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THE PREDICTIVE ROLE OF OBESITY FOR MATERNAL AND CHILD HEALTH IN THE FIRST YEAR OF LIFE

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Abstract. Over the past few decades, the prevalence of obesity worldwide has reached epidemic proportions. Obesity and overweight during pregnancy are associated with worse maternal and child outcomes. In addition, studies show that maternal obesity can lead to long-term consequences for the offspring, increasing the risk of neuropsychiatric disorders, metabolic, atopic diseases, and possible changes in the immune / inflammatory status. In addition to genetic mechanisms, a growing body of evidence suggests the induction of epigenetic changes by maternal obesity, which may influence offspring phenotype, thereby influencing later risk of obesity and cardiometabolic disease. However, the mechanisms linking the maternal environment to adverse short and long term outcomes remain poorly understood. This review presents current knowledge about the impact of maternal obesity on a child in the first year of life. Understanding these processes is key to developing therapeutic interventions to prevent future cardiovascular and metabolic pathologies in future generations.

Key words: *maternal obesity; perinatal period; metabolic syndrome; offspring of obese mothers; mother–placenta–fetus.*

ПРОГНОСТИЧЕСКАЯ РОЛЬ ОЖИРЕНИЯ ДЛЯ ЗДОРОВЬЯ МАТЕРИ И РЕБЕНКА В ПЕРВЫЙ ГОД ЖИЗНИ

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Резюме. За последние несколько десятилетий распространенность ожирения во всем мире достигла масштабов эпидемии. Ожирение и избыточный вес во время беременности связаны с ухудшением исходов для матери и ребенка. Кроме того, исследования показывают, что материнское ожирение может привести к долгосрочным последствиям для потомства, увеличивая риск развития психоневрологических расстройств, метаболических, атопических заболеваний, а также возможных изменений иммунного / воспалительного статуса. В дополнение к генетическим механизмам все больше данных свидетельствует об индукции эпигенетических изменений материнским ожирением, которые могут влиять на фенотип потомства, тем самым программируя риск ожирения и кардиометаболических заболеваний. Однако механизмы, связывающие материнскую среду с неблагоприятными краткосрочными и долгосрочными последствиями, остаются плохо изученными. В данном обзоре представлены современные знания о влиянии материнского ожирения во время беременности на ребенка в первый год жизни. Понимание этих процессов имеет ключевое значение для разработки терапевтических вмешательств с целью предотвращения будущих сердечно-сосудистых и метаболических патологий у последующих поколений.

Ключевые слова: *материнское ожирение; перинатальный период; метаболический синдром; потомство матерей с ожирением; мать–плацента–плод.*

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INTRODUCTION

Obesity is a serious medical and social problem in modern medicine, it reaches epidemic proportions worldwide. In 2022, according to the World Health Organization report on obesity in Europe, about 55.5% of adult population is overweight and obese. The prevalence of obesity in women of childbearing age is steadily increasing [1]. In 2017–2018, the prevalence of obesity in women of childbearing age in the US was about 40% [2–4], in the UK, 21.6% of women had obesity and 27.4% were overweight. In Scotland in 2021, 25.9% of women were obese by the time of pregnancy [3]. Statistical data in the Russian Federation echo the global trend. Thus, according to the results of the epidemiologic study ESSE-RF (Epidemiology of cardiovascular diseases and their risk factors in the regions of the Russian Federation) in 2013–2014, obesity was found in almost every third citizen of Russia. The second wave of the ESSE-RF program, conducted in 2017, included 17 regions and more than 26,000 participants of both sexes aged from 20 to 64 years. The results of the study showed that obesity was registered in 27.9% of men and 31.8% of women, the prevalence of obesity in women of childbearing age reached 25% [5]. Currently, the problem of obesity in women of childbearing age is urgent, according to recent studies demonstrating the adverse effect of maternal obesity on the health of offspring. Obesity significantly complicates the course of pregnancy and labor, contributing to obstetric complications 2–3 times more often than in women with normal body mass index [6–8]. In addition, women with obesity are more likely than women with normal body mass index (BMI) to have excessive gestational weight gain, which has also been shown to increase obstetric and perinatal risks [9–12].

THE IMPACT OF MATERNAL OBESITY ON FETAL GROWTH AND DEVELOPMENT. PERINATAL RISKS

Numerous studies have proven the role of maternal obesity in the formation of various complications of pregnancy and childbirth, such as pregnancy failure, preeclampsia, gestational diabetes mellitus, gestational arterial hypertension, labor anomalies, increased incidence of operative delivery, bleeding in labor and early postpartum period, maternal and fetal traumas, surgical infections, and delayed fetal intrauterine development [14–18]. In addition to complications of pregnancy and labor, perinatal risks, the mechanisms of long-term effects of maternal obesity on offspring are actively studied. Currently, there are sporadic studies investigating the impact of maternal obesity in the first year of a child's life, the influence of genetic and epigenetic factors.

During pregnancy, significant anatomical and physiological changes occur in many organs and systems of a woman's body to ensure nutrition and development of the fetus. One of the important mechanisms of physiologic adaptation of the maternal body to pregnancy is the controlled production of cytokines, inflammatory and proinflammatory factors by different cell subtypes at the maternal-fetal interface, since strict regulation of inflammatory factors is required for implantation, placentation, and continuation of pregnancy [19, 20]. Maternal obesity is associated with changes in the profile of the inflammatory response, which directly affects physiologic adaptation. Pregnancy with obesity and excessive body weight results in low-grade chronic inflammation secondary to an impaired immune cell profile, subsequently leading to activation of pro-inflammatory mechanisms. This condition has the name "metaflammation" in the current literature. Nowadays, metaflammation is recognized as a major factor affecting offspring health in early life [21, 22]. Three immunological stages based on the body's inflammatory response during pregnancy have been described [20, 23]. In the first trimester, the initial pro-inflammatory stage is important for implantation and placentation. With the onset of the II trimester, Th2-type anti-inflammatory and immune stage appears, which is necessary for fetal growth. In the III trimester, the pro-inflammatory stage and Th1-type immune activation initiate labor and delivery [20–23]. In addition to the important role of Th1 and Th2 cells during pregnancy, other T-helper cells such as T-helper 17 (Th17), T-helper 22 (Th22), follicular T-helper (Tfh) and regulatory T-cells (Treg) of the mother and fetus contribute to the continuation of a healthy pregnancy. Th17 and Th22 cells are involved in the induction of immunity against extracellular pathogens at the maternal-fetal interface [20–22]. Uncontrolled Th1 and Th17 response is associated with implantation failure and pregnancy failure [21–28]. Treg cells enhance fetal immune tolerance by suppressing excessive Th1 and Th17 activity and autoimmune response [29]. Follicular T-helper cells in the third trimester provide humoral immunity by activating B-cells to initiate an antibody response outside the follicular and germinal center [30]. Type 1 (Th1) and type 2 (Th2) T-helper cells represent the two major subsets of CD4 T-helper cells that regulate the adaptive immune response [31]. Th1 cells produce high levels of interferon-γ (IFN-γ), interleukin-2 (IL-2), tu-

mor necrosis factor (TNF) and are responsible for phagocyte-dependent inflammation as well as for defense against intracellular pathogens [31]. They also play an important role in the development of organ-specific autoimmune diseases and chronic inflammatory diseases [31]. Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, which leads to an excessive immune response by switching B cells, activating eosinophils and inhibiting phagocytic activity [32]. Despite some inconsistent results, a lot of studies, found in the current literature, show that mothers with obesity before pregnancy have increased levels of pro-inflammatory cytokines such as IL-8, IL-6, CRP, TNF-α and IFN-γ and altered levels of adipokines [33–40]. Inflammation occurring against a background of maternal obesity leads to impaired placental development, which affects both maternal and placental inflammatory profiles [41–43]. Nowadays, the influence of cytokines on implantation and remodeling of spiral arteries has been proven. For example, abnormally high levels of TNF-α can lead to impaired remodeling of spiral arteries [44], and IL-6 increases trophoblast cell migration and invasion, while TNF-α decreases it [45–48]. Recent studies have demonstrated that maternal obesity is associated with increased placental mass and decreased placental efficiency, indicating an adaptation to increased nutrient availability to regulate fetal growth [49–54]. A linear correlation between placental mass and birth weight has also been found [49, 54]. Placental transport has a significant influence on the fetal intrauterine environment [55]. In pregnancies with a background of obesity, abnormal placental vasculature is the most common placental pathology [53, 56–59]. Placental vascular growth is regulated by angiogenic factors including VEGF, placental growth factor (PlGF) forming growth factor-β (TGF-β) and leptin, as well as anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) [7–9, 51]. By the end of the second trimester, the villous vessels begin to form loops and wriggle, dramatically increasing the surface area for nutrient and gas exchange [60]. The imbalance between pro- and anti-angiogenic factors is considered an important link in the pathogenesis of preeclampsia and intrauterine developmental delay [65]. Obesity has been proven to be associated with increased placental expression of VEGF, decreased levels of circulating PlGF and sFlt-1 [66, 67]. Thus, maternal obesity impairs the development of placental architecture, potentially jeopardizing fetal growth and survival [60].

In the early stages of physiologically normal pregnancy, insulin sensitivity is increased, which promotes glucose uptake by adipose tissue, which in turn prepares the body for increased energy requirements later in pregnancy [61]. Obese women have 50–60% higher postprandial insulin concentrations than women with normal body mass in both early and late pregnancy [62]. Women with obesity also have greater glucose tolerance compared to pregnant women with normal BMI, as evidenced by higher fasting glucose levels 1 and 2 hours after the oral glucose tolerance test (OGTT) [62]. Although glycemic values may not meet the criteria for gestational diabetes mellitus (GDM), an abnormal response to the OGTT in obese women is associated with the risk of delivering a fetus large for gestational age [63]. In addition, in obese or overweight pregnant women, increased levels of circulating cytokines in the maternal blood, such as TNF-α and IL-6, have been reported. This association has been proven in the development of insulin resistance in the first and second trimesters of pregnancy [64–66].

In studies carried out on animal models and then repeated in humans, it was found that maternal obesity leads to decreased transport of oleic acid in the placenta in male children, which is associated with decreased expression of the CD36 transporter (fatty acid translocase) and intracellular fatty acid binding protein (FABP 5) [67]. Increased lipid transfer to the fetus contributes to the development of adipose tissue, and thus the risk of developing overweight offspring [68]. Hyperlipidemia and vascular dysfunction may be an important mediator of cardiometabolic diseases observed in offspring born to obese mothers. Considering all the above mechanisms, it can be concluded that maternal obesity has deleterious effects on offspring health. Short-term adverse fetal outcomes in infants of obese mothers include increased risk of fetal overgrowth, stillbirth, and neonatal hypoglycemia [69, 70]. A meta-analysis of published data from 38 cohorts showed that maternal obesity and even small increases in BMI were associated with an increased risk of intrauterine and infant death. For women with BMI >30 kg/m^2, the absolute risk per 10,000 pregnancies was 102 and 43 intrauterine and infant deaths, respectively [71]. Pregnancies of overweight women are associated with a 2–3-fold increased risk of fetal macrosomia; this is associated with an increase in absolute fetal size and its fat mass [72–74]. Some studies suggest that the programming of obesity in offspring by maternal obesity may be partially sex-specific, basically, male offspring have a greater susceptibility to the risks of developing of obesity compared to female offspring born to obese mothers

[75]. Fetal overgrowth is the main reason for the increased incidence of cesarean section [76, 77]. Severe neonatal hypoglycemia occurs in 10–15% of neonates and can lead to nervous system damage [78]. In maternal obesity, neonatal hypoglycemia is usually transient and occurs because of inadequate, persistent hyperinsulinemia caused by higher than normal concentrations of glucose in the womb [79].

REGULATORY FACTORS AT THE LEVEL OF MOTHER-PLACENTA-FETUS IN MATERNAL OBESITY

Data from recent studies demonstrate that adipose tissue is an important endocrine organ involved in metabolism through several mechanisms, the most important of which is the secretion of bioactive mediators by adipocytes and other cells [80–88]. These bioactive substances, collectively referred to as "adipokines", are important in the pathophysiology of insulin resistance, hyperlipidemia, inflammation, and metabolic syndrome [89–100]. Metabolic adaptation begins early in pregnancy and is accompanied by changes in maternal hormone production, including prolactin, estrogen, progesterone, and cortisol [101, 102]. Placental hormone secretion, which begins immediately after implantation and continues all pregnancy, is important for maternal metabolic adaptation through indirect modeling of endocrine axes and direct changes in maternal metabolic systems [103].

Glucose metabolism. Glucose is a major substrate for placental and fetal energy metabolism, and normal pregnancy causes marked changes in maternal glucose metabolism, including insulin resistance, activation of hepatic glucose production, and increased insulin release by pancreatic β-cells with higher plasma C-peptide levels; these mechanisms contribute to placental and fetal glucose delivery [61]. Early in gestation, fasting glycaemia levels decrease (compared with pre-pregnancy glucose levels), in part due to hemodilution associated with an increase in maternal circulating blood volume. Maternal fasting glycaemia remains consistently low in the second trimester and reaches even lower values in the third trimester: this is due to increased glucose utilization by the fetal-placental complex [62]. Maternal fasting hypoglycemia during pregnancy is compensated for by increased hepatic gluconeogenesis, which contributes to elevated blood glucose levels and helps maintain nutrient supply to the fetus [63–69]. In contrast, postprandial glucose levels progressively increase during pregnancy compared to pre-pregnancy levels [106, 107]. This is due to impaired peripheral tissue sensitivity to insulin and hence decreased maternal glucose utilization after meals [108]. Obese women have a higher glucose profile than women with normal BMI [70–73]. Maternal glycaemia is a strong determinant of fetal growth, as evidenced by the continuous association of maternal glucose levels with increasing birth weight [65–67].

Insulin. Early in pregnancy, the mother has increased secretin levels and insulin sensitivity, which stimulates lipogenesis and decreases fatty acid oxidation, causing maternal fat accumulation. In mid-pregnancy, insulin resistance develops to direct available nutrients for fetal growth and development. This state of insulin resistance is exacerbated in pregnant women with a background of GDM or obesity [68–71]. Insulin resistance in obesity leads to maternal hyperglycemia and, consequently, fetal hyperglycemia, because glucose freely passes through the placenta [72–78]. It is already known, that insulin plays a neurotrophic role for many brain regions; it inhibits neuronal apoptosis through activation of protein kinase B and protein kinase C, resulting in increased neuronal survival [79–85]. High insulin levels are essential for proper brain maturation [86]. However, chronic hyperinsulinemia, which is proven to be more common in obese mothers, corresponds to high fetal insulin levels, which contributes to fetal insulin resistance [87–94]. Maternal obesity is also associated with characteristic changes in the release of adipokines, which have systemic effects on metabolism and energy homeostasis [95–98].

Adiponectin. Adiponectin is one of the adipokines produced by adipocytes and the most abundant product of adipose tissue and accounts for 0.01% of total plasma proteins. It plays an important role in the relationship between adipose tissue and other metabolic tissues such as liver and skeletal muscle [45–47]. Adiponectin suppresses hepatic gluconeogenesis and contributes to insulin sensitization [45–59]. As opposed to other adipokines, although it is secreted by adipocytes and its plasma concentration is inversely correlated with BMI [56, 99–102]. During pregnancy, adiponectin levels decrease as the insulin resistance develops in pregnant women, which contributes to decreased glucose uptake and increased lipolysis, moving nutrients such as glucose and lipids to the fetus [103–109]. Studies in mice have shown that in maternal obesity, fetal adiponectin enhances fetal fat deposition, thereby increasing fetal body weight, proving the important role of adiponectin in the regulation of maternal meta-

bolism, placental function, and fetal development [110–114].

Leptin. Leptin is released from adipose tissue in proportion to its mass. Leptin levels increase throughout pregnancy, reaching a maximum level in the third trimester. Overweight or obese mothers have higher levels of serum leptin before pregnancy, so throughout pregnancy, leptin concentrations are higher in mother and fetus compared to mothers with normal BMI [85, 87]. Leptin involved in the development of the nervous system as it is an important trophic factor. In studies, leptin has been shown to bind to the receptors of the satiety center in the hypothalamus and form a negative feedback loop, suppressing increased food intake and thus preventing obesity [36]. It is shown in studies that have been carried out on animal models that obesity is associated with hyperleptineamia in both females and their offspring, and maternal obesity leads to the formation of resistance to leptin and, consequently, the inability of leptin to cause anorexic effects [92].

Ghrelin. Ghrelin is a gut hormone with a strong orexigenic signal. After entering the bloodstream, ghrelin circulates in two major forms: acyl ghrelin and des-acyl ghrelin. The maternal concentration of total ghrelin decreases slightly throughout pregnancy, and there is a positive correlation between the ratio of acylated to total circulating ghrelin in mothers in the third trimester of pregnancy and the baby's birth weight [106–110]. Levels of total ghrelin in cord blood are inversely correlated with neonatal birth weight [115–117]. Studies in animal models and humans have shown that maternal ghrelin regulates fetal development in late pregnancy. Administration of ghrelin to mice during the last week of gestation caused a 10–20% increase in body weight in the offspring [118]. In studies on mice, it was shown that ghrelin has an inhibitory role in the development of neural connections of hypothalamus, acting as a "break" in the balance of the neurotrophic action of leptin, and, therefore, proper expression of ghrelin in the neonatal period is important for children and in older age.

Pre-adipocyte factor. Pre-adipocyte factor (PREF-1) is a secreted protein that inhibits adipocyte differentiation both in vitro and in vivo. Pre-adipocyte factor is synthesized as a transmembrane protein whose ectodomain containing repeats of epidermal growth factor, is cleaved by tumor necrosis factor-α-converting enzyme to release a biologically active soluble form [104–108, 118]. The importance of PREF-1 in adipogenesis has been demonstrated in animal models. Mice experimentally deprived of pre-adipocyte factor had growth retardation, skeletal abnormalities, tendency to obesity, impaired insulin sensitivity and decreased glucose tolerance, which confirms the role of PREF-1 in the regulation of adipocyte differentiation [13]. During embryonic development, PREF-1 is widely expressed in numerous embryonic tissues: multipotent mesenchymal stem cells, pancreatic glandular cells, ovarian and male glandular cells, and is also involved in the differentiation of the central nervous system, hepatocytes, respiratory epithelial cells, mesodermal cells of the renal proximal tubule, and adrenal cortex [119–121]. Increased levels of PREF-1 are detected in serum, urine, and amniotic fluid during the second trimester of pregnancy [53]. After birth, PREF-1 expression ceases in most tissues and is observed in a limited number of cells: preadipocytes, pancreatic islet cells, thymus stromal cells, and adrenal cortex cells [28, 97].

Growth hormone. Growth hormone is well known for its function in stimulating cell growth, reproduction, and regeneration, so it is extremely important for development. Recent research findings suggest that the brain is an important target for growth hormone in the regulation of food intake, energy expenditure and glycaemia, especially in response to various forms of metabolic stress such as glucoprivation, food restriction and exercise [122–125]. During pregnancy, growth hormone action is associated with the regulation of maternal food intake, insulin and leptin sensitivity, suggesting that growth hormone and other gestational hormones are important in preparing the maternal body for the metabolic needs of the offspring [126]. Currently, little is known about the programming effects of maternal and/or fetal growth hormone on hypothalamic development in the offspring. There is some evidence that growth hormone regulates hypothalamic neurocircuits that control energy homeostasis [59].

Pro- and anti-inflammatory cytokines. Numerous studies show that maternal obesity further increases concentrations of pro-inflammatory cytokines such as IL-6, TNF-α, monocyte chemoattractant protein 1 (MCP-1), IL-8 and C-reactive protein in plasma, supporting the concept that the low pro-inflammatory state associated with normal pregnancy is exacerbated by maternal obesity [127]. The biological effects of pro-inflammatory cytokines are counterbalanced by anti-inflammatory cytokines such as IL-1, IL-4, IL-6, IL-10, IL-11 and IL-22 [63]. Obesity is now considered as a key factor in the development of chronic inflammation [96, 128], which is important in the pathogenesis

of pre-eclampsia, gestational diabetes mellitus [129]. Chronic inflammation has unfavorable significance for fetal programming. In a recent animal study, it was shown that the offspring of rats injected with IL-6 throughout pregnancy had more body fat compared to the control group, and male offspring had reduced insulin sensitivity [130].

Lipids. During pregnancy, in maternal organism, a lipid accumulation occurs in the I and II trimesters, and subsequently there is an increase in adipose tissue lipolysis. The catabolic state of female adipose tissue in late pregnancy is associated with hyperlipidemia, mainly corresponding to an increase in plasma triglyceride levels, and a smaller increase in phospholipid and cholesterol levels [70]. Maternal obesity is associated with increased lipid levels, higher triglyceride and very-low-density lipoprotein (VLDL) levels and lower cholesterol, high-density lipoprotein (HDL) levels than women with normal BMI [131]. Several recent studies have shown that maternal postprandial triglycerides and free fatty acids are stronger predictors of neonatal weight gain than maternal glucose levels in obese pregnancies [45]. The amount and nature of fatty acid intake during pregnancy are important for brain development and hypothalamic function in the offspring. Hypothalamic dysfunction was observed in the offspring of mice and rats born to animals that consumed increased amounts of saturated or trans fatty acids [132, 133]. Excessive nutrition usually activates hypothalamic inflammatory signaling through increased endoplasmic reticulum stress in the hypothalamus, which serves as a mechanism for the energy imbalance underlying obesity [76]. In obese pregnant women, offspring have increased level of inflammation in the hypothalamus [58] due to elevated levels of circulating fatty acids [134–138]. It has been suggested that fatty acids play an important role in the hypothalamic dysfunction observed in offspring born to mothers who consume increased amounts of saturated or trans fatty acids, and the mechanisms underlying these changes may be related to endoplasmic reticulum stress and hypothalamic inflammation.

Nowadays, the role of brain-derived neurotrophic factor and peptide YY in regulation at the maternal-placenta-fetal level in maternal obesity and their further effects on child growth and development remain poorly understood [102, 113, 139–141].

THE IMPACT OF MATERNAL OBESITY ON OFFSPRING HEALTH

In addition to adverse intrapartum and perinatal outcomes, maternal obesity is also associated with the development of chronic diseases in children later in their life. In 1990, David Barker proposed an "adult disease origins" model in which he hypothesized that exposure to a suboptimal environment early in life shapes an individual's future health [80]. Initially, he showed that adults born with low birth weight secondary to intrauterine developmental delay due to inadequate nutrient intake were at higher risk of developing metabolic and cardiovascular diseases. Conversely, conditions associated with intrauterine "overeating" and increased inflammation, such as gestational diabetes mellitus and maternal obesity, negatively impact the long-term health of the offspring. Evidence from recent studies suggests that activation of the proinflammatory state during pregnancy is associated with long-term offspring diseases, including childhood obesity, neuropsychiatric disorders, and allergic diseases [135].

Neuropsychiatric disorders. In recent years, there is increasing evidence that children born to obese mothers are more prone to neurodevelopmental and neuropsychiatric disorders. There is evidence that children born to obese mothers have lower intelligence quotient (IQ), higher rates of autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), cerebral palsy (CP), and mood disorders [45, 47, 136–138]. In studies on animal models, maternal obesity more often led to neuropsychiatric diseases in offspring, which is associated with significant changes in brain structure in the form of decreased proliferation of neural precursors in the hippocampus, reduced apoptosis in the hippocampus and neuronal differentiation in the dentate gyrus, atrophy of dendrites in the hippocampus and amygdala, and reduced myelination in the cerebral cortex in offspring (predominantly male offspring) [205–209]. It was also shown that offspring born to obese mothers had problems in education, behavioral disorders in the form of hyperactivity, anxiety, decreased sociability, addictive behavior, and food intake disorders [139]. Edlow et al. in their study found that the offspring of mice born to obese animals had increased production of TNF-α in response to polysaccharide exposure in placental CD11b cells compared to control group [140]. The increase in pro-inflammatory cytokines was more significant in male offspring, which may correlate with the prevalence of some neuropsychiatric diseases associated with maternal obesity in males [140–142]. From these findings, it has been hypothesized that it is neuroinflammation and oxidative stress, which arise through increased expression of proinflammatory cytokines,

increased lipid peroxidation and microglia activation in offspring born to obese mothers, that play an important role in adverse neurodevelopmental outcomes [26]. The pro-inflammatory environment affects the metabolism of brain-derived neurotrophic factor (BDNF), which is essential for hippocampal neurogenesis. Alterations in BDNF metabolism and tryptophan hydroxylase (TPH2) expression are associated with anxiety disorder in adulthood [29, 130].

Impact on the immune system. There is evidence that maternal obesity and chronic inflammation during pregnancy increase the risk of developing different chronic diseases in offspring. A lot of such diseases have features of altered immune/inflammatory activation [143–145]. Reviews in recent years have provided evidence of altered fetal immunity in response to maternal obesity [36–38]. In a study conducted by Enninga et al. an increased number of CD4+ lymphocytes and decreased levels of IL-12p40 and chemokines were detected in the cord blood of infants born to obese mothers [146]. In another small cohort study, cord blood from the placenta of obese mothers showed increased numbers of CD3+, CD4+, CD8+, NK and CD8 + CD25 + Foxp3 + Treg lymphocyte subpopulations, while CD34 cells were decreased [40]. Moreover, the effect of maternal obesity on decreased response of fetal monocytes and dendritic cells to toll-like receptor ligands has been proved [147]. The toll-like receptor family plays a key role in the proinflammatory response to bacterial infections; consequently, dysregulation of toll-like receptor signaling is associated with bacterial diseases, including necrotizing enterocolitis [148]. Most of these studies are performed using circulating immune cells and probably do not reflect the specificity of immune cells in different organ systems. Kamimae-Lanning investigated the effect of maternal obesity on hematopoietic stem cells (HSCs) and progenitor cells isolated from the liver of fetal mice [149]. The results showed that female mice that were continuously fed a high-fat diet exhibited not only signs of adverse fetal programming, including growth restriction, but also a decrease in HSCs and progenitor cells in the fetal liver. Despite the decrease in the total number of HSCs and progenitor cells, the proportion of B220+ lymphoid and Gr1+/Ter119+ myeloid cells in the liver was increased, indicating a tendency toward myeloid and B-cell differentiation [43].

Atopic diseases. Several studies and meta-analyses show that children born to obese mothers are at higher risk of developing atopic diseases, including atopic dermatitis and bronchial asthma [44–51]. Probably, this is due to altered function of immune checkpoints in offspring born to obese mothers that regulate development of allergy. Elevated levels of maternal TNF-α and pro-inflammatory cytokines, which are significantly elevated in obese mothers, have been associated with frequent lower respiratory tract infections and wheezing in offspring [52, 150]. In animal models, MacDonald et al. showed that the contents of bronchoalveolar lavage in offspring born to obese mice had an increased percentage of neutrophils and an increased concentration of IL-6, which allowed them to propose a theory about the role of the influence of an active proinflammatory state in reactive respiratory diseases in children born to obese mothers [151]. In the same study, increased bronchial hyperreactivity was observed during methacholine provocation test [34]. In 2019, Smoothy et al. found increased concentrations of Th1 (TNF-α) and Th2 (IL-5, IL-33) cytokines in bronchoalveolar lavage of obese mice, without any neutrophilia or eosinophilia, and it was hypothesized that these mice are more prone to hyperreactivity to further exposure to allergens or exposure to viruses [152]. Another study found that offspring born to obese mice exhibited an enhanced sensitization reaction in response to allergen (ovalbumin) administration, which was characterized by overproduction of IL-4, IL-13, TNF-α and TGF-β1 [153]. The same study demonstrated that mice born to obese mothers exhibited increased eosinophilic/neutrophilic infiltration in the parenchyma of lungs, increased collagen deposition and increased mucus hypersecretion [56]. A study conducted by Castro-Rodriguez et al. in 2020 showed an association of high levels of leptin in cord blood with a higher risk of bronchial asthma in children aged 3 years born to obese mothers [154].

Cardiometabolic diseases. The effect of maternal obesity on the risk of cardiometabolic disease in offspring in childhood and adult life has been demonstrated in human and animal models [58, 155]. Cardiometabolic diseases are a complex phenotype of cardiovascular and metabolic dysfunction characterized by insulin resistance, impaired glucose tolerance, dyslipidaemia, obesity, arterial hypertension, and cardiovascular diseases. Recent studies have demonstrated that children born to obese mothers are at higher risk of future cardiovascular disease (excluding congenital heart disease) [155], and a positive correlation was found between maternal pre-pregnancy BMI and increased blood pressure in the child, regardless of the child's BMI [23, 156]. In addition to cardio-

vascular diseases, children born to obese mothers are susceptible to developing of obesity at early age. Evidence from observational studies of mothers and their children in Europe, North America and Australia showed that high maternal BMI before pregnancy and increased body weight during pregnancy were associated with an increased risk of overweight and obesity in offspring throughout childhood [26]. Recent studies have demonstrated the important role of levels of adipokine and leptin in the formation of obesity in children and adults. Obesity is associated with a state of hyperleptinemia and decreased tissue sensitivity to leptin, which subsequently leads to impaired regulation of energy homeostasis [69]. Leptin is secreted into the blood by adipocytes, regulates appetite, metabolism and energy homeostasis, and increases insulin secretion by pancreatic β-cells [157, 158]. During pregnancy, leptin levels regulate fetal development and growth and are positively correlated with neonatal body weight and fat mass [71–75]. Several studies have shown that low levels of cord blood leptin in children predict increased body weight and body length at 2–3 years of age [159]. Leptin and insulin control metabolism of glucose by acting at peripheral and central units [160]. Insulin is a key regulator of leptin metabolism; hyperinsulinemia leads to an increase in serum leptin concentrations [144–159]. Such infants were more resistant to insulin with a positive correlation with neonatal fat deposition [42, 94]. In the view of fact, that leptin and insulin are factors that influence the development of hypothalamus, nervous system, and involved in appetite regulation. It is shown that maternal obesity programs obesity in their offspring with occurrence of hyperphagia. The hyperphagia has been observed in several different rodent models of maternal obesity in both male and female offspring [161]. Considered, that this hyperphagic phenotype may be caused by altered development and function of hypothalamic circuits that regulate appetite and energy expenditure. The timing of the maximum level of neonatal leptin in rodents is a critical window for the development and maturation of hypothalamic neural connections, because the correct levels and timing of influences are required for proper hypothalamic development. Thus, any influences that result in under- or over-exposure to leptin during these critical periods of development may have negative consequences. In animal models, newborn rats born and obese animals have been shown to have an enhanced and prolonged postnatal leptin surge [162]. Studies both in human and animals show that maternal obesity has sex-specific effects on glucose metabolism and cardiometabolic profiles in male offspring [163]. One theory is differences in pancreatic β-cell function that are partially associated with increased oxidative stress in the islets of Langerhans and decreased plasma estradiol levels in male offspring. Maternal obesity induces insulin resistance and impairs pancreatic β-cell function, accompanied by inflammation in adipose tissue and hepatic steatosis with marked sex differences [91]. Estrogen in female offspring may play a protective role against oxidative stress induced by the effects of maternal obesity [164].

Diseases of urinary system. Recent studies have shown an association between maternal obesity and congenital abnormalities of the urinary system and reduced volume of fetal kidney in late pregnancy compared with fetal body weight [93–95]. Since kidney volume is proposed as an approximate measure of the number of nephrons, maternal obesity may be associated with a reduction in the number of fetal nephrons, potentially leading to hyperfiltration with further development of chronic kidney disease [165, 166]. In contrast, a study in animal models (rats) showed no effect on the number of fetal nephrons late in pregnancy in obese females [108]. However, there was evidence of increased cellular stress, inflammation and apoptosis in the kidneys of fetuses of obese females [167]. In the postnatal period, studies in rodent have shown that offspring from obese mothers show abnormalities in kidney structure due to oxidative stress and fibrosis [99–102, 168, 169]. A potential mechanism for programming renal dysfunction in offspring is the depression of sirtuin 1 (SIRT1) expression induced by maternal obesity [170, 171]. Sirtuin 1 is a key regulator that promotes lipid utilization and suppresses lipogenesis. It's well known, SIRT1 is reduced in cells with high insulin resistance [109, 110]. Maternal obesity during intrauterine development can lead to increased formation of glomerulosclerosis in response to inflammation with further decline in renal function [60].

Features of breastfeeding. Mother's milk realizes the connection between the health of the mother and the offspring. The triad "mother — breast milk — infant" is a unified system, the basic mechanisms of which have not yet been fully elucidated. The nature of nutrition of a pregnant woman significantly affects the development of the fetus, the state of health of the child in the future. Obese women are less likely to initiate breastfeeding than normal-weight women, and are more at risk of lactation difficulties, which may lead to discontinuation of breastfeeding [61].

Lactation function in women with obesity is affected by physiological (delayed lactogenesis or reduced prolactin production in response to suckling) and psychosocial factors [62–64]. The trophic status of a lactating woman affects the composition of breast milk and, consequently, the rate of growth and development of the infant. One of the main sources of energy is lipids. A systematic review of 11,373 publications found a positive correlation between maternal BMI and the amount of fat in breast milk. For every unit of maternal BMI, 0.56 g/L of fat was added to breast milk, and this association was observed from the 1st to the 6th month after delivery. There was no significant association between maternal BMI and the energy value of milk, lactose content and total protein [168, 169]. There is also evidence that the milk of an obese mother contributes to the formation of components of metabolic syndrome in the child in the future life.

MATERNAL OBESITY AND GUT MICROBIOTA IN CHILDREN

The hypothesis that the gut microbiota is an important factor in the pathogenesis of obesity has led to the investigation of its diversity in a group of overweight and obese individuals. The first evidence suggesting a link between the gut microbiota and obesity was suggested by Ley et al. in a study using 16SrRNA genome sequencing. In their work in animal models, they identified the two most abundant types of bacteria, *Firmicutes* (60–80%) and *Bacteroidetes* (20–40%), which differed proportionally in obese mice compared to mice with normal BMI [170]. Specifically, obese mice showed a 50% decrease in the *Bacteroidetes* population and a proportional increase in *Firmicutes*. Of particular interest were the results which revealed that after dietary treatment, the relative abundance of *Bacteroidetes* increased and *Firmicutes* decreased [171–180]. Turnbaugh et al. confirmed the increased ratio of *Firmicutes* and *Bacteroidetes* in obese mice compared to lean mice in animal models using the latest DNA metagenomic sequencing technique [176, 179]. Moreover, obese mice had a higher proportion of archaea in the microbial communities of the caecum [43]. Armougom et al. in their study evaluated the expression profiles of gut microbiota using real-time PCR and found significantly reduced levels of *Bacteroidetes* in obese individuals compared to those with normal BMI, whereas the concentration of *Firmicutes* was similar in the compared groups [173]. Species-specific variations of *Lactobacillus* in patients with obesity, such as *L. reuteri* and *L. Gasseri*, and lower concentrations of *Ruminococcus* flavefaciens, a subgroup of *Ruminococcus* flavefaciens belonging to the bacterial subdivision *Firmicutes*, were also observed in obese individuals [45, 146]. In another study investigating the relationship between gut microbiota, genotype and host's weight, Turnbaugh et al. analyzed the composition of the gut microbiota in monozygotic and dizygotic twins with normal BMI and obesity and their mothers [170]. The results showed that obesity was associated with a low proportion of *Bacteroidetes* and a higher proportion of *Actinobacteria* in obese individuals compared to lean people, but no differences in the phylum *Firmicutes* were found between groups [176, 179]. Numerous studies in recent years have focused on the dynamics of changes in the levels of the bacterial types *Bacteroidetes* and *Firmicutes* in people both with obesity and loss of weight, but there are researches linking obesity in mice to specific bacteria, particularly *Halomonas* and *Sphingomonas*, and decreased numbers of *Bifidobacteria* [180]. A special place in the genesis of obesity is also allocated to archaea — *Methanobrevibacter* is the main representative of archaea in the gut microbiota [149]. Zhang and Armougom et al. found higher numbers of *M. smithii* in obese people compared to a group of people with normal BMI [131, 138, 153, 178]. Currently, there are several putative mechanisms that contribute to the development of obesity. The first is that different strains of the gut microbiota are able to induce low-grade inflammation by stimulating the production of pro-inflammatory cytokines [181–196]. Gram-negative bacteria such as *Bacteroidetes* produce lipopolysaccharide (LPS, endotoxin), which is an important component of the cell wall [197–215]. Cani et al. described that a high-fat diet increases LPS levels, and observational studies have reported diurnal fluctuations in plasma LPS concentration, termed "metabolic endotoxemia" [216]. The pattern of weight gains, visceral and subcutaneous obesity in LPS-injected mice was similar to those observed in mice fed a high-fat diet [217]. In addition, "metabolic endotoxemia" triggered the expression of inflammatory cytokines and serum amyloid A (SAA) proteins. Overgrowth of Gram-negative bacteria such as *Veillonella* in obese individuals can lead to a higher dose of LPS in the intestine, consequently it can disrupt the intestinal barrier through activation of the TLR4/MyD88/IRAK4 signaling pathway in intestinal epithelial cells, resulting in the movement of LPS from the intestine into the bloodstream [183, 184]. When circulating systemically, LPS is able to initiate an immune response in adipose tissue and liver. LPS

first binds to lipopolysaccharide-binding protein, forming a complex with CD14, further inducing the expression of activator protein 1 and nuclear factor kappa B (NF-kB) by activating toll-like receptor 4 (TLR4), expressed on macrophages and adipose tissue, which promotes the secretion of pro-inflammatory cytokines and chemokines including TNF-α, IL-6, and monocyte chemoattractant protein-1 (MCP-1) [218, 219]. These cytokines can influence adipocytes and stimulate cytokine and chemokine secretion by autocrine and paracrine pathways [185–191, 220–224]. Moreover, MCP-1 overexpression in adipose tissue has been shown to be associated with increased macrophage infiltration in rodents [225].

It's known, the gut microbiota is involved in the central modulation of appetite through the production of gut hormones such as peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and neurotransmitters. *Bifidobacterium* and *Lactobacillus* can produce lactate, which serves as a substrate for neuronal cells, thereby prolonging the postprandial feeling of satiety [226]. Acetate is able to activate the citric acid cycle in the hypothalamus and further alter the expression profile of neuropeptides regulating satiety [194]. Butyrate affects appetite and eating behavior of the host by activating the vagus nerve and hypothalamus, it is able to cross the blood-brain barrier [193]. Bile acids, short-chain fatty acids and indoles are closely related to the secretion of intestinal hormones by neuroendocrine cells [195–198]. GLP-1 and PYY are the potent anorexigenic hormones that can influence host appetite and eating behavior by binding to their receptors locally distributed in intestinal neurons, vagus nerve afferents, hypothalamus and brainstem [51, 199, 227–230]. The gut microbiota also leads to the production of neurotransmitters, including γ-aminobutyric acid (GABA) and serotonin [37]. GABA, as the predominant inhibitory neurotransmitter of the nervous system, has the ability to stimulate appetite, while serotonin contributes to appetite suppression through regulation of melanocortin neurons [200–204].

In addition, the gut microbiota influences the food center and eating behavior through the regulation of mood. On the one hand, gut microbiota is able to alter mood by affecting the production of bacterial metabolites, gut hormones and neurotransmitters that act as important messengers in gut-brain interactions and further regulate host appetite and eating behavior [47, 205]. On the other hand, the gut microbiota is involved in the regulation of mood and reward pathways, which presumably influence brain circuits related to eating behavior [206–210, 231].

MATERNAL OBESITY IN PREGNANCY AND CHANGES IN GUT MICROBIOTA

The composition of gut microbiota in pregnant women with obesity differs from that of pregnant women with normal BMI. Physiological shifts in the gut microbiota during pregnancy are necessary to adapt the mother to pregnancy and promote optimal fetal growth and development. During pregnancy on the background of obesity, changes in the gut microbiota may lead to metabolic disturbances of mother, which may indirectly affect the growth and development of the child and the establishment of its own gut microbiota [211–218, 232–242]. Collado et al. in their study observed significant differences in microbial composition in pregnant women depending on their BMI. They found higher numbers of *Bacteroides* and *Staphylococcus aureus* in obese women compared to women with normal BMI [187, 243, 244]. Interestingly, the composition of the microbiota varied with weight gain throughout pregnancy: *Bacteroides* showed a positive correlation both with pre-pregnancy BMI and with weight gain during pregnancy; each kilogram of weight gain was proportionally accompanied by an increase in the number of *Bacteroides* by 0.006 logarithmic units [220–235]. Various studies have shown that the gut microbiota remodels and fluctuates during pregnancy depending on gestational age [221, 236–238]. Zacarias et al. demonstrated that pregnant women with obesity have a high ratio of *Firmicutes* and *Bacteroidetes*, increased numbers of actinobacteria in the second and third trimester of pregnancy, and decreased bacterial diversity in the third trimester [239]. Santacruz et al. studied the fecal microbiota of 50 pregnant women (group 1 — overweight pregnant women, group 2 — pregnant women with normal BMI) to evaluate the relationship between changes in the composition of the gut microbiota during pregnancy and biochemical parameters depending on their BMI. It was found that higher concentration of *Staphylococcus* was significantly correlated with increased serum cholesterol levels, higher number of *Enterobacteriaceae* and *E. coli* was correlated with increased serum ferritin and decreased transferrin levels, while higher number of *Bifidobacterium* was correlated with decreased ferritin and increased transferrin and folic acid levels. The number of *Bacteroides* was associated with higher levels of cholesterol, HDL, and folic acid [240].

THE ROLE OF MATERNAL MICROBIOTA IN PROGRAMMING OF BABY'S OBESITY

It is well known that the first microbial influence on the child is exerted by the maternal microbiota during pregnancy, suggesting that the maternal gut microbiota has a direct influence on the child's gut microbiota and subsequent metabolic and immunologic programming. Both animal and human studies have shown that changes in the diversity and abundance of gut microbial composition in obese mothers were associated with changes in the gut microbiota of the offspring at early and later ages. Soderborg et al. showed in their study that germ-free mice colonized with stool microbes from the stools of two-week-old infants born to obese mothers had increased gut permeability, impaired macrophage activity, and increased inflammation compared to mice colonized with stool microbes from infants born to normal weight mothers [241]. In addition, these mice showed accelerated body weight gain at follow-up [242]. When comparing the gut microbiota in obese and normal weight children, studies have demonstrated an increased ratio of *Firmicutes/ Bacteroidetes* in the obese group [243, 244]. Recent studies also show a decrease in the level of bifidobacteria in the intestinal microbiota in obese and overweight children [245]. A study on 77 children born to obese mothers and women with normal BMI showed that the number of *Parabacteroides* spp. and *Oscillibacter* spp. in the gut microbiota was higher in children born to obese mothers. In addition, amounts of *Blautia* spp. and *Eubacterium* spp. were lower [245–251]. Vael et al. in a prospective study demonstrated high intestinal concentrations of *Bacteroides fragilis* and low concentrations of *Staphylococcus* in infants aged from three weeks to one year, which is associated with a higher risk of obesity later in life [247, 252]. Nadal et al. found significantly reduced levels of *Clostridium hystoliticum, Eubacterium rectale* and *Clostridium coccoides* correlated with weight loss in obese adolescents [253].

Changes in the gut microbiota of offspring born to obese mothers are still controversial and require further investigation.

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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PROBIOTIC PROPERTIES OF *LACTOBACILLUS REUTERI (L. REUTERI)* STRAINS

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Abstract. Probiotic status is given to microorganisms that are considered safe and meet certain criteria. *Lactobacillus reuteri* DSM 17938 (*L. reuteri*) is a well-studied bacterium that can colonize various parts of the body in humans. The strain in use today, L. reuteri DSM 17938, recently renamed *Limosilactobacillus reuteri* (*L. reuteri*), is a probiotic well identified for its beneficial effects on several gastrointestinal diseases. The probiotic effect of *L. reuteri* is due to a whole range of special properties. *L. reuteri* is able to influence the biodiversity, composition and metabolic function of the gut, oral and vaginal microbiota. These effects are largely strain-specific. The main therapeutic target of *L. reuteri* is infantile colic. In infants, in addition to relieving colic and modulating the intestinal microbiota, *L. reuteri* is able to enhance the mucosal barrier function, which is necessary to block the entry of external antigens and toxins. Literature data indicate the effectiveness of *L. reuteri* in acute watery diarrhea, against *H. pylori* and other diseases: atopic dermatitis, obesity, caries, autism spectrum disorders, autoimmune diseases, incl. inflammatory bowel disease and systemic lupus erythematosus, etc. The safety and tolerability of *L. reuteri* has been proven by numerous clinical studies. There are several strains of *L. reuteri* with different origins and many of the probiotic functions of *L. reuteri* are strain dependent. Therefore, in the future, it may be advantageous to combine different strains of *L. reuteri* in order to maximize their beneficial effects.

Key words: *probiotic; L. reuteri; Limosilactobacillus reuteri; infant colic*

ПРОБИОТИЧЕСКИЕ СВОЙСТВА ШТАММОВ *LACTOBACILLUS REUTERI (L. REUTERI)*

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Резюме. Статус «пробиотик» присваивается тем микроорганизмам, которые считаются безопасными и соответствуют определенным критериям. *Lactobacillus reuteri* DSM 17938 (*L. reuteri*) — хорошо изученная бактерия, способная колонизировать у людей различные участки тела. Штамм, который используется сегодня, *L. reuteri* DSM 17938, недавно переименованный в *Limosilactobacillus reuteri* (*L. reuteri*), является пробиотиком, хорошо идентифицированным по его благотворному влиянию на некоторые желудочно-кишечные заболевания. Пробиотический эффект *L. reuteri* обусловлен целым комплексом особенных свойств. *L. reuteri* способен влиять на биоразнообразие, состав и метаболическую функцию микробиоты кишечника, полости рта и влагалища. Эти эффекты в значительной степени штаммоспецифичны. Основной терапевтической мишенью воздействия *L. reuteri* являются младенческие колики. У младенцев, помимо купирования

колик и модуляции кишечной микробиоты, *L. reuteri* способны усиливать барьерную функцию слизистой оболочки, которая необходима для блокирования проникновения внешних антигенов и токсинов. Литературные данные свидетельствуют об эффективности *L. reuteri* при острой водянистой диарее, против *H. pylori* и при других заболеваниях: атопическом дерматите, ожирении, при кариесе, расстройствах аутистического спектра, аутоиммунных заболеваниях, в том числе воспалительных заболеваниях кишечника и системной красной волчанке и др. Безопасность и переносимость *L. reuteri* доказана многочисленными клиническими исследованиями. Существует несколько штаммов *L. reuteri* с различным происхождением, и многие из пробиотических функций *L. reuteri* зависят от штамма. И поэтому в будущем, возможно, может быть выгодно комбинировать различные штаммы *L. reuteri*, чтобы максимизировать их полезные эффекты.

***Ключевые слова*:** *пробиотик; L. reuteri; Limosilactobacillus reuteri; младенческие колики*

Lactobacillus reuteri DSM 17938 (*L. reuteri*) is a well-studied bacterium capable of colonising a wide range of vertebrates, including pigs, rodents and chickens. Evolution has adapted the bacterium to a large number of mammals [1]. In humans, *L. reuteri* is found in various body sites including the gastrointestinal tract, urinary tract, skin and breast milk [2, 3]. *L. reuteri* was first described in 1962 as a heterofermentative species that grows in oxygen-limited atmospheres and colonises the proximal gastrointestinal tract of humans and animals [17]. Around 1990, the probiotic properties of the parent strain of *L. reuteri*, ATCC 55730, were clinically proven [5]. After deletion of gene-bearing antibiotic resistance plasmids from *Lactobacillus reuteri* ATCC 55 730, the strain used today, *L. reuteri* DSM 17938, was generated [6]. It belongs to the genus *Lactobacillus*, which includes many other Gram-positive oxygen-resistant fermentative bacteria such as *L. acidophilus, L. bulgaricus, L. casei* and *L. rhamnosus* [7]. Lactobacillus reuteri DSM 17938, recently renamed Limosilactobacillus reuteri (*L. reuteri*), is a probiotic well identified for its beneficial effects on several gastrointestinal diseases [2, 4, 8–10].

The probiotic effect of *L. reuteri* is due to a whole complex of special properties. Due to its ability to form biofilms [4, 11], *L. reuteri* colonies are resistant to low pH values and bile salts [12]. *L. reuteri* has been shown to be able to attach to mucin, intestinal epithelium, and intestinal epithelial cells in a number of vertebrates [13]. The adhesion mechanism is thought to be due to the binding of bacterial surface molecules to the mucus layer. Mucus-binding proteins (MUBs) and MUB-like proteins encoded by *Lactobacillales*-specific clusters of protein encoding genes act as adhesins [14]. The considerable diversity of MUBs among *L. reuteri* strains and differences in the number of MUBs on the cell surface correlate with their ability to bind mucus [15]. The strain-specific role of MUBs in the recognition of mucus elements and/or their ability to stimulate aggregation may explain the contribution of MUBs to *L. reuteri* adhesion. Factors that mediate attachment to surfaces include many large surface proteins, MUB A, glucosyltransferase A (GtfA) and inulosucrase (Inu) and D-alanyl ester [2]. The relationship between bacterial adhesion to the epithelium of the host gastrointestinal tract and the ability of bacteria to form biofilms has been studied. Numerous experiments *in vitro* and on different animals, including microbe-free rodents, have shown that biofilm formation of *L. reuteri* strains depends on the origin of the host strains. For example, biofilm formation of *L. reuteri* TMW1.106 is associated with GtfA and Inu molecules [16]; *L. reuteri* 70902 and the secA2-SecY2 system were key factors regulating biofilm formation from L. reuteri 100–23 in germ-free mice [17]; the bfrKRT and cemAKR two-component systems are associated with biofilm formation of *L. reuteri* 100–23 [18]; *L. reuteri* RC-14 is able to penetrate into the mature biofilm of *E. coli* and become part of it [19].

The probiotic potential of *L. reuteri* is also associated with the production of their metabolites with antimicrobial and immunomodulatory effects [2]. The most studied is reuterin, which is a mixture of different forms of 3-hydroxypropionic aldehyde (3-HPA) [20]. Most strains of *L. reuteri* can metabolise glycerol to form reuterin in a glycerol dehydratase dependent reaction mediated by coenzyme B_{12} [21, 22]. Some other bacteria can also produce 3-HPA [23], but only *L. reuteri* is capable of secreting it in significant amounts above the bioenergetic requirement [24]. An important compound in the antimicrobial activity of reuterin is the acrolein-cytotoxic electrophile into which 3-HPA can be spontaneously converted. Conjugation of heterocyclic amines also depends on the formation of acrolein [25]. Reuterin can inhibit a wide range of microorganisms, mainly Gram-negative bacteria, while *L. reuteri* strains themselves show pronounced resistance to reuterin [26].

Some strains of *L. reuteri*, in addition to reuterin, produce other antimicrobial substances: a lactic acid, an acetic acid, an ethanol, and a reutericycline [21]. Due to the synthesis of these substances, *L. reuteri* is effective against various bacterial infections of the gastrointestinal tract: *Helicobacter pylori, E. coli, Clostridium difficile* and Salmonella [27–30]. In addition, due to metabolites having antiviral properties, *L. reuteri* is effective against pneumoviruses, circoviruses, rotaviruses, coxsackie viruses and papillomaviruses [31–34]. There are reports that *L. reuteri* also stops the growth and kills various *Candida* species [35].

Some strains of *L. reuteri* (for example, the human commensal bacterium *L . reuteri* 6475) convert the amino acid L-histidine into histamine [36], which suppresses tumour necrosis factor (TNF) production from stimulated human monocytes by activating histamine H_2-receptors, increasing intracellular cAMP and protein kinase A, and inhibiting MEK/ERK signal transduction [37]. Numerous experimental studies demonstrate the involvement of histamine in suppressing intestinal inflammation in mouse models of colitis [38, 39].

Tryptophan catabolites of *L. reuteri* have been recognised as ligands for the aryl hydrocarbon receptor (AhR). By activating AhR, *L. reuteri* can stimulate local production of IL-22 from innate lymphoid cells (ILCS) and induce the development of regulatory $CD4^+CD8aa^+$ double-positive intraepithelial lymphocytes [50, 51]. Given that AhR is expressed ubiquitously, *L. reuteri* and its metabolites may affect many other immune cell types besides ILCs and T cells [52].

Four strains of *L. reuteri* of different origins have been detected, among which the most studied are *L. reuteri* CRL1098 and *L. reuteri* JCM1112, which are capable of producing different types of vitamins, including vitamin B_{12} (cobalamin) and B_9 (folic acid). Vitamin B_{12} is vital for the production of reuterin, as a B_{12}-dependent coenzyme is required to reduce glycerol to 3 GPA [40–42].

L. reuteri can also produce gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system [57]. It is possible that this accounts for the effect of the microorganism on visceral sensitisation [58].

The exopolysaccharide (EPS) synthesised by the *L. reuteri* is important for biofilm formation and adhesion of *L. reuteri* to epithelial surfaces [11]. Numerous experimental works on animals have shown that EPS can inhibit the adhesion of *E . coli* to epithelial cells [43, 44], inhibit gene expression of proinflammatory cytokines that are induced by *E. coli* infection, including IL-1β and IL-6, inhibit the binding of enterotoxigenic *E. coli* to animal erythrocytes [45], and induce Foxp3+ regulatory T cells (Treg) in the spleen [46].

The property of *L. reuteri* to induce Treg is highly strain dependent. *L. reuteri ATCC PTA, 6475, L. reuteri DSM 17938, L. reuteri 100–23, L. reuteri ATCC 23272, L. reuteri RC-14* have been described to mediate Treg cell induction in obesity, necrotising enterocolitis, inflammatory bowel disease (IBD), atopic dermatitis, systemic lupus erythematosus, wound healing and other conditions [2]. In addition to acting on Treg cells, L. reuteri can suppress Th1/Th2 responses in Treg-deficient mice [47]. Some strains of L. reuteri are able to reduce the production of many pro-inflammatory cytokines (MCP-1, TNF, IL-6, TNF, IL-22) [48, 49]. At the same time, studies investigating the effect of Lactobacillus reuteri on the levels of free secretory IgA (sIgA) in various tissues (blood, saliva, breast milk) give contradictory results, which is apparently due to the use of different strains [53–56].

The immune system of humans and animals is closely interrelated with the intestinal microbiota [59]. It has been shown that disturbances of the microbiota can contribute to the development of diseases, and restoration of the microbiota prevents or improves the course of some diseases [60]. *L. reuteri* is able to influence the biodiversity, composition and metabolic function of the gut, oral and vaginal microbiota. These effects are largely strain specific [18, 61, 62]. In rodent models, *L. reuteri* DSM17938 was demonstrated to increase the number of Firmicutes types and the genera *Lactobacillus* and *Oscilospira* in the gut [47], while reducing multi-organ inflammation; *L. reuteri* 6475 resulted in increased microbiota biodiversity in both jejunum and ileum [63]; *L. reuteri* C10–2-1 modulates the diversity of intestinal microbiota in ileum [53].

A number of researchers have studied the effect of *L. reuteri* DSM 17938 on the intestinal microbiota of infants. In one study, the administration of this strain to children aged 2 weeks to 4 months born by caesarean section reduced the number of enterobacteria and increased the number of bifidobacteria, that is, modulated the development of the intestinal microbiota in the direction of the composition of the microbiota found in infants born vaginally. At the same time, the structure of the intestinal microbiota of newborns born vaginally remained unchanged after taking *L. reuteri* supplements. [62]. In a study made by Savino et al. (2015) administration of the same *L. reuteri* strain to infants resulted in 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 was significantly reduced [64]. The differences in the results of the two studies may be related to the different ages of the subjects, the duration of treatment, the method of administration and dosage.

The *L. reuteri* strain NCIMB 30242, which is administered as delayed-release capsules for 4 weeks, increased the ratio of *Firmicutes* to *Bacteroidetes* in healthy adults [65]. The mechanism of modulation of the intestinal microbiota in them is associated with the ability of this strain to activate the hydrolase of bile salts and increase the content of circulating bile acid in the blood [66]. Modulation of the intestinal microbiota using the *L. reuteri* DSM 17938 strain was also performed in patients with type 2 diabetes mellitus and cystic fibrosis [2].

In addition to modulating the intestinal microbiota, *L. reuteri* is able to enhance the barrier function of the mucous membrane, which is necessary to block the penetration of external antigens and toxins [67]. It has been demonstrated in animal models that *L. reuteri* can reduce the movement of bacteria from the gastrointestinal tract to mesenteric lymph nodes, increase the expression of dense compound proteins (TJ) in intestinal epithelial cells, which suppresses the translocation of proinflammatory molecules such as LPS [68–70]. *L. reuteri* is able to reduce intestinal permeability in children with atopic dermatitis; at the same time, the clinical picture of the disease is significantly improved [71].

In addition to influencing the gut microbiota and intestinal permeability, *L. reuteri* can influence the microbiota of other biotopes. The effects of two strains of *L. reuteri* — DSM 17938 and PTA 5289 — on the microbiota of the oral cavity have been most studied: changes in the composition of the microbiota, reduction in the number of periodontal pathogens in the sub-gingival microbiota [72]. There are studies demonstrating the positive effect of *L. reuteri* RC-14 on the vaginal microbiota in postmenopausal women and in patients with bacterial vaginosis [73, 74].

Due to its pronounced modulating effects on the host microbiota and immune responses, and its good safety profile, *L. reuteri* is a worthy candidate for the prevention and/or treatment of various diseases. The therapeutic potential of different strains of *L. reuteri* has been studied in various diseases and the results have been promising in many cases [2, 60].

The main therapeutic target of *L. reuteri* is infantile colic [75]. Colic in infants is characterised by restlessness or excessive crying; it occurs in 10–30% of cases. The exact cause and effective treatment of this condition remain unclear [76]. The clinical efficacy of *L. reuteri* DSM 17938 [77–81] and *L. reuteri* ATCC 55730 [86] in reducing restlessness and duration of crying has been demonstrated in a large number of clinical trials. There are reports that the use of *Lactobacillus reuteri* DSM 17938 has shown a positive therapeutic and preventive effect exclusively in breastfed infants (use for 21–28 days), whereas no positive result was obtained with artificial feeding [82, 83]. This may be due to the fact that *L. reuteri* is found in the breast milk of most women [87]. F. Savino et al. noted an increase in the number of lactobacilli and a decrease in *E. coli* in the faecal microbiota against the background of *L. reuteri* administration along with the clinical effect [81]. At the same time, there are studies that did not confirm the effect of *L. reuteri* on the gut microbiota [84] and on the duration of crying in infants [85]. Since most clinical studies were successful, experts consider the clinical efficacy of *L. reuteri* DSM 17938 proven [88, 89]. The failure of some studies may be explained by differences in the dosage of *L. reuteri* the age of the infants when the studies were initiated, or the basic structure of the microbiota of the subjects.

The use of *Lactobacillus reuteri* DSM 17938 was effective in the prevention and treatment of regurgitation in infants [77, 90], management of functional abdominal pain [91, 92], treatment of constipation in children and adults [10], and prevention and treatment of diarrhea [10].

A considerable amount of work has been devoted to the study of the effectiveness of *L. reuteri* in constipation. The mechanism of action of *L. reuteri* efficacy is associated with its ability to produce short-chain fatty acids (SCFA), reduce intraluminal intestinal pH level and also contribute to colonic peristalsis by affecting the frequency and speed of its myoelectric cells [93]. Current evidence suggests that *L. reuteri* improved defecation in patients (both children and adults) with chronic constipation [8, 9], but did not affect stool consistency [93]. Kubota et al. [8] reported that *L. reuteri* administered to children with chronic constipation, twice daily for four weeks, induced changes in the composition of the intestinal microbiota (reduction of *Clostridiales* genera such as *Oscillospira, Megasphaera* and *Ruminococcus*), increasing intestinal peristalsis and decreasing stool transit time, with significant results at week four *L. reuteri* improved stool frequency but not stool consistency [8]. *Coccorullo* et al. [94] proved that *L. reuteri* has a positive effect on functional constipation

in infants, improving the frequency of defecation at the 2nd, 4th and 8th weeks of administration. Indrio et al. [77] emphasised that *L. reuteri* reduced constipation during the first three months of life. A number of researchers have reported the efficacy of L. reuteri for constipation in adult patients [9, 95–97]; The mechanism of positive action is attributed to the reduction of methane (CH_4) production by intestinal microbiota (*Methanobrevibacter smithii*), modulation of serum levels of serotonin (5-HT) and brain-derived neurotrophic factor (BDNF) by this probiotic strain, activation of afferent sensory nerves affecting intestinal motility, and increase in excitability of myeenteric neurons due to the action on 5-HT pathways. At the same time, a number of studies have not observed a positive effect of *L. reuteri* in constipation in children [98] and adults [93], and no significant changes in the microbiota and its relationships with the dynamics of constipation have been found [98]. According to experts, to recommend the inclusion of *L. reuteri* in constipation therapy protocols, additional studies are needed to investigate the efficacy of probiotics in constipation and the mechanisms by which *L. reuteri* modulates intestinal motility with effects on constipation in children and adults [99–101].

Literature data indicate the effectiveness of *L. reuteri* in acute watery diarrhea [36, 102–107, 114, 115] and in the prevention of new episodes of diarrhea, including diarrhea after long-term antibiotic treatment [108, 109]. A.V. Shornikova et al. [110, 111] investigated the role of *L. reuteri* in acute watery diarrhea in children and in rotavirus gastroenteritis. In a randomised controlled clinical trial involving 86 children aged 6 to 36 months with rotavirus enteritis, *L. reuteri* administration was shown to reduce the duration of acute watery diarrhea with a dose-dependent effect. The mean duration of acute watery diarrhoea was 1,5 days in the group dosed with 10^{10} colony forming units (CFU) of *L. reuteri*, 1,9 days in the group dosed with107 CFU of *L. reuteri*, and 2,5 days in the group receiving placebo. By the second day of *L. reuteri* treatment, acute watery diarrhea persisted among 48% of people taking the high dose, 70% of people taking the low dose, and 80% of people treated with placebo. In another randomised placebo-controlled clinical trial [106], supplementation with *L. reuteri* at a dose of 4×10^8 CFU/day for 7 days was demonstrated to reduce the duration of acute watery diarrhoea in children aged 3 months to 3 years, with a maximum effect on the second and third day, with no reported side effects. Other studies [107, 112] found that administration of 5 drops containing 10^8 CFU of *L. reuteri* could reduce the duration of acute watery diarrhoea by up to 15 h in children aged 3 months to 5 years. A meta-analysis including 1229 children receiving *L. reuteri* at a dosage of 10^8 CFU daily for 5–7 days demonstrated a reduction in the duration of diarrhoea by 1 day with a maximum beneficial effect on the second day. Although the analysed studies were heterogeneous in duration and dosage of *L. reuteri* the authors confirmed the beneficial effect of this probiotic in the treatment and prevention of acute watery diarrhea [113]. Another review and meta-analysis [116] of 4 studies comparing the effects of L. reuteri at different doses with placebo or no treatment on the duration of diarrhea and stool volume, on the course of diarrhea, on the duration of diarrhea of 7 days or less and on the duration of hospitalisation. It was observed that L. reuteri reduced the duration of diarrhea by about 21 hours and the duration of hospitalisation in children by about 13 hours. Thus, most authors believe that *L. reuteri* may be a useful and safe, supportive measure for the treatment and prevention of diarrhea, reducing both its duration and intensity of symptoms [116].

L. reuteri strain DSM 17938 has been successfully used in preterm infants [117, 118]. Various authors have found a reduction in food intolerance and length of hospital stay in infants, but one study noted no effect on the incidence of necrotising enterocolitis (NEC) [118].

The use of *L. reuteri* strain DSM 122460 (from 19070–2) for 6 weeks [119] and *L. reuteri* strain ATCC 55730 for 8 weeks [120] was effective in atopic dermatitis. *L. reuteri* strain ATCC 55730 in infants with a family history of allergies was effective in preventing IgE-associated eczema, but did not provide protection against the common occurrence of eczema [121] and had no effect on the prevalence of asthma, eczema or other allergic diseases later in life [122].

The potential of *L. reuteri* in the treatment of obesity is actively debated. It has been shown in experimental and clinical studies that depending on the strain, *L. reuteri* can have different effects on body weight. For example, vancomycin-resistant *L. reuteri* in the intestinal microbiota has been identified as a predictor of increased body weight during vancomycin treatment [123]. In contrast, in a randomised, double-blind and placebo-controlled clinical trial, administration of *L. reuteri* JBD301 for 12 weeks significantly reduced body weight in overweight adults [124]. Experts of the European Paediatric Society of Gastroenterology, Hepatology and Nutrition (ESPGHAN), based on a review of a significant number of studies, con-

cluded that supplementation of infant formula with *L. reuteri* does not increase body weight in infants [125].

The clinical efficacy of *L. reuteri* against *H. pylori* has been described in a number of studies. It has been shown that adjuvant therapy with *L. reuteri* against antibiotics in eradication regimens can improve the tolerability of the regimens, reduce abdominal pain, diarrhoea, nausea, vomiting and abdominal bloating, restoring the balance of intestinal microflora [30, 126]. Dore et al. [127] showed that *L. reuteri* prevents *H. pylori* colonisation of human intestinal mucosa by inhibiting the binding of *H. pylori* to glycolipid receptors. It also increases the production of mucin, reuterin and antioxidant substances, stabilises the mucosal barrier and stimulates mucosal immunity [127, 128] with beneficial health effects in intestinal microbiota dysbiosis after the use of antibiotics and antisecretory treatments. A number of authors have noted that due to the above described properties, *L. reuteri* accelerates the eradication of *H. pylori* [129–131].

Experimental and clinical studies of *L. reuteri* efficacy in caries, autism spectrum disorders, autoimmune diseases including inflammatory bowel disease and systemic lupus erythematosus have been conducted [2].

In the last few decades, there has been a decline in *L. reuteri* in humans, probably caused by modern lifestyles (antibiotic use, western diet, improved hygiene). This decline coincides with an increase in inflammatory and autoimmune diseases over the same period. Although evidence is currently insufficient to establish a correlation, it is possible that increased colonisation of *L. reuteri* may be a new and relatively safe strategy against inflammatory diseases.

Conclusion. The safety and tolerability of *L. reuteri* has been proven by a large number of clinical studies. There are several strains of *L. reuteri* with different origins, and many of the probiotic functions of *L. reuteri* are strain dependent. And so in the future, it may be advantageous to combine different strains of *L. reuteri* to maximise their beneficial effects.

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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CHRONIC CONSTIPATION AND DEFECATION DISORDERS IN A NEUROLOGICAL PATIENT WITH LIMITED MOBILITY

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Abstract. Chronic constipation in neurological patients with limited mobility is a common problem among children and adults. About 98% of patients with limited mobility with cerebral palsy in the Russian Federation have constipation, and there are no data on its prevalence among children with other neurological pathologies in our country. The versatility of causes, ranging from impaired nerve conduction at different levels, ending with the psychological state of the patient and his family, only proves the need for a more attentive attitude to this problem and to find ways to solve it. This literature review presents the results of modern studies of compatriots and foreign colleagues on the problem of chronic constipation and defecation disorders among patients with limited mobility.

Key words: *chronic constipation; limited mobility patient; cerebral palsy; Spina Bifida.*

ХРОНИЧЕСКИЕ ЗАПОРЫ У МАЛОМОБИЛЬНОГО ПАЦИЕНТА НЕВРОЛОГИЧЕСКОГО ПРОФИЛЯ

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Резюме. Хронические запоры у маломобильных пациентов неврологического профиля являются часто встречающейся проблемой среди детского и взрослого населения. Около 98% маломобильных пациентов с детским церебральным параличом (ДЦП) в Российской Федерации имеют запор, а данные о его распространенности среди детей с иной неврологической патологией на территории нашей страны отсутствуют. Многогранность причин, начиная от нарушения нервной проводимости на разных уровнях, заканчивая психологическим состоянием пациента и его семьи, только доказывает необходимость в более внимательном отношении к данной проблеме и в поиске путей к ее решению. В литературном обзоре представлены результаты современных исследований соотечественников и зарубежных коллег проблемы хронических запоров и нарушения дефекации среди маломобильных пациентов.

Ключевые слова: *хронический запор; маломобильный пациент; ДЦП; Spina Bifida.*

Constipation is a disorder of intestinal function, which is manifested by a shortening (compared to the individual physiological norm) of the age-related rhythm of the defecation act, its difficulty, systematically insufficient emptying of the intestine and/or changes in the shape and nature of stool [1, 2–4]. Constipation affects about 12% of the world's population, with people in the Americas and Southeast Asia being twice as likely to be constipated as Europeans (17.3 and 8.75%, respectively) [1]. Studies published over the last decade have reported constipation rates in children ranging from 10 to 25%, with only sporadic data on the prevalence of chronic constipation (CC) in low-mobility patients (LMP), especially in children, with a high proportion of functional constipation [5, 6]. Patients with severe chronic diseases in the decompensation stage, neurological pathology, diseases of the muscular system, oncological diseases, morbid obesity, as well as with various traumas and terminal illnesses are usually considered to be LMP. It has been found that 98% of LMP with cerebral palsy have CC, and its incidence among oncological patients ranges from 32 to 87% and increases to 90% in the case of opioid use [7]. During normal evacuation the intestinal contents stretch the ampulla of the rectum and irritate baro- and mechanoreceptors. Through afferent pathways, the signal from them reaches the centre of involuntary defecation, which is located in the lumbosacral spinal cord. Under the influence of descending signals there is a relaxation of the internal sphincter of the anus. In turn, the arbitrary act of defecation occurs with the participation of the cortex: under the influence of efferent impulses, the external sphincter of the anus and the puborectal muscle relax [8]. The enteric nervous system regulates rhythmic contractions of the rectum, facilitating faecal movement [9]. Adequate control of the muscles of the anterior abdominal wall and pelvic diaphragm also contributes to proper and timely defecation by increasing intra-abdominal pressure. Disruption of nerve impulse transmission at each level can lead to disorders of the act of defecation (neurogenic bowel dysfunction — NBD) and CC. Chronic constipation and faecal incontinence often coexist; sometimes there is "overflow" diarrhea (when solid stools accumulated above the rectum allow only watery stools to pass by, resulting in incontinence of liquid faeces)

[10]. The term NBD implies autonomic and/or somatic denervation of the bowel. The problem of NBD in the paediatric literature is not sufficiently considered, and there is no standardised approach to therapy in national guidelines.

Causes of defecation disorders are tumours or organic lesions of the brain, pathology at the level of the spinal tract, infiltration of sacral nerves, disorder of autonomic innervation of the colon. The causes and manifestation of NBD in children and adolescents differ from adult forms. In most cases, paediatric NBD is caused by congenital problems such as cleft spine and cerebral palsy. Acquired forms caused by trauma, infection and other causes are similar to the clinical presentation in adult patients [11].

Cerebral palsy is defined as a congenital neurological condition due to non-progressive trauma (usually presumed post-hypoxic) or brain malformation occurring in the foetal or perinatal period [12]. The incidence of cerebral palsy is about 1,5 per 1000 births, making it the most common neurological condition encountered in paediatrics. Cerebral palsy encompasses a group of disorders of varying degrees of movement and postural development. Up to 90% of children with cerebral palsy suffer from constipation and 47% from faecal incontinence, although the majority suffer to a minor degree [13]. In patients with cerebral palsy, due to motor pathway damage at different levels, muscle hypertonicity occurs, limiting the development of motor function, which in some cases makes it difficult and almost impossible to control the abdominal muscles and pelvic diaphragm. There is evidence of lesions of the mesenteric and submucosal nerve plexuses as coordinators of intestinal peristalsis, controlled by the central nervous system (CNS), which is also a risk factor for the development of constipation in patients with cerebral palsy [14]. There is a direct correlation between the degree of motor skills development, according to the GMFCS classification, and the frequency of constipation in patients [15, 16]. About half of people with cerebral palsy are intellectually disabled [17, 18], which affects what treatments of NBD and CC can be used. In multiple sclerosis, lesions in the spinal cord and hypothalamic region of the brain will cause problems similar to reflex bowel emptying after spinal cord injury (Table 1) [19].

Another illustrative example of nerve conduction disturbance as a cause of NBD and CC development is the presence of a spinal hernia of various sizes in a child with *Spina Bifida*. A meningocele, meningoradiculocele, myelomeningocele, and myelocystocele are distinguished depending on the contents of the hernial sac. Myelomeningocele (MMC) is the most common and myelocystocele is the most rare [20, 21]. The vast majority of MMC cases involve the lumbar spi-

nal cord and sacral roots that innervate the bladder, distal colon and their respective sphincters, so some degree of neurogenic bladder and bowel dysfunction is almost universal in this population [22]. The frequency of urethrovesical dysfunction in myelomeningocele is not completely known, but most studies suggest that it is very high [23]. Similarly, anorectal dysfunction is also common. In contrast, in meningocele, the dura mater protrudes through the spinal canal defect, but the nerve elements remain confined within the canal and therefore are usually not damaged either antenatally or postnatally. In *Spina Bifida occulta* the bony lesions are not open, so in most cases there are no obvious signs of neurological damage [24]. Bowel dysfunctions such as constipation and faecal incontinence have a significant impact on the quality of life and well-being of individuals with spina bifida, as well as their parents. The *Spina Bifida Association* in 2019 surveyed adult patients, parents and children with the condition to assess the extent to which bowel dysfunctions such as constipation and faecal incontinence affect quality of life; half of the parents surveyed rated it as the biggest problem [25–29].

Muscular dystrophies and mitochondrial disorders are also accompanied by symptoms of bladder and bowel dysfunction. Constipation in X-linked Duchenne muscular dystrophy can be life-threatening, but fecal incontinence is usually the most disabling [30, 31]. The cause of constipation in these patients is functional anorectal obstruction [30], altered gastrointestinal transport and possible sensory impairment due to expression of the DP116 dystrophin isoform in peripheral nervous tissue and autosomal DP116 homologues in sensory ganglia [30], as well as decreased myoelectric slow-wave activity along with decreased nitric oxide (NO) availability due to the absence of dystrophin acting as an anchor for NO synthase [30]. Loss of alpha-dystroglycan-laminin interaction due to defective glycosylation of alpha-dystroglycan underlies a group of congenital muscular dystrophies often associated with brain malformations called dystroglycanopathies [31]. Mitochondrial neurogastrointestinal encephalomyopathy is often associated with chronic intestinal obstruction. The pathophysiology leading to impaired peristalsis and movement of intestinal contents is related to impaired neuromuscular coordination due to the myopathy (affecting intestinal contraction), neuropathy (affecting coordination of intestinal reflexes) or mesenchymopathy (associated with abnormalities of interstitial cells of Cajal). In addition, mitochondrial abnormalities may contribute to impaired homeostasis of the intestinal microbiota, which in turn may be involved in the manifestation of gastrointestinal dysmotility seen in neurogastrointestinal encephalomyopathy [32]. In Wolfram's syndrome, diabetes mellitus and optic atrophy debut in the first decade of life, the other symptoms appear later, may be severely delayed by non-suggestive diabetes, hearing impairment and usually bowel and bladder dysfunction [33]. In all these muscular disorders, muscular dystrophies and mitochondrial cytopathy, NBD and urinary incontinence symptoms may change as the disease progresses.

Acquired brain injury (ABI) represents the leading cause of death and neurological disability in children after infancy. Today, the number of survivors of traumatic brain injury is increasing and these patients constitute a large proportion of patients in neurorehabilitation units. Functional impairments (motor, behavioural, learning and cognitive) including CC and NBD are common and may persist during all life [34].

Acquired damage to the nerves innervating the pelvic organs is iatrogenic in most cases, but rarely may also occur as a result of the impact. Any pelvic surgery in infants and children for anorectal malformation or Hirschprung's disease [35, 36], neuroblastoma, ganglioneuroma, sacrococcygeal teratoma are theoretically capable of damaging the pelvic parasympathetic nerves of the rectum, anus, bladder and genitalia. In addition, pelvic irradiation can cause damage to adjacent nerve fibres, resulting in altered function, as can some cytotoxic drugs [36].

Acquired spinal cord injury leads to different types of defecation disorders: faecal incontinence, chronic constipation or a combination of both [37]. According to electromyography of the external anal sphincter, 25–33% of patients with spinal cord injury had bilateral or unilateral abnormalities of muscle action during defecation, and 88.5% had pelvic floor dysfunction [38]. The mean rectal volume for generating defecation urge was also elevated in them.

There are two models of bowel dysfunction are distinguished depending on the level of the conductive tract lesion relative to the *conus medullaris*: supraconal disorder, or "upper bowel motor neuron syndrome", or "hyperreflexic bowel", or "spastic bowel", and infraconal disorder, "lower motor neuron type", or "areflexic bowel" [39]. [39]. In the case of supraconal disorder, there is an increase in tone of the colon wall, pelvic floor and spasmodically constricted state of the external anal sphincter, which causes stool retention [39]. When the

anal sphincter cannot be relaxed arbitrarily, the signals between the colon and the brain become disconnected: the reflex that triggers bowel emptying is still working, but the child may not feel it coming, resulting in sudden unplanned passage of stool whenever the rectum is full. These disorders are characterised by high anal resting tone, anal and bulbocavernous reflex present. The situation is different in the case of an areflexic bowel: loss of colorectal tone and reduced amplitude of the rectoanal inhibitory reflex leads to a cyclic pattern of rectal filling and progressive distension of the rectum, eventually leading to faecal incontinence. In a situation of sluggish bowel, there is decreased movement in the colon, decreased peristalsis, and the anal sphincter is in a more relaxed state than normal. This can lead to constipation with frequent stool leakage. Typically, these patients have any or low anal resting tone and lack of anal and bulbocavernous reflexes [40].

The extent of symptoms also depends on the degree of injury: severe spinal injury has been shown to result in the most severe form of NBD with loss of control of the external anal sphincter [41].

Transverse myelitis is a rare immune-mediated disease resulting in spinal cord injury [42]. Approximately 20% of acute myelitis cases occur in children, in whom one of the most common initial symptoms is pain (60%). Other common symptoms in children include motor deficits, numbness, ataxic gait and loss of bowel or bladder control. Constipation can be severe and may be accompanied by a marked feeling of fullness in the left lower quadrant. Long-term autonomic sphincter dysfunction has been reported in 22–80% of children [43].

Multiple sclerosis (MS) is the most common progressive neurological disorder in young adults with a median age in the early 30s and a prevalence of 40–220 cases per 100,000 people in Europe [44], with similar rates in North America [45]. The incidence of childhood onset of multiple sclerosis is low, ranging from 0.3–0.9 per 100,000 people. The prevalence of childhood MS is 5–10% of all MS cases [46, 47]. Constipation in MS is observed in 31–54% of patients [48].

Defecation disorders have been described in 15% of patients in Guillain-Barré syndrome [49, 50], cauda equina syndrome (damage to nerve roots from L2 to S4) [51, 52], central lumbar disc prolapse, spinal cord tumour, spinal canal stenosis, spinal malformations and iatrogenic causes (during spinal surgery or spinal anaesthesia) [53].

Other rare paediatric neurological diseases affecting cells in the anterior horn of motor neurons that control voluntary skeletal muscle activity (i.e. the external anal sphincter, not the bowel itself, have been described, although they can also indirectly affect bowel function due to weakened muscles and abdominal immobility). They are associated with a very poor prognosis as they are often progressive and there is currently no known cure (treatment is limited to symptomatic relief and support of basic vital functions such as breathing and feeding). Such diseases include spinal muscular atrophy, amyotrophic lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy and primary lateral sclerosis [54], X-linked adrenoleukodystrophy [55], and Menkes disease [56]. Theoretically, any congenital or acquired disease that affects neurological and/or cognitive development and behaviour and results in limited mobility could also have secondary effects on the bowel (and bladder) of a child or adolescent.

Nutrition plays an important role in the development of constipation. Often people with neurological pathology have a reduced appetite and receive insufficient amounts of food and fluids [57]. Children on tube feeding or through a gastrostomy require the use of specialised high-calorie therapeutic mixtures enriched with dietary fibre [58]. However, constipation may occur even if the correct dietary regime is followed, if there is no possibility of comfortable defecation or if there is a negative experience associated with it. Thus, hard faeces when passing through the anus can traumatise it, causing pain. A vicious circle is created: the unwillingness to experience the painful sensation again makes the patient arbitrarily delay stool. Further, due to the reverse absorption of water by the intestine, the faecal masses become harder, which causes even more negative emotions in subsequent acts of defecation. There are other factors in the development of CC in LMP, such as metabolic and absorption disorders, side effects of certain medications (opioids, iron preparations, antacids, etc.), disruption of the intestinal microbiocenosis due to frequent antibiotics and a diet low in fibre, and lack of parental control and interest in the defecation of a child with low mobility [59–61].

DIAGNOSTICS

Diagnosis of CC begins with the complaints, but these may not be present due to various circumstances: disinterest of the patient or his/her representative, inability to assess the extent to which constipation affects quality of life, etc. When collecting anamnesis, it is necessary to assess whether the underlying disease, concomitant

Table 1. Possible bowel problems and associated neurological conditions [19]

Таблица 1. Возможные проблемы с кишечником и связанные с ними неврологические состояния [19]

Neurological pathology/ Неврологическая патология	Bowel and urinary problems / Проблемы с кишечником и мочеиспусканием
Spinal cord injury / Повреждение спинного мозга	• Loss of control and sensation of the need to defecate / Потеря контроля и ощущения потребности в дефекации. • Urinary incontinence and/or constipation / Недержание мочи и/или запор
Spina Bifida	• Constipation / Запор. • Stool incontinence / Недержание стула
Multiple sclerosis / Рассеянный склероз	• Constipation / Запор. • Stool incontinence / Недержание стула
Stroke and brain injury / Инсульт и черепно-мозговая травма	• Loss of conscious desire for defecation / Утрата осознанного желания дефекации. • Constipation / Запор. • Urinary incontinence / Недержание мочи
Cerebral palsy / Детский церебральный паралич	• Constipation / Запор
Parkinson's disease / Болезнь Паркинсона	• Constipation / Запор. • Less commonly urinary incontinence / Реже недержание мочи

pathology in LMP or previous gastrointestinal diseases influence the occurrence of constipation. It is necessary to find out when difficulties in defecation appeared, whether their appearance is connected with pelvic or spinal surgery, with trauma; what sensations the patient experiences against this background (a discomfort, its localisation, an increased gas formation, a feeling of incomplete emptying of the rectum after stool discharge, pain and other symptoms such as nausea, vomiting, decreased appetite, signs of dysuria) and how often stool is discharged. It should be clarified whether there are factors that improve or worsen the situation, such as a change in the amount of food or drink, taking certain medications, or changes in motor activity. Particular attention should be paid to the quality of the stool, its colour, density, odour, quantity and presence of abnormal impurities such as blood or mucus. When the last stool occurred, whether the patient has urges to defecate and whether he or she needs to push. During the discussion, the doctor should determine the patient's understanding of the importance of constipation management, as some patients and their parents may not be bothered by such difficulties. Attention should also be paid to social factors, such as how the patient and family feel about the problem, the importance the patient attaches to constipation, and whether there is privacy and a comfortable environment for defecation [62]. It is likely that the patient has already tried to control constipation, so it is necessary to clarify how this occurred and whether there was an effect. Percussion to look for bowel bloating may be performed, as well as abdominal palpation and palpebral rectal examination. The patient's examination should form an opinion about the nature of the constipation: functional and/or organic [63].

An additional diagnostic method is the research of intestinal transit using X-ray contrast markers [64]. The colonic transit time can be used only in extremely unclear cases as a differential sign between functional constipation and functional faecal incontinence without constipation.

TREATMENT

The approach to the treatment of constipation in LMP varies according to the pathogenetic basis of constipation. In patients with hyperreflexic bowel, stimulation of the rectum (chemically or mechanically) results in evacuation of any rectal stool. The goal in hyperreflexic bowel is to achieve a relatively soft stool consistency to stimulate evacuation. In these patients, stool softeners and stimulant laxatives with mechanical stimulation of the anorectal area can provide stool relief. Patients with areflexic bowel may require abdominal muscle exercises and manual evacuation of stool. In patients who have low anal sphincter tone at rest, more formed stools may help reduce episodes of incontinence, so excessive use of stool softeners and stimulant laxatives should be avoided [65]. In patients with lesion levels at T6 or above any treatment that results in rapid rectal emptying carries the risk of precipitating life-threatening autonomic dysreflexia [66]. Patients at risk or carers

should be made aware of this risk and informed of appropriate emergency treatment (nifedipine).

In general, the treatment of CC in LMP should be staged, with the aim of finding the least invasive intervention that normalises stool consistency and frequency. The treatment approaches proposed by foreign researchers are presented in Figure 1. Treatment should be carried out for at least two weeks consecutively before considering further modification of the program.

First of all, dietary adjustments are required: an increase in the amount of fibre or other bulking agents in the diet and optimization of water balance [63, 68, 69]. For LMP with cognitive impairment, diet should be treated very carefully: an abdominal bloating and subsequent pain associated with flatulence cause them to scream and become uncontrollably anxious. Increased motor activity and traditional positioning during defecation also cannot be used in LMP. The use of technical rehabilitation devices (TRD) for daily positioning can improve bowel peristalsis and resolution of constipation with nutritional therapy. Rehabilitative aids are individually selected by orthopaedists and/or occupational therapists, and may include sitting supports, standing supports, walkers with additional body support, including for patients with cerebral palsy [70]. Abdominal massage activates intestinal stretch receptors, which causes increased contraction of the bowel and rectum, excites waves of contraction of the rectus abdominis muscles, decreases colon transit time, and stimulates the parasympathetic nervous system, thereby leading to increased intestinal secretion and motility and relaxation of sphincters in the digestive tract [71]. Mechanical effects may also be observed in lean LMP. Abdominal massage in children is usually performed starting at the right iliac region, using a gentle, squeezing, kneading motion in an inverted "U" direction around the top of the umbilicus to the left iliac fossa and then deep into the suprapubic region to help move gas and stool along the course of the colon to the rectum [72].

Anal/rectal stimulation [73] is a well-established technique used in LMP with constipation to facilitate bowel evacuation. The LMP caregiver inserts a lubricated finger (in medical glove) into the rectum and performs a rotary motion, dilating the anal canal and relaxing the pubic muscle, resulting in a reduction of the anorectal angle. Both of these effects result in reduced resistance to the passage of stool, thereby promoting bowel emptying [73]. This method of stimulation is very different from manual evacuation, where stool is extracted directly with the finger and which is generally not suitable as a regular treatment for the older child. Some studies have demonstrated the efficacy of non-invasive nerve stimulation, such as percutaneous electrical nerve stimulation [74], posterior tibial nerve stimulation [75] in the treatment of constipation.

If there is no effect from dietary changes, oral laxatives may be used, aimed at changing the rate of fecal passage. However, the side effects of the drugs used should be taken into account: a mineral oil, an osmotic laxative (polyethylene glycol preparations, lactulose) can aggravate fecal incontinence. Intestinal peristalsis stimulants such as Senna extract and bisacodyl are widely used. Rectal-sigmoid emptying can be carried out with a small-volume enema, glycerin suppositories. Sodium phosphate enemas should be avoided in children with renal impairment [3]. If there is no effect, the use of a larger volume enema administered through a conical tip or a special catheter, which provides transanal irrigation, is recommended [76]. The final step is the use of an antegrade enema administered through commercially available transanal irrigation systems. For the LMP and carers daily suppositories are more convenient and comfortable to use than transrectal irrigations, because with constant use it avoids fecal blockage and the need for 'high' enemas.

Surgical treatment of constipation in LMP should be considered taking into account all of

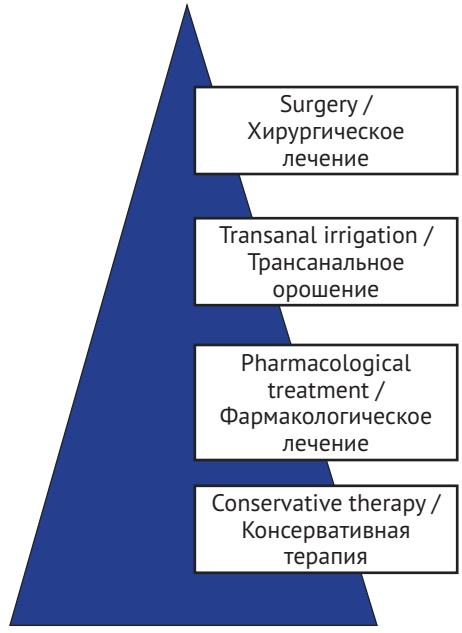

Fig. 1. Pyramid of recommendations for the treatment of neurogenic bowel dysfunction (adapted from [67])

Рис. 1. Пирамида рекомендаций по лечению нейрогенной дисфункции кишечника (адаптировано по [67])

Table 2. Guidelines for bowel care and function for people with spina bifida in different age periods [77]

Таблица 2. Руководящие принципы по уходу и функции кишечника для людей с расщелиной позвоночника в разные возрастные периоды [77]

Age group / Возрастная группа	Guidelines / Руководящие принципы
0-11 months / 0–11 месяцев	1. Monitor stool frequency, consistency and quantity / Контролируйте частоту стула, консистенцию и его количество. 2. Use dietary treatment, in particular breastfeeding if possible, as breast milk is easier to digest and provides a better recovery of the microbiome after surgery / Используйте диетическое лечение, в частности грудное вскармливание, если это возможно, так как грудное молоко легче усваивается и обеспечивает лучшее восстановление микробиома после операции. 3. Consider dietary treatment (fibre and fluids) before pharmacological supplements and/or rectal stimulants (glycerine suppositories) to treat constipation / Рассмотрите диетическое лечение (клетчатка и жидкости) перед фармакологическими добавками и/или ректальными стимуляторами (глицериновые суппозитории) для лечения запоров. 4. Use barrier creams to protect the perineal area as needed / Используйте барьерные кремы для защиты области промежности по мере необходимости.
1–2 years 11 months / 1–2 года 11 месяцев	1. Discuss toilet training and habits with parents / Обсудите с родителями обучение туалету и привычкам. 2. Set a goal to work towards correcting stool incontinence / Установите цель работы в направлении коррекции недержания стула. 3. Use fibre, sufficient fluids by mouth, exercise and a chronobiological approach (defecation in the morning after meals) / Используйте клетчатку, достаточное количество жидкости через рот, физические упражнения и хронобиологический подход (дефекации утром после еды). 4. Consider prescribing oral and rectal interventions for constipation / Рассмотрите назначение пероральных и ректальных вмешательств для борьбы с запорами. 5. Use dietary treatment (fibre and fluids), pharmacological supplements (sennoside, polyethylene glycol) and/or rectal stimulants (glycerin, docusate sodium or bisacodyl suppositories) to treat constipation and faecal incontinence / Используйте диетическое лечение (клетчатка и жидкости), фармакологические добавки (сеннозид, полиэтиленгликоль) и/или ректальные стимуляторы (глицерин, докузат натрия или бисакодил- суппозитории) для лечения запоров и недержания кала. 6. Use barrier creams to protect the perineal area as needed / Используйте барьерные кремы для защиты области промежности по мере необходимости. 7. Consult a *Spina Bifida* clinic or a specialist with expertise in bowel management bowel management for *Spina Bifida* / Обратитесь в клинику *Spina Bifida* или к специалисту с опытом в области управления кишечником при *Spina Bifida*.
3–5 years 11 months / 3–5 года 11 месяцев	1. Discuss the consequences of constipation and bowel incontinence (including shunt malfunction, urinary tract infections (UTIs), skin maceration, social isolation / Обсудите последствия запоров и недержания кишечника (включая неисправность шунтов, инфекции мочевыводящих путей (ИМП), мацерацию кожи, социальную изоляцию). 2. Set a treatment goal and establish a bowel control programme, using the recommendations given / Установите цель лечения и установите программу контроля за работой кишечника, используя приведенные рекомендации. 3. Use fibre, adequate oral fluids, exercise, and a chronobiological approach, exercise and a chronobiological approach (defecation in the morning after meals) / Используйте клетчатку, достаточное количество жидкости через рот, физические упражнения и хронобиологический подход (дефекации утром после еды). 4. Consider prescribing oral and rectal interventions to control management of constipation / Рассмотрите назначение пероральных и ректальных вмешательств для борьбы с запорами. 5. Use dietary treatment (fibre and fluids), pharmacological supplements (sennoside, polyethylene glycol) and/or rectal stimulants (glycerin, sodium docusate or bisacodyl suppositories) to treat constipation and faecal incontinence / Используйте диетическое лечение (клетчатка и жидкости), фармакологические добавки (сеннозид, полиэтиленгликоль) и/или ректальные стимуляторы (глицерин, докузат натрия или бисакодил-суппозитории) для лечения запоров и недержания кала. 6. Use barrier creams to protect the perineal area from maceration as needed / Используйте барьерные кремы для защиты области промежности от мацерации по мере необходимости. 7. Consult a *Spina Bifida* clinic or a specialist with experience in bowel management for *Spina Bifida* / Обратитесь в клинику *Spina Bifida* или к специалисту с опытом управления кишечником при *Spina Bifida*

the patient's problems, including general prognosis, mental function, and trophological status, not just defecation problems that are not resolved by therapeutic methods.

There are no consensus documents on the management of constipation and defecation disorders in LMP; only for children with spina bifida has a standardized approach to the management of bowel dysfunction been developed [77]. Guidelines for bowel care and function for people with spina bifida at different ages are summarized in Table 2. For older age, the recommendations are the same.

In summary, the management of constipation and defecation disorders in pediatric LMP is challenging and has significant psychosocial implications for both the patient and carers. Clinical guidelines are needed to provide a proactive, systematic and rational approach to the management of bowel dysfunction, including fecal incontinence and constipation. Collaborative efforts between multidisciplinary specialists are needed to overcome research barriers and provide innovative solutions.

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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IRON DEFICIENCY ANEMIA IN THE STRUCTURE OF CHRONIC DISEASES (LITERATURE REVIEW)

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Abstract. Iron deficiency anemia is an important problem in modern medicine. The disease is common among the population around the world and accompanies many diseases, especially common against the background of chronic diseases. Timely diagnosis and treatment of this pathology is an important element of the therapy of chronic pathological processes, since anemia aggravates the course of the underlying disease, worsening the quality of life of patients. This literature review considers a number of chronic diseases accompanied by iron deficiency anemia.

Key words: *iron deficiency anemia; chronic disease.*

ЖЕЛЕЗОДЕФИЦИТНАЯ АНЕМИЯ В СТРУКТУРЕ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. Железодефицитная анемия — важная проблема современной медицины. Заболевание распространено среди населения во всем мире и сопровождает многие острые и хронические патологические процессы. Своевременная диагностика и лечение данного клинико-гематологического синдрома является важным элементом терапии хронических болезней, поскольку анемия усугубляет течение основного патологического состояния, ухудшая качество жизни пациентов. В данном литературном обзоре рассмотрен ряд хронических заболеваний, сопровождающихся железодефицитной анемией.

Ключевые слова: *железодефицитная анемия; хроническое заболевание.*

INTRODUCTION

Iron deficiency disorders (IDD) are an important problem in pediatrics. Primarily, it is determined by the widespread prevalence of these conditions worldwide [1, 2]. Iron deficiency anemia (IDA) is a medical and social problem due to its impact on growth, development, cognitive function, intelligence, and behavioral responses in children [3, 4].

Iron is an essential element involved in many biological processes, one of the most important components of the mitochondrial respiratory chain. It is absolutely necessary for the proper functioning of the organism [5]. Iron is capable to

give and receive electrons and plays an important role in fundamental biological processes, including oxygen and electron transport, cellular respiration and DNA synthesis [4]. Iron deficiency (even in the absence of anemia) aggravates the course of many chronic diseases and increases the risk of mortality. The main organs regulating iron metabolism are liver and kidneys [6].

Iron deficiency anemia is an acquired disease characterized by a decrease in iron content in blood serum, bone marrow and tissue depots which resulting in impaired formation of hemoglobin and erythrocytes, hypochromic anemia and trophic disorders in tissues. The disease is polyetiologic [7]. Hermic hypoxia progresses and, subsequently, secondary metabolic disorders develop within this condition. IDA can develop in children with chronic inflammatory diseases even without persistent blood loss [8–10]. Anemia associated with such conditions is commonly referred to as anemia of chronic diseases (ACD), although this term is arbitrary since anemia can also occur in acute inflammation, particularly in suppurative processes (apostematous nephritis, lung abscess, etc.).

EPIDEMIOLOGY

According to the World Health Organization (WHO), about 1.62 billion people, or 24.8% of the total world population, suffer from various pathogenetic forms of anemia. In 2008, the WHO published a report analyzing the prevalence of anemia syndrome, with high rates among preschool children (76.1%), pregnant (69.0%) and non-pregnant women (73.5%). Iron deficiency anemias account for 90% of all anemias in childhood and 80% of all anemias in adults [11].

Iron deficiency anemia is associated with a large number of chronic pathologies:

1) autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, vasculitis, sarcoidosis, Crohn's disease, nonspecific ulcerative colitis) [12–15];
2) infections (acute ones: sepsis, pneumonia, septic endocarditis, peritonitis; chronic ones: osteomyelitis, tuberculosis, lung abscess, HIV);
3) tumors [16];
4) chronic heart failure (anemia is found in 17% of patients with first diagnosed CHF; it is an independent prognostic factor of mortality);
5) critical patients (intensive care patients);
6) endocrine pathology;
7) liver diseases;
8) chronic non-inflammatory diseases (severe trauma, thermal burns);
9) mixed diseases — alcoholic cirrhosis of the liver, circulatory insufficiency, thrombophlebitis, ischemic heart disease [17, 18].

PATHOPHYSIOLOGY

Three pathophysiological mechanisms of anemia development are distinguished:

A slight shortening of erythrocyte lifespan which is attributed to increased hemophagocytosis by macrophages occur in patients with inflammatory diseases;

Erythropoiesis is impaired due to decreased erythropoietin (EPO) production and reduced bone marrow response.

Iron metabolism is altered due to increased levels of hepcidin, which inhibits iron absorption and recycling, resulting in iron sequestration. Hepcidin, a protein synthesized in the liver, plays an important role in iron homeostasis. Inflammation results in the release of large amounts of mediators such as interleukin-6, interleukin-13, which in turn leads to an increase of hepcidin levels. It induces ferroportin blockade, impaired function of duodenal enterocytes, liver kupffer cells, and spleen macrophages; such changes result in reduced iron absorption and recycling [19, 20].

DIAGNOSTICS

The diagnostic basis for IDA associated with chronic disease is the presence of a long-standing condition, such as tumor, infectious-inflammatory, or autoimmune disease. By the moment, diagnostic criteria for the pathology have been developed:

1) clinical signs (depend on the disease: inflammatory, tumor or infectious);
2) pathology (hypoproliferative anemia, impaired iron release from cells of the mononuclear phagocyte system for furhter hemoglobin synthesis, reduced life span of erythrocytes);
3) data of laboratory tests [21, 22].

Clinical manifestations of chronic IDA largely depend on the associated disease. There is a direct correlation between the degree of IDA and severity of an underlying disease.

IDA and diseases of gastrointestinal tract (GIT). Obviously, when searching for the cause of anemia, first of all, it is necessary to exclude diseases that create conditions for blood loss. However, iron deficiency may be caused by impaired intestine absorption of the element. Iron is absorbed in the duodenum and in the initial part of the jejunum. The element passes through the following stages: capture of divalent iron by the cells of the mucous membrane (villi) of the small intestine and its oxidation into trivalent iron in the membrane of

microvilli; transfer of iron to the proper membrane, where it is captured by transferrin and quickly passes into the plasma. In this regard, small intestinal pathology may cause iron deficiency anemia [23–25].

The debut of celiac disease may manifest with anemia; therefore, children with chronic IDA are at risk for celiac disease, so should be screened. Iron deficiency can be observed both in the typical manifestation of celiac disease and in the absence of diarrhea and weight loss. Anemia occurs in 23.75–50% of patients with celiac disease and may be the sole symptom [8, 26].

The stomach plays a major role in iron absorption processes.

Hydrochloric acid converts ionic trivalent iron into the divalent form. In this regard, atrophic gastritis may cause IDA. The second, most common form of atrophic gastritis is associated with prolonged exposure to *Helicobacter pylori* (*H. pylori) infection*, which has been considered as a trigger factor in the development of idiopathic anemia in recent years [9, 14, 27, 28].

At the same time, the peculiarities of IDA in children with Helicobacter infection are insufficiently explored. In the course of the study (67 children with IDA aged 11–15 years) the authors found out that *Helicobacter* infection was detected in every third child with anemia. Anemia associated with Helicobacter infection was characterized by a refractory course, lower increase of hemoglobin and erythrocyte levels compared to children with IDA without *Helicobacter* infection. After successful eradication of *H. pylori*, there was obtained a positive dynamic in treatment with a significant increase of hemoglobin level in children [29].

Anemic syndrome is a frequent companion of inflammatory bowel disease (IBD). About two-thirds of patients with IDA suffer from concomitant anemia, which significantly impairs their quality of life. As a rule, the etiopathogenesis of anemia in IBD is multicomponent since it has no isolated single cause. Anemic syndrome in IBD is a combined variant of iron deficiency and anemia of chronic diseases. The course of the disease is aggravated by additional metabolic disorders, vitamin deficiency, as well as the effect of drugs used for the treatment of IBD [30].

Hemocolitis is one of the main causes of IDA in children with IBD, the incidence is 83–84% in ulcerative colitis and 22–43% in Crohn's disease. In case full recovery of iron depot is not taken into account, the correction of iron deficiency might be inadequate which lead to latent iron deficiency, and then to recurrence of anemic syndrome. As a result, decreased iron intake and increased iron losses have a negative effect on the parameters of iron metabolism [31].

Iron deficiency in overweight. IDA and iron deficiency in excessive adipose tissue accumulation have long been recognized, however, the mechanisms of their interaction continue to be studied. In recent years, 3 main hypotheses of hypoferremia in obesity have been proposed. Nutritional hypothesis: iron deficiency is a comorbid condition in obesity due to insufficient dietary iron intake or insufficient absorption due to concomitant gastroduodenal pathology. Blood volume hypothesis: as body weight increases, blood volume increases. Inflammation hypothesis: based on the involvement of systemic inflammation in the disturbance of iron metabolism in obesity. This hypothesis is the most convincing, it logically fits with the data on low-active inflammation found in obesity [1, 4].

Iron metabolism in kidney disease. Iron metabolism is disturbed in any form of renal pathology. Nephrogenic anemia is one of the pathogenetic variants related to IDA, which naturally complicates the course of chronic kidney disease [5]. This pathology is usually characterized by normocellular, normochromic, hypoproliferative anemia.

Reduced production of erythropoietin produced by kidneys plays a leading role in the mechanisms of anemia development in chronic kidney disease (CKD). However, other factors also contribute to its formation: shortening of erythrocyte lifespan, chronic blood loss, iron or folic acid deficiency, secondary hyperparathyroidism, chronic inflammation and others. Hepsidine excess is considered to be the main cause of impaired iron homeostasis and anemia in CKD due to decreased absorption of dietary iron and mobilization of iron from the depot [32]. The highest incidence of IDA is registered when creatinine clearance is decreased to 40–60 ml/min, and sometimes at earlier stages of the disease. Early development of this form of anemia is most common for diabetic nephropathy [33].

The main causative agent of urinary tract infections currently remains Escherichia coli. This group secretes a number of toxins, including lipopolysaccharide (the main component of membranes of Gram-negative bacteria). Iron is an essential element for survival, reproduction, and virulence of intestinal microorganisms. Hypoferremia is a protective response to infection and inflammation which reduce the amount of iron available for pathogens. Lipopolysaccharide is known to

activate Toll-like receptors (TLRs). TLR activation causes hypoferremia mainly by increasing hepcidin levels. Progression of inflammatory processes in chronic pyelonephritis is accompanied by an increase in the proportion of divalent iron in the structure of sideremia against the background of a decrease in the total iron-binding capacity of serum and reticulocytes and an increase in the concentration of ferritin [5].

Anemia in autoimmune disease. Anemia associated with systemic connective tissue diseases is caused by impaired erythropoietin synthesis due to blood loss from ulcers and erosions of the gastrointestinal tract which develop during prolonged use of anti-inflammatory drugs [34]. Rheumatoid arthritis is accompanied by anemia in 16–65% of cases. The development of anemia in rheumatoid arthritis is promoted by an increased level of inflammatory cytokines. About half of patients with systemic lupus erythematosus have anemia with a hemoglobin content of less than 100 g / l, it is either hypo- or normochromic type. A close relationship between hepcidin levels and IDA in patients with rheumatoid arthritis (RA) has been demonstrated: patients with RA have higher hepcidin levels than healthy individuals, patients with RA and anemia have higher hepcidin levels compared to patients with normal hemoglobin levels, and finally, hepcidin levels in patients with RA and IDA are higher than in cases where systemic inflammation is combined with iron deficiency [35, 36].

IDA in endocrine disease Anemia is quite common in endocrine diseases. At the same time, all morphological forms of anemia might be developed. Thus, parathyroid hormone has a direct inhibitory effect on the synthesis of endogenous erythropoietin, as well as on erythrocyte precursors in the bone marrow and their life span, which determines the presence of anemic syndrome in parathyroid gland pathology. Hypothyroidism is accompanied by anemia in 30–60% of patients. As a rule, hypochromic anemia develops. It is caused by a reduced iron absorption in the small intestine and the lack of stimulating effects on erythropoiesis which is induced by thyroid hormones. Anemia in hypopituitarism occurs in 32–46% of cases [37]. The cause is neoplasms or pubertal underdevelopment of the pituitary gland, accompanied by deficiency of thyroid hormones, adrenal hormones, androgens [38]. Diabetes mellitus is a frequent cause of IDA. The etiology is multifactorial: decreased synthesis of erythropoietin (due to diabetic nephropathy), low absorption of iron and vitamins, medications. Falsely elevated hematocrit level is determined in the blood samples of patients with diabetes mellitus, ketoacidosis might cause acute hemolysis [39].

Thus, iron deficiency anemia is quite common, especially against the background of chronic pathology, often aggravating the clinical course of an underlying disease. Early detection of iron deficiency anemia can accelerate the diagnostic search for the underlying disease, which undoubtedly leads to an earlier start of therapy and improved prognosis.

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

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NUTRITIONAL APPROACHES TO THE PREVENTION OF OBESITY IN CHILDREN

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Abstract. Prevention of obesity in children is a priority way to reduce the prevalence of obesity and, consequently, cardiovascular risk, both in the pediatric and adult populations. Preventive measures are aimed at correcting lifestyle and include optimizing nutrition and increasing physical activity. This review analyzes the effectiveness of modern nutritional interventions used to prevent overweight and obesity in children. Nutritional approaches are most promising from conception to 2 years of age. Encouraging breastfeeding and reducing the amount of protein in a child's diet in the first 12–24 months of life reduces the risk of obesity later in life, and avoiding complementary foods until 4 months of age is also recommended. Starting at 2 years of age, approaches that combine changes in diet and physical activity are used. Obesity prevention interventions carried out in children's educational institutions, including with the participation of the family, are most effective. Promising methods for correcting food stereotypes are the Mediterranean diet, reducing the consumption of sugary drinks and increasing the consumption of fruits, vegetables and foods rich in dietary fiber, which has a positive effect on various health parameters.

Key words: *obesity; children; prevention; breastfeeding; school meals.*

НУТРИЦИОЛОГИЧЕСКИЕ ПОДХОДЫ К ПРОФИЛАКТИКЕ ОЖИРЕНИЯ У ДЕТЕЙ

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Резюме. Профилактика ожирения у детей является приоритетным способом снижения распространенности ожирения и, следовательно, кардиоваскулярного риска как в детской, так и во взрослой популяции. Профилактические мероприятия направлены на коррекцию образа жизни и включают оптимизацию питания и повышение физической активности. В представленном обзоре проанализирована эффективность современных нутрициологических вмешательств, используемых для профилактики избыточной массы тела и ожирения у детей. Подходы, направленные на питание, наиболее перспективны в возрастном периоде от зачатия до 2 лет. Поощрение грудного вскармливания и снижение содержания белка в рационе ребенка в первые 12–24 месяцев жизни снижают риск ожирения в дальнейшие возрастные периоды. Также рекомендуется избегать введения прикорма до 4-месячного возраста. Начиная с двухлетнего возраста применяют подходы, сочетающие изменения в питании и физической активности. Наибольшей эффективностью обладают вмешательства по профилактике ожирения, проводимые в условиях детских образовательных учреждений, в том числе с участием семьи. Перспективными методами коррекции пищевых стереотипов являются средиземноморская диета, сокращение потребления сладких напитков и повышение потребления фруктов, овощей и продуктов, богатых пищевыми волокнами, что оказывает положительное влияние на различные параметры здоровья.

Ключевые слова: *ожирение; дети; профилактика; грудное вскармливание; школьное питание.*

INTRODUCTION

Overweight and obesity in children is increasing worldwide. It is an urgent problem both in high-income and low-income countries [1, 2]. The chronic course of the disease, its persistence in adulthood and the lack of effective treatment methods determine the importance of preventing its outbreak and spread [2–4].

According to H. Jebeille et al. (2022), the prevalence of obesity in the global pediatric population is 5.6% among girls and 7.8% among boys aged 5–19 years [5]. In the Russian Federation, according to a systematic review and meta-analysis that included the results of a survey of more than 350,000 children (2022), the prevalence of obesity is 1.2–25.3%, depending on age, sex, and region of residence [6].

Excess body weight is caused by a prolonged positive energy balance [1]. More than 600 genes have been associated with the risk of developing obesity [7]; however, in most cases obesity has no clear genetic cause because it results from the interaction of multiple factors that disrupt metabolism [8]. It is believed that more than 95% of obesity cases develop due to the inability of genetically predisposed individuals to adjust their behavior to obesogenic environment [7]. The obesogenic (obesity) environment, including high availability of foods with added sugars and saturated fats, cultural traditions and social behaviors of patients and their families, place of residence, inadequate availability of sports facilities, and other factors that contribute to increased energy intake and inadequate energy expenditure, increases the risk of developing obesity through epigenetic regulatory mechanisms over the lifespan. Treatment of obesity is a complex proble. Currently, it does not lead to sufficiently effective results in both adults and children [9, 10].

In contrast, prevention represents a promising strategy to combat obesity [11]. It is generally recognized that prevention of overweight in children and adolescents is a priority way to reduce the prevalence of obesity and, consequently, cardiovascular risk [2, 12, 13]. According to the recommendations of the European Society of Endocrinologists (2017), which most completely illuminate this problem, the prevention of overweight and obesity in children should include interventions aimed at correcting nutrition, physical activity, and lifestyle in general [14]. A large number of programs have been developed to promote behavioral changes from early life (pregnancy, infancy, and early early childhood) throughout childhood and adolescence involving the family, school, society, media, and government agencies [2, 11]. In 2022, methodological recommendations "Early prevention of obesity in children" created by FGBUN "FIC Nutrition and Biotechnology" (the Russian Federation) were published. They include modern approaches to targeted prenatal and postnatal nutritional optimization [15]. The development and implementation of effective intervention strategies and reduction of the long-term negative health effects of obesity is an important task of the modern medical community.

AIM

The aim of the review is to analyze the effectiveness of existing nutritional interventions directed to prevent underweight and obesity in children.

OBESITY PREVENTION IN CHILDREN DURING THE PRE-CONCEPTION PERIOD AND THE FIRST 1000 DAYS OF LIFE

Interventions before conception and during pregnancy

Согласно According to the concept of nutritional programming (metabolic imprinting), the nature of a child's diet determines the metabolic patterns of the child in the following age periods. Nutrition is considered to influence a child most significantly during the "first 1,000 days", from early gestation period up to 24 months. During this period, nutrition can modulate the risk of developing diseases in the presence of genetic predisposition [16].

Insufficient nutrition in the intrauterine period and the birth of an infant with low weight or body length have been shown as risk factors for obesity, arterial hypertension and type 2 diabetes subsequently. Excessive weight gain in women during pregnancy, even in case of initially normal body mass index (BMI), has a programmatic influence as well. Obesity and gestational diabetes mellitus among mothers are the best known risk factors for obesity in offspring [17]. Thus, there is a necessity to correct the nutritional status of women before pregnancy.

The evidence on interventions in the pre-conception period which were directed to prevent non-communicable diseases (NCDs), including obesity in children and adults, is scarce. This is partly due to heterogeneity in the definition of the pre-conception period [18]. In 2019 C.M. Jacob et al. analyzed the way different preventive approaches influence on etiological factors of NCDs during pre-conception period [19]. Thus, it was shown that the use of balanced protein-energy

products in combination with nutritional counseling and physical activity can reduce the risk of giving born to an infant with low length and weight in a certain gestational age by 21% and 27%, respectively, especially in mothers with weight deficiency [20]. A lower risk of developing gestational diabetes was found among women with high levels of physical activity [21]. Pregnant women which received intervention in the form of nutritional counseling and physical activity gained less weight compared to the control group [22].

A number of studies have shown that a pregnant woman's diet with excessive energy and fat content increases the risk of obesity in the offspring. There is no cerrelation with the nutritional status of the woman [23–28]. Current nutritional interventions during pregnancy show low efficacy in reducing the prevalence of childhood obesity, however, they have a positive effect on maternal and neonatal risk factors for the disease [29, 30]. Excessive weight gain was less common in pregnant women who were counseled on a low glycemic index diet (-24%) or counseled on nutrition and physical activity (-16%). Another study reported that nutritional counseling for pregnant women reduced the risk of developing gestational diabetes by 46% [30].

Interventions in the 0–2 years age group

Breastfeeding

Breastfeeding is one of the most studied aspects of early prevention measures in childhood obesity. The breastfading has a protective effect on the formation of overweight which is confirmed by studies [31]. Breastfeeding reduces the probability of excessive weight gain in childhood and adulthood by 13% [32]. The duration of exclusive breastfeeding has not been confirmed to influence the risk of obesity [31].

The duration of exclusive breastfeeding has not been confirmed to influence the risk of obesity [31]. It is most likely that brief breastfeeding is less protective against obesity than longer breastfeeding, regardless of whether it is exclusive or not. The benefits of prolonged exclusive breastfeeding with regard to obesity, have lack of evidence base due to the heterogeneity of the studies conducted and the lack of analysis of anthropometric data in children [33–36]. In addition, the studies did not take into account the associated factors which may influence the outcome.

Characteristics of formulas

Studies evaluating the relationship between the composition of formula used in the first year of life and obesity risks are mainly focused on the protein content. The use of formula with lower protein content is associated with lower body weight and Z-score of body weight at 6–12 months, BMI between 1 and 6 years, and risk of obesity at 6 years in the absence of conclusive data on body composition [37]. This pattern has been confirmed in many studies; however, there has been noted ambiguity in the criteria used to categorize formulae as low (1.1–2.1 g/100 ml) and high protein (1.5–3.2 g/100 ml) [38, 39].

Thus, reducing the protein content in formulas is a promising approach to obesity prevention. However, further study is required in order to assess its effectiveness in the long term [37]. The protein content of formula for infants under 1 y.o., recommended by the European Food Safety Authority (EFSA) is 1.8–2.5 g/100 kcal [40]. The consensus of the European Society of Pediatric Gastroenterologists, Hepatologists and Nutritionists (ESPGHAN, 2018) recommends adhering to the lowest protein concentration regarding the above mentioned range for children 1–3 years of age [41].

In addition to the protein content of formulas, protein hydrolysates and their possible protective role in children's obesity have been studied. P. Rzehak et al. [42] indicated that children who received formula with high-hydrolyzed casein had a slower increase in BMI in the first year of life. However, further observation of the same children up to the age of 10 years revealed no differences in anthropometric indices compared to breastfed children or those who received standard formula. Moreover, the rate of weight gain did not depend on the degree of protein hydrolysis. J.A. Mennella et al. demonstrated that the use of formula containing highly hydrolyzed protein in infants aged 2.5–7.5 months was accompanied by lower Z-score of body weight to growth compared to children receiving standard formula [43].

The protective effect of other infant formula components (prebiotics, probiotics, long-chain polyunsaturated fatty acids (PUFAs), soy protein) on obesity is currently unproven [31, 44].

Complementary feeding

Introduction of complementary foods and protein intake in infants and toddlers are the most studied controllable risk factors for the development of obesity.

The ESPGHAN consensus on complementary feeding reports an association between the introduction of complementary foods before 4 months of age and an increase in fat mass. The ESPGHAN

consensus recommends to introduce complementary foods not earlier than 4 and not later than 6 months of age [45].

L.A. Daniels et al. summarized the results of 26 studies and showed that the introduction of complementary foods before 4 months of age increases the risk of obesity in children [46]. In contrast, the EFSA consensus (2019) found no significant association between the time of complementary food introduction and the risk of obesity. Additionally, the EFSA consensus (2019) does not define a single introduction time of complementary foods for European children, and recommends focusing on the individual characteristics of children, especially in cases of prematurity [47].

With respect to protein intake, the ESPGHAN consensus [41] suggests not to exceed 15% of total energy intake during complementary feeding in order to prevent overweight and obesity.

Parenting interventions

Numerous studies that examined the effects of family-centered interventions on children's anthropometric measures have heterogeneous characteristics and endpoints, making it impossible to draw general conclusions. In the study by K.J. Campbell et al.,the authors gave parents recommendations on children's diet, physical activity, and duration of television watching and performed a further follow-up [48]. Beneficial effects of this approach were found at the age of 20 months and resulted in low consumption of sugary snacks and decreased TV time, however, no statistically significant effect on BMI was detected. A. Morandi et al. provided parents with information about their children's eating habits, including responsiveness to hunger and satiety cues. Despite a higher frequency of breastfeeding on demand at 3 months of age, there was no statistically significant effect on obesity prevalence at 2 years of age [49]. In the work of L.A. Daniels et al. [50, 51] the intervention began at 4–6 months of age. It was focused on healthy eating and growth patterns. Children in the control group had a higher Z-score BMI at 14 months of age, and their mothers were more likely to use "non-responsive" feeding practices. However, at age of 2 years, there were no significant differences in both Z-score BMI and the prevalence of overweight and obesity although intergroup differences in feeding practices were maintained.

In a study by I.M. Paul et al. [52], parents were trained to recognize the child's hunger and satiety cues and other sources of possible anxiety besides hunger; at the age of 1 year, children in the intervention group had a significantly lower weight-for-height percentile than the control group. The American Heart Association mentions that parental responsiveness to a child's hunger and satiety cues contributes to good "self-regulation of eating" and low risk of obesity [53]. The necessity to create a structured environment that defines dietary rules, food restrictions, availability of healthy foods, and role modeling is emphasized. Educational interventions for parents are required as a part of a strategy to reduce obesity and cardiometabolic risk across the lifespan.

OBESITY PREVENTION IN PRESCHOOL AND SCHOOCHILDREN

It becomes more difficult to combat the risk of obesity in children over 3 years of age, as the child's eating behavior, family eating patterns and parental feeding style have been sufficiently formed by this time.

The nutritional pattern for obesity prevention in children includes adequate consumption of vegetables and fruits rich in dietary fiber, as well as minimization of fast food and sugar-sweetened beverages. Additionally, the amount of fruit juice should be controlled, as exceeding the recommended amount (180–200 ml per day) contributes to excess body weight [54].

In the context of promoting a healthy lifestyle, it is recommended both to adhere to a balanced diet, and to form and maintain healthy eating habits in the family [2, 12, 55]. The daily amount of food should be divided into no more than 5 meals (3 main meals and no more than 2 snacks). It is also recommended to encourage eating at home, as opposed to eating outside [2, 12, 56]. In addition, providing children with a daily breakfast is an important guideline to prevent overweight and obesity [12, 56].

Prevention of obesity in preschool

Regular nutrition classes conducted by a nutritionist or a pediatrician are effective for preschool children. Preschoolers are explained the rules of healthy eating and nutritional behavior.

The most effective interventions are weekly nutrition lessons. They are focused on 5 rules: "drink water", "eat fruits and vegetables", "eat regularly", "make good choices" and "turn off your gadget while eating". The program also included increasing physical activity and modifying the surrounding space for sufficient mobility of preschoolers. The 4-month intervention resulted in a decrease of fat body mass in the main group and no effect on BMI [57]. S.N. Bleich et al. analyzed 5 randomized

controlled trials (RCTs) and 1 pilot study on the prevention of overweight in preschool children [58]. All five RCTs included the family as an additional intervention target. Three studies showed positive results: two of them included only physical activity intervention [59, 60], while the third used a multicomponent intervention with nutritional correction [61]. The positive results referred to decreased BMI in children aged 4–5 years in the first two studies. The third study found a less significant increase in BMI percentile and an increase in fruit and vegetable intake in children in the intervention group compared to the control group. Two other studies evaluated the effectiveness of an obesity prevention program aimed at preschoolers. They focused on both physical activity and nutrition, and reported no differences in outcomes between intervention and control groups [62, 63]. Z. Zhou et al. found a positive effect of a nutrition intervention in preschoolers. The study involved family and neighborhood, and resulted in changes of body composition (decreased body fat and increased muscle mass) after 12 months of follow-up, although no significant changes in BMI and Z-score were observed [64].

Obesity prevention in schools

The school-based interventions are mainly focused on elementary and middle school students. Food stereotypes were corrected by reducing portion sizes in school canteens, increasing the availability and interest in various fruits and vegetables, installing drinking water fountains, and eliminating foods with added sugar and saturated fats from school cafeterias. Lessons on healthy eating were conducted for children and parents as part of prevention programs. The lessons related to food choice, controlling the consumption of fast food and sugary drinks, the importance of breakfast for schoolchildren, and limiting eating outside the home. A number of studies included cooking workshops for schoolchildren and their families. About half of the studies analyzed by Y. Wang et al. in the systematic review demonstrated statistically significant positive effects of nutritional interventions on a number of obesity characteristics [65]. School-based interventions which were maintained at home appeared to be more effective. Only schools have shown moderate evidence of a preventive effect on obesity, when programs with nutrition or physical activity interventions were implemented. Programs involving both school and home environments appeared to be ineffective for isolated nutritional intervention and, in contrast, highly effective for increasing physical activity. A meta-analysis of RCTs examining the role of school-based interventions showed a Z-score BMI trend of –0.05 (95% CI –0.10, –0.01) and BMI of –0.30 kg/m^2 (95% CI –0.45, –0.15). Most of the results had a moderate level of evidence [65].

S.N. Bleich et al. reported that among 24 RCTs focusing on obesity prevention in schools, 17 had statistically significant favorable effects for at least one obesity-related endpoint [58]. Most of the effective programs combined nutrition and physical activity intervention and included the home environment as a secondary intervention target. Differences in BMI between intervention and control groups ranged from –0.33 to +0.05 kg/m^2 with follow-up ranging from 6 months to 6 years. These preventive interventions consisted of various combinations of programs whith increased intensity and duration of physical activity, educational courses on nutrition and self-regulation, and environmental modifications.

A systematic review by C.T. Bramante et al. summarized 33 studies aimed at preventing obesity in children and adolescents, 6 of which were school-based [66]. Five studies included food environment interventions, three of which obtained positive effects on BMI. Interventions with proven effectiveness included programs to provide access to drinking water at school [67], improving the in- and out-of-school nutrition environment [68], and modifying the range of food and beverages available in school cafeterias [69].

Obesity prevention in families and social groups

Y. Wang et al. showed that interventions directed at dietary change solely at home were not effective for obesity-related outcomes [65]. It is worth noting that Interventions conducted by the outpatient health care level were not successful, whereas school and community interventions showed positive results in obesity prevention (moderate level of evidence).

Community-based interventions show conflicting results and have a low level of evidence [58, 70]. The 2019 Cochrane Review reported the effectiveness of both home- and community-based interventions for childhood obesity [71], with lower financial costs per child and greater adherence to recommendations [72]. Approaches which modify the food environment (food advertising, range of vending machines at school, installation of drinking fountains) and facilitate access to physical activity are more appropriate for adolescents [2, 71]. Interventions directed to amend fast food marketing and financial support for low-income population groups are also useful [55].

ROLE OF SPECIFIC NUTRIENTS IN OBESITY PREVENTION

Healthy dietary habits that guide food and meal choices play a key role in the prevention of overweight and obesity. Some of the most studied nutrients in this regard include fat, added sugar, and dietary fiber.

Two recent Cochrane Reviews have focused on fat intake and its impact on body weight. Cohort studies have demonstrated a trend toward an increased incidence of obesity with increasing total fat intake [73]. There have been performed an analysis of three RCTs among children 4–13 years old. It was found out that educational interventions aimed at reducing dietary fat (≤30% vs. >30% of total energy intake) led to a decrease in both total and saturated fat intake, which was accompanied by a decrease in BMI (–1.5 kg/m^2, 95% CI –2.45, –0.55; moderate level of evidence). The protective effect of PUFAs on obesity does not have enough evidence base, since the results of a number of interventions conducted from birth to the first years of life are not sufficient [31].

The effect of total energy intake corection in early childhood which may influence on physical development in subsequent ages has not been proven so far [31].

The WHO Guideline: sugars intake for adults and children (2015) states that there is moderate evidence for an association between reduced intake of free sugars and decreased body weight, as well as weak evidence for an association between increased intake of free sugars and increased body weight [74, 75].

Four systematic reviews have reported the reduction in consumption of beverages with added sugars as a result of nutritional interventions [31, 55, 66, 76].

The results of long-term studies examining the way sugary beverage consumption affects weight gain in the early years of life are contradictory. Probably, weight gain might be explained by other dietary habits of the participants [31]. Nevertheless, reducing the consumption of sugary drinks is likely to have a positive impact on obesity in children [77, 78]. A recent position paper from the World Federation of International Societies of Pediatric Gastroenterologists, Hepatologists and Nutritionists (FISPGHAN) recommends to promote drinking water instead of sugary drinks from early childhood [2]. The effect of sugar substitutes on body weight continues to be debated and their safety in children has not been proven to date [79].

The impact of dietary fiber on health indicators has been analyzed by A.N. Reynholds et al. It was based on the results of 45 observational studies conducted in children aged 1 to 19 years. Increased consumption of fiber and foods rich with fiber content resulted in positive influence on body weight, blood lipid, glucose levels, and blood pressure [80]. A decrease in appetite and triglyceride absorption with dietary fiber supplementation was demonstrated after a single intake in the postprandial period in obese children [81]. Regarding the consumption of fruits and vegetables, C.T. Bramante et al. reported positive results of interventions at school in 2 out of 5 studies conducted [66].

Finally, several recommendations suggest adherence to the Mediterranean diet for obesity prevention [2, 56]. S. Fernández-Barrés et al. [82] demonstrated a positive effect of the Mediterranean diet during pregnancy, since it positively influenced on abdominal circumference in children at the age of 4 years with no effect on Z-score BMI. In contrary, L. Pereira-da-Silva et al. proved an inverse relationship between adherence to the Mediterranean diet and the risk of overweight in children [83].

DISCUSSION

Despite the heterogeneity of the conducted studies and the insufficient length of follow-up, many of the nutritional interventions resulted in new skills, lifestyle and environmental modifications. These changes may have favorable effects on obesity prevention that persist beyond the end of the study [84]. The Cochrane Review by T. Brown et al. emphasized that nutrition and physical activity behaviors learned in childhood persist throughout life [71]. It is plausible that small changes detected in the short term may provide long-term benefits for various aspects of health, including obesity prevention.

Parent-targeted interventions from conception to the first 2 years of life are generally effective in terms of behavior change but do not always have an impact on physical developmental parameters or obesity risk [44, 76]. Interventions at the family level are more effective than interventions at the level of health care providers or the community of a child [55].

The most effective interventions for the prevention of overweight and obesity are provided by pediatric educational institutions [58, 65, 66], including family-based interventions [58, 65]. This may be explained by the fact that children spend a significant part of the day in kindergarten or school and often have more than one meal in these institutions. In addition, school fulfills

the tasks of education and changing habits [72]. Family involvement is also important, taking into account the way family and home environment influence children's health behaviors.

Nutrition-focused interventions appeared to be the most promising approaches to prevent obesity in the age period from conception to 2 years. Encouraging breastfeeding and reducing the protein content of formula and the diet in general during the first 12–24 months of life are effective in minimizing the risk of overweight and obesity at later ages [31, 32, 37, 41, 44, 45, 76]. It is also recommended to avoid the introduction of complementary foods until 4 months of age [31, 45]. Starting from the age of 2 years, approaches combining changes in nutrition and physical activity are applied [58, 65, 71, 72]. Furthermore, a number of studies have shown separate effectiveness of nutrition and physical activity, which depends on the age and the context of application [58, 65, 66, 71]. The universal advice for individuals of all age groups is to adopt a healthy diet with emphasis on the Mediterranean diet model for the prevention of overweight and obesity, since many studies devoted to this topic have been conducted [31, 44, 66, 76, 82, 83]. Reduction in the consumption of sugary drinks may also lead to a lower overweight [77–79]. Consumption of fruits, vegetables and foods rich in dietary fiber has positive impacts on various health parameters (adequate satiety, body weight regulation, glycemic control, blood lipid levels, modulation of intestinal microbiota) [80, 83].

Many studies have confirmed the importance of a multidisciplinary approach to obesity prevention in children in order to improve its effectiveness. The WHO Commission on Ending Childhood Obesity suggests that intervention measures on changing eating behavior are not effective due to the fact they target one individual [85]. The most promising approach involves interventions at the level of a child, family, educational institution, health care providers, community organizations, and public health policy [86].

CONCLUSION

Prevention of childhood obesity is a major challenge for the scientific community. Nutritional interventions, especially in the early stages of child development, can prevent the development of obesity later in life. Long-term complex interventions, combining dietary modification with increased physical activity, appear to be the most effective at the level of the educational institution and the family. There is a strong need for further exploration of promising intervention targets in order to prevent overweight and obesity in children, with a focus on early adolescence. It is advisable to use not only BMI, but also the amount of body fat and muscle mass as well as quality of life as indicators of the intervention impact. Pediatricians monitoring a child from birth play a key role in the implementation of preventive interventions and, if there is a risk of obesity, should implement the above-mentioned measures as early as possible in cooperation with the family.

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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ADJUVANT THERAPY FOR GIARDIASIS

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Abstract. Giardiasis remains an urgent problem in Russia due to its proximity to endemic foci, insufficient control of the incidence, especially among the adult population, and the low level of hygiene literacy among adolescents. The progression of the disease leads to a wide symptom complex, aggravates the course of comorbid pathology and provokes the development of functional disorders. Used pathogenetic therapy allows to achieve complete elimination of the pathogen. This article provides information on the use of adjuvant therapy, which can reduce the duration of treatment and reduce the number of residual effects.

Key words: *giardiasis; protozoal infection; intestinal microbiota; antibiotic therapy; probiotics; adjuvant therapy.*

АДЪЮВАНТНАЯ ТЕРАПИЯ ЛЯМБЛИОЗА

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Резюме. Лямблиоз остается актуальной проблемой в России по причине близости к эндемичным очагам, недостаточного контроля заболеваемости, особенно среди взрослого населения, и низкого уровня гигиенической грамотности среди подростков. Прогрессирование заболевания приводит к широкому симптомокомплексу, отягощает течение коморбидной патологии и провоцирует развитие функциональных расстройств. Используемая патогенетическая терапия позволяет добиться полной элиминации возбудителя. В данной статье приводятся сведения о применении адъювантной терапии, которая позволяет уменьшить сроки лечения и снизить количество остаточных явлений.

Ключевые слова: *лямблиоз, протозойная инфекция; кишечная микробиота; антибактериальная терапия; пробиотики; адъювантная терапия.*

INTRODUCTION

Giardiasis is the most common human protozoal disease in the world. Despite the fact that some scientific sources classify this disease as a "forgotten tropical disease", according to the World Health Organization (WHO), the number of the population infected with Giardia is 10–20% [1, 2]. Thus, within the period of 2017–2021, 1,924 cases of the disease were registered in the Leningrad region, 1,513 of total number of cases (79%) accounted for children [3].

The causative agent of *Giardia intestinalis* (*Giardia lamblia*) is a flagellated protozoan; infection occurs after the ingestion of cysts in the gastrointestinal tract. The source is a sick person — in 1 g of feces there are up to 250 thousand cysts, and inoculation dose is only 10–100 cysts. Cysts are stable in the external environment, they free-

ly cross the gastric barrier and then pass to the stage of trophozoites under the influence of duodenal contents in the small intestine, feeding with the products of membrane digestion. The cycle is completed by spontaneous transition of Giardia into the form of cysts and their exit with feces [4]. Clinical recommendations of the Ministry of Health and treatment protocols for giardiasis in Russia are absent. Various options are discussed in the literature: from monotherapy with antiparasitic agents [5–8] to long-term three-stage complex therapy [9–12]. The use of adjuvant therapy is associated with increasing resistance of the parasite to antiprotozoal drugs [13–16] and low efficacy of monotherapy [17, 18].

AIM

To analyze scientific studies evaluating the efficacy of complex therapy for giardiasis compared to monotherapy with antiprotozoal drugs.

MATERIALS AND METHODS

Cyberleninka, UpToDate, PubMed, Medscape, PLOS and e-library databases were used as sources of foreign and domestic literature. The following keywords were used: giardiasis, protozoal infection, intestinal microbiota, antibiotic therapy, probiotics, intestinal adsorbents, immunomodulators, hepatoprotectors, adjuvant therapy. 34 sources were analyzed.

RESULTS

The classical domestic approach to the therapy of giardiasis, outlined in a number of practical guidelines for physicians, requires a step-by-step and complex treatment, reduced to three consecutive actions: elimination of factors contributing to the "failure to thrive" — proper antiparasitic therapy — post-eradication support [4, 19–21]. However, no evidence-based studies on the effectiveness of this approach have been found; the recommendations are based on an empirical approach. There have been found only one study comparing the efficacy of giardiasis treatment in preschool children. The treatment included following variations: antiparasitic agents alone (A), antiparasitic agents combined with a prebiotic with sorption properties (A+S), antiparasitic agent in combination with a prebiotic with sorption properties and a choleretic drug (A+C+Ch) and antiparasitic agent in combination with a prebiotic with sorption properties, a choleretic drug and a hepatoprotector (A+C+Ch+H) [22, 23]. The authors report that the effectiveness of Giardia eradication did not depend on the treatment regimen used. However, combined regimens (especially A+C+Ch) helped to stabilize stools, abdominal pain, nausea, and normalize the autonomic nervous system according to cardiointervalography [22, 23].

Since the role of the intestinal microbiocenosis in the pathogenesis of giardiasis has been proven [24–27], the most widely studied treatment is the combination of antiprotozoal agents with probiotics.

A recent publication [28] indicated that a constantly maintained normal composition of the intestinal microbiota protects against various microorganisms and protozoa. It is suggested that probiotics may disrupt the cellular architecture of parasites and modulate the immune response in addition to direct effects on the intestinal epithelium (restoration of the mucosal barrier, increase in the number of epithelial and bocaloid cells). A comparative study [29] showed that the use of a complex treatment (*Saccharomyces bouvardia* CNCM I-745 were used as probiotics) significantly improved the efficacy of therapy by enhancing the gut microbiota compared to monotherapy. Similar data were obtained by E.A. Kornienko in 2008 [18]. It is worth noting that studies with an experimental model of giardiasis showed that probiotics as monotherapy have anti-giardia effect as well, which makes them useful in the treatment of resistant forms of parasitic infestation [31]. The influence of enterosorbents in the therapy of giardiasis is less studied. Foreign sources do not provide such studies. There are single publications in the domestic literature proving the effectiveness of adsorbents, including dietary supplements, in the complex therapy of giardiasis [32, 33].

One of the studies evaluated the efficacy of enterosorbent Zosterin-Ultra in the complex therapy of children with giardiasis. Sixty children aged 3 to 17 years with giardiasis were examined. The patients were divided into 3 groups: the first group — 20 children, with inclusion of Zosterin-Ultra 30% in complex treatment against the background of albendazole treatment; the second group — 20 children, with inclusion of Zosterin-Ultra 60% in complex treatment against the background of albendazole treatment; the third group (comparison group) — 20 children, treated with albendazole only. All children treated with Zosterin-Ultra as part of the complex therapy, were significantly less often suffered from pain syndrome and asthenic complaints compared to monotherapy. The maximum percentage of Giardia eradication was observed with adjuvant therapy with Zosterin-

Ultra 60% against the background of albendazole treatment. Inclusion of adsorbents led to complete elimination of meteorism and flattulence, as well as normalization of appetite. Based on the obtained data, the authors recommend including Zosterin-Ultra in the complex treatment of giardiasis in children [33].

Single publications recommend including vitamin and mineral supplements in the treatment regimen of giardiasis [34]. However, there are no studies confirming the efficacy of this approach. There are also no data on the effectiveness of hepatoprotectors, immunomodulators, and antihistamines in giardiasis.

CONCLUSION

The presence of Giardia resistance to antigiardia drugs requires new approaches to the therapy. The study of complex therapy remains the subject of detailed research; more randomized trials are needed to incorporate complex therapy into national programs and clinical guidelines as soon as possible.

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 CLINICAL PRESENTATION AND DIAGNOSIS OF CYSTIC FIBROSIS

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Abstract. Cystic fibrosis is a common hereditary disease caused by a mutation of the *CFTR* gene responsible for the synthesis, preservation of the structure and function of the CFTR protein, manifested primarily by pathology of the gastrointestinal tract and respiratory system. The lack of protein function in cystic fibrosis leads to an increase in the viscosity of the secretion of exocrine glands, obturation of organs and disruption of their functions. As a result, it causes steatorrhea, malabsorption, diabetes mellitus, metabolic disorders, with developmental delay and chronic bronchopulmonary process. This article will consider the main aspects of the clinical course and diagnosis of this disease.

Key words: *cystic fibrosis; diagnostics*

ОСОБЕННОСТИ КЛИНИЧЕСКОЙ КАРТИНЫ И ДИАГНОСТИКИ МУКОВИСЦИДОЗА

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Резюме. Муковисцидоз, или кистозный фиброз, — распространенное наследственное заболевание, обусловленное мутацией гена *CFTR*, ответственного за синтез, сохранение структуры и функции белка CFTR. Муковисцидоз проявляется, в первую очередь, патологией со стороны желудочно-кишечного тракта и дыхательной системы. Недостаток функции белка при данной патологии приводит к повышению вязкости секрета экзокринных желез, обтурации органов и нарушению их функций, как следствие возникают стеаторея, мальабсорбция, сахарный диабет, нарушение метаболизма, задержка физического развития и хронический бронхолегочный процесс. В данной статье будут рассмотрены основные аспекты особенностей клинического течения и диагностики данного заболевания.

Ключевые слова: *муковисцидоз; диагностика*

INTRODUCTION

Cystic fibrosis (CF) — is a widespread hereditary disease caused by mutation in the CFTR gene (cystic fibrosis transmembrane regulator) responsible for the synthesis, conservation and function of protein CFTR. [1, 2]. Recently, pneumonia and malabsorption were the causes of death in children with CF in early childhood and first year of

life. Nowadays, CF changed its classification from "fatal" to chronic disease, with over than 25% of adults in patients with CF in 2019 year. Active research of the CFTR gene, CFTR protein, and its functions has contributed to the development of new possibilities for a personalized approach to the pharmacotherapy for patients with CF aimed at restoring the structure and function of the CFTR protein.

The average age of patients was 13.7±9.7 years, according to the "Register of patients with cystic fibrosis in the Russian Federation" in 2020. The eldest patient in the reporting year was observed in Saint Petersburg. His age was 63.1 years, and the youngest patient was 3 weeks old. The proportion of adult patients (≥18 years of age) was 26.5%. Among the patients with CF, a slight predominance of males was 52.0%, and females were 48.0%. Neonatal screening allowed to diagnose 52.3% of patients [3].

ETIOLOGY AND PATHOGENESIS OF THE DISEASE

Cystic fibrosis has autosomal-recessive inherence; the responsible gene is localized on the long arm of chromosome 7. It codes the membrane-associated protein CFTR, which is a cyclic adenosine monophosphate (cAMF). The cAMPF-controlled chloride movement channel regulates the transport of chlorides, salts, and bicarbonates throw membranes of epithelial cells of respiratory tract, saliva, sweat glands, pancreas, and intestine.

All variations of the CFTR gene's nucleotide sequence fall into one of seven main classes based on the effect of the CFTR protein [4, 5]. Not all polymorphisms of the CFTR gene's nucleotide sequence are categorized, and it is known that a single mutation might disrupt a protein's structure or function in multiple ways.

Mutations of the CFTR gene disrupt not only transport, but also the secretion of chlorine ions. When glandular cells reabsorb more sodium due to the difficulty of their passage throw the cell membrane, the disruption of the lumen's electrical potential occurs. In this causes a change in the electrolyte composition and dehydration of the secretion of the glands of external secretion. As the result, allocated secret becomes excessively thick and viscous. The deficiency of the function of protein in CF leads to the disruption of the chloride channel located on the apical part of cells of the exocrine glands. As the result of such defect, chloroanions are retained in the cell, increasing the absorption of sodium cations and water. Loss of water from the lumen of exocrine glands leads to an increase in the viscosity of secretion, obturation of organs and impairment of functions [6, 7].

The bronchial secretion in the lungs dehydrates, thickens, and interferes with the removal of mucus from the rhinoceros epithelium. Due to this condition, bacterial infections may occur; *Staphylococcus aureus, Pseudomonas aeruginosa*, multi-resistant strains of *Stenotrophomonas maltophilia*, and Burkholderia cepacia are the main pathogens. The spectrum of microorganisms associated with respiratory tract infections in CF continues to expand. The studies of the pulmonary microbiome in this category of patients demonstrate a complex synergy between cultivated and non-cultivated microorganisms [8]. Features of chronic lung infection in patients with cystic fibrosis include the fact that the infection is produced by an association of microorganisms in 2/3 of cases rather than by a monoculture [9].

Chronic respiratory tract infection with pathogenic microorganisms causes morphological changes in the bronchial tree and interstitium of lungs. The typical changes in CF are bronchiectasis and bronchiectasis, focal points of intersticial fibrosis, cystic changes, bullous emphysema, and atelectasis of segments. Chronic pulmonary aspergillosis is a slowly progressive, destructive process in the lungs caused by the mushrooms of Aspergills spp. in previous bronchiectasis. The development of pulmonary aspergillosis in patients with CF is promoted by impaired mucociliary clearance and immune response, as well as prolonged antibacterial and glucocorticosteroid therapy [10, 11].

In the pancreas, there is an early obturation of the conduits with viscous secretion and fibrocystic changes in the parenchyma. Such condition contributes to the autolysis of gland tissue with the formation of typical fibrosis, cavernosa pancreatitis, steatorrhea, malabsorption and associated deficiency of fat-soluble vitamins A, D, E, and K. This causes a delay in physical development. As the result of the defects of the islets of Langerhans, endocrine pancreatic insufficiency develops, which leads to the formation of diabetes mellitus.

Pathological changes in the liver are characterized by obstruction of the intrahepatic ductuses, accompanied by inflammatory infiltration, proliferation of stroma with the formation of micronodular cirrhosis of the livers. Patients have fatty liver disease, gallbladder hypoplasia, often with the formation of gallstones [12].

The World Health Organization (WHO), International Cystic Fibrosis Association, and European Cystic Fibrosis Society currently adopt the following classification:

1. Classical cystic fibrosis with pancreatic insufficient (mixed or pulmonary-intestinal form of the disease), E84.8.
2. Classical cystic fibrosis with pancreatic-sufficient (mainly pulmonary form of the disease), E84.0.
3. Cystic fibrosis unspecified (uncertain diagnosis in positive neonatal screening for cystic fibrosis (CRMS/CFSPID)), E84.9.
4. Diseases associated with the CFTR gene: isolated obstructive azoospermia; chronic pancreatitis; disseminated bronchiectasis.

FEATURES OF CLINICAL PICTURE OF CYSTIC FIBROSIS

The advancement of modern technology has made it feasible to recognize the indicators that suggest cystic fibrosis in prenatal and neonatal periods: the presence of hyperechogenic bowel according to the data of ultrasound (US), the existence of meconium ileus in newborn, prolonged neonatal jaundice, and vitamin K-dependent hemorrhagic conditions.

The clinical picture of cystic fibrosis has some features. Therefore, this pathology can be detected at early age in the form of such manifestations: obsessive cough like whooping cough; often recurring respiratory infections with phenomena of bronchitis and pneumonia; wheezing; shortness of breath; cough with purulent sputum, including outside periods of exacerbation; various lung sounds of different localizations depending on the prevalence of the process.

Meconium ileus is one of the syndromes that can be observed in children with CF from birth. It is characterized by the manifestation of bowel obstruction, which is caused by mechanical causes — accumulation in the lumen of a dense meconium block [13]. Meconium ileus is diagnosed in 15–20% of newborns with cystic fibrosis. The percentage of patients with meconium ileus at birth in the group of children of the first year of life was 22.1%, reflecting its true incidence, according to the Russian Federation's register of patients with cystic fibrosis [14].

Patients with CF are characteristic of delayed weight gain, frequent abundant steatorrhoea, increased appetite, episodes of rectal prolapse, and stool retention with clinical manifestations of partial or complete bowel obstruction (so-called distal intestinal obstruction syndrome). At an early age, there are also episodes of manifestations of cerebral salt wasting syndrome (hypokalemia, hyponatremia, hypochloremia) in the form of weight loss, regurgitation, vomiting, lethargy, and refusal of food. Insufficient intake of salts with food and water, and also due to loss of electrolytes through the gastrointestinal tract and with sweat fluid, especially in conditions of increased sweating (fever, hot weather), can lead to the development of pseudo-Bartter syndrome (PBS). The syndrome manifests mainly at the first year of life in patients with CF. Because of its potential for fatality, it is regarded as a severe and dangerous complication of cystic fibrosis that, in some situations, a reason to call for emergency medical care. PBS can be the first symptom of CF. The clinical manifestations of this syndrome are varied, from a delay in physical development to an acute condition, occurring with refusal to eat and drink, lethargy, regurgitations, and vomiting—signs of dehydration. This syndrome is frequently confused with adrenogenital syndrome, kidney pathology, and acute intestine infection [8].

One of the manifestations of cystic fibrosis is cystic fibrosis — associated liver disease (CFLD), which includes a variety of nosologies in the form of biliary cirrhosis with or without portal hypertension, persistent elevation of liver enzymes, fibrosis, steatosis, and gallstones disease [15, 16]. Globally, the incidence of hepatobiliary pathology associated with cystic fibrosis is estimated to be 37.9%, with 2.5% of deaths resulting from liver disease decompensation. [17]. Biliary cirrhosis with portal hypertension in the Russian Federation in 2017 was recorded in 4.5% of patients, without portal hypertension in 2.3%, liver cirrhosis (hypertension is unknown) in 0.7% of patients, and liver damage without cirrhosis in 15.9%. In 1.5% of patients, liver damage is the first clinical symptom of CF. That is why it is recommended to include a sweat test in the diagnostic algorithm for cirrhosis of the liver of unclear etiology [15, 16]. Like many other phenotypic manifestations of cystic fibrosis (CF), liver damage depends more on modifying genes outside the *CFTR* locus, not just on the genetic defect and type of mutation of this gene.

Patients with CF often have age-related endocrine insufficiency of the pancreas — cystic fibrosis-related diabetes (CFRD), which is typically asymptomatic and can be undiagnosed for a long time. At the same time, it is known that already 2–4 years before the manifestation of CFDR, indicators of nutritional status and respiratory function deteriorate. The combination of CF and diabetes mellitus has a negative impact on life expectancy [18].

Mostly male patients have reduced fertility. In most cases, the fertility in women with cystic fibrosis is preserved. However, in certain cases it is possible infertility caused by anovulatory cycle and

secondary amenorrhea, due to protein-energy deficiency. The most common cause of decreased fertility in patients with a normal ovulatory cycle is a change in the water and electrolyte composition of cervical mucus due to a large amount of *CFTR* in the cylindrical epithelium of the cervix. As a result, the cervical secretion becomes too viscous, which reduces the ability to fertilize [19, 20].

Osteoporosis, often found in these patients, is always secondary. The causes of its development in CF include chronic microbial-inflammatory processes, low calcium intake, low physical activity, hypoxia and hypercapnia, diabetes mellitus in the context of CF, bone mass deficit, violation of bone microarchitecture due to inadequate acquisition of peak bone mineral density during the period of active growth, and excessive bone loss in adults. Osteoporosis for CF in childhood and adolescents is between 20 and 50% and increases after 18 years of life (50–75%) [21].

Allergic bronchopulmonary aspergillosis (ABPA) in patients with CF is proceeds chronic with periodic exacerbations. The main clinical signs of exacerbation of ABPA are: uncontrolled course of CF, attacks of suffocation, cough with sputum containing brown or black inclusions and mucous block, bronchial obstructive syndrome and/or the occurrence of infiltrates with eosinophilia, chest pain, refractory increase in fever to the use of antibacterial drugs, as well as a decrease in lung function [22].

The duration of pulmonary aspergillosis for more than 3 months may indicate the development of a chronic form of the disease (chronic pulmonary aspergillosis (CPA)). It is manifested by a productive cough, shortness of breath, hemoptysis, a progressive decrease in lung function, as well as intoxication syndrome. CPA is often mistaken for exacerbating CF caused by a bacterial pathogen and prescribes inefficien reserve antibacterial therapy in these cases [10, 11, 22].

Cystic fibrosis in adults can be divided into two groups: patients with a typical form of the disease, who became ill in early childhood and lived to adulthood; and patients with an atypical form, with late manifestation. The first group is characterized by low nutritional status, ongoing, recurrent infection, and an inflammatory process in the lungs with noticeable, long-lasting bronchial wall alterations, the formation massive bronchiolo- and bronchiectasis, widespread pneumofibrosis, and obstructive and bullous emphysema. The respiratory tract of these patients is much more often to be infected with gram-negative microflora: there are cirrhosis changes, pansinusitis, hemoptysis, diabetes mellitus (20%) and other pulmonary and extrapulmonary complications [23].

FEATURES OF DIAGNOSIS OF CYSTIC FIBROSIS

ДThe diagnosis of CF is confirmed if there are one or more characteristic phenotypic manifestations of it in combination with evidence of *CFTR* dysfunction, such as the detection of clinically significant mutations of the *CFTR* gene during genotyping or an increase in the level of chlorides in the secretion of the patient's sweat glands. To address the challenges associated with CF diagnosis, a set of criteria has been established. According to which mandatory for CF is the existence of a distinctive clinical symptom and evidence of any malfunction related to the functioning of the chlorine canal one of the methods proven.

Nowadays, professionals use a number of variations of the CF diagnosis criteria [6, 8].

The most common, national consensus and European Standards-approved diagnostic criteria are used, which call for the patient to comply with two requirements:

1) a positive sweat test result and/or two *CFTR* mutations;
2) neonatal hypertrypsinogenaemia or characteristic clinical manifestations (diffuse bronchiectasis, expulsion from sputum of pathogenic microflora relevant to CF, exocrine pancreatic insufficiency, salt wasting syndrome, obstructive azoospermia) [6, 24].

In the diagnosis of obstructive intestinal obstruction (including meconium ileus) in the neonatal period, attention should be paid to the presence of signs of intrauterine small bowel perforation or transferred intrauterine necrotizing enterocolitis (intrauterine formation of adhesions, peritonitis), and also to the violation of colon obstruction under normal formation of its neural apparatus. Since the disorders mentioned are related to late fetopathies them can be visualized in the third trimester. DNA testing for cystic fibrosis is recommended if the child continues to exhibit intrauterine symptoms of hyperechogenic bowel in order to determine the most prevalent mutations. The infant is susceptible to developing intestinal blockage and meconium ileus after birth.

After birth, diagnosis of intestinal obstruction and complications is necessary in accordance with clinical practice of patients with meconium ileus. A cystic fibrosis specialist consultation, sweat test, and DNA test are required. If the sweat test is not possible, a DNA-test should be performed [24].

A child is diagnosed with pseudo-Bartter syndrome if they have established diagnosis of cystosis fibrosis, the classic clinical presentation, biochemical abnormalities in the blood: hyponatremia, hypokalemia, hypochloremia, and metabolic alkalosis [8].

Since many diagnostic criteria overlap with the common symptoms of the underlying disease, diagnosing aspergillosis in patients with cystic fibrosis is hard and frequently delayed. To determine a diagnosis, a complex specialist examination is necessary. According to the consensus of the Cystic Fibrosis Foundation (2003), the diagnostic criteria for ABPA include [25]:

- deterioration of the course of cystic fibrosis: cough with sputum containing mucous tubes, shortness of breath, suffocation attacks, reduction of TLC (lung capacity of the lungs), FEV_1 (the forced expiratory volume in 1 second), acute or persistent deterioration of the condition, not related to other causes;
- total IgE >500 IU/ml;
- presence of specific *Aspergillus* IgE or positive *aspergillus* antigen skin test;
- presents of specific *aspergillus* IgG;
- changes in the X-ray or CT [25–27].

When diagnosing liver cirrhosis in people with cystic fibrosis, it is important to consider the existence of the following symptoms: increased alanine aminotransferase, aspartate transferase and gamma-glutamyl transferase for more than 6 months with the exception of other causes [28, 29]; palpatory increase in the size of liver and spleen [29]; prolonged prothrombin (thromboplastin) time in the blood or in the plasma [29, 30]; a characteristic ultrasound (heterogeneous echogenicity of parenchyma, severity, rounded borders hepatic, growth of connective tissue in the gate of the liver), finding of a significant amount of free fluid in the abdominal cavity, which indicates ascites [31, 32]; depletion of venous blood flow and discovered portal vein hypertension formation indicators through hepatic duplex ultrasound scanning (DUS); the presence of cirrhosis or fibrosis-related symptoms as determined by indirect liver elastometry research, with signs of fibrosis severity determined by morphological classification METAVIR (Meta-Analysis of Histological Data in Viral Hepatitis); identifying of stomach and esophageal varices while performing an esophagogastroduodenoscopy (EGD). In clinical practice, the severity and degree of compensation of liver cirrhosis associated with CF is determined by the Child-Pugh score [34].

The presence of early morning hyperglycemia (fasting blood glucose ≥7.0 mmol/l), "diabetic" blood glucose levels in the standard glucose tolerance test (fasting blood glucose <7,0 mmol/l and fasting blood glucose level after 2 hours in the oral glucose tolerance test ≥11,1 mmol/l), or postprandial hyperglycemia — which is determined by continuous monitoring of glycose in the absence of symptoms — are the diagnostic criteria for diabetes related to cystic fibrosis [35].

Patients with cystic fibrosis (CF) can be diagnosed with osteoporosis through laboratory methods of investigation, clinical picture evaluation, and bone density scanning.

The diagnosis of osteoporosis in cystic fibrosis (CF) is established when there are one or more vertebral body compression fractures that are not connected to a high-energy injury or a localized disease that results in a change in MBD or when there is a history of fracture and MBD by z-criterion ≤–2 SD (standard deviations) [36].

In the Russian Federation, neonatal screening for cystic fibrosis is done on all newborns to diagnose the condition. Early diagnosis and prompt treatment initiation lower the risk of serious complications, enhance physical development, decelerate the rate of lung function loss, and minimize the need for hospital stays [6, 8, 24]. There are three required steps in the screening protocol: immunoreactive trypsin (IRT) test and sweat test. The first step involves measuring the amount of IRT in a dried drop of blood from newborns (4–5 days for full-term, 7–8 days for premature). Administer blood is carried out in accordance with Order No. 185 of 22th of March 2006 "On mass screening of newborn children for hereditary diseases". In the second step, if the IRT threshold level (cut-off >99.5 centile) is exceeded a retest is conducted on the 21–28th day of life. In the third step, in the event of a positive re-test, a sweat test is conducted. In the fourth step, with the sweat test's borderline outcome, additional testing techniques, such as DNA analysis and measuring the intestinal potential difference. When a sweat test is positive, it is considered a positive screening result, and the patient is sent to the cystic fibrosis center (or the profile unit). All children with meconium ileus require a sweat test because of the possibility of a false-negative result, regardless of the level of IRT. The first two months of life are the best time to diagnose and begin monitoring a patient identified by the neonatal screening program [8, 24].

The sweat test is the "gold standard" for the diagnosis of cystic fibrosis. It takes at least two positive results to establish a diagnosis. It is possible to conduct the sweat test on a child who weighs at least 2 kg and is 48 hours old [6, 8, 24].

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There are two types of sweat test methods used in the Russian Federation.

1. The classical direct method of determining the electrolyte composition of sweat (chlorine or sodium) by the method of pilocarpine electrophoresis by Gibson and Cooke (1959). The norm is up to 30 mmol/l, the borderline significance is 30–59 mmol/ll, the positive result is 60 mmol/l and above (with a hose of sweat of at least 100 mg). If the chloride content exceeds 150 mmol/l, it should be questioned [6–8].
2. Sweat sample collection was first used in the mass screening of newborns. Sweat analysis with specialized equipment was widely used to help determine the conductivity of perspiration. This correlates with the measurement of the chloride content and enables the measurement of 3–10 µl of sweat to yield a sufficient result. For the purpose of assessing conductivity, a positive result for cystic fibrosis is defined as an indicator that is greater than 80 mmol/l; the borderline significance is 50–80 mmol/l; normal — up to 50 mmol / l. When conductivity exceeds 170 mmol/l, it is cause to be questioned. The time to collect sweat should not exceed 30 min, the minimum permissible amount of sweat is 75–100 mg (15 µl in the Macroduct collector), the rate of sweating should be at least 1 g/m^2 per minute [24]. It is necessary to thoroughly cleanse the patient's skin beforehand [8].

The following could be the cause of the sweat test's border results: individual characteristics in people without cystic fibrosis, especially in adults; improper preparation for the test; carrying soft mutations in cystic fibrosis [24]. It is advised to employ various techniques for determining sweat chloride levels in this situation: carrying out repeated research, performing advanced DNA analysis (gene sequencing), extended clinical laboratory tests, and instrumental examination (coprological examination, determining the pancreatic elastase-1 stool test, the biochemical analysis of electrolytes of blood, sputum or swab culture from the posterior wall of the throat, chest X-ray, sinus X-ray, spermogram), the procedure to identify variations in nasal potentials or measuring the electrical current in the intestinal biopsy and finding a function violation in the chlorine canal.

It may be suggested that patients who exhibit suspicions of cystic fibrosis undergo an additional test for intestinal current measurement, particularly in cases that are questionable (at the boundary values of the sweat test, with unexpressed symptoms, and/or with incomplete classical manifestations of the disease) [6–8].

For the following indications, a genetic molecular testing to identify *CFTR* gene mutations is advised: newborns with positive IRT and positive or limit values of the sweat test, meconium ileus; people with limit value of sweat test; patients with clinical manifestations of classical or monosymptomatic CF; in *CFTR*-associated diseases (pancreatitis, congenital bilateral absence of the vas deferens / obstructive azoospermia); relatives of patients with CF (to media status determination as desired); women after the birth of the first child with cystic fibrosis, as well as during subsequent pregnancies in the presence of a child with cystic fibrosis; intrauterine child in 10–12 weeks of gestation with suspicion of CF (siblings with CF) or exposure of hyperechogenic bowel during ultrasound examination; to gamete donors and embryos in vitro fertilization programs (IVF), intrauterine insemination; when there are no limitations or contraindications, married couples with high genetic risk cystic fibrosis (CF) who want to undergo IVF (preimplantation genetic testing) on CF to prevent the birth of a child with CF [8, 24].

The Consensus guidelines and the regularly updated databases should be taken into consideration when evaluating the clinical significance of the genetic variants that have been detected.

The molecular genetic testing strategy for cystic fibrosis involves multiple phases.

1. The first stage involves searching for the most prevalent mutation variants in the population that the subject is a member of [8].
2. In the second phase, an advanced search for more rare variants is carried out using Sanger sequencing or High Performance Genomic Sequencing (MPS/NGS). The analysis includes the study of the entire CFTR gene encoding sequence (27 exons), exon-intron compound areas, 5'- and 3'-noncoding regions (up to 200–300 nucleotides), as well as the deep introne areas where the variants with established pathogenicity are found.
3. The third stage is when minor alterations in the gene sequence can be found using standard scanning techniques, such as sequencing: nucleotide replacement, small deletion or insertion. These methods are not effective in detecting modifications that involve multiple exons or introns. It is advised to use the following technologies: MLPA (multiplex-ligation dependent probe amplification) or QF-PCR (fluorescent quantitative multiplex PCR) [24, 37].

The European Consensus on CF states that in 98% of cases, a pathogenic variant can be identified through a thorough molecular analysis of the

CFTR gene. This could be because of the following: the methods employed precluded the examination of the gene's regions containing pathogenic genetic variants, the phenomenon of uniparental disomy, or the CF phenocopy [24].

OTHER LABORATORY TESTS FOR CYSTIC FIBROSIS DIAGNOSTIC AND MONITORING OF PATIENTS WITH CYSTIC FIBROSIS

All CF patient must undergo a blood test to determine their level of inflammation, track how their medication is affecting these markers, and participate in a complex nutritional status evaluation [8, 38]. Also, it is advised that all CF patients have a urinalysis performed during primary diagnosis and dynamic observation in order to identify kidney damage early on.

It is advised that laboratory testing be done on all patients who have CF suspicion or who are confirmed to have the disease in order to assess the degree of pancreatic insufficiency (measurement of the pancreatic elastase-1 stool test), the degree of correction of the pancreatic insufficiency, and the stool test with the measurement of neutral fat in stool [6, 8, 24].

All patients with CF (or with suspicion of CF) are shown sputum analysis (induced sputum or tracheal aspirate). In exceptional situations (for infants), oropharyngeal swab and/or bronchoalveolar lavage (BAL) to identify the pathogen/pathogens and determine the sensitivity of the secreted microflora [6–8, 24].

The study is conducted during the primary diagnosis and dynamic observation processes, including therapy efficiency monitoring at least once every three months, based on indications — preferably more frequently. To assess the efficacy of eradication in the initial seeding of *P. aeruginosa* and other multidrug-resistant gram-negative microflora, a control study is also conducted 10–14 days following an antimicrobial therapy.

Sending a monthly microbiological examination is advised in cases of chronic multidrug-resistant gram-negative microflora in CF patients to assess the effectiveness of pathogen eradication therapy. To send kids under five years old for a deep throat saliva test to diagnose their microbiological flora. Prioritizing sputum analysis is advised for adults and children older than 5–6 years old.

Laboratory tests should be considered to diagnose allergic bronchopulmonary aspergillosis: the total IgE test (IgE), *Aspergillus fumigatus* specific IgE and IgG antibodies. The same tests are recommended in case of suspicion of CPA and the determination of galactomannan (metabolite *Aspergillus fumigatus*) in the blood (definition of fungal metabolites) [6, 8, 10, 24, 25].

Patients with CF with suspicion of ABPA are shown the *aspergillus* antigen skin test to exclude/confirm mycogenic sensitization [25].

All patients with CF are recommended to conduct a biochemical blood test (protein total, albumin, determination of the activity of Aspartate aminotransferase, alanine amino transferase, gamma-glutamyl transferase, alkaline phosphatase, amylase, lipase, study of the level of cholesterol, triglycerides, sodium, potassium, chlorides, total bilirubin, free and albumin-bound bilirubin, C-reactive protein in blood) annually, according to indications — more often. The purpose of the study is to track chronic inflammation, pancreatic function, electrolyte metabolism, and liver health based on indicators [8, 38].

Patients with CF should have tests for acid-base blood, potassium, and sodium to rule out PBS and to keep track of PBS therapy [8, 30].

It is advised that all patients with cirrhosis of the liver and a primary diagnosis of cystic fibrosis undergo a coagulogram, a reference study of the hemostasis system, 1 every 3 to 6 months in order to track the function of their livers, synthesis of proteins, and timely prevention of hemorrhagic complications [24].

For the purpose of tracking the pancreatic endocrine system, all patients with CF should have a blood glucose assessment once every 6 months. As a screening for the timely diagnosis of CFRD, it is recommended to consider performing a glucose tolerance test with a glucose load of 1.75 g/kg (no more than 75 g; control points — on an empty stomach, after 60 min, after 120 min) for all children over 10 years of age (as indicated — earlier) annually during the period of clinical stability. The use of glycated hemoglobin (HbA1c) as a screening test is not required because there is not enough information available to patients with CF about these indications [35].

For the complex diagnosis of osteoporosis and the diagnostic of kidney pathology, patients with CF are recommended to determine the level of total and ionized calcium, phosphate in blood, serum blood creatinine and creatinine clearance (calculated according to the Cockcroft-Gault formula), alkaline phosphatase [8].

For all male patients with CF who are 15 years of age or older, spermogram and molecular genetics testing (which, if not done previously, analyzes mutations in the *CFTR* gene) in order to ascertain the prognosis and strategies for resolving

the issue of reproduction. All male patients with cystic fibrosis (CF) who are 15 years of age or older should have testing for total testosterone and steroid-binding proteins in their blood serum to rule out hypogonadism [39, 40].

For patients with CF or suspected CF, chest organ computed tomography (CT) and X-ray are advised in order to assess the type and degree of lung tissue damage [6, 8, 24].

X-rays can reveal such signs as deformation and enhancement of the pulmonary pattern, pneumofibrosis, peribronchial cuffing, consolidation (atelectasis), bronchiectasis, pleural bullae, manifestations of bronchial obstruction (local emphysema, increased retrosternal airspace, flattening of the diaphragm), bronchial wall thickening, mucus plugs, and kyphosis. In the past, X-rays were more frequently used in different centers that care for patients with CF, including foreign ones, for dynamic observation; a number of centers used CT. [24]. Now the main method of diagnosis of changes in the lungs in CF.

To clarify the method for reducing radiation exposure with repeated control of the inflammation process, patients with CF are recommended to perform magnetic resonance imaging (MRI) of the chest organs. Up to 7 years in conditions of conscious sedation, after free-breathing [41].

It is recommended to perform CT of the paranasal sinuses (PC) (cone beam or multislice) or MRI of the PC in the initial assessment of the pathological process in the paranasal sinuses and in preparation for each rhinosurgery [41]. Children are not recommended to perform CT paranasal sinuses without clinical indications (for the purpose of dynamic observation). This significantly increases the total radiation exposure (due to the need for periodic chest CT scans).

In cases of suspicion of CF and in patients with CF, it is recommended to examine the function of external respiration. The spirometry is done on average every 3 months (study of unprovoked respiratory volumes and flows, if necessary; additional study of breathing volumes with the use of drugs). Body plethysmography is performed annually, on indications and on average, in order to determine the dynamic control of pulmonary function and the reversibility of airway obstruction in its presence (in the absence of age or other contraindications) [6, 8, 24]. An external respiratory function study (spirometry) is possible in children from 5 to 6 years of age if the patient can perform a forced exhalation maneuver. For children under five, the study's diagnostic value is lower. Spirometry allows an indirect assessment of lung capacities. The body plethysmography is carried out to more accurately evaluate the lung capacities according to indications.

Pulse oximetry and/or blood gas analysis should be performed at each hospitalization for all patients with CF suspicions and all CF patients, depending on the indications (exacerbation of the chronic bronchopulmonary process, presence of respiratory failure, needing oxygen therapy) —more often [8]. All patients with suspicion of CF and patients with CF are recommended to perform abdominal ultrasounds and liver ultrasounds. To detect changes typical of the disease and their dynamics, special attention should be given to the pancreatic structure in order to ascertain the type of liver blood flow. It is also recommended to perform liver elastometry in all patients with CF to assess the severity of fibrosis on the METAVIR scale [8, 24].

All male patients aged over 15 years with CF should undergo a urological/andrological examination with an ultrasound of the genitals to detect structural and morphological changes.

Regular periodic doppler echocardiography (measurement of the pulmonary arteriovenous pressure) is recommended in patients with CF, as with this pathology, especially with widespread damage. The development of pulmonary hypertension and the formation of pulmonary heart is possible [8].

It is recommended to perform an electrocardiography of patients with CF in PBS to monitor the effect of electrolyte disorders on heart activity. Also, before starting therapy with proton pump inhibitors, drugs against nontuberculous mycobacterial infections (NTMs), with prolonged use of azithromycin for other indications, against the background of high-doses of selective Beta 2-adrenergic agonists (2 weeks) therapy to evaluate the *Q–T* interval [30].

When a CF patient needs a BAL microbiological examination in addition, tracheobronchoscopy is advised. This method is used for the purpose of rehabilitation, should conservative therapy prove ineffective in an effort to rectify lung lobe atelectasis [6, 8, 10].

Nasal endoscopy in patients with CF is recommended for indications: if necessary, assessment of the severity of chronic rhinosinusitis, degree of nasal polyps, clarification of indications for surgical treatment on the nose, evaluation of the results of endoscopic endonasal surgical interventions.

EGD (esophagogastroduodenoscopy) is recommended for all patients with CF with cirrhosis of the liver to monitor esophageal varices — 1 time every 6–12 months. If you suspect erosive-ulcera-

tive lesions, inflammatory diseases of the stomach and esophageal mucosa, or gastroesophageal reflux disease [8].

Sigmoidoscopy with biopsy is advised in order to assess the variation in intestinal potential for patients suspected of having CF.

CONCLUSION

Patients with cystic fibrosis require active dispensary observation and clinical monitoring. Improving the prognosis for this disease is closely related to an early and adequate diagnosis. So, it is crucial to consider not only the patient's objective state but also information regarding the clinical picture, diagnosis, and course of treatment. Multidisciplinary care and collaborative patient observation by experts with diverse backgrounds are essential in the treatment for CF in patients, because the illness requires complex therapy and damages numerous organs and systems.

ADDITIONAL INFORMATION

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

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CLINICAL AND LABORATORY FEATURES OF ACUTE INTESTINAL INFECTIONS CAUSED BY *KLEBSIELLA PNEUMONIAE* IN CHILDREN

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Abstract. The *aim* of the work is to study the clinical and laboratory features of intestinal infections caused by *Klebsiella pneumoniae* in combination with viruses and other enterobacteria to optimize their diagnosis, prognosis and therapy in young children. *Patients and methods*. In the department of intestinal Infections of the Children's Scientific and Clinical Center for Infectious Diseases of the FMBA of Russia in the period 2019–2021, 65 young children who were on inpatient treatment for AII caused by *K. pneumoniae* were observed. Depending on the etiological forms of the disease, the patients formed 4 groups: *K. pneumoniae* monoinfection — group "Kp" (n=29); combination of *K. pneumoniae* with intestinal viruses — group "Kp+V" (n=14); combination of *K. pneumoniae* with opportunistic enterobacteria (OEB) — group "Kp+OB" (n=14); combination of *K. pneumoniae* with intestinal viruses and OEB — group "Kp+V+OEB" (n=8). Clinical and laboratory data were evaluated in all children. The degree of intestinal dysbiosis, in addition to the generally accepted criteria, was characterized by the content of atypical *E. coli* in feces (lg CFU/g). Etiological diagnosis of AII was performed using the bacteriological method and polymerase chain reaction. During statistical processing, the average values of indicators, the average frequency of deviations of indicators from the norm (M±σ; P±σ) were determined, differences in groups were revealed using the t-test and Pearson's criterion χ^2; they were considered reliable at $p < 0.05$. Methods of variance and discriminant analysis were used. *Results*. The higher age of children in the groups "Kp+V" and "Kp+V+OEB" was revealed. The association of *K. pneumoniae* with viruses in these groups was accompanied by an increase in the frequency of diarrhea ($p < 0.05$). The frequency of thrombocytosis and monocytosis differed in the groups of children ($p < 0.05$) and was maximal in the groups "Kp+OEB" and "Kp+V", respectively. The content of atypical *E. coli* in faeces in the "Kp" group was lower than in the "Kp+OEB" group ($p < 0.05$). The duration of inpatient treatment was longer in the "Kp" and "Kp+V+OEB" groups. The discriminant model included the following signs: age of children (p=0.0015); complaints of lethargy (p=0.02); complaints of vomiting (p=0.08); platelet count in the hemogram (p=0.006); amylorrhea in the coprogram (p=0.0008); stool pH (p=0.12); duration inpatient treatment (p=0.004); combination of *K. pneumonia*e with OEB ($p < 0.00001$). The overall diagnostic significance of the model was 89.2%. *Conclusion*. Using discriminant analysis, it was found that the features of clinical and laboratory signs of acute intestinal infections caused by *K. pneumoniae* in young children are more determined by the combination of *K. pneumoniae* with opportunistic enterobacteria than by the combination with viruses.

Key words: *intestinal infections; children; early age; Klebsiella pneumoniae; intestinal viruses; opportunistic enterobacteria; clinical and laboratory features; diagnostics.*

КЛИНИКО-ЛАБОРАТОРНЫЕ ОСОБЕННОСТИ ОСТРЫХ КИШЕЧНЫХ ИНФЕКЦИЙ, ВЫЗВАННЫХ *KLEBSIELLA PNEUMONIAE*, У ДЕТЕЙ

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Резюме. *Цель работы* — изучить клинико-лабораторные особенности кишечных инфекций, вызванных *Klebsiella pneumonia,* в сочетании с вирусами и другими энтеробактериями для оптимизации их диагностики, прогнозирования и терапии у детей раннего возраста. *Пациенты и методы*. В отделении кишечных инфекций ДНКЦИБ ФМБА России в период 2019–2021 гг. наблюдали 65 детей раннего возраста, находившихся на стационарном лечении по поводу ОКИ, вызванных *K. pneumoniae*. В зависимости от этиологических форм заболевания пациенты образовали 4 группы: моноинфекция *K. pneumoniae* — группа «Кр» (n=29); сочетание *K. pneumoniae* с кишечными вирусами — группа «Кр+В» (n=14); сочетание *K. pneumoniae* с условно-патогенными бактериями (УПЭ) — группа «Кр+УПЭ» (n=14); сочетание *K. pneumoniae* с кишечными вирусами и УПЭ — группа «Кр+В+УПЭ» (n=8). У всех детей оценивали клинико-лабораторные данные. Степень дисбиоза кишечника дополнительно к общепринятым критериям характеризовали по содержанию атипичной *E. coli* в фекалиях (lg КОЕ/г). Этиологическую диагностику ОКИ выполняли при помощи бактериологического метода и полимеразной цепной реакции. При статистической обработке определяли средние значения показателей, среднюю частоту отклонений показателей от нормы (M±σ; P±σ), выявляли различия в группах с помощью t-критерия и критерия χ^2 Пирсона; считали их достоверными при p <0,05. Использовали методы дисперсионного и дискриминантного анализа. *Результаты*. Выявлен более высокий возраст детей в группах «Кр+В» и «Кр+В+УПЭ». Ассоциация *K. pneumoniae* с вирусами в этих группах сопровождалась увеличением частоты диареи (p <0,05). Частота тромбоцитоза и моноцитоза отличалась в группах детей (p <0,05) и была максимальной в группах «Кр+УПЭ» и «Кр+В» соответственно. Содержание атипичной *E. coli* в фекалиях в группе «Кр» было ниже, чем в группе «Кр+УПЭ» (p <0,05). Длительность стационарного лечения была больше в группах «Кр» и «Кр+В+УПЭ». В дискриминантную модель вошли признаки: возраст детей (p=0,0015); жалобы на вялость (p=0,02); жалобы на рвоту (p=0,08); количество тромбоцитов в гемограмме (p=0,006); амилорея в копрограмме (p=0,0008); pH кала (p=0,12); длительность стационарного лечения (p=0,004); сочетание *K. pneumoniae* с УПЭ (p <0,00001). Общая диагностическая значимость модели составила 89,2%. *Заключение.* С помощью дискриминантного анализа установлено, что особенности клинико-лабораторных признаков ОКИ, вызванных *K. pneumoniae,* у детей раннего возраста в большей степени определяются сочетанием *K. pneumoniae* с УПЭ, чем сочетанием с вирусами.

Ключевые слова: *кишечные инфекции; дети, ранний возраст; Klebsiella pneumoniae; кишечные вирусы; условно-патогенные энтеробактерии; клинико-лабораторные особенности; диагностика.*

INTRODUCTION

In the etiological structure of the incidence of acute intestinal infections (AIE) in Russian children in recent years, the importance of opportunistic pathogens has remained significant, among which the leading role belongs to *Klebsiella pneumoniae* [1, 2]. Attention to the study of *Klebsiella* etiology was attracted by its severity and tendency to defeat children in the early age group. The increase in the incidence of Klebsiella, the similarity of local changes in

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the gastrointestinal tract with other intestinal infections makes it important to study this pathology. This especially relevant in the appearance of carbapenem resistant strains of *Klebsiella* [3].

When the *Klebsiella* invasion nature of AII is established, the disease is more often diagnosed as a mono-infection [4, 5]. The majority of hospitalized patients with this pathology are young children with unformed intestinal microbiota and immature immune system. Moreover, they have other constitutional anomalies, deficiency conditions, feeding disorders, which reduce the non-specific resistance of the body and predispose to manifestation of AII [6–9].

In the study of epidemiology AII described combinations of Klebsiella infection with other conditionally pathogenic representatives of the family Enterobacteriaceae (conditionally pathogenic enterobacteria — CPE). As well as the combination of CPE with respiratory viruses in young children [10]. As concomitant infections increase [11], the problem of AIIs remains unresolved since AIIs are caused by the combination of conditionally-pathogenic pathogens with intestinal viruses in children [12]. There is a very few information on resistance of *K. pneumoniae* of extra-hospital to antibiotics and Bacteriophages that cause intestinal infections young children [13]. The laboratory feature of out-of-hospital AII caused by Klebsiella and other pathogens of bacterial and viral nature remain poorly studied.

AIM

To study clinical and laboratory features of acute intestinal infections caused by *Klebsiella pneumoniae* in combination with viruses and other enterobacteria to optimize their diagnosis, prognosis and treatment in young children.

MATERIALS AND METHODS

65 children aged from 1 month to 3 years were observed in hospital treatment for AII associated with *K. pneumoniae* in the period 2019–2021, in the Department of Intestinal Infections of the Children's Research and Clinical Center for Infectious Diseases of the Federal Medical and Biological Agency of Russia. The sampling was based on the diagnosis of AII mono- and combined etiology associated with *K. pneumoniae*. Patients formed four groups: "Kp group" (n=29) — monoinfection with *K. pneumoniae*; "Kp+V group" (n=14) — combined AII caused by *K. pneumoniae* and intestinal viruses; "Kp+CPE group" (n=14) — AII caused by the K. pneumoniae and other CPEs; and "Kp+V+CPE" group (n=8) — combined AII caused by the *K. pneumoniae*, intestine viruses and CPE.

The etiological significance of *K. pneumoniae* and CPE in AII genesis was determined when detected in feces. The condition was the detection of at least 5 lg CFU/g and the absence of other bacterial pathogens in the bacteriological method. Results of fecal studies by PCR method using the set of reagents "AmpliSens® OKI screen-FL", intended for molecular-genetic diagnosis of bacterial (Shigella, Salmonella, Yersinia, Campylobacter, Escherichia coli) and viral (Rotavirus, Norovirus, Enterovirus, Astrovirus, Adenovirus) pathogens. Value determined by serological response in the diagnosis of indirect hemagglutination in some cases [14].

The severity of intestinal dysbiosis was assessed indirectly by the excretion of atypical *E. coli* from the feces in a quantity of not less than 5 lg CFU/g.

There has been performed evaluation of patients' complaints (weakness, fever, vomiting, diarrhea), medical history (duration of pre-hospital stage of disease, treatment) and life (food allergies, atopic dermatitis, past illnesses, vaccination history), objective status, results of clinical tests of blood and urine, biochemical blood tests (ALT, C-reactive protein, glucose, urea, electrolytes), stool test data. The severity of exicosis in children with AII was assessed on the basis of clinical recommendations.

K. pneumoniae sensitivity to antibacterial drugs (ampicillin/sulbactam, ceftriaxone, gentamicin, nalidixic acid, nitrofurantoin, trimetoprim/sulfamethoxazole) was determined by microdiffusion on Muller-Hinton agar using standard ACS strains 700603. The sensitivity of K. pneumoniae to bacteriophages ("Bacteriophage Klebsiella polyvalent purified" and "Bacteriaphage Klebsiella pneumoniae purifying" JSC "NGO "Mikrogen"", Ufa) was studied. The lithium activity of bacteriophages was assessed using the "sterile spot" method according to MP 3.5.1.0101–15.

Treatment of children with AII was carried out according to clinical recommendations of the Ministry of Health of Russia. The results of treatment in different children's groups were evaluated. According to the duration of hospitalization and outcomes (recovery, improvement).

During statistical processing, the average values of indicators, the average frequency of deviations of indicators from the norm (M±σ; P±σ) were determined, differences in groups were revealed using the t-test and Pearson's criterion χ^2; they were considered reliable at $p < 0.05$. To prove the possibility of separating groups of children with AII of mono- and combined etiology associated with *K. pneumoniae*, the discriminant

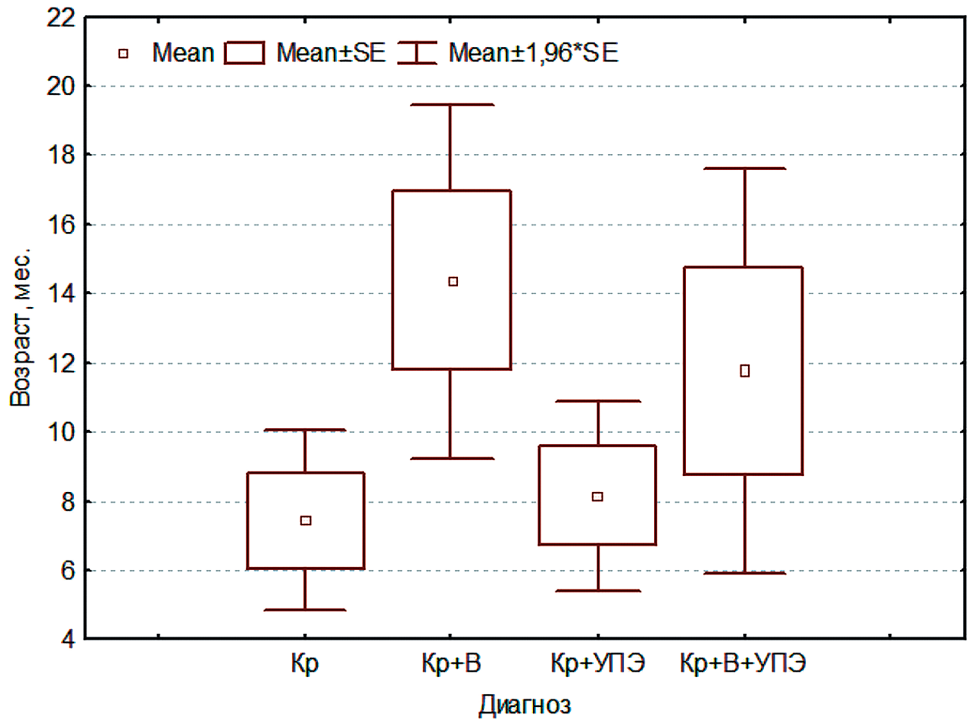

Fig. 1. Average values of the age of children in groups (number of months)
Рис. 1. Средние значения возраста детей в группах (число месяцев)

analysis method was used. By identifying the signs of determinants that significantly influence the assignment of a particular patient to one of the four groups, coefficients were calculated for the identified signs and subsequent solution of discriminant functions.

RESULTS AND DISCUSSION

The gender composition of the children in the sample shows a small predominance of boys in the group in the "Kp+V" and "Kp+CPE" groups (48.3%; 64.3%; 57.1%; 37.5%; χ^2=1.82; p=0.61). (These groups are presented here and will be listed in the following order: "Kp", "Kp+V", "Kp+CPE", "Kp+V+CPE"). The age composition was characterized by a relatively high proportion of children of the first year of life in the "Kp" and "Kp+CPE" groups (79.3%; 50%; 85.7%; 62.5%; χ^2=05.83; p=0.12) (Fig. 1), when visiting children's organized groups, it is normal for children older than one year to have more contact with viral infectious agents [15]. A comparison of the median age values of children revealed differences between the "Kp" and "Kp+V" groups (7.4±7.3 and 14.4±9.7 months; p=0,007) and the "Kp+V" and "Kp+CPE" groups (14.4±9.7 and 8.1±5.3 months; p=0.036) (Fig. 1).

In children in the grip "Kp+V" rotavirus was detected in 50% of cases, norovirus — in 35.7%, enteroviruses — in 7.15%. The combination of rotaviruses with norovírus — in 7,15%. In children in the group "Kp+V+CPE" rotavirus was detected in 25% of cases, norovirus — in 50%, adenovirus — in 12.5%. In this group the combination of rotaviruses with noroviruses — in 12,5%.

The frequency of discharge of different CPE in stool was at high titers in children in the "Kp+CPE" and "Kp+V+CPE" groups decreased in the following rows: *S. aureus* (45,8%); *P. mirabilis* (20,8%); *Enterobacter* (12,5%); *C. freundii* (8.3%); *H. alvei* (4.2%); *A. baumani* (4.2%); *P. aeruginosa* (4,2%).

At the time of admission at the hospital, the majority of the children in all groups had exicosis of the 1 degree (65,5%; 78.6%; 57.1%; 62.5%; χ^2=3.88; p=0.69), exicosis of the 2 degree — 6.9% of "Kp" children and 14.3% of the "Kp+CPE". The combination of AII with acute respiratory infection was diagnosed in children in all groups (37.9%; 28.6%; 21.4%; 33.3%; χ^2=1.42; p=0.70), of which 10.3%; 14.4%; 7.1%; 12.5% cases (χ^2=0.40; p=0.94). Febrile seizures were observed in children in the groups "Kp", "Kp+V", "Kp+CPE" (3.4%; 7.1%; 7,1%; χ^2=8.40; p=0.49). Urinary tract infections were diagnosed in a small part of children in all groups (6.9%; 7.1%; 7,1%; 12.5%; χ^2=8.40; p=0.49). Atopic dermatitis was detected in children in the "Kp", "Kp+V", "Kp+V+CPE" groups (20.7%; 7.1%; 25%; χ^2=4.75; p=0.19).

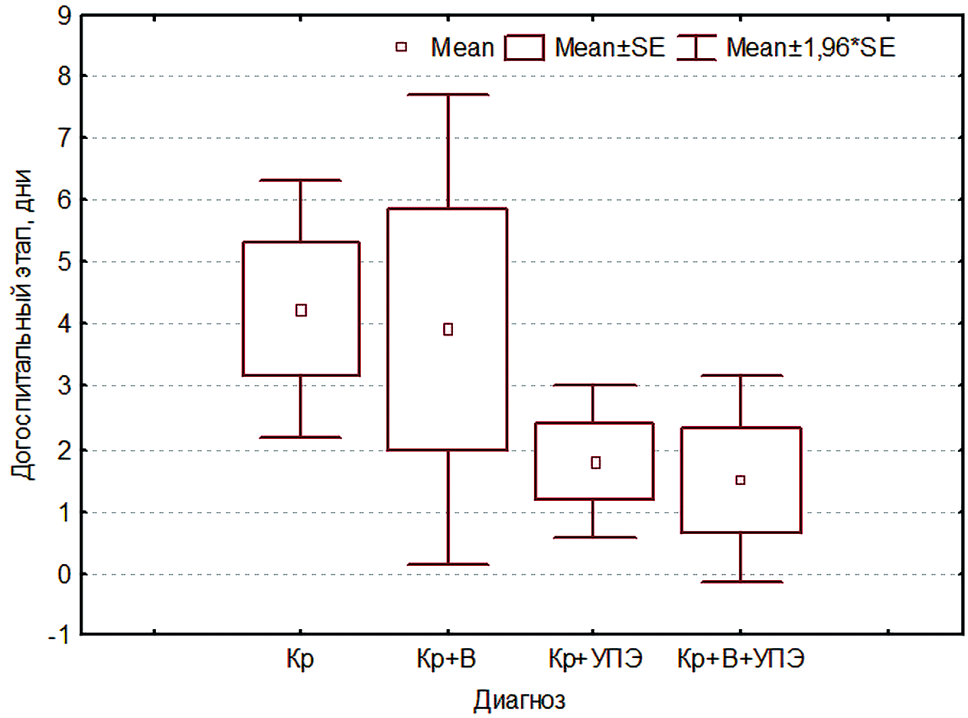

Fig. 2. The average duration of the prehospital stage of treatment of children in groups (number of days)
Рис. 2. Средняя длительность догоспитального этапа лечения детей в группах (число дней)

The pre-hospital stage by time was slightly greater in children in the "Kp" and "Kp+V" groups (4.2±5.7 days; 3.9±7.2 days) compared to those in the "Kp+CPE" and "Kp+V+CPE" groups (1.8±2.3 days; 1.5±2.4 days) (p >0.05) (Fig. 2). Nifuroxazide treatment was equally often during this period in all groups: 6.9%; 14.3%; 7.1%; 25%; χ^2=2,51; p=0.47; Antibiotic treatment was received by 13.8% of children in the "Kp" group, 7.1% of those in the "Kp+V" group and 7.1% in the "Kp+CPE" group (χ^2=1.68; p=0.64).

The incidence of diarrhea in the children's groups was high: 79.3%; 100%; 71.4%; 100% (p_{1-2} <0.05; p_{1-4} <0.05) and the incidence of vomiting was lower than 44.8%; 71.04%; 50%; 87.5% (χ^2=6.0; p=0.099). The incidence of lethargy (24.1%; 50%, 64.3%, 37.5%) and fever (41.4%; 64.3%; 50%; 75%) in the children's groups did not differ significantly (χ^2=4,0; p=0,27 and χ^2=2,92; p=0,40).

Inflammatory changes in the blood analysis were manifested by leukocytosis in children in the "Kp" and "Kp+V+CPE" groups (13.8%; 37.5%; χ^2=11.66; p=0.07), leukopenia in children of the "Kp", "Kp+V", "Kp+CPE" groups (20.7%; 14.3%; 28.6%; χ^2=11. 66; p = 0.07), thrombocytosis — frequently in children from the "Kp" and "Kp+CPE" groups (37.9%, 21.4%, 57.1%, 7.5%; χ^2=12.8; p=0.46), monocytosis — significantly frequently among children of "Kp+V" and "Kp+CPE" groups (6.9%, 42.9%, 28.6%, 12.5%; χ^2=8.61; p=0.34). Children in the "Kp" and "Kp+V+CPE" groups experienced increases in ESR more frequently (20.7%; 7.1%; 7,1%; 37.5%; χ^2=8.42; p=0.21).

Increases in C-reactive protein in the blood were frequently in the "Kp", "Kp+V", "Kp+V+CPE" groups (20.7%; 21.4%; 7.1%; 37.5%; χ^2=3.0; p=0.39). An increase in the level of alanine transaminase — an indicator of reactive changes in the liver in AII. Increase ALT was slightly more commonly observed in the groups "Kp+CPE" and "Kp+V+CPEs" (6.9%; 7.1%; 21.4%; 50%; χ^2=2.3; p=0.51). An increase in urea was also found slightly more frequently in the group "Kp+CPE", "Kp+V+CPE" (44.8%; 42.9%; 50%: 50%; 50%, χ^2=0.2; p=0.97). Dehydration-related elevated potassium blood levels associated with electrolyte disorders were a little less common in the "Kp" group (3.4%; 14.3%;14.3%; 12.5%; χ^2=2.1; p=0,55).

There were variations found in the kids' rates of decline in the groups' percentage relative urine density (44.8±14.4%; 42.9±22.1%; 64.3±16.9%; 0%; χ^2=15.1; p=0.19; $p_{"Kp" - "Kp+V+CPE"}$ <0.01; $p_{"Kp +CPE" - "Kp+V+CPEs"}$ <0.01). This was explained by the difference in the kidney concentrating capacity, since the age of children in groups «Kp» and «Kp+CPE» was lower than in the group «Kp+V» and "Kp+V+CPE» (Fig. 1). There was a difference in the frequency of detection of ketones in urine (10.3%;

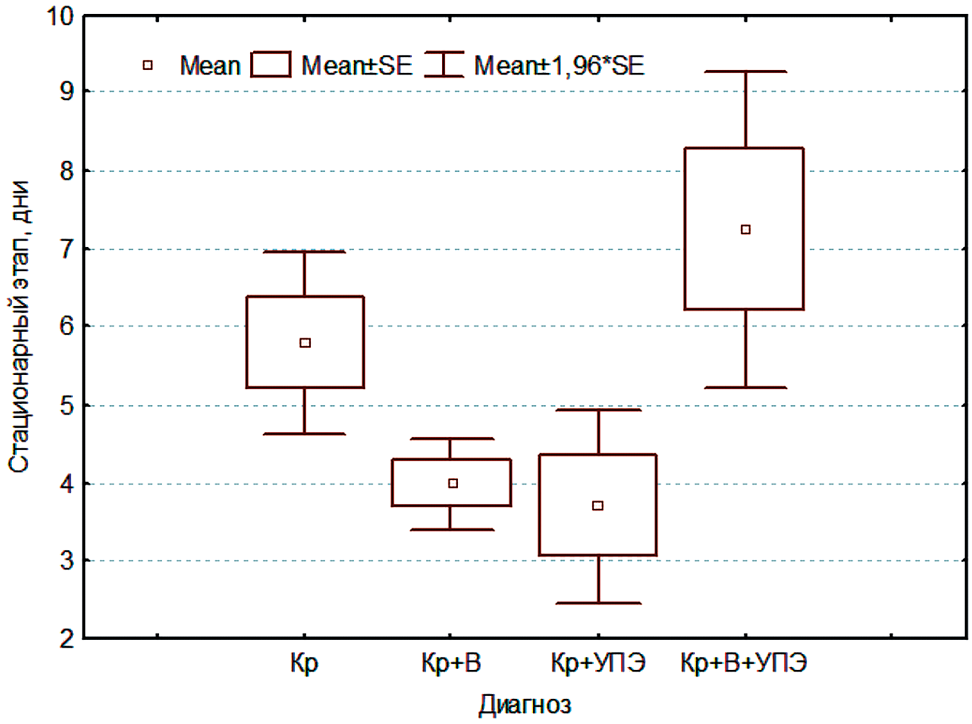

Fig. 3. Average duration of inpatient treatment of children in groups (number of days)
Рис. 3. Средняя длительность стационарного лечения детей в группах (число дней)

28.6%; 7.1%; 37.5%; χ^2=19,4; p=0,080). This indicating a more frequent acidosis in children of the "Kp+V" and "Kp+V+CPE" groups, in which intestinal infections were involved in the combination AII. Elevated leukocyte counts in the urine were somewhat more frequently seen in children in the "Kp" and "Kp+V+CPE" groups (41.4%; 21.4%;21.4%; 62.5%; χ2=5.4; p=0.14).

The changes in the stool test were characterized by a relatively more frequent decrease in fecal pH in children in the "Kp", "Kp+V", "Kp+CPE" groups (69%; 78.6%; 92.9%; 50%; χ^2=6.86; p=0.33). This due to fermentation dyspepsia with malabsorption in the small intestine. In the "Kp" (17.2% of cases) and "Kp+CPE" (14.3%) groups, amylorrhea was noted, and in 6.9 and 7.1% of cases, respectively, steatorrhea type 2. All child groups showed signs of colitis syndrome in stool test with high leukocyte detection (58.6%; 28.6%; 35.7%; 25%; χ^2=5.4; p=0.14) and mucus abundance (69%; 35,7%; 50%; 37.5%; χ^2=5.46; p = 0.14).

A high titer of atypical *E. coli* was observed in the overwhelming majority of children in all groups (65,5%; 71.4%; 78.6%; 75%; χ^2=0.87; p=0.83). In the same time the average titer for atypic *E. coli* in the feces in the "Kp" group was lower than in the "Kp+CPE" group (4.7±1.9 and 5.8±0.4; t=2.1; p <0.05). This confirmed a more pronounced microbiocenosis disorder in AII caused by the combination of *K. pneumoniae* with CPE than in monoinfection with *K. pneumoniae*.

Multiple antibiotic resistance to *K. pneumoniae* (to three or more drugs) was detected only in "Kp" (6.9±4.7%) and "Kp+V" (14.3±9.7%) children (p >0.05). In all child groups, *K. pneumoniae* resistance to bacteriophages was noted (48.3%; 21.4%; 42.3%; 62.5%; χ^2=11.3; p=0.51).

The duration of hospital treatment for children was maximum in the "Kp" and "Kp+V+CPE" groups (5.8±3.2 days; 4.0±1.1 days; 3.7±2.4 days; 7.3±2.9 days; $p_{"Kp" - "Kp+V"}$=0.04; $p_{"Kp"-"Kp+CPE"}$=0.02; $p_{"Kp+V" - "Kp + V+CPE"}$=0.008; $p_{"Kp + CPE"-"Kp+V+CPE"}$= 0.004) (Fig. 3). Most of the kids in the groups were discharged from the hospital "with improvement" (75.9%; 85.7%; 100%; 75%; χ^2=4.4; p=0.22).

Discriminant analysis was applied considering similarities and differences of clinical-laboratory manifestations in groups. It was used to prove the possible separation of AII mono- and combined etiology associated with *K. pneumoniae*. The discriminant model includes the following interrelated signs: children's age (months of life; p=0,0015); complaints of lethargy (0 — no, 1 — yes; p=0,02); complaints of vomiting (0 — none, 1 — yes, p=0,08); platelet count (0 — normal, 1 — lowered, 2 — elevated; p=0,006); amylorrhea in the stool test (0 — not, 1 — yes; P=0,0008); feces pH (0 — normal, 1 — decreasing, 2 — increasing; p=0.12);

Table 1. Complex of clinical and laboratory signs of discriminant model of differential diagnosis of intestinal infections associated with *K. pneumoniae*, codes and coefficients of detected signs

Таблица 1. Комплекс клинико-лабораторных признаков дискриминантной модели дифференциальной диагностики ОКИ, ассоциированной с *K. Pneumoniae*, коды и коэффициенты выявленных признаков

Наименование признаков / Name of signs	Коды / Codes	Коэффициенты признаков линейных дискриминантных функций (ЛДФ) / Feature coefficients of linear discriminant functions (LDF)			
		$ЛДФ_1$ / LDF_1	$ЛДФ_2$ / LDF_2	$ЛДФ_3$ / LDF_3	$ЛДФ_4$ / LDF_4
Возраст детей / Age of children	X_1	0,23	0,38	0,69	0,73
Жалобы на вялость / Complaints of lethargy	X_2	–0,12	2,54	–3,59	–1,93
Жалобы на рвоту / Vomiting complaints	X_3	3,00	4,08	0,37	3,37
Количество тромбоцитов в крови / The number of platelets in the blood	X_4	1,77	0,82	5,13	4,17
Амилорея в копрограмме / Amylorrhea in the coprogram	X_5	3,39	–3,33	3,64	0,42
pH кала / Fecal pH	X_6	3,47	4,77	–0,09	0,59
Длительность стационарного лечения / Duration of inpatient treatment	X_7	1,18	0,85	0,68	1,29
Сочетание *K. pneumoniae* с другими условно-патогенными бактериями / Combination of *K. pneumoniae* with other opportunistic bacteria	X_8	–0,92	–1,10	48,20	43,27
Константа / Constant		–8,24	–10,78	–30,95	–32,99

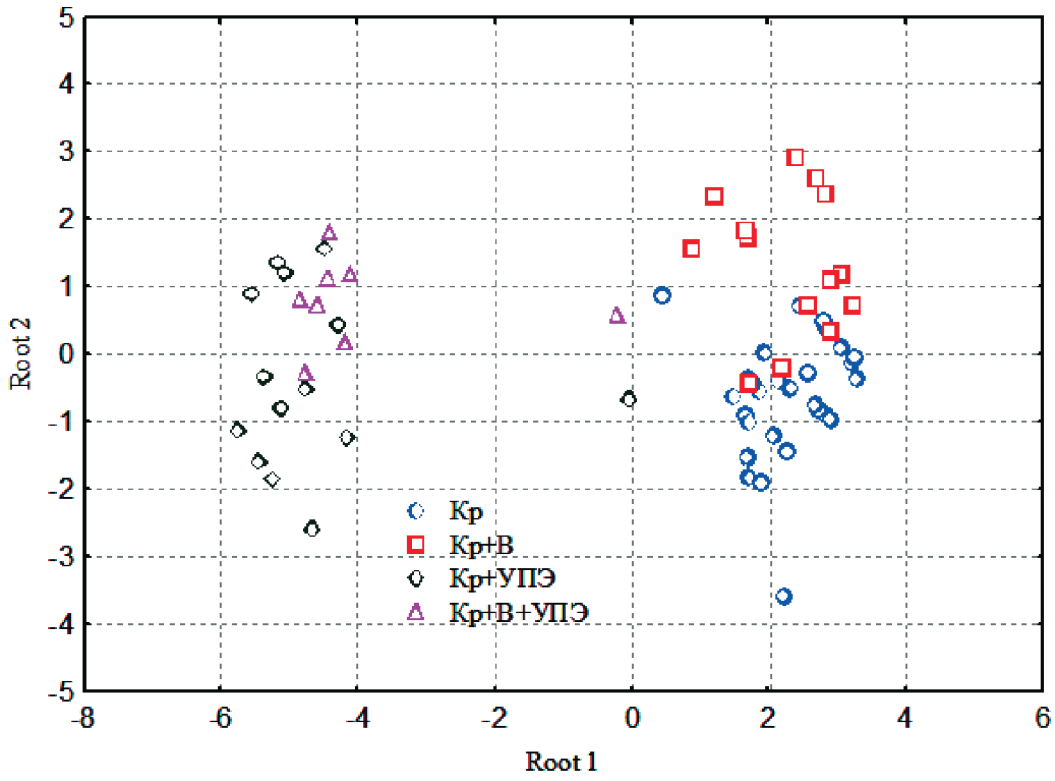

Fig. 4. The position of the objects of the four groups in the coordinates of the first and second canonical LDF

Рис. 4. Положение объектов четырех групп в координатах первой и второй канонических ЛДФ

duration of hospital treatment (days; p=0,004); combination of *K. pneumoniae* with other CPE (0 — no,1 — yes; p <0,00001).

Decisive diagnostic rules expressed as linear discriminatory functions (LDFs): LDF1 (monoinfection of *K. pneumoniae* — "Kp"), LDF2 (AII caused by *K. pneumoniae* and intestinal viruses — "Kp+V"), LDF3 (AII caused by *K. pneumoniae* and other CPE — "Kp+CPE"), LDF4 (AII caused by *K. pneumoniae*, intestinal viruses, and CPE — "Kp+V+CPE"). Table 1 shows the complex of clinical laboratory features affecting the patient's assignment to one of the four groups, the codes and coefficients of these traits.

The following formulae were used to carry out the LDF decision:

$$LDF_1 = -8{,}24 + 0{,}23X_1 - 0{,}12X_2 + 3{,}00X_3 + 1{,}77X_4 + 3{,}39X_5 + 3{,}47X_6 + 1{,}18X_7 - 0{,}92X_8,$$

$$LDF_2 = -10{,}78 + 0{,}38X_1 + 2{,}54X_2 + 4{,}08X_3 + 0{,}82X_4 - 3{,}33X_5 + 4{,}77X_6 + 0{,}85X_7 - 1{,}10X_8,$$

$$LDF_3 = -30{,}95 + 0{,}69X_1 - 3{,}59X_2 + 0{,}37X_3 + 5{,}14X_4 + 3{,}64X_5 - 0{,}09X_6 + 0{,}68X_7 + 48{,}20X_8,$$

$$LDF_4 = -32{,}99 + 0{,}73X_1 - 1{,}93X_2 + 3{,}37X_3 + 4{,}17X_4 + 0{,}42X_5 + 0{,}59X_6 + 1{,}29X_7 + 43{,}27X_8,$$

where X_1–X_8 correspond to the numerical values of the characteristics. The patient is assigned to the group for which LDF will take the maximum value.

The model's sensitivity for kids in the "Kp" group was 96.6%, 78.6% for the "Kp+V" group, 92.9% for the "Kp+CPE" group, and 75%. The model's overall diagnostic significance was high — 89.2%.

The position of the objects of the four groups in the coordinates of the first and second canonical LDFs (with a level of significance of p <0,001) is shown in Fig. 4. This figure demonstrates that the combination of *K. pneumoniae* with other CPEs, rather than the association of K. pneumoniae with intestinal viruses. In children under three years of age is more determined by the combination of *K. pneumoniae* with other CPE than with intestinal viruses.

The less accurate diagnosis of the discriminatory model for the "Kp+V" and "Kp+V+CPE" groups, representing viral-bacterial variants of AII, is due to the significant overlap of clinical and laboratory symptoms in children of the groups "Kp" and "Kp+V", "Kp + CPE" and "Kp+V+CPE". This shows how similar pairs of groups' manifestations of the disease were influenced by common bacterial pathogens. *K. pneumoniae* was present in groups "Kp" and "Kp+V," as well as *K. pneumoniae* combined with CPE in groups "Kp+V+CPE" and "Kp+V" Put another way, variations in the degree of intestinal dysbiosis clearly explained the features and severity of clinical and laboratory signs of AII in similar pairs of groups.

One article describes intestinal infections that are not associated with hypervirulent Klebsiella [16]. However, more dangerous by pathogenicity factors may appear among the population of community-acquired *Klebsiella*. These strains may not have sensitivity to phages and antibiotics which can cause serious complications. Community-acquired strains of *Klebsiella* are among pathogens that provoke AII in young children, they do not have high pathogenicity and pronounced antibiotic resistance. Community-acquired strains of Klebsiella deserve close attention since they are commonly combined with other infectious agents, including representatives of intestinal microbiocenosis. This increasing the likelihood of adverse outcome of the disease.

The manifestation of intestinal infections caused by *K. pneumonia* and other CPE in young children is associated with an increase in their microbiotic representation. It is accompanied by distinct clinical and laboratory manifestations of inflammatory nature.

CONCLUSION

The conducted study allowed to define the features of clinical laboratory signs of mono- and combined intestinal infections associated with *K. pneumoniae* in young children. This study shows that the nature and severity of these signs to a greater extent determines the combination of *K. pneumoniae* with other conditionally-pathogenic enterobacteria than a combination with intestine viruses. Also it confirms the relationship of the symptoms of these intestinal infections with the gravity of bowel dysbiosis, which is main significant in reducing the non-specific resistance of the organism.

ADDITIONAL INFORMATION

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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THE ROLE OF INTESTINAL DYSBACTERIOSIS IN THE GENESIS OF MICROBIAL ECZEMA IN CHILDREN

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Abstract. Recently there has been an increase in the incidence of eczema in the world. Up to 40% of all skin diseases are due to this pathology. A large proportion among various types of eczema is microbial eczema, which tends to be more severe with frequent, progressive relapses, a significant spread of the pathological process and is characterized by resistance to conventional methods of treatment. The available data on the important pathogenetic significance in the development and course of eczema of the pathology of the gastrointestinal tract are not well understood and often in practice they are not given much importance. The aim of this work was to analyze individual intestinal microbiota in children under 6 years of age suffering from microbial eczema. Comparison of laboratory indicators of stool analysis was made with the control group, consisted of patients with scleroderma. For various different between local games popular Fisher's exact criterion. An increase in the frequency of dysbiotic groups among children with microbial eczema was revealed, in particular, the detection of candidiasis, which requires the inclusion of relevant studies in the diagnostic search for the select the right therapy.

Key words: *microbial eczema; intestinal dysbacteriosis; microbial sensitization*

РОЛЬ ДИСБАКТЕРИОЗА КИШЕЧНИКА В ГЕНЕЗЕ МИКРОБНОЙ ЭКЗЕМЫ У ДЕТЕЙ

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Резюме. В последнее время отмечается увеличение заболеваемости экземой в мире. До 40% всех кожных заболеваний приходится на данную патологию. Большой удельный вес среди различных видов экзем составляет микробная экзема, имеющая тенденцию к более тяжелому течению с частыми, продолжительными рецидивами, значительным распространением патологического процесса и характеризующаяся резистентностью к общепринятым методам лечения. Имеющиеся данные о важном патогенетическом значении в развитии и течении экземы патологии желудочно-кишечного тракта недостаточно изучены, и часто на практике им не придается большого значения. Цель данной работы — анализ нарушений микробиоты кишечника у детей до 6 лет, страдающих микробной экземой. Производилось сравнение лабораторных показателей анализа кала с контрольной группой, которую составили пациенты со склеродермией. Для

выявления различий между двумя группами использовался точный критерий Фишера. Установлено достоверное увеличение частоты дисбиотических нарушений в группе детей с микробной экземой, в частности выявление кандидоза, что требует включения в диагностический поиск соответствующих лабораторных исследований для подбора рациональной терапии.

Ключевые слова: *микробная экзема; дисбактериоз кишечника; микробная сенсибилизация*

INTRODUCTION

Eczema (from the Greek *ekzeo* — I boil out) is a chronic recurrent allergic skin disease, formed under the influence of exogenous and endogenous trigger factors, characterized by the appearance of a polymorphic rash [9]. The disease occurs with itching, sleep disturbance and deterioration in quality of life. Recently, there has been an increase in the incidence of eczema in the world. Up to 40% of all skin diseases are due to this pathology. Urban residents get sick more often (60–65%) [10, 16]. Eczema appears at any age and can have an acute, subacute or chronic course [17].

Microbial eczema (ME) is one of the clinical forms of eczema. This is a polyetiological disease that develops as a result of the interaction of hereditary (polygenic multifactorial inheritance with pronounced expressivity and penetrance of genes), metabolic, neuroendocrine, vegetative-vascular, infectious-allergic and external factors [16]. In recent years, ME has acquired a tendency toward a more severe course with frequent, prolonged relapses, a significant spread of the pathological process, and is characterized by resistance to conventional treatment methods [2]. In the acute stage, ME is clinically manifested by asymmetrically located foci of edematous hyperemia with clear boundaries of different localization, the central part is covered with purulent and serous crusts, after removal of which an erosive surface with weeping in the form of "wells" is exposed. Secondary lesions (eczematids) may appear on large areas of the skin [16]. The clinical types of ME found in children include numular (coin-shaped) and post-traumatic. When skin scrapings from skin lesions in patients with eczema, *S. aureus* is detected in 80% of cases, *S. haemolyticus* in 14%, and yeast of the genus *Candida* in 40.7% [3, 7, 8, 11, 15]. In the pathogenesis of the disease, the leading role is given to bacterial sensitization, which is promoted both directly by microbial allergens and by skin autoantigens formed under the influence of bacterial and fungal flora [11].

An important pathogenetic significance in the development and further course of eczema, especially in children, is the pathology of the gastrointestinal tract and hepatobiliary system [4–6, 14, 17, 18], accompanied by enzymopathies, dyskinesias, intestinal dysbacteriosis, leading to impaired membrane digestion and malabsorption syndrome, which in turn creates additional antigenic stimulation of the body. Contrary to popular belief, gut microflora affects not only the metabolism of the body as a whole, but also the shaping of skin microbiome. It has been established that patients with ME have pronounced skin dysbiosis both in lesions and on unaffected skin [7, 12, 16]. Against this background, the microflora is transformed into a more pathogenic one, which contributes to the chronicization of dermatoses [12]. A direct connection between the state of the intestinal biocenosis and the course of allergic skin diseases was discovered. In particular, an increase in the frequency of seeding of *S. aureus* has been established, as well as a close relationship between its proliferation of the skin and intestines in patients with an acute form of ME, and a decrease in representatives of the autochthonous intestinal bacterial flora (bifidobacteria and lactobacilli) in the chronic course [12]. It has also been proven that the inclusion in therapy of probiotic drugs leads to a significantly faster resolution of clinical symptoms, a decrease in the frequency of exacerbations and relapses of the disease [1, 12, 18]. However, standards of medical care do not include the use of drugs to correct dysbiosis [13].

It remains unclear whether changes in the composition of the gut microbiome precede the development of ME or whether changes in the gastrointestinal (GI) tract are secondary. The most probable is the assumption about the existence of a so-called "vicious circle" in the relationship between allergic diseases and GI pathologies [4–6].

AIM

The aim of this study is to analyze disturbances of the gut microbiota in children with microbial eczema and assess its effect on the underlying condition.

MATERIALS AND METHODS

The study is based on a comparative analysis of laboratory data characterizing the state of gut microbiota of two groups of patients who were examined and treated in the dermatovenerological department of the clinic of Saint Petersburg State Pediatric Medical University for 6 years from 2011 to 2023. The first group consisted of children (n=12) with an average age of 3 years 5 months, who were

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diagnosed with ME based on complaints and clinical and anamnestic data. The control group included children with localized scleroderma (n=12) with an average age of 4 years 8 months. All subjects underwent stool analysis for conditionally pathogenic microflora and/or stool analysis for dysbacteriosis. Statistical data analysis was carried out using the Excel program. Differences in proportions independent variables were assessed by Fisher's exact test. The criterion of reliability at $p < 0.05$ was considered statistically significant for indicators.

RESULTS AND DISCUSSION

A comparative analysis of identified deviations in gut microbiota in two groups of children is presented in Table 1.

Intestinal dysbacteriosis due to the proliferation of pathogenic or opportunistic bacteria and/or fungi of the genus *Candida* was detected in 83% of cases when analyzing the stool of children with ME, which is 2 times more frequent than in patients with scleroderma (42%). In particular, proliferation of fungi of the genus *Candida* was detected significantly more often (in 58% of cases versus 8%, respectively). Another important pathogen, which was more common in the children of the first group, was *Staphylococcus aureus* (33% versus 8%), but the difference in the two groups was not statistically significant. Among the less common pathogens in the group of children with ME, *Proteus mirabilis, Citrobacter freundii, Klebsiella oxytoca, and hemolytic Escherichia coli* were identified. It was not possible to conduct a comparative analysis of disturbances of the normal autochthonous microbiota, including bifidobacteria and lactobacilli, since a detailed stool analysis for dysbacteriosis was not carried out for all subjects. However, a decrease in lacto- and/or bifidobacteria was detected in 100% of cases when performing this analysis in children with ME, which was not observed in the second group.

The results obtained confirm the presence of dysbiotic changes in the intestines of patients with ME and their direct relationship with the disease, which allows us to talk about disorder of the intestinal microbiocenosis as one of the links of pathogenesis. At the same time, the etiological structure of pathogens that we identified does not differ qualitatively from that in previously conducted studies, however, the largest share was made up of *Candida*, and not the coccal flora. It should be noted that the species composition may differ depending on the region of residence and the age group of patients.

CONCLUSION

Dysbiotic disorders in the intestine are an important component of the pathogenesis of ME. Changes in the intestinal microbiocenosis in children with ME under 6 years of age are characterized by an increase in the number of various pathogenic flora; fungi of the genus *Candida* are most often identified. The polyetiological disease requires a comprehensive approach, including diagnosis and correction of the intestinal dysbacteriosis.

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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Table 1. Pathological deviations in the intestinal microbiocenosis in in the main and control groups of children

Таблица 1. Патологические отклонения в микробиоценозе кишечника в основной и контрольной группах детей

Identified pathological deviations in the intestinal microbiocenosis / Выявленные патологические отклонения в микробиоценозе кишечника	Children with microbial eczema, n=12 / Дети с микробной экземой, n=12	Control group, n=12 / Контрольная группа, n=12	Reliability of differences, p / Достоверность различий, p
Yeast-like fungi of the genus *Candida* / Дрожжеподобные грибы рода *Candida*	7*	1	0,01
Staphylococcus aureus	4	1	0,14
Proliferation of pathogenic or opportunistic bacteria and/or fungi of the genus *Candida* / Пролиферация патогенных или условно-патогенных бактерий и/или грибов рода *Candida*	10*	5	0,04

*Statistically significant differences / * Статистически значимые различия.

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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ASSESSMENT OF PARENTS' COMMITMENT TO SPECIFIC TREATMENT OF CHILDREN WITH TUBERCULOSIS

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Abstract. One of the leading factors influencing the outcome of tuberculosis is the attitude of patients to long-term combination therapy. Children's adherence to TB treatment is a problem that is not presented in domestic and foreign sources. Children with tuberculosis cannot fully appreciate the importance of adherence to therapy. The aim of the study was to assess the level of commitment of parents to anti-tuberculosis treatment of their children. On the basis of the tuberculosis department of St. Petersburg GBUZ DIB No. 3, an analysis of 30 case histories of children aged 2–13 years with an established tuberculosis infection requiring anti-tuberculosis treatment for at least 6 months was carried out. An anonymous questionnaire was conducted for the parents of patients, which included four blocks of information: data on awareness of tuberculosis infection, knowledge about the prevention of tuberculosis, determination of awareness of parents' attitude to anti-tuberculosis treatment, as well as their personal attitude to people with tuberculosis and to their children. Parents of children with tuberculosis infections revealed an insufficient level of basic knowledge about tuberculosis (30.0%), about tuberculosis prevention measures (30.0%), the need to follow long-term comprehensive anti-tuberculosis treatment (37.5%), in some cases parents' personal fear for their health (13.3%). A timely study of the factors leading to low adherence of parents to the treatment of their children will allow them to be corrected in a timely manner by conducting social and educational work and individual consultations, if necessary, providing psychological assistance.

Key words: *tuberculosis; children; parents; tuberculosis therapy; adherence to treatment.*

ОЦЕНКА ПРИВЕРЖЕННОСТИ РОДИТЕЛЕЙ К СПЕЦИФИЧЕСКОМУ ЛЕЧЕНИЮ ДЕТЕЙ, БОЛЬНЫХ ТУБЕРКУЛЕЗОМ

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Резюме. Одним из ведущих факторов, влияющих на исход туберкулеза, является отношение пациентов к длительной комбинированной терапии. Детская приверженность к противотуберкулезному лечению — проблема, которая не представлена в отечественных и иностранных источниках. Дети, болеющие

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туберкулезом, не могут в полной мере оценить важность приверженности к терапии. Целью исследования было оценить уровень приверженности родителей к противотуберкулезному лечению их детей. На базе туберкулезного отделения СПб ГБУЗ ДИБ № 3 проведен анализ 30 историй болезни детей в возрасте 2–13 лет с установленной туберкулезной инфекцией, требующей осуществления противотуберкулезного лечения не менее 6 месяцев. Родителям пациентов проведено анонимное анкетирование, включающее четыре блока сведений: данные об осведомленности о туберкулезной инфекции, знания о предупреждении заболевания туберкулезом, определение осознанности отношения родителей к проведению противотуберкулезного лечения, а также их личное отношение к болеющим туберкулезом лицам и к своим детям. У родителей детей с туберкулезной инфекцией был выявлен недостаточный уровень основных знаний о туберкулезе (30,0%), о мерах предупреждения туберкулеза (30,0%), необходимости следования длительному комплексному противотуберкулезному лечению (37,5%), в ряде случаев присутствовало личное опасение родителей за свое здоровье (13,3%). Своевременное изучение факторов, ведущих к низкой приверженности родителей к лечению их детей, позволит данные факторы корректировать путем проведения социально-просветительной работы и индивидуальных консультаций, при необходимости — оказания психологической помощи.

Ключевые слова: *туберкулез; дети; родители; противотуберкулезная терапия; приверженность к лечению.*

Tuberculosis is a socially significant disease that remains dangerous in our time. Every year, more than 10 million people worldwide fall ill with tuberculosis, and more than 1 million people die [1]. Children account for 5–11% of the number of tuberculosis patients; the need for their long-term treatment represents a special psychological, medical and social problem [2–5].

The term "adherence to treatment" was first defined by a special report of the World Health Organization (WHO) in 2003 [6]. According to the WHO definition, adherence to treatment is the extent to which a person's behavior in taking medications, following a diet and/or other lifestyle changes corresponds to the recommendations from a doctor.

Commitment to the treatment of tuberculosis patients and their attitude to long-term combination therapy is the most important factor determining the outcome of the process [7]. Currently, low adherence to treatment is recognized as a proven factor that reduces the effectiveness of therapy and increases the risk of complications and secondary drug resistance. All this makes it difficult to achieve a clinical cure, leads to a worsening of the disease prognosis and quality of life, and also increases treatment costs [8, 9]. The determining direction in increasing adherence to treatment in adult patients is the correction of the adverse social factors during complex treatment and rehabilitation of patients [10, 11]. Commitment to anti-tuberculosis treatment in children is a problem that is poorly represented in the scientific literature. Obviously, due to psychosocial immaturity, children cannot fully appreciate the importance of adherence to therapy [12]. That is why the main task of parents is to help children understand the importance of treatment and follow it. However, parents themselves, especially from socially disadvantaged families, do not always have an adequate attitude towards diagnosis, preventive measures and necessary therapy. Children from such families are the most vulnerable, since parents often do not consider it advisable to adhere to the treatment regimen and a set of doctor's appointments.

AIM

The aim of this study is to assess the level of adherence of parents to anti-tuberculosis treatment of their children in order to develop recommendations for increasing it.

MATERIALS AND METHODS

The analysis of 30 case histories of children from 2 to 13 years, with an identified tuberculosis infection and undergoing treatment on the basis of the tuberculosis department of infectious diseases hospital No. 3 of Saint Petersburg was carried out. All children underwent an in-depth phthisiological examination, including analysis of epidemiological anamnesis data; results of specific immunodiagnosis (Mantoux test with 2TE, a skin test with tuberculosis recombinant allergen (TRA), if indicated — *in vitro* tests: Quantiferon test (QuantiFERON®-TB Gold) or TB-FERON test); radiological methods, including multislice computed tomography and laboratory tests. Patients were prescribed anti-tuberculosis treatment lasting from 6 to 12 months or more. The parents of the observed children were given an anonymous survey, including four blocks of information.

The first block of the survey characterized the level of awareness about tuberculosis infection in general and was aimed at analyzing knowledge about the danger of tuberculosis, ways of infection, diagnostic methods and factors influencing the course of the disease. The first block included 4 questions, 4 answer options.

The second block of the survey (5 questions) revealed the existence of knowledge about the prevention of tuberculosis. It included questions about the need for vaccination, immunodiagnosis and the regular fluorographic examination.

The third block of the survey (7 questions) determined the parents' attitude directly to the conduct of anti-tuberculosis treatment. It contained questions about the need for long-term, combined treatment of tuberculosis, the possibility of undergoing treatment at a sanatorium, as well as questions about observance of the sanitary and hygienic regime.

The fourth block (4 questions) determined personal attitude towards people suffering from tuberculosis and towards their children. Thus, in total, the survey contained 20 questions.

All parents gave voluntary informed consent to the survey.

Statistical data processing was performed using computer program STATISTICA 6.1. Data are presented as arithmetic mean ± standard error of the arithmetic mean. To determine the reliability of differences, Student's t-test was used. Differences were considered statistically significant at $p < 0.05$.

RESULTS

The majority of the examined patients were vaccinated against tuberculosis (90.0% of children); only two children were not vaccinated; one of them had parents who refused a BCG vaccination, and the second had contraindications. Tuberculosis contact was established in 50.0% of children, and 40.0% of identified contacts were long-term: family or related. Based on the results of diagnosis of tuberculosis, the following types of tuberculosis infection were established: active forms of tuberculosis of the respiratory organs (tuberculosis of the intrathoracic lymph nodes and primary tuberculosis complex) were diagnosed in 56.6% (17 children), they were prescribed the main course of chemotherapy lasting 6–12 months; in the remaining children — residual post-tuberculosis changes and latent tuberculosis infection were newly identified — in 43.4% (13 children), they were prescribed a preventive course of chemotherapy lasting 6 months.

The results of answers to the first block of questions (awareness of tuberculosis infection) revealed that 86.6% of parents have an idea about the epidemic danger of tuberculosis, 40.0% about the ways of spreading infection, 76.6% about the clinical signs of the disease, and 30.0% about the possibility of a cure (Fig. 1).

It was noted that only 19.0% of respondents recognized the fact of having family or related contact, while this type of contact with a tuberculosis patient was established in 40.0% of patients.

Fig. 1. Assessment of the basic knowledge of parents with tuberculosis infection about the danger, spread, signs and possibilities in the treatment of tuberculosis

Рис. 1. Оценка основных знаний родителей детей с туберкулезной инфекцией об опасности, распространении, признаках и возможности лечения туберкулеза

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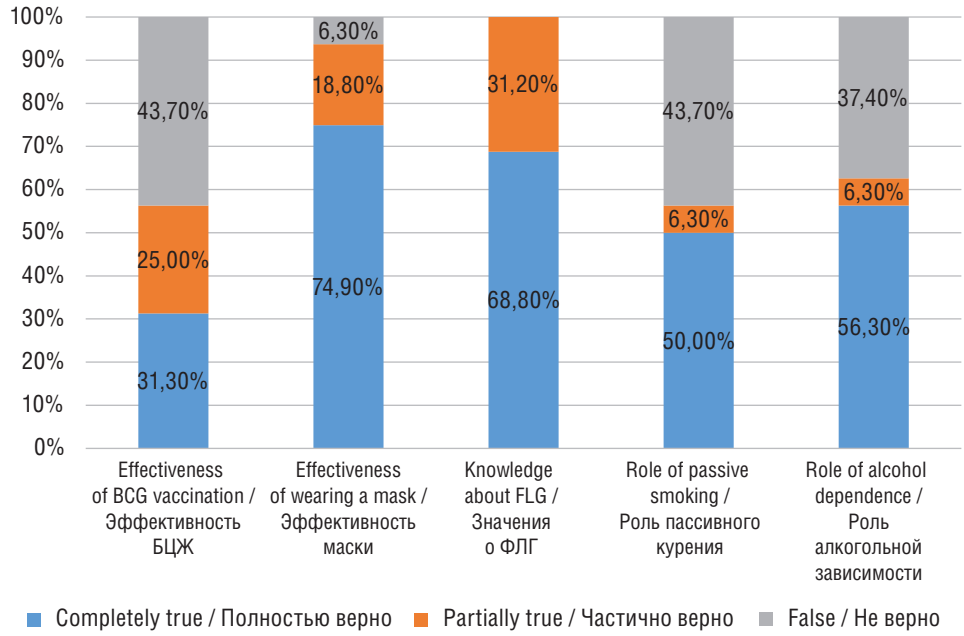

Fig. 2. Knowledge of patients' parents about measures to prevent tuberculosis. BCG — bacillus Calmette-Guerin. FLG — fluorographic examination

Рис. 2. Знания родителей пациентов о мерах предупреждения туберкулеза. БЦЖ — бацилла Кальметта–Герена; ФЛГ — флюорография

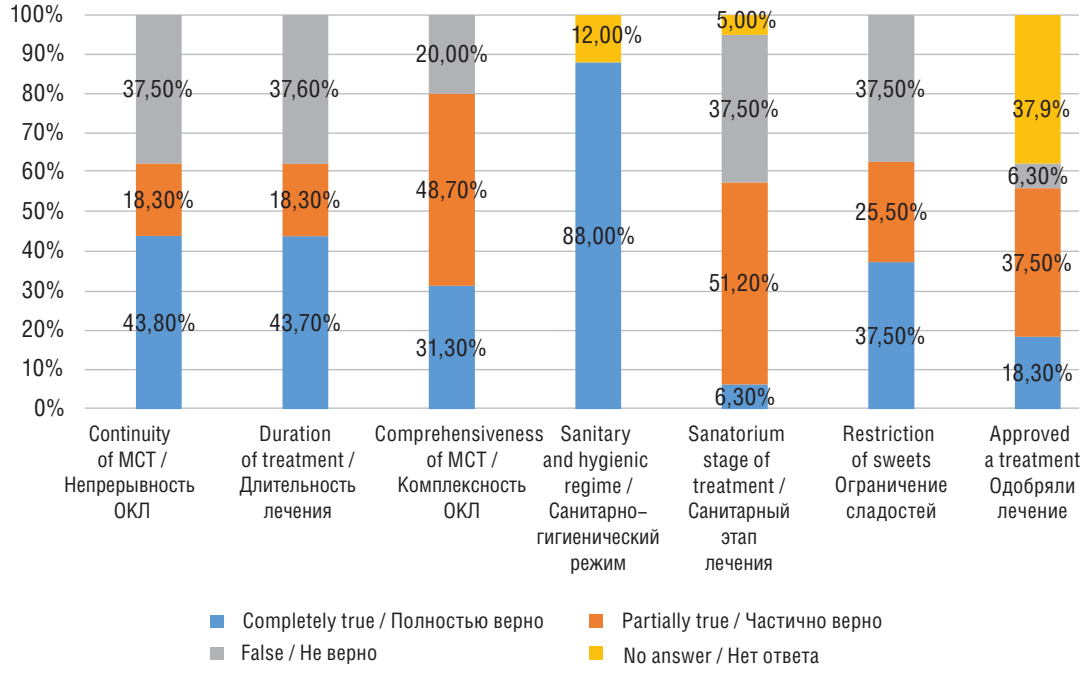

Fig. 3. Assessment of the need for comprehensive anti-tuberculosis treatment. MCT — main course of treatment

Рис. 3. Оценка необходимости проведения комплексного противотуберкулезного лечения. ОКЛ — основной курс лечения

Analysis of the data from the second block of the questionnaire (the existence of knowledge about the prevention of tuberculosis disease) determined that 31.3% of respondents recognized the effectiveness of vaccination against tuberculosis, while the efficiency of wearing a mask was noted more frequently — in 74.9% of cases ($p < 0.05$) (Fig. 2).

The importance of regular fluorographic examination for the tuberculosis prevention were aware 68.8% of parents. The harm of passive smoking for their child recognized 50% of respondents and the harm of alcohol dependence of parents — 56.3% of respondents.

Data from the third block of questions (recognition of the need for complex anti-tubercu-

losis therapy) revealed the following: 43.8% of parents agreed with the continuity of treatment, and 37.5% of parents agreed with the treatment duration (Fig. 3). Only 31.3% of respondents understood the need for comprehensive treatment. 25.0% of respondents agreed to maintain the sanitary and hygienic regime.

Analysis of parents' personal attitudes showed that the majority of parents (86.7%) understand that the forms of the disease in children are not dangerous for them, since children rarely excrete Mycobacteria into the external environment, and do not worry about their health; only 13.3% expressed concern about their infection from a child.

After summing up the data from all four blocks of the survey, the following results were obtained: 30% of respondents had completely correct ideas about tuberculosis, 30.0% also about measures to prevent the disease, only 23.3% of parents were perfectly prepared to comply with the necessary conditions and anti-tuberculosis therapy regimen.

CONCLUSION

1. Parents of children with tuberculosis infection requiring long-term anti-tuberculosis therapy revealed an insufficient level of basic knowledge about tuberculosis (30.0%), about measures to prevent the incidence of tuberculosis (30.0%), the need to follow long-term comprehensive anti-tuberculosis treatment (23, 3%), parents expressed concern for their health (13.3%).

2. Problems of commitment to anti-tuberculosis therapy in children with tuberculosis infection are caused by insufficient awareness of parents about tuberculosis, the possibility of its timely prevention, the need for long-term complex treatment to achieve clinical cure, and therefore, reluctance to follow recommendations on the regimen and comprehensive treatment.

3. Timely study of the reasons leading to low adherence of parents to the treatment of their children will make it possible to reduce the influence of these factors through socio-educational action and individual consultations, and, if necessary, providing psychological assistance.

4. Volunteers, especially from among students and clinical residents, can be involved in the work to improve the health literacy of parents, which can increase the commitment of parents and children to anti-tuberculosis activities without additional material investments.

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.

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

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AICARDI–GUTIER SYNDROME IN A PATIENT WITH CEREBRAL PALSY

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Abstract. Rare genetic diseases and their symptoms are unusual for doctors, especially if the disease is heterogeneous, and this poses a serious medical problem. There are about 7000 different rare diseases in the world, 80% of them are genetically determined, and more and more newly discovered ones are appearing. Approximately 50% of patients suffering from rare diseases are children, which determines the importance of studying these diseases in pediatric science. On the example of a clinical case, the manifestations of the Aicardi–Goutieres syndrome in a 17-year-old child admitted to the St. Petersburg State Pediatric Medical University clinic with the main diagnosis: nephrotic syndrome with diffuse membranous glomerulonephritis are considered. The main data of history and clinical and laboratory examination are reflected. The description of mutations leading to the emergence of Aicardi–Goutieres syndrome, as well as the forms of this disease, is presented. Special attention is paid to the differential diagnosis of Aicardi–Goutieres syndrome with other clinically similar nosological forms.

Key words: *rare (orphan) diseases; Aicardi–Goutieres syndrome; AGS; children.*

СИНДРОМ АЙКАРДИ–ГУТЬЕРА У ПАЦИЕНТА С ДЕТСКИМ ЦЕРЕБРАЛЬНЫМ ПАРАЛИЧОМ

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Резюме. Редкие наследственные заболевания и их симптоматика являются необычными для врачей, особенно если заболевание гетерогенно, и это представляет серьезную медицинскую проблему. В мире существует около 7000 различных редких заболеваний, из них 80% — генетически детерминированы. Появляется все больше вновь обнаруженных орфанных болезней. Приблизительно 50% пациентов, страдающих редкими заболеваниями, — это дети, что обусловливает важность изучения данных болезней в педиатрической науке. На примере клинического случая рассмотрены проявления синдрома Айкарди–Гутьера у ребенка 17 лет, госпитализированного в клинику СПбГПМУ с основным диагнозом: нефротический синдром при диффузном мембранозном гломерулонефрите. Отражены основные данные анамнеза и клинико-лабораторного обследования. Представлено описание мутаций, приводящих к возникновению синдрома Айкарди–Гутьера, а также формы данного заболевания. Особое внимание отведено дифференциальной диагностике синдрома Айкарди–Гутьера с другими клинически схожими нозологическими формами.

Ключевые слова: *редкие (орфанные) заболевания; синдром Айкарди–Гутьера; AGS; дети.*

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INTRODUCTION

Rare diseases have recently begun to attract the attention of doctors. Of the 7000 nosological forms, 80% of rare diseases are genetically determined, and 50% of those suffering from these diseases are pediatric patients [1]. About 30% of children with rare diseases do not survive beyond 5 years of age [10].

If a disease has a prevalence of 10 cases per 100 thousand population, it is classified as an orphan disease. All orphan diseases have a chronic lifelong course and often progressive nature [6]. For 2018–2020 there was an increase in the total number of patients due to almost all nosological forms of orphan diseases [13, 14]. Compared to 2019, in 2021 the budget for orphan diseases in Saint Petersburg has increased. The number of patients with a separate nosological form, idiopathic thrombocytopenic purpura, is 2 times higher than the average [13]. Due to the steady increase in rare congenital pathologies, it is necessary to ensure that children are protected from the severe consequences of such diseases.

In the Russian Federation, regulations have been developed governing the provision of assistance to patients suffering from rare diseases [9]. In particular, Decree of the President of the Russian Federation dated June 1, 2012 № 761 "On the national strategy of action in the interests of children for 2012–2017" emphasizes the importance of establishing a federal register of children with rare diseases and organizing targeted funding for such children at the expense of budgetary allocations of the federal budget according to this register [8]. There is also a departmental program "Improving the system of organizing medical care and drug provision for citizens suffering from diseases included in the list of life-threatening and chronic diseases", the indicators of which in the "pediatrics" section are: reduction in mortality and disability of children under 18 years of age suffering from these diseases, increase their life expectancy and improvement of their quality of life. An important document is the Order of the President of the Russian Federation V.V. Putin dated January 16th, 2014 № Pr-78 "On the concept of providing early assistance to children with genetic disorders" [12].

Rare diseases are characterized by non-specific symptoms, manifestation of signs at different age periods, progressive nature, and also require careful differential diagnosis with clinically similar pathologies. These factors make diagnosis difficult and can lead to delays in providing medical care. Issues of drug provision for patients suffering from orphan diseases are very complex due to the high cost of necessary therapy and limited budgetary funds. The lack of necessary therapy leads to a reduction in the life expectancy of patients, and in some cases, to death [11]. Complex diagnostics, absence of a unified comprehensive strategy for providing medical assistance to patients with orphan diseases, and the severe consequences of diseases without timely treatment determine the relevance of studying rare diseases at the present time. A solution to this problem can be neonatal screening for orphan diseases.

We present a case of Aicardi–Goutières syndrome (ICD-10 code G31.8), which is classified as an orphan disease based on the List of Orphan Diseases of the Russian Ministry of Health [7] in a 17-year-old child to illustrate the importance of studying rare diseases.

CLINICAL CASE

For examination and determination of tactics for further management, a young man with periodic proteinuria for 10 years (since 2013) was hospitalized in the department of the Saint Petersburg State Pediatric Medical University clinic in a planned manner. Upon admission, a preliminary diagnosis was made: nephrotic syndrome with diffuse membranous glomerulonephritis.

A disabled child (cerebral palsy, spastic diplegia, flexion contractures in the knee joints) is on the dispensary of a neurologist due to Aicardi-Goutières syndrome, which is inherited in an autosomal dominant mode. The child has spastic tetraparesis with predominantly damage to the lower extremities, hyperkinetic syndrome, cognitive disorders, psychovegetative syndrome with cerebrovascular disorders, migraine-like headaches. As a treatment for hyperkinetic syndrome, he receives a centrally acting muscle relaxant (tizanidine or sirdalud). The orthopedist diagnosed kyphoscoliosis, lower extremity joint contractures, valgus deformity of the left foot, cavovalgus deformity of the right foot, deformity of the first fingers and toes, rotational displacement of C_1. Due to subclinical hypothyroidism diagnosed by an endocrinologist, he receives L-thyroxine. Suffers from myopia, astigmatism, nosebleeds. The patient has stage 2 secondary arterial hypertension; during dynamic observation, episodes of increased pressure up to 170/90 mmHg are noted. Chronic tonsillitis. Childhood infections denied, negative tuberculosis anamnesis, injuries denied.

From the anamnesis collected from the words of the grandmother and from the presented medical documentation, it is known: the mother of the child has spastic paraparesis since the age of 4, is

intellectually intact, the father has cerebral palsy. A child from the first pregnancy, the first emergency delivery by cesarean section, birth weight 2450 g, height 47 cm, discharged from the maternity hospital on the 7th day, artificial feeding. In the first days of life hyperkinesis the lower extremities was noted; he crawled from 8 months, sat from 8–9 months, and began to walk from 1 year 2 months. At the age of 1 year 4 months, febrile tonic-clonic seizures appeared and were reduced independently. From this moment on, a rapid progression of the lower extremity spasticity, the formation of paraparesis, and regression of neurological skills were noted. Febrile seizures repeated twice, after which the acquired skills were lost. Further rate of development: rolls over from 2.5 years old, crawls from 3 years old, sits from 4 years old, walks with support from 4 years old. Since 2010, blood tests have consistently shown high ESR levels. In 2013, proteinuria was detected for the first time. In 2014, he underwent surgical treatment at H.Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery — adductor tenotomy tenomyotomy with cutting of the tendinous portion of the *m. iliopsoas*, lengthening of the tibia flexors on both sides. Arthrodesis of the talonavicular joint on the right. Due to the appearance of fever, proteinuria, and elevated ESR, he was transferred to the specialized department of the Saint Petersburg State Pediatric Medical University clinic. Ultrasound revealed renal pelvis dilatation on the left, without signs of vesicoureteral reflux. Subsequently, the elevation of ESR remained, proteinuria constantly observed in urine tests up to a maximum of 5 g/day. Proteinuria without impairment of renal function was detected. Subsequently, the increase in ESR and proteinuria in urine tests remained constant, up to a maximum of 5 g/day. In 2017, an MRI of the brain was performed – low lying cerebellar tonsillar position. An MRI of the brain in 2021 revealed basal ganglia calcifications up to 5 mm in size in the substance of both frontal lobes. Enlarged perivascular spaces are identified in the basal ganglia. According to the results of a genetic research for the "neurodegenerative diseases" block, a variant with an unknown clinical significance c.2636A>G of the IFIH1 gene in a heterozygous state was identified. The child's mother was detected the same genetic variant in a heterozygous state. The child was consulted by a geneticist: Strumpell's disease was excluded, as well as Singleton–Merten syndrome 1, associated with mutations in this gene, but the clinical picture was not consistent with this disease. Taking into account the genetic variant, clinical picture data, and MRI of the brain, this case may correspond to the diagnosis of Aicardi–Goutières syndrome 7; no increased level of interferon-α was detected.

Objective status. The condition is of moderate severity due to the neurological manifestations of cerebral palsy. Contactable, answers questions. Well-being is satisfactory. Forced position in bed, sits up independently, turns himself in bed with support on his hands. There are no complaints at the time of examination. The skin is clean, regular coloring, and there is no infectious rash. Peripheral edema is absent. Visible mucous membranes are clean. Peripheral lymph nodes are not enlarged. The pharynx is not hyperemic. Nasal breathing is free. Respiration is vesicular, carried out in all lung fields; there are no abnormal respiratory sounds or wheezing. The peripheral pulse in the peripheral arteries is satisfactory in all respects. Heart sounds are clear, rhythmic, sonorous, they are heard over the entire surface of the heart, the ratio of sounds is correct, there are no additional muscle sounds, there is no splitting or bifurcation of tones at the 2nd and 3rd points of auscultation, extracardiac murmurs are not heard. Temperature — 36.6 °C. Heart rate — 80 beats/min. Blood pressure — 130/90 mm Hg. On palpation, the abdomen participates evenly in the act of breathing, soft, painless in all areas. The liver borders are normal. The spleen is not palpable.

Tapping in the lumbar regions is negative on both sides. Urination is free, painless, there is no dysuria. Diuresis is sufficient. The stool is regular and formed. Joint status: all joints are not warm, soft nodules are palpable above the joints of the first fingers and metacarpophalangeal joints of the second fingers of both hands, the range of motion in the joints is not limited. The lower limbs are in a forced position, the knee joints are straightened, the ankle joints are in plantar flexion.

The physical development of the patient was assessed, taking into account motor activity and diagnosed cerebral palsy GMFCS III, as well as the component composition of the body using bioimpedance analysis (Fig. 1).

In consideration of the family anamnesis, clinical picture, MRI and genetic research data, the patient was prescribed a coagulogram with a lupus anticoagulant test in order to exclude monogenic variants of systemic lupus erythematosus.

Based on the results of an examination of the patient by a nutritionist, mild protein-energy malnutrition was detected, corrected using a formula (+500 kcal). For 6 years, the child received subsidies with Modulen IBD formula in a volume of 500 ml in fractional per day. Body weight 39.4 kg, height 155 cm (calculated using the leg method), BMI = 16.40, which is below normal.

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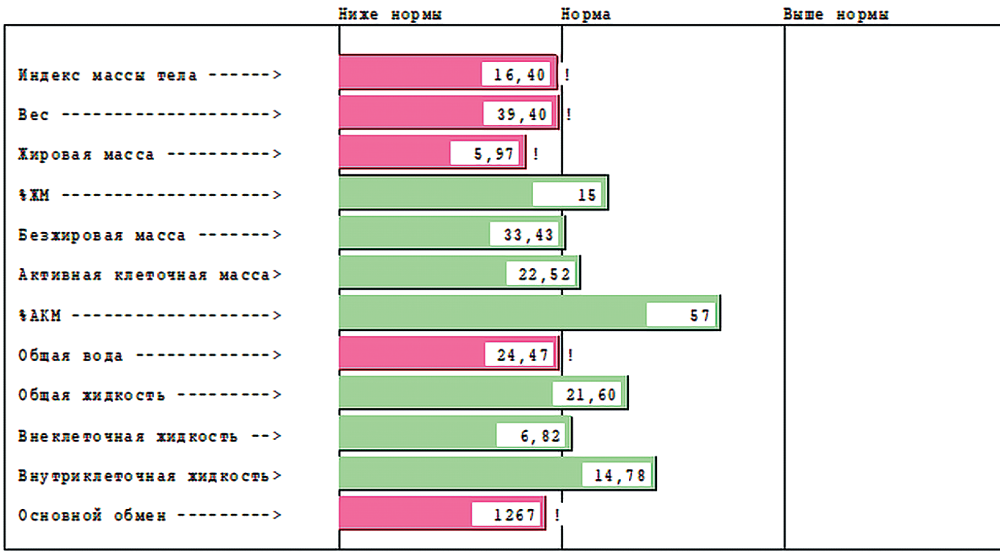

ПОКАЗАТЕЛЬ		Должные	% долж.	Измерен.	% измер.	Отклон.	%от долж
ИМТ	(кг/м2.)	18,53		16,40			
Вес	(кг)	44,51	100,00	39,40	100,00	-5,11	-11,48
ЖМ	(кг)	7,50		5,97		-1,53	-20,43
%ЖМ	(%)	17		15			
БЖМ	(кг)	37,01	83,15	33,43	84,85	-3,58	-9,67
АКМ	(кг)	24,55		22,52		-2,03	-8,29
%АКМ	(%)	55		57			
ОВ	(л)	27,39	61,53	24,47	62,11	-2,91	-10,64
ООЖ	(л)	22,51		21,60		-0,90	-4,02
ОВнек.Ж.	(л)	7,50		6,82		-0,68	-9,09
ОВнук.Ж.	(л)	15,00		14,78		-0,22	-1,49
ОО	(ккал)	1481		1267		-215	-14,50

Fig. 1. Body Composition Data

Рис. 1. Данные компонентного состава тела

Antibodies to the herpes simplex virus, cytomegalovirus, and Epstein–Barr virus were not found. Total IgE levels are elevated. Antiphospholipid antibodies were not detected. No increase in the level of interferon-α was identified. The dynamics of the patient's laboratory examination parameters are presented in Table 1.

DISCUSSION

Aicardi–Goutières syndrome is a rare genetic disease. About 400 cases of the syndrome have been described in the world. Various names for the disease are mentioned in the literature: Aicardi–Goutier(es) syndrome, Aicardi–Gutier(es), Ekardi-Goutie(es). The article gives the name Aicardi–Goutières. Aicardi–Gouthières syndrome (AGS) is a genetically determined interferonopathy, a monogenic inflammatory encephalopathy caused by mutations in any of nine genes (*TREX1, RNASEH2A/B/C, SAMHD1, ADAR1, IFIH1, LSM11* and *RNU7–1*) encoding the proteins involved in nucleic acid metabolism and detection [15]. The disease is characterized by non-specific clinical manifestations. Most patients suffering from Aicardi–Goutières syndrome have neurological disorders of varying degrees: from spastic paraparesis with relatively preserved cognitive functions to tetraparesis and severe mental retardation [2]. 75% of patients develop epilepsy, which in half of the cases is resistant to therapy with a predominance of tonic-clonic seizures [4]. Interferonopathy is associated with early onset neurological disability and systemic inflammation. Taking into account that each AGS subtype has common characteristics, cases of varying severity of course and subsequent complications occur. However, regardless of the specific variant, all forms of the syndrome lead to increase in the level of interferon-α [16]. Because of this heterogeneity, it is important to fully characterize the trajectory of the syndrome [3]. Forms with the onset of the disease in the neonatal period are clinically more severe than forms with onset after the first months of a child's life, and are associated with high mortality (up to 34% in the first year of life). If the onset of the disease occurred after the first months of the child's life, such patients have a longer life expectancy and

Table 1. Indicators of laboratory observation of the patient

Таблица 1. Динамика показателей лабораторного обследования пациента

Параметр / Parameter	Референтный интервал / Referential interva	Даты проведения исследования / Dates of the study		
		30.08.2022	05.09.2022	09.09.2022
Лабораторные показатели крови / Laboratory blood parameters				
Лейкоциты, $\times10^9$/л / Leukocytes, $\times10^9$/L	4–9	6.40		11.90
Эритроциты, $\times10^{12}$/л / Red blood cells, $\times10^{12}$/L	4,2–5,6	5,02		5,02
Гемоглобин, г/л / Hemoglobin, g/L	117–166	151		149
Тромбоциты, $\times10^9$/л / Platelets, $\times10^9$/L	150–400	198,00		289,00
Микроальбумин, мг/л / Microalbumin, mg/L	(0,0–30,0)	500		
Микроальбумин/креатинин, мг/л / Microalbumin to creatinine ratio, mg/L	(0,00–2,50)	71,40		
Фибриноген (Клаусс), г/л / Fibrinogen level (Clauss method), g/L	(2,00–4,00)	5,08	3,16	
Волчаночный антикоагулянт подтв. / Lupus anticoagulant confirmatory test	(0,90–1,20)		0,98	
Холестерин, ммоль/л / Cholesterol, mmol/L	(3,60–5,18)		5,59	6,93
Холестерин ЛПНП, ммоль/л / LDL cholesterol, mmol/L	(0,00–2.60)	4,39		
Альбумин, % / Albumin, %	(55,8–66,1)		48,4	
Альфа 2, % / Alpha-2, %	(7,1–11,8)		18,3	
Альбумин, г/л / Albumin, g/L	(34,80–48,10)		29,04	
Альфа 2, г/л / Alpha-2, g/L	(6,10–8,40)		10,98	
Глюкоза, ммоль/л / Glucose, mmol/L	(3,33–5,55)		7,94	3,86
Антистрептолизин-О, МЕ/мл / Antistreptolysin O titre, IU/mL	(166,00–250,00)		<50	
Мочевая кислота, ммоль/л / Uric acid, mmol/L	(0,21–0,42)		0,53	
IgE общий (R), МЕ/мл / Total IgE (R), IU/mL	(0,00–110,00)		999,95	
Лабораторные показатели мочи / Laboratory parameters of urine				
Белок, г/л / Protein, g/L		6,50	7,60	
Удельный вес, г/мл / Specific gravity, g/mL		1,012	1,017	1,015
Цвет / Color		Светло-желтый / Light yellow	Светло-желтый / Light yellow	Светло-желтый / Light yellow
Эритроциты, кл/мкл / Red blood cells, cells/μL		4,00	10,00	4,00
Цилиндры гиалиновые, кл/мкл / Hyaline casts, cells/μL			3,00	

better intellectual potential, as well as lower mortality (8%). According to the literature, patients with a late-onset form die within 10 years of life [4], however, a patient at the Saint Petersburg State Pediatric Medical University clinic was hospitalized at the age of 17 years 6 months.

The disease is often diagnosed as intrauterine or perinatal viral infections. If intrauterine infection is excluded, it is necessary to diagnose congenital genetic syndromes [4]. Aicardi–Goutières syndrome is manifested by progressive encephalopathy with onset in early childhood, accompanied by hepatosplenomegaly with elevated transaminase levels, thrombocytopenia, basal ganglia calcifications, lymphocytosis, leukodystrophy, increased the level of interferon-α in the cerebrospinal fluid in the absence of data on the presence of a viral infection [4]. Among the hematologic abnormalities in AGS are neutropenia, anemia and thrombocytopenia, severe cases of which were detected with the use

of baricitinib [16]. Patients with AGS have a higher risk of developing autoimmune diseases, including systemic lupus erythematosus [4]. The child in the presented clinical case was admitted with a diagnosis of nephrotic syndrome with diffuse membranous glomerulonephritis. In modern literature, there is a description of kidney damage in Aicardi–Goutières syndrome: in a 19-year-old patient, laboratory analysis showed severe renal failure (creatinine 2.85 mg/dL, GFR 30 ml/min) with arterial hypertension. After 1 month of providing palliative care, he died. Histopathological analysis of the kidney revealed fibrin thrombi and intimal proliferation, signs of thrombotic microangiopathy [18].

Pathogenesis of the disease: interferon-α, the source of which is astrocytes, causes microangiopathy (microinfarcts in the neocortex and cerebellar cortex), calcification of the basal ganglia and perivascular space of small vessels, leukodystrophy (diffuse heterogeneous demyelination with astrocytosis). The basis of such damage is lymphocytic vasculitis with fibrinoid necrosis and microthrombosis. The level of interferon-α in the cerebrospinal fluid increases at the onset of the disease and can normalize during the development and stabilization of the disease, as happened in the patient in the described clinical case.

Diagnosis of this syndrome is difficult, since the onset of the disease and clinical course resemble intrauterine infections, inherited metabolic diseases, epilepsy, so the true prevalence of the disease is unknown. The criteria for the diagnosis of the syndrome are: early appearance of a rash resembling frostbite, the appearance of calcifications in the central nervous system, leukodystrophy, developmental delay, dystonia, positive antinuclear antibody test, increased levels of interferon-α without confirmed infection. Attention is also drawn to patients with systemic lupus erythematosus of atypical manifestations who are not responsive to conventional treatment methods [17]. Long-term dynamic observation, application of neuroimaging techniques and genetic research are necessary [4]. An evaluation of vital organ function is required.

Treatment is symptomatic. The prognosis directly depends on the age of onset of symptoms of the disease, the severity of developmental defects, the severity of clinical symptoms and associated complications [5]. Therapy includes antiepileptic drugs, physical therapy, treatment of concomitant infections, adequate caloric nutrition, endocrinological and ophthalmological monitoring, and prevention of hypothermia. The use of hormonal therapy and high doses of immunoglobulin did not show effectiveness, however, with the administration of corticosteroids, a decrease in the level of interferon-α was noted [4].

CONCLUSION

The discovery of genetic interferonopathies, which include the orphan disease "Aicardi-Goutieres syndrome", on the example of the presented clinical case leads us to understand the systemic effect of interferon overexpression on the body, convinces us of the need for long-term observation of such patients, careful diagnosis of the syndrome and symptomatic treatment, the prognosis of which depends on the age of onset of the disease, its severity and severity of symptoms.

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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DISEASE TAKAYASUS IN A TEENAGER. CLINICAL OBSERVATION AND COMMENT

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Abstract. Nonspecific aortoarteritis (NAA), or Takayasu disease, is a rare pathology related to large vascular vasculitis. Its characteristic feature is the weakening and asymmetry of the pulse. Diagnosis of NAA is difficult due to nonspecific manifestations in the onset of the disease, an extremely wide range of differential diagnostics and insufficient awareness of primary care physicians. The features of NAA in children have not been sufficiently studied. The article provides a clinical observation of a 14-year-old girl with Takayasu disease proven in accordance with international criteria.

Key words*: nonspecific aortoarteritis; Takayasu disease; children; pulse asymmetry.*

БОЛЕЗНЬ ТАКАЯСУ У ПОДРОСТКА. КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ И КОММЕНТАРИЙ

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Резюме. Неспецифический аортоартериит (НАА), или болезнь Такаясу, — редкая патология, относящаяся к васкулитам крупных сосудов. Его характерной особенностью является ослабление и асимметрия пульса. Диагностика НАА затруднена из-за неспецифических проявлений в дебюте заболевания, чрезвычайно широкого круга дифференциальной диагностики и недостаточной осведомленности врачей первичного звена. Особенности НАА у детей изучены недостаточно. В статье приводится клиническое наблюдение девочки 14 лет с доказанной в соответствии с международными критериями болезнью Такаясу.

Ключевые слова: *неспецифический аортоартериит; болезнь Такаясу; дети; асимметрия пульса.*

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INTRODUCTION

Nonspecific aortoarteritis (NAA), or Takayasu's disease, is a rare pathology related to vasculitis, predominantly affecting large arteries — the aortic arch, its branches, and less often the descending aorta. NAA, along with giant cell arteritis (GCA), belongs to large-vessel vasculitis (LVVs). While GCA is the most common primary vasculitis in adults, Takayasu's disease occurs at a frequency of 1,2 to 6,3 cases per 1 million population. NAA was first described in 1908 as a series of retinal vascular disorders by Japanese ophthalmologist Mikito Takayasu [1]. The association of this pathology with absent or weakened pulses in the peripheral vessels has led to the term "pulseless disease" [2]. Synonyms are used in the literature: Takayasu's arteritis, Takayasu's disease, pulseless disease (ICD-10 code: M31) [3]. Early descriptions of the disease included persons of Japanese ancestry, but NAA is now found worldwide. The classification of NAA was proposed in 1994 (Takayasu Conference, 1994) and is based on the predominant localization of vascular lesions [4]. There are 5 types:

- Type I — aortic arch and arteries branching from it;
- Type IIa — ascending aorta, arch and its branches;
- Type IIb — ascending aorta, arch and its branches, descending thoracic aorta;
- Type III — descending thoracic, abdominal aorta and (or) renal arteries;
- Type IV — abdominal aorta and (or) renal arteries;
- Type V is a mixed version of types IIb and IV.

In children, the prevalence and clinical features have not been sufficiently studied. It is known that the manifestation of the disease in most patients occurs in early adolescence. Rapid diagnosis and early treatment are key to good patient outcomes, but diagnosis of NAA is challenging and typically delayed because clinical manifestations are nonspecific, the range differential diagnosis is quite broad, and assessment of disease activity is difficult.

EPIDEMIOLOGY OF NONSPECIFIC AORTOARTERITIS

In Japan, where Takayasu's disease was first described, it is detected annually at a frequency of 1–2 cases per million people. In Europe, the annual incidence ranges from 0,4 to 3,4 per million. Age of onset usually ranges from 10 to 40 years and is the main epidemiological feature that distinguishes NAA from GCA, although late-onset NAA has become more common [5]. In Europe, 80–90% of NAA are female; in China, India, Japan, and Thailand, the ratio of female to male varies from 3:1 to 4:1 [6, 7]. It is noteworthy that the nature of the disease may vary depending on the patient's age at the onset of the disease, as well as between men and women. In the national literature, the largest number of observations of children with Takayasu's disease (51 children) were presented by Moscow pediatricians [8]. According to their data, the ratio of the frequency of NAA between boys and girls under 7 years of age is almost the same: 1:1.25; in the group of children over 7 years old, girls significantly predominated — 1:7,4. The most common symptoms were malaise (90%) and fever (67.3%). Remarkably, the authors noted the absence or weakening of the pulse only in 35% of cases.

PATHOGENESIS

The pathogenesis of LVV has been studied mainly in relation to GCA as a more common pathology, but the main links also apply to NAA. Under physiological conditions, the walls of medium and large arteries are protected from inflammation and autoimmune reactions by immune tolerance. LVV is characterized by a loss of immune tolerance, which leads to the launch of a cascade of pro-inflammatory mediators and progressive tissue damage. At the onset of the disease, vasculitis is difficult to notice and quantify. Aneurysm formation and progressive arterial occlusion occur decades after onset. Over the past few years, the role of mast cells in the pathogenesis of NAA lesions has been identified. In a series of *in vitro* and *in vivo* experiments using serum and aortic tissue from both healthy individuals and patients with NAA, mast cells were responsible for increased vascular permeability, neovascularization, and fibrosis; these cells represent a potential therapeutic target [9]. Vascular inflammation in LVV is often combined with extravascular systemic inflammation. This systemic inflammatory response manifests as anemia, thrombocytosis, liver dysfunction, and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in the blood, with clinical symptoms of fever, malaise, and myalgia. Systemic inflammation is associated with a change in the number of circulating B cells and an increase in their ability to produce interleukin-6 (IL-6). Identification of anti-endothelial cell antibodies in patients with NAA suggests vascular autoimmune reactions [10].

We present our own observation of clinical case of Takayasu's disease in a 14-year-old teenager

Girl M., 14 years old, was admitted to the clinic urgently with a diagnosis of community-acquired pneumonia. From the anamnesis it is known that 3 months before hospitalization, pain appeared in the left hypochondrium, which intensified in the supine position and at the depth of inspiration. The onset of pain could

not be associated with any disease, injury, or stress. At the local clinic she was examined several times by a pediatrician and a neurologist; intercostal neuralgia was diagnosed, for which she received symptomatic therapy with NSAIDs and physiotherapy treatment, but the pain syndrome persisted over time. Upon repeated examination, a neurosis-like condition was diagnosed, treatment was also without effect. Due to the child's persistent complaints of pain in the left hypochondrium, an outpatient chest x-ray was performed, which revealed infiltrative changes in the lower parts of the left lung. The condition was considered pneumonia, and therefore the patient was hospitalized.

From the anamnesis vitae it is known that the girl was born from a second, normal pregnancy, an urgent physiological delivery. Breastfed up to 1.5 years. She grew and developed according to age. Vaccinated according to the National calendar. *Menses* from the age of 13, regular periods. She was rarely sick and suffered from a mild form of acute upper respiratory infection. No allergic pathology was observed in relatives. Heredity is burdened: the first child in the family died from a congenital pulmonary malformation.

Upon admission, the child's condition was moderate. Body temperature — 36.8 °C, heart rate — 102 beats/min. Weak filling pulse, respiratory rate — 18 per min. Blood pressure on the right arm is 150/70 mm Hg, on the left arm — 130/75 mm Hg. The pulse in the legs was almost not palpable, and blood pressure was not determined. General well-being is satisfactory. Consciousness is clear. There are no meningeal symptoms. The position in bed is active. The skin and visible mucous membranes pale coloration, there are no pathological rashes. The body type is asthenic. The subcutaneous fat layer is not sufficiently developed. Tissue turgor and skin elasticity are preserved. Nasal breathing is free. The mucous membrane of the pharynx is pale pink. The tonsils are hypertrophied, grade 1–2, there are no plaques. Peripheral lymph nodes are small, mobile. Heart sounds are muffled, rhythmic, rough systolic murmur over the entire surface of the heart, carried out extracardially, the murmur is heard along the entire abdominal aorta. There is no peripheral edema. The chest is of normal shape. Percussion sound is pulmonary. There is vesicular breathing in the lungs, carried out in all fields, there are no wheezes, during forced inhalation the girl complains of chest pain on the left. The abdomen is soft, painless. The lumbar region is visually unchanged, the symptom of tapping on both sides is negative. The liver and spleen are not enlarged. Physiological functions are normal.

Urine analysis: pH 6.5; specific gravity — 1.025; white blood cells — 8–10 per HPF; squamous epithelial cells — a large number per HPF; protein — 0.34 g/L.

Examination by an ophthalmologist: vessels of the eye fundus without pathology. A disseminated bronchopulmonary process has been excluded (Mantoux test with 2TE dated 29.10.21 — 12 mm, the girl was consulted by a phthisiatrician — there is no tuberculosis data).

Laboratory examination data upon admission are shown in Tables 1–3.

As can be seen from Tables 1 and 2, the patient has moderate iron-deficiency anemia, and markers of active inflammation are sharply increased.

An immunological study (Table 3) revealed high titers of immunoglobulins of classes A and M and anti-beta 2-glycoprotein I antibodies of IgGAM class (antiphospholipid antibodies).

Table 1. Complete blood count

Таблица 1. Клинический анализ крови

Hb, g/L / Hb, г/л	RBC, 10^{12}/L / Эр., 10^{12}/л	CI / ЦП	Ht, % Ht, %	MCV, fl / MCV, фл	MCHC / MCHC	Plt, 10^9/L / Тромбоциты, 10^9/л	WBC, 10^9/l / Лей 10^9/л	Neu, % / Нейт. %	Lym, % / Лимф. %.	Bas, % / Баз. %	Eos, % / Эоз. %	Mon, % / Мон. %	ESR, mm/hr / СОЭ мм/ч
80	4,64	55,6	27,9	60	285	383	7,8	57,9	26,2	0,8	2,7	12,4	67

Table 2. Biochemical blood test

Таблица 2. Биохимический анализ крови

Parameter / Показатель	Result / Результат	Normal /Норма
Total protein, g/L / Общий белок, г/л	82	60–80
CRP, mg/L / СРБ, мг/л	55,71	0,00–5,00
Iron, µmol/L / Железо, мкмоль/л	3,4	4,7–19,7
Transferrin, g/L / Трансферрин, г/л	2,1	3,0–3,8
TIBS of serum, µmol/L / ОЖСС сыворотки, Мкмоль/л	45	52–79

Table 3. Immunogram

Таблица 3. Иммунограмма

Parameter, g/L / Показатель, г/л	Result / Результат	Normal / Норма
Immunoglobulin A / Иммуноглобулин А	6,14	0,47–2,40
Immunoglobulin M / Иммуноглобулин М	2,76	0,15–1,88
Immunoglobulin G / Иммуноглобулин G	21,5	6,58–15,34

Instrumental examinations

- According to the results of computed tomography of the chest organs with intravenous bolus contrast-enhanced of the lungs, there is a picture of diffuse lesion of the thoracic, abdominal parts of the aorta and its branches, the pulmonary trunk, focal consolidation in the lower lobe of the left lung (pulmonary infarction localized in S_8 on the left) (Fig. 1), subcortical defect of contrast of the left kidney (infarction in the upper pole of the left kidney) (Fig. 3).
- By the data of duplex imaging of the abdominal aorta and its visceral branches, there is a picture of aortoarteritis of abdominal aorta, arteritis of the superior mesenteric artery, severe stenosis of the celiac trunk (Fig. 2, 4); Duplex imaging of the renal arteries — signs of stenosis at the mouth of the right renal artery, stenosis of the left renal artery.
- Color-coded triplex scanning of the transcranial and brachiocephalic arteries revealed stenosis of the right subclavian artery, arteritis of the common carotid artery, the upper third of the internal carotid artery on both sides (Fig. 5).
- As the results of echocardiography — moderate dilatation of the ascending aorta, mild aortic insufficiency; left ventricular concentric remodeling, increased fluid content in the pericardial cavity.

During the examination, the range of differential diagnosis included a disseminated pulmonary process, pneumonic infiltration, diffuse connective tissue diseases and small-vessel vasculitis, pulmonary infarction, infectious endocarditis, rheumatoid arthritis, neoplastic process, primary immunodeficiency.

Based on the totality of the results of the anamnesis, clinical, laboratory and instrumental examinations, namely the presence of 4 out of 5 criteria proposed by EULAR/PRINTO/PReS [11], the diagnosis was established: "Systemic vasculitis: nonspecific aortoarteritis (Takayasu's disease), debut, type V. Secondary antiphospholipid syndrome.

Complications: pulmonary infarction localized in S_8 on the left. Infarction in the upper pole of the left kidney. Moderate microcytic hypochromic anemia. Arterial hypertension. Mild aortic insufficiency".

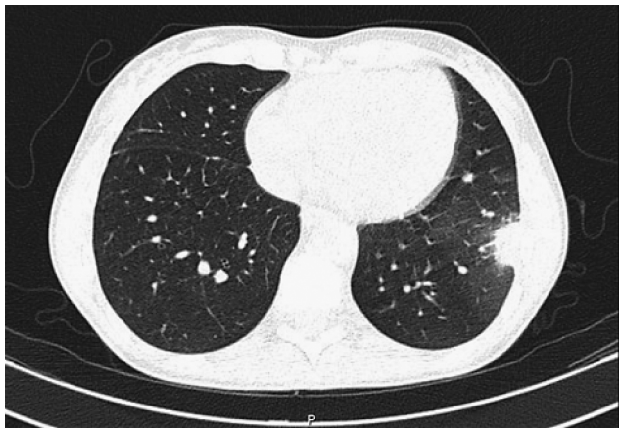

Fig. 1. Computed tomography of the chest organs with intravenous bolus contrast-enhanced: focal consolidation in the lower lobe of the left lung (pulmonary infarction localized in S_8)

Рис. 1. Компьютерная томография органов грудной полости с внутривенным болюсным контрастированием: очаговое уплотнение в нижней доле левого легкого (инфаркт легкого с локализацией в S_8)

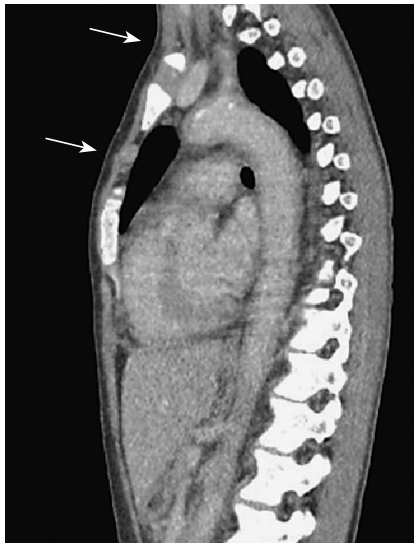

Fig. 2. Computed tomography of the chest organs with intravenous bolus contrast-enhanced (angiography): CT picture of diffuse lesion of the thoracic, abdominal parts of the aorta and its branches, the pulmonary trunk. Arrows indicate calcifications in the aortic arch and diffuse lesions of the thoracic aorta

Рис. 2. Компьютерная томография органов грудной полости с внутривенным болюсным контрастированием (ангиография): КТ-картина диффузного поражения грудного, брюшного отделов аорты и ее ветвей, легочного ствола. Стрелками обозначены кальцинаты в дуге аорты и диффузное поражение грудного отдела аорты

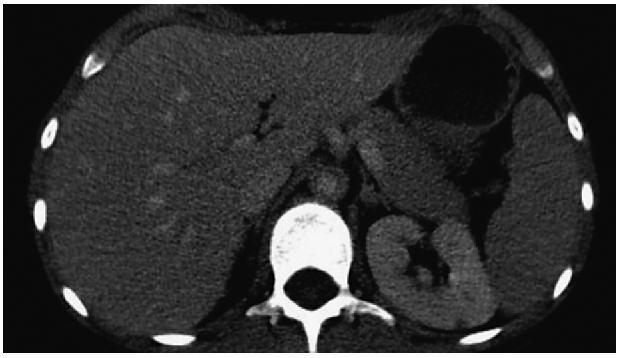

Fig. 3. Computed tomography of the chest organs with intravenous bolus contrast-enhanced: subcortical defect of contrast of the left kidney (infarction in the upper pole of the left kidney)

Рис. 3. Компьютерная томография органов грудной полости с внутривенным болюсным контрастированием: субкортикальный дефект контрастирования левой почки (инфаркт в верхнем полюсе левой почки)

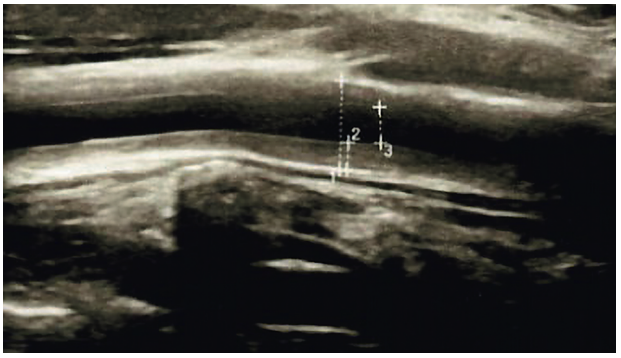

Fig. 5. Color-coded triplex scanning of the transcranial and brachiocephalic arteries: stenosis of the right subclavian artery, arteritis of the common carotid artery, the upper third of the internal carotid artery on both sides

Рис. 5. Цветовое триплексное сканирование транскраниальных и брахиоцефальных артерий: стеноз правой подключичной артерии, артериит общей сонной артерии, верхней трети внутренней сонной артерии с обеих сторон

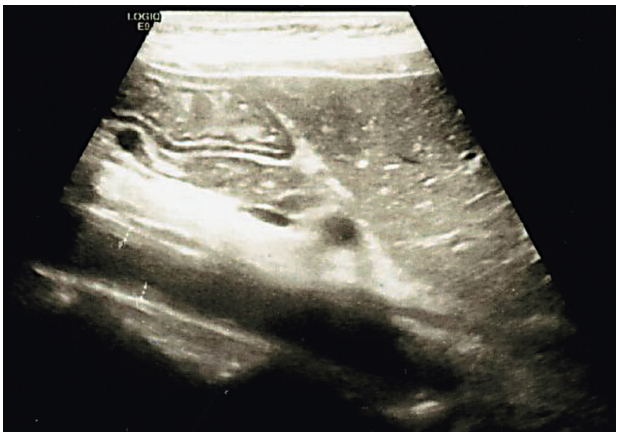

Fig. 4. Duplex imaging of the abdominal aorta and its visceral branches: picture of aortoarteritis of abdominal aorta, arteritis of the superior mesenteric artery, severe stenosis of the celiac trunk

Рис. 4. Дуплексное исследование брюшного отдела аорты и ее висцелярных ветвей: картина аортоартериита брюшного отдела аорты, артериита верхней брыжеечной артерии, выраженного стеноза чревного ствола

At the department, intravenous methylprednisolone pulse therapy was started at a dose of 1000 mg once a daily for 3 days, with subsequent administration of oral prednisolone at a dose of 50 mg once a day. Anticoagulant, antihypertensive, antibacterial and symptomatic therapy were also carried out. A positive effect was achieved: pain in the left half of the chest, dizziness, headaches were relieved; an increase in hemoglobin was noted (from 80 to 104 g/L), a decrease in ESR was observed (from 67 to 34 mm/hr), as well as a decrease in CRP (from 55 to 10 mg/L), and normalization of coagulogram parameters.

According to the results of control instrumental examinations (ultrasound of the abdominal aorta and its visceral branches, renal vessels, echocardiography) — no dynamics.

MSCT of the chest circumference described positive dynamics — a reduction in the size of the focal consolidation of the left lung; Ground-glass opacities are marked on both sides.

To continue treatment of systemic vasculitis and secondary antiphospholipid syndrome, the patient was transferred to a specialized pediatric rheumatology center, where she was prescribed targeted therapy: infliximab (anti-TNF-α group), methotrexate, and combination antihypertensive therapy.

CONCLUSION

Diagnosis of NAA is difficult; clinical manifestations depend on the preferential damage to certain vessels. This pathology can occur under the "masks" of other diseases, have a polymorphic course and not be recognized for a long time. This requires special alertness of pediatricians and doctors of other specialties to this pathology. Correct diagnosis and timely initiation of therapy help prevent the development of serious complications that are associated with a high risk of disability, morbidity and mortality of patients.

ADDITIONAL INFORMATION

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

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

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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CLINICAL CASE: TREACHER COLLINS SYNDROME

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Abstract. Treacher Collins syndrome is a congenital developmental disorder of the craniofacial region associated with an anomaly in the differentiation of the first and second pharyngeal arches. This syndrome is a rare pathology, its frequency of occurrence is 1 per 50,000 cases of live births, but we had the opportunity to observe a patient with this syndrome on the basis of the St. Petersburg Orphanage. *Aim.* To analyze the literature, present a description of the Treacher Collins syndrome and analyze a clinical case in a patient under observation in a children's home (St. Petersburg). *Materials and methods*. International and domestic scientific publications, analysis of clinical cases in the literature, medical documentation of the orphanage. *Results.* In our article, we assess the severity of congenital malformations in a patient at the orphanage, and give a conclusion about the specificity of the severity of his condition for Treacher Collins syndrome.

Key words: *Treacher Collins syndrome; STC; Franceschetti's syndrome; mandibular dysostosis.*

КЛИНИЧЕСКИЙ СЛУЧАЙ: СИНДРОМ ТРИЧЕРА КОЛЛИНЗА

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Резюме. Синдром Тричера Коллинза — врожденное нарушение развития черепно-лицевой области, связанное с аномалией дифференцировки первой и второй глоточных дуг. Данный синдром является редкой патологией, частота его встречаемости — 1 на 50 000 случаев живорожденных, но нам представилась возможность наблюдать пациента с данным синдромом на базе Санкт-Петербургского дома ребенка. *Цель.* Провести анализ литературы, представить описание синдрома Тричера Коллинза и разобрать клинический случай у пациента, находящегося под наблюдением в доме ребенка (Санкт-Петербург). *Материалы и методы.* Международные и отечественные научные публикации, разбор клинических случаев в литературе, медицинская документация дома ребенка. *Результаты.* В нашей статье мы даем оценку степени выраженности врожденных пороков развития у пациента дома ребенка и делаем заключение по поводу характерности тяжести его состояния для синдрома Тричера Коллинза.

Ключевые слова: *синдром Тричера Коллинза; СТК; синдром Франческетти; нижнечелюстно-лицевой дизостоз.*

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INTRODUCTION

Treacher Collins syndrome (TCS, Franceschetti syndrome or mandibulofacial dysostosis) is a congenital developmental disorder of the craniofacial region. The cause of the syndrome is an anomaly in the differentiation of the first and second pharyngeal arches, which occurs during intrauterine development of the fetus [1, 2]. The disease is characterized by bilateral symmetrical oto-mandibular dysplasia without limb anomalies and leads to a number of head and neck defects [1].

EPIDEMIOLOGY

The incidence of Treacher Collins syndrome has been estimated by various researchers to range from 1 in 25,000 to 1 in 70,000 live births (most often reported as 1 in 50,000) [1–3].

OBJECTIVE

The aim of this study is to analyze the literature, present a description of the Treacher Collins syndrome and review a clinical case in a patient under observation in an orphanage (St. Petersburg).

MATERIALS AND METHODS

International and national scientific publications, analysis of clinical cases in the literature, medical documentation of the orphanage.

DISCUSSION AND RESULTS

Treacher Collins syndrome has an autosomal dominant and, less commonly, autosomal recessive pattern of inheritance, but, despite some well-known familial cases, for the most part (the authors note, 60% or more) the mutation is sporadic [4–6].

TCS is genetically and phenotypically heterogeneous. Based on the mutation of a specific gene, authors distinguish from three to four types of TCS.

1) type 1 — mutation in the *TCOF1* gene;
2) type 2 — mutation in the *POLR1D* gene;
3) type 3 — mutation in the *POLR1C* gene;
4) type 4 — mutation in the *POLR1B* gene.

Up to 93% of all cases of Treacher Collins syndrome are type 1 syndrome. TCS type 1 is associated with mutations in the *TCOF1* gene, which is located on chromosome 5q32-q33.1 [1, 2, 5, 7, 8]. The mode of inheritance is autosomal dominant with 90% penetrance and variable expressivity, including patients within the same family. There are known observations of children with pronounced clinical manifestations of the syndrome in one family, while one of the parents was found to have the same mutation without pronounced clinical manifestations of the disease [1, 4].

Type 2 of Treacher Collins syndrome is caused by a mutation in the *POLR1D* gene on chromosome 13q12; Type 3 — mutation in the *POLR1C* gene on chromosome 6p21 [1, 6, 7].

The first 3 types of Treacher Collins syndrome are noted by the authors of the articles, and the authors in more recent publications distinguish the 4th type of TCS based on the newly identified mutation in the *POLR1B* gene [2].

According to the authors of the researched publications, there is no correlation between the clinical features of patients and the gene in which mutations occur, therefore the classification of the syndrome by type of affected chromosome is conditional [3, 9, 11].

The authors also note a large share of intrafamilial phenotypic variability in this syndrome. For example, in one familial case, the proband suffered from severe craniofacial deformities and conductive hearing loss, while the proband's mother was a carrier of the same gene mutation variant but had mild lesions [8].

CLINICAL MANIFESTATIONS

Treacher Collins syndrome is a condition with high phenotypic variability, both in intrafamilial and in sporadic cases.

People with TCS have characteristic facial dysmorphism with bilateral symmetrical malar hypoplasia (95% of cases) and mandibular hypoplasia (78% of cases), leading to micrognathia and malocclusion.

Abnormalities of the external ear, such as microtia or anotia, external auditory canal atresia, and abnormal development of the auditory ossicles (60% of cases), are often observed, causing conductive hearing loss [7, 9, 10].

Pharyngeal hypoplasia is common, which in turn can contribute to feeding problems and/or difficulty breathing.

Choanal atresia and eyelid coloboma have been described (69% of cases), accompanied by the absent eyelashes. Features include complex disorders in the structure of the temporomandibular joint, which leads to a limited ability to open the mouth of varying degrees of severity [1, 7].

People with TCS may develop hearing loss due to sound waves not passing through the middle ear (conductive hearing loss, 77% of cases). The outer ear may be crumpled or rotated, but the inner ear is usually not affected [1].

The severity of deformities does not increase with age [2, 8]. The syndrome is not a progressive disease.

Mental retardation occurs in 5% of people with TCS [1]. 60% of children have poor speech quality resulting from hearing impairment [11, 12].

As a result of the above, we can make the assumption that the likelihood of developing mental retardation correlates with the pathology of the auditory system, which complicates the development of active speech and leads to problems with mastering the curriculum.

CLINICAL CASE

Patient F., 08.09.2022 (9 months), has been in the orphanage since 6 months 12 days. From the anamnesis vitae, it is known that the mother's pregnancy proceeded against the background: class 2 obesity, stage 2 hypertension, varicose veins of the lower extremities, vaginitis, gestational diabetes mellitus, preeclampsia, chronic kidney disease, uterine scar. The delivery was preterm, operative, at a gestational age of 33 3/7 weeks. At birth, body weight was 1130 g, body length 37 cm. Apgar score was 4/6/7 points.

From the moment of birth, a serious condition due to respiratory failure, circulatory failure, immaturity, intra-amniotic infection, intrauterine growth restriction. He was intubated in the delivery room. From the first days of life to 6 months, he received antibiotics (including from the reserve group), inhaled corticosteroids, was on artificial ventilation, and had blood transfusions due to regularly occurring infections. At 2 months of life, a tracheostomy was performed. At 5 months, percutaneous endoscopic gastrostomy was carried out.

Anamnesis morbi. At birth, the phenotype allowed us to suspect Treacher Collins syndrome, because multiple congenital malformations (CM) were identified: underdevelopment of the zygomatic bones, ptosis of the upper and lower eyelids, abnormally developed low-set ears, flat nasal bone, high-arched palate, incomplete cleft of the upper gum, micrognathia, retrognathia, glossoptosis. Subsequently, the presumptive diagnosis of TCS was confirmed by laboratory tests.

The patient has the following congenital malformations (with noticed frequency of their occurrence within the framework of the TCS):

1) hypoplasia of the bones of the facial part of the skull, including: underdevelopment of the zygomatic bones, flat nasal bone, stenosis of the nasolacrimal duct OU, mandibular hypoplasia, micrognathia, retrognathia, glossoptosis, high-arched palate (in the sources these symptoms are described as very common, they are registered in 91–97% of cases);
2) CM of the organ of vision, including: OU — blepharophimosis, hypertelorism, grade 3 bilateral microtia (reported in sources in 77% of cases);
3) CM of the hearing organ, including: abnormally developed low-set ears (reported in sources in 60% of cases).

This patient also has symptoms classified as rare within the TCS:

- choanal atresia on both sides (up to 25% of cases);
- incomplete hard palate cleft and complete soft palate cleft (up to 33% of cases).

The operations performed on him (gastrostomy and tracheostomy) in the studied sources are also classified as rare:

- gastrostomy (up to 28% of cases);
- tracheostomy (up to 18% of cases).

The above allows us to infer that in most cases, patients with TCS have less pronounced phenotypic manifestations than the presented clinical case.

The boy was extremely premature at the time of birth, but a study of the sources allows us to conclude that this situation is in many ways rare. In the literature we studied, only one clinical case indicated preterm delivery (at 37 weeks of gestation); in most cases, delivery was urgent and spontaneous [6, 10].

At the moment, the child has a physical developmental delay, which is assessed by the centile method as very low, with retarded growth and body weight (corresponding to 6 months of age). There is no underweight.

CONCLUSION

The child has common congenital malformations characteristic of TCS: hypoplasia of the bones of the facial part of the skull, congenital defects of the organ of vision, congenital anomalies of the organ of hearing, which initially made it possible to phenotypically suspect this syndrome, which was later confirmed by laboratory tests.

At the same time, this patient has rare CM: choanal atresia on both sides, incomplete hard palate cleft and complete soft palate cleft. The following operations were performed: tracheostomy and gastrostomy (which are also rare for this syndrome).

The causes of prematurity, physical developmental delay, and the generally more severe condition of our patient compared to other clinical cases of TCS were the mother's pregnancy pathology (uterine scar, chronic infection, preeclampsia, stage 2 hypertension, class 2 obesity, gestational

diabetes mellitus), which led to preterm surgical delivery, as well as intrauterine infection, which complicated the patient's condition and led to an undulating course infectious process for up to 6 months of his life.

INFERENCE

Treacher Collins syndrome is characterized by multiple congenital malformations of the facial part of the skull. The syndrome is transmitted in an autosomal dominant type and is characterized by preserved intelligence.

In the clinical case presented by us, the child has multiple CM, typical of TCS, but the severity of the child's condition is due to prematurity at 33 3/7 weeks of gestation, which is not characteristic of the described syndrome.

Due to the fact that TCS is not a progressive disease, patients often have preserved intelligence, so the child has a relatively favorable clinical prognosis for managing the disease and satisfactory rehabilitation potential using modern medical and surgical treatment methods, as well as methods of habilitation and rehabilitation of children.

ADDITIONAL INFORMATION

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

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

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Consent for publication. The authors obtained written consent from the patients' legal representatives for the publication of medical data.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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ПРАВИЛА ДЛЯ АВТОРОВ

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

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

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

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

В Журнале печатаются ранее не опубликованные работы по профилю Журнала.

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

Размещение публикаций возможно только после получения положительной рецензии.

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

ПРЕДСТАВЛЕНИЕ РУКОПИСИ В ЖУРНАЛ

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

СОПРОВОДИТЕЛЬНЫЕ ДОКУМЕНТЫ

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

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

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При представлении рукописи в Журнал Авторы несут ответственность за раскрытие

своих финансовых и других конфликтных интересов, способных оказать влияние на их работу. В рукописи должны быть упомянуты все лица и организации, оказавшие финансовую поддержку (в виде грантов, оборудования, лекарств или всего этого вместе), а также другое финансовое или личное участие.

АВТОРСКОЕ ПРАВО

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

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2) территория, на которой разрешается использовать авторский материал, — Российская Федерация и сеть Интернет;
3) срок действия Договора — 5 лет. По истечении указанного срока Редакция оставляет за собой, а Автор подтверждает бессрочное право Редакции на продолжение размещения авторского материала в сети Интернет;
4) Редакция вправе по своему усмотрению без каких-либо согласований с Автором заключать договоры и соглашения с третьими лицами, направленные на дополнительные меры по защите авторских и издательских прав;
5) Автор гарантирует, что использование Редакцией предоставленного им по настоящему Договору авторского материала не нарушит прав третьих лиц;
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7) Редакция предоставляет Автору возможность безвозмездного получения справки с электронными адресами его официальной публикации в сети Интернет;
8) при перепечатке статьи или ее части ссылка на первую публикацию в Журнале обязательна.

ПОРЯДОК ЗАКЛЮЧЕНИЯ ДОГОВОРА И ИЗМЕНЕНИЯ ЕГО УСЛОВИЙ

Заключением Договора со стороны Редакции является опубликование рукописи данного Автора в журнале «Children's medicine of the North-West» и размещение его текста в сети Интернет. Заключением Договора со стороны Автора, т. е. полным и безоговорочным принятием Автором условий Договора, является передача Автором рукописи и экспертного заключения.

ОФОРМЛЕНИЕ РУКОПИСИ

Редакция журнала приветствует полностью двуязычные статьи.

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

1. **Заглавие** (Title) должно быть кратким (не более 120 знаков), точно отражающим содержание статьи.

2. **Сведения об авторах** (публикуются). Для каждого автора указываются: фамилия, имя и отчество, место работы, почтовый адрес места работы, e-mail, ORCID. Фамилии авторов рекомендуется транслитерировать так же, как в предыдущих публикациях или по системе BGN (Board of Geographic Names), см. сайт http://www.translit.ru.

3. **Резюме** (Summary) (1500–2000 знаков, или 200–250 слов) помещают перед текстом статьи. Резюме не требуется при публикации рецензий, отчетов о конференциях, информационных писем.

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

Рекомендуемая структура аннотации: введение (Background), цели и задачи (Purposes and tasks), методы (Materials and methods), результаты (Results), выводы (Conclusion). Предмет, тему, цель работы нужно указывать, если они не ясны из заглавия статьи; метод или методологию проведения работы целесообраз-

но 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.

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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.

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Описание Интернет-ресурса

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

Kealy M. A., Small R. E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women's accounts in Victoria, Australia. BMC Pregnancy and Childbirth. 2010. Available at: http://www.biomedcentral.com/1471–2393/10/47/. (accessed 11.09.2013).

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

По новым правилам, учитывающим требования международных систем цитирования, библиографические списки (References) входят в англоязычный блок статьи и, соответственно, должны даваться не только на языке оригинала, но и в латинице (романским алфавитом). Поэтому авторы статей должны давать

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

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

Технология подготовки ссылок с использованием системы автоматической транслитерации и переводчика.

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

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

2. Копируем транслитерированный текст в готовящийся список References.

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

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

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

Примеры транслитерации русскоязычных источников литературы для англоязычного блока статьи

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

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

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

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

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

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

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

Тезисы докладов, материалы научных конф.

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

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

Авторефераты

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

Описание Интернет-ресурса

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

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

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

СТРУКТУРА ОСНОВНОГО ТЕКСТА СТАТЬИ

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

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

Объем рукописей.

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

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

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

РЕЦЕНЗИРОВАНИЕ

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

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

АДРЕС РЕДАКЦИИ

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

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

ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

ОРТОПЕДИЧЕСКАЯ СТОМАТОЛОГИЯ. ПРОТЕЗИРОВАНИЕ НЕСЪЁМНЫМИ КОНСТРУКЦИЯМИ ЗУБНЫХ ПРОТЕЗОВ

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

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

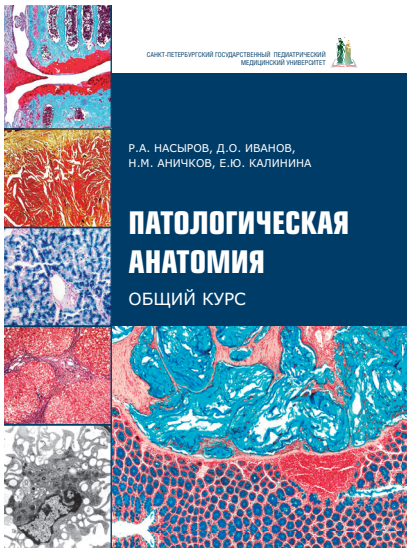
Авторы будут признательны за критические замечания и дополнения.

Твердый переплет, цветные иллюстрации, 464 страницы.

Приобрести издание можно в интернет-магазине Лабиринт:
https://www.labirint.ru/books/877708/

ПАТОЛОГИЧЕСКАЯ АНАТОМИЯ. ОБЩИЙ КУРС

Р.А. Насыров, Д.О. Иванов, Н.М. Аничков, Е.Ю. Калинина



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

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

Твердый переплет, цветные иллюстрации, 280 страниц.

Приобрести издание можно в интернет-магазине Лабиринт:
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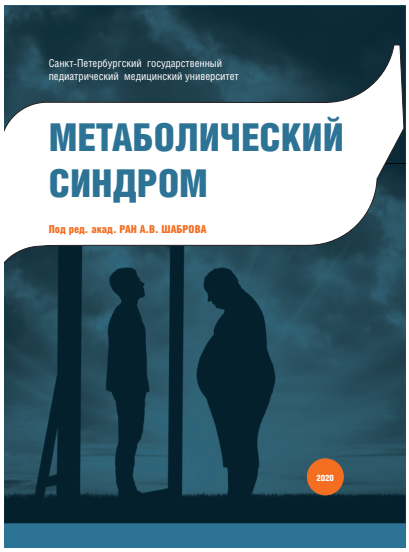
ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

МЕТАБОЛИЧЕСКИЙ СИНДРОМ

Под ред. акад. РАН А.В. Шаброва



Монография посвящена одной из ведущих проблем современного здравоохранения — метаболическому синдрому. Представлены исторические аспекты изучения метаболического синдрома и ассоциированных с ним заболеваний сердечно-сосудистой системы, критерии диагностики, эпидемиологические данные, проанализирована роль таких факторов, как микробиом кишечника, адипокины, оксидативный стресс, нарушение пищевого поведения в патогенезе метаболического синдрома. Рассмотрено влияние метаболического синдрома на бронхолегочную патологию, гастроэнтерологическую патологию, половые дисфункции. Описаны перспективные методы обследования пациентов с метаболическим синдромом, современные подходы к терапии. Монография будет интересна врачам терапевтических специальностей, научным работникам, преподавателям, аспирантам, студентам медицинских вузов.

Твердый переплет, 496 страниц.

Приобрести издание можно в интернет-магазине Лабиринт:
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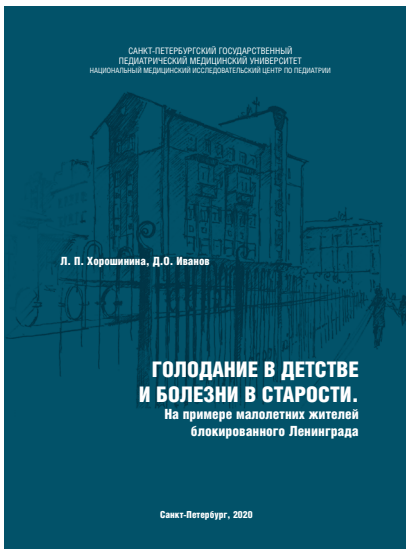
ГОЛОДАНИЕ В ДЕТСТВЕ И БОЛЕЗНИ В СТАРОСТИ

Л.П. Хорошинина, Д.О. Иванов



Книга посвящена малоизученным медицинским проблемам у людей старших возрастных групп, переживших в детстве длительные периоды голодания. Авторами изучаются отдаленные последствия длительного голодания детей и подростков в блокированном Ленинграде (1941–1944). Литературный обзор и полученные данные свидетельствуют об особенностях соматических заболеваний у бывших малолетних жителей блокированного Ленинграда, ставших ныне взрослыми. Книга переиздается повторно, текст её дополнен и исправлен.

Издание может быть интересно патологам, врачам-клиницистам, специалистам по организации здравоохранения и всем гражданам, интересующимся историей блокады Ленинграда.

2-е издание, переработанное и дополненное.

Твердый переплет, 176 страниц.

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https://www.labirint.ru/books/777647/