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ORIGINAL STUDIES

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CHARACTERISTICS OF INTESTINAL MICROBIOTA PARAMETERS IN YOUNG PEOPLE WITH METABOLIC SYNDROME

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ХАРАКТЕРИСТИКА ПАРАМЕТРОВ МИКРОБИОТЫ КИШЕЧНИКА У ЛИЦ МОЛОДОГО ВОЗРАСТА С МЕТАБОЛИЧЕСКИМ СИНДРОМОМ

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Objective. To study the features of the colon microbiota, as well as the associations of microbial representatives with anthropometric, anamnestic and biochemical parameters in young patients with metabolic syndrome.
Materials and methods. 118 young people took part in a single-center, one stage, controlled study. 87 of them were diagnosed with obesity, and 31 people with normal body weight formed the control group ("C").

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87 obese patients were divided into 2 groups: "MS-" which consisted of 43 people (49.4 %), and "MS+" including 44 people (50.6 %) with metabolic syndrome. When stratifying the groups, the NCEP ATP III criteria were used. Blood for biochemical test was taken from all the participants, and the condition of the colon microbiota was assessed using polymerase chain reaction («Colonoflor-16 (premium)»). The Microsoft Excel 2010 and IBM SPSS Statistics 26.0 application software package were used for statistical calculations. The results were evaluated as statistically significant at a level of $p < 0.05$.

Results. In the MS+ group *Fusobacterium nucleatum* (*Fusobacteriaceae* family) was detected statistically significantly more often than in individuals from group "C" (40.5 %). Differences in the bacterial composition of the intestinal microbiota between two groups of obese people were revealed: in the "MS+" group there was a significant decrease in bacteria of the genus *Bifidobacterium* (*Bifidobacteriaceae* family), *Prevotella* (*Prevotellaceae* family) and *Faecalibacterium prausnitzii* (*Ruminococcaceae* family) ($p < 0.05$). In addition, correlation patterns between the species and generic composition of the microbiota on the one hand and age, BMI, waist circumference, hip circumference, breastfeeding duration, indicators of carbohydrate (glucose, insulin, HOMA-IR index) and lipid (total cholesterol, triglycerides, low-density lipoproteins, very low-density lipoproteins, high-density lipoproteins) metabolism, CRP on the other hand have been established.

Conclusions. The colon microbiota in obese patients is characterized by proinflammatory changes. For the metabolically unhealthy phenotype of obesity these changes are most characteristic. It is clear that further research is needed to determine the mechanisms underlying the influence of bacterial-fungal associations on metabolism in obese individuals, as these mechanisms are likely to play a key role in the development of metabolic diseases.

Keywords. Intestinal microbiota, Colonophlor-16 (premium), obesity, metabolic syndrome.

Цель. Изучить особенности микробиоты толстой кишки, а также ассоциации микробных представителей с антропометрическими, анамнестическими и биохимическими параметрами у молодых пациентов с метаболическим синдромом.

Материалы и методы. Проведено одноцентровое, одномоментное, контролируемое исследование с участием 118 молодых людей, из них у 87 человек диагностировано ожирение и у 31 человека нормальная масса тела, которые составляли группу контроля («К»). Из 87 пациентов с ожирением 43 человека (49,4 %) входили в группу «МС-», 44 человека (50,6 %) имели метаболический синдром и составляли группу «МС+». При стратификации групп руководствовались критериями NCEP ATP III. Всем участникам проводился биохимический анализ крови, а также оценка состояния микробиоты толстой кишки методом ПЦР («Колонофлор-16 (премиум)»). Для статистических расчетов был использован пакет прикладных программ Microsoft Exel 2010, IBM SPSS Statistics 26.0. Результаты оценивались как статистически значимые при уровне $p < 0,05$.

Результаты. В группе «МС+», по сравнению с лицами из группы «К», статистически значимо чаще выявляется *Fusobacterium nucleatum* (семейство *Fusobacteriaceae*) (40,5 %). Выявлены различия в бактериальном составе микробиоты кишечника между двумя группами лиц с ожирением, в частности, в группе «МС+» отмечалось достоверное снижение бактерий рода *Bifidobacterium* (семейство *Bifidobacteriaceae*), *Prevotella* (семейство *Prevotellaceae*) и *Faecalibacterium prausnitzii* (семейство *Ruminococcaceae)* ($p \leq 0,05$). Кроме того, установлены корреляционные закономерности между видовым и родовым составом микробиоты, с одной стороны, и возрастом, индексом массы тела, окружностью талии, окружностью бедер, продолжительностью грудного вскармливания, показателями углеводного (глюкоза, инсулин, индекс HOMA-IR) и липидного (общий холестерин, триглицериды, липопротеиды низкой плотности, липопротеиды очень низкой плотности, липопротеиды высокой плотности) обмена, СРБ – с другой.

Выводы. Микробиота толстой кишки у пациентов с ожирением, характеризуется изменениями провоспалительного характера. В наибольшей степени эти изменения свойственны для метаболически нездорового фенотипа ожирения. Очевидно, что необходимы дальнейшие исследования для определения механизмов, лежащих в основе влияния бактериально-грибковых ассоциаций на обмен веществ у лиц с ожирением, поскольку эти механизмы, вероятно, играют ключевую роль в развитии метаболических заболеваний.

Ключевые слова. Микробиота кишечника, «Колонофлор-16 (премиум)», ожирение, метаболический синдром.

INTRODUCTION

The prevalence of obesity and related diseases is increasing worldwide[1]. Obesity is a major risk factor for metabolic diseases. Recently, the concept of "metabolically healthy obesity" (MHO) has been actively used, which means the absence of components of the metabolic syndrome in an obese person [1]. People with MHO are characterized by a lower degree of systemic inflammation, more favorable profiles of the immune system and liver function [2]. However, MHO is a condition that eventually develops into metabolic syndrome (MS). Thus, approximately 30 to 50 % of people with MHO develop "metabolically unhealthy obesity" (MUHO) over a period of 4–20 years [3].

Recently, the theory of the involvement of the intestinal microbiota in the development of obesity and metabolic syndrome has been increasingly discussed. This was initiated by a series of studies conducted by Cani et al. in 2007. The scientists have found that chronic consumption of high-fat diet (HFD) products leads to increased permeability of the intestinal barrier, resulting in higher permeability to byproducts of bacterial metabolism and others antigens, in particular bacterial lipopolysaccharides (LPS), into the systemic circulation with the development of so-called metabolic endotoxemia [4]. Bacterial LPS, activating TLRs (Toll-like receptors), cause an immune response that disturbs insulin sensitivity, and inhibit the normal glycemic response. Thus, the central role of intestinal permeability in chronic low-grade inflammation makes the microbiota a central link in the initiation of metabolic disorders. To date, although we can clearly establish a causal relationship between intestinal microbial profiles and metabolic syndrome in animal experiments, the association between them in the human body does not seem so certain and requires further study. Therefore, further clinical studies are needed to clarify the role of the microbiota in the formation of metabolic disorders, as well as in the prevention and treatment of metabolic syndrome.

The objective of the study was to investigate the features of the colon microbiota, as well as the associations of microbial representatives with anthropometric, anamnestic and biochemical parameters in young patients with metabolic syndrome.

MATERIALS AND METHODS

On the basis of the clinic of Tyumen State Medical University, a single–center, one-stage, cross-sectional, controlled study was conducted with the participation of 118 young people: 87 patients with obesity and 31 patients with a normal body weight who formed the control group ("C"). Obese patients, in turn, were divided into two groups depending on the presence or absence of metabolic syndrome. 43 obese patients (49.4 %) were metabolically healthy and were assigned to the "MS-" group, whereas 44 patients (50.6 %) had metabolic syndrome and were assigned to the "MS+" group. The stratification of the groups was carried out based on the NCEP ATP III criteria.

[1] World Obesity Atlas. World Obesity Federation; 2022, available at: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022

Inclusion criteria for obese patients. Age from 18 to 44 years, signed informed consent, BMI over 30 kg/m^2, absence of somatic pathology.

Inclusion criteria for persons in the control group. Age from 18 to 44 years, signed informed consent, normal body weight (BMI 18.5–24.9 kg/m^2), absence of somatic pathology.

Criteria for non-inclusion. Acute inflammatory diseases during the month before the study, the use of drugs affecting microbial composition and intestinal motility within 3 months before the study, pregnancy/lactation, alcohol abuse.

Each participant was provided with a questionnaire, specially designed in accordance with the objectives of this study. All the participants underwent anthropometric examinations.

The biochemical examination included the determination of total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), triglycerides (TG), glucose levels, C-reactive protein (CRP). The study of biochemical parameters was carried out on the BS-380 Mindray biochemical analyser (China). The level of glycated hemoglobin was determined with the EKF-diagnostic GmbH reagent (Germany) using the Quo-Lab Analyser System (Germany). The insulin level was detected with a set of ELISA reagents manufactured by DRG Techsystems (ЗАО «ДРГ Техсистемс», Russia). All the participants were examined for insulin resistance (HOMA-IR) and evaluation of the functioning of β-cells (HOMA-β). The assessment of the condition of microbiota of the colon was carried out using quantitative real-time polymerase chain reaction (qPCR) with a set of reagents "Colonoflor-16 Premium" by Alfalab LLC ("Колонофлор-16 премиум", ООО «АльфаЛаб», Russia) with fluorescent detection of the results of amplification BioRad CFX96 (USA). The analyses were performed on the basis of the clinical and biochemical laboratory of the Multidisciplinary University Clinic of the Tyumen State Medical University of the Ministry of Health of the Russian Federation (head of the laboratory – Candidate of Medical Sciences N.Yu. Yuzhakova).

This study was conducted in accordance with the protocol approved by the Ethics Committee at the Tyumen State Medical University of the Ministry of Health of the Russian Federation dated March 13, 2023.

For statistical calculations, the Microsoft Excel 2010 and IBM SPSS Statistics 26.0 software was used. The data are presented in the form of median and interquartile range (Me [Q_{25}; Q_{75}]) using the Mann – Whitney and Kruskal–Wallis tests. Spearman's rank correlation method was used to evaluate and identify the associations between variables. The Bonferroni correction was used for multiple comparisons. The results were evaluated as statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The average age of patients in the "MS-" group was 25 [22; 31] years, in the "MS+" group – 32.5 [25; 40] years ($p = 0.002$). The

average age of the control group was 29 [26; 34] years, which did not significantly differ from the "MS+" and "MS-" groups ($p = 0.310$ and $p = 0.100$, respectively). The study participants in all three groups did not significantly differ in gender. Obese patients in the "MS-" and "MS+" groups did not significantly differ in BMI ($p = 0.848$) waist circumference (WC) (in men, $p = 0.898$, in women, $p = 0.225$), hip circumference (HC) (in men, $p = 0.976$, in women, $p = 0.513$), systolic blood pressure ($p = 0.506$), and diastolic blood pressure ($p = 0.319$), while in comparison with the control group, there were statistically significant differences in all the listed parameters.

According to the level of TC, groups "C", "MS-" and "MS+" had no statistically significant differences ($p = 0.310$). LDL levels did not differ significantly in the "MS-" and "MS+" groups ($p = 0.413$), however, they were statistically higher in the "MS-" ($p = 0.016$) and "MS+" ($p = 0.001$) groups, compared with the "C" group. All three groups differed statistically significantly from each other in terms of VLDL, HDL, TG, as well as the ATG index ($p = <0.001$). Thus, in the patients with a metabolically unhealthy obesity phenotype, the most atherogenic plasma lipid profile was revealed, characterized by a significant increase in LDL cholesterol, VLDL cholesterol, TG and ATG index, as well as a significant decrease in HDL. Glucose levels differed significantly between groups "C" and "MS+" ($p < 0.001$), "MS-" and "MS+" ($p = 0.015$), whereas in groups "C" and "MS-" there were no statistically significant differences ($p = 0.140$). The levels of insulin, calculated HOMA-IR, HOMA-β indices, as well as CRP differed statistically significantly between groups "C" and "MS-" ($p < 0.001$), "C" and "MS+" ($p < 0.001$), while the differences between groups "MS-" and "MS+" were statistically insignificant. However, it is necessary to note a distinct tendency towards the increase of insulin levels, the HOMA-IR index and HbA1c in the "MS+" patients.

When analyzing the intestinal microbiota, differences were found depending on the metabolic status in obese patients (Table). When comparing the microbiota of the "C" and "MS+" groups, it was revealed that *F. nucleatum* (*Fusobacteriaceae* family) was statistically more often found in "MS+" patients (40.5 %), compared with those from the "C" group (10.3 %) ($p = 0.018$). It is known that *Fusobacterium* spp. synthesize a significant amount of butyrate, which is the main source of energy for colonocytes, on the other hand, *F. Nucleatum* is a powerful proinflammatory and protumorogenic agent [5] due to increased secretion of cytokines such as IL-1β, IL-6 and IL-17, increased expression of various TLRs, activation of the STAT3 (signal transducer and activator of transcription 3) signaling pathway, increased proliferation of $CD4^+$ T cells and differentiation into Th-1 and Th-17 [6]. This microorganism is able to disrupt the integrity of the epithelial barrier and increase intestinal permeability by suppressing the expression of the tight junction proteins – zonula occludens-1 (ZO-1) and occludin, which are the markers of the barrier function of the intestinal mucosa. There are differences in the prevalence of *A. mucini-*

phila (family *Akkermansiaceae*) between the groups ($p = 0.013$). Although the differences between groups "C" and "MSMS-" and "MS+" ($p = 0.165$) are unreliable, the statistical significance between groups "C" and "MS+" could not be calculated due to insufficient sampling. However, *A. muciniphila* is an important species capable of maintaining intestinal barrier function, thereby reducing its permeability and translocation of antigenic structures [7]. Therefore, this type of metabolic disorders deserves further study.

When quantifying the number of microorganisms, there was a statistically significant decrease in bacteria of the *Bifidobacterium* genus (*Bifidobacteriaceae* family) ($p = 0.040$) in the "MS+" group. As shown in numerous animal studies, representatives of the genus *Bifidobacterium* have a pronounced anti–inflammatory effect due to their ability to synthesize antibacterial peptides, such as bacteriocins, linoleic acid, acetate.

Animal studies have revealed that the addition of *Bifidobacterium* spp. reduces bacterial translocation, thereby leading to a decrease in endotoxemia and normalization of metabolic parameters [8]. In a randomized, double-blind, placebo-controlled, parallel-group study involving persons with abdominal obesity, Anna Pedret et al. discovered that the intake of *Bifidobacterium Animalis* subsp. led to a decrease in waist circumference (WC), waist circumference to height ratio (WC/H), conicity index (CI), body mass index (BMI) [9]. In the "MS+" group, a statistically significant decrease in another genus of bacteria *Prevotella* (*Prevotellaceae* family) was also found ($p = 0.036$). These bacteria are involved in ensuring the integrity of the intestinal barrier, which is due to their ability to destroy mucins, which make up the mucosal layer surrounding the walls of the digestive tract. At the same time, bacteria of this genus have pro-inflammatory properties realized through the ability to stimulate the production of pro-inflammatory cytokines IL-8, IL-6 by epithelial cells [10].

In the "MS+" patients, the number of *Faecalibacterium prausnitzii* (*F. prau*) ($p = 0.030$) (*Ruminococcaceae* family) was significantly reduced. The number of *F. prau* was also lower in comparison with the control group ($p = 0.006$). As is known, *F.prau* is one of the main butyrate-producing bacteria, which is associated with its pronounced anti-inflammatory properties. In particular, the anti-inflammatory effect was demonstrated in Caco-2 cells in a study in mice with induced colitis by Sokol et al. [11]. Metabolites secreted by *F.prau* blocked the activation of "kappa-bi" nuclear factor (NF-κB) and reduced the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukins IL-12 and IL-8, while stimulating the secretion of anti-inflammatory IL-10. The study by Furet et al. [12] revealed a stable correlation between *F. prau* and chronic inflammation, which demonstrated a negative relationship with serum concentrations of circulating inflammatory markers such as C-reactive protein (CRP) and IL-6. In addition, *F. prau* play an important role in the intestinal barrier integrity

Comparison of quantitative indicators of microbial phylotypes in the feces of healthy people and patients with metabolic health issues (*Me* [Q_1; Q_3])

Phylotypes, quantitative indicators	Control, $n = 31$	"MS-", $n = 43$	"MS+", $n = 44$	p
Total bacterial mass	$1 \cdot 10^{13}$ [$4 \cdot 10^{12}$; $3 \cdot 10^{13}$]	$1 \cdot 10^{13}$ [$3 \cdot 10^{12}$; $4 \cdot 10^{13}$]	$1 \cdot 10^{13}$ [$2 \cdot 10^{12}$; $4 \cdot 10^{13}$]	0.840
Lactobacillus spp.	$1 \cdot 10^{7}$ [$5 \cdot 10^{6}$; $3 \cdot 10^{7}$]	$9 \cdot 10^{6}$ [$2 \cdot 10^{6}$; $3 \cdot 10^{7}$]	$4 \cdot 10^{6}$ [$3 \cdot 10^{5}$; $2 \cdot 10^{7}$]	0.331
Bifidobacterium spp.	$3 \cdot 10^{10}$ [$1 \cdot 10^{9}$; $1 \cdot 10^{11}$]	$2 \cdot 10^{10}$ [$4 \cdot 10^{9}$; $2 \cdot 10^{11}$]	$5 \cdot 10^{9}$ [$4 \cdot 10^{8}$; $4 \cdot 10^{10}$]	0.022 $p_{C-MS-} = 1.000$ $p_{C-MS+} = 0.078$ $p_{MS-MS+} = 0.040$
Escherichia coli	$2 \cdot 10^{8}$ [$4 \cdot 10^{7}$; $7 \cdot 10^{8}$]	$6 \cdot 10^{8}$ [$1 \cdot 10^{8}$; $2 \cdot 10^{9}$]	$3 \cdot 10^{8}$ [$2 \cdot 10^{7}$; $2 \cdot 10^{9}$]	0.170
Bacteroides spp.	$1 \cdot 10^{13}$ [$4 \cdot 10^{12}$; $2 \cdot 10^{13}$]	$1 \cdot 10^{13}$ [$3 \cdot 10^{12}$; $3 \cdot 10^{13}$]	$1 \cdot 10^{13}$ [$2 \cdot 10^{12}$; $3 \cdot 10^{13}$]	0.928
Faecalibacterium prausnitzii	$8 \cdot 10^{11}$ [$1 \cdot 10^{11}$; $2 \cdot 10^{12}$]	$3 \cdot 10^{11}$ [$1 \cdot 10^{11}$; $1 \cdot 10^{12}$]	$9.5 \cdot 10^{10}$ [$7 \cdot 10^{9}$; $4 \cdot 10^{11}$]	0.003 $p_{C-MS-} = 1.000$ $p_{C-MS+} = 0.006$ $p_{MS-MS+} = 0.030$
Eubacterium rectale	$8 \cdot 10^{9}$ [$4 \cdot 10^{8}$; $4 \cdot 10^{10}$]	$1 \cdot 10^{10}$ [$1.5 \cdot 10^{9}$; $1 \cdot 10^{11}$]	$3 \cdot 10^{9}$ [$8.5 \cdot 10^{7}$; $5 \cdot 10^{10}$]	0.171
Acinetobacter spp.	$8.5 \cdot 10^{6}$ [$2 \cdot 10^{6}$; $3 \cdot 10^{7}$]	$2 \cdot 10^{7}$ [$3 \cdot 10^{6}$; $7 \cdot 10^{7}$]	$6 \cdot 10^{6}$ [$2 \cdot 10^{6}$; $5 \cdot 10^{7}$]	0.294
Roseburia inulinivorans	$7 \cdot 10^{9}$ [$1 \cdot 10^{8}$; $2 \cdot 10^{10}$]	$7 \cdot 10^{9}$ [$5 \cdot 10^{8}$; $2 \cdot 10^{10}$]	$2 \cdot 10^{9}$ [$3 \cdot 10^{7}$; $2 \cdot 10^{10}$]	0.192
Prevotella spp.	$3 \cdot 10^{7}$ [$4 \cdot 10^{6}$; $4 \cdot 10^{10}$]	$3 \cdot 10^{10}$ [$1 \cdot 10^{9}$; $1 \cdot 10^{12}$]	$1 \cdot 10^{9}$ [$4 \cdot 10^{6}$; $2 \cdot 10^{11}$]	0.004 $p_{C-MS-} = 0.006$ $p_{C-MS+} = 0.374$ $p_{MS-MS+} = 0.036$
Bacteroides thetaomicron	$2 \cdot 10^{10}$ [$4 \cdot 10^{8}$; $4 \cdot 10^{10}$]	$7 \cdot 10^{9}$ [$7 \cdot 10^{8}$; $2 \cdot 10^{10}$]	$3 \cdot 10^{9}$ [$2 \cdot 10^{8}$; $2 \cdot 10^{10}$]	0.654
Ruminococcus spp.	$2 \cdot 10^{8}$ [$3.5 \cdot 10^{6}$; $1 \cdot 10^{9}$]	$1.5 \cdot 10^{8}$ [$1 \cdot 10^{7}$; $3.5 \cdot 10^{9}$]	$2 \cdot 10^{8}$ [$9 \cdot 10^{6}$; $3 \cdot 10^{9}$]	0.743
Streptococcus spp.	$6.5 \cdot 10^{6}$ [$4 \cdot 10^{5}$; $4 \cdot 10^{7}$]	$3.5 \cdot 10^{7}$ [$4 \cdot 10^{6}$; $8 \cdot 10^{8}$]	$7 \cdot 10^{6}$ [$1 \cdot 10^{6}$; $1 \cdot 10^{8}$]	0.085
Blautia spp.	$2 \cdot 10^{7}$ [$2 \cdot 10^{6}$; $2 \cdot 10^{8}$]	$1 \cdot 10^{8}$ [$6 \cdot 10^{7}$; $2 \cdot 10^{9}$]	$1 \cdot 10^{8}$ [$3 \cdot 10^{7}$; $4 \cdot 10^{9}$]	0.313
Enterobacter spp.	$4 \cdot 10^{7}$ [$4 \cdot 10^{5}$; $2 \cdot 10^{8}$]	$2 \cdot 10^{7}$ [$5 \cdot 10^{6}$; $2 \cdot 10^{8}$]	$5 \cdot 10^{6}$ [$8 \cdot 10^{5}$; $4 \cdot 10^{7}$]	0.424
Staphylococcus aureus	$2.5 \cdot 10^{6}$ [$1 \cdot 10^{6}$; $1 \cdot 10^{7}$]	$1.65 \cdot 10^{7}$ [$1.5 \cdot 10^{6}$; $8.5 \cdot 10^{7}$]	$4.5 \cdot 10^{6}$ [$1.5 \cdot 10^{6}$; $8.5 \cdot 10^{6}$]	0.752
Parvimonas micra	$2.5 \cdot 10^{8}$ [$7.5 \cdot 10^{5}$; $4.5 \cdot 10^{16}$]	$3 \cdot 10^{6}$ [$9 \cdot 10^{5}$; $1 \cdot 10^{11}$]	$3 \cdot 10^{6}$ [$1 \cdot 10^{6}$; $1.7 \cdot 10^{8}$]	0.987
Fusobacterium nucleatum	$2 \cdot 10^{5}$ [$2 \cdot 10^{5}$; $7 \cdot 10^{6}$]	$1 \cdot 10^{6}$ [$5 \cdot 10^{5}$; $4 \cdot 10^{6}$]	$8 \cdot 10^{5}$ [$3 \cdot 10^{5}$; $3 \cdot 10^{6}$]	0.578
Escherichia coli enteropathogenic	$1.2 \cdot 10^{4}$ [$4 \cdot 10^{3}$; $2 \cdot 10^{4}$]	$2 \cdot 10^{6}$ [$7 \cdot 10^{5}$; $2 \cdot 10^{6}$]	$3 \cdot 10^{4}$ [$2 \cdot 10^{3}$; $1 \cdot 10^{8}$]	–
Akkermansia muciniphila		$1 \cdot 10^{10}$ [$3 \cdot 10^{6}$; $4 \cdot 10^{10}$]	–	–

system by maintaining tight junction proteins, stimulating ZO-1 expression and proliferation of colon epithelial cells [13].

During the correlation analysis, numerous interrelations of certain microorganisms with anthropometric, biochemical parameters and anamnestic data were revealed. A negative correlation of the total bacterial mass was found (r = -0.336; p = 0.030), *Lactobacillus* spp. (r = -0.365; p = 0.018), *E. coli* (r = -0.310; p = 0.046), *Bacteroides* (r = -0.305; p = 0.050), *Acinetobacter* (r = -0.469; p = 0.002), a positive correlation of *S. aureus* (r = 0.614; p = 0.034) and *P. micra* (r = 0.715; p = 0.046) with age. These data can be considered an indirect confirmation of the hypothesis of a decrease in the diversity and active properties of the microbiota with an increase of patients' age.

The qualitative and quantitative composition of microbiota phyla demonstrated close correlations with anthropometric parameters in obese patients. Thus, positive correlations were found between BMI with *Bifidobacterium* (r = 0.375; p = 0.014), *Bacteroides* (r = 0.310; p = 0.045), *Acinetobacter* (r = 0.342; p = 0.027), and a negative correlation *with F. nucleatum* (r = -0.522; p = 0.031). The value of WC was positively correlated with *Lactobacillus* spp. (r = 0.328; p = 0.034), *Bifidobacterium* spp. (r = 0.412; p = 0.007), a negative correlation was found with *Ruminococcus* spp. (r = -0.387; p = 0.031). The value of HC was positively correlated with the total bacterial mass (r = 0.368; p = 0.017), *Lactobacillus* spp. (r = 0.387; p = 0.011), *Bifidobacterium* spp. (r = 0.443; p = 0,003), *Bacteroides* spp. (r = 0,335; p = 0,030), *B. thetaomicron* (r = 0,359; p = 0,029), *Acinetobacter* spp. (r = 0,388; p = 0,011), *E. rectale* (r = 0,316; p = 0,047).

The decisive role of breastfeeding in shaping the qualitative and quantitative composition of the microbiota was confirmed by the presence of negative correlation dependencies with *Lactobacillus* spp. (r = -0.335; p = 0.035), *B. thetaomicron* (r = -0.356; p = 0.036), and *F. nucleatum* (r = -0.573; p = 0.026). The study also established a positive correlation of *Blautia* spp. with glucose levels (r = 0.419; p = 0.041), *E. rectale* with insulin (r = 0.357; p = 0.024) and the HOMA-IR index (r = 0.343; p = 0.030), as well as *Streptococcus* spp. with the duration of obesity (r = 0.537; p = 0.004).

Significant correlations were found with lipid metabolism indicators: *S. aureus* positively correlated with TG (r = 0.749; p = 0.005), HDL (r = 0.597; p = 0.040), and LDL (r = 0.749; p = 0.005). *M. Smithii* had a positive correlation with HDL (r = 0.810; p = 0.015). Negative correlation dependencies were found for *Acinetobacter* spp. with TC (r = -0.319; p = 0.039) and TG (r = -0.316; p = 0.042), as well as for *Streptococcus* spp. with TC (r = -0.402; p = 0.038). The identified correlation dependencies related to such an important factor characterizing inflammation, as CRP, are also noteworthy. The analysis revealed a positive correlation of CRP with BMI (r = 0.317; p = 0.036), as well as CRP with *Acinetobacter* spp. (r = 0.314; p = 0.043).

CONCLUSION

The microbiota of the large intestine in patients with obesity is characterized by changes of a pro-inflammatory nature. These

changes are most pronounced in the metabolically unhealthy phenotype of obesity. In particular, in the "MS+" group, compared to the "C" group, *F. nucleatum* (*Fusobacteriaceae* family) was statistically more frequently identified (40.5 %). Additionally, in the "MS+" group, compared to the "MS-" group, there was a statistically significant decrease in the bacteria of the genera *Bifidobacterium* (*Bifidobacteriaceae* family) and *Prevotella* (*Prevotellaceae* family). At the species level, the quantity of *F. prau* (*Ruminococcaceae* family) was significantly reduced in the "MS+" group. Correlations were found between representatives of the microbiota and age, BMI, WC, obesity duration, duration of breastfeeding, indicators of carbohydrate metabolism (glucose, insulin, HOMA-IR index), lipid metabolism (TC, TG, LDL, HDL), and CRP.

Clearly, further research is needed to determine the mechanisms underlying the influence of bacterial-fungal associations on metabolism in persons with obesity, as these mechanisms likely play a key role in the development of metabolic diseases.

References

1. *Drapkina O.M., Samorodskaya I.V., Starinskaya M.A., Kim O.T., Neymark A.E.* Ozhirenie: otsenka i taktika vedeniya patsientov. Kollektivnaya monografiya. Moscow: FGBU «NMICz TPM» Minzdrava Rossii; OOO «Siliceya-Poligraf»; 2021 (in Russian).

2. *Iacobini C., Pugliese G., Blasetti Fantauzzi C., Federici M., Menini S.* Metabolically healthy versus metabolically unhealthy obesity. Metabolism. 2019; 92: 51–60. DOI: 10.1016/j.metabol.2018.11.009

3. *Kouvari M., Panagiotakos D.B., Yannakoulia M., Georgousopoulou E., Critselis E., Chrysohoou C., Tousoulis D., Pitsavos C.* ATTICA Study Investigators. Transition from metabolically benign to metabolically unhealthy obesity and 10-year cardiovascular disease incidence: The ATTICA cohort study. Metabolism. 2019; 93: 18–24. DOI: 10.1016/j.metabol.2019.01.003

4. *Cani P.D., Amar J., Iglesias M.A., Poggi M., Knauf C., Bastelica D., Neyrinck A.M., Fava F., Tuohy K.M., Chabo C., Waget A., Delmée E., Cousin B., Sulpice T., Chamontin B., Ferrières J., Tanti J.F., Gibson G.R., Casteilla L., Delzenne N.M., Alessi M.C., Burcelin R.* Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes. 2007; 56 (7): 1761–1772. DOI: 10.2337/db06-1491

5. *Engevik M.A., Danhof H.A., Ruan W., Engevik A.C., Chang-Graham A.L., Engevik K.A., Shi Z., Zhao Y., Brand C.K., Krystofiak E.S., Venable S., Liu X., Hirschi K.D., Hyser J.M., Spinler J.K., Britton R.A., Versalovic J.* Fusobacterium nucleatum Secretes Outer Membrane Vesicles and Promotes Intestinal Inflammation. mBio. 2021; 12 (2): e02706–20. DOI: 10.1128/mBio.02706-20

6. *Liu H., Hong X.L., Sun T.T., Huang X.W., Wang J.L., Xiong H.* Fusobacterium nucleatum exacerbates colitis by damaging epithelial barriers and inducing aberrant inflammation. J Dig Dis. 2020; 21 (7): 385–398. DOI: 10.1111/1751-2980.12909

7. *Depommier C., Everard A., Druart C., Plovier H., Van Hul. M., Vieira-Silva S., Falony G., Raes J., Maiter D., Delzenne N.M., de Barsy M., Loumaye A., Hermans M.P., Thissen J.P., de Vos W.M., Cani P.D.* Sup-

plementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nat Med. 2019; 25 (7): 1096–1103. DOI: 10.1038/s41591-019-0495-2

8. *Cani P.D., Neyrinck A.M., Fava F., Knauf C., Burcelin R.G., Tuohy K.M., Gibson G.R., Delzenne N.M.* Selective increases of bifidobacteria in gut microflora improve high-fat-diet-induced diabetes in mice through a mechanism associated with endotoxaemia. Diabetologia. 2007; 50 (11): 2374–2383. DOI: 10.1007/s00125-007-0791-0

9. *Pedret A., Valls R.M., Calderón-Pérez L., Llauradó E., Companys J., Pla-Pagà L., Moragas A., Martín-Luján F., Ortega Y., Giralt M., Caimari A., Chenoll E., Genovés S., Martorell P., Codoñer F.M., Ramón D., Arola L., Solà R.* Effects of daily consumption of the probiotic Bifidobacterium animalis subsp. lactis CECT 8145 on anthropometric adiposity biomarkers in abdominally obese subjects: a randomized controlled trial. Int J Obes (Lond). 2019; 43 (9): 1863–1868. DOI: 10.1038/s41366-018-0220-0

10. *Nichols F.C., Yao X., Bajrami B., Downes J., Finegold S.M., Knee E., Gallagher J.J., Housley W.J., Clark R.B.* Phosphorylated dihydroceramides from common human bacteria are recovered in human tissues. PLoS One. 2011; 6 (2): e16771. DOI: 10.1371/journal.pone.0016771

11. *Sokol H., Pigneur B., Watterlot L., Lakhdari O., Bermúdez-Humarán L.G., Gratadoux J.J., Blugeon S., Bridonneau C., Furet J.P., Corthier G., Grangette C., Vasquez N., Pochart P., Trugnan G., Thomas G., Blottière H.M., Doré J., Marteau P., Seksik P., Langella P.* Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A. 2008; 105 (43): 16731–16736. DOI: 10.1073/pnas.0804812105

12. *Furet J.P., Kong L.C., Tap J., Poitou C., Basdevant A., Bouillot J.L., Mariat D., Corthier G., Doré J., Henegar C., Rizkalla S., Clément K.* Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. Diabetes. 2010; 59 (12): 3049–3057. DOI: 10.2337/db10-0253

13. *Sugawara Y., Kanazawa A., Aida M., Yoshida Y., Yamashiro Y., Watada H.* Association of gut microbiota and inflammatory markers in obese patients with type 2 diabetes mellitus: post hoc analysis of a synbiotic interventional study. Biosci Microbiota Food Health. 2022; 41 (3): 103–111. DOI: 10.12938/bmfh.2021-081

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CLINICAL AND NON-HEMORRHAGIC NEUROIMAGING INDICATORS OF PROBABLE CEREBRAL AMYLOID ANGIOPATHY AS A CAUSE OF NON-TRAUMATIC LOBAR HEMATOMAS

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КЛИНИЧЕСКИЕ И НЕГЕМОРРАГИЧЕСКИЕ НЕЙРОВИЗУАЛИЗАЦИОННЫЕ ИНДИКАТОРЫ ВЕРОЯТНОЙ ЦЕРЕБРАЛЬНОЙ АМИЛОИДНОЙ АНГИОПАТИИ КАК ПРИЧИНЫ НЕТРАВМАТИЧЕСКИХ ЛОБАРНЫХ ГЕМАТОМ

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Objective. To identify clinical and non-hemorrhagic neuroimaging indicators of probable CAA in patients with acute non-traumatic lobar hematomas. Cerebral amyloid angiopathy (CAA) is a microangiopathy affecting the leptomeningial and cortical vessels of the brain due to the deposition of pathological β-amyloid in them. The most common clinical manifestation of CAA is lobar hematomas (LH) – spontaneous intracerebral hemorrhages localized between the cerebral cortex and basal ganglia. LH can also occur in hypertensive cere-

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bral microangiopathy (hCMA) in patients with arterial hypertension. Since the tactics of managing patients with CAA and hCMA differ, it is important to determine the genesis of LH correctly.

Materials and methods. A comparative analysis of clinical and neuroimaging characteristics of acute non-traumatic hypertension in 32 patients with probable CAA and hCMA was carried out. Along with neurological examination and neuroimaging, all patients underwent a study using the Montreal Cognitive Assessment Scale and the Benson Complex Figure Test to reveal visuospatial impairments. The diagnosis of probable CAA was carried out in accordance with the updated Boston criteria of 2010, the diagnosis of hCMA was based on clinical data, anamnesis and results of neuroimaging of the brain.

Results. Probable CAA was diagnosed in 16 patients, and in all these cases it was combined with hCMA (1st subgroup). Isolated hCMA as a cause of LH was also observed in 16 patients (2nd subgroup). Patients of subgroup 1 were statistically significantly more likely to have clinically pronounced visual impairments, performed the MoCA subtest and the Benson Complex Figure Test worse, and the overall assessment of their cognitive functions according to Mo SA was lower than in patients of subgroup 2. According to neuroimaging data, in the 1st subgroup of patients, an expansion of perivascular spaces in the semi-oval center and a zero or negative value of the front-occipital gradient were more often detected. The application of the logistic regression method made it possible to integrate potential CAA indicators and create a prognostic model for revealing this pathology in patients with hypertension.

Conclusions. Clinically pronounced disorders of primary and higher visual functions, a negative front-occipital gradient and expansion of perivascular spaces in the semi-oval centers can serve as indicators of probable CAA in patients with acute lobar hematoma. On admission of such patients to the vascular center, it is advisable to include iron-sensitive pulse sequences in the neuroimaging screening protocol to verify the diagnosis of CAA.

Keywords. Cerebral amyloid angiopathy, lobar hematoma, intracerebral hemorrhage, hypertensive microangiopathy, perivascular spaces, front-occipital gradient.

Цель. Выявление клинических и негеморрагических нейровизуализационных индикаторов вероятной церебральной амилоидной ангиопатии у пациентов с острыми нетравматическими лобарными гематомами. Церебральная амилоидная ангиопатия (ЦАА) – микроангиопатия, поражающая лептоменингиальные и кортикальные сосуды головного мозга вследствие отложения в них патологического β-амилоида. Наиболее частое клиническое проявление ЦАА – лобарные гематомы (ЛГ), т.е. спонтанные внутримозговые кровоизлияния, локализующиеся между корой головного мозга и базальными ганглиями. ЛГ также встречаются и при гипертензивной церебральной микроангиопатии (гЦМА) у больных артериальной гипертензией. Поскольку тактика ведения пациентов с ЦАА и гЦМА различается важно правильно определить генез ЛГ.

Материалы и методы. Проведен сравнительный анализ клинико-нейровизуализационных характеристик острых нетравматических ЛГ у 32 человек с вероятной ЦАА и гЦМА. Наряду с неврологическим осмотром и нейровизуализацией всем пациентам проводилось исследование с применением шкалы МоСА и теста сложной фигуры Бенсона для выявления зрительно-пространственных нарушений. Диагностика вероятной ЦАА осуществлялась в соответствии с обновленными Бостонскими критериями 2010 г., диагностика гЦМА основывалась на клинико-анамнестических данных и результатах нейровизуализации.

Результаты. Вероятная ЦАА была диагностирована у 16 больных, и во всех случаях сочеталась с гЦМА (1-я подгруппа). Изолированная гЦМА как причина ЛГ также отмечалась у 16 больных (2-я подгруппа). Больные 1-й подгруппы статистически значимо чаще имели клинически выраженные зрительные нарушения, хуже выполняли субтест МоСА и тест сложной фигуры Бенсона, общая оценка когнитивных функций по МоСА была ниже, чем во 2-й подгруппе. По данным нейровизуализации в 1-й подгруппе пациентов чаще обнаруживалось расширение периваскулярных пространств в полуовальном центре и нулевое или отрицательное значение фронтоокципитального градиента. Применение метода логистической регрессии позволило интегрировать потенциальные индикаторы ЦАА и создать прогностическую модель для выявления этой патологии у пациентов с ЛГ.

Выводы. Клинически выраженные нарушения первичных и высших зрительных функций, отрицательный фронтоокципитальный градиент и расширение периваскулярных пространств в полуовальных центрах могут служить индикаторами наличия вероятной ЦАА у больных с острой ЛГ. Таким пациентам при поступлении в сосудистый центр в протокол нейровизуализационного обследования целесообразно включать железочувствительные импульсные последовательности для верификации диагноза ЦАА.

Ключевые слова. Церебральная амилоидная ангиопатия, лобарная гематома, внутримозговое кровоизлияние, гипертензивная микроангиопатия, периваскулярные пространства, фронтоокципитальный градиент.

INTRODUCTION

Hemorrhagic stroke accounts for 10–15 % of all types of cerebral circulation disorders, with intracerebral hemorrhages being the primary component. The medical and social significance of intracerebral hemorrhages (non-traumatic intracerebral hematomas) is underscored by a mortality rate that reaches 50 % or higher, while the disability rate among surviving patients exceeds 3.0 per 1000 population [1].

The most common cause of intracerebral hemorrhages (up to 35 %) is arterial hypertension and the associated hypertensive cerebral microangiopathy (hCMA). It is important to differentiate this pathology from cerebral amyloid angiopathy (CAA), which is a less common, but possible (up to 20 %) cause of intracerebral hematomas in the elderly [2].

The importance of diagnosing CAA as a cause of intracerebral hematomas is determined by the specific management strategies for patients and the prognosis of the disease. In particular, with CAA, the risk of recurrent intracerebral hemorrhage is significantly higher, and antihypertensive therapy is not as effective in preventing it compared to hCMA [3]. Furthermore, patients with CAA have restrictions on the use of antithrombotic therapy and statins for the prevention of ischemic stroke, which is also a risk in both CAA and hCMA [4; 5].

Cerebral amyloid angiopathy (CAA) is a pathology of the brain vessels characterized by the deposition of beta-amyloid in the walls of medium and small-caliber arteries (up to 2 mm in diameter), arterioles, and capillaries of the cerebral cortex, leptomeningeal vessels, and some other vessels, and less frequently in venules [6]. CAA is one of the common causes of strokes [7]. Since CAA primarily affects the cortical and leptomeningeal vessels, the most common manifestations of CAA are multiple superficial microhemorrhages and lobar (i.e., localized in the cortical or subcortical areas of the brain) intracerebral hematomas [8].

The diagnosis of CAA is established based on the Modified Boston Criteria of 2010, which include patients' age over 55 years, results from clinical examinations, laboratory data, and neuroimaging findings (CT or MRI of the brain) [9]. According to the currently applicable Modified Boston Criteria, neuroimaging indicators of CAA include only hemorrhagic markers, specifically – single or multiple lobar hematomas (LH), multiple cortical-subcortical microhemorrhages, and focal or disseminated cortical superficial siderosis (cSS).

The identification of LH in a patient based on CT or MRI data increases the likelihood of CAA; however, in the absence of information about cortical microhemorrhages, this is insufficient for the diagnosis of CAA [10]. At the same time, recognizing small cortical hemorrhages and cSS requires the use of additional MRI pulse sequences, which are not employed in most vascular

centers during the initial examination of patients with strokes. All of the above highlights the importance of searching for such signs, the detection of which would indicate the need for additional inclusion of MRI sequences sensitive to microhemorrhages and their transformation products (SWI, SWAN, or T2*GRE) in the neuroimaging assessment of patients with LH [11].

Since CAA is characterized by LH, which are more often localized in the posterior regions of the brain, the corresponding "indicator" clinical signs of a high likelihood of CAA may include acutely occurring visual and visuospatial disturbances. As non-hemorrhagic neuroimaging biomarkers indicative of a high probability of CAA, it is appropriate to discuss the enlargement of perivascular spaces (PVS) in the centrum semiovale, as well as the predominance of white matter hyperintensity (WMH) in the posterior parts of the brain, evidenced by a negative fronto-occipital gradient (FOG). At the same time, the informativeness of the listed signs for differentiating CAA and hCMA as causes of LH has not been studied [12].

The objective of the study was to identify clinical and non-hemorrhagic neuroimaging indicators of probable cerebral amyloid angiopathy in patients with acute non-traumatic lobar hematomas.

MATERIALS AND METHODS

Thirty-two patients diagnosed with acute hemorrhagic stroke were observed during examination and treatment at the Nizhny Novgorod Regional Vascular Center. The diagnosis of "probable CAA" was made according to the Modified Boston Criteria of 2010, based on the presence of the following signs: age over 55 years; presence of multiple hemorrhagic cerebral lesions; restricted localization of hemorrhages in cortical and subcortical (lobar) regions of the brain; and the absence of other causes of bleeding (arteriovenous malformation, traumatic brain injury, brain tumour, vasculitis, anticoagulation, etc.) [9].

The diagnosis of hCMA was established in the presence of a verified history of arterial hypertension, clinical and neuroimaging signs of cerebral microangiopathy, and the establishment of a causal relationship between them, while the manifestations of the disease did not comply with the Boston criteria for CAA [9].

All patients underwent neurological examination, neuropsychological assessment, and neuroimaging studies. The neurological examination was supplemented by a quantitative assessment of impairments using the NIHSS scale. Based on the collection of complaints, analysis of anamnesis, and neurological evaluation, the presence of motor impairments (paresis), somatic sensory disturbances (hypoaesthesia), coordination disorders, and cranial nerve dysfunctions were considered for each patient. Special attention during the examination and neuropsychological assessment was given to identifying potential clinical indicators of likely CAA, such as visual disturbances of varying levels (hemianopsia, central metamorphopsia, visual agnosias, visuospatial disorders) [13].

For the quantitative assessment of visuospatial praxis and gnosis, a cube copying task was used as a component of the MoCA

test (0 points – no impairments in cube copying, 1 point – impairments in cube copying), as well as the Benson Complex Figure Test [14]. The Benson Complex Figure Test is a simplified version of the Rey-Osterrieth Complex Figure Test used to assess visuoconstructive abilities and visual memory. A patient was asked to copy the figure and then reproduce it from memory after 10–15 minutes [15]. Each element of the figure in this test is scored out of 2 points if the element is accurately drawn and correctly positioned on the figure (1 point for accuracy, 1 point for placement). 1 point is awarded if the element is poorly drawn but correctly placed, or accurately drawn but not in its correct position, and 0 points is given if the element is neither drawn nor placed correctly. A bonus point is awarded when the figure is well-drawn (i.e. each element must be accurately drawn, all elements must be correctly placed, all elements must be drawn in proper proportions, all connections between elements must be clear, and no extraneous lines should be present). The total score is calculated, with a maximum possible value of 17 points [15].

For the quantitative integral assessment of the degree of cognitive dysfunction, the Montreal Cognitive Assessment (MoCA) scale was used [16].

The neuroimaging study was conducted using a General Electric Signa Infinity HiSpeed Plus MRI scanner with a magnetic field strength of 1.5 T. The research protocol included T2, T1, and FLAIR pulse sequences in three planes, as well as a T2*GRE pulse sequence to verify areas of hemoglobin derivative deposits (including regions of microhemorrhages).

To determine the nature and localization of the brain lesion, all patients underwent CT and MRI of the brain.

Neuroimaging data were used to assess the presence of LH, microhemorrhages, cSS, and PVS. Additionally, the frontal-occipital gradient (FOG) was calculated to evaluate the varying degrees of T2 hyperintensities in white matter between the frontal and occipital lobes.

The localization of intracerebral hematomas (lobar vs deep) was determined according to the approach of G.J. Falcone et al. (2013). A lobar (subcortical) hematoma was defined as an intracerebral hemorrhage localized in the cortex and the adjacent subcortical area, while a deep hematoma was defined as a hemorrhage affecting only the thalamus, basal ganglia, internal capsule, and deep periventricular white matter [10]. In addition, the localization of lobar hematomas was conditionally divided into two categories: the first – frontal, parietal, and frontoparietal localization of hematomas; the second – temporal, occipital, and temporo-occipital.

Cerebral superficial microhemorrhages and their count were assessed using axial T2*-weighted images. The number of microhemorrhages was classified as small (0–4), medium (5–9), and large (≥10). Similarly, the evaluation of deep microhemorrhages (located in the deep white matter) was performed in the same manner.

Cortical superficial siderosis (cSS) was assessed based on MRI results in T2* mode (gradient echo) as follows: 0 points – no

cSS, 1 point – focal, limited to involvement of 1–2 sulci of the brain, 2 points – multifocal, involving 3 or more sulci of the brain [17]. The detection of multiple microhemorrhages and cSS was necessary for diagnosing CAA according to its criteria.

Alongside this, the analysis included those non-hemorrhagic neuroimaging markers that, although not included in the current Boston criteria for diagnosing CAA, may be important for differentiating it from hCMA, namely PVS and FOG.

To determine the FOG, images in FLAIR mode were used in the axial plane. Calculations were performed using the method by Zhu et al. (2012) [18]. For this purpose, the scores (each of which could range from 0 to 2 points on the Zhu scale) of hyperintensity in the periventricular, juxtacortical, and deep white matter were first summed in the frontal region, then in the occipital region, after which the difference in total scores in the specified areas was calculated. The total FOG score can range from -6 to +6 points.

The perivascular spaces (PVS) were assessed using the method by F.N. Doubal et al. (2010) with clarifications by A. Charidimou et al. (2019) on axial T2-weighted images (T2-WI), separately in the basal ganglia and separately in the semioval centre of each hemisphere. The presence of visualised PVS was regarded as a sign of their expansion. The assessment was carried out using a 4-point visual rating scale as follows: 0 points – no visualised PVS, 1 point – ≤ 10 PVS, 2 points – 11–20, 3 points – 21–40, and 4 points – ≥ 40 visualised PVS [17]. All relevant slices were reviewed, and the presence of PVS on each side of the brain was assessed, after which a score corresponding to the side and slice with the highest number of identified PVS was assigned [19].

Statistical analysis of the data was conducted using the SPSS 23 software package. Normality testing for quantitative variables was not performed due to the small sample size and the established groups. Therefore, within the framework of descriptive statistics, the median and interquartile range (*Me* [Q1; Q3]) were calculated for all quantitative and ordinal parameters. Qualitative (binary) variables were described by calculating the proportions (%) of individual categories of patients in the studied sample and in the groups. Pairwise comparisons of groups for quantitative and ordinal parameters were conducted using the Mann-Whitney U test. The assessment of differences in binary traits was conducted using the analysis of contingency tables. Differences in binary variables were assessed using chi-squared (χ^2) tests and Fisher's exact test (when the values in the cells of the contingency tables were less than 5). Differences were considered statistically significant at $p < 0.050$.

To provide an integral assessment of the prognostic ability of the identified predictors of CAA in patients with LH, a binary classifier was developed based on the use of a logistic regression model. For training, specialized libraries of the Python programming language (Pandas[1], Numpy [20], Scikit-Learn[2])

[1] pandas-dev/pandas: Pandas. Zenodo, available at: https://zenodo.org/records/10426137

were used, as well as the software package AutoStatPack (Certificate of state registration of the computer program No. 2020663190).

RESULTS AND DISCUSSION

The medical history data and cardiological examination results indicated the presence of stage III hypertension in all 32 examined individuals. Signs of probable CAA, according to the modified Boston criteria, were observed in 16 patients. In all these cases, CAA was associated with hCMA. Patients with LH against the background of combined CAA and hCMA comprised the first subgroup (8 men and 8 women, mean age 68.5 [67.0; 82.2] years). The second subgroup included 16 individuals with LH against the background of isolated hCMA (9 men and 7 women; median age 67.5 [63.0; 73.5] years). The groups did not have statistically significant differences in age and sex, nor in the frequency of motor, coordination, and somatic sensory disturbances.

Patients with CAA had statistically significantly more frequent LH localized in the temporal, occipital, and temporo-occipital regions compared to those with hCMA (Table 1). This fact appears to be quite logical, as it has previously been established that intracerebral hemorrhages in the occipital and parietal lobes are more characteristic of CAA [21]. Some authors attribute this to the fact that occipital vessels, for some reason, have thicker walls and can therefore accommodate significantly more amyloid compared to vessels in other areas of the brain [3; 8].

Alongside this, patients in the first subgroup exhibited statistically significantly more frequent visual disturbances, such as hemianopsia, metamorphopsia, visual agnosia, and spatial apraxia, compared to those in the second subgroup. There were also statistically significant differences in the results of tasks involving cube copying, figure copying, and memory drawing of the Benson figure and MoCA (see Table 1). Such a high frequency of primary visual function and visuospatial disturbances can be explained by the predominant involvement of the posterior regions of the brain in CAA [22]. Our data are supported by the findings of the study by Y. Su et al. (2021), which discovered that clinically detectable visuospatial dysfunction may serve as an independent marker for the presence of CAA in non-demented patients [22].

In the first subgroup of patients, multiple visible (i.e., enlarged) perivascular spaces (PVS) in the centrum semiovale were also more frequently detected than in the second subgroup (see Table 1). In this regard, it should be noted that several authors point out the nonspecific nature of PVS enlargement, which can be observed with aging and arterial hypertension, not only in cases of CAA [23]. However, our data suggest the potential use of this indicator as a neuroimaging marker of CAA, which aligns with the opinion of A. Charidimou et al. (2019), who even propose including it in the new version of the Boston criteria for CAA diagnosis.

[2] scikit-learn/scikit-learn: Scikit-learn 1.3.2. Zenodo, available at: https://zenodo.org/records/10039710

Table 1

Comparative characteristics of patients

Parameter	Overall group, $n = 32$	CAA patients (1), $n = 16$	hCMA patients (2), $n = 16$	p
Age, years, *Me* [Q_1; Q_3]	68.0 [63.2; 74.0]	68.5 [67.0; 82.2]	67.5 [63.0; 73.5]	0.450
Women, abs. (%)	15 (46.9)	8 (50.0)	7 (43.8)	1.000
Men, abs. (%)	17 (53.1)	8 (50.0)	9 (56.2)	1.000
Localization				
Frontal, parietal, fronto-parietal, abs. (%)	20 (62.5)	8 (50.0)	12 (75.0)	0.144
Temporal, occipital, and temporo-occipital, abs. (%)	18 (56.3)	13 (81.3)	5 (31.3)	0.011
Clinically manifest visual disturbances, abs. (%)	16 (50.0)	12 (75.0)	4 (25.0)	0.012
Neuropsychological tests				
Cube copying test, number of patients with disturbances (%)	19 (59.4)	14 (87.5)	5 (31.2)	0.003
Benson test, points: *Me* [Q_1; Q_3]	16 [14.0; 17.0]	14 [14.0; 15.8]	17 [16.0; 17.0]	< 0.001
Benson test after 10 minutes, points: *Me* [Q_1; Q_3]	8.5 [7.25; 12.5]	8.0 [6.0; 8.0]	12.5 [10.0; 14.0]	< 0.001
MoCA, points: *Me* [Q_1; Q_3]	18.0 [12.0; 20.0]	12.0 [10.0; 18.0]	20.0 [18.0; 24.3]	< 0.001
Non-hemorrhagic neuroimaging markers				
Enlarged perivascular spaces (PVS) in the centrum semiovale, abs. (%)	18 (56.3)	16 (100.0)	2 (12.5)	< 0.001
Fronto-occipital gradient (FOG) greater than 0, abs. (%)	9 (28.1)	0 (0.0)	9 (56.3)	0.001

The values of FOG in the first subgroup ranged from 0 to -4, while in the second subgroup, they ranged from 1 to 5 points.

These results contradict the findings of S. Phuach et al. (2022), who did not find a predominance of white matter hyperintensity (WMH) in the posterior parts of the brain in cases of CAA, but are consistent with the opinion of A. Charidimou et al. (2016), who consider negative values of FOG to be typical for CAA, in which white matter damage predominates in the occipital regions of the brain and in the periventricular white matter around the posterior horns of the lateral ventricles [24; 25]. In contrast, with hypertensive cerebral microangiopathy (hCMA), WMH, according to neuroimaging data, is uniformly expressed throughout the entire periventricular region [25].

At the next stage of the work, an analysis was performed on the predictive value of the clinical and non-hemorrhagic neuroimaging indicators that demonstrated statistically significant intergroup differences and could therefore serve as potential indicators of CAA in patients with LH. For this purpose, the entire group of patients was divided into training and testing samples in a ratio of 60/40 (19 and 13 patients, respectively). The proportion of patients with CAA (coded as 1) in the training sample was 53 % compared to 46 % in the testing sample. Structural differences in the specified samples regarding the presence of CAA were not significant (p = 0.570). The predictive model was constructed using data from the training sample, and the quality of the model was evaluated on the testing

sample. The resulting equation of the logistic regression model is as follows:

$$P = \frac{1}{1 + e^{-(-0,23+0,51 \cdot X_1 + 0,64 \cdot X_2 + 0,15 \cdot X_3 - 0,5 \cdot X_4 - 0,43 \cdot X_5 - X_6 + 0,79 \cdot X_7)}},$$

where P is the probability of the presence of CAA (coded as 1) in a patient, x1–7 are the values of the predictors in the model (see Table 2).

The decision regarding the presence of CAA in a patient was made when $P \geq 0,5$, and for the absence of CAA when $P < 0,5$. The accuracy of the model was 100 [84.3; 100] % for the test sample, indicating excellent classification quality. However, it should be understood that the performance of the model may decline in real clinical practice (within the confidence interval) when non-classical cases arise that may not have been present in the training and test samples during model development. Given the small size of the training and test samples, additional evaluation of the model's prognostic ability and correction of binary classification quality metric values are required when analyzing an expanded data set.

From the data in Table 3, it follows that the obtained model, which includes the clinical and neuroimaging indicators we selected, provides a high quality of personalized diagnosis of probable CAA in a patient.

Conclusion

Data from the patients with lobar hematomas and probable CAA differed from those in the patients with hypertensive cerebral microangiopathy by a more frequent occurrence of primary visual function impairments and visuospatial disturbances

Table 2

Clinical and neuroimaging indicators included as predictors in the logistic regression model for predicting CAA = 1

Code	Description and Data Entry Format	Feature Type
X_1	Temporo-occipital localization: yes – 1, no – 0	Binary
X_2	Visual disturbances: yes – 1, no – 0	Binary
X_3	Cube copying test: yes – 1, no – 0	Binary
X_4	Benson test, points	Quantitative
X_5	MoCA, points	Quantitative
X_6	Fronto-occipital gradient	Quantitative
X_7	Perivascular spaces, enlargement – 1, no enlargement – 0	Binary

Table 3

Prediction quality metrics

Sl.№	Metrics, %	Metric value [95 % confidence interval]
1	Accuracy	100 [84.3; 100]
2	Sensitivity	100 [84.3; 100]
3	Specificity	100 [84.3; 100]
4	Positive Predictive Value (PPV)	100 [84.3; 100]
5	Negative Predictive Value (NPV)	100 [84.3; 100]

in the clinical presentation of the disease, as well as a more pronounced overall decline in cognitive functions.

Lobar hematomas, associated with CAA, compared to hypertensive lobar hematomas, were statistically significantly more likely to have temporo-occipital localization and were more frequently associated with the enlargement of perivascular spaces in the semioval centers of the cerebral hemispheres and with a negative fronto-occipital gradient of hyperintensity of white matter.

Clinically significant impairments of primary and higher visual functions, a negative fronto-occipital gradient, and the enlargement of perivascular spaces in the semioval centers may serve as indicators of probable CAA in patients with acute lobar hematoma. An integral logistic regression model that included these indicators as predictors provided excellent quality in predicting CAA with an accuracy of 100 [84.3; 100] %. For patients with a high suspicion index of CAA based on the application of the proposed model, it is advisable to additionally include iron-sensitive pulse sequences in the neuroimaging protocol upon admission to a vascular center for verification of the corresponding diagnosis.

References

1. *Gusev E.I., Martynov M.Yu., Shchukin I.A., Fidler M.S., Kol'cov I.A.* The influence of the volume of hemorrhage, perifocal edema and blood breakthrough into the ventricular system on functional recovery according to the Barthel scale in patients with hemorrhagic stroke of hemispheric localization. *Bulletin of neurology, psychiatry and neurosurgery* 2019; (11): 3–10. DOI: 10.33920/med-01-1910-01 (in Russian).

2. *Kulesh A.A.* Modern approaches to diagnosis of intracerebral hemorrhage. *Neurology, neuropsychiatry, psychosomatics* 2020; 12 (2): 4–11. DOI: 10.14412/2074-2711-2020-2-4-11 (in Russian).

3. *Sharma R., Dearaugo S., Infeld B., O'Sullivan R., Gerraty R.P.* Cerebral amyloid angiopathy: Review of clinico-radiological features and mimics. Journal of Medical Imaging and Radiation Oncology 2018; 62 (4): 451–463. DOI: 10.1111/1754-9485.12726

4. *Weber S.A., Patel R.K., Lutsep H.L.* Cerebral amyloid angiopathy: diagnosis and potential therapies. Expert Review of Neurotherapeutics 2018; 18 (6): 503–513. DOI: 10.1080/14737175.2018.1480938

5. *Cannistraro R.J., Meschia J.F.* The Clinical Dilemma of Anticoagulation Use in Patients with Cerebral Amyloid Angiopathy and Atrial Fibrillation. Current cardiology reports 2018; 20 (11): 106. DOI: 10.1007/s11886-018-1052-1

6. *Kulesh A.A., Gorst N.H., Kuzina E.V., Drobaha V.E., Shestakov V.V., Karakulova Yu.V.* Amyloid angiitis and progressive cortical superficial siderosis as aggressive phenotypes of cerebral amyloid angiopathy: principles of rational management. *Russian Neurological Journal* 2019; 24 (6): 29–38. DOI: 10.30629/2658-7947-2019-24-6-29-38 (in Russian).

7. *Chan E., Bonifacio G.B., Harrison C., Banerjee G., Best J.G., Sacks B., Harding N., Mas M.D.R.H., Jäger H.R., Cipolotti L., Werring D.J.* Domain-specific neuropsychological investigation of CAA with and without intracerebral haemorrhage. Journal of Neurology 2023; 270 (12): 6124–6132. DOI: 10.1007/ s00415-023-11977-8

8. *Teo K.C., Fong S.M., Leung W.C., Leung I.Y., Wong Y.K., Choi O.M., Yam K., Lo R.C.N., Cheung R.T.F., Ho S.L., Tsang A.C.O., Leung G.K.K., Chan K.H., Lau K.K.* Location-specific hematoma volume cutoff and clinical outcomes in intracerebral hemorrhage. Stroke 2023; 54 (6): 1548–1557. DOI: 10.1161/STROKEAHA.122.041246

9. *Charidimou A., Boulouis G., Frosch M.P., Baron J.C., Pasi M., Albucher J.F., Banerjee G., Carmen Barbato, Bonneville F., Brandner S., Calviere L., Caparros F., Casolla B., Cordonnier C., Delisle M.B., Deramecourt V., Dichgans M., Gokcal E., Herms J., Hernandez-Guillamon M., Jäger H.R., Jaunmuktane Z., Linn J., Martinez-Ramirez S., Martínez-Sáez E., Mawrin C., Montaner J., Moulin S., Olivot J.M., Piazza F., Puy L., Raposo N.,Rodrigues M.A., Roeber S., Romero J.R., Samarasekera N., Schneider J.A., Schreiber S., Schreiber F., Schwall C., Smith C., Szalardy L., Varlet P., Viguier A., Wardlaw J.M., Warren A., Wollenweber F.A., Zedde M., Van Buchem M.A., Gurol M.E., Viswanathan A., Salman R.Al.S., Smith E.E., Werring D.J.* The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI–neuropathology diagnostic accuracy study. The Lancet Neurology 2022; 21 (8): 714–725. DOI: 10.1016/S1474-4422(22)00208-3

10. *Falcone G.J., Biffi A., Brouwers H.B., Anderson C.D., Battey T.W., Ayres A.M., Vashkevich A., Schwab K., Rost N.S., Goldstein J.N., Viswanathan A., Greenberg S.M., Rosand J.* Predictors of hematoma volume in deep and lobar supratentorial intracerebral hemorrhage. JAMA neurology 2013; 70 (8): 988–994. DOI: 10.1001/jamaneurol.2013.98

11. *Roh D., Boehme A., Young C., Roth W., Gutierrez J., Flaherty M., Rosand J., Testai F., Woo D., Elkind M.S.* Hematoma expansion is more frequent in deep than lobar intracerebral hemorrhage. Neurology 2020; 95 (24): e3386–e3393. DOI: 10.1212/WNL.0000000000010990

12. *Das A.S., Gurol M.E.* Not all lobar hemorrhages are created equal. Stroke 2020; 51 (12): 3485–3486. DOI: 10.1161/STROKEAHA.120.032404

13. *Onomura H., Shimizu T., Kobayashi R., Suzuki J., Nakai N., Okuda S., Itoa Y.* Palinopsia as an initial symptom of cerebral amyloid angiopathy-related inflammation. Eneurologicalsci 2021; 25: 100375. DOI: 10.1016/j.ensci.2021.100375

14. *Culhane J.E., Chan K.C., Teylan M.A., Chen Y.C., Mock C., Gauthreaux K., Kukull W.A.* Factor consistency of neuropsychological test battery versions in the NACC Uniform Data Set. Alzheimer disease and associated disorders 2020; 34 (2): 175. DOI: 10.1097/WAD.0000000000000376

15. *Jiskoot L.C., Russell L.L., Peakman G., Convery R.S., Greaves C.V., Bocchetta M., Poos J.M., Seelaar H., Giannini L.A.A., Van*

Swieten J.C., Van Minkelen R., Pijnenburg Y.A.L., Rowe J.B., Borroni B., Galimberti D., Maselli M., Tartaglia C., Finger E., Butler C.R., Graff C., Laforce R., Sanchez-Valle R., De Mendonça A., Moreno F., Synofzik M., Vandenberghe R., Ducharme S., le Ber I., Levin J., Otto M., Pasquier F., Santana I., Cash D.M., Thomas D., Rohrer J.D. The Benson Complex Figure Test detects deficits in visuoconstruction and visual memory in symptomatic familial frontotemporal dementia: A GENFI study. Journal of the Neurological Sciences 2023; 446: 120590. DOI: 10.1016/j.jns.2023.120590

16. *Toups K., Hathaway A., Gordon D., Chung H., Raji C., Boyd A., Hill B.D., Hausman-Cohen S., Attarha M., Chwa W.J., Jarrett M., Bredesen D.E.* Precision medicine approach to Alzheimer's disease: Successful pilot project. Journal of Alzheimer's Disease 2022; 1: 1–11. DOI: 10.3233/JAD-215707

17. *Charidimou A., Frosch M.P., Salman R.A.S., Baron J., Cordonnier C., Hernandez-Guillamon M., Linn J., Raposo N., Rodrigues M., Romero J.R., Schneider J.A., Schreiber S., Smith E.E., van Buchem M.A., Viswanathan A., Wollenweber F.A., Werring D.J., Steven M. Greenberg for the International CAA Association.* Advancing diagnostic criteria for sporadic cerebral amyloid angiopathy: study protocol for a multicenter MRI-pathology validation of Boston criteria v2. 0. International Journal of Stroke 2019; 14 (9): 956–971. DOI: 10.1177/1747493019855888

18. *Zhu Y.C., Chabriat H., Godin O., Dufouil C., Rosand J., Greenberg S.M., Smith E.E., Tzourio C., Viswanathan A.* Distribution of white matter hyperintensity in cerebral hemorrhage and healthy aging. Journal of neurology 2012; 259: 530–536. DOI: 10.1007/s00415-011-6218-3

19. *Doubal F.N., MacLullich A.M., Ferguson K.J., Dennis M.S., Wardlaw J.M.* Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. Stroke 2010; 41 (3): 450–454. DOI: 10.1161/STROKEAHA.109.564914

20. *Harris C.R., Millman K.J., van Der Walt S.J., Gommers R., Virtanen P., Cournapeau D., Wieser E., Taylor J., Berg S., Smith N.J., Kern R., Picus M., Hoyer S., van Kerkwijk M.H., Brett M., Haldane A., Del Río J.F., Wiebe M., Peterson P., Gérard-Marchant P., Sheppard K., Reddy T., Weckesser W., Abbasi H., Gohlke C., Oliphant, T.E.* Array programming with NumPy. Nature 2020; 585 (7825): 357–362. DOI: 10.1038/s41586-020-2649-2

21. *Jung Y.H., Jang H., Park S.B., Choe Y.S., Park Y., Kang S.H., Lee J.M., Kim J.S., Kim J., Kim J.P., Kim H.J., Na D.L., Seo S.W.* Strictly Lobar Microbleeds Reflect Amyloid Angiopathy Regardless of Cerebral and Cerebellar Compartments. Stroke 2020; 51 (12): 3600–3607. DOI: 10.1161/STROKEAHA.119.028487

22. *Su Y., Fu J., Zhang Y., Xu J., Dong Q., Cheng X.* Visuospatial dysfunction is associated with posterior distribution of white matter damage in non-demented cerebral amyloid. European Journal of Neurology 2021; 28 (9): 3113–3120. DOI: 10.1111/ene.14993

23. *Francis F., Ballerini L., Wardlaw J.M.* Perivascular spaces and their associations

with risk factors, clinical disorders and neuroimaging features: A systematic review and meta-analysis. International Journal of Stroke 2019; 14 (4): 359–371. DOI: 10.1177/1747493019830321

24. *Phuah C.L., Chen Y., Strain J.F., Yechoor N., Laurido-Soto O.J., Ances B.M., Lee J.M., for the Alzheimer's Disease Neuroimaging Initiative.* Association of data-driven white matter hyperintensity spatial signatures with distinct cerebral small vessel disease etiologies. Neurology 2022; 99 (23): e2535–e2547. DOI: 10.1212/WNL.0000000000201186

25. *Charidimou A., Boulouis G., Haley K., Auriel E., van Etten E.S., Fotiadis P., Reijmer Y., Ayres A., Vashkevich A., Dipucchio Z.Y., Schwab K.M., Martinez-Ramirez S., Rosand J., Viswanathan A., Greenberg S.M., Gurol M.E.* White matter hyperintensity patterns in cerebral amyloid angiopathy and hypertensive arteriopathy. Neurology 2016; 86 (6): 505–511. DOI: 10.1212/WNL.0000000000002362

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Grigoryeva V.N. – problem formulation, development of the research concept, preparation and editing of the text, involvement in the scientific design, approval of the final version of the work, consultation.

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ASSESSMENT OF FUNCTIONAL DISORDERS IN CHILDREN WITH NARROWING OF DENTITION FROM THE PERSPECTIVE OF THE INTERNATIONAL CLASSIFICATION OF FUNCTIONING

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ОЦЕНКА ФУНКЦИОНАЛЬНЫХ НАРУШЕНИЙ У ДЕТЕЙ С СУЖЕНИЕМ ЗУБНЫХ РЯДОВ С ПОЗИЦИИ МЕЖДУНАРОДНОЙ КЛАССИФИКАЦИИ ФУНКЦИОНИРОВАНИЯ

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Objective. To assess functional disorders in children with narrowing of the dentition from the perspective of the international classification of functioning.
Materials and methods. The indicators of the components of the international classification of functioning were analyzed and assessed in 75 children with narrowing of the dentition aged 6–9.
Results. Nasal breathing impairments and speech disorders were found in children with narrowing of the dentition.
Conclusions. Orthodontists, otorhinolaryngologists, and speech therapists can use the parameters of the international classification of functioning to assess functional disorders in children with narrowing of dentition. It will help interdisciplinary planning in early diagnosis and treatment.
Keywords. International Classification of Functioning, rhinomanometry, nasal breathing.

Цель. Оценить функциональные нарушения у детей с сужением зубных рядов с позиции Международной классификации функционирования. Деформации зубного ряда часто являются причинами развития функциональных нарушений зубочелюстной системы, а при наличии ротового дыхания у детей существующие отклонения усугубляются. Оценка нарушенных функций с использованием меж-

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дународной классификации функционирования поможет сформировать комплексный подход к лечению детей с сужением зубных рядов.
Материалы и методы. Проведен анализ доменов и оценка показателей составляющих Международной классификации функционирования у 75 детей с сужением зубных рядов в возрасте 6–9 лет.
Результаты. У детей с сужением зубных рядов выявлены нарушения носового дыхания и изменения функций речи.
Выводы. Врачи-ортодонты, оториноларингологи, а также логопеды могут использовать параметры международной классификации функционирования для оценки функциональных нарушений у детей с сужением зубных рядов, что помогает междисциплинарному планированию в ранней диагностике и лечении.
Ключевые слова. Международная классификация функционирования, риноманометрия, носовое дыхание.

INTRODUCTION

Modern studies reveal that the narrowing of the upper jaw leads to impaired nasal breathing. Others believe that the impairment of nasal breathing results in narrowed dental arches. The narrowing of the dental arches in children with impaired nasal breathing increases with every year of a child's life. This is especially pronounced at the beginning of tooth change, when improper tooth eruption prevails.

MATERIALS AND METHODS

To determine functional disorders in children, we used the domains of the international classification of functioning in 75 children aged 6–9 years undergoing orthodontic treatment at the Department of Pediatric Dentistry and Orthodontics of Perm State Medical University and the "Lyubimyi doctor" ("Favorite Doctor") medical center, Perm. The main and additional examination methods were carried out in the following sequence: collection of complaints, anamnesis, examination, photometric analysis of the face, cephalometric and morphometric calculation, determination of the condition of the upper respiratory tract by an otorhinolaryngologist, speech assessment by a speech therapist. To determine the degree of narrowing of the upper jaw, we used the measurement of the width of the dental arch using the Pont index – the distance between the points of the first permanent molars of the upper jaw. Moreover, the patients underwent orthopantomographic and teleroentgenographic studies with the description of the condition of the maxillary sinuses and nasal septum. For an objective assessment of nasal breathing, otorhinolaryngologists used the method of anterior active rhinomanometry with the Rhinoscan SRE 2000 INTERACOUSTIC equipment. The results were generated into an Excel database and processed using the SPSS Statistics 5.0 software. The average value of the analyzed indicators, standard deviation, average error and Student's *t*-test were calculated. The differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

75 examined children aged 6–9 years were divided into two groups: 42 children with

habitual mouth breathing and narrowing of the upper dental arch, where the distance between the palatine surfaces of the first permanent molars was less than 35 mm (main group). The comparison group included 33 children with nasal breathing and with a sufficient width of the upper dental arch.

We evaluated the indicators and selected domains suitable for our study from the components of the International Classification of Functioning (ICF): "functions and structure of the body", "activity and participation". Then we used the ICF evaluation system for children with distal occlusion and functional disorders and assessed the selected domains.

For effective analysis, the ICF evaluation displays were used for the presented classification components ("functions", "structures", "activity and participation"), which were assigned codes. Differences in treatment dynamics were analyzed using a color scale opposite each code.

Among the components of the classification of "functions", we selected the following domains: articulation functions (b320), voice functions (b310), respiratory functions (b440); among the "structure" components: teeth (s3200), nose structure (s310), mouth structure (s320), respiratory system structure (s430), hard palate (s32020); among the "activity and speech" components: speech (d330), oral care (d520), conversation (d350), parent–child relationship (d7600).

Each domain was evaluated in a comprehensive clinical examination using the methods brought to the unified definitions of the ICF:

xxx.0. NO problems (none, not present, negligible, ...) 0–4 %.

xxx.1. MINOR problems (insignificant, mild, ...) 5–24 %.

xxx.2. MODERATE problems (average, significant, ...) 25–49 %.

xxx.3. SEVERE problems (high, intense...) 50–95 %.

xxx.4. ABSOLUTE problems (complete, ...) 96–100 %.

xxx.8. Not identified (NI).

xxx.9. Not applicable (NA).

Special displays were compiled to work with children who had verified narrowing of the dentition, as well as speech and breathing disorders. They are shown in the figure.

As a result, it was found that, despite the presence of narrowing of the dentition in children of both groups, statistically significant differences were revealed between them in the components of the classification of "functions", "structures" and "activity and speech", assessed with the Mann-Whitney *U*-test ($p = 0.034$).

When analyzing the children in the main group, three domains were identified as being most significantly disrupted in the "functions" component of the classification, five in the "structures" component, and four in the "activity and speech" component. In contrast, in the children from the comparison group, there were only one, two, and one maximally disrupted parameter in each of these components of the classification respectively.

In a comparative analysis, the average functional impairment in children from the main group ranged from 32 % to 51 %, while in patients from the comparison group, it ranged from 6 % to 23 % ($p = 0.026$). In addition, more pronounced impairment in the categories of "activity and speech" was identified among children with narrowing of the dentition, reaching 52 % compared with those in the comparison group (up to 23 %). This was mainly manifested in the assessment of the domains of speech, conversation, and parent-child relationship ($p = 0.021$).

A comparative analysis of the components of the "structures" domain in assessing the size of the upper dentition revealed a narrowing and shortening of the dental arch in patients with impaired nasal breathing. The narrowing of the upper dental arch leads to a decrease in space in the dentition, which can cause crowding or retention of teeth. The narrowing of the upper jaw results from a complex interaction between various factors that affect the myodynamic balance in the maxillofacial region.

The impairment of the myodynamic balance affects both the growth of the jaw and the position of the teeth. Lip closure becomes disrupted, the position of the tongue changes, and the imbalance of the chewing muscles increases.

Conclusion

The application of the International Classification of Functioning in children with narrowing of the dental arches reveals the breadth of assessment of impaired functions and the possibility of its use in dynamics to analyze the effectiveness of complex treatment. The developed evaluation display facilitates the process of diagnosing disorders in children with narrowing of the dentition using the International Classification of Functioning and will allow assessing these disorders in the dynamics of treatment.

Evaluation at the beginning of treatment								
Components of ICF		Definition of ICF						
Functions		0	1	2	3	4	NI	NA
b 440	Respiratory functions							
b 310	Voice functions							
b 320	Articulation functions							
Structures		0	1	2	3	4	NI	NA
s 310	Nose structure							
s 320	Mouth structure							
s 430	Respiratory system structure							
s3200	Teeth							
s32020	Hard palate							
Activity and speech		0	1	2	3	4	NI	NA
d 330	Speech							
d 350	Conversation							
d 520	Oral care							
d7600	Parent-child relationship							

Fig. The ICF Evaluation Display for patients with narrowing of the dentition and functional disorders

An integrated approach to early detection and correction of the dentition narrowing, assessed in accordance with the International Classification of Functioning, at an early age, facilitates normal child development.

References

1. *Gvozdeva Yu.V., Danilova M.A.* Rationale for carrying out preventive measures aimed at correcting myofunctional disorders during the period of occlusion of primary teeth. *Pediatric dentistry and dental prophylaxis* 2009; 8 (1): 51–56 (in Russian).

2. *Gvozdeva Yu.V., Tsarkova O.A., Danilova M.A.* Assessment of the harmony of the facial profile in children with various types of myofunctional disorders. *Kazan Medical Journal* 2010; 2: 173–176 (in Russian).

3. *Danilova M.A., Machulina N.A., Zalazaeva E.A.* The experience of joint work of the Department of Pediatric Dentistry and Orthodontics of the PGMA and the KGAU "Center for Comprehensive Rehabilitation of the disabled". *Pediatric dentistry and dental prophylaxis* 2013; 1 (44): 70–72 (in Russian).

4. *Evdokimova N.A., Popov S.A.* The effect of oral breathing on the formation of the nasomaxillary complex in children with adenoids. *The Scientific and Practical Journal «The Dental Institute»* 2010; 4: 64–65 (in Russian).

5. *Grigorenko N.Y.* Formation of pronunciation skills in children of early and preschool age with mild abnormalities of articulation organs. *Pedagogical education in Russia* 2016; (3): 113–119 (in Russian).

6. *Khamidov A.G., Lekishvili M.V., Melanin V.D., Serebryakova I.Yu., Shiraliev M.R.* The use of acoustic rhinometry and anterior active rhinometry for differential diagnosis of pathologies of intra-nasal structures in nasal obstruction. *Rossiiskaya otorinolaringologiya* 2009; (42): 113–119 (in Russian).

7. *Tsarkova O.A., Danilova M.A.* Evaluation of the results of complex treatment of children with nasal breathing disorders. *Orthodontics* 2007; 3: 83 (in Russian).

8. *Shilenkova V.V.* About some functions of the nasal cavity in children. *Pediatric otorhinolaryngology* 2013; (2): 23–26 (in Russian).

9. *Tesch F.C., Oliveira B.H., Leão A.* Measuring the impact of oral health problems on children's quality of life: conceptual and methodological issues. Cad Saúde Pública 2007; 23 (11): 2555– 2564.

10. *Zicari A.M., Albani F., Ntrekou P. et al.* Oral breathing and dental malocclusions. Eur J Paediatr Dent. 2009; 10 (2): 59–64.

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METABOLIC FATTY LIVER DISEASE AS A RISK FACTOR FOR EARLY RENAL DYSFUNCTION IN WOMEN OF REPRODUCTIVE AGE

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МЕТАБОЛИЧЕСКИ АССОЦИИРОВАННАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ КАК ФАКТОР РИСКА РАННЕЙ РЕНАЛЬНОЙ ДИСФУНКЦИИ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА

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Objective. To study the correlation of adipocytokines with early renal dysfunction indicators in women of reproductive age with obesity and metabolic fatty liver disease.
Materials and methods. The study included 100 obese females divided into 2 groups. The 1st group consisted of patients ($n = 50$) diagnosed with metabolic fatty liver disease aged 40.5 ± 2.8, and the 2nd group contained patients ($n = 50$) without metabolic fatty liver disease (MFLD). The level of insulin, cystatin C, resistin, leptin, monocyte chemoattractant protein (MCP-1), vascular endothelial growth factor (VEGF), interleukin 6 (IL-6), tumor necrosis factor α (TNF) were determined in blood serum by enzyme-linked immunosorbent assay (ELISA) method. Albumin-to-creatinine ratio, TNF- α, MCP-1, IL 6, cystatin C, β_2-microglobulin, VEGF were determined in morning urine.
Results. Increased levels of pro-inflammatory cytokines and endothelial dysfunction were revealed in group 1 in relation to both the comparison and control groups. In patients with MFLD associations of resistin level were the following: with HOMA($r = 0.60$), alanine aminotransferase (ALT) ($r = 0.54$), aspartate aminotransferase ($r = 0.71$), gamma-glutamyl transpeptidase ($r = 0.71$), high-density lipoprotein (HDL) ($r = -0.54$), VEGF ($r = 0.54$), TNF-α ($r = 0.44$), MCP-1 ($r = 0.57$) $p<0.05$. In the 1st and 2nd groups cytokine urinary excretion and renal dysfunction markers were higher than in the control group. Associations of urinary excretion of β_2-microglobulin with BMI ($r = 0.33$), HOMA ($r = 0.34$), resistin ($r = 0.30$), uric acid level ($r = 0.50$),

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creatinine ($r = 0.34$), thyroglobulin ($r = 0.31$), urinary MCP-1($r = 0.60$), IL-6 ($r = 0.70$) $p<0.05$ were revealed in the 1st group. In group 1 associations of urinary IL 6 with BMI ($r = 0.35$), waist/hip circumference (WC/HC) ($r = 0.33$), uric acid level ($r = 0.44$), urinary MCP-1($r = 0.74$) were positive, and associations with HDL ($r = -0.44$) $p<0.05$.
Conclusions. Resistin can be considered as an unfavourable marker of cardiometabolic disturbances in patients with MFLD. The association of subclinical inflammation markers and endothelial dysfunction with the markers of early renal impairment in patients with MFLD which was determined allows to expand the understanding of cardio-renal-metabolic continuum.
Keywords. Metabolic non-alcoholic fatty liver disease, early renal dysfunction, adipocytokines, obesity.

Цель. У женщин репродуктивного возраста с ожирением и МАЖБП изучена взаимосвязь адипоцитокинов с показателями ранней ренальной дисфункции.
Материалы и методы. В исследование были включены 100 женщин с ожирением, которых распределили по группам: 1-я группа – пациенты ($n = 50$) с установленной МАЖБП, возраст 40,5 ± 2,8 г., 2-я группа – пациенты ($n = 50$) без МАЖБП. В сыворотке крови методом ИФА определяли: уровень инсулина, цистатина С, резистина, лептина, моноцитарный хематтрактантный протеин (МСР-1), васкулоэндотелиальный фактор роста (ВЭФР), интерлейкин 6 (IL-6), фактор некроза опухоли альфа (ФНО-α). В утренней порции мочи определяли соотношение «альбумин/креатинин», ФНО-α, МСР-1, IL-6, цистатин С, β_2-микроглобулин, ВЭФР.
Результаты. В 1-й группе выявлены повышенные уровня провоспалительных цитокинов и дисфункции эндотелия относительно как данных группы сравнения, так и группы контроля. В группе с МАЖБП получены ассоциации уровня резистина с HOMA ($r = 0,60$), АЛТ ($r = 0,54$), АСТ ($r = 0,71$), ГГТП ($r = 0,71$), ЛПВП ($r = -0,54$), ВЭФР ($r = 0,54$), ФНО-α ($r = 0,44$) и МСР-1 ($r = 0,57$) $p < 0,05$. В 1-й и 2-й группах мочевая экскреция цитокинов и маркеров ренальной дисфункции превышала значения группы контроля. В 1-й группе выявлены связи мочевой экскреции β_2-микроглобулина с ИМТ ($r = 0,33$), HOMA ($r = 0,34$), резистина ($r = 0,30$), уровнем мочевой кислоты ($r = 0,50$), креатинина ($r = 0,34$), ТГ ($r = 0,31$), мочевыми МСР-1 ($r = 0,60$) и IL-6 ($r = 0,70$), $p < 0,05$. В 1-й группе IL-6 мочи имел положительные связи с ИМТ ($r = 0,35$), ОТ/ОБ ($r = 0,33$), уровнем мочевой кислоты ($r = 0,44$), мочевым МСР 1 ($r = 0,74$) и отрицательную с ХС ЛПВП ($r = -0,44$) $p < 0,05$.
Выводы. Резистин может быть рассмотрен в качестве неблагоприятного маркера кардиометаболических нарушений у лиц с МАЖБП. Установленная взаимосвязь маркеров субклинического воспаления и дисфункции эндотелия с маркерами раннего почечного повреждения у больных с МАЖБП позволяет расширить представления о кардио-рено-метаболическом континууме.
Ключевые слова. Метаболически ассоциированная неалкогольная жировая болезнь печени, ранняя ренальная дисфункция, адипоцитокины, ожирение.

INTRODUCTION

There are 33 million obese people in the Russian Federation*. It has been proven that metabolic syndrome in combination with non-alcoholic fatty liver disease (NAFLD) is associated with an increased risk of cardiovascular death, in this regard, in 2020, the European Society of Gastroenterologists proposed to combine the combination of metabolic syndrome with fatty liver disease into the concept of metabolically associated fatty liver disease (MAFLD) [1; 2]. The number of patients with chronic kidney disease (CKD) is increasing annually in the world, as of 2019, the disease was detected in 850 million people [3]. The significant contribution of fatty disease to the development and progression of CKD is beyond doubt. The prevalence of CKD in patients with fatty liver disease is 20–50 % [4; 5]. The mechanism of renal dysfunction in patients with MAFLD has not been fully studied. The liver is a generator of markers of inflammation, endothelial dys-

function and fibrosis, which can serve as binding components in the development of renal dysfunction in patients with MAFLD [6]. In turn, adipose tissue secretes a number of hormones that can have a simultaneous damaging effect on hepatocytes and nephron, triggering a cascade of cardio-hepato-reno-metabolic disorders [7]. The study of the involvement of MAFLD in the development of renal dysfunction in women of reproductive age is of clinical interest.

The objective of the study was to investigate the relationship of adipocytokines with indicators of early renal dysfunction in women of reproductive age with obesity and MAFLD.

MATERIALS AND METHODS

Groups under supervision:

Group 1 consisted of 50 women with obesity and MAFLD having no signs of alcoholic liver damage, suffering from hypertension, diabetes mellitus, functional and organic kidney damage. The average age of the patients was 40.5 ± 2.8 years and body mass index (BMI) = 35.6 ± 3.4 kg/m^2.

Group 2: 50 women without MAFLD. The average age was 39.6 ± 1.8 years and BMI = 34.7 ± 3.2 kg/m^2.

Control group: 30 healthy women, whose average age was 39.6 ± 4.3 years, BMI = 21.7 ± 1.8 kg/m^2.

The diagnosis of MAFLD was established in accordance with clinical recommendations EASL–EASD–EASO for the diagnosis and treatment of this disease [2]. Liver steatosis was determined by ultrasound diagnostics. Liver fibrosis was assessed using fibroelastography. Serum levels of cystatin C, insulin, leptin, resistin, monocyte chemattractant protein (MCP-1), interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF-α) were determined by ELISA (enzyme-linked immunosorbent assay). TNF-α, MCP-1, albumin-to-creatinine ratio, IL-6, β_2-microglobulin, cystatin C, and VEGF were tested in the morning urine portion. The glomerular filtration rate (GFR) was calculated using the CKD-EPI equation. The following biochemical parameters were studied in blood serum: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (γ-GTP), glucose, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), tyriglycerides (TG), creatinine. The Fatty Liver Index (FLI) included an assessment of the level of TG and γ-GTP, body mass index (BMI) and waist circumference (WC). Follicle-stimulating hormone (FSH) was evaluated using immunochemiluminescence analysis (IHLA). The statistical processing of the obtained data was carried out with Statistica 12.0 software. The 3 groups were compared using the Kruskal – Wallis test, a pairwise comparison of groups with a normal distribution was performed using the Bonferroni–corrected *t*-test, in groups with an abnormal distribution the Mann – Whitney *U*-test was used. A statistically significant dependence was calculated at $p < 0.05$.

RESULTS AND DISCUSSION

The metabolic profile in the groups is presented in the table.

It is noteworthy that, despite abdominal obesity and proven liver steatosis, markers of metabolic syndrome were not fully represented in Group 1 patients. Naturally, an increase in the HOMA index, TG and uric acid levels was obtained, while the level of glucose and LDL and HDL cholesterol did not differ in Group 1 and Group 2 patients. Despite the increased level of cystatin C in Group 1, there were no significant differences in the calculated GFR between the groups. Group 2 patients demonstrated an increase in blood glucose, uric acid, and γ-GTP levels, while the parameters remained in the reference range. In Group 2, ALT was associated with HOMA ($r = 0.36$), γ-GTP ($r = 0.42$), LDL cholesterol ($r = 0.39$) $p < 0.05$. In the group without MAFLD, FLI was correlated with the levels of HOMA, glucose ($r = 0.4$ and $r = 0.3$, $p < 0.05$) and resistin ($r = 0.1$, $p < 0.05$).

During the study, adipocytokine activity was analyzed in comparison groups. As expected, levels of cytokines were significantly higher in the group with obesity and MAFLD relative to the data of the comparison group: resistin – (4.0 [2.5; 4.9] vs. 3.1 [2.7; 4.3] ng/ml, $p = 0.04$), leptin – (23.6 [17.2; 31.8] vs. 18.5 [11.8; 19.9] ng/ml, $p = 0.04$), TNF-α – (1.7 [1; 2.1] vs. 0.9 [0.6; 1.6] pg/ml, $p = 0.04$), VEGF – (293.7 [120.5; 435.2] vs. 155.9 [80.9; 255.6] pg/ml, $p = 0.04$), MCP-1 – (207.6 [148.7; 265.9] vs. 163.2 [125.8; 230.8] pg/ml, $p = 0.04$), IL-6 (1.8 [1.2; 2.2] vs. 1.10 [1; 1.3] pg/ml, $p = 0.03$).

Metabolic parameters in the groups ($M \pm 2m$); Kruskal – Wallis test H (2, $N = 130$)

Parameter	Group 1 $n = 50$	Group 2 $n = 50$	Control, $n = 30$	p
SBP, mmHg	128.2 ± 10.0	111.9 ± 7.0	113.3 ± 9.0	$p = 0.40$ $p_{1-2} = 0.04$ $p_{1-c} = 0.04$ $p_{2-c} = 0.40$
DBP, mmHg	84.1 ± 5	75.8 ± 4.2	79.8 ± 4.2	$p = 0.33$ $p_{1-2} = 0.04$ $p_{1-c} = 0.05$ $p_{2-c} = 0.10$
WC/HC	1.0 ± 0.1	0.8 ± 0.3	0.8 ± 0.2	$p = 0.65$ $p_{1-2} = 0.04$ $p_{1-c} = 0.04$ $p_{2-c} = 0.90$
TC, mmol/l	5.3 ± 0.6	5.05 ± 0.8	5.04 ± 0.8	$p = 0.80$ $p_{1-2} = 0.60$ $p_{1-c} = 0.10$ $p_{2-c} = 0.90$

Continuation of the table

Parameter	Group 1 *n*= 50	Group 2 *n*= 50	Control, *n*= 30	*p*
LDL-C, mmol/l	3.6 ± 0.6	3.0 ± 0.7	2.5 ± 0.5	$p = 0.22$ $p_{1-2} = 0.1$ $p_{1-c} = 0.04$ $p_{2-c} = 0.06$
HDL-C, mmol/l	1.3 ± 0.1	1.5 ± 0.2	1.5 ± 0.1	$p = 0.51$ $p_{1-2} = 0.05$ $p_{1-c} = 0.05$ $p_{2-c} = 0.90$
TG, mmol/l	2.7 ± 0.7	1.0 ± 0.3	1.0 ± 0.1	$p = 0.04$ $p_{1-2} = 0.02$ $p_{1-c} = 0.02$ $p_{2-c} = 0.10$
ALT U/l	45.3 ± 10.3	14.4 ± 6.8	14.3 ± 7.3	$p = 0.01$ $p_{1-2} = 0.001$ $p_{1-c} = 0.001$ $p_{2-c} = 0.1$
AST U/l	30.7 ± 16.2	17.5 ± 8.2	17.9 ± 9.5	$p = 0.04$ $p_{1-2} = 0.01$ $p_{1-c} = 0.01$ $p_{2-c} = 0.10$
Glucose, mmol/l	5.2 ± 0.6	4.9 ± 0.4	4.5 ± 0.2	$p = 0.10$ $p_{1-2} = 0.06$ $p_{1-c} = 0.04$ $p_{2-c} = 0.04$
Uric acid, μmol/l	306 ± 45.8	256 ± 58.3	220.2 ± 35.7	$p = 0.05$ $p_{1-2} = 0.04$ $p_{1-c} = 0.02$ $p_{2-c} = 0.04$
γ-GTP, U/l	48.7 ± 15.6	23.7 ± 13.5	16.7 ± 5.8	$p = 0.03$ $p_{1-2} = 0.01$ $p_{1-c} = 0.001$ $p_{2-c} = 0.04$
Cystatin C, ng/ml	0.90 ± 0.1	0.85 ± 0.1	0.83 ± 0.1	$p = 0.05$ $p_{1-2} = 0.04$ $p_{1-c} = 0.03$ $p_{2-c} = 0.07$
Creatinine, μmol/l	76.2 ± 4.9	74.0 ± 6.9	75.1 ± 7.0	$p = 0.60$ $p_{1-2} = 0.05$ $p_{1-c} = 0.09$ $p_{2-c} = 0.10$
GFR, ml/min/ 1,73 m^2 (CKD-EPI)	85.3 ± 11.5	90.3 ± 14.6	86.3 ± 9.8	$p = 0.30$ $p_{1-2} = 0.05$ $p_{1-c} = 0.09$ $p_{2-c} = 0.05$

End of the table

Parameter	Group 1 n= 50	Group 2 n= 50	Control, n= 30	p
Insulin, μIU/ml	14.3 ± 6.7	6.5 ± 2.4	4.5 ± 0.5	$p = 0.01$ $p_{1-2} = 0.001$ $p_{1-c} = 0.001$ $p_{2-c} = 0.05$
HOMA	3.5 ± 1.0	1.3 ± 0.5	1.3 ± 0.6	$p = 0.10$ $p_{1-2} = 0.03$ $p_{1-c} = 0.03$ $p_{2-c} = 0.80$
FSH, mIU/ml	8.7 ± 2.3	7.1 ± 1.9	6.7 ± 2.0	$p = 0.10$ $p_{1-2} = 0.06$ $p_{1-c} = 0.04$ $p_{2-c} = 0.05$
FLI, U.	84.3 ± 6.9	42.3 ± 4.3	39.7 ± 2.1	$p = 0.03$ $p_{1-2} = 0.01$ $p_{1-c} = 0.01$ $p_{2-c} = 0.05$
Albumin/creatinine, mg/g	10.7 ± 1.3	7.7 ± 1.2	3.0 ± 0.3	$p = 0.07$ $p_{1-2} = 0.05$ $p_{1-c} = 0.04$ $p_{2-c} = 0.05$

Note: SBP – systolic blood pressure; DBP – diastolic blood pressure; WC/HC – waist circumference/hip circumference ratio, TC – total cholesterol, LDL-C – low density lipoproteins cholesterol, HDL-C – high density lipoproteins cholesterol, TG – triglycerides, HOMA – insulin resistance index, GFR – glomerular filtration rate, ALT – alanine aminotransferase, AST – aspartaminotransferase, γ-GTP – gamma-glutamyltransferase; FSH – follicle stimulating hormone; FLI – fatty liver index; p – 5 % significance level of the differences, at which the differences were considered reliable; unrel. – the differences are statistically unreliable.

Notably, with an equal BMI in the comparison groups, in Group 1, the levels of leptin and resistin exceeded the values of Group 2. In the comparison groups, leptin levels correlated with BMI (r = 0.52 and r = 0.46), $p < 0.05$. In the MAFLD group, the level of resistin was associated with TNF-α with HOMA (r = 0.63 and r = 0.28), ALT (r = 0.52 and r = 0.50), AST (r = 0.68 and r = 0.35), GGT (r = 0.72 and r = 0.63), HDL-C (r = -0.50; r = -0.42) and fibroelastography findings (r = 0.75 and r = 0.32). In addition, the correlations of resistin with the level of VEGF (r = 0.52), TNF-α (r = 0.41) and MCP-1 (r = 0.55) were revealed. TNF-α was associated with the level of MCP-1 (r = 0.51) and VEGF (r = 0.31); IL-6 – with the level of γ-GTP (r = 0.57). In the group without MAFLD, the association of the VEGF level with HOMA-IR (r = 0.45), MCP-1 (r = 0.55) and IL-6 (r = 0.53), $p < 0.05$ was revealed.

We studied the urinary excretion of markers of subclinical kidney damage and assessed their relationship with hormonal

and metabolic parameters. Despite the equivalent level of GFR in the studied groups, we obtained significant differences in the level of urinary inflammatory cytokines of kidney damage: TNF-α (0.3 [0.2; 0.5] vs. 0.20 [0.03; 0.3] pg/ml, $p = 0.04$), MCP-1 (125.5 [83.5; 155.8] vs. 92.3 [39.5; 142.7] pg/ml, $p = 0.02$), VEGF (124.3 [75.4; 255.3] vs. 105.8 [64.2; 154.8] pg/ml, $p = 0.04$), IL-6 (0.82 [0.4; 2.7] vs. 0.43 [0.04; 1.3], pg/ml, $p = 0.01$), cystatin C (44.7 [30.7; 97.5] vs. 35.6 [18.9; 87.3] ng/ml, $p = 0.04$), β_2-microglobulin (1.1 [0.5; 1.7] vs. 0.6 [0.2; 1.2] pg/ml, $p = 0.04$).

In the MAFLD group, the urinary excretion of cytokines and markers of early renal dysfunction exceeded the values of the group without MAFLD. In the studied groups we determined the corresponding associations of urinary cystatin C with the level of MCP-1 ($r = 0.53$ and $r = 0.47$), VEGF ($r = 0.72$ and $r = 0.73$), β_2-microglobulin ($r = 0.59$ and $r = 0.65$), IL-6 ($r = 0.63$ and $r = 0.54$). In the MAFLD group, we obtained an association with the level of resistin and uric acid ($r = 0.48$ and $r = 0.36$), $p < 0.05$. In addition, the associations of β_2-microglobulin with BMI ($r = 0.27$), HOMA-IR ($r = 0.39$), resistin ($r = 0.48$), creatinine ($r = 0.52$), TG ($r = 0.35$), urinary MCP-1 ($r = 0.72$), IL-6 ($r = 0.69$), and uric acid ($r = 0.72$), $p < 0.05$ were revealed. There were no significant associations in the group without MAFLD. In the group with MAFLD urinary IL-6 was associated with BMI ($r = 0.28$), WC/HC ratio ($r = 0.31$) uric acid level ($r = 0.56$), urinary MCP-1 ($r = 0.74$) and has a negative correlation with HDL-C ($r = -0.52$) $p < 0.05$.

Fatty liver disease produces a large number of hormone-like active substances, one of which is resistin. The expression of resistin is stimulated by inflammatory cytokines, while resistin itself enhances the formation of proinflammatory cytokines by macrophages [8]. A number of authors have shown that suppression of resistin at the genetic level restores tissue sensitivity to insulin and improves glucose homeostasis [9]. According to literature data, about 25 % of circulating IL-6 is synthesized by white adipose tissue. It has been stated in the literature that changes in the content of IL-6 in kidney tissue play an important role in the progression of CKD. VEGF is produced by macrophages and endotheliocytes, and serves as a marker of endothelial damage and a stimulator of fibrogenesis. It has been proven that an increase in the serum level of VEGF is associated with the progression of insulin resistance, enthelial dysfunction, and the development of NAFLD [10]. VEGF also plays a significant role in the differentiation and proliferation of mesangial cells; it has been proven that excessive production of VEGF contributes to the development of nephrosclerosis [11]. An association of increased TNF-α production with an accelerated rate of decrease in glomerular filtration rate and the development of cardiovascular pathology and metabolic diseases has been established in a number of publications [12]. In modern literature, much attention is paid to the study of MCP-1 in blood and urine in patients with metabolic diseases and CKD [13–15]. In our study, se-

rum and urinary levels of IL-6, MCP-1, VEGF and TNF-α in the groups with a combination of obesity and MAFLD were higher compared to the group with obesity without MAFLD. In the group with MAFLD, the association of blood and urine cytokines with the HOMA index, resistin, uric acid, cystatin C and β_2-macroglobulin was obtained, whereas in the obesity group without MAFLD, these associations were not revealed. Thus, it can be stated that obesity in combination with MAFLD contributes to endothelial dysfunction and activation of subclinical inflammation, causing a damaging effect on the glomerular and tubular apparatus of the kidneys.

Conclusion

1. Resistin can be considered as an unfavorable marker of cardio-metabolic disorders in people with MAFLD.

2. The association of markers of subclinical inflammation and endothelial dysfunction with markers of early renal dysfunction in women of reproductive age with MAFLD, established during the study, allows us to expand the understanding of the cardio-reno-metabolic continuum.

References

1. *Maev I.V., Andreev D.N., Kucheryavyy Yu.A.* Metabolically associated fatty liver disease – a disease of the 21st century: A review. *Consilium Medicum* 2022; 24 (5): 325–332. DOI: 10.26442/20751753.2022.5.201532 (in Russian).

2. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016, 64 (6): 1388–402. DOI: 10.1016/j.jhep.2015.11.004

3. *Jager K.J., Kovesdy C., Langham R., Rosenberg M., Jha V., Zoccali C.* A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. Kidney Int. 2019 Nov; 96 (5): 1048–1050. DOI: 10.1016/j.kint.2019.07.012. Epub 2019 Sep 30. PMID: 31582227.

4. *Musso G., Cassader M., Cohney S. et al.* Emerging Liver-Kidney Interactions in Nonalcoholic Fatty Liver Disease. Trends Mol Med 2015; 21: 645–662.

5. *Statsenko M.E., Turkina S.V., Ermolenko A.A., Gorbacheva E.E., Sabanov A.V.* Non-alcoholic fatty liver disease – a new risk factor for the development of chronic kidney disease. *Journal of Volgograd State Medical University* 2018; 2 (66): 125–130. DOI: 10.19163/1994-9480-2018-2(66)-125-130 (in Russian).

6. *Drapkina O.M., Zyatenkov E.V.* The involvement of kidneys in chronic heart failure patients with liver steatosis. *Cardiovascular Therapy and Prevention* 2016; 15 (1): 26–30. DOI: 10.15829/1728-8800-2016-1-26-30 (in Russian).

7. *Verbovoy A.F., Verbovaya N.I., Dolgikh Yu.A.* Obesity is the basis of metabolic syndrome. *Obesity and metabolism* 2021; 18 (2): 142–149. DOI: 10.14341/omet12707 (in Russian).

8. *Janke J., Engeli S., Gorzelniak K. et al.* Resistin gene expression in human adipocytes is not related to insulin resistance. Obes. Res. 2002; 10: 1–5.

9. *Tripathi D., Kant S., Pandey S., Ehtesham N.Z.* Resistin in metabolism, inflammation, and disease. FEBS J. 2020 Aug; 287 (15): 3141–3149. DOI: 10.1111/febs.15322. Epub 2020 Apr 21. PMID: 32255270

10. *Park S., Kim J.W., Kim J.H.* Differential Roles of Angiogenesis in the Induction of Fibrogenesis and the Resolution of Fibrosis in Liver. Biol Pharm Bull. 2015; 38 (7): 980–985.

11. *Gulyaeva I.L., Bulatova I.A., Pestrenin L.D.* Role of vascular endothelial growth factor in the pathogenesis of hepatic steatosis and dyslipidemia. *Pathological physiology and experimental therapy* 2020; 64 (4): 31–36. DOI: 10.25557/0031-2991.2020.04.31-36 (in Russian).

12. *Murkamilov I.T., Aitbaev K.A., Fomin V.V., Murkamilova Zh.A., Yusupov F.A., Redzhapova N.A., Rayimzhanov Z.R., Schastlivenko A.I.* Study of endothelial vascular growth factor, markers of inflammation and vascular stiffness in chronic kidney disease. *Clinical nephrology* 2020; 2: 41–51. DOI: 10.18565/nephrology.2020.2.43-51 (in Russian).

13. *Chen J., Bundy J.D., Hamm L.L., Hsu C.Y., Lash J., Miller E.R. 3rd, Thomas G., Cohen D.L., Weir M.R., Raj D.S., Chen H.Y., Xie D., Rao P., Wright J.T. Jr, Rahman M., He J.* Inflammation and Apparent Treatment-Resistant Hypertension in Patients With Chronic Kidney Disease. Hypertension. 2019; 73 (4): 785–793. DOI: 10.1161/HYPERTENSIONAHA.118.12358. PMID: 30776971; PMCID: PMC6416070

14. *Satirapoj B., Dispan R., Radinaha6 med P., Kitiyakara C., Satirapoj B., Dispan R., Radinahamed P., Kitiyakara C.* Urinary epidermal growth factor, monocyte chemoattractant protein 1 or their ratio as predictors for rapid loss of renal function in type 2 diabetic patients with diabetic kidney disease. BMC Nephrol 2018; 19 (1): 246.

15. *Thakur V., Chattopadhyay M.* Early Urinary Markers for Diabetic and Other Kidney Diseases. Curr Drug Targets. 2018; 19 (7): 825–831. DOI: 10.2174/1389450119666180319124639. PMID: 29552988.

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PREVALENCE OF MAIN RISK FACTORS AND CYTOKINE PROFILE IN PATIENTS WITH ACUTE CORONARY SYNDROME AND DIFFERENT SERUM MYOSTATIN LEVELS

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РАСПРОСТРАНЕННОСТЬ ОСНОВНЫХ ФАКТОРОВ РИСКА И ЦИТОКИНОВЫЙ ПРОФИЛЬ У ПАЦИЕНТОВ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ И РАЗНЫМ УРОВНЕМ МИОСТАТИНА СЫВОРОТКИ КРОВИ

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Objective. To study the prevalence of the main risk factors and the value of proinflammatory cytokines in patients with acute coronary syndrome (ACS) depending on the determined level of serum myostatin.
Materials and methods. 120 patients with ST elevation ACS (STE-ACS) and non-ST-segment elevation ACS (NSTE-ACS), hospitalized in the cardiology department of the regional vascular center were examined.

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In 86 patients, the level of serum myostatin and proinflammatory cytokines was determined on the 5th day of the development of acute coronary syndrome.
Results. Patients were divided into two subgroups depending on the level of serum myostatin which was determined: group 1 – with a lower level of myostatin, group 2 – with a higher level of myostatin. Group 1 (serum myostatin level from 0.038 to 0.084 ng/ml) consisted of 23 patients (16 males). Group 2 (serum myostatin level from 0.137 to 0.630 ng/ml) contained 21 patients (14 males). The main risk factors for cardiovascular diseases such as family history of early development of cardiovascular diseases, smoking, dyslipidemia, obesity, arterial hypertension and type 2 diabetes mellitus were assessed.
The levels of pro-inflammatory cytokines were determined. Tumor necrosis factor alpha (TNF-alpha) and interleukin 18 (IL-18) levels were significantly higher in patients with higher myostatin levels. Correlation analysis revealed a relationship between serum myostatin concentration and TNF-alpha level ($r = 0.34$; $p = 0.0016$).
Conclusions. No differences in the prevalence of risk factors in patients with ACS and different myostatin levels, except for smoking were revealed in the study, the frequency of smoking was higher in the group with higher myostatin levels. Greater activity of pro-inflammatory cytokines TNF-alpha and IL-18 was revealed in patients with higher levels of myostatin, as well as a significant correlation between the level of myostatin and TNF-alpha.
Keywords. Myostatin, proinflammatory cytokines, acute coronary syndrome.

Цель. Изучить распространенность основных факторов риска и значения провоспалительных цитокинов у пациентов с острым коронарным синдромом (ОКС) в зависимости от определяемого уровня сывороточного миостатина.
Материалы и методы. Обследовано 120 пациентов с ОКС с подъемом (ОКСпST) и без подъема сегмента ST (ОКСбпST), госпитализированных в отделение кардиологии на базе регионального сосудистого центра. У 86 пациентов из госпитализированных был определен уровень сывороточного миостатина и провоспалительных цитокинов на 5-е сутки развития острого коронарного синдрома.
Результаты. Пациентов разделили на две подгруппы в зависимости от определяемого уровня сывороточного миостатина: группу 1 – с более низким уровнем миостатина, группу 2 – с более высоким уровнем миостатина. Группу 1 (уровень сывороточного миостатина от 0,038 до 0,084 нг/мл) составили 23 пациента (из них 16 мужчин). Группу 2 (уровень сывороточного миостатина от 0,137 до 0,630 нг/мл) – 21 пациент (из них 14 мужчин). Были оценены основные факторы риска сердечно-сосудистых заболеваний: наследственная отягощенность по раннему развитию сердечно-сосудистых заболеваний, курение, дислипидемия, ожирение, артериальная гипертензия и сахарный диабет 2-го типа.
Определены уровни провоспалительных цитокинов. Уровни фактора некроза опухоли альфа (ФНО-α) и интерлейкина 18 (IL-18) были достоверно выше у пациентов с более высоким уровнем миостатина. По данным корреляционного анализа выявлена взаимосвязь между концентрацией миостатина сыворотки и уровнем ФНО-α ($r = 0,34$; $p = 0,0016$).
Выводы. В исследовании не выявлено различий по распространенности факторов риска у пациентов с ОКС и разным уровнем миостатина, за исключением курения, частота которого была выше в группе с более высоким уровнем миостатина. Зафиксирована большая активность провоспалительных цитокинов ФНО-α и IL-18 у пациентов с более высокими уровнями миостатина, а также достоверная корреляция между уровнем миостатина и ФНО-α.
Ключевые слова. Миостатин, провоспалительные цитокины, острый коронарный синдром.

INTRODUCTION

Myostatin (growth differentiation factor 8) is a member of the superfamily of the transforming growth factor-β whose primary target is myoblasts. It is secreted primarily by skeletal muscle, although small amounts of myostatin are also produced by the myocardium and adipose tissue [1]. It is secreted primarily by skeletal muscles, although small amounts of myostatin are also produced by the myocardium and adipose

tissue [1]. Myostatin inhibits skeletal muscle development and regulates fibroblast proliferation in skeletal muscle, i.e. the properties of the extracellular matrix [2], and also affects the structure and function of tendons [3]. The role of myostatin in influencing the cardiac muscle or myofibroblasts in coronary heart disease (CHD) and myocardial infarction (MI) is less clear. Recent studies in transgenic animals have shown that long-term overexpression of myostatin in the mouse heart reduces ejection fraction (EF) and stroke volume, increases end-systolic and diastolic volumes, induces the development of fibrosis and a decrease in heart weight, whereas the removal of myostatin has the opposite effect – it leads to myocardial hypertrophy [1]. In mice, Sarina Lim et al. found significant differences in outcomes between myostatin-null and wild-type mice after MI. The myostatin-null group had better EF recovery, less myocardial collagen deposition, and lower mortality. The researchers hypothesized that low myostatin levels are associated with better cardiac function after MI, possibly by limiting the extent of fibrosis [4].

There are isolated studies concerning the concentration of myostatin in the serum after myocardial infarction in humans. The study by Oliveira et al. [5] included 102 patients with MI and showed a decrease in the concentration of myostatin, compared to that in healthy people. Mortality among patients with lower concentrations of serum myostatin was higher than among patients with less reduced levels.

Thus, there are quite contradictory data on the direction of changes in myostatin concentration in the post-infarction period in the experiment and in clinical observations. Obviously, additional studies are needed to study the relationship between the myostatin level and the course of the disease in patients with acute coronary syndrome.

The aim of the study was to investigate the prevalence of major risk factors and the significance of proinflammatory cytokines in patients with acute coronary syndrome depending on the determined level of serum myostatin.

MATERIALS AND METHODS

A total of 120 patients with acute coronary syndrome with and without ST elevation were examined, hospitalized in the Cardiology Department at the Regional Vascular Center of the S.N. Grinberg City Clinical Hospital (RVC S.N. Grinberg City Clinical Hospital) from 2019 to 2021.

The inclusion criteria for the study were: diagnosis of acute coronary syndrome according to the clinical guidelines of the Russian Ministry of Health and the recommendations of the European Society of Cardiology[1]; age 30–90 years; voluntary informed consent of the patient to participate in the study. Exclusion criteria were non-coronary heart disease, malignant neoplasms, kidney and liver diseases with impaired function, blood diseases, acute infectious diseases, the presence of heart failure stage IIB–III and functional class III–IV before hospitalization.

Examination and treatment of patients was carried out in accordance with the Clinical Guidelines of the Russian Ministry of Health, Guidelines of the European Society of Cardiology[2], in force at the time of the study.

All patients underwent collection of clinical and anamnestic data; physical examination with measurement of blood pressure (BP), heart rate (HR), height and weight with calculation of body mass index (BMI), waist circumference (WC) and hip circumference (HC) with calculation of the WC / HC ratio.

Standard laboratory testing included a complete blood count; follow-up of biochemical markers of cardiocytolysis (Troponin I-high sensitive, creatine phosphokinase-MB (CPKMB)); urea content, blood creatinine with calculation of the glomerular filtration rate (cGFR); aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, glucose, blood lipids (total cholesterol (TC), low-density lipoprotein (LDL), very low-density lipoproteids (VRDL), high density lipoproteins (HDL), triglycerids (TG) with calculation of the atherogenic coefficient (AC) and non-high-density lipoprotein cholesterol).

In 86 patients, the level of serum myostatin and proinflammatory cytokines was determined on the 5th day of development of acute coronary syndrome.

Blood sampling for the study was performed from the cubital vein on an empty stomach in the morning. Venous blood, obtained without anticoagulants in vacuum tubes with gel, was left to stand for 30 minutes at room temperature until a clot is formed. The tubes were then centrifuged for 10 min at 1500 rpm. The separated serum was transferred to clean Eppendorf tubes, frozen and stored at -30 °C.

The concentration of myostatin was determined by enzyme immunoassay using the ELISA Kit for Myostatin (MSTN), USA, catalog No: CEB653Hu.

Also, by the enzyme immunoassay method, interleukin 6 (IL-6) was determined using the Interleukin-6-IFA-BEST reagent kit (A-8768) from ZAO Vector-Best (Russia) (series 42), interleukin 18 (IL-18) using the Interleukin-18-IFA-BEST reagent kit (A-8770) from ZAO Vector-Best (Russia) (series 28), and tumor necrosis factor alpha (TNF-α) using the Alpha-TNF-IFA-BEST reagent kit (A-8756) from ZAO Vector-Best (Russia) (series 65).

Instrumental diagnostic studies included electrocardiography (ECG); Holter ECG monitoring (HM ECG); echocardiography (EchoCG); chest radiography; selective coronary angiography (CAG).

Electrocardiographic examination (Nihon Kohden Cardiofax C ECG-2150, Japan)

[2] ESC Guidelines for the Management of Patients with Acute Myocardial Infarction without ST Elevation 2015. Russian Journal of Cardiology 2016, 3 (131): 9-63. DOI: 10.15829/1560-4071-2016-3-9-63; ESC Guidelines for the Management of Patients with Acute Myocardial Infarction with ST Elevation 2017. Russian Journal of Cardiology 2018; 23 (5): 103-158. DOI: 10.15829/1560-4071-2018-5-103-158; Clinical Guidelines of the Ministry of Health of the Russian Federation. "Acute Myocardial Infarction without ST Elevation of Electrocardiogram". Russian Society of Cardiology in Conjunction with the Association of Cardiovascular Surgeons of Russia. M. 2020; Clinical Guidelines of the Ministry of Health of the Russian Federation. "Acute Myocardial Infarction with ST Elevation of the Electrocardiogram." Russian Society of Cardiology in Conjunction with the Association of Cardiovascular Surgeons of Russia. M. 2020.

was performed in 12 standard leads upon admission of patients to hospital and then daily. To identify rhythm and conduction disturbances, the presence and duration of myocardial ischemia episodes, Holter ECG monitoring was performed (Astrocard Holtersystem-2f, AO MEDITEK, Russia).

Selective coronary angiography (CAG) was performed by specialists from the Department of X-ray Surgical Diagnostic and Treatment Methods of the S.N. Grinberg Regional Vascular Centre of the City Clinical Hospital using standard techniques and radial access.

All patients with acute coronary syndrome with persistent ST elevations (STE-ACS) underwent emergency CAG with subsequent reperfusion of the infarct-related artery. The decision on the necessity and urgency of CAG with possible percutaneous coronary intervention in patients with NSTE-ACS was made after risk stratification according to the GRACE[3] Scale.

Patients received therapy in accordance with Clinical Guidelines[3]: dual antiplatelet therapy, anticoagulant therapy (low molecular weight heparins), beta-blockers, mineralocorticoid receptor antagonists, drugs from the group of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, statins.

Statistical processing of the obtained data was carried out using the Statistica 10.0 program (StatSoft, Inc., USA). The Kolmogorov-Smirnov criterion was used to determine the normality of the distribution of features. To describe quantitative characteristics, the median (Me) and quartiles (Q_1, Q_3) were used. When assessing the statistical significance of differences (d) in independent samples for quantitative characteristics, the Mann – Whitney *U*-test (*U*) was used. The reliability of differences for qualitative characteristics was assessed using the nonparametric XI table test (χ^2). The relationship between the quantitative characteristics under study was determined using the correlation coefficient (*r*). The correlation was considered statistically reliable at $p < 0.05$.

RESULTS AND DISCUSSION

The distribution pattern of myostatin levels in patients differed from normal (Figure). The distribution median was 0.1131 ng/ml, the interquartile range (25–75 %) was 0.0835–0.134 ng/ml. To study the characteristics of patients with different levels of serum myostatin, two subgroups were taken for analysis: the 1st one included patients with low myostatin levels (1st quartile), the 2nd – with high (4th quartile).

[3] ESC Guidelines for the Management of Patients with Acute Coronary Syndrome without Persistent ST Elevation 2015. Russian Journal of Cardiology 2016, 3 (131): 9-63. DOI: 10.15829/1560-4071-2016-3-9-63; ESC Guidelines for the Management of Patients with Acute Myocardial Infarction with ST Elevation 2017. Russian Journal of Cardiology 2018; 23 (5): 103-158. DOI: 10.15829/1560-4071-2018-5-103-158; Clinical Guidelines of the Ministry of Health of the Russian Federation. "Acute Coronary Syndrome without ST Elevation of the Electrocardiogram." Russian Society of Cardiology with the Participation of the Association of Cardiovascular Surgeons of Russia. Russian Society of Cardiology in Conjunction with the Association of Cardiovascular Surgeons of Russia. M. 2020; Clinical Guidelines of the Ministry of Health of the Russian Federation. "Acute Myocardial Infarction with ST Elevation of Electrocardiogram". Russian Society of Cardiology with the Participation of the Association of Cardiovascular Surgeons of Russia. M. 2020.

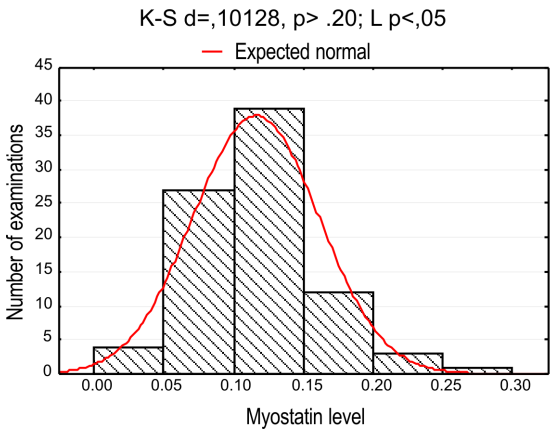

Fig. Histogram of Distribution of Myostatin Values in Patients with ACS

Group 1 (level of serum myostatin from 0.038 to 0.084 ng/ml) consisted of 23 patients (including 16 men). Group 2 (level of serum myostatin from 0.137 to 0.630 ng/ml) – 21 patients (including 14 men). The average age in Group 1 was 68 [58; 72] years, in Group 2 – 60 [51; 69] years. There were no statistically significant differences between the groups in terms of gender and age. The clinical characteristics of patients in both groups are presented in Table 1.

As can be seen from Table 1, the frequency of occurrence of the main risk factors for cardiovascular diseases (except smoking), concomitant diseases, and the history of coronary heart disease did not differ between the groups. Smokers were more common in the group with higher myostatin levels ($p = 0.011$). The smoking index did not differ and was 25.0 [14.0; 39.0] in group 2 versus 27.0 [19.5; 28.5] pack-years in group 1, respectively ($p = 0.876$). The groups were comparable in the structure of the final clinical diagnosis: 11 patients in each group were diagnosed with myocardial infarction, unstable cardiac angina was diagnosed in 12 people in group 1 and in 10 in group 2 ($p = 0.788$).

Table 2 presents the values of the studied proinflammatory cytokines. The levels of TNF-α and IL-18 were significantly higher in patients of the 2nd group. The values of IL-6 did not differ.

According to the correlation analysis, a relationship was found between the concentration of serum myostatin and the level of TNF-α ($r = 0.34$; $p = 0.0016$).

In recent decades, much new data has been obtained on various myokines and their local and systemic effects [6]. In particular, it has been shown that myostatin suppresses muscle tissue growth by reducing proliferation, myocyte differentiation, and protein synthesis [7; 8].

J. Dong et al. demonstrated in an experiment an increase in fibroblast division under the influence of myostatin, which may result in muscle tissue fibrosis [9]. In the cardiac muscle, this process can influence the remodeling of cardiac sections in coronary heart disease and heart failure. Animal experiments have shown that in case of cardiac pathology the level of myostatin production in cardiac tissue increases several times [10]. In myocardial infarction, myostatin transcription increases in cardiomyocytes located around the damaged area [11], and the increase in concentration persists in animals after 8 weeks from the moment of MI [12]. In clinical studies, myostatin levels were found

Table 1

Clinical Performance of Patients

Characteristic Value	Group 1, $n = 23$	Group 2, $n = 21$	p
Sex (male / female), %	69.6/30.4	66.7/33.3	0.899
Age, years	68 [58; 72]	60 [51; 69]	0.693
BMI, kg/m^2	28.7 [24.8; 31.2]	29.1 [26.1; 32.5]	0.148
Waist circumference (WC), cm	92 [86; 96]	95 [89; 103]	0.111
Hip circumference Окружность бедер (HC), cm	96 [90; 100]	103 [99; 106]	0.001
WC/HC, relative units	0.96 [0.90; 0.98]	0.96 [0.87; 1.02]	0.925
Heart rate, bpm	74 [70; 74]	74 [68; 78]	0.239
SAP, mm Hg	130 [120; 140]	140 [130; 160]	0.205
DBP, mm Hg	80 [70; 90]	90 [80; 90]	0.307
Hereditary load for early development of cardiovascular diseases, abs./%	5/21.7	5/23.8	0.871
Smoking, abs./%	3/13	10/47.6	0.011
Dyslipidemia, abs./%	21/91.3	20/95.2	0.243
Obesity, abs./%	8/34.8	6/28.6	0.637
AH, abs./%	19/82.6	20/95.2	0.196
Type 2 diabetes, abs./%	6/26.1	8/36.4	0.626
CAD H/O, abs./%	14/60.9	16/76.2	0.550
PC H/O, abs./%	5/21.7	10/47.6	0.182

Notice: MAP – systolic arterial pressure. DBP – diastolic blood pressure. AH – arterial hypertension. Diabetes – diabetes mellitus.

Table 2

Serum Interleukin Levels in Patients with Different Serum Myostatin Levels (*Me* [Q_1; Q_3])

Characteristic Value	Group 1, $n = 23$	Group 2, $n = 21$	p
TNF-α, pg/ml	1.5 [1.1; 2.7]	3 [2.6; 3.4]	0.012
IL-18, pg/ml	175.4 [133.9; 264.2]	259.9 [187.9; 300.4]	0.043
IL-6, pg/ml	5.3 [1.6; 9.5]	3.6 [3.3; 7.3]	0.991

to be increased in left ventricular myocardial samples from patients suffering from ischemic or dilated cardiomyopathy (DCM) [13].

The main source of myostatin in the systemic circulation is skeletal muscle, but in cardiac pathology, cardiac myostatin also contributes to this indicator. This was shown in an experiment on mice [14].

It can be assumed that high production of myostatin in patients with acute coronary syndrome may lead to more pronounced fibrosis processes in the myocardium, systemic lipid metabolism disorders and atherogenesis, as well as sarcopenia [6].

This study revealed greater activity of proinflammatory cytokines TNF-α and IL-18

in patients with higher myostatin levels, as well as a significant correlation between myostatin levels and TNF-α. It can be assumed that elevated myostatin levels are associated with metabolic imbalance and systemic inflammatory response with hyperexpression of proinflammatory cytokines [4; 15]. Our data are supported by the results of experimental work, which showed that tumor necrosis factor-alpha (TNF-alpha) increases the expression of myostatin [12].

Study limitation

This study is limited by the sample size of patients, further research in this direction requires a larger sample size.

Conclusion

The study found no differences in the prevalence of major risk factors in patients with acute coronary syndrome and different levels of myostatin, with the exception of smoking, the frequency of which was higher in the group with higher levels of myostatin. Greater activity of proinflammatory cytokines TNF-α and IL-18 was found in patients with higher levels of myostatin, as well as a direct relationship between the level of myostatin and TNF-α.

References

1. *Knapp M., Supruniuk E., Górski J.* Myostatin and the Heart. Biomolecules. 2023 Dec 12; 13 (12): 1777. DOI: 10.3390/biom13121777. PMID: 38136649; PMCID: PMC10741510.

2. *Mendias C.L., Gumucio J.P., Bakhurin K.I. et al.* Physiological loading of tendons induces scleraxis expression in epitenon fibroblasts. J. Orthop. Res. 2012; 30 (4): 606.

3. *Kjær M., Langberg H., Heinemeier K. et al.* From mechanical loading to collagen synthesis, structural changes and function in human tendon. Scand. J. Med. Sci. Sport. 2009; 19 (4): 500.

4. *Sarina Lim, Chris D. McMahon, Kenneth G. Matthews, Gerard P. Devlin, Marianne S. Elston, John V. Conaglen.* Absence of Myostatin Improves Cardiac Function Following Myocardial Infarction, Heart, Lung and Circulation, 2018; 27 (6): 693–701. DOI: 10.1016/ j.hlc.2017.05.138

5. *Oliveira P.G.S., Schwed J.F., Chiuso-Minicucci F., Duarte S.R.S., Nascimento L.M., Dorna M.S., Costa N.A., Okoshi K., Okoshi M.P., Azevedo P.S. et al.* Association Between Serum Myostatin Levels, Hospital Mortality, and Muscle Mass and Strength Following ST-Elevation Myocardial Infarction. Heart Lung Circ. 2022; 31: 365–371.

6. *Golovskoj B.V., Berg M.D., Bulatova I.A.* The muscular system in maintaining health and preventing chronic non-infectious diseases. *Perm Medical Journal* 2021; 38 (1): 72–86. DOI: 10.17816/pmj38172-86. EDN TPOYTR (in Russian).

7. *Ríos R., Carneiro I., Arce V.M., Devesa J.* Myostatin is an inhibitor of myogenic differentiation. Am J Physiol Physiol. 2002; 282 (5): C993-C999. DOI: 10.1152/ajpcell.00372.2001

8. *Taylor W.E., Bhasin S., Artaza J. et al.* Myostatin inhibits cell proliferation and protein synthesis in C 2 C 12 muscle cells. Am J Physiol Metab. 2001; 280 (2): E221-E228. DOI: 10.1152/ajpendo.2001.280.2.E221

9. *Dong J., Dong Y., Chen Z., Mitch W.E., Zhang L.* The pathway to muscle fibrosis depends on myostatin stimulating the differentiation of fibro/adipogenic progenitor cells in chronic kidney disease. Kidney Int. 2017; 91 (1): 119–128. DOI: 10.1016/j.kint.2016.07.029

10. *Shyu K.G., Lu M.J., Wang B.W. et al.* Myostatin expression in ventricular myocardium in a rat model of volumeoverload heart failure. Eur. J. Clin. Invest. 2006; 36 (10): 713.

11. *Sharma M., Kambadur R., Matthews K.G. et al.* Myostatin, a transforming growth factor-β superfamily member, is expressed in heart muscle and is upregulated in cardiomyocytes after infarct. J. Cell. Physiol. 1999; 180 (1): 1.

12. *Lenk K., Schur R., Linke A. et al.* Impact of exercise training on myostatin expression in the myocardium and skeletal muscle in a chronic heart failure model. Eur. J. Heart Fail. 2009; 11 (4): 342.

13. *George I., Bish L.T., Kamalakkannan G. et al.* Myostatin activation in patients with advanced heart failure and after mechanical unloading. Eur. J. Heart Fail. 2010; 12 (5): 444.

14. *Breitbart A., Auger-Messier M., Molkentin J.D., Heineke J.* Myostatin from the heart: local and systemic actions in cardiac failure and muscle wasting. Am. J. Physiol. Heart Circ. Physiol. 2011; 300 (6): H1973.

15. *Ilich J.Z., Kelly O.J., Inglis J.E. et al.* Interrelationship amond muscle, far, fnd bone: Connecting the dots on cellular, hormonal, and whole body levels. Ageing Res Rev. 2014; 15: 51–60. DOI: 10.1016/j.arr.2014.02.007. PMID: 24632496.

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LITERATURE REVIEW

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POST-COVID-19 COGNITIVE IMPAIRMENTS (LITERATURE REVIEW)

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ПОСТКОВИДНЫЕ КОГНИТИВНЫЕ НАРУШЕНИЯ (ОБЗОР ЛИТЕРАТУРЫ)

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Post-COVID-19 condition (PCC) is a condition that occurs in patients with a history of SARS-CoV-2 infection 3 months after the onset of COVID-19 with symptoms that last at least 2 months and are not explained by any other diseases. PCC affects from 17 % to 28 % of patients and includes a wide range of clinical manifestations, including cognitive dysfunction. Cognitive dysfunctions can be manifested by a wide range of symptoms, such as memory impairment, attention deficit, executive dysfunction, and reduced information processing speed. Risk factors for developing PCC, with or without cognitive impairment, include late adulthood, pre-existing medical conditions, and severity of acute illness. The underlying mechanisms remain unclear, but suspected factors include neuroinflammation, hypoxia, vascular damage and latent reactivation of the virus,

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this does not exclude the possibility of direct viral central nervous system invasion. The analysis of retrospective cohort studies showed that the risk of cognitive deficits, dementia, psychotic disorders and seizures remained elevated even 2 years after the infection of SARS-CoV-2. It is interesting to note that there were no differences in the risks of neurological and psychiatric outcomes between infections caused by Omicron (B.1.1.529) or Delta (B.1.617.2) variants. Recent researches show that cognitive deficits after infection of SARS-CoV-2 persist for two years after the infection and were the greatest in individuals with more severe SARS-CoV-2 infection [2]. COVID-19 can impair the function of the interoceptive network of the brain selectively, while exteroceptive brain processing remains undamaged [3].
Keywords. Post-COVID-19 condition, cognitive impairment, post-COVID disorders.

Изучены последние данные литературы о постковидных когнитивных нарушениях. Post-COVID-19 condition (PCC) – это состояние, которое возникает у пациентов с инфекцией SARS-CoV-2 в анамнезе через 3 месяца после начала COVID-19 с симптомами, длящимися не менее 2 месяцев и не объясняющимися никакими иными заболеваниями. PCC поражает от 17 до 28 % пациентов и включает в себя широкий спектр клинических проявлений, в том числе когнитивную дисфункцию. Когнитивные дисфункции могут проявляться в виде широкого спектра симптомов, включая ухудшение памяти, дефицит внимания, исполнительную дисфункцию и снижение скорости обработки информации. Факторы риска развития PCC, с когнитивными нарушениями или без них, включают пожилой возраст, ранее существовавшие заболевания и тяжесть острого заболевания. Лежащие в основе механизмы остаются неясными, но предполагаемые факторы включают нейровоспаление, гипоксию, повреждение сосудов и латентную реактивацию вируса, не исключая возможности прямой вирусной инвазии в центральную нервную систему.
Анализ ретроспективных когортных исследований привел к выводу, что риск когнитивного дефицита, слабоумия, психотических расстройств и судорог оставался повышенным даже через 2 года после заражения SARS-CoV-2. Интересно также то, что не наблюдалось различий в рисках неврологических и психиатрических исходов между инфекциями, вызванными вариантами «Омикрон» (B.1.1.529) или «Дельта» (B.1.617.2). Последние исследования подводят к выводу, что когнитивный дефицит после заражения SARS-CoV-2 сохранялся через два года после заражения и был наибольшим у лиц с более тяжелой инфекцией SARS-CoV-2, а также показывают, что COVID-19 может избирательно нарушать функцию интероцептивной сети мозга, оставляя нетронутой экстероцептивную обработку мозга.
Ключевые слова. COVID-19, post-COVID-19 condition, когнитивные нарушения.

INTRODUCTION

The new coronavirus infection has led to long-term consequences in the form of cognitive impairment in the working population, since vaccination against SARS-CoV-2 was not a completely reliable protection against the post-COVID-19 condition (PCC). Today, there is still insufficient data on what causes cognitive dysfunction in patients with PCC, and even less is known about the most effective rehabilitation measures [1; 2]. The latest foreign data on cognitive impairment associated with SARS-CoV-2 infection and their prevalence in the population were analyzed through the PubMed® search engine. The novelty (2022–2023) was the main criteria for selecting articles. The following queries were entered into the search: cognitive dysfunction in post-COVID-19; the effects of COVID-19 on cognitive; persistent symptoms after COVID-19; post-COVID syndrome; main symptoms of long-COVID.

According to the World Health Organization (WHO), PCC is a condition that

occurs in patients with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months after the onset of COVID-19, with symptoms that last at least 2 months and are not explained by any other diseases (World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. Geneva, Switzerland). PCC includes a wide range of clinical manifestations affecting multiple organ systems. In most people with PCC, symptoms gradually resolve over time, but in some patients, they persist for many months or even years after SARS-CoV-2 infection and have a significant impact on quality of life [1].

Long-term cognitive dysfunction is one of the most common impairments in PCC, affecting 17 to 28 % of people more than 12 weeks after infection and persisting for several years in some cases [3]. Cognitive dysfunction can be manifested as a wide range of symptoms, including memory impairment, attention deficit, executive dysfunction, and reduced information processing speed. Risk factors for developing PCC, with or without cognitive impairment, include late adulthood, pre-existing medical conditions, and severity of acute illness. The underlying mechanisms remain unclear, but suspected factors include neuroinflammation, hypoxia, vascular damage and latent reactivation of the virus, this does not exclude the possibility of direct viral central nervous system invasion [1].

The most common symptoms in PCC are fatigue, memory problems, decreased concentration, and impaired attention. Large meta-analyses by F. Ceban et al. and Q. Han et al. summarize that the overall proportion of individuals with cognitive impairment is 19–22 %. Cognitive impairment is also accompanied by sleep disturbances, anxiety, and depression [3; 4].

In the study by Rija Aziz et al. patients reported that the most common symptoms of PCC were fatigue (89 %), forgetfulness or "brain fog" (89 %), and difficulty concentrating (77 %). The Montreal Cognitive Assessment (MoCA) showed that 46 % had mild cognitive dysfunction. And in a study by Jedsada Khieukhajee, the prevalence of cognitive impairment after COVID-19, defined as a total MoCA score below 25 points, was 61.76 % [5; 6]. Testing the health of patients who had recovered from the new coronavirus infection using the PHQ-9 (Patient Health Questionnaire) in a study by Rija Aziz et al. showed that 42 % had moderate to severe depression. Moderate to severe anxiety was also detected in 38 % of COVID-19 survivors, as assessed by the General Anxiety Disorder-7 (GAD-7) test. Symptom severity was similar across gender, age, and initial disease severity. Patients with PCC presenting to an academic hospital after COVID-19 experienced multiple multisystem symptoms and functional impairments, regardless of initial COVID-19 disease severity [5].

Mihaela-Camelia Vasile et al. [7] assessed COVID-19-related neuropsychiatric disorders in a prospective study using the Mini-Mental State Examination (MMSE) and

MoCA questionnaires, which were administered to hospitalized COVID-19 patients who had experienced moderate to severe forms of the disease. Tests were performed at discharge and re-evaluated after 6 and 12 months. Baseline cognitive dysfunction was detected in 12.4 % of patients according to the MMSE test and in 19.7 % according to the MoCA scale. Overall cognitive dysfunction in COVID-19 normalized after 6 months, but some symptoms were quite severe, such as impaired concentration, short-term memory, and task performance skills. Male gender and the degree of hypoxia associated with the severity of COVID-19 infection were associated with cognitive dysfunction in the study group [7].

An analysis of retrospective cohort studies led M. Taquet et al. to the conclusion that the risk of cognitive deficit, dementia, psychotic disorders and seizures remained elevated even 2 years after SARS-CoV-2 infection [8]. It is interesting to note, that no differences in the risks of neurological and psychiatric outcomes were observed between infections caused by the Omicron (B.1.1.529) or Delta (B.1.617.2) variants [1]. Given that attentional functions define the fundamental basis of cognitive processes, they are crucial for managing our daily lives. Impaired attentional functions, even in cases of mild changes, directly affect performance in both daily tasks and professional activities.

Fatigue is a characteristic symptom in both acute COVID-19 and PCC. The prevalence rates of post-COVID fatigue range from 32 to 46 % in different studies, and from 18 to 39 % in a meta-analysis of one-year follow-up. In neurological conditions, decreased attention, slower processing speed, and tiredness were associated with the feeling of fatigue, but also showed a significant correlation with depression and sleep disturbances [5].

A recent meta-analysis by Tsampasian et al. showed that female gender, age, high BMI, and smoking were associated with an increased risk of developing PCC symptoms. The presence of concomitant diseases and previous hospitalization, including admission to the intensive care unit, were found to be associated with an even higher risk of PCC developing. Markers of systemic inflammation are associated with persistent fatigue and cognitive symptoms with significant functional impairment. Most authors indicate a significant proportion (40–80 %) of hospitalized patients experiencing post-COVID consequences in the form of neuropsychiatric symptoms. In line with this, vaccination against SARS-CoV-2, which reduces the risk of severe COVID-19 for most people, appears to reduce the risk of developing PCC after infection [1].

The following pathophysiological mechanisms have been discussed to explain the persistence of symptoms after infection with the SARS-CoV-2 virus: direct brain injury during acute SARS-CoV-2 infection, low-level persistence of viral antigens to SARS-CoV-2 in the CNS, reactivation of latent herpes viruses, epigenetic response, central and peripheral hypoxia, ongoing

systemic inflammation, neuroinflammation and autoimmune response, microvascular inflammation and microthrombosis, glucose metabolism in the brain [1].

A study by Nathan J. Cheetham et al. found that cognitive deficits following SARS-CoV-2 infection were detected nearly two years after infection and were greatest in individuals with longer duration of symptoms, persistent symptoms, and/or more severe infection. However, no such deficits were found in individuals who reported full recovery from COVID-19 [2].

The results of Siri-Maria Kamp et al. show that COVID-19 can selectively disrupt the function of the brain's interoceptive network while leaving exteroceptive processing intact. Dysfunctional interoceptive processing may be associated with attention/concentration deficits and poor mental health outcomes such as depression and anxiety [9].

In a study by C. Gouraud et al., patients with persistent symptoms following COVID-19 underwent a multi-faceted assessment to describe their symptoms, provide medical reports (diagnoses and recommendations), and assess satisfaction with treatment. Among 286 patients (mean age: 44 years; 70 % women), the most common symptoms were fatigue (86 %), shortness of breath (65 %), joint/muscle pain (61 %) and cognitive dysfunction (58 %), with a mean duration of 429 days. Physical activity rehabilitation was recommended to 91 % of patients. The median patient satisfaction with the rehabilitation program was 8 out of 10. Most patients attending this program had long-term symptoms and severe impairment in quality of life, received a diagnosis of functional somatic disorder and reported high levels of satisfaction with the program [10].

A study by M. Jayasekera et al. examined 153 patients treated for COVID infection at the University Hospital, Kotelawala Defence University of Sri Lanka in July 2021. Of the patients, 92 (60.2 %) had severe disease, 43 (28.1 %) had moderate disease, and 18 (11.7 %) had mild disease. The mean age was 57.2 (± 16.3) years, of which 83 (54.2 %) were men. Cognitive impairment was detected in 26 patients (13 women, 13 men). The authors did not find any difference in gender and age, and no relationship with fatigue was found. The condition returned to normal within 3 months. According to this publication, patients diagnosed with cognitive impairment experienced difficulties with concentration, memory, speech perception, and executive functions. However, the authors concluded that it is impossible to judge cognitive impairment without clear evidence of patient's premorbid intelligence [11]. Disease severity and age over 60 years were risk factors for the development of post-COVID syndrome. According to the study results, vaccination reduced post-COVID symptoms. Quality of life and cognitive impairment improved after 12 weeks. This may indicate that at least 12 weeks are required to detect true dementia in patients after COVID-19 [11; 12].

PCC may also be of great concern in the pediatric population, even in patients who do not require hospitalization. D. Buonsenso et al. [13] reported that symptoms persisted 120 days after COVID-19 infection in more than half of the children, in 42.6 % of whom these disorders limited daily activities. Fatigue, muscle and joint pain, headache, insomnia, difficulty breathing and increased heart rate were particularly common. Cognitive disorders were recorded in 34.3 % of patients who had recovered from COVID-19 [14]. The authors emphasize the need to monitor children for several months after hospitalization to maintain their mental health. According to the authors, the inclusion of psychological assessment in the diagnosis of children with post-COVID syndrome is a practical necessity. In May 2023, an Italian prospective cohort study was conducted to identify risk factors for post-COVID syndrome in children, and the authors noted the following factors: age over 10 years, concomitant diseases, acute phase of novel coronavirus infection in the intensive care unit, multisystem inflammatory syndrome, recently diagnosed Kawasaki syndrome [15].

In the pediatric cohort, cognitive impairment in the post-COVID syndrome is associated with asthenic syndrome. Common manifestations of cognitive impairment in children in the post-COVID period include: decreased concentration, visual gnosis, impaired visual-spatial perception, dynamic and kinesthetic praxis, and decline in thinking. Based on the concept of A.R. Luria, it can be assumed that the cognitive profile and nature of neurological complaints of children in the main group indicate that the temporo-parietal-occipital, mediobasal frontal-temporal regions of the brain, and the limbic-reticular complex are involved in the topic of disorders [16]. This requires a diagnostic algorithm and the development of correctional and educational programs for children with post-COVID cognitive impairment. According to K.S. Korotaeva et al., when examining children with the consequences of COVID-19, the most sensitive hematological indices were the degree of entropy of the leukocyte formula according to A.V. Gorelov, indicating a violation of the dynamic constancy of the leukocyte formula, indices of the ratio of neutrophils and monocytes, the ratio of lymphocytes and monocytes, showing the presence of a viral infection [17].

A study by M. Fotuhi et al. on the pathogenetic mechanisms of neurocognitive deficit caused by COVID-19 in adults divides the formation of neurological changes into three variants: 1) cytokine storm, but the brain is not affected; 2) cytokine storm causes inflammation of blood vessels; 3) cytokine storm damages the blood-brain barrier. In the first case, cognitive impairment does not seem to be observed. However, the emerging symptoms of COVID-19 include nausea, vomiting, sore throat, fever, anosmia and ageusia, the last two indicating damage to the peripheral nervous system. In the second variant, neurological impairment develops, leading

to partial hemiplegia, aphasia, brain fog, pain, blurred vision and ataxia. Working memory, attention deficit and cerebellar dysfunction are symptoms of cognitive impairment during this period. At this stage, COVID-19 symptoms include fatigue, body aches or discomfort, headache, insomnia, depression and/or anxiety. In the third and most severe variant of the disease, the patient develops encephalitis, coma, seizures and delirium. If the patient survives, motor functions, attention, memory, speech and executive functioning are significantly impaired. COVID-19 manifestations include chest discomfort, confusion, shortness of breath or difficulty breathing, and changes in blood pressure and heart rate [18].

Burak Yulug and other authors believe that SARS-CoV-2 may be a risk factor for Alzheimer's disease. The scientists compared 17 patients with COVID-19 with 20 control patients and assessed the impact of COVID-19 on overall cognitive performance, hippocampal volume and its connections. They showed that COVID-19 patients had significantly worse cognitive functioning and increased hippocampal connectivity, as evidenced by a strong correlation between hippocampal connectivity and cognitive performance. These findings of increased hippocampal connectivity in the absence of observable hippocampal morphological changes even in mild cases of COVID-19 infection may indicate a pre-structural compensatory mechanism to stimulate additional neural resources to combat cognitive dysfunction, as has been shown in the prodromal stages of degenerative cognitive disorders [19].

A systematic review and meta-analysis of 20 studies by Zoe Marjenberg et al. on the risks of prolonged manifestation of the main symptoms of COVID-19 after SARS-CoV-2 infection found that SARS-CoV-2 infection is associated with a significantly higher risk of memory problems and difficulty concentrating. However, the authors highlight that these risks are likely to change continually as vaccines, reinfections and new variants alter global immunity [20].

Conclusions

Long-term cognitive dysfunction is a common disorder affecting children and adults with PCC. Risk factors for the development of PCC in general include female gender, age, pre-existing medical conditions, and severity of acute illness, in pediatric practice – multisystem inflammatory syndrome, Kawasaki syndrome on the eve. Proposed mechanisms contributing to the development of PCC and cognitive impairment include neuroinflammation, hypoxia, vascular injury, latent viral reactivation, and direct viral invasion of the central nervous system. Treatment of cognitive dysfunction that persists for more than six months after the acute period of infection in PCC requires a multifaceted approach, including neuropsychological examination and individual rehabilitation, as well as systematic screening for early diagnosis of progressive brain pathologies. Further research on this

topic is needed to conduct evidence-based interventions specific to cognitive impairment associated with COVID-19.

References

1. *Möller M., Borg K., Janson C. et al.* Cognitive dysfunction in post-COVID-19 condition: Mechanisms, management, and rehabilitation. J Intern Med. 2023; 27. DOI: 10.1111/joim.13720

2. *Cheetham N.J., Penfold R., Giunchiglia V. et al.* The effects of COVID-19 on cognitive performance in a community-based cohort: a COVID symptom study biobank prospective cohort study. E Clinical Medicine. 2023; 62: 102086. DOI: 10.1016/j.eclinm.2023.102086

3. *Ceban F., Ling S., Lui L.M.W. et al.* Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis. Brain Behav Immun. 2022; 101: 93–135. DOI: 10.1016/j.bbi.2021.12.020

4. *Han Q., Zheng B., Daines L., Sheikh A.* Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. Pathogens. 2022; 11 (2): 269. DOI: 10.3390/pathogens11020269

5. *Aziz R., Siles N., Kelley M. et al.* Clinical characteristics of Long COVID patients presenting to a dedicated academic post-COVID-19 clinic in Central Texas. Sci Rep. 2023; 13 (1): 21971. DOI: 10.1038/s41598-023-48502-w

6. *Khieukhajee J., Rojana-Udomsart A., Srisarakorn P. et al.* Cognitive Impairment and Risk Factors in Post-COVID-19 Hospitalized Patients. Dement Geriatr Cogn Dis Extra. 2023; 13 (1): 18–27. DOI: 10.1159/000531743

7. *Vasile M.C., Vasile C.I., Arbune A.A. et al.* Cognitive Dysfunction in Hospitalized Patient with Moderate-to-Severe COVID-19: A 1-Year Prospective Observational Study. J Multidiscip Healthc. 2023; 16: 3367–3378. DOI: 10.2147/JMDH.S432969

8. *Taquet M., Sillett R., Zhu L. et al.* Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. Lancet Psychiatry. 2022; 9 (10): 815–827. DOI: 10.1016/S2215-0366(22)00260-7

9. *Kamp S.M., Buntić N., Amtmann J. et al.* Reduced concentration performance and heartbeat-evoked potential in individuals with a history of a SARS-CoV-2 infection. Neurosci Lett. 2023; 814: 137466. DOI: 10.1016/j.neulet.2023.137466

10. *Gouraud C., Thoreux P., Ouazana-Vedrines C. et al.* Patients with persistent symptoms after COVID-19 attending a multidisciplinary evaluation: Characteristics, medical conclusions, and satisfaction. J Psychosom Res. 2023; 174: 111475. DOI: 10.1016/j.jpsychores.2023.111475

11. *Jayasekera M.M.P.T., De Silva N.L., Edirisinghe E.M.D.T. et al.* A prospective cohort study on post COVID syndrome from a tertiary care centre in Sri Lanka. Sci Rep. 2023; 13 (1): 15569. DOI: 10.1038/s41598-023-42350-4

12. *Kozik V., Reuken P., Utech I. et al.* Characterization of neurocognitive deficits in patients with post-COVID-19 syndrome: persistence, patients' complaints, and clini-

cal predictors. Front Psychol. 2023; 14: 1233144. DOI: 10.3389/fpsyg.2023.1233144

13. *Buonsenso D., Munblit D., De Rose C., Sinatti D., Ricchiuto A., Carfi A., Valentini P.* Preliminary evidence on long COVID in children. Acta Paediatr. 2021; 110 (7): 2208–2211. DOI: 10.1111/apa.15870. Epub 2021 Apr 18. PMID: 33835507; PMCID: PMC8251440.

14. *Almeria M., Cejudo J.C., Sotoca J., Deus J., Krupinski J.* Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment. Brain Behav Immun Health. 2020; 9: 100163. DOI: 10.1016/j.bbih.2020.100163. Epub 2020 Oct 22. PMID: 33111132; PMCID: PMC7581383.

15. *Morello R., Mariani F., Mastrantoni L., De Rose C., Zampino G., Munblit D., Sigfrid L., Valentini P., Buonsenso D.* Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study. E Clinical Medicine. 2023

16. *Troitskaya L.A., Plotnikova I.A., Avakyan G.G., Erokhina V.A., Badalyan O.L., Muraveva A.V., Zelentsova V.L., Khodko O.K., Safarova S.T., Shirokova E.I., Rusina E.A., Sanina N.P., Terentev K.V., Rachin A.P.* Neuropsychological evaluation of cognitive disorders in children after COVID-19. Eur J Transl Myol. 2022; 32 (3): 10685. DOI: 10.4081/ejtm.2022.10685. PMID: 35838578; PMCID: PMC9580531.

17. *Korotaeva K.S., Furman E.G., Sumlivaya O.N.* Integral'nye pokazateli lejkocitarnoj formuly u detej s koronavirusnoj infekciej COVID-19. *Permskij medicinskij zhurnal* 2022; 39 (1): 27–34 (in Russian).

18. *Shariff S., Uwishema O., Mizero J. et al.* Long-term cognitive dysfunction after the COVID-19 pandemic: a narrative review. Ann Med Surg (Lond). 2023; 85 (11): 5504–5510. DOI: 10.1097/MS9.0000000000001265.

19. *Yulug B., Ayyıldız B., Ayyıldız S. et al.* Infection with COVID-19 is no longer a public emergency: But what about degenerative dementia? J Med Virol. 2023; 95 (9): e29072. DOI: 10.1002/jmv.29072.

20. *Marjenberg Z., Leng S., Tascini C. et al.* Risk of long COVID main symptoms after SARS-CoV-2 infection: a systematic review and meta-analysis. Sci Rep. 2023; 13 (1): 15332. DOI: 10.1038/s41598-023-42321-9.

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THE EFFECTIVENESS OF PHOTODYNAMIC THERAPY IN PEDIATRIC PRACTICE

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ЭФФЕКТИВНОСТЬ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ В ПЕДИАТРИЧЕСКОЙ ПРАКТИКЕ

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Photodynamic therapy (PDT) is a relatively young but rapidly developing method of treatment. Currently, PDT is widely used in dentistry, dermatology, oncology and other fields of medicine. Cases of successful treatment of tumors of the head and neck, brain, lungs, pancreas, colon, breast, prostate, bladder, cervix and skin using PDT are described in literature. In addition, the effectiveness of PDT in the treatment of bacterial and fungal infections has been repeatedly proved. To date, there are a large number of studies on the use of PDT in various diseases in adults, but few data on this subject in children. The authors have been searching for publications in the electronic databases PubMed, Google Scholar and eLibrary by the following keywords: "PDT", "photodynamic therapy", "pediatrics", "children", "dermatology", "dentistry", "pulmonology", "ophthalmology", "oncology". The search was conducted from the moment of the foundation of the corresponding database to August 2023. PDT is an innovative method of treating neoplasms and bacterial infections. On the basis of the data obtained while conducting the study, it can be confirmed that applying PDT allows to reduce the number of surgical interventions and achieve the best treatment results. All the studies and clinical cases with the use of PDT in the treatment of various diseases in children, which are presented in this review, demonstrated that the treatment results were better than those with standard therapy. However, certain limitations must be taken into account, these include difficulties in selecting a photosensitizer and its route of administration. At present PDT is being actively studied in the pediatric population, but there are still many gaps that require additional large-scale studies.
Keywords. Photodynamic therapy, PDT, dermatology, pediatrics, children, oncology; ophthalmology, dentistry.

Осуществлен анализ литературных данных, посвященных использованию фотодинамической терапии (ФДТ) при различных заболеваниях в педиатрической популяции. ФДТ – относительно молодой, но быстро развивающийся метод лечения. В настоящее время ФДТ активно применяется в стоматологии, дерматологии, онкологии и других областях медицины. В литературе описаны случаи успешного лечения опухолей головы и шеи, головного мозга, легких, поджелудочной железы, толстой кишки, молочной железы, простаты, мочевого пузыря, шейки матки и кожи с использованием ФДТ. Кроме того, неоднократно доказывалась эффективность использования ФДТ в терапии бактериальных и грибковых инфекций. На сегодняшний день имеется большое количество исследований, посвященных применению ФДТ при различных заболеваниях у взрослых, однако данные по детям ограничены. Авторами был проведен поиск публикаций в электронных базах данных PubMed, Google Scholar и ELibrary. Поиск проводился по следующим ключевым словам: PDT, photodynamic therapy, pediatric, children, dermatology, dentistry, pulmonology, ophthalmology, oncology, «ФДТ», «фотодинамическая терапия», «педиатрия», «дети», «дерматология», «стоматология», «пульмонология», «офтальмология», «онкология». Поиск проводился во временном интервале с момента основания соответствующей базы данных по август 2023 г.
ФДТ является инновационным методом лечения новообразований и бактериальных инфекций. Основываясь на имеющихся данных, можно утверждать, что ФДТ позволяет сократить количество хирургических вмешательств и добиться наилучших результатов лечения. Все исследования и клинические случаи использования ФДТ в терапии различных заболеваний у детей, представленные в настоящем обзоре, продемонстрировали, что результаты лечения были лучше, чем при проведении стандартной терапии. Однако необходимо учитывать наличие определенных ограничений, включая трудности с подбором фотосенсибилизатора и его пути введения. На сегодняшний день ФДТ активно изучается в педиатрической популяции, однако остается много пробелов, которые требуют проведения дополнительных масштабных исследований.
Ключевые слова. Фотодинамическая терапия, ФДТ, дерматология, педиатрия, дети, онкология, офтальмология, стоматология.

INTRODUCTION

Photodynamic therapy (PDT) is a relatively young but rapidly developing method of treatment [1]. Currently, PDT is widely used in dentistry, dermatology, oncology and other fields of medicine [2; 3]. Cases of successful treatment of tumors of the head and neck, brain, lungs, pancreas, colon, breast, prostate, bladder, cervix and skin using PDT are described in literature [4–6]. In addition, the effectiveness of PDT in the treatment of bacterial and fungal infections has been repeatedly proved [7]. To date, there are a large number of studies on the use of PDT in various diseases in adults, but few data on this subject in children. Thus, the aim of this study is to analyze the literature data on the use of PDT for various diseases in the pediatric population.

MATERIALS AND METHODS

The authors have been searching for publications in the electronic databases PubMed, Google Scholar and eLibrary by the following keywords: "PDT", "photodynamic therapy", "pediatric", "children", "dermatology", "dentistry", "pulmonology", "ophthalmology", "oncology", «ФДТ», «фотодинамическая терапия», «педиатрия», «дети», «дерматология», «стоматология», «пульмонология», «офтальмология», «онкология». The search was conducted in the time interval from the moment the corresponding database was founded until August 2023. The authors independently analyzed article titles and abstracts, after which the full text of relevant studies was extracted.

MECHANISM OF ACTION OF PDT AND APPLICATION SCOPE

The PDT mechanism is based on the oxidation of biomolecules under the influence of light of the appropriate wavelength due to the preliminary introduction of a so-called photosensitizer into the irradiated area. A photosensitizer is a pharmacological drug capable of selectively accumulating in pathologically altered tissues. When the area treated with photosensitizer is locally illuminated with laser radiation of a certain wavelength, the so-called photocytotoxic effect occurs. This process can proceed according to two mechanisms [8; 9].

Type I – light energy is transferred from excited molecules to biomolecules via electron / hydrogen transfer upon direct contact, where it accumulates and causes specific damage to biomolecules.

Type II – light energy is transferred to molecular oxygen, which then produces singlet oxygen, which is extremely reactive and can damage both cellular proteins and DNA [8].

In addition to the direct cytotoxic effect leading to cell apoptosis, there are other destructive mechanisms such as occlusion of blood vessels and the release of lymph and cytokines [9]. The degree of damage and the mechanism of action depend on the type of photosensitizer used, as well as the type of cells being affected, the concentration of the photosensitizer itself, and the wavelength of the light used. To date, the effectiveness of PDT has been proven and introduced into clinical practice in the treatment of superficial lesions [5; 11]. However, in the case of deeper

lesions, certain difficulties arise associated with the placement of the photosensitizer and the limited penetrating ability of the light wave. Thanks to the rapid development of technology, fiber optic endoscopes make it possible to penetrate hard-to-reach places and directly deliver light with the required wavelength [12; 13]. Photosensitizers themselves are also constantly modified by the addition of various organ-specific carriers. This allows the photosensitizer to be delivered to the target organ after intravenous administration. At the same time, it has a protective effect on other organs in the case of potential pathological effects of PDT on healthy tissues [14; 15]. Attempts have also been made to introduce photosensitizers that bind to receptors on the surface of cancer cells, such as estrogen, progesterone, or EGFR [16; 17].

The use of PDT allows patients to avoid complex surgical procedures. In addition, PDT has recently begun to be used in dentistry, particularly in endodontics, to achieve an antimicrobial effect [18].

USE OF PDT FOR SKIN DISEASES IN CHILDREN

The occurrence of skin cancer in childhood is rare. However, some genetic syndromes, such as Gorlin syndrome or xeroderma pigmentosum, may predispose to the development of skin tumors from childhood.

Basal cell nevus syndrome (BCNS), also known as Gorlin syndrome, is caused by mutations in the PTCH1 gene and is inherited in an autosomal dominant pattern. BCNS is characterized by multiple basal cell carcinomas (BCC) in combination with dental, bone, ophthalmological, and neurological defects. C. Girard et al. used PDT to treat Gorlin syndrome in children. The authors showed that the effectiveness of PDT using 5-aminolevulinic acid (5-ALA) for superficial lesions ranged from 78 to 100 %. The researchers did not report any signs of toxicity [19]. A.R. Oseroff et al. performed several sessions of 10 % ALA PDT in children using a laser for smaller diameter areas (2 to 7 cm) and a lamp for larger diameter areas (up to 16 cm in diameter). Each patient required four to seven sessions. Patients reported no new BCCs at PDT sites during 6 years of examination [20]. The results of therapy of 33 patients with BCNS in the age range of 9–79 years were described by J. Loncaster et al. [21]. The authors used ALA-PDT and MAL (methylaminolevulinic acid)-PDT, obtaining different results depending on the thickness of the lesions. The authors performed ultrasound to assess lesion thickness and used topical PDT to treat only superficial lesions (<2 mm thick). To reach deeper lesions, a systemic photosensitizer was administered. At 12 months, local control rates were 73.0 % for lesions < 1 mm, 40.8 % for lesions 1 to 2 mm, and 59.3 % for lesions > 2 mm [21]. Patients with Gorlin syndrome are highly susceptible to DNA damage from treatments such as ionizing radiation. However, A.R. Oseroff et al. found no evidence that ALA-PDT induces or promotes the development of BCC in pediatric patients [20]. It is important to note that the effective radiation dose may be reduced due to the different pigmentation of BCC. Preliminary removal of pigmented BCC may help to cope with this problem. In a group of adult patients, A.G. Salvio et al. performed the removal of 30 pigmented BCCs before

MAL-PDT and obtained a complete response to therapy in 100 % of cases with no relapses after 24 months of examination [22]. The suitability of this method should also be investigated in the pediatric population.

There is a report of a 12-year-old boy with Bowen's disease who underwent therapy using MAL-PDT. After two PDT sessions, which were carried out with breaks for 3 weeks, the lesion was completely removed. Nine months after the procedure, no relapses were observed [23].

M. Xu et al. conducted a study involving 12 children with pointed condyloma. The children underwent PDT therapy using the photosensitizer 5-ALA. Red light with a wavelength of 635 nm was used as a light source for 20 min. Positive changes were observed after using PDT. In addition, no relapse of the disease was observed. The authors showed that PDT is highly effective for perianal and intraanal lesions with minimal side effects [24].

Flat warts (FW) are a superficial viral skin disease that is extremely common in childhood. F. Borgia et al. evaluated the efficacy of conventional PDT (C-PDT) compared to daylight PDT (DL-PDT) using 10 % ALA. The authors included 30 patients under 18 years of age with FW on the face in the study. The patients were divided equally into two groups: Group 1 – received C-PDT; Group 2 – DL-PDT. The therapeutic intervention was performed three times with a monthly interval. The treatment results were assessed at 4, 8, 12, and 24 weeks. The authors identified the following criteria for the effectiveness of the therapy: excellent (reduction in the total number of FWs by 75–100 %); very good (reduction by 74–50 %); good (reduction by 49–25 %); weak (reduction by less than 25 % or no response). The study found that DL-PDT in combination with 5-ALA is a safer and more effective method. Patients reported better tolerability and absence of pain [25]. In another study, the same authors described a clinical case of an 8-year-old girl who received PDT for FW on the eyelids, nose, and cheeks. t5-ALA was applied topically as a photosensitizer, and sunlight was the light source. The method was used twice, with an interval of one month between treatments. Six weeks after the last treatment session, the scars had completely disappeared without recurrence [26].

The effectiveness of PDT was also demonstrated in the description of a clinical case of a 6-year-old girl who had a history of multiple warts on her foot for a year. Physical examination revealed a subungual papilloma and multiple hyperkeratotic plaques on the dorsum of the left foot. Cryotherapy performed 3 months earlier was ineffective; therefore, PDT was used. After 6 weeks, the lesions were removed without any side effects. PDT may be an alternative treatment for warts, especially in patients who are not responsive to routine treatment. Regression of FW is promoted by two main mechanisms: 1) generation of cytotoxic radicals that destroy keratinocytes via apoptosis; 2) stimulation of specific immune responses releasing various cytokines (IL-1β, IL-2 and tumor necrosis factor alpha). In this study, FWs were removed after only two sessions [27; 28].

A. Ding et al. performed PDT using 5-ALA as a photosensitizer in six patients diagnosed with squamous cell carcinoma localized on the face. The results of the study showed complete removal of foci within a month of

therapy [29]. Thus, it can be assumed that ALA-PDT is highly effective, especially in cases where other therapy does not show results [29]. M. Chen et al. demonstrated the effectiveness of PDT using the example of a 9-year-old girl with papillary lesions in the vulva. Just one hour after PDT, tumor cells began to fragment with pronounced damage to organelles, and after 4 hours, the authors noted cell necrosis. The papillary lesion completely disappeared after one week of PDT. Electron microscopy showed that PDT mainly damaged acanthocytes and koilocytes in virus-infected tissue [30].

Nevus flammeus (port-wine stain) is a congenital permanent developmental defect that occurs in 0.1–2 % of newborns. It appears as a unilateral or bilateral spot of irregular shape, clearly defined, bright pink or purple color [31]. There have been several attempts to use PDT in the treatment of nevus flammeus in children. T. Chun-Hua et al. conducted a retrospective study by evaluating 439 case histories of children with nevus flammeus, whose therapy was carried out using PDT [32]. Hematoporphyrin monomethyl ether was used as a photosensitizer, and a green laser with a wavelength of 532 nm was used as a light source, which was applied for approximately 20–25 min. The results of the study showed that 95 % of patients demonstrated an effective response to the therapy. Transient side effects in the form of edema, purpura and pigmentation were leveled without additional treatment and only 2 % of patients had scars. Y. Huang et al. conducted a similar study, which included 212 patients with a mean age of 13.01 ± 12.67 years [33]. The authors found that patients who received more than three PDT sessions demonstrated a better response compared to those who received less than three sessions ($p = 0.003$). In general, PDT with hemoporphyrin is an effective treatment for nevus flammeus in children [31–36], but there are reports of the impossibility of complete removal of lesions located deeper or having a larger diameter due to limited penetration of light into the skin [37].

USE OF PDT IN PEDIATRIC DENTISTRY

The scope of PDT application in dentistry is extremely broad and includes the treatment of acute and chronic gingivitis, alveolitis, and peri-implantitis. In addition, PDT has begun to be actively used in endodontics for the purpose of antibacterial treatment of prepared carious cavities and root canals of teeth [38].

A. Alsaif et al. showed a reduction in the total number of bacteria by approximately 95 % when PDT affected oral biofilm. The authors concluded that PDT contributes to increased clinical efficacy by reducing the overall treatment time for oral diseases [39]. M. Bargrizan et al. showed that antibacterial PDT removes planktonic bacteria, plaque, and oral biofilm [40]. E.P. Rosa et al. evaluated the effectiveness of antibacterial PDT in patients with braces. The authors included 34 patients of both sexes with gingivitis who had been wearing braces for more than 12 months. Methylene blue was used as a photosensitizer, and a red laser diode with a wavelength of 660 nm was used as a light source. PDT resulted in significant removal of biofilm, which in turn reduced the extent of tissue damage [41]. Other authors have also confirmed that antibacterial PDT, this

time using chlorine, has a pronounced bactericidal effect on biofilms, making it an effective treatment for acute and recurrent oral diseases [42]. L.P. Kiselnikova and G.I. Kuznetsova presented the results of treatment of 81 adolescent children with chronic gingivitis, who were divided into two groups: 1st – treatment using photoactivated antisepsis; 2nd – standard therapy. Patients in group 1 showed a more pronounced decrease in the PMA and CPI indices compared to patients in group 2 [43]. C.B. Okamoto et al. assessed the effectiveness of PDT in eliminating microorganisms from inside the root canals of the tooth. Methylene blue was used as a photosensitizer, and the light source was a laser with a wavelength of 660 nm. The result of the experiment was the complete (with 100 % efficiency) removal of bacteria in the root canals [44]. Similar results regarding the antibacterial treatment of root canals were obtained by K.G. Karakov et al. [45].

S.L. Pinheiro et al. evaluated the effectiveness of PDT therapy in children with pulp necrosis in primary teeth by quantitatively determining live bacteria. PDT was performed using a diode after the introduction of toluidine blue as a photosensitizer. As a result, a reduction in the number of microorganisms with an efficiency of 98.37 % was observed. The study concluded that PDT is a therapy that helps reduce the population of microorganisms in primary teeth with pulp necrosis [46].

N.K.S. Mslik and O.H. Alkadhi evaluated the effectiveness of PDT therapy against oral candidiasis in children with gingivitis. The average age of patients was 16 years. The results of the study showed a statistically significant decrease in the number of candida in the oral cavity [47].

V.C. Ribeiro da Silva et al. studied the effectiveness of PDT in the treatment of stomatitis in children [48]. The study included 29 patients aged 10 months to 18 years, who were divided into two groups. Patients in the first group received PDT using 0.01 % methylene blue as a photosensitizer and a red laser (660 nm) as a light source; patients in the second group received low-level laser therapy. In both groups, patients reported a significant reduction in pain.

One of the main tasks in pediatric dentistry is the preservation of baby teeth with pulpitis caused by caries or traumatic impact. De Sant'Anna presented a clinical case of post-traumatic pulpitis that developed in a 5-year-old boy with type I diabetes [49]. The author successfully applied PDT for root canal disinfection using methylene blue (50 μ / ml) as a photosensitizer. The advantages of PDT included a reduction in procedure time, which is extremely important when working with children. A.C. Da Mota et al. also evaluated the effectiveness of PDT in the treatment of pulpitis in primary teeth [50]. The study included children aged 3–6 years with pulpitis.

The authors divided the patients into two groups: 1st – experimental (PDT); 2nd – control (standard therapy). Methylene blue at a concentration of 0.005 % was used as a photosensitizer. The light source was a laser (660 nm) with an energy of 4 J and an average power of 100 MW, the effect was carried out for 40 s. Based on the results of the study, the authors concluded that antibacterial PDT is highly effective against microorganisms, does not cause resistance, and is a comfortable method for patients, since it does not cause pain.

R. Fekrazad et al. evaluated the effectiveness of antibacterial PDT in children with severe caries [51]. The study group consisted of 22 children with severe caries aged 3–6 years. The oral cavity was treated with toluidine blue for 1 min and irradiated with a LED for 150 s. Saliva samples from each treated child were collected in three stages: before the examination, 1 hour after the procedure, and 7 days after the procedure. At each stage, the authors determined the amount of Streptococcus mutans. After the experiment, the authors concluded that the amount of Streptococcus mutans in saliva decreased significantly after 1 hour, but 7 days after the treatment, their number returned to the original values. Similar conclusions were presented by L.V.G.L. Alves et al., who confirmed the effectiveness of PDT against cariogenic microorganisms after selective removal of caries without damaging composite dental materials [52]. A. Potapchuk et al. conducted a study involving 35 children with caries aged 12–15 years who underwent PDT. The antibacterial effect was assessed using polymerase chain reaction. The authors found a statistically significant reduction in microorganisms such as Enterococcus faecalis, Veilonella and Candida albicans. After the experiment, it was established that PDT in the treatment of dentin caries is a highly effective and pathogenetically proven method, providing a significant reduction in facultative and obligate types of carious microorganisms [53]. L.T. Carvalho et al. described the effectiveness of antibacterial PDT in a 9-year-old patient with deep caries of the first molar of the right lower jaw. Six months after treatment, no traces of caries were found, which confirmed the effectiveness of the technique used [54]. PDT is characterized by a high level of comfort for pediatric patients, as it has a low level of noise and vibration, as well as painlessness.

USE OF PDT IN RECURRENT RESPIRATORY PAPILLOMATOSIS

Recurrent respiratory papillomatosis (RRP) is one of the most challenging problems among benign tumors of the upper and lower respiratory tract. Dissemination of the tumor process and damage to the lung tissue not only create the possibility of malignancy, but also complicate the choice of treatment tactics and in many ways limit surgical options, necessitating a multidisciplinary approach [55]. RRP is characterized by a relapsing course, as well as extremely rapid growth of neoplasms, which can be life-threatening. In most cases, treatment of RRP requires complex surgical interventions. PDT can be used as an adjuvant treatment for RRP. For example, A. Lieder et al. found that PDT, both as an independent therapy and in combination with surgical treatment, brings therapeutic benefits in children and adults with RRP [56]. Another example of the use of PDT in RRP is a clinical study conducted by M.J. Shikowitz et al. [57], which included 23 patients (children and adults) diagnosed with RRP. Hydroxyphenyl chlorine was used as a photosensitizer. The authors demonstrated that PDT contributed to an improvement in the immune response and prognosis of the disease.

USE OF PDT IN CHILDREN'S OPHTHALMOLOGY

Choroidal neovascularization (CNV) is a pathological mechanism common to

many eye diseases. It involves the proliferation of small vessels originating from the choroidal capillaries that penetrate through Bruch's membrane into the space beneath the retinal pigment epithelium, as well as into the cells of the retinal pigment epithelium and photoreceptors. Newly formed vessels are highly fragile and have a tortuous structure. If these vessels are damaged, blood accumulates in the subretinal space, causing hemorrhagic retinal detachment, which ultimately leads to the formation of a discoid fibrous vascular scar [58]. S. Ozdek et al. used PDT to treat CNV in four children, and clinical efficacy was assessed using fluorescein angiography and optical coherence tomography [59]. All patients responded well to PDT. The efficiency of visual acuity improvement was 80 %. Improvement or stabilization of visual acuity was maintained for an average of 25 months of observation. The aim of the study by A. Lipski et al. was to determine the therapeutic potential of PDT using verteporfin in patients with CNV [60]. The results of the study demonstrated high efficacy and tolerability of PDT in a group of patients with visual impairment. D. Sьsskind et al. assessed the effectiveness of PDT in the treatment of exudative limited choroidal hemangioma [61]. According to the results of the study, the authors noted an improvement in visual acuity in all patients. In turn, the average thickness of the retina was reduced. It has been proven that PDT is an effective and safe procedure in the treatment of exudative choroidal hemangioma. Similar results were presented by C. Y ld r m et al. in a description of a clinical case of a 10-year-old girl with CNV who lost vision in her right eye. The authors used PDT with verteporfin. Improvement of visual acuity up to 80 % and resorption of subretinal fluid were observed after four months of therapy [62]. After one year of observation, no relapses of the disease were observed. In turn, in the study of F. Giansanti et al., which included five patients aged 7–15 years who were treated with PDT, infiltration decreased and atrophic changes occurred in the retinal pigment epithelium. Visual acuity was stable [63].

Sturge-Weber syndrome is an encephalotrigeminal angiomatosis that is related to hereditary neurocutaneous syndromes (phakomatoses). Eye lesions occur in 30–70 % of cases and are represented by a disruption in the formation of the capillary wall of the conjunctiva, episclera and iris, glaucoma, an increase in the size of the cornea, and choroidal hemangioma [64]. R. Nugent et al. described a clinical case of a 6-year-old girl with Sturge-Weber syndrome who was treated using PDT. As a result of the therapy, the exudate completely resolved within 3 months after treatment [65]. M. Mauget-Faяsse et al. assessed the efficacy and safety of PDT in combination with verteporfin in children and young people with subfoveal choroidal neovascularization [66]. As a result of PDT, visual acuity improved, vascular anastomosis was formed, and no serious side effects were observed. M.E. Farah et al. evaluated the role of PDT using verteporfin in the treatment of subfoveal choroidal neovascularization in Vogt-Koyanagi-Harada syndrome. A case of a 9-year-old patient was analyzed in which complete regression of the lesion within one week after the start of treatment was observed [67].

USE OF PDT IN CASE OF MALIGNANT NEOGLOMS IN CHILDREN

Brain tumors occurring in the pediatric population have significant differences from those in adults, which is expressed mainly in their localization and histopathology. The selection of therapeutic tactics must be carefully considered, since not all forms of treatment used in adult patients can be used in children. To date, there is data on the use of PDT in childhood oncological diseases both in vitro and in vivo. M. Schwake et al. evaluated the antitumor activity of PDT in vitro on four different cell lines of brain tumors that arise in childhood. The authors used a diode with a wavelength of 635 nm, the exposure time was 250 s. 5-ALA and protoporphyrin were used as photosensitizers. The results of the study showed the destruction of all malignant cells in the studied lines [68]. M.H. Schmidt et al. conducted a study involving 20 patients with recurrent malignant brain tumors who were treated using PDT [69]. Porphyrin was used as a photosensitizer, while a light-emitting diode was used as a light source. All treated patients showed stabilization of tumor growth, which was assessed using MRI. P.J Lou et al. analyzed interstitial PDT (injection of the drug directly into the tissues). Clinical trials have supported the hypothesis that interstitial PDT provides pain relief in terminal advanced head and neck cancer. It is a treatment option that should be added to those available for complex head and neck cancer syndromes [70].

PDT is an extremely promising method for adjuvant treatment of oncological diseases. One of the main advantages of PDT is the low number of side effects, which is especially important in the treatment of children. PDT is increasingly being used in children worldwide with satisfactory results. Expanding research into the use of PDT in childhood cancers provides an opportunity to develop an effective adjuvant therapy method and forms the basis for reducing the need for surgical interventions. In addition, PDT opens up prospects for increasing the survival rate of cancer patients.

DIFFICULTIES IN USING PDT IN CHILDREN

Despite the undeniable advantages described above, PDT may have certain limitations when used in children. One of the limitations is the choice of the least toxic photosensitizer, as well as the correct titration of its dose for each specific case. Because of the need to administer a photosensitizer prior to exposure to the light source, the patient may have varying reactions to a relatively long waiting period, which can range from a few minutes to several days. For deep lesions, the photosensitizer is administered intravenously, which can be difficult, especially in children.

CONCLUSIONS

PDT is an innovative method for treating neoplasms and bacterial infections. Based on the available data, it can be stated that PDT allows to reduce the number of surgical interventions and achieve the best treatment results. All studies and clinical cases of using PDT in the treatment of various diseases in children presented in this review demonstrated that the treatment results were better than with standard therapy. However, it is necessary to take into account the presence of certain limitations,

including difficulties in selecting a photosensitizer and its route of administration. To date, PDT is actively studied in the pediatric population, but there are many gaps that require additional large-scale studies.

References

1. *Daniell M.D., Hill J.S.* A history of photodynamic therapy. Aust N Z J Surg. 1991; 61 (5): 340–348. DOI: 10.1111/j.1445-2197.1991.tb00230.x

2. *Acedo P., Stockert J.C., Cañete M., Villanueva A.* Two combined photosensitizers: a goal for more effective photodynamic therapy of cancer. Cell Death Dis. 2014; 5 (3): 1122. DOI: 10.1038/cddis.2014.77

3. *Dos Santos A.F., Terra L.F., Wailemann R.A., Oliveira T.C., Gomes V.M., Mineiro M.F., Meotti F.C., Bruni-Cardoso A., Baptista M.S., Labriola L.* Methylene blue photodynamic therapy induces selective and massive cell death in human breast cancer cells. BMC Cancer. 2017; 17 (1): 194. DOI: 10.1186/s12885-017-3179-7

4. *Bozzini G., Colin P., Betrouni N., Nevoux P., Ouzzane A., Puech P., Villers A., Mordon S.* Photodynamic therapy in urology: what can we do now and where are we heading? Photodiagnosis Photodyn Ther. 2012; 9 (3): 261–273. DOI: 10.1016/j.pdpdt.2012.01.005

5. *Civantos F.J., Karakullukcu B., Biel M., Silver C.E., Rinaldo A., Saba N.F., Takes R.P., Vander Poorten V., Ferlito A.* A Review of Photodynamic Therapy for Neoplasms of the Head and Neck. Adv Ther. 2018; 35 (3): 324–340. DOI: 10.1007/s12325-018-0659-3

6. *Korshunova O.V., Plekhova N.G.* Photodynamic therapy in oncology: present and future. *Pacific Medical Journal* 2020; (4): 15–19. DOI: 10.34215/1609-1175-2020-4-15-19 (in Russian).

7. *Kolarikova M., Hosikova B., Dilenko H., Barton-Tomankova K., Valkova L., Bajgar R., Malina L., Kolarova H.* Photodynamic therapy: Innovative approaches for antibacterial and anticancer treatments. Med Res Rev. 2023; 43 (4): 717–774. DOI: 10.1002/med.21935

8. *Bataev S.M., Cilenko K.S., Osipov A.N., Reshetnikov A.V., Bataev A.S., Sosnova S.P.* Fundamentals of photodynamic therapy, clinical practice and prospects of application in pediatric surgery. Literature review. *Russian Bulletin of Pediatric Surgery. Anesthesiology and Resuscitation* 2023; 12 (4): 461–472. DOI: 10.17816/psaic936 (in Russian).

9. *Tserkovskiy D.A., Prokopovich E.L., Stupak D.S.* The main aspects of the use of photosensitizing agents in photodynamic therapy. *Oncological Journal* 2019; 13 (2), 79–99 (in Russian).

10. *Kwiatkowski S., Knap B., Przystupski D., Saczko J., Kędzierska E., Knap-Czop K., Kotlińska J., Michel O., Kotowski K., Kulbacka J.* Photodynamic therapy – mechanisms, photosensitizers and combinations. Biomed Pharmacother. 2018; 106: 1098–1107. DOI: 10.1016/j.biopha.2018.07.049

11. *Meulemans J., Delaere P., Vander Poorten V.* Photodynamic therapy in head and neck cancer: indications, outcomes, and future prospects. Curr Opin Otolaryngol Head NeckSurg. 2019; 27 (2): 136–141. DOI: 10.1097/MOO.0000000000000521

12. *Mallidi S., Anbil S., Bulin A.L., Obaid G., Ichikawa M., Hasan T.* Beyond the barriers of light penetration: strategies, perspectives and possibilities for photody-

namic therapy. Theranostics. 2016; 6 (13): 2458–2487. DOI: 10.7150/thno.16183

13. *Pogue B.W., Elliott J.T., Kanick S.C., Davis S.C., Samkoe K.S., Maytin E.V., Pereira S.P., Hasan T.* Revisiting photodynamic therapy dosimetry: reductionist & surrogate approaches to facilitate clinical success. Phys Med Biol. 2016; 61 (7): 57–89. DOI: 10.1088/0031-9155/61/7/R57

14. Sazhnev D.I., Andreev A.A., Ostroushko A.P. Photodynamic therapy in surgical practice. *Bulletin of Experimental and Clinical Surgery* 2019; 12: 2: 141–146. DOI: 10.18499/2070-478X-2019-12-2-141-146 (in Russian).

15. *Hodgkinson N., Kruger C.A., Abrahamse H.* Targeted photodynamic therapy as potential treatment modality for the eradication of colon cancer and colon cancer stem cells. Tumour Biol. 2017; 39 (10): 1010428 317734691. DOI: 10.1177/1010428317734691

16. *Zhao X., Li M., Sun W., Fan J., Du J., Peng X.* An estrogen receptor targeted ruthenium complex as a two-photon photodynamic therapy agent for breast cancer cells. Chem Commun. 2018; 54: 7038–7041. DOI: 10.1039/C8CC03786H

17. *Stuchinskaya T., Moreno M., Cook M.J., Edwards D.R., Russell D.A.* Targeted photodynamic therapy of breast cancer cells using antibody-phthalocyanine-gold nanoparticle conjugates. Photochem Photobiol Sci. 2011; 10 (5): 822–831. DOI: 10.1039/ c1pp05014a

18. *Abrahamse H., Hamblin M.R.* New photosensitizers for photodynamic therapy. Biochem J. 2016; 473 (4): 347–364. DOI: 10.1042/BJ20150942

19. *Girard C., Debu A., Bessis D., Blatière V., Dereure O., Guillot B.* Treatment of Gorlin syndrome (nevoid basal cell carcinoma syndrome) with methylaminolevulinate photodynamic therapy in seven patients, including two children: interest of tumescent anesthesia for pain control in children. J Eur Acad Dermatol Venereol. 2013; 27 (2): 171–175. DOI: 10.1111/j.1468-3083.2012.04538.x

20. *Oseroff A.R., Shieh S., Frawley N.P., Cheney R., Blumenson L.E., Pivnick E.K., Bellnier D.A.* Treatment of diffuse basal cell carcinomas and basaloid follicular hamartomas in nevoid basal cell carcinoma syndrome by wide-area 5-aminolevulinic acid photodynamic therapy. Arch Dermatol. 2005; 141 (1): 60–67. DOI: 10.1001/archderm.141.1.60

21. *Loncaster J., Swindell R., Slevin F., Sheridan L., Allan D., Allan E.* Efficacy of photodynamic therapy as a treatment for Gorlin syndrome-related basal cell carcinomas. Clin Oncol (R Coll Radiol). 2009; 21 (6): 502–508. DOI: 10.1016/j.clon.2009.03.004

22. *Salvio A.G., Requena M.B., Stringasci M.D., Bagnato V.S.* Photodynamic therapy as a treatment option for multiple pigmented basal cell carcinoma: Long-term follow-up results. Photodiagnosis Photodyn Ther. 2021; 33: 102154. DOI: 10.1016/ j.pdpdt.2020.102154

23. *Hyun D.J., Seo S.R., Kim D.H., Yoon M.S., Lee H.J.* Periungual Bowen's Disease in a 12-Year-Old Boy Treated with Photodynamic Therapy. Pediatr Dermatol. 2016; 33 (2): 82–83. DOI: 10.1111/pde.12753

24. *Xu M., Lin N., Li J., Jiang L., Zeng K.* Photodynamic therapy as an alternative therapeutic option for pediatric condyloma acuminata: A case series. Photodiagnosis Photodyn Ther. 2018; 24: 179–181. DOI: 10.1016/j.pdpdt.2018.09.010

25. *Borgia F., Giuffrida R., Coppola M., Cannavò S.P.* Successful photodynamic therapy in a pediatric patient with difficult warts. Dermatol Ther. 2020; 33 (3): 13391. DOI: 10.1111/dth.13391

26. *Borgia F., Coppola M., Giuffrida R., Cannavò S.P.* Excellent cosmetic result of daylight photodynamic therapy for facial flat warts in a child. Photodiagnosis Photodyn Ther. 2019; 26: 27–28. DOI: 10.1016/j.pdpdt.2019.02.021

27. *Borgia F., Giuffrida R., Coppola M., Cannavò S.P.* Successful photodynamic therapy in a pediatric patient with difficult warts. Dermatol Ther. 2020; 33 (3): e13391. DOI: 10.1111/dth.13391

28. *Chun-Hua T., Li-Qiang G., Hua W., Jian Z., Si-Li N., Li L., Yi W., Can L., Xiao-Yan L., Guang-Hui W.* Efficacy and safety of hemoporfin photodynamic therapy for port-wine stains in paediatric patients: A retrospective study of 439 cases at a single centre. Photodiagnosis Photodyn Ther. 2021; 36: 102568. DOI: 10.1016/j.pdpdt.2021.102568

29. *Ding A., Li C., Zhang J.* Topical 5-aminolevulinic acid photodynamic therapy in the treatment of verruca plana: Report of 6 cases. Photodiagnosis Photodyn Ther. 2021; 35: 102438. DOI: 10.1016/j.pdpdt.2021.102438

30. *Chen M., Xie J., Han J.* Photodynamic therapy of condyloma acuminatum in a child. Pediatr Dermatol. 2010; 27 (5): 542–544. DOI: 10.1111/j.1525-1470.2010.01279.x

31. *Belysheva T.S., Moiseenko E.* Laser therapy of vascular skin formations in children. S*arcomas of bones, soft tissues and skin tumors* 2011; (3): 37–47 (in Russian).

32. *Chun-Hua T., Li-Qiang G., Hua W., Jian Z., Si-Li N., Li L., Yi W., Can L., Xiao-Yan L., Guang-Hui W.* Efficacy and safety of hemoporfin photodynamic therapy for port-wine stains in paediatric patients: A retrospective study of 439 cases at a single centre. Photodiagnosis Photodyn Ther. 2021; 36: 102568. DOI: 10.1016/j.pdpdt.2021.102568

33. *Huang Y., Yang J., Sun L., Zhang L., Bi M.* Efficacy of influential factors in hemoporfin-mediated photodynamic therapy for facial port-wine stains. J Dermatol. 2021; 48 (11): 1700–1708. DOI: 10.1111/1346-8138.16094

34. *Wang S., Lee L.Y., Liu S.X.* Photodynamic therapy for port-wine stains in extremities: Report of 4 cases. Photodiagnosis Photodyn Ther. 2020; 30: 101781. DOI: 10.1016/j.pdpdt.2020.101781

35. *Xiao Q., Li Q., Yuan K.H., Cheng B.* Photodynamic therapy of port-wine stains: long-term efficacy and complication in Chinese patients. J Dermatol. 2011; 38 (12): 1146–1152. DOI: 10.1111/j.1346-8138.2011.01292.x

36. *Cai H., Yang Q.Q., Ma C., Zou D.X., Wang Y.X., Sun P., Ju A.Q., Fang F., Gong S., Liu W.* Photodynamic therapy in the treatment of xeroderma pigmentosum: A case report. Photodiagnosis Photodyn Ther. 2020; 30: 101761. DOI: 10.1016/j.pdpdt.2020.101761

37. *Li Y., Wang X., Liu Y., Tao J.* Dermoscopy predicts outcome in hemoporfin-mediated photodynamic therapy of port-wine stains: A prospective observational study. J Am Acad Dermatol. 2020; 83 (6): 1765–1767. DOI: 10.1016/j.jaad.2020.03.063

38. *Mishutina O.L., Volchenkova G.V., Kovaleva N.S., Vasil'cova O.A., Fabradova V.A.* Photodynamic therapy in dentistry (literature review). *Smolensk Medical Almanac* 2019; (3): 102–111 (in Russian).

39. *Alsaif A., Tahmassebi J.F., Wood S.R.* Treatment of dental plaque biofilms using photodynamic therapy: a randomised controlled study. Eur Arch Paediatr Dent. 2021; 22 (5): 791–800. DOI: 10.1007/s40368-021-00637-y

40. *Bargrizan M., Fekrazad R., Goudarzi N., Goudarzi N.* Effects of antibacterial photodynamic therapy on salivary mutans streptococci in 5- to 6-year-olds with severe early childhood caries. Lasers Med Sci. 2019; 34 (3): 433–440. DOI: 10.1007/s10103-018-2650-2652

41. *Rosa E.P., Murakami-Malaquias-Silva F., Schalch T.O., Teixeira D.B., Horliana R.F., Tortamano A., Tortamano I.P., Buscariolo I.A., Longo P.L., Negreiros R.M., Bussadori S.K., Motta L.J., Horliana A.C.R.T.* Efficacy of photodynamic therapy and periodontal treatment in patients with gingivitis and fixed orthodontic appliances: Protocol of randomized, controlled, double-blind study. Medicine (Baltimore). 2020; 99 (14): 19429. DOI: 10.1097/MD.0000000000019429

42. *Luke-Marshall N.R., Hansen L.A., Shafirstein G., Campagnari A.A.* Antimicrobial Photodynamic Therapy with Chlorin e6 Is Bactericidal against Biofilms of the Primary Human Otopathogens. mSphere. 2020; 5 (4): e00492-20. DOI: 10.1128/mSphere.00492-20

43. *Kiselnikova L.P., Kuznetsova G.I.* Application of photodynamic therapy in the treatment of gingivitis in childhood. *Clinical dentistry* 2016; 2 (78): 4–8 (in Russian).

44. *Okamoto C.B., Motta L.J., Prates R.A., da Mota A.C.C., Gonçalves M.L.L., Horliana A.C.R.T., Mesquita Ferrari R.A., Fernandes K.P.S., Bussadori S.K.* Antimicrobial Photodynamic Therapy as a Co-adjuvant in Endodontic Treatment of Deciduous Teeth: Case Series. Photochem Photobiol. 2018; 94 (4): 760–764. DOI: 10.1111/php.12902

45. *Karakov K.G., Hachaturyan E.E., Uzdenov M.B., Uzdenova L.H., Hachaturyan A.E., Eremenko A.V., Usnunc Yu.K.* A modern look at the antibacterial treatment of the root canal using laser photodynamic therapy. *Problemy stomatologii* 2019; 15 (1): 23–27. DOI: 10.18481/2077-7566-2018-15-1-23-27 (in Russian).

46. *Pinheiro S.L., Schenka A.A., Neto A.A., de Souza C.P., Rodriguez H.M., Ribeiro M.C.* Photodynamic therapy in endodontic treatment of deciduous teeth. Lasers Med Sci. 2009; 24 (4): 521–526. DOI: 10.1007/s10103-008-0562-2

47. *Malik N.K.A., Alkadhi O.H.* Effectiveness of mechanical debridement with and without antimicrobial photodynamic therapy against oral yeasts in children with gingivitis undergoing fixed orthodontic therapy. Photodiagnosis Photodyn Ther. 2020; 31: 101768. DOI: 10.1016/j.pdpdt.2020.101768

48. *Ribeiro da Silva V.C., da Motta Silveira F.M., Barbosa Monteiro M.G., da Cruz M.M.D., Caldas Júnior A.F., Pina Godoy G.* Photodynamic therapy for treatment of oral mucositis: Pilot study with pediatric patients undergoing chemotherapy. Photodiagnosis Photodyn Ther. 2018; 21: 115–120. DOI: 10.1016/j.pdpdt.2017.11.010

49. *de Sant'Anna G.* Photodynamic therapy for the endodontic treatment of a traumatic primary tooth in a diabetic pediatric patient. J Dent Res Dent Clin Dent Prospects. 2014; 8 (1): 56–60. DOI: 10.5681/joddd.2014.010

50. *da Mota A.C., Gonçalves M.L., Bortoletto C., Olivan S.R., Salgueiro M., Godoy C., Altavista O.M., Pinto M.M., Horliana A.C.,*

Motta L.J., Bussadori S.K. Evaluation of the effectiveness of photodynamic therapy for the endodontic treatment of primary teeth: study protocol for a randomized controlled clinical trial. Trials. 2015; 16: 551. DOI: 10.1186/s13063-015-1086-2

51. *Fekrazad R., Seraj B., Chiniforush N., Rokouei M., Mousavi N., Ghadimi S.* Effect of antimicrobial photodynamic therapy on the counts of salivary Streptococcus mutans in children with severe early childhood caries. Photodiagnosis Photodyn Ther. 2017; 18: 319–322. DOI: 10.1016/j.pdpdt.2017.03.007

52. *Alves L.V.G.L., Curylofo-Zotti F.A., Borsatto M.C., Salvador S.L.S., Valério R.A., Souza-Gabriel A.E., Corona S.A.M.* Influence of antimicrobial photodynamic therapy in carious lesion. Randomized split-mouth clinical trial in primary molars. Photodiagnosis Photodyn Ther. 2019; 26: 124–130. DOI: 10.1016/j.pdpdt.2019.02.018

53. *Potapchuk A.M., Almashi V.M., Lomnitsky I.Y., Rusyn V.V., Hegedush V.* The use of photodynamic therapy in the treatment of dental caries in children of contaminated areas of the ecosystem of the upper tysa region. Wiad Lek. 2020; 73 (3): 483–488.

54. *Carvalho L.T., Belém F.V., Gonçalves L.M., Bussadori S.K., Paschoal M.A.B.* Chemo-mechanical and photodynamic approach in A deep dental cavity: A case report. Photodiagnosis Photodyn Ther. 2020; 32: 101954. DOI: 10.1016/j.pdpdt.2020.101954

55. *Ryabova M.A., Molodcova V.P., Portnov G.B., Akopov A.L.* Recurrent respiratory papillomatosis with lung involvement and malignancy. *Pulmonology* 2022; 32 (2): 261–269. DOI: 10.18093/0869-0189-2022-32-2-261-269 (in Russian).

56. *Lieder A., Khan M.K., Lippert B.M.* Photodynamic therapy for recurrent respiratory papillomatosis. Cochrane Database Syst Rev. 2014; (6): CD009810. DOI: 10.1002/14651858.CD009810.pub2

57. *Shikowitz M.J., Abramson A.L., Steinberg B.M., DeVoti J., Bonagura V.R., Mullooly V., Nouri M., Ronn A.M., Inglis A., McClay J., Freeman K.* Clinical trial of photodynamic therapy with meso-tetra (hydroxyphenyl) chlorin for respiratory papillomatosis. Arch Otolaryngol Head Neck Surg. 2005; 131 (2): 99–105. DOI: 10.1001/archotol.131.2.99.

58. *Ioyleva E.E., Belyanina S.I.* Treatment of choroidal neovascularization associated with optic disc druses. *Rossijskaya detskaya oftalmologiya* 2022; 3: 51–57 (in Russian).

59. *Ozdek S., Ozmen M.C., Tufan H.A., Gurelik G., Hasanreisoglu B.* Photodynamic therapy for best disease complicated by choroidal neovascularization in children. J Pediatr Ophthalmol Strabismus. 2012; 49 (4): 216–21. DOI: 10.3928/01913913-20111004-01

60. *Lipski A., Bornfeld N., Jurklies B.* Photodynamic therapy with verteporfin in paediatric and young adult patients: long-term treatment results of choroidal neovascularisations. Br J Ophthalmol. 2008; 92 (5): 655–660. DOI: 10.1136/bjo.2007.134429

61. *Süsskind D., Inhoffen W., Gelisken F., Völker M.* Photodynamic therapy with double duration for circumscribed choroidal haemangioma: functional and anatomical results based on initial parameters. Clin Exp Ophthalmol. 2018; 46 (5): 495–501. DOI: 10.1111/ceo.13096

62. *Yıldırım C., Çetin E.N., Yayla K., Avunduk A.M., Yaylalı V.* Photodynamic therapy for unilateral idiopathic peripapil-

lary choroidal neovascularization in a child. Int Ophthalmol. 2011; 31 (4): 333–335. DOI: 10.1007/s10792-011-9442-z

63. *Giansanti F., Virgili G., Varano M., Tedeschi M., Rapizzi E., Giacomelli G., Menchini U.* Photodynamic therapy for choroidal neovascularization in pediatric patients. Retina. 2005; 25 (5): 590–696. DOI: 10.1097/00006982-200507000-00009

64. *Ol'shanskaya A.S., SHnajder N.A., Dmitrenko D.V., Kozina E.V., CHeshejko E.Yu., Il'enkov S.S., Cuprikova M.E.* Damage to the organ of vision in Sturge-Weber syndrome. *Zabajkalskij medicinskij vestnik* 2019; (2): 196–203 (in Russian).

65. *Nugent R., Lee L., Kwan A.* Photodynamic therapy for diffuse choroidal hemangioma in a child with Sturge-Weber syndrome. J AAPOS. 2015; 19 (2): 181–183. DOI: 10.1016/j.jaapos.2014.10.032

66. *Mauget-Faÿsse M., Mimoun G., Ruiz-Moreno J.M., Quaranta-El Maftouhi M., De Laey J.J., Postelmans L., Soubrane G., Defauchy M., Leys A.* Verteporfin photodynamic therapy for choroidal neovascularization associated with toxoplasmic retinochoroiditis. Retina. 2006; 26 (4): 396–403. DOI: 10.1097/01.iae.0000238552.76412.ae

67. *Farah M.E., Costa R.A., Muccioli C., Guia T.A., Belfort R.Jr.* Photodynamic therapy with verteporfin for subfoveal choroidal neovascularization in Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol. 2002; 134 (1): 137–139. DOI: 10.1016/s0002-9394(02)01456-3

68. *Schwake M., Nemes A., Dondrop J., Schroeteler J., Schipmann S., Senner V., Stummer W., Ewelt C.* In-Vitro Use of 5-ALA for Photodynamic Therapy in Pediatric Brain Tumors. Neurosurgery. 2018; 83 (6): 1328–1337. DOI: 10.1093/neuros/nyy054

69. *Schmidt M.H., Meyer G.A., Reichert K.W., Cheng J., Krouwer H.G., Ozker K., Whelan H.T.* Evaluation of photodynamic therapy near functional brain tissue in patients with recurrent brain tumors. J Neurooncol. 2004; 67 (1–2): 201–207. DOI: 10.1023/b: neon.0000021804.50002.85

70. *Lou P.J., Jäger H.R., Jones L., Theodossy T., Bown S.G., Hopper C.* Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. Br J Cancer. 2004; 91 (3): 441–446. DOI: 10.1038/sj.bjc.6601993

71. *Yu W., Zhu J., Wang Y., Wang J., Fang W., Xia K., Shao J., Wu M., Liu B., Liang C., Ye C., Tao H.* A review and outlook in the treatment of osteosarcoma and other deep tumors with photodynamic therapy: from basic to deep. Oncotarget. 2017; 8 (24): 39833–39848. DOI: 10.18632/oncotarget

72. *Markichev N.A., Eliseenko V.I., Alekseev YU.V., Armichev A.A.* Photodynamic therapy of basal cell skin cancer with the use of a photosensitizer of the chlorin series. *Laser medicine* 2005; 9 (1): 16–19 (in Russian).

73. *Esposito S., Garziano M., Rainone V., Trabattoni D., Biasin M., Senatore L., Marchisio P., Rossi M., Principi N., Clerici M.* Immunomodulatory activity of pidotimod administered with standard antibiotic therapy in children hospitalized for community-acquired pneumonia. J Transl Med. 2015; 13: 288. DOI: 10.1186/s12967-015-0649-z

74. *Nicolò M., Desideri L.F., Vagge A., Traverso C.E.* Current Pharmacological Treatment Options for Central Serous Chorioretinopathy: A Review. Pharmaceuticals (Basel). 2020; 13 (10): 264. DOI: 10.3390/ph13100264

75. *Seitz G., Fuchs J., Schaefer J.F., Warmann S.W.* Molecular imaging and photodynamic therapy in hepatoblastoma. Front Biosci (Elite Ed). 2012; 4 (1): 487–492. DOI: 10.2741/e394

76. *Stefini A., Salzer S., Reich G., Horn H., Winkelmann K., Bents H., Rutz U., Frost U., von Boetticher A., Ruhl U., Specht N., Kronmüller K.T.* Cognitive-Behavioral and Psychodynamic Therapy in Female Adolescents With Bulimia Nervosa: A Randomized Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2017; 56 (4): 329–335. DOI: 10.1016/j.jaac.2017.01.019

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NON-ALCOHOLIC FATTY LIVER DISEASE AND PREGNANCY

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НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ И БЕРЕМЕННОСТЬ

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The issues of epidemiology, risk factors, and pathogenetic mechanisms of non-alcoholic fatty liver disease during pregnancy are considered in the review. The impact of liver steatosis and obesity on the course and outcome of pregnancy, the perinatal state of the mother and fetus are described. Fluctuations in the hormonal spectrum, an increase in body weight, which can affect the development and progression of liver steatosis, occur during pregnancy. Women of reproductive age with metabolic syndrome, obesity require a thorough examination and, if it is necessary, optimization of metabolic health before planning pregnancy. Pregnant women with liver pathology need dynamic control and prevention of disease progression and associated obstetric complications.
Keywords. Liver, pregnancy, non-alcoholic fatty liver disease, obesity.

В обзоре рассмотрены вопросы эпидемиологии, факторов риска, патогенетических механизмов неалкогольной жировой болезни печени при беременности. Описано влияние стеатоза печени и ожирения на течение и исход беременности, перинатальное состояние матери и плода. При беременности происходят колебания гормонального спектра, увеличение массы тела, что может влиять на развитие и прогрессирование стеатоза печени.

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Женщинам репродуктивного возраста с метаболическим синдромом, ожирением до планируемой беременности требуется тщательное обследование и при необходимости оптимизация метаболического здоровья. Беременным женщинам с патологией печени показан динамический контроль и профилактика прогрессирования заболевания и ассоциированных с ним акушерских осложнений.
Ключевые слова. Печень, беременность, неалкогольная жировая болезнь печени, ожирение.

INTRODUCTION

Fatty liver disease is quite common during pregnancy and occurs in two completely different conditions: non-alcoholic fatty liver disease (NAFLD) and acute fatty liver disease across pregnancy. The prevalence of NAFLD increases every year and is registered in 10–20 % of women of childbearing age [1; 2], 10–15 % of pregnant women [3], which is associated with the obesity pandemic and the increasing age of pregnant women, especially in Western countries. The number of pregnant women with fatty liver disease is expected to increase in the coming years [4]. During pregnancy, there are fluctuations in the hormonal spectrum and an increase in body weight, which can affect the development and progression of liver steatosis [5]. The issues of diagnosis and principles of correction of NAFLD in pregnant women, the features of maternity care, childbirth and the postpartum period in these women are also discussed.

EPIDEMIOLOGY AND RISK FACTORS FOR NAFLD IN PREGNANCY

Recently, there has been an increase in obstetric and perinatal pathology caused by hepatocellular insufficiency. Pathology of the hepatobiliary system occurs in women 4.7 times more often than in men, which leads to an increase in the number of pregnant women with liver diseases [6; 7]. Liver pathology is registered in 3–5 % of pregnant women and is characterized by a variety of etiological forms, which are divided into two main groups: liver damage caused by pregnancy itself (with uncontrollable vomiting of pregnancy, intrahepatic cholestasis of pregnancy, acute fatty liver disease of pregnancy, liver damage in preeclampsia, eclampsia and HELLP syndrome), and liver diseases not directly caused by pregnancy (acute diseases that developed during pregnancy and chronic diseases that preceded pregnancy, including NAFLD) [8; 9]. Over the past 10 years, there has been a trend towards an increase in the prevalence of NAFLD among women [10], as well as a sharper increase in mortality compared to men [11].

NAFLD is associated with an increase in the prevalence of risk factors in the population, such as metabolic syndrome (MS), obesity, diabetes mellitus and dyslipidemia [5]. In women, MS develops 2.4 times more often than in men [12], in women of childbearing age, MS is recorded in 7.6–15.7 % [13; 14], the increase in the prevalence of MS among pregnant women, according to some data, over a period of 1988–2015 amounted to from 3 to 42 % [15].

Recently, the problem of obesity and overweight, according to WHO, has become a pandemic of global proportions. By 2025, the number of obese people worldwide is expected to reach approximately 300 million. Obesity has a detrimental effect on every aspect of reproductive health and during pregnancy can have enormous consequences and increase the risk of obstetric pathologies such as gestational hypertension, preeclampsia, gestational diabetes and preterm birth [16–18]. For one in five women of reproductive age, obesity has a high socioeconomic cost due to increased risk of maternal and neonatal complications [19]. It has been established that gestational diabetes mellitus occurs significantly more frequently in obese pregnant women, regardless of the type of fat deposition. The visceral type of fat tissue distribution is associated with an increased risk of gestational diabetes mellitus in women with normal and excess body weight [20; 21].

Dyslipidemia is diagnosed in 40–50 % of the population and is often asymptomatic [22]. Pregnancy changes lipid parameters as early as the 12th week, causing physiological hyperlipidemia, which can affect the outcome of pregnancy [23]. According to research, all obese pregnant women in the third trimester have dyslipidemia with a predominance of the atherogenic fraction of lipoproteins and hypertriglyceridemia, 12 % have hyperfermentemia, and 52 % have signs characteristic of liver steatosis according to ultrasound data. Moreover, premature and late births were significantly more common in the group of women with obesity compared to pregnant women with normal BMI [24]. Pregnancy alters lipid parameters from the 12th week of amenorrhea and causes physiological hyperlipidemia. The lipid profile of patients may influence obstetric outcome. There is an increased risk of gestational diabetes (33 %), preeclampsia (25 %) and gestational cholestasis [25–27].

The characteristics of MS make it difficult to conduct retrospective studies to determine the contribution of each metabolic risk factor to the development of NAFLD during pregnancy. Prospective studies are needed to clarify the association between NAFLD and pregnancy-specific features and to assess the actual impact of NAFLD on pregnancy outcomes [2].

Pathogenetic mechanisms linking NAFLD and pregnancy

The pathogenesis of NAFLD is currently considered as a complex multifactorial process of a combination of adipose tissue dysfunction with hyperproduction of proinflammatory cytokines, insulin resistance, activation of lipolysis, dyslipidemia, impaired hepatic lipid clearance, oxidative stress, mitochondrial and endothelial dysfunction, and intestinal microbiota disorders [2; 14; 28–33].

There is currently no evidence that pregnancy can provoke the development of NAFLD, but it has been proven that estrogen imbalance, weight gain and insulin

resistance (IR) due to pregnancy itself, as well as the result of obesity before and during pregnancy, are important in the pathogenesis of liver steatosis during pregnancy. Leptin and insulin levels directly correlate with gestational age [2; 34]. It has been established that IR in obese pregnant women is based on proinflammatory processes, since visceral adipose tissue synthesizes proinflammatory cytokines, which leads to the development of systemic inflammation and changes in endocrine and immune functions [35–37].

There is evidence that the production of proinflammatory cytokines in obese pregnant women may increase in adipose tissue, blood, placenta and mucous membranes, including the intestines, where an increase in the number of opportunistic microorganisms is recorded. Gut microbiota is involved in whole-body metabolism, influencing energy balance, glucose metabolism, and low-grade inflammation associated with obesity and associated metabolic disorders [38]. The number of microorganisms increases from the first to the third trimester of pregnancy. High concentrations of bacteroides are associated with excessive weight gain during pregnancy [39].

The mechanisms of pathogenesis of insulin resistance, endothelial dysfunction underlying the formation of placental insufficiency and preeclampsia, thrombophilia, against the background of a chronic inflammatory reaction in pregnant women with obesity have been described [37]. It has been established that clinical manifestation of previously asymptomatic NAFLD may occur during pregnancy [27].

Influence of NAFLD on the course and outcome of pregnancy

Obesity and NAFLD can affect the course of pregnancy, labor, and the postpartum period. Complications such as miscarriage, preeclampsia, premature birth, bleeding, infections are registered, and the risk of congenital anomalies and fetal death increases [14; 41–44].

A large meta-analysis involving patients of childbearing age showed an association of liver steatosis with the risk of developing miscarriage, preeclampsia and eclampsia, gestational hypertension and diabetes mellitus, premature birth, and bleeding in the postpartum period [45–48]. There is evidence that NAFLD is associated with an increased risk of low birth weight and more frequent Cesarean sections. The risk of developing preeclampsia and gestational diabetes is increased in pregnant women with NAFLD even in the absence of obesity or overweight [48]. There is also an increase in the incidence of rapid development of liver cirrhosis as an outcome of NAFLD [49] and a higher risk of developing this pathology in infants born to mothers with NAFLD [50; 51]. There is also an increase in the incidence of rapid development of liver cirrhosis as an outcome of NAFLD [49] and a higher risk of developing this pathology in infants born to mothers with NAFLD [50; 51].

The pathophysiological mechanisms of the influence of NAFLD on the perinatal state of the mother and fetus are not completely clear. There is an opinion that IR associated with NAFLD activates the sympathoadrenal and renin-angiotensin-aldosterone systems, leads to endothelial dysfunction, which can contribute to the development of hypertension [52]. The development of preeclampsia in NAFLD and obesity is associated with an imbalance of adipose tissue hormones [53–55].

Conclusions

Structural and functional changes in the liver affect the course of pregnancy and require timely adequate correction. Women of fertile age with MS and obesity require a thorough examination and, if necessary, optimization of metabolic health before the planned pregnancy.

Pregnant women with NAFLD require dynamic monitoring and prevention of disease progression and associated obstetric complications. The complex of preventive measures should include recommendations to prevent excessive weight gain during pregnancy (diet and exercise), as well as hepatotropic agents as indicated. Appropriate counseling and monitoring of patients with or at risk for hepatic steatosis during pregnancy may have significant health benefits for the mother and child.

References

1. *Younossi Z.M., Koenig A.B., Abdelatif D. et al.* Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64: 73–84.

2. *Hershman M., Mei R., Kushner T.* Implications of nonalcoholic fatty liver disease on pregnancy and maternal and child outcomes. Gastroenterol Hepatol (N Y) 2019; 15: 221–228.

3. *Yki-Jarvinen H.* Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol. 2014; 2: 901–10.

4. *Azzaroli F., Mazzella G., Marchesini G. et al.* Fatty liver in pregnancy: a narrative review of two distinct conditions. Expert Rev Gastroenterol Hepatol. 2020; 14 (2): 127–135.

5. *Livzan M.A., Syrovenko M.I., Krolevets T.S.* Non-alcoholic fatty liver disease and women's health. breast cancer. *Medical Review* 2023; 7 (5): 310–317. DOI: 10.32364/2587-6821-2023-7-5-9 (in Russian).

6. *Novruzova D.R., Sosnova E.A.* Features of the state of the hepatobiliary system during the physiological course of pregnancy and against the background of taking medications. *V.F. Snegirev Archive of Obstetrics and Gynecology* 2018; 2 (5): 60–64. DOI: 10.18821/2313-8726-2018-5-2-60-64 (in Russian).

7. *Allen A.M., Kim W.R., Larson J.J. et al.* The epidemiology of liver diseases unique to pregnancy in a US Community: a population-based study. Clin. Gastroenterol. Hepatol. 2016; 14 (2): 287–94.e2. DOI: 10.1016/j. cgh.2015.08.022.

8. *Grigorenko E.I., Maksimova E.V., Klaritskaya I.L.* Liver diseases in pregnant women. *KTZ* 2020; 2: 21–31 (in Russian).

9. *Palgova L.K., Mozgovaya E.V., Zhestkova N.V.* at al. Liver disease and pregnancy. Analysis of current clinical recommendations and own experience. Part one. Liver diseases associated with pregnancy. Experimental and Clinical Gastroenterology 2018; 151 (3): 105–114 (in Russian).

10. *Arshad T., Golabi P., Paik J. et al.* Prevalence of nonalcoholic fatty liver disease in the female population. Hepatol Commun. 2019; 3 (1): 74–83. DOI: 10.1002/hep4.1285

11. *Paik J.M., Henry L., De Avila L. et al.* Mortality related to nonalcoholic fatty liver disease is increasing in the United States. Hepatol Commun. 2019: 3 (11): 1459–1471. DOI: 10.1002/hep4.1419

12. *Lee C., Tsenkova V.K., Boylan J.M. et al.* Gender diff erences in the pathways from childhood disadvantage to metabolic syndrome in adulthood: An examination of health lifestyles. SSM Popul Health. 2018; 4: 216–224.

13. *Szostak-Węgierek D., Waśkiewicz A., Piotrowski W. et al.* Metabolic syndrome and its components in Polish women of childbearing age: a nationwide study [published correction appears in BMC Public Health. 2017; 18 (1): 15.

14. *Ivanyuk E.S., Salikova S.P., Ivanyuk G.Y.* Metabolic syndrome and pregnancy. Is there a gastroenterological trace? *Experimental and clinical gastroenterology* 2020; 183 (11): 74–79. DOI: 10.31146/1682-8658-ecg-183-11-74-79 (in Russian).

15. *Tavares H.P., Arantes M.A., Tavares S.B. et al.* Metabolic Syndrome and Pregnancy, Its Prevalence, Obstetrical and Newborns Complications. Open Journal of Obstetrics and Gynecology 2015; 5 (11) 618–625.

16. *Poston L., Harthoorn L.F., van der Beek E.M.* Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement. Pediatr Res 2011; 69 (2): 175–180.

17. *Hamsir F., As'ad S., Tahir A.M. et al.* Macro- and micronutrient of junk food and preeclampsia on pregnant women. Open Access Maced J Med Sci 2022; 10: 1–6.

18. *Gete D.G., Waller M., Mishra G.D.* Effects of maternal diets on preterm birth and low birth weight: a systematic review. Br J Nutr 2020; 123 (4): 446–461. DOI: 10.1017/S0007114519002897

19. *Jarvie E., Hauguel-de-Mouzon S., Nelson S.M. et al.* Lipotoxity in obese pregnancy outcome and obesity in the offspring. Clin. Sci. (Lond). 2010; 119 (3): 123–9. DOI: 10.1042/CS20090640

20. *Chabanova N.B., Vasilkova T.N., Shevlyukova T.P.* The importance of visceral obesity in increasing the risk of gestational diabetes mellitus in women depending on body mass index. *Ural University Medicine* 2018; 4 (15): 44–45 (in Russian).

21. *Chabanova N.B., Vasilkova T.N., Polyakova V.A., Shevlyakova T.P.* Assessment of the nature of fat deposition in the dynamics of the gestational process according to ultrasound data. *Russian Electronic Journal of Radiation Diagnostics* 2018; 1 (8): 129–136 (in Russian).

22. *Haslam D.E., Peloso G.M., Herman M.A. et al.* Beverage consumption and longitudinal changes in lipoprotein concentrations and incident dyslipidemia in US adults: the Framingham heart study. JAHA 2020; 9 (5): e014083

23. *Jin W.-Y., Lin S.-L., Hou R.-L., Chen X.-Y., Han T., Jin Y. et al.* Associations between maternal lipid profle and pregnancy complications and perinatal outcomes: a population-based study from China. BMC Pregnancy Childbirth 2016; 16 (1): 60.

24. *Makarov I.O., Borovkova E.I., Kazakov R.D.* Prevalence of non-alcoholic fatty liver disease in obese pregnant women. Obstetrics. Gynecology. Reproduction 2012; 4 (6): 18–21 (in Russian).

25. *El Jamaly H., Eslick G.D., Weltman M.* Systematic review with meta-analysis: non-alcoholic fatty liver disease and the association with pregnancy outcomes. Clin Mol Hepatol 2022; 28 (1): 52–66.

26. *Cordivani J., Clotilde L., Michel B. et al.* Non-alcoholic steatohepatitis in pregnancy: a case report. Bull Natl Res 2023; 136. DOI: 10.1186/s42269-023-01110-0

27. *Sarkar M., Grab J., Dodge J.L. et al.* Non-alcoholic fatty liver disease in pregnancy is associated with adverse maternal and perinatal outcomes. J Hepatol 2020; 73 (3): 516–522.

28. *Bulatova I.A., Shchekotova A.P., Karlysheva K.N. et al.* Leptin, proinflammatory cytokines and functional liver tests in metabolic syndrome in combination with fatty liver disease. *Perm Medical Journal* 2014; 2 (31): 86–91 (in Russian).

29. *Shchekotova A.P., Krivtsov A.V., Bulatova I.A., Zagorodskikh E.B.* Endothelial dysfunction and polymorphism of the endothelial nitric oxide synthase (NOS3) gene in chronic liver diseases. *Modern problems of science and education* 2012; 2: 109 (in Russian).

30. *Shchekotova A.P., Bulatova I.A., Paducheva S.V.* Clinical and diagnostic problems of liver fibrosis/cirrhosis. *Perm Medical Journal* 2018; 5 (35): 98–107 (in Russian).

31. *Bulatova I.A., Shchekotova A.P., Suzdaltseva K.N. et al.* Superoxide dismutase glutathione reductase in chronic hepatitis C and non-alcoholic fatty liver disease. *Fundamental research* 2014; 7: 455–459 (in Russian).

32. *Shchekotova A.P., Bulatova I.A.* The role of vascular endothelial growth factor and its gene in the pathogenesis of hepatobiliary pathology. *Perm Medical Journal* 2020; 4 (37): 36–45 (in Russian).

33. *Bulatova I.A., Miftakhova A.M., Gulyaeva I.L.* The severity of inflammatory syndrome and endothelial dysfunction in steatosis and liver fibrosis. *Perm Medical Journal* 2021; 4 (38): 54–62 (in Russian).

34. *Estes C., Razavi H., Loomba R. et al.* Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018; 67 (1): 123–133. DOI: 10.1002/hep.29466

35. *Salem S.Y., Kessous R., Pariente G. et al.* Obesity in pregnancy: whats next? Long-term cardiovascular morbidity in a follow-up period of more than a decade. Am J Obstet Gynecol 2014; 210 (1.): 45–68.

36. *Tarasenko K.V., Mamontova T.V., Vesnina L.E.* Interrelations of insulin resistance and hyperinsulinemia with markers of systemic inflammation in pregnant women with obesity of varying degrees. *Protection of motherhood and childhood* 2014; 2: 48–51 (in Russian).

37. *Chabanova N.B., Mataev S.I., Vasilkova T.N., et al.* The role of systemic inflammation in the development of pregnancy complications in obese women. *Akusherstvo i ginekologiya* 2017; 10: 12–8. DOI: 10.18565/aig.2017.10.12-18 (in Russian).

38. *Cani P.D., Osto M., Geurts L. et al.* Involvement of gut microbiota in the development of low-grade infl ammation and type 2 diabetes associated with obesity. Gut microbes. 2012; 3: 279–288.

39. *Collado M.C., Isolauri E., Laitinen K. et al.* Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. American Journal of Clinical Nutrition 2008; 88: 894–899.

40. *Chabanova N.B., Mataev S.I., Vasilkova T.N. et al.* The role of systemic inflammation in the development of pregnancy complications in obese women. *Obstetrics and gynecology* 2017; 10: 12–18 (in Russian).

41. *Santangeli L., Sattar N., Huda S.S.* Impact of maternal obesity on perinatal and childhood outcomes. Best Pract Res Clin Obstet Gynaecol. 2015; 29 (3): 438–448.

42. *Kautzky-Willer A., Harreiter J., Winhofer-Stöckl Y. et al.* Gestations diabetes (GDM) (Update 2019). Wien Klin Wochenschr. 2019; 131 (1): 91–102.

43. *Grieger J.A., Bianco-Miotto T., Grzeskowiak L.E. et al.* Metabolic syndrome in pregnancy and risk for adverse pregnancy outcomes: A prospective cohort of nulliparous women. PLoS Med. 2018; 15 (12): e1002710.

44. *Khromylev A.V.* Metabolic syndrome and pregnancy. *Obesity and metabolism* 2014; 2: 3–7 (in Russian).

45. *De Souza L.R., Berger H., Retnakaran R. et al.* Non-alcoholic fatty liver disease in early pregnancy predicts dysglycemia in mid-pregnancy: prospective study. Am J Gastroenterol. 2016; 111: 665–670. DOI: 10.1038/ajg.2016.43

46. *Koralegedara I.S., Warnasekara J.N., Dayaratne K.G. et al.* Non-alcoholic fatty liver disease (NAFLD): a signifcant predictor of gestational diabetes mellitus (GDM) and early pregnancy miscarriages – prospective study in Rajarata Pregnancy Cohort (RaPCo). BMJ Open Gastroenterol 2022; 9: e000831

47. *Lee S.M., Kwak S.H., Koo J.N. et al.* Non-alcoholic fatty liver disease in the fi rst trimester and subsequent development of gestational diabetes mellitus. Diabetologia. 2019; 62 (2): 238–248.

48. *Hagström H., Höijer J., Ludvigsson J.F. et al.* Adverse outcomes of pregnancy in women with non-alcoholic fatty liver disease. Liver Int. 2016; 36 (2): 268–274.

49. *Sarkar M., Djerboua M., Flemming J.A.* NAFLD Cirrhosis Is Rising Among Childbearing Women and Is the Most Common Cause of Cirrhosis in Pregnancy. Clin Gastro-

enterol Hepatol. 2022; 20 (2): e315–e318. DOI: 10.1016/j.cgh.2021.01.022

50. *Sarkar M., Brady C.W., Fleckenstein J. et al.* Reproductive Health and Liver Disease: Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021; 73 (1): 318–365. DOI: 10.1002/hep.31559

51. *Shulman G.I.* Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med. 2014; 371: 1131–1141. DOI: 10.1056/ NEJMra1011035

52. *Zhou M.-S., Schulman I.H., Zeng Q.* Link between the rennin – angiotensin system and insulin resistance: implications for cardiovascular disease. Vasc Med 2012; 17 (5): 330–341.

53. *Park M.J., Lee D.H., Joo B.S. et al.* Leptin, leptin receptors and hypoxia-induced factor-1α expression in the placental bed of patients with and without preeclampsia during pregnancy. Mol Med Rep. 2018; 17 (4): 5292–5299.

54. *Pérez-Pérez A., Toro A., Vilariño-Garcia T. et al.* Leptin action in normal and pathological pregnancies. J Cell Mol Med. 2018; 22 (2): 716–727.

55. *Th agaard I.N., Hedley P.L., Holm J.C. et al.* Leptin and Adiponectin as markers for preeclampsia in obese pregnant women, a cohort study. Pregnancy Hypertens 2019; 15: 78–83.

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CERVICAL MUSCULAR DYSTONIA. MODERN APPROACHES TO TREATMENT

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ЦЕРВИКАЛЬНЫЕ МЫШЕЧНЫЕ ДИСТОНИИ. СОВРЕМЕННЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ

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Cervical dystonia is a disease of the nervous system characterized by forcible discoordinated abnormal postures of the head and neck. There are several approaches to the treatment of dystonia: conservative drug treatment, botulinum therapy and neurosurgery. The latter includes deep brain stimulation, radiofrequency ablation, focused ultrasound, gamma knife. Literature data on this problem from open statistical and information databases such as Web of Science, PUBMED, Movement Disorders Society; International Association of Parkinsonism and Related Disorders were analyzed. Through a comparative approach, the advantages and disadvantages of modern approaches and interventions used in the treatment of cervical dystonia are noted. Among the modern methods of treating cervical dystonia, there are a large number of approaches that improve the methods of managing such patients. This review allowed us to summarize the experience of their application. A significant growth of abilities of stereotactic techniques used in the treatment of cervical dystonia was also noted.
Keywords. Cervical muscular dystonia, focused ultrasound, deep brain stimulation, radiofrequency ablation, gamma-knife, botulinum therapy.

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Цервикальная дистония – заболевание нервной системы, характеризуемое насильственными дискоординированными, патологическими позами головы и шеи. Поражая преимущественно трудоспособное население, заболевание приводит к социально-бытовой дезадаптации, что являет собой актуальную проблему. На сегодняшний день существует несколько подходов к лечению дистонии – консервативная фармакотерапия, ботулинотерапия и нейрохирургические вмешательства, такие как глубинная стимуляция головного мозга, радиочастотная абляция, фокусированный ультразвук, гамма-нож. Среди используемых подходов следует выделить наиболее эффективные тенденции, подходящие к условиям современного лечения дистоний.

Осуществлен анализ имеющейся литературы по исследуемой тематике из открытых статистических и информационных баз данных Web of Science, PUBMED, Movement Disorders Society; International Association of Parkinsonism and Related Disorders. Посредством компаративистского подхода отмечены преимущества и недостатки современных подходов и вмешательств, используемых при лечении цервикальных дистоний. Среди современных методов лечения цервикальных дистоний существует значительное количество подходов, совершенствующих методы помощи таким пациентам. Приведенный обзор позволил обобщить опыт их применения. Так же мы отметили существенный рост возможностей стереотаксических методик, используемых при лечении цервикальной дистонии.

Ключевые слова. Цервикальная мышечная дистония, фокусированный ультразвук, глубинная стимуляция мозга, радиочастотная абляция, гамма-нож, ботулинотерапия.

INTRODUCTION

Cervical dystonia (CD) – this is a common neurological syndrome characterized by involuntary contractions of the neck muscles, leading to violent, uncoordinated, twisting and repetitive movements with an unnatural pathological position of the head and neck, which is up to 50 % of all cases of focal dystonia (according to Mark S. LeDoux, S. Fahn [1]). Its prevalence in the population is up to 30–60 cases per 100,000 people [2]. The true pathogenetic mechanisms of the disease have not yet been clarified. A number of authors attribute a role to anomalies in the processes of inhibition, sensomotor integration, neural plasticity, and disorders in the functioning of calcium channels [3].

Clinically, cervical dystonia is classified according to the EFNS-MDS recommendations using the Western Toronto Spasmodic Torticollis Scale (TWISTRS) depending on the presence of exogenous or hereditary-degenerative genesis into acquired and idiopathic forms, respectively (the latter are associated with mutations in the loci of the DYT family of genes) [4]. Among the motor signs, postural and action patterns stand out, including dystonic positioning of the head and neck (torticollis, laterocollis, anterocollis, retrocollis, anterocaput, retrocaput, laterocaput, torticaput), dystonic tremor (usually action tremor that does not stop at the “zero point”). Among non-motor symptoms, anxiety-depressive disorders (48–53 % of patients, more among women), muscle pain syndrome (97.5 % of patients) were statistically significantly distinguished [5; 6]. Some authors also distinguish dyssomnia, cognitive and emotional disorders, emphasizing their primary implementation in the pathogenesis of dystonia [7]. Pathognomonic specific corrective gestures and movements (in-

cluding when imagining them) are a result of the inclusion of a sensory component in the pathogenesis [8; 9].

Treatment of dystonia initially consisted of physiotherapy and drug therapy, including central anticholinergic drug, muscle relaxants, benzodiazepines and levodopa. Oral medications are usually ineffective and have significant side effects, so today the gold standard of treatment is injections of chemodenervating botulinum toxins type A (BTA), classic examples of which are abobotulinumtoxin, incobotulinumtoxin and onabotulinumtoxin. The use of BTA medications showed a significant decrease in TWISTRS scores on average from –12.9 to –3.2 (at the 4th week and at the end of the cycle, respectively) with an injection frequency of 3–4 months [10; 11]. Their use in the treatment of spasticity, depression, headaches, and other conditions has also been described [12; 13]. According to the Cochrane review ($n = 1144$), when using botulinum toxins, the proven improvement in the baseline TWISTRS level (43.5 on average) ranges from 18.4 to 56 % (by the 4th week and by the end of use, respectively). It is summarized that the frequency of unsatisfactory results largely depends on the anatomical verification of the muscles affected by the dystonic pattern, the starting dose of the drug, the level of compliance, and the presence or absence of the titer of neutralizing antibodies.

Among the modern possible ways to improve the results of botulinum therapy, it is possible to note the use of a combined synergy of two methods – EMG assistance and ultrasound navigation (the so-called "double control" method), since up to 37 % of unsuccessful treatment cases depend on inaccurate verification of target muscles [14]. The technique allows to significantly reduce the frequency of trauma to the vascular-nervous bundles and increase the frequency of precise injections, which significantly increases the effectiveness of therapy [15; 16]. It has been established that the combination of the two techniques is more effective than each taken separately [17]. Also, experience of botulinum therapy using F18-FDG PET/CT navigation data ($n = 78$) with a positive response in 50 % of patients, a reduction in symptoms assessed using the TWISTRS Scale by more than 30 % (by 15.0 points, respectively) has been declared. The advantages of PET navigation have made it possible to predict the response to therapy by assessing the degree of hypermetabolism in muscles and visualize the deep muscles of the neck [18]. "Functional isotope navigation" has opened up prospects for performing targeted surgical interventions for selective denervation with myotomy in cases of dystonia refractory to botulinum therapy [19]. In a double-blind randomized trial ($n = 122$), the use of Tc99m-sestamibi SPECT also allowed identification of affected muscles with a sensitivity and specificity of 93.2 % and 88.5 %, respectively. It was shown that in the long-term period, visualization improved the

effectiveness with an assessment on the TWISTRS Scale to −4.86 (95 % CI from −9.40 to −0.32; $R = 0.036$) in patients, compared with the group where botulinum therapy was carried out in the classical way. The first documented experience of CT-assistance with improvement of long-term treatment results was given by Russian authors [20]. The problem of the absence of a pronounced effect in 20 % of patients is explained by W. Poewe et al. by the unequal effectiveness of different dosages (using placebo as an example), confirming the best results of high starting doses at the beginning of therapy, however, it is worth remembering the precedents of general reactions [21; 22]. In addition, methods of combining therapy with BTA drugs with venlafaxine are proposed, which correct pain syndrome and compliance to a greater extent and show positive treatment dynamics [23]. O.R. Orlova et al. noted that, in addition to the local synaptotropic effect of botulinum toxin, the reduction of non-motor symptoms, in particular pain syndrome, is associated with additional central afferent mechanisms mediated by retrograde axonal transport, which determines the effect on the sensomotor pathogenetic component at the segmental and suprasegmental level, which is confirmed by the data of Z.A. Zaljalova et al. [7; 24]. The use of venlafaxine appears to enhance these effects to a certain level, but the case of its induction of dystonic symptoms should be kept in mind [25]. It is known that from 39 to 83 % of patients during the treatment cycle experience a decrease in the effect of BTA and a return of symptoms on average at 10.5 weeks (with a 12-week cycle), which leads to a decrease in satisfaction with the results, low compliance and, as a consequence, refusal to continue therapy [26]. Thus, over time, control over the severity of the disease is lost, worsening its form. Works with a small number of observations on the different duration of the effect of different forms of BTA drugs have been published, which is important for choosing the time of the subsequent injection [27]. Several studies have noted that additional injections into the inferior oblique muscle may increase the subjective improvement in patients' quality of life [28]. It should be taken into account that non-motor symptoms such as chronic pain syndrome and anxiety-depressive disorders (aggravated by alcohol consumption), often accompanying CD, significantly affect the subjective perception of the effectiveness of botulinum therapy, for example, pessimistically assessing its results [4; 29].

Despite the effectiveness of botulinum therapy and significant experience in its use, some patients do not achieve stable control of the disease symptoms or develop individual refractoriness [30]. In addition, the treatment is not without significant drawbacks. These include the need for periodic injections (every 3–4 months), and unequal effectiveness in various forms of CD, such as anterocollis, retrocollis, and shift. Up to 46.5 % of patients refuse therapy due to the development of muscle weak-

ness, dysphagia, dry mouth and headache [31]. This leads to the consideration of neurosurgical interventions in the maintenance of patients with CD.

The first surgical operations, dating back to the 19th century, usually included posterior rhizotomy according to Foerster, unilateral or bilateral transection of motor or sensory roots, or decompression of the accessory nerve [32]. They were used only to a limited extent due to such known complications as high mortality and, at the same time, low efficiency. The experiments of W. Hess and R. Hassler, who used functional pallidotomy in the area of Forel's H1 field and thalamotomy in the projection of the ventrooral, ventrointermedial nuclei, and the internal nucleus of the globus pallidus (GPi), opened the era of stereotactic interventions in dystonia [33].

DEEP BRAIN STIMULATION (DBS)

This is deep brain stimulation – a currently widely used invasive implantation procedure for high-frequency chronic stimulation in focal, segmental, cervical and generalized dystonias. It involves the presence of a subcutaneous stimulator installed on the anterior chest wall, acting on the target of interest through inhibitory stimulation, as well as through action on A1-adenosine receptors, desynchronizing pathological impulses of nuclei, while allowing for correction of the supplied frequencies and partial control of the symptoms of the disease. Also, through the neuromodulatory effect, a local change in metabolism occurs, which has a therapeutic effect due to the influence on neuroplasticity processes. The main target for cervical dystonia is the pallidothalamic tract (PTT), the ventrointermediate nucleus (Vim) (in dystonic tremor) and ventrooral nucleus (Vo).

Retrospective studies conducted in 2012 described the analysis of positive responses after the DBS-GPi procedure for primary idiopathic segmental dystonia at 6 months, 3 and 5 years, respectively, in 83, 94 and 81 % of adult patients ($n = 40$) with a reduction in symptoms according to the Burke – Fahn – Marsden Dystonia Rating Scale (BFMDRS or BFM) by 54.5, 49.4 % [34]. The mentioned analysis also included data from a French multicenter study (Stimulation du Pallidum Interne dans la Dystonie, SPIDY) ($n = 31$). These included a corresponding response rate after surgery of 67 and 60 % at comparable 3- and 5-year examination and a regression of dystonia symptoms of 44.8 % in the first 6 months and 67.0 % by the end of long-term examination. Using the same scales, other authors obtained improvements in treatment results, assessed using quantitative scales by 69 and 79 %, respectively [35].

Studies comparing the outcomes of patients who underwent DBS intervention ($n = 102$) reported an improvement of at least 20 % from baseline in the motor portion of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [36]. Studies comparing the outcomes of patients who underwent DBS intervention

(n = 102) reported an improvement of at least 20 % from baseline in the motor portion of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) [36]. In combination with the indicators of pain syndrome severity and the relative decrease in the severity of CD according to other subscales and the comparative evidence of effectiveness with DBS imitation, the results allow us to present this study as clinically successful. The complications from bilateral implantation reported by the authors include a smaller proportion of affected patients from the total number (36 %), but, among other things, are supplemented by postoperative stroke and hemiparesis. When comparatively analyzing the results of 24 non-conforming studies (n = 532) with patients of comparable age and duration of observation, it is possible to conclude that the intervention is effective, since a decrease in the median on the BFMDRS Scale by 58.6 % was noted after 6 months (with the greatest effect of 51.8 % in those operated on with primarily generalized and focal cervical forms) and 65.2 % after 3 years, respectively (40 and 70 % are similar for the TWSTRS Scale) [37]. The complications listed in the cited works included both correctable (electrode fracture, technical malfunctions) and other complications in the form of bleeding; however, it is necessary to take into account the comparatively smaller proportion of dysarthria and dysphagia when extrapolating their frequencies to the spectrum of pallidotomy complications. As in previous studies, the need for careful selection of patients was indicated, since there is a strong relationship between young age, onset and severity of the condition according to the analyzed scales. Recent analytical reviews on cervical dystonias highlight articles comparing the use of GPi and effects on the subthalamic (STN) nuclei. But if we compare the effectiveness of the operations (while extrapolating metadata to 2020) with the reduction of symptoms according to the Western Toronto Scale, then based on the data obtained in 59 and 60 %, we can conclude that they are equally effective. DBS has proven itself as a method that provides the ability to modify adjustable parameters individually for each patient with subsequent regulation of clinical symptoms over time. As a rule, the clinical phenotypes of laterocollis and torticollis are the most favorable in terms of response to stimulation, while retcollis and shift forms have a very controversial prognosis, since the above-mentioned works contain indications of complications occurring with a fairly high frequency.

The main disadvantages of DBS are the need for periodic replacement or recharging of the electrostimulator batteries depending on the value of the frequencies set, the need to select a stimulation program, the invasiveness of the procedure, the high cost of the necessary equipment and the installation of foreign implants, which do not exclude complications such as 0.4 % mortality. This causes a mixed attitude towards the results of this method among a number of authors.

RADIOFREQUENCY ABLATION (RFA)

This is a medical procedure that is a minimally invasive technique based on the transmission of radiofrequency alternating current using a needle probe into various anatomical structures with subsequent irreversible destruction. The essence of the method is to create a lesion by means of heat through an intracranial insulated electrode (except for the tip). The electric field between the two electrode contacts oscillates and causes nearby ions in the electrolyte medium to move back and forth in space with the same frequency. The tissues are heated by friction generated by the radiofrequency oscillations of the ions, which results in tissue heating and induces damage to the area of interest. The target structures for RFA operations are the ventroral, ventrointermediate nucleus, pallidothalamic tract and GPi. The results of treatment of patients with primary dystonia using RFA after unilateral pallidotomy and contralateral pallidothalamic tractotomy are presented, where the presented results in 6-month dynamics, assessed using the BFMDRS Scale, showed a reduction in symptoms by 88.6 % [38]. The authors summarized the decisive role of bilateral ablation, with a few exceptions such as laryngeal symptoms, citing the experience of previous studies with achieved results of reduction in BFMDRS scores after 6 months, 5 and 10 years by 70.5; 45.7 and 31.1 %, respectively. Cases of cervical dystonia have been described, the symptoms of which regressed along with pain syndrome in up to 90 %, while the need for other supportive therapy was completely eliminated [39]. Recently, several relevant CT-guided studies have been reported, one of which was cited as a successful treatment option with a symptom reduction assessed by the BFMDRS of 77.4 % [40].

However, when analyzing data from a few interventions, episodes of facial paresis are reported due to local impact on adjacent targets. Common complications of RFA include intracerebral hemorrhage, damage to nearby structures directly during the procedure, and a high risk of surgical infection. The RFA technique is an alternative for the treatment of cervical dystonia when DBS is contraindicated.

GAMMA KNIFE ABLATION (GKA)

It is a radiosurgical procedure using the isotope cobalt-60, which emits a known number of gamma radiation beams that converge on the target of interest with high precision. The technique uses ionizing radiation without the need for invasive electrodes, thereby reducing the risk of infectious complications. At the isocenter, the beams create a high total radiation dose, which is corrected by collimators and sectors of different sizes, ensuring high targeting accuracy using the Elekta system. The mechanism of ablation action consists of damaging the DNA of the target cell and creating a focus of radiation necrosis. This allowed

the method to be successfully applied in neuro-oncology. A relatively small number of cases of dystonia treatment using this approach have been published. However, a pooled review of the use of GKA in 16 patients was reported, of which only 30 % achieved significant improvement [41]. These results are not sufficient to recommend gamma knife therapy, but it may be an option in certain patient groups, particularly those with coagulopathies, cardiovascular disease, and the elderly.

Focused ultrasound under magnetic resonance guidance (MRgFUS)

The greatest emphasis today is placed on the use of focused ultrasound under magnetic resonance guidance (MRgFUS) – a technology for non-invasive ultrasound surgical intervention without the use of ionizing radiation and foreign implants. It allows the creation of a thermal ablation focus with a precision of up to 1 mm by focusing beams of high-intensity ultrasound energy under MR guidance through bone tissue, reaching deep-lying nuclei and structures, creating a thermal ablation and cavitation effect. This method involves a step-by-step effect on the selected area with subtherapeutic and therapeutic temperatures (45° and 55–60 °C, respectively, under the control of MR thermometry), the result of which is a formed zone of coagulation necrosis. Another feature of the method is the constant monitoring of the patient's symptoms, while the patient remains conscious throughout the entire operation.

Despite the small number of studies devoted to high-intensity ultrasound, a retrospective analysis of the treatment results of 13 patients with cervical dystonia was presented. The study reported a decrease in TWSTRS scores from 22 before treatment to 6 points after. In 4 patients, bilateral Vo-thalamotomy with PTT-tomy was used, while in the rest, depending on the dominant symptoms, one target or a combination was selected. Overall, 70.6 % improvement was achieved [42]. No serious complications related to the surgery were noted, except for one case of logorrhea and micrographia that regressed after three weeks. In 2017, a 6-month observance of three cured patients with cervical dystonia and dystonic tremor was reported [43]. The use of ultrasonic thermocoagulation of the Vim nucleus with Morel mapping resulted in a decrease in scores on the BFMDRS Scale from an average of 15.0 ± 3.0 to 8.0 ± 2.0 against the background of minor paresthesia of the lip, which regressed before the end of the study.

In addition to such contraindications to the operation as excessive thickness of the skull bones due to aberration of the rays and excessive heating of the tissues, there is a significant attachment mainly to the deep structures of the brain, since this reduces the accuracy of focusing. Another disadvantage worth mentioning is the small number of authorized centers involved in MRgFUS, due to the high cost of their initial establishment.

Conclusions

Dystonia remains a current problem that requires various treatment methods. The effectiveness of botulinum therapy undoubtedly depends on the accuracy of intramuscular injection, which has been greatly improved by various navigation and monitoring methods. Individual selection of dosages and injection cycles with correction of pain syndrome and emotional background of the patient allows to increase the level of compliance and, possibly, slow down the progression of cervical dystonia. The presence of a course of this form of dystonia that is refractory to botulinum therapy forces us to resort to a surgical array – from radiofrequency and gamma knife ablation, deep brain stimulation to the use of focused ultrasound. Among modern interventions, DBS occupies a strong position as the most studied invasive method with additional effects from the stimulation therapy produced with comparable results in the reduction of dystonic patterns. When comparing non-invasive techniques, the best results were achieved using MRgFUS, which was confirmed in studies showing greater efficiency and less positioning error than when using RFA. Imagine the small number of documented cases of treatment of cervical dystonia by the MRgFUS method, which is rather associated with a short period of clinical use due to the novelty of the technique. It is worth considering that, if there are indications, the use of GKA and RFA, which can be effective in certain groups of patients, is not excluded.

References

1. *LeDoux M.S.* Dystonia: phenomenology. Parkinsonism and related disorders 2012; 18 (1): S162-S164.

2. *Ahmadeeva L.R. i dr.* The use of botulinum neuroprotein type A in the treatment of focal muscular dystonia. *Medicinskij vestnik Bashkortostana* 2017; 12 (4): 63–65 (in Russian).

3. *Munasipova S.Je., Zaljalova Z.A., Terehova A.A.* Etiological and pathogenetic mechanisms of muscle dystonia formation. Prakticheskaja medicina 2023; 21 (3) (in Russian).

4. *Zaljalova Z.A.* Modern classifications of muscular dystonia, treatment strategy. *Zhurnal nevrologii i psihiatrii im. SS Korsakova* 2013; 113 (3): 85–9 (in Russian).

5. *Druzhinina O.A., Zhukova N.G., Shperling L.P.* Quality of life at cervical distonia. *Bulletin of Siberian Medicine* 2020; 19 (1): 43–49. DOI: 10.20538/1682-0363-2020-1-43-49 (in Russian).

6. *Druzhinina O.A. et al.* Cervical dystonia: non-motor aspects. *Nevrologija, nejropsihiatrija, psihosomatika* 2020; 12 (3): 69–74 (in Russian).

7. *Hajatova Z.G., Zaljalova Z.A.* Clinical variants of affective, dyssomnic and motor manifestations of craniocervical dystonia (literature review). *Obozrenie psihiatrii i medicinskoj psihologii imeni V.M. Behtereva* 2020; 2: 47–56 (in Russian).

8. *Orlova O.R.* Focal dystonia: modern approaches to diagnosis and the possibilities of botulinum therapy. *Nervnye bolezni* 2016; 4: 3–12 (in Russian).

9. *Schramm A., Classen J., Reiners K., Naumann M.* Characteristics of sensory trick-like manoeuvres in jaw-opening dystonia. Mov. Disord. 2007; 22 (3): 430–433.

10. *Simpson D.M. et al.* Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016; 86 (19): 1818–1826.

11. *Trosch R.M., Misra V.P., Maisonobe P., Om S.* Impact of abobotulinumtoxinA on the clinical features of cervical dystonia in routine practice.Clin Park Relat Disord. 2020; 3: 100063. DOI: 10.1016/j.prdoa.2020.100063.eCollection 2020.

12. *Ahmadeeva L.R. i dr.* Clinical recommendations for the diagnosis and treatment of tension headaches. *RMZh.* 2016; 24 (7): 411–419 (in Russian).

13. *Ahmadeeva L.R., Derevjanko H.P.* The use of drugs of botulinum toxin type A in neurological practice not according to the instructions. *Vestnik Rossijskoj voenno-medicinskoj akademii* 2018; 2 (62): 195 (in Russian).

14. *Erro R., Picillo M., Pellecchia M.T., Barone P.* Improving the Efficacy of Botulinum Toxin for Cervical Dystonia: A Scoping Review. Toxins 2023, 15, 391. DOI: 10.3390/toxins 15060391

15. *Salazar G., Ferreiro S., Fragoso M. et al.* Ultrasound and Electromyography as Guidance Tools for the Botulinum Toxin Therapy. J. Behav. Brain Sci. 2021; 11 (2): 49–57.

16. *O'Brien CF.* Injection Techniques for Botulinum Toxin Using Electromyography and Electrical Stimulation. Muscle Nerve. 1997; 6: S176-80. DOI: 10.1002/(SICI)1097-4598(1997)6+<176::AID-MUS12>3.0.CO;2-4

17. *Tijssen M.A.J. et al.* Descending control of muscles in patients with cervical dystonia. Movement disorders: official journal of the Movement Disorder Society 2002; 17 (3): 493–500.

18. *Kwon H.R., Lee H., Sung D.H., Choi J.Y.* Therapeutic Efficacy and Prediction of 18F-FDG PET/CT-Assisted Botulinum Toxin Therapy in Patients With Idiopathic Cervical Dystonia. Clin Nucl Med. 2022; 47 (12): e725-e730. DOI: 10.1097/RLU.0000000000004383. Epub 2022 Sep 6. PMID: 36342802.

19. *Miura I. et al.* Myotomy and Selective Peripheral Denervation Based on 18F-FDG PET/CT in Intractable Cervical Dystonia: A Case Report. NMC Case Report Journal 2023; 10: 99–102.

20. *Mokina T.V., Pavlov Ju. I., Zaljalova Z.A.* Possibilities of using computed tomography in the treatment of complex cervical dystonia with botulinum toxin type A. *Nevrologija, nejropsihiatrija, psihosomatika* 2016; 8 (2): 68–73 (in Russian).

21. *Zaljalova Z.A.* High technologies in the treatment of extrapyramidal diseases. *Vrach* 2010; 3: 5–10 (in Russian).

22. *Poewe W. et al.* Efficacy and safety of abobotulinumtoxinA liquid formulation in cervical dystonia: A randomized-controlled trial. Movement Disorders 2016; 31 (11): 1649–1657.

23. *Salouhina, N.I., Nodel M.R., Tolmacheva V.A.* Cervical dystonia: ways to achieve long-term treatment effects and improve patients' quality of life. *Russian neurological journal* 2023; 28 (4): 16–23 (in Russian).

24. *Zaljalova Z.A., Abdulgalimova D.M.* Pain syndrome before and after the use of Dysport in patients with spastic torticollis. *Zhurnal nevrologii i psihiatrii im. CC Korsakova* 2010; 110 (11–2): 62–65.

25. *Fonseca L., Rodrigues M., Machado A.* Psychogenic movement disorder after a venlafaxine-induced dystonia. Movement Disorders: Official Journal of the Movement Disorder Society. 2010; 25 (4): 506–507. DOI: 10.1002/mds.22910. PMID: 20014065.

26. *Samotus O., Jog M.* Conversion to abobotulinumtoxinA increases waning time and efficacy for cervical dystonia. Movement Disorders Clinical Practice 2023.

27. *Esquenazi A. et al.* Duration of symptom relief between injections for AbobotulinumtoxinA (Dysport®) in spastic paresis and cervical dystonia: Comparison of evidence from clinical studies. Frontiers in neurology 2020; 11: 576117.

28. *Bessemer R.A., Jog M.* Botulinum Toxin Injections to the Obliquus Capitis Inferioris Muscle for Dynamic Cervical Dystonia Improves Subjective Patient Outcomes. Toxins 2024; 16: 76. DOI: 10.3390/toxins16020076

29. *Druzhinina O.A., Zhukova N.G., Shperling L. P* Non-motor conditions in patients with cervical dystonia. *Zhurnal nevrologii i psihiatrii im. CC Korsakova* 2020; 120 (10): 7–13 (in Russian).

30. *Simpson D.M. et al.* Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016; 86 (19): 1818–1826.

31. *Erro R., Picillo M., Pellecchia M.T., Barone P.* Improving the Efficacy of Botulinum Toxin for Cervical Dystonia: A Scoping Review. Toxins 2023; 15: 391. DOI: 10.3390/toxins15060391

32. *Popov V.A., Tomskij A.A., Gamaleja A.A., Sedov A.S.* History of the study of the pathogenesis and surgical treatment of cervical dystonia. *Zhurnal nevrologii i psihiatrii im. S.S. Korsakova* 2020; 120 (7): 128–133 (in Russian).

33. *Hassler R., Hess W.R.* Experimental and anatomic studies of rotatory movements and their control mechanisms. Arch. Psychiatr. Nervenkr. 1954; 192: 488–526. DOI: 10.1152/jn.1962.25.4.455

34. *Volkmann J. et al.* Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. The Lancet Neurology 2012; 11 (12): 1029–1038.

35. *Vidailhet M. et al.* Deep brain stimulation for dystonia. Handbook of Clinical Neurology 2013; 116: 167–187.

36. *Volkmann J. et al.* Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. The Lancet Neurology 2014; 13 (9): 875–884.

37. *Moro E. et al.* Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta analysis. European journal of neurology 2017; 24 (4): 552–560.

38. *Horisawa, Shiro, et al.* Radiofrequency ablation for DYT 28 dystonia: short term follow up of three adult cases. Annals of Clinical and Translational Neurology 2020; 7 (10): 2047–2051.

39. *Dey S., Ghosh S.* Cervical Dystonia Refractory to Botulinum Toxin Responding to Radiofrequency Ablation: A Case Report. J Pain Res. 2020; 13: 2313–2316. DOI: 10.2147/JPR.S271945. PMID: 32982394; PMCID: PMC7509331

40. *Horisawa S., Kamba R., Sato M., Sueki A., Kawamata T., Nishimura K., Taira T.* Improvement of obsessive-compulsive disorder after pallidothalamic tractotomy for cervical dystonia. Ann Clin Transl Neurol. 2023; 10 (5): 832–835. DOI: 10.1002/acn3.51764. Epub 2023 Mar 23. PMID: 36950926; PMCID: PMC10187716.

41. *Verma S., Agrawal D., Singh M.* Role of Gamma Knife Radiosurgery in the Management of Functional Disorders – A Literature Review. Neurol India. 2023; 71 (Suppl.): S49–S58. DOI: 10.4103/0028-3886.373644. PMID: 37026334.

42. *Galimova R.M. et al.* Focused ultrasound under MRI control for cervical dystonia. *Annaly klinicheskoj i jeksperimental'noj nevrologii* 2023; 17 (4): 28–34 (in Russian).

43. *Alfonso Fasano, Maheleth Llinas, Renato P. Munhoz, Eugen Hlasny, Walter Kucharczyk, Andres M. Lozano.* MRI-guided focused ultrasound thalamotomy in non-ET tremor syndromes. Neurology 2017; 89 (8): 771–775. DOI: 10.1212/WNL.0000000000004268

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RISK FACTORS FOR EXOGENOUS-CONSTITUTIONAL OBESITY AND POSSIBILITIES OF ITS PREVENTION IN CHILDREN AND ADOLESCENTS

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ФАКТОРЫ РИСКА ФОРМИРОВАНИЯ ЭКЗОГЕННО-КОНСТИТУЦИОНАЛЬНОГО ОЖИРЕНИЯ И ВОЗМОЖНОСТИ ЕГО ПРОФИЛАКТИКИ У ДЕТЕЙ И ПОДРОСТКОВ

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The problem of obesity becomes more and more urgent due to its rising incidence and unfavourable effects on health of both children and adults. Various factors leading to an increased energy consumption while its output is reduced at different periods of life (from conception to adulthood) are considered in the article. Different ways of exogenous-constitutional obesity prevention in children and adolescents are described. Influence of phones/television/computers on the formation of hypodynamia and inadequate nutrition which can result in an excess body weight and obesity is characterized. The significance of behavioral response in the pathogenesis of obesity which should be considered while developing preventive methods is stressed. Thus, the problem of obesity requires further studies and discussion.
Keywords. Obesity, children, adolescents, risk factors, prevention.

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Проблема ожирения становится всё более актуальной в связи с его возрастающей распространённостью и неблагоприятными последствиями для здоровья детей и взрослых. Рассматриваются многообразные факторы, приводящие к повышенному потреблению энергии на фоне снижения её расходования в разные периоды жизни, от момента зачатия ребёнка до его перехода во взрослую жизнь. Описаны различные способы предупреждения экзогенно-конституционального ожирения у детей и подростков. Охарактеризовано влияние телефонов/телевидения/компьютеров на формирование гиподинамии и нерационального питания, следствием чего может быть избыток массы тела и ожирение. Подчёркнуто значение поведенческих реакций в патогенезе ожирения, которые необходимо учитывать при разработке методов профилактики. Таким образом, проблема ожирения, безусловно, требует дальнейшего углублённого изучения и обсуждения.
Ключевые слова. Ожирение, дети, подростки, факторы риска, профилактика.

INTRODUCTION

The negative impact of excess body weight on human health is felt not so much in childhood as in the patient's later life. Obesity prevention helps to reduce severe, difficult-to-treat diseases in the population and increases the value of a person as a member of society [1].

It is now well known that the likelihood of developing obesity, in addition to genetic factors, significantly depends on lifestyle, diet, energy expenditure, and the duration of use of modern devices (television, computers, tablets, smartphones). Timely and rational prevention of excess body weight accumulation prevents the development of obesity, preserving the health of the nation and the country's financial resources [2; 3].

Up to 99 % of all types of obesity are exogenous-constitutional or simple obesity. Other forms of obesity – hypothalamic, iatrogenic, syndromic – are much less common, and some types of monogenic obesity account for only 10–20 clinical cases [4].

Childhood obesity can lead to both short-term and long-term complications for somatic and psychosocial health. Obesity disrupts all types of metabolism, primarily fat and carbohydrate metabolism, and, accordingly, increases the risk of developing cardiovascular diseases, diabetes, fatty hepatosis, musculoskeletal pathology, mental disorders and oncology; quality of life and its duration decrease [5; 6].

EPIDEMIOLOGY OF OBESITY

In recent decades, overweight and obesity have become a major problem in many countries. According to the World Health Organization (WHO), more than a billion people on the planet are overweight and about 300 million are obese.

30 million children and adolescents are overweight, 15 million are obese [7].

Over 40 years (1975–2016), the number of children suffering from obesity has increased more than 8-fold (from 5 to 74 million). Another 213 million children and adolescents were overweight in 2016 [8], while, according to Lobstein et al. (2016), at least 42 million children were overweight or obese by the age of 5 [9; 10].

Similar trends are also evident in Russia. According to I.I. Dedov et al., in 2007, in the regions of Russia, obesity was present in 5.5 % of examined children in rural areas,

8.5 % in urban areas, and another 5.5–11.8 % of children were overweight. [11].

Currently, obesity is diagnosed by the body mass index (BMI) and the standard deviation (*SD*) from the median, i.e. from its average value.

In children, the standard deviation coefficient (*SDS*) of BMI from -2.0 to +1.0 is accepted as the norm. With BMI *SDS* +1.0 ... +2.0, excess body weight is diagnosed, and with BMI *SDS* over 2.0 – obesity.

RISK FACTORS

The main cause of childhood obesity is considered to be a hereditary predisposition and an imbalance between energy intake and expenditure [12–14]. Modern conditions of civilization and favorable socio-economic factors relieve both adults and children from labor-intensive household duties, which inevitably leads to a decrease in energy expenditure and, accordingly, to the accumulation of fat mass. Gadgets (TV, computer, telephone) make a certain contribution to the decrease in sufficient physical activity. A clear link has been established between time spent in front of the TV and obesity [15].

During the period of intrauterine development and in the first months of postnatal life, metabolic processes are highly plastic and have the ability to quickly respond to changes in environmental conditions. Insufficient nutrition of a pregnant woman, impaired utero-placental circulation, anemia, stress and other unfavorable factors during the gestational period lead to a delay in physical development, the birth of a low-weight child, and the formation of an "economical" phenotype with a tendency to accumulate. In older age, this is short stature, early puberty, obesity. In addition, nutrient deficiency in the fetus and low birth weight lead to a decrease in the number of β-cells in the pancreas and their damage [16–20].

Excessive consumption of trans fats and sweets by a woman leads to the birth of a large child, who subsequently often develops obesity and metabolic syndrome (MS), while individual components of the metabolic syndrome are detected in some children already at an early or preschool age [21].

Adipocytes are laid down mainly in the last trimester of pregnancy and in the first two years of life, so overfeeding during this period leads not only to an increase in their volume, but also to an increase in the number of fat cells [14].

OPERATIVE DELIVERY (CAESAREAN SECTION)

Operative delivery increases the risk of developing obesity in later life [22].

According to the study by Singh et al., during operative delivery, the child is not in contact with the mother's vaginal and intestinal microflora. As a result, the intestines are populated with microflora from the environment, the number of bifidobacteria decreases, and dysbiosis develops. Subsequently, impaired colonization persists for several months and even years [23]. According to the studies by Carl Vael et al., excessive concentrations of *B. fragilis* in infants are associated with the possibility of subsequent development of obesity [24].

INFANCY

Excessive weight gain in infants can be associated with feeding with any anxiety, and in the case of artificial feeding – with excessive protein content in the formula and the child's inability to independently regulate the amount of feeding, since parents strive to fully consume the available formula [25].

The growth rate in infancy correlates with the protein content in the diet. With its excess consumption, the level of hormones that have an adipogenic effect (insulin, IGF-1) increases. Excessive growth in the first months of life programs obesity and metabolic syndrome (MS) in the future, and a decrease in protein intake reduces the likelihood of developing MS in older age [25].

The likelihood of developing obesity also increases with the early introduction of supplemental feeding, as well as the appointment of juices and fruit purees in the first six months of life. Sweet foods at this age disrupt eating behavior, since children subsequently refuse vegetable dishes [26; 27].

Tight swaddling, prolonged stay in fixing devices, lack of therapeutic exercises and conditions for crawling are risk factors for the development of obesity in the future [28].

A decrease in the duration of sleep has an adverse effect on metabolism and is one of the factors that increases the likelihood of developing obesity [28; 29].

EARLY AGE

Nutritional characteristics of children over one year of age are largely determined by family traditions and taste preferences. In most cases, children receive more protein than recommended by WHO, which may be due to excessive consumption of milk used to quench their thirst. After 12 months, children often eat from the common table. During this period, pediatricians less strictly control the nature of nutrition. Parents are poorly oriented in matters of rational nutrition; they feed their children with confectionery, fast food, chips, and other products containing a lot of trans fats. Some mothers give their children milk instead of water to quench their thirst. While, children do not receive enough vegetables and fruits [30].

Parents often turn on entertainment content for their children on TV or phone in order to do their own things, thus creating another factor in childhood obesity [31–33].

PRESCHOOL AND JUNIOR SCHOOL AGE

Typical food preferences during this period are pasta, chips, various baked goods, combined with a negative attitude towards fish and vegetables. Weight gain can be facilitated by the abuse of industrially produced juices, which contain a large amount of sugar and are high in calories [34].

The easiest way to please a child is to offer him something tasty, so parents often abuse candies, cakes and other sweets, thus forming deviant (emotionogenic) eating behavior. The formation of emotional eating behavior is also facilitated by the use of food as a reward or consolation. The stimulus for eating in the future is not hunger, but a low mood [35].

The demand of parents to eat all the food on the plate, regardless of its volume and the child's desire, leads to overeating and can provoke external eating behavior – the child gets used to eating all the food he sees. As a result, increased sensitivity to external signs that stimulate appetite develops: a bright shop window, a beautifully set table, spectacular advertising of food products, and the person eats without being hungry [35].

Excessive use of devices and television contributes to weight gain, since it not only reduces physical activity and duration of sleep, but is also often accompanied by food intake, while the child does not monitor the quality and quantity of food consumed, since his attention is occupied with something else [31–33].

ADOLESCENCE

Against the background of the pubertal growth spurt, with the observance of the basic principles of a healthy lifestyle, it is possible to lose weight. Some teenagers become motivated to lose weight. Against the background of a normal-calorie diet and increased physical activity, obesity recedes. However, a significant portion of teenagers who are overweight continue to lead a sedentary lifestyle, eat when fell stressed, and obesity progresses [36]. The consequence of prolonged starvation with restrictive eating behavior (diets) are episodes of overeating and the development of "dietary depression" [37]. Studies of the quality of life of adolescents suffering from obesity have established a significant decrease in it in comparison with healthy peers and even with patients suffering from diabetes, especially on the scales of "social" and "physical" function. Quality of life suffers to a greater extent in girls [38; 39].

The literature has studied the influence of various modern technologies on the formation of obesity [40].

During adolescence, the time spent in front of TV screens increases from 2.7 ± 0.17 h at 11 years of age to 3.4 ± 0.25 h at 15 years of age. At 11 years of age, 18.3 % of children spend four hours or more daily in front of TV screens, and by 15 years of age, this number increases to 38.5 %. With age, the number of schoolchildren eating in front of a screen increases: 33.4 % at 11 years of age and 47.4 % at 15 years of age [15].

Often, the use of computers/ phones/ gadgets leads to a reduction in night sleep, affects cognitive functions, mood, quality of life and somatic health of the patient [41].

When using gadgets, there is often background content that advertises various food products that are not always healthy [42].

Previously, when digital technologies were not used so widely, schoolchildren's entertainment included a wide range of active games and various competitions, which is currently significantly reduced due to unlimited access to gadgets [15].

A teenager should do physical exercises of varying degrees of difficulty at least an hour daily [28].

The risk of developing excess body weight in a child depends not only on the long-term use of phones, television, tablets, but also on the expansion of school programs that leave a minimum amount of time for

physical activity. As a result, children spend significantly less energy than they receive [43].

Treatment

Obesity treatment requires a lot of time and efforts, it costs many times more than obesity prevention. In addition to a normal-calorie diet and mandatory physical exercise, children over 12 years of age may use medications. In Russia, orlistat and liraglutide are used to treat obesity [44–46].

Prevention

Prevention of obesity is significantly more effective than subsequent treatment [47].

At the stage of pregnancy planning, women who are overweight (in Russia, 1/4 of women over 20 years of age are overweight) should try to normalize their body weight. It is necessary to review the nature of nutrition and monitor weight [48].

The first thousand days of life from the moment of conception is a "critical window" for subsequent human development. During this period, metabolic processes are highly plastic. Obesity can be prevented through coordinated actions of specialists who prepare a woman for childbirth, monitor her during pregnancy, and carry out dispensary observation of the child [49].

During pregnancy, special attention should be paid to women with diabetes and obesity. In some countries (Australia, Finland), these women are visited by specially trained mid-level health workers, who teach them the rules of rational nutrition, monitor their weight and eating behavior [50].

Timely diagnosis and treatment of gestational diabetes can reduce the risk of obesity in a child. Of particular importance for preventing insufficient fetal weight gain is the prevention of pregnancy complications [50].

The child's eating habits are formed during the period of intrauterine development, so a woman should limit sweets, confectionery, monitor the calorie content of food, and limit the consumption of saturated fats [51–56].

In order to prevent disruption of the normal intestinal microbiota of the child, it is advisable to perform a cesarean section strictly according to indications [22–24].

To avoid overfeeding, do not feed the child at any anxiety and completely exclude force-feeding. When signs of hunger relief appear, the child may tightly squeeze his mouth and even spit out food; in this situation, continuing feeding is inappropriate. At the same time, persistence should be shown when introducing new supplemental foods: return to them again, give them in small portions, combine with favorite foods, etc. [26; 27].

Juices and fruit purees should not be introduced into the diet in the first six months of life, so that children do not refuse vegetable dishes later [26; 27].

At an early age, instead of cow's milk, it is possible to use special baby food with a reduced amount of fat and a complex of vitamins and microelements in the composition.

It is necessary to limit the consumption of juices, especially industrially produced ones, containing a large amount of sugar, and give preference to fresh fruits.

For a smooth transition of children to the "common" table, you can use industrially produced cereals with the addition of pieces of fruit and flakes, which help develop chewing skills, as well as meat with vegetable and fish with vegetable purees [30].

You cannot limit the child's motor activity. Clothes, including those of the baby, should not restrict movement [28].

Tight swaddling is unacceptable. Parents should do gymnastics with the child, give him a massage, put the child in the playpen, stimulate crawling.

The child should be involved in active games, and conditions for active movement should be created for him. Children successfully master bicycles without pedals already in the 2nd year of life. Walking on rough terrain, climbing, swimming, scootering, cycling, etc. should become habitual for a child in the first years of life. A horizontal bar, a skipping rope, an expander and other “mini-stadium” items are necessary in every family [28].

Uncontrolled use of modern electronic devices (television, computers, smartphones) affects behavioral habits. It is necessary to learn to live in harmony with new technologies, to form a behavior program in such a way as to allow digitalization into our lives and at the same time not to lose our health [31–33].

Developing an effective obesity prevention program is a global problem at the international level. It is necessary to identify a risk group of children with excess body weight and develop a system of preventive measures for them. The strategy for controlling excess body weight in children should include planned preventive measures with patients of all ages [57].

A promising strategy for obesity prevention should be multicomponent and begin at the pre-pregnancy preparation stage. Compliance with the rules of rational nutrition and optimal physical activity at different periods of life can prevent the development of obesity even in cases of a burdened heredity [30].

Conclusions

Endocrinologists and pediatricians know the risk factors for the development of obesity, but there is currently no generally accepted system for its prevention. Identifying a risk group and planned work with it could significantly change the situation.

At the moment, there is a need to develop a comprehensive program for preventing obesity at different periods of life. Preventing obesity requires the friendly work of the family, school, health workers, the media and government agencies.

References

1. *August G.P., Caprio S., Fennoy I., Freemark M., Kaufman F.R., Lustig R.H., Silverstein J.H., Speiser P.W., Styne D.M., Montori V.M.* Accelerating Progress in Obesity Prevention institute of medicine 2012.

2. *Wang Y., Lim H.* The global childhood obesity epidemic and the association between socio-economic status and childhood obesity. Int. Rev. Psychiatry 2012; 24: 176–188.

3. *Borodich T.S.* The modifiable risk factors for obesity and overweight in early childhood period. *Obesity and metabolism*

2015; 12 (2): 51. DOI: 10.14341/OMET2015251 (in Russian).

4. *Peterkova V.A., Vasyukova O.V.* About the new classification of obesity in the children and adolescents. *Problems of Endocrinology* 2015; 61 (2): 39–44. DOI: 10.14341/probl201561239-44 (in Russian).

5. Primary Prevention of Cardiovascular Disease and Type 2 Diabetes in Patients at Metabolic Risk: An Endocrine Society Clinical Practice Guideline JCEM 2008; 93 (10): 3671–3689.

6. *Afshin A., Forouzanfar M.H., Reitsma M.B. et al.* Global health effects of overweight and obesity. N Engl J Med. 2017; 377 (1): 80–81. DOI: 10.1056/NEJMoa1614362

7. *Mladovsky P., Allin S., Masseria C. Hernadez-Auevedo C., McDaid D., Mossialios E.* Health in the European Union. Trends and analysis. Copenhagen: WHO Regional office for Europe 2009.

8. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017; 390 (10113): 2627–2642 DOI: 10.1016/ S0140-6736 (17) 32129-3

9. *Lobstein T., Jackson-Leach R., Moodie M.L., Hall K.D., Gortmaker S.L., Swinburn B.A., James W. P.T., Wang Y., McPherson K.* Child and adolescent obesity: part of a bigger picture. Lancet 2015; 385 (9986): 2510–2520. DOI: 10.1016/ S0140-6736(14)61746-3

10. *Baranov A.A., Kuchma V.R., Namazova-Baranova L.S., Sukhareva L.M., Ilyin A.G., Rapoport I.K., Shirokova V.I., Levitskaya A.A., Chumakova O.V., Antonova E.V., Albitsky V.Yu., Zvezdina I.V., Chubarovsky V.V., Sokolova N.V., Sergeeva A.A.* Strategy "Health and development of adolescents in Russia" (harmonization of European and Russian approaches to the theory and practice of protecting and promoting the health of adolescents. Moscow 2010 (in Russian).

11. *Dedov I.I., Melnichenko G.A., Butrova S.A., Savelyeva L.V.* Obesity in adolescence. Results of a Russian epidemiological study. *Ter. archive*. 2007; 10: 28–32 (in Russian).

12. *Weihrauch-Blüher S., Wiegand S.* Risk Factors and Implications of Childhood Obesity. Curr Obes Rep. 2018; 7 (4): 254–259. DOI: 10.1007/s13679-018-0320-0

13. *Martínez-Villanueva J., González-Leal R., Argente J., Martos-Moreno G.Á.* La obesidad parental se asocia con la gravedad de la obesidad infantil y de sus comorbilidades [Parental obesity is associated with the severity of childhood obesity and its comorbidities]. An Pediatr (Barc). 2019; 90 (4): 224–231.DOI: 10.1016/j.anpedi.2018.06.013

14. *Netrebenko O.K., Ukraintsev S.E., Melnikova I.Yu.* Obesity in children: new concepts and directions for prevention. Literature review. *Issues of modern pediatrics* 2017; 16 (5): 399–405. DOI: 10.15690/vsp.v16i5.1804 (in Russian).

15. *Namazova-Baranova L.S., Kovtun O.P., Anufrieva E.V., Naboychenko E.S.* The value of behavioral determinants in the formation of overweight and obesity in adolescents. *Russian Journal of Preventive Medicine* 2019; 22 (4): 2043–2048. DOI: 10.17116/profmed20192204243 (in Russian).

16. *Wallby T., Lagerberg D., Magnusson M.* Relationship Between Breastfeeding and Early Childhood Obesity: Results of a Prospective Longitudinal Study from Birth to 4 Years. Breastfeed Med. 2017; 12: 48 53. DOI: 10.1089/bfm.2016.0124

17. *Baran J., Weres A., Czenczek-Lewandowska E. et al.* Excessive Gestational Weight Gain: Long-Term Consequences for the Child. J Clin Med. 2020; 9 (12): 3795. DOI: 10.3390/jcm9123795

18. *Jimenez-Chillaron J.C., Duaz R., Martinez D., Pentinat T., Ramon-Krauel M., Ribo S., Plosch T.* The role of nutrition on epigenetic modifications and their implications on health. Biochimie 2012; 94: 2242–2263.

19. *Ng S.F., Lin R.C., Laybutt D.R., Barres R., Owens J.A., Morris M.J.* Chronic high – fat diet in fathers programs betacell dysfunction in female rat offspring. Nature 2010; 467: 963–966.

20. *Carone B.R., Fauquier L., Habib N.* Paternally induced transgenerational environmental reprogramming of metabolic gene expression in mammals. Cell. 2010; 143: 1084–1096.

21. *Wallby T., Lagerberg D., Magnusson M.* Relationship Between Breastfeeding and Early Childhood Obesity: Results of a Prospective Longitudinal Study from Birth to 4 Years. Breastfeed Med. 2017; 12: 48–53. DOI: 10.1089/bfm.2016.0124

22. *Mueller N.T., Mao G., Bennet W.L. et al.* Does vaginal delivery mitigate or strengthen the intergenerational association of overweight and obesity? Findings from the Boston Birth Cohort. Int J Obes (Lond). 2017; 41 (4): 497–501. DOI: 10.1038/ijo.2016.219

23. *Singh S.B., Madan J., Coker M. et al.* Does birth mode modify associations of maternal pre-pregnancy BMI and gestational weight gain with the infant gut microbiome? Int J Obes (Lond). 2020; 44 (1): 23–32. DOI: 10.1038/s41366-018-0273-0

24. *Vael C., Verhulst S.L., Nelen V., H Goossens & Kristine N.* Desager Intestinal microflora and body mass index during the first three years of life: an observational study. Gut Pathog. 2011; 3 (1): 8. DOI: 10.1186/1757-4749-3-8

26. *Wang J., Wu Y., Xiong G. et al.* Introduction of complementary feeding before 4 months of age increases the risk of childhood overweight or obesity: A meta-analysis of prospective cohort studies. Nutr Res. 2016; 36: 759–770. DOI: 10.1016/j.nutres.2016.03.003

27. *Grote V., Theurich M., Luque V. et al.* Complementary Feeding, Infant Growth, and Obesity Risk: Timing, Composition, and Mode of Feeding. Nestle Nutr Inst Workshop Ser. 2018; 89: 93–103. DOI: 10.1159/000486495

28. *Peterkova V.A., Bezlepkina O.B., Bolotova N.V. et al.* Clinical guidelines «Obesity in children». *Problems of Endocrinology* 2021; 67 (5): 67–83. DOI: 10.14341/probl12802 (in Russian).

29. *Taveras E.M., Rifas-Shiman S.L., Oken E. et al.* Short sleep duration in infancy and risk of childhood overweight. Arch Pediatr Adolesc Med. 2008; 162 (4): 305–311. DOI: 10.1001/archpedi.162.4.305

30. *Aleksandrov A.A., Peterkova V.A., Vasyukova O.V.* Rekomendatsii po diagnostike, lecheniyu i profilaktike ozhireniya u detei i podrostkov. Moscow: Praktika 2015; 136 (in Russian).

31. *Robinson T.N., Banda J.A., Hale L. et al.* Screen Media Exposure and Obesity in Children and Adolescents. Pediatrics. 2017; 140 (S2): 97–101. DOI: 10.1542/peds.2016-1758K

32. *Bickham D.S., Blood E.A., Walls C.E. et al.* Characteristics of screen media use associated with higher BMI in young adolescents. Pediatrics. 2013; 131 (5): 935–941. DOI: 10.1542/peds.2012-1197

33. *Li C., Cheng G., Sha T. et al.* The Relationships between Screen Use and Health Indicators among Infants, Toddlers, and Preschoolers: A Meta-Analysis and Systematic Review. Int J Environ Res Public Health 2020; 17 (19): 7324. DOI: 10.3390/ijerph17197324

34. *He B., Long W., Li X. et al.* Sugar-Sweetened Beverages Consumption Positively Associated with the Risks of Obesity and Hypertriglyceridemia Among Children Aged 7–18 Years in South China. J Atheroscler Thromb. 2018; 25 (1): 81–89. DOI: 10.5551/jat.38570

35. *Dedov I.I., Melnichenko G.A.* Obesity. Moscow: MIA 2004; 456 (in Russian).

36. *Simmonds M., Burch J., Llewellyn A.* The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: A systematic review and meta-analysis. Health Technol Assess. 2015; 19: 1–336. DOI: 10.3310/hta19430

37. *Van Strien T., Bazelier F.G.* Perceived parental control of food intake is related to external, restrained and emotional eating in 7–12-year old boys and girls. Appetite 2007; 49 (3): 618–625.

38. *Endokrinologiya: novosti, mneniya, obucheniye* 2018; 7 (2): 51–59. DOI: 10.24411/2304-9529-2018-12005 (in Russian).

39. *Akhmedova R.M., Sofronova L.V., Vladimirova K.N.* Assessment of the quality of life of adolescents suffering from endocrine diseases. *Pediatrician* 2016; 7 (1): 16–21. DOI: 10.17816/PED7116-21 (in Russian).

40. *Boswell N., Byrne R., Davies P.S.W.* Aetiology of eating behaviours: A possible mechanism to understand obesity development in early childhood. Neurosci Biobehav Rev. 2018; 95: 438–448. DOI: 10.1016/j.neubiorev.2018.10.020

41. *Berdin O.N.* The role of sleep and its disorders in the formation of cognitive functions in childhood. *Bulletin of the VSSC SB RAMS* 2014; 6 (100) (in Russian).

42. *Norman J., Kelly B., McMahon A.T. et al.* Sustained impact of energy-dense TV and online food advertising on children's dietary intake: a withinsubject, randomised, crossover, counter-balanced trial. Int J Behav Nutr Phys Act. 2018; 15 (1): 37. DOI: 10.1186/s12966-018-0672-6

43. *Drapkina O.M., Karamnova N.S., Kontsevaya A.V., Gorny B.E., Dadaeva V.A., Drozdova L.Yu., Yeganyan R.A., Eliashevich S.O., Izmailova O. V., Lavrenova E.A., Lischenko O.V., Skripnikova I.A., Shvabskaya O.B., Shishkova V.N.* Russian Society for the Prevention of Noncommunicable Diseases (ROPNIZ). Alimentary-dependent risk factors for chronic non-communicable diseases and eating habits: dietary correction within the framework of preventive counseling. Methodological Guidelines. *Cardiovascular Therapy and Prevention* 2021; 20 (5): 2952. DOI: 10.15829/1728-8800-2021-2952 (in Russian).

44. *Kelly A.S., Auerbach P., Barrientos-Perez M. et al.* A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. N Engl J Med. 2020; 382 (22): 2117–2128. DOI: 10.1056/NEJMoa1916038

45. *Mastrandrea L.D., Witten L., Carlsson Petri K.C. et al.* Liraglutide effects in a paediat-

ric (7-11 y) population with obesity: A randomized, double-blind, placebo-controlled, short-term trial to assess safety, tolerability, pharmacokinetics, and pharmacodynamics. Pediatr Obes. 2019; 14 (5): e12495. DOI: 10.1111/ijpo.12495

46. *Robert H. Lustig, Pamela S. Hinds, Karen Ringwald-Smith, Robbin K. Christensen, Sue C. Kaste, Randi E. Schreiber, Shesh N. Rai, Shelly Y. Lensing, Shengjie Wu, Xiaoping Xiong* Octreotide Therapy of Pediatric Hypothalamic Obesity: A Double-Blind, Placebo-Controlled Trial. The Journal of Clinical Endocrinology & Metabolism 2003; 88 (6): 2586–2592. DOI: 10.1210/jc.2002-030003

47. *Pandita A., Sharma D., Pandita D. et al.* Childhood obesity: prevention is better than cure. Diabetes Metab Syndr Obes. 2016; 9: 83–89. DOI: 10.2147/DMSO.S90783

48. *Razina A.O., Runenko S.D., Achkasov E.E.* Obesity: Current Global and Russian Trends. *Annals of the Russian Academy of Medical Sciences* 2016; 71 (2): 154–159. DOI: 10.15690/vramn655 (in Russian).

49. *Belyaeva I.A., Namazova-Baranova L.S., Turti T.V.* Introduction of complementary feeding as a measure to prevent overweight and obesity in children from the perspective of the "first 1000 days" concept. *Issues of modern pediatrics* 2020; 19 (3): 220–227. DOI: 10.15690/vsp.v19i3.2118 (in Russian).

50. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. Diabetic Medicine 2011; 844–854.

51. *Shenderov B.A.* The role of nutrition and intestinal microflora in the programming and implementation of the epigenome of healthy and sick people. *Bulletin of restorative medicine* 2013; 1: 102–107 (in Russian).

52. *Tutelyan V.A., Kon I.Ya.* Baby food: A guide for doctors. Moscow: Medical Information Agency 2013; 744 (in Russian).

53. *Netrebenko O.K.* Infantile origins of obesity and cardiovascular disease in children. *Nestle News Bulletin* 2012; 34: 4–6 (in Russian).

54. *Baturin A.K., Kon I.Ya., Gmoshinskaya M.V., Ukraintsev S.E.* Rational nutrition for pregnant and lactating women. Information mail. Moscow 2009; 16 (in Russian).

55. *Kon I.Ya., Gmoshinskaya M.V.* Nutrition of women during pregnancy. *Consilium medicum. Application "Pediatrics"* 2006; 1: 57–62 (in Russian).

56. *Kamalova AA.* Current approaches to preventing childhood obesity. *Rossijskij vestnik perinatologii i pediatrii* 2016; 61 (6): 43–48. DOI: 10.21508/1027-4065-2016-61-6-43-48 (in Russian).

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PREDICTING THE PROBABILITY OF COMPLICATIONS DURING PROSTATECTOMY IN PATIENTS WITH PROSTATE CANCER USING MACHINE LEARNING METHODS

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ПРОГНОЗИРОВАНИЕ МЕТОДАМИ МАШИННОГО ОБУЧЕНИЯ ВЕРОЯТНОСТИ РАЗВИТИЯ ОСЛОЖНЕНИЙ ПРИ ПРОСТАТЭКТОМИИ У ПАЦИЕНТОВ С РАКОМ ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ

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Objective. To determine the probabilities of predicting possible complications after surgery in patients with the diagnosis of prostate cancer using artificial intelligence methods.

Materials and methods. Case histories of 701 patients who underwent prostatectomy were analyzed in the study. The anamnesis, findings of clinical, laboratory and instrumental study, as well as objective data of clinical observations were evaluated. The average age was 64.72. On the basis of the set of examination results, patients were selected according to the following inclusion criteria: prostate cancer patients without confirmed metastases with disease stage from T1N0M0 to T3N0M0; absence of previous and concomitant special treatment (immunotherapy or targeted therapy); informed consent to the surgery. Logistic regression, a binary classifier using a sigmoidal activation function on linear combinations of features, was used as a machine learning model.

Results. It was determined that the logistic regression model based on selected parameters (prostate volume, pain syndrome, disease duration), predicts the probability of complications quite well (TPR = 1). The overall accuracy of the model is: Accuracy = 0.98. At the same time, it can be noticed from the agreement matrix that the trained model plays it safe and classifies some cases without complications incorrectly in 5.3 % (FNR = 0.053). However, the model never made an error and did not classify cases with a high risk of complications as those in which such a possibility was unlikely.

Conclusions. The results obtained show that on the basis of just three parameters (prostate volume, pain syndrome, duration of the disease), it is possible to build a fairly good predictive model of the probability of complications after prostatectomy based on such machine learning method as logistic regression.

Keywords. Prostate cancer; prostatectomy; diagnostics; early detection of complications; prediction of complications; logistic regression.

Цель. Определение возможностей прогнозирования вероятности возникновения осложнений после перенесенного оперативного вмешательства у пациентов, поступивших с диагнозом раком предстательной железы, с помощью методов искусственного интеллекта.

Материалы и методы. В исследовании были проанализированы данные историй болезни 701 пациента, которым была выполнена простатэктомия. Проведена оценка анамнеза, данных клинико-лабораторных и инструментальных методов исследования, а также объективных данных клинических наблюдений. Средний возраст пациентов составил 64,72 г. Исходя из комплекса результатов обследования, были отобраны пациенты, соответствующие следующим критериям включения: больные раком предстательной железы без подтвержденных метастазов со стадией заболевания от T1N0M0 до T3N0M0; отсутствие предшествующего и сопутствующего специального лечения (иммунотерапия или таргетная терапия); наличие информированного согласия на проводимое оперативное вмешательство. В качестве модели машинного обучения применялась логистическая регрес-

сия – бинарный классификатор, использующий сигмоидную функцию активации на линейные комбинации признаков.

Результаты. Установлено, что на отобранных параметрах (объем простаты, болевой синдром, длительность заболевания) модель логистической регрессии достаточно хорошо предсказывает вероятность возникновения осложнений (TPR = 1). Общая точность модели составляет Accuracy = 0,98. При этом из матрицы согласования видно, что обученная модель «перестраховывается» и классифицирует часть случаев без осложнений неправильно – в 5,3 % (FNR = 0,053). Однако модель ни разу не ошиблась и не отнесла случаи, в которых высока вероятность возникновения осложнений, к случаям, где такая возможность маловероятна.

Выводы. Полученные результаты показывают, что на основе всего трех параметров (объем простаты, болевой синдром, длительность заболевания) можно построить достаточно хорошую предсказательную модель вероятности возникновения осложнений после простатэктомии на основе такого метода машинного обучения, как логистическая регрессия.

Ключевые слова. Рак предстательной железы, простатэктомия, диагностика, раннее выявление осложнений, прогнозирование осложнений, логистическая регрессия.

INTRODUCTION

The incidence of prostate cancer (PC) has been rapidly increasing over the last decade in Russia. PC is on the 4th place (6.9 % of tumors of all localizations) after lung cancer, gastric cancer and skin tumors in the structure of malignant neoplasm morbidity among males [1–4]. The number of patients with localized forms of prostate cancer has increased significantly after the implementation of screening programs using prostate specific antigen (PSA) testing [5–7]. A recurrence of PC occurs among 10–30 % of patients after surgical interventions. PC is determined by an increase in PSA level values in the early stages [8–11]. Improvement of the prostatectomy technique proceeds accordingly to the evolution of the study of the anatomy of this area, more accurate understanding of the peculiarities of the location and structure of the fascial layers and functionally important anatomical structures [12; 13]. Due to the active development of AI, it is possible to create an aid system for making medical decisions on predicting the occurrence of complications of various diseases, including PC. Currently, clinical decision support systems for physician based on retrospective analysis of outpatient charts and clinical history are already being developed and implemented; real-time systems for ICU patients that allow to warn the medical personnel about the onset of critical conditions; wearable systems for monitoring and subsequent retrospective analysis of anamnesis data.

One of the ways of improving the outcomes of post-prostatectomy PC treatment is to identify and predict the postoperative survival rate of patients and the rate of complications at an early stage by using gradient-boosting methods, which will undoubtedly be able to greatly simplify the construction and strategy of treatment.

The aim of the study is to determine the possibilities of predicting the probability

of complications after surgical intervention among patients diagnosed with PC using AI methods.

MATERIALS AND METHODS

The study analyzed data from the clinical histories of 701 patients who had a prostatectomy. The anamnesis, data of the clinical laboratory and instrumental methods of research, as well as objective data of clinical observations were conducted. The average age was 64,72 y. All included in the study patients received a comprehensive examination according to clinical guidelines for diagnosis and treatment of prostate cancer patients. Morphologic examinations of the obtained material (after surgical treatment) was conducted according to the standard technology. The slices colored by hematoxylin and eosin were used in the observational morphological analysis to determine the histological type of the tumor, the degree of differentiation, the severity of secondary changes, and the prevalence of the tumor process according to the WHO classification. eosin were used to determine the histological type of tumor, the degree of differentiation, the intensity of secondary changes and the prevalence of the tumor process according to the WHO classification. Patients were selected according to a set of examination results. They met the following inclusion criteria: cancer patients without confirmed metastases with the disease stage from T1N0M0 to T3N0M0; absence of previous and concomitant special treatment (immunotherapy or targeted therapy); informed consent to undergoing surgical intervention and participation in the study. The exclusion criteria were: PC patients with confirmed metastases, previous and concomitant special treatment, and also the presence of exacerbations of chronic diseases. During clinical examination, PSA levels were determined to range from 3.98 to 30.49 ng/mL; the Glisson number was from 3 to 7, and the prostate tumor size ranged from 33.04 to 143.88 cm^3.

Logistic regression is a binary classifier that uses a sigmoid activation function on linear combinations of features. It was used as a machine learning model. This machine learning method is the simplest classifier that still shows reasonably good results for certain tasks. At the same time, it allows us to find out the presence of linearly dependent parameters of the dataset.

The following metrics were used here:

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

An approval matrix in the form of:

$$\begin{bmatrix} TPR & FNR \\ FPR & TNR \end{bmatrix},$$

where

$$TPR = \frac{TP}{TP + FP}; \quad FPR = \frac{FP}{TP + FP};$$

$$TNR = \frac{TN}{TN + FN}; \quad FNR = \frac{FN}{TN + FN};$$

TPR is the share of patients who had a complication and the model predicted the

complication, out of all patients who had a predicted complication; *FPR* is the share of patients who did not have a complication, but the model predicted a complication, out of all patients who had a predicted complication; *FNR* is the share of patients who had complications but the model did not predict a it, out of all patients who had a predicted absence of complications; *TNR* is the share of patients who did not have a complication and the model predicted the absence of a complication, out of all patients who had a predicted absence of a complication; *TP* is the amount of patients who had a complication and the model predicted the complication; *FP* is the amount of patients who did not have a complication but the model predicted a complication; *FN* is the amount of patients who had complications but the model did not predict a complication; *TN* is the amount of patients who did not have a complication and the model predicted the absence of a complication.

Permission for conducting this study was reflected by the Local Ethical Committee (LEC) of the V.I. Razumovsky Saratov State Medical University (LEC protocol No. 2 of 16.09.2023). The study was conducted in the presence of voluntary informed consent of patients in accordance with the declaration of compliance with international as well as Russian ethical principles and standards (excerpt from Minutes No. 19 of the Bioethics Committee of 26th October, 2018). The study was conducted in accordance with the requirements of the World Medical Association Declaration of Helsinki (revised in 2013).

RESULTS AND DISCUSSION

In addition to TNM staged diagnoses (at the time of hospitalization and after histological confirmation), the collected data set contained the following parameters (*I* – range of values, *m* – average, *s* – standard deviation), shown in Table 1.

Table 1

Parameters of the studied dataset

Name of parameter	Value range	Code
Age, years	*I* = [50...80] *m* = 64.73 *s* = 8.14	AGE
Duration of disease, months	*I* = [7...120] *m* = 26.87 *s* = 19.08	DD
PSA level before surgery, ng/mL'	*I* = [3.98...30.49] *m* = 17.21 *s* = 7.74	PSABS
TNM Glisson score for surgery	*I* = [3.00...7.00] *m* = 4.90 *s* = 1.42	GLISSONFS

End of Table 1

Name of parameter	Value range	Code
Prostate ultrasound at the time of hospitalization, cm	I = [3.00...5.89] m = 4.28 s = 0.71	US1
Prostate ultrasound after surgery, cm	I = [2.91...8.78] m = 4.23 s = 0.83	US2
Prostate ultrasound at the time of discharge, cm	I = [2.89...9.70] m = 4.25 s = 0.86	US3
Prostate volume, cm^3	I = [25.90...180.20] m = 87.84 s = 32.05	PV
Was there residual urine	Yes/No	RU
Infected urine before surgery (All patients had a value of "No". The parameter was excluded from the study)	Yes/No	
Comorbidity	Yes/No	COMORB
Coexisting diseases of the cardiovascular system	Yes/No	CCVD
Coexisting gastrointestinal diseases	Yes/No	GIT
Coexisting diseases of the respiratory system	Yes/No	RS
Surgical history	Yes/No	SH
Surgery type (patients underwent the following surgeries depending on the stage of the tumor process: posterior radical prostatectomy; laparoscopic posterior radical prostatectomy; radical perineal prostatectomy)	Posterior prostatectomy Laparoscopic prostatectomy Perineal prostatectomy	SURT
TNM Glisson score after surgery	I = [3.00...10.00] m = 6.45 s = 2.17	GLISSONAS
Diagnostic concordance according to the Glisson scale	Yes/No	GLISSONCON
Impurity of blood in urine after surgery	Yes/No	BLOODURINE
Duration of hospitalization after surgery, days	I = [7.00...41.00] m = 19.69 s = 8.34	HOSPIT
Discharged with a catheter	Yes/No	CATHETER
Blood loss	Yes/No	BLOODL
Demand for blood transfusion	Yes/No	TRANSF
Interoperative complications	Yes/No	INTEROP
Postoperative complications	Yes/No	POSTOP
Complications which are not directly related to the surgery	Yes/No	COMPLIC
Sluggish urine stream before surgery	Yes/No	SLUGSTREAM
Severe pain syndrome	Yes/No	PAINSYN
Nocturia	Yes/No	NOCT

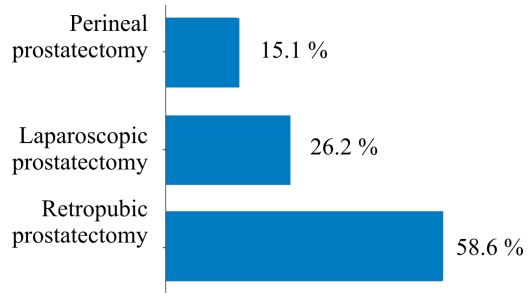

Fig. 1. Percentage of patients by surgery type

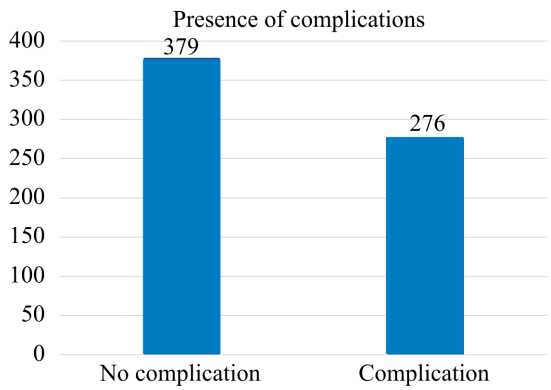

Fig. 2. Patients distribution by presence and absence of complications: 0 – there were no complications, 1 – there were complications

Figure 1 shows the percentage of patients according to the type of surgery, figure 2 shows the distribution of patients according to age.

According to the data of Fig. 1, the information set is unbalanced by the type of performed operation. The majority of patients (58.6 %) had a retropubic prostatectomy. Laparoscopic prostatectomy was conducted for 26.2 % of patients and perineal prostatectomy for 15.1 %. At the same time, the amount of patients with and without complications was approximately the same, as can be seen from Fig. 2.

For further study, parameters with values that were either unique or the same for all patients were removed. As a result, the following parameters remained: “AGE” (age of the patients), ‘DD’ (duration of disease (in months)), ‘TNM.T’ (tumor size according to TNM classification), ”TNM. N“ (stages with lymph node involvement according to TNM classification), ‘PSABS (preoperative PSA level, ng/mL’)”, “GLISSONFS” (TNM Glisson score for surgery), “US1” (prostate ultrasound at the time of hospitalization, cm), “US2” (prostate ultrasound after surgery, cm), “US3” (prostate ultrasound at the time of discharge, cm), “PV” (prostate volume, cm3), ‘RU’ (was there residual urine), ‘CCVD’ (coexisting diseases of the cardiovascular system), ‘GIT’ (coexisting gastrointestinal diseases), ‘RS’ (coexisting diseases of the respiratory system), ‘SH’ (surgery history), ‘SURT’ (surgery type (patients underwent the following surgeries depending on the stage of the tumor process: posterior radical prostatectomy; laparoscopic posterior radical prostatectomy; radical perineal prostatectomy), “GLISSONAS” (TNM Glisson score after surgery), “gTNM. T” (histologic verification of tumor according to TNM classification), ‘GLISSONCON’ (diagnostic concordance according to the Glisson scale), ‘BLOODURINE’ (impurity of blood in urine after surgery), “CATHETER” (discharged with a catheter), ‘BLOODL’ (blood loss), ‘TRANSF’ (demand for blood transfusion), ‘PAINSYN’ (severe pain syndrome), ‘NOCT’ (nocturia). Target variable for predicting “POSTOP” (postoperative complications).

Logistic regression was used to identify parameters that were linearly dependent from the others. The calculation results of the significance of the remaining linearly independent parameters are summarized in Table 2.

Table 2

Calculation results of the importance of the remaining independent parameters

Model	Logit		Method	MLE		
Dependent Variable:	AS		Pseudo R-squared:	0.853		
Date:	2024-03-29 20:26		AIC:	186.4373		
No. Observations:	701		BIC:	291.1450		
Df Model:	22		Log-Likelihood:	-70.219		
Df Residuals:	678		LL-Null:	-478.59		
Converged:	1.0000		LLR p-value:	1.6073e-158		
No. Iterations:	11.0000		Scale:	1.0000		
	Coef.	Std.Err.	z	P > |z|	[0.025	0.975]
AGE	-0.0220	0.0270	-0.8158	0.4146	-0.0750	0.0309
DD	-0.0204	0.0091	-2.2558	0.0241	-0.0382	-0.0027
TNM.T	-0.0465	0.6236	-0.0745	0.9406	-1.2688	1.1759
TNM.N	0.0198	1.9323	0.0102	0.9918	-3.7674	3.8069
PSABS	0.0146	0.0320	0.4565	0.6480	-0.0480	0.0772
GLISSONFS	-0.1571	0.1754	-0.8955	0.3705	-0.5009	0.1867
US1	-0.0702	0.3461	-0.2028	0.8393	-0.7486	0.6082
US2	-0.4671	0.2545	-1.8349	0.0665	-0.9659	0.0318
US3	-0.0195	0.2300	-0.0850	0.9323	-0.4704	0.4313
PV	-0.0148	0.0073	-2.0188	0.0435	-0.0292	-0.0004
RU	0.0001	0.0329	0.0018	0.9985	0.0645	0.0646
CCVD	-1.0520	1.1430	-0.9204	0.3574	-3.2923	1.1883
GIT	-0.6683	0.5550	-1.2041	0.2286	-1.7560	0.4195
RS	1.1087	1.5938	0.6956	0.4866	-2.0150	4.2324
SH	1.0268	0.9198	1.1163	0.2643	-0.7760	2.8297
SURT	0.3699	0.4353	0.8499	0.3954	-0.4832	1.2231
GLISSONAS	-0.0891	0.1207	-0.7381	0.4605	-0.3256	0.1475
gTNM.T	1.1078	0.8687	1.2752	0.2022	-0.5948	2.8104
GLISSONCON	-0.0751	0.5762	-0.1303	0.8963	-1.2044	1.0542
BLOODURINE	0.0498	1.4686	0.0339	0.9730	-2.8286	2.9281
CATHETER	-0.9088	0.7519	-1.2087	0.2268	-2.3824	0.5649
BLOODL	-0.0786	1.4563	-0.0539	0.9570	-2.9329	2.7758
PAINSYN	10.4449	1.5913	6.5636	0.0000	7.3259	13.5638

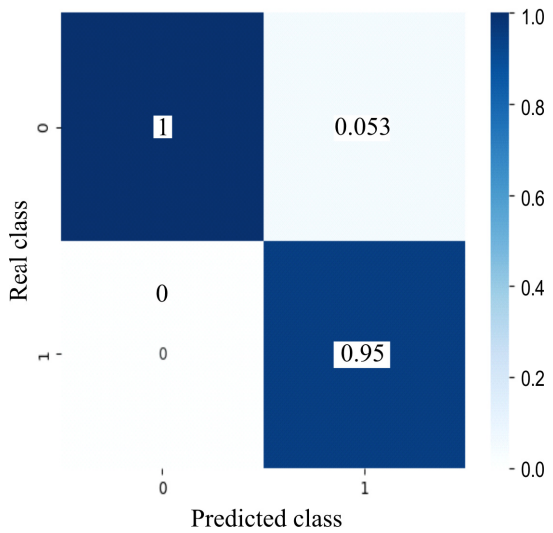

Fig. 3. Approval matrix

As we can see from the data presented in Table 2, the most important parameters determining the likelihood of complications are prostate volume (PV, $p = 0.0435$), pain syndrome (PAINSYN, $p = 0.0000$), and disease duration (DD, $p = 0.0241$).

Then, logistic regression was trained on these parameters to determine the probability of complications.

The original data set was divided in the proportion of 70 %/30 % for training and metrics calculation such that the distributions of the target variable (AS) were statistically indistinguishable in the training and variation metrics.

The Accuracy metric was 0.98 as a result of testing the trained model on the validation sample. The concordance matrix is shown in Fig. 3. As it can be seen, the share of patients who had complications and among patients to whom the model predicted complications was TPR = 1. The model never made an error and did not categorize patients with complications to patients without complications (FPR = 0). In this case, the model "reinsured" and it predicted the occurrence of complications for 5.3 % of patients, although they did not get a complication (FNR = 0.053 and TNR = 0.95).

It is necessary to mention that the certificate of state registration of computer programs "System of prediction of complications prediction during prostatectomy for prostate cancer" (No. 2024613673)1 has also been obtained to date.

Conclusions

As can be seen from the obtained metrics, the logistic regression model predicts the probability of complications reasonably well (TPR = 1) on the selected parameters (prostate volume (PV), pain syndrome (PAINSYN), duration of disease (DD)). The overall accuracy of the model is 0.98. However, as can be seen from the concordance matrix, the model "reinsures" and classifies a part of cases without complications incorrectly. Thus, 5.3 % (FNR = 0.053) were misclassified as cases with a high likelihood of complications. At the same time, the model never made an error in categorizing cases in which there was a high probability of complications to cases where such a possibility was low.

Thus, the obtained results show that on the basis of only three parameters

(prostate volume (PV), pain syndrome (PAINSYN), duration of disease (DD)), it is possible to build a reasonably good predictive model of the probability of complications after prostatectomy based on such a machine learning method as logistic regression. If the model metrics need to be improved, further the patient sample can be increased and the model can be trained using more sophisticated machine learning and AI methods.

References

1. *Sekhoacha M., Riet K., Motloung P., Gumenku L., Adegoke A., Mashele S.* Prostate Cancer Review: Genetics, Diagnosis, Treatment Options, and Alternative Approaches. Molecules. 2022; 27 (17): 5730.

2. *Alipov V.V., Takhmezov A.E., Polidanov M.A., Musaelyan A.G., Kondrashkin I.E., Volkov K.A., Alipov A.I.* Improvement of the results of treatment and diagnosis of postoperative complications in abdominal surgery with the use of multifunctional device. *Medical Science and Education of the Urals* 2023; 24 (1–113): 67–71 (in Russian).

3. *Wasim S., Lee S.Y., Kim J.* Complexities of Prostate Cancer. Int J Mol Sci. 2022; 23 (22): 142–157.

4. *Desai K., McManus J.M., Sharifi N.* Hormonal Therapy for Prostate Cancer. Endocr Rev. 2021; 42 (3): 354–373.

5. *Achard V., Putora P.M., Omlin A., Zilli T., Fischer S.* Metastatic Prostate Cancer: Treatment Options. Oncology. 2022; 100 (1): 48–59.

6. *Williams I.S., McVey A., Perera S., O'Brien J.S., Kostos L., Chen K., Siva S., Azad A.A., Murphy D.G., Kasivisvanathan V., Lawrentschuk N., Frydenberg M.* Modern paradigms for prostate cancer detection and management. Med J Aust. 2022; 217 (8): 424–433.

7. *Rizzo A., Santoni M., Mollica V., Fiorentino M., Brandi G., Massari F.* Microbiota and prostate cancer. Semin Cancer Biol. 2022; 86: 1058–1065.

8. *Eifler J.B., Feng Z., Lin B.M., Partin M.T., Humphreys E.B., Han M., Epstein J.I., Walsh P.C., Trock B.J., Partin A.W.* An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. BJU Int. 2023; 111 (1): 22–29.

9. *Pushkar D.Y., Rasner P.I.* Diagnostics and treatment of localized prostate cancer. Moscow: MEDpress-Inform 2008: 320 (in Russian).

10. *Veliev E.I., Golubtsova E.N., Tomilov A.A.* Surgical treatment for progressive prostate cancer: A clinical case. *Onkourologiya* 2014; 3: 95–100 (in Russian).

11. *Veliev E.I., Tomilov A.A., Bogdanov A.B.* Salvage lymphadenectomy in patients with PET/CT-confirmed oligometastatic recurrence of prostate cancer. *Oncourology* 2018; 4: 79–86 (in Russian).

12. *Evsyukova O.I., Chernyaev V.A., Khalmurzaev O.A., Khafizov K.A., Khachaturyan A.V., Tkhakokhov M.M., Matveev V.B.*

Evaluation of safety and feasibility of salvage lymphadenectomy in patients with lymphogenic metastases of prostate cancer after radical treatment. *Oncourology* 2017; 4: 64–69 (in Russian).

13. *Perepechai V.A., Vasiliev O.N.* Laparoscopic radical prostatectomy. *Bulletin of Urology* 2018; 3: 57–72 (in Russian).

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EARLY PREDICTION OF BRONCHOPULMONARY DYSPLASIA IN EXTREMELY PREMATURE INFANTS: A COHORT STUDY

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РАННЕЕ ПРОГНОЗИРОВАНИЕ БРОНХОЛЕГОЧНОЙ ДИСПЛАЗИИ У ГЛУБОКО НЕДОНОШЕННЫХ ДЕТЕЙ: КОГОРТНОЕ ИССЛЕДОВАНИЕ

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Objective. To develop the model for early prediction of clinically significant bronchopulmonary dysplasia in extremely premature infants.

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Materials and methods. 226 premature infants with gestational age less than 31 weeks, birth weight from 490 to 999 g, age from 0 to 7 days, and respiratory failure requiring ventilatory support (ventilator support) were included into a retrospective study conducted in the Perm Regional Perinatal Center. Machine learning algorithms such as logistic regression, support vector machine, random forest method, and gradient boosting method were used for the prognostic model building. Five variables were used: birth weight, Apgar score in the 5th minute of life, Silverman score, number of days of invasive ventilatory support, median oxygen fraction in the inhaled air measured daily during the first seven days of life.
Results. In the 36th week of postconceptional age 148 out of 182 infants (81.3 %) in the study cohort developed bronchopulmonary dysplasia (BPD), among them 15.4 % had a mild form, 29.7 % a moderate one, and in 36.3 % of patient it was severe. Among the four studied prediction algorithms, logistic regression model was chosen as the final model with metrics: AUC = 0.840, accuracy 0.818, sensitivity 0.972, specificity 0.666. The practical application of the modeling results was implemented in the form of a probability calculator.
Conclusions. In the early neonatal period of extremely premature infants, a combination of clinical predictors such as birth weight, Apgar score in the 5th minute of life, Silverman score, number of days of invasive ventilatory support, median oxygen fraction in the inhaled air measured during the first seven days of life can be used to predict the development of bronchopulmonary dysplasia. The logistic regression model shows high sensitivity that minimizes the probability of an error of second kind. Thus, its application is useful in the early prediction of bronchopulmonary dysplasia in premature infants.
Keywords. Bronchopulmonary dysplasia, prematurity, prediction, machine learning.

Цель. Разработка алгоритма раннего прогнозирования развития клинически значимой бронхолегочной дисплазии у глубоко недоношенных детей.
Материалы и методы. В ретроспективное исследование, проведенное в Пермском краевом перинатальном центре, были включены 226 глубоко недоношенных детей, со сроком гестации менее 31 недели, весом при рождении от 490 до 999 г., в возрасте от 0 до 7 дней, с наличием дыхательной недостаточности, потребовавшей аппаратной поддержки. Для построения прогностической модели использовались алгоритмы машинного обучения: логистическая регрессия, метод опорных векторов, метод случайного леса, метод градиентного бустинга. Использовали пять переменных характеристик: масса тела при рождении, оценка по шкале Апгар на 5-й мин жизни, оценка по шкале Сильвермана, количество дней инвазивной ИВЛ, медианное значение доли кислорода во вдыхаемом воздухе, измеряемое ежедневно в первые семь дней жизни.
Результаты. На 36-й неделе постконцептуального возраста у 148 из 182 новорожденных исследуемой когорты (81,3 %) развилась бронхолегочная дисплазия (БЛД): у 15,4 % она была отнесена к легкой, у 29,7 % – к средней тяжести, и у 36,3 % – к тяжелой. Из четырех изученных алгоритмов прогнозирования в качестве итоговой выбрана модель логистической регрессии с метриками: AUC = 0,840, точность 0,818, чувствительность 0,972, специфичность 0,666. Прикладное применение результатов моделирования осуществлено в виде калькулятора вероятности.
Выводы. В раннем неонатальном периоде глубоко недоношенных детей для прогнозирования развития БЛД можно использовать сочетание клинических предикторов, таких как масса тела при рождении, оценка по шкале Апгар на 5-й мин, оценка по шкале Сильверман, количество дней инвазивной ИВЛ, медианное значение доли кислорода во вдыхаемом воздухе измеряемое в первые семь дней жизни. Модель логистической регрессии показывает высокие значения чувствительности, которые позволяют минимизировать вероятность ошибки второго рода, что делает ее применение полезным в задачах раннего прогнозирования развития БЛД у глубоко недоношенных детей.
Ключевые слова. Бронхолегочная дисплазия, недоношенные, прогнозирование, машинное обучение.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most crucial complications of preterm labor as it has long-term consequences [1]. Due to the advances in modern neonatal care, the survival rate of profoundly premature infants has improved significantly,

which is contributing to the increasing incidence of BPD worldwide [2]. The optimization of strategies for the prevention and treatment of BPD is based on scientific prediction of the probability of its development, the main goal of which is to ensure a personalized approach to each child.

Many BPD prediction models have been developed in recent years. For example, T. C. Kwok (2023) included 64 studies with 53 prediction models in his review [3], H. B. Peng (2022) described 21 prediction models from 13 studies [4], M. Romijn (2023) examined 65 studies, including 158 development models and 108 externally validated models, however, the problem is that the existing models are of varying quality and they may produce contradictory results, and this leads to difficulties about the kind of model to use or to recommend [5]. Mathematical approaches in medical prediction include the use of statistical methods and machine learning. Statistical methods can be used to analyze disease data, patient data, and epidemiological trends to identify patterns and factors that affect health. Machine learning allows to create models based on large amounts of data, which helps in predicting diagnoses, treatment results and possible complications [6; 7]. Various algorithms have been effectively applied to process data generated in neonatology over the past decade, for example, for the prediction of the hemodynamic significance of a functioning ductus arteriosus among preterm neonates [8; 9]. The model based on machine learning of support vectors was proposed in Denmark in 2021 to predict the occurrence of BPD by combining postpartum clinical characteristics and the amount of nitrogen in exhaled gas, the accuracy of the model was about 90 % [10]. In another study was created a machine learning model to predict serious BPD using clinical data and genomics, the AUC of the model was 0.872 [11]. The results of BPD prediction based on deep machine learning technologies, particularly with the help of neural networks, have been published now [12; 13]. Traditionally, all researchers identify risk factors for BPD's development by classifying preterm infants for the presence or absence of BPD at 28 days postnatal period or 36 weeks postconceptional age (PCA). Then researchers examine all factors that influenced risk up to the time of diagnosis. Most BPD's prediction models use clinical indicators, including prenatal, perinatal, and postnatal factors. Although there were a lot of attempts to examine the correlation between biomarkers and BPD in the majority of studies, only few biomarkers have been included in prediction models (14). Today the main known risk factors for BPD's development listed in studies are low birth weight, gestational age, male sex, open ductus arteriosus, sepsis, and artificial pulmonary ventilation. Nevertheless, considering the fact that the development of BPD is determined by the influence of a large number of factors, the interrelationship of which is still controversial, the optimal set of factors predicting the development of BPD is still unknown.

The aim of the study is to develop an algorithm for early prediction of the development of clinically significant bronchopulmonary dysplasia among profoundly premature infants. It is hypothesized that there is an optimal combination of predictive features (predictors) that will result in the highest probability of BPD's development.

MATERIALS AND METHODS

A retrospective study, conducted at the Perm Regional Perinatal Center, included 226 profoundly premature infants that were born between October 2015 and April 2020. Conditions of inclusion in the observation groups were: gestational age less than 31 weeks, birth weight from 490g to 999g, age from 0 to 7 days, respiratory insufficiency requiring artificial pulmonary ventilation (ALV), main diagnosis according to ICD-10: P 27.1 – bronchopulmonary dysplasia that occurred in the perinatal period. Exclusion criteria: serious congenital malformations such as chromosomal abnormalities, congenital lung disease, congenital heart defects (except open ductus arteriosus (OAD) and atrial septal defect) and malformations of the central nervous system, as well as incomplete clinical data. The information was obtained by retrospective examination of medical records of reporting forms No. 112/y. In our study, we defined BPD according to the wording of R.D. Higgins (2018) stated in the clinical recommendations: bronchopulmonary dysplasia is a chronic diffuse parenchymatous (interstitial) lung disease that occurs among premature infants as an outcome of respiratory distress syndrome and/or pulmonary hypoplasia, diagnosed on the basis of oxygen dependence at 28 days of life and/or 36 weeks postconceptional age [15]. 60 potential prognostic features were identified based on literature review and our own hypotheses, and 37 of them were excluded as uninformative in subsequent analysis. As a result, 5 variable characteristics (predictors) of the early neonatal period were used to develop a prediction model: birth weight, the 5-minute Apgar score, Silverman score, the amount of days of invasive ALV, and the median value of the fraction of oxygen in the respired oxygen (FiO_2) recorded daily during the first seven days of life. Invasive ALV was defined as any type of assisted ventilation requiring intubation and artificial ventilation from a CPAP machine. The indication for ALV was frequent apneas, increasing symptoms of RI in the form of participation of auxiliary muscles in the breathing process, persistent respiratory acidosis in blood gasses, increasing $PaCO_2 > 50$ mm Hg at FiO_2 60 % in the supplied mixture. Laboratory methods of research included general clinical blood analysis (Sysmex XN 9000 analyzer), biochemical blood analysis (Sapphire 400 analyzer). Echocardiographic study (echocardiography) was conducted among all infants on the 1st, 3rd, 7th, and 28th days of life with Vivid&GE (USA), 12S-RS and 8S-RS transducers. Neurosonographic study (NSG) was conducted on the 1st and 3rd day of life using a Vivid&General Electric ultrasound multifunctional scanner

(USA) with color coded Doppler flow mapping. Standard ECG recordings were conducted among all infants using an electrocardiograph "Alton EKZT-12-03 (2007)" on the second day of life. Chest organ radiography (OGC) was conducted on the 1st, 3rd, 28th days and at 36 weeks of PCA (TMS 300 RDR mobile X-ray unit). Round-the-clock monitoring of vital functions was conducted among all infants and included monitoring of heart rate, saturation and blood pressure.

The results were subjected to statistical processing by using parametric and non-parametric analysis methods. Quantitative indices, which distribution differed from normal, were described using median (Me) values with quartiles ($Q_1 - Q_3$) corresponding to the 25–75 % interval. Nominal data were described by stating the absolute value and percentage. Arithmetic mean (*M*), standard deviation (*SD*) and 95 % confidence interval (95 % CI) limits were calculated for quantitative indices having normal distribution. The Student's t-criterion (for normal distribution) and the Mann – Whitney (U) criteria for non-normal distribution were calculated for comparative analysis of mean values. Nominal data were compared using Pearson's ^{2} test. Differences were considered statistically significant if the level of significance was determined to be $p < 0.05$. The connection between the phenomena, which were represented by quantitative data, was evaluated using Spearman's rank correlation coefficient. The following algorithms were used to develop the model: logistic regression, support vector machines (SVM), Random Forest Classifier and Gradient Boosting Classifier. Continuous variables were standardized such that their values ranged from 0 to 1. Non-binary categorical variables were converted to binary variables via One Hot Encoder. Models were developed using the training dataset and evaluated using 5-fold cross-validation. The test dataset was used for internal validation. The area under the ROC curve (AUC) of each model was calculated to evaluate the characteristics of the models. The evaluation of the following metrics were used: Accuracy, Precision, Recall, and F1 Score.

Data accumulation, adjustment, summarization and visualization were accomplished in standard Microsoft Office Excel 2016 spreadsheets. Jamovi, SPSS 26.0 software was used for statistical analysis.All experiments were conducted in Python 3.9.5 using the following libraries: scikit-learn 0.24.1, matplotlib, scipy. All procedures in this research involving human people were conducted in accordance with the Declaration of Helsinki (revised in 2013). The study was approved by the local ethical committee of the Federal State Budgetary Educational Institution of Higher Education "Perm State Medical University named after Academician E.A. Wagner" of the Ministry of Health of the Russian Federation (Perm, Russia). Written informed consent was obtained from the patients' parents or legal guardians.

RESULTS AND DISCUSSION

A total of 226 infants, born before 30 weeks gestation, were enrolled in the study. Retrospectively, 44 infants were excluded from the study due to death before the 28th

day of life, 21 dropped out of the study because of other reasons. Thus, there were a total of 182 children included in the final analysis, including 94/182 (51.6 %) girls and 88/182 (48.4 %) boys. The median birth weight was 880.0 g with an interquartile range ($Q_1 - Q_3$) from 770 to 960.0 g, the average gestational age was 26.7 ± 1.74 weeks, and the average mother's age was 27.2 ± 6.5. 148 out of 182 infants (81.3 %) diagnosed with BPD at the 36th week of postconceptional age, 28/182 (15.4 %) of them were categorized as mild, 54/182 (29.7 %) as moderately severe, and 66/182 (36.3 %) as serious. Considering the insignificant clinical manifestations of mild BPD, it was decided to divide the data into two groups: moderate/serious BPD (main group, 120 patients) and absence/mild BPD (comparison group, 62 children). There were significant differences between the groups, such as median weight in the main group was 806 (720–900) g, in the comparison group it was 949 (893–990) g, $p < 0.001$, the average gestational age in the main group was 26.1 ± 1.5, in the comparison group it was 28 ± 1.5 – ($p < 0.001$). The length of stay in the intensive care unit was prolonged among infants with BPD (in average of 52.2 days vs. 21.7 days without BPD ($p < 0.001$)). Apgar score was lower among patients with later BPD's progression (main group): 6.13 ± 0.91 vs. 7.06 ± 0.86, $p < 0.001$. The Silverman scale score (respiratory disease severity score) in the main group was 5.98 ± 0.80 vs. 5.11 ± 0.88 points, $p < 0.001$. The average amount of days on ALV was significantly higher in the main group (5.18 ± 2.54 vs. 1.44 ± 2.51, $p < 0.001$). The median value of respired oxygen fraction FiO2 in the first 7 days of life was significantly higher in the main group: 28.70 (25.5–33.0) vs. 23.50 (22.00–27.00), $p < 0.001$ (Table 1).

Four machine learning algorithms were used to develop a BPD prediction model. The task type is binary classification, the target variable is the probability of BPD progression, it takes one of two possible values – 0 or 1, the independent variables are a set of five studied features. Data preparation was conducted, outliers (four values) were removed, and the final dataset size for the simulation was 178 observations. The dataset was randomly divided into two subsets: the training dataset, which consisted of 75 % of the cohort (133 children), and the test dataset, which consisted of the remaining 25 % (45 children). The following variables were used as predictors: birth weight, the 5-minute Apgar score, Silverman score, number of days of invasive ALV and median FiO_2 value. In our work, in the context of the task of predicting the probability of developing BPD among preterm infants, we chose the Recall metric as the leading one, because it is important to minimize false negative results. When the model incorrectly predicts the absence of BPD of the infant, as the wrong treatment tactics may be chosen. We reduce the number of such errors by choosing the model with the maximum Recall value. The logistic regression model showed the highest Recall value among the four used algorithms (Table 2).

Table 1

Clinical characteristics of profoundly premature infants

Patients	Main group, $n = 120$	Comparison group, $n = 62$	p-value
Birth weight, g	806 (720–900)	949 (893–990)	0.001
Birth gestational age, weeks	26 ± 1.5	28 ± 1.5	0.001
Apgar score, score	6.13 ± 0.91	7.06 ± 0.86	0.001
Silverman scale score, score	5.98 ± 0.80	5.11 ± 0.88	0.001
Days on ALV	5.18 ± 2.54	1.44 ± 2.51	0.001
FiO_2, median share, %	28.70 (25.5–33.0)	23.50 (22.00–27.00)	0.001

Table 2

Classification characteristics (metrics) of the final models

№	Model	Accuracy	Precision	Recall	F1 Score	AUC
1	Logistic Regression	0.818	0.795	0.972	0.875	0.840
2	Random Forest	0.763	0.780	0.888	0.831	0.830
3	Gradient Boosting	0.740	0.823	0.777	0.799	0.800
4	SVC	0.720	0.733	0.916	0.814	0.800

A logistic regression equation was developed on the basis of the obtained results with the coefficients intercept = 1.18, variable "Birth weight" = –0.68, variable "Silverman score" = 0.67, variable "Apgar score" = –0.62, variable "Number of days on ALV" = 0.37, variable "FiO_2 fraction" = 0.78. The final equation is provided to the user in a convenient format in the form of a calculator (Web interface). Our final logistic regression model has the following classification characteristics (metrics): Recall 0.972; AUC 0.840; Accuracy 0.818, which allow its application in clinical practice (Figure).

The advantage of this study is that the proposed algorithm is conducted on the seventh day of the infant's life, providing clinicians the opportunity of early prognosis. In addition, the used predictors are uncomplicated and available in clinical practice. A limitation of our study is the relatively small number of participants. It can lead to potential bias. Therefore, further larger studies are needed to confirm the findings and determine their clinical utility.

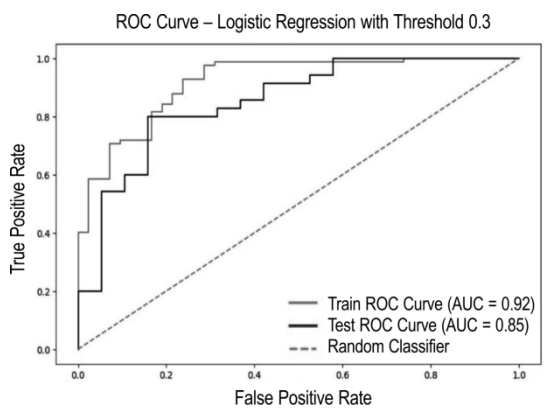

Fig. ROC-curve graph for the logistic regression model

CONCLUSIONS

A combination of clinical predictors such as: birth weight, the 5-minute Apgar score, Silverman score, number of days of

invasive ALV, median respired oxygen fraction measured in the first seven days of life can be used to predict the development of BPD in the early neonatal period of profoundly premature infants. The logistic regression model shows high sensitivity values that allow minimizing the probability of the second type of error, which makes its application useful in the tasks of predicting the BPD progression among premature infants with ELBW in the early neonatal period.

References

1. *Cheong J.L.Y., Doyle L.W.* An update on pulmonary and neurodevelopmental outcomes of bronchopulmonary dysplasia. Semin Perinatol. 2018; 42 (7): 478–484. DOI: 10.1053/j.semperi.2018.09.013

2. *Lui K., Lee S.K., Kusuda S., Adams M., Vento M., Reichman B., Darlow B.A., Lehtonen L., Modi N., Norman M., Håkansson S., Bassler D., Rusconi F., Lodha A., Yang J., Shah P.S.* International Network for Evaluation of Outcomes (iNeo) of neonates Investigators. Trends in Outcomes for Neonates Born Very Preterm and Very Low Birth Weight in 11 High-Income Countries. J Pediatr. 2019; 215: 32–40.e14. DOI: 10.1016/j.jpeds

3. *Kwok T.C., Batey N., Luu K.L., Prayle A., Sharkey D.* Bronchopulmonary dysplasia prediction models: a systematic review and meta-analysis with validation. Pediatr Res. 2023; 94 (1): 43–54. DOI: 10.1038/s41390-022-02451-8

4. *Peng H.B., Zhan Y.L., Chen Y., Jin Z.C., Liu F., Wang B., Yu Z.B.* Prediction Models for Bronchopulmonary Dysplasia in Preterm Infants: A Systematic Review. Front Pediatr. 2022; (12): 10: 856159. DOI: 10.3389/fped.2022.856159

5. *Romijn M., Dhiman P., Martijn J.J. Finken, Anton H. van Kaam, Trixie A. Katz, Joost Rotteveel, Ewoud Schuit, Gary S. Collins, Wes Onland, Heloise Torchin.* Prediction Models for Bronchopulmonary Dysplasia in Preterm Infants: A Systematic Review and Meta-Analysis. J Pediatr. 2023; Jul: 258 (113370). DOI: 10.1016/j.jpeds.2023.01.024

6. *Kuchumov A.G., Golub M.V., Rakisheva I.O., Doroshenko O.V.* An algorithm for creation of metamodel for predicting hemodynamics in the aortas of children with congenital heart defects. Sbornik nauchnyh trudov VII kongressa biofizikov Rossii. Sbornik materialov kongressa. Krasnodar 2023; 228–229 (in Russian).

7. *Ter-Levonian, A.S., Koshechkin K.A.* Review of machine learning technologies and neural networks in drug synergy combination pharmacological research. Research Results in Pharmacology 2020; 6 (3): 27–32. DOI: 0.3897/rrpharmacology.6.49591

8. *Porodikov A.A., Bijanov A.N., Permjakova A.V., Tuktamyshev V.S., Kuchumov A.G., Pospelova N.S., Furman E.G., Onoprienko M.N.* N-terminal pro-brain natriuretic peptide as a predictor of hemodynamic significance of functioning ductus arteriosus in premature newborns. *Perm Medical Journal* 2021; 38 (1): 5–15 (in Russian).

9. *Permyakova A.V., Porodikov A., Kuchumov A.G., Biyanov A., Arutunyan V., Furman E.G., Sinelnkov Y.S.* Discriminant

Analysis of Main Prognostic Factors Associated with Hemodynamically Significant PDA: Apgar Score, Silverman–Anderson Score, and NT-Pro-BNP Level. *J. Clin. Med.* 2021; 10 (3729). DOI: 10.3390/jcm10163729

10. *Verder H., Heiring C., Ramanathan R., Scoutaris N., Verder P., Jessen T.E., Höskuldsson A., Bender L., Dahl M., Eschen C., Fenger-Grøn J., Reinholdt J., Smedegaard H., Schousboe P.* Bronchopulmonary dysplasia predicted at birth by artificial intelligence. Acta Paediatr. 2021; 110 (2): 503–509. DOI: 10.1111/apa.15438

11. *Dai D., Chen H., Dong X., Chen J., Mei M., Lu Y., Yang L., Wu B., Cao Y., Wang J., Zhou W., Qian L.* Bronchopulmonary Dysplasia Predicted by Developing a Machine Learning Model of Genetic and Clinical Information. Front Genet. 2021; 2 (12): 689071. DOI: 10.3389/fgene.2021.689071

12. *Na J.Y., Kim D., Kwon A.M., Jeon J.Y., Kim H., Kim C.R., Lee H.J., Lee J., Park H.K.* Artificial intelligence model comparison for risk factor analysis of patent ductus arteriosus in nationwide very low birth weight infants cohort. Sci Rep. 2021: 11 (1): 22353. DOI: 10.1038/s41598-021-01640-5

13. *Son J., Kim D., Na J.Y., Jung D., Ahn J.H., Kim T.H., Park H.K.* Development of artificial neural networks for early prediction of intestinal perforation in preterm infants. Sci Rep. 2022; 12: 12112. DOI: 10.1038/s41598-022-16273-5

14. *Zhuravleva L.N., Novikova V.I., Derkach Ju.N.* Determining the possibility of developing bronchopulmonary dysplasia by determining the cytokine profile in premature infants. *International journal of Immunopathology, allergology, infectology* 2021; 3: 21–27. DOI: 10.14427/jipai.2021.3.21

15. *Higgins R.D., Jobe A.H., Koso-Thomas M., Bancalari E., Viscardi R.M., Hartert T.V., Ryan R.M., Kallapur S.G., Steinhorn R.H., Konduri G.G., Davis S.D., Thebaud B., Clyman R.I., Collaco J.M., Martin C.R., Woods J.C., Finer N.N., Raju T.N.K.* Bronchopulmonary Dysplasia: Executive Summary of a Workshop. J Pediatr. 2018; 197: 300–308. DOI: 10.1016/j.jpeds.2018.01.043

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ANALYSIS OF POPULATION MORTALITY FROM ENDOCRINE DISEASES AND DIABETES MELLITUS IN THE REPUBLIC OF SAKHA (YAKUTIA) SINCE 2018 TO 2022

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АНАЛИЗ СМЕРТНОСТИ НАСЕЛЕНИЯ ОТ ЭНДОКРИННЫХ ЗАБОЛЕВАНИЙ И САХАРНОГО ДИАБЕТА В РЕСПУБЛИКЕ САХА (ЯКУТИЯ) ЗА 2018–2022 ГГ.

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Objective. To analyze the mortality from endocrine pathology of the population in the Republic of Sakha (Yakutia).
Materials and methods. A retrospective analysis of the mortality rates from endocrine diseases and diabetes mellitus of the population of the Republic of Sakha (Yakutia) from 2018–2022 was carried out. The analysis was based on the data of YARMIAC and the republican register of diabetes mellitus.
Results. An increase in the death rate from endocrine pathology, from diabetes mellitus was noted during the analyzed period. In the structure of mortality from endocrine pathology, deaths from diabetes mellitus were 96 %. The structure of causes of death in patients with diabetes mellitus includes renal failure, CHF, acute myocardial infarction, PE and pneumonia.
Conclusions. The results obtained during the study will allow us to justify the need for improving the endocrinological service in the Republic of Sakha (Yakutia) scientifically and will form the basis for the regional program "Combating diabetes mellitus".
Keywords. Morbidity, mortality, endocrine pathology, diabetes mellitus, Yakutia.

Цель. Анализ смертности населения от эндокринной патологии в Республике Саха (Якутия).
Материалы и методы. Проведен ретроспективный анализ показателей смертности населения от эндокринных заболеваний и от сахарного диабета в Республике Саха (Якутия) за 2018–2022 гг. по данным ЯРМИАЦ и Республиканского регистра сахарного диабета.
Результаты. За анализируемый период отмечается повышение показателя смертности населения от эндокринной патологии. В структуре смертности от эндокринной патологии – смертность от сахарного диабета составляет 96 %. В структуре причин смерти пациентов с сахарным диабетом – почечная недостаточность, ХСН, острый инфаркт миокарда, ТЭЛА и пневмония.
Выводы. Полученные результаты позволят научно обосновать необходимость совершенствования эндокринологической службы в Республике Саха (Якутия) и лягут в основу региональной программы «Борьба с сахарным диабетом».
Ключевые слова. Заболеваемость, смертность, эндокринная патология, сахарный диабет, Якутия.

INTRODUCTION

The spread of diabetes mellitus is becoming more important from year to year in the world in general and particularly in the Russian Federation. This disease is a global medicosocial threat to the person and society as a whole [1; 2]. The Russian Federation has accepted the series of strategic documents for improvement of endocrinological service and medical care organization for this group of patients. It is necessary to point out that there are not many works devoted to the analysis of mortality of patients suffering from diabetes mellitus, especially in the regions of the Russian Federation. The study of epidemiological characteristics of diabetes mellitus will allow to develop effective organizational mechanisms for reducing morbidity, disability, and mortality [3–5].

According to the data of federal and regional registers of diabetes mellitus morbidity in recent years and in the postpandemic period, there is a clear increase of 1 and 2 diabetes mellitus type among the population [1; 5]. Therefore, it is particularly important to study the mortality rates of the population from diabetes mellitus.

The Republic of Sakha (Yakutia) is one of the regions of the Far Eastern Federal District with a well-organized endocrinology department. All specialized medical care in the field of endocrinology is located in

Yakutsk. There is a unified register of patients. The population of the republic is quite heterogeneous in terms of ethnicity. In connection with the above, the republic has the potential to become a pilot northern region for monitoring the epidemiological characteristics of diabetes mellitus and for improving the endocrinological department in the Arctic zone of the Russian Federation.

MATERIALS AND METHODS

The retrospective analysis of population mortality rates from endocrine diseases and diabetes mellitus in the Republic of Sakha (Yakutia) for the period 2018–2022 was conducted. The official statistics data are taken from the Yakutsk Republican Medical Information and Analytical Center (YRMIAAC), which is the republican register of diabetes mellitus of the Republic of Sakha (Yakutia).

RESULTS AND DISCUSSION

Since 2018–2022, the main classes of mortality causes of the population demonstrate a steady growth of the number of deaths, including diseases of the endocrine system and diabetes mellitus. The highest mortality rates from all causes are identified in 2021 (1,067.8 per 100,000 of population). The highest mortality rates from endocrine diseases, eating disorders and metabolic disorders are registered in 2020 (27.6 per 100,000 of population) and mainly because of mortality from diabetes mellitus (26.0 per 100,000 of population). The total mortality rate from all causes increased by 5.7 % in the changes for the analyzed period – from 784.1 in 2018 to 828.5 in 2022, including diseases of the endocrine system – by 26.4 %, from 17.8 to 22.5, including diabetes mellitus – by 31.7 %, from 16.4 to 21.6 per 100 thousand of the population, respectively (Table 1).

The largest share in the mortality structure from endocrine diseases is mortality from diabetes mellitus (average from 92.8 % to 96.0 %). At the same time, the number of deaths from insulin-independent diabetes mellitus is significantly higher than from non-insulin-dependent diabetes mellitus. The dynamics over the five-year period shows an increase in the share of deaths caused by diabetes mellitus from 92.8 % in 2018 to 96.0 % in 2022, mainly because of the non-insulin-dependent form of diabetes. Thus, the specific volume of the number of deaths from non-insulin-dependent diabetes mellitus in 2018 was 69.0 %, in 2022 – 86.5 %. The specific volume of the number of deaths from insulin-dependent form of diabetes in changes, on the contrary, is decreasing: if in 2018 the specific volume of deaths from insulin-dependent form of diabetes amounted to 25.3 %, then in 2022 – 12.1 % (Table 2).

From 13.7 % to 17.8 % of endocrine diseases deaths from 2018 to 2022 are registered in the working age group (2018 – 14 %; from 2022 – 17.8 %), the majority of which are men (more than 53.1–75 %). Women share is from 25 % to 46.9 % in this age category. The overwhelming majority of deaths from endocrine diseases are registered annually at the

Table 1

Changes of mortality rate of the population of the Republic of Sakha (Yakutia) according to classes and individual causes of death, 2018–2022 (per 100 thousand of the population)

Rate	2018	2019	2020	2021	2022	Increase/ decrease, in % 2022 to 2018
Deaths from all causes, including:	784.1	784.0	929.5	1 067.8	828.5	5.7
diseases of the endocrine system, eating disorders, metabolic disorders	17.8	18.1	27.6	21.6	22.5	26.4
of them from diabetes mellitus	16.4	16.7	26.0	20.6	21.6	31.7

Table 2

Changes of the population mortality structure from endocrine diseases in the Republic of Sakha (Yakutia), 2018–2022

The cause of death	2018		2019		2020		2021		2022	
	abs.n.	%	abs.n.	%	abs.n.	%	abs.n.	%	abs.n.	%
Endocrine diseases	172	100	175	100	270	100	213	100	224	100
Diabetes mellitus, including:	158	92.8	162	92.6	254	94.1	203	95.3	215	96.0
insulin-dependent diabetes mellitus	40	25.3	36	22.2	29	11.4	19	9.4	26	12.1
non-insulin-dependent diabetes mellitus	109	69.0	120	74.1	218	85.8	182	89.7	186	86.5
other forms of diabetes	9	5.7	6	3.7	7	2.8	2	0.9	3	1.4
Malnutrition	0	0	1	0.6	4	1.5	0	0	3	1.3
Other endocrine diseases, eating disorders and metabolic disorders	14	8.1	12	6.9	12	4.4	10	4.7	6	2.7

age above working age – from 77.2 % to 84.9 %, of which women prevail – more than 60 %. The share of men was from 20.5 % to 33.5 % during the analyzed period.

The number of deaths from endocrine diseases increased in both age categories in the changes for 2018–2022: of working age – to 66.7 % and above working age – to 18.5 %.

The number of deaths from diabetes mellitus in 2022 increased, in comparison with 2018. It increased to 36.1 % (57 people). The women's share of population prevails in the structure of mortality of the republic from diabetes mellitus (2018 – 70.9 %; 2022 – 69.3 %), the men's share of population is less than 40 % (2018 – 29.1 %; 2022 – 30.6 %).

The majority deaths from diabetes mellitus are registered above working age (2018 – 86.7 %; 2022 – 77.7 %), in 2018 – 78.8 % of women and 21.2 % of men; in 2022, 66.4 % of women and 33.5 % of men. 17.2 % of deaths from diabetes mellitus were registered among the able-bodied population for 2022 (2018 – 13.3 %), among men prevail – 67.5 %, women's share is for about 32.4 % (in 2018, the share of men – 81 %, the share of women – 19 %).

The number of deaths from diabetes mellitus in both age categories increased in the changes for 2018–2022: at working age by 76.2 % and above working age by 21.9 %.

The urban population prevails in the structure of population mortality from diabetes mellitus (2018 – 71.2 %; 2022 – 69.6 %), there were 69.4 % of women in 2018 and 30.6 % of men; in 2022 – 60.6 % of women and 39.4 % of men.

The rural population is about 30 % (2018 – 28.8 %; 2022 – 30.4 %), in 2018 – 69.4 % of women and 30.6 % of men; in 2022, 59.7 % of women and 40.3 % of men.

The changes for 2018–2022 shows an increase in the number of deaths from diabetes mellitus in both population categories: rural population to 26.5 % and urban population to 17.4 %.

The largest share in the structure of immediate causes of mortality of patients with diabetes mellitus in 2022 were: renal failure (20.0 %), chronic heart failure (18.6 %), acute cerebral circulatory failure (7.9 %), acute myocardial infarction (5.1 %), PATE and pneumonia (4.2 % each).

The following changes occurred over the five-year period: the share of deaths from renal failure increased (from 15.8 % in 2018 to 20.0 % in 2022), pneumonia (from 1.3 % to 4.2 %), PATE (from 3.2 % to 4.3 %); the share of deaths from a sepsis decreased (from 1.9 % in 2018 to to 0.9 % in 2022), acute myocardial infarction (from 7.0 % to 5.1 %), acute cerebral circulatory failure (from 10.8 % to 7.9 %), chronic heart failure (from 31.0 % to 18.6 %) (Table 3).

Comparing the immediate causes of death among patients with diabetes mellitus in 2022 and in 2018, there is a 33.3 % decrease from sepsis deaths, decrease from chronic heart failure deaths to 18.4 %, and to 100.0 % decrease from gastrointestinal diseases deaths. However, there was an increase of deaths from pneumonia to 350.0 % (from 2 cases in 2018 to 9 cases in 2022), PATE to 80.0 % (from 5 to 9 cases respectively), and renal failure to 72.0 % (from 25 to 43 cases). The highest number of deaths among patients with diabetes mellitus occurred from sepsis, acute myocardial infarction, and acute cerebral circulatory failure in 2020 (it is the beginning of the occurrence and spread of the incidence of a new coronavirus infection). The highest number of deaths among patients with diabetes mellitus occurred from renal failure and chronic heart failure in 2021. The mortality rate among diabetic patients increased to 15.9 % (Table 4) in changes over the five-year period.

Table 3

Changes of the structure of immediate causes of death among patients with diabetes mellitus, 2018–2022

Rate	2018		2019		2020		2021		2022	
	abs.n.	%	abs.n.	%	abs.n.	%	abs. n.	%	abs.n.	%
Deaths from diabetes mellitus, the number of people	158	100	162	100	254	100	203	100	215	100
Sepsis	3	1.9	4	2.5	7	2.8	5	2.5	2	0.9
AMI	11	7.0	11	6.8	18	7.1	6	3.0	11	5.1
PATE	5	3.2	3	1.9	8	3.1	7	3.4	9	4.2
AFCC	17	10.8	15	9.3	24	9.4	8	3.9	17	7.9
Pneumonia	2	1.3	1	0.6	7	2.8	7	3.4	9	4.2
Renal failure	25	15.8	19	11.7	43	16.9	45	22.2	43	20.0
Gangrene		0.0	1	0.6	1	0.4	2	1.0		0.0
CHF	49	31.0	49	30.2	42	16.5	47	23.2	40	18.6
GI	1	0.6	2	1.2	3	1.2		0.0		0.0

Table 4

Changes of immediate causes of death among patients with diabetes mellitus, 2018–2022

Rate	2018	2019	2020	2021	2022	Increase/decrease 2022 to 2018, in %
The immediate cause of death of patients with diabetes mellitus in total of which:	113	105	153	127	131	15.9
sepsis	3	4	7	5	2	–33.3
acute myocardial infarction	11	11	18	6	11	–
PATE	5	3	8	7	9	80.0
acute cerebral circulatory failure	17	15	24	8	17	–
pneumonia	2	1	7	7	9	350.0
renal failure	25	19	43	45	43	72.0
gangrene	0	1	1	2	0	0
chronic heart failure	49	49	42	47	40	–18.4
gastrointestinal diseases	1	2	3	0	0	–100

CONCLUSIONS

There is an increase in the mortality rate of the population from endocrine pathology to 26.4 %, from diabetes mellitus to 31.7 % in the changes for the analyzed period of 2018–2022. Mortality from diabetes mellitus is 96 % in the structure of mortality from endocrine pathology, of which 86.5 % is mortality from non-insulin-dependent diabetes mellitus; 77 % are disabled people, 66 % are women. In the structure of causes

of death of patients with diabetes mellitus – 20 % renal failure, 18.6 % – CHF, 5 % – acute myocardial infarction, 4.2 % – PATE and pneumonia. During the coronavirus pandemic, the pattern of causes of death among patients differed significantly from the pre-pandemic period. The obtained results will allow to substantiate scientifically the necessity of improvement of the endocrinological department in the Republic of Sakha (Yakutia) and will form the basis of the regional program "Fighting Against Diabetes Mellitus".

References

1. *Dedov I.I., Shestakova M.V., Vikulova O.K., Zheleznjakova A.V., Isakov M.A.* Diabetes mellitus in the Russian Federation: prevalence, morbidity, mortality, parameters of carbohydrate metabolism and structure of hypoglycemic therapy according to the Federal register of diabetes mellitus, status 2017. *Saharnyj diabet* 2018; 21 (3): 144–159 (in Russian).

2. *Mironova V.R., Zavorotnij A.A.* Statistical analysis of the impact of the incidence of diabetes mellitus in the population of the Central Federal District on mortality from myocardial infarction. *Innovacionnye nauchnye issledovanija* 2022; 12–4 (24): 43–52 (in Russian).

3. *Makisheva R.T., Hromushin V.A., Prilepa S.A., Lastoveckij A.G.* Gender-specific mortality of patients with diabetes mellitus in the Tula region. *Vestnik novyh medicinskih tehnologij* 2015; 22 (2): 60–67 (in Russian).

4. *Sabgajda T.P., Tarasov N.A., Evdokushkina G.N.* Mortality from diabetes mellitus from the perspective of multiple causes of death: coding problems. *Problemy social'noj gigieny, zdravoohranenija i istorii mediciny* 2019; 27 (6): 1043–1048 (in Russian).

5. *Dorofeev Ju.Ju., Koljado V.B., Koljado E.V., Tribunskij S.I.* Dynamics of mortality from diseases of the endocrine system in the Altai Territory. *Medicina v Kuzbasse* 2018; 17 (1): 55–58 (in Russian).

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CLINICAL CASE

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CLINICAL CASE OF HETEROTOPIC PREGNANCY AFTER IN VITRO FERTILIZATION

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КЛИНИЧЕСКИЙ СЛУЧАЙ ГЕТЕРОТОПИЧЕСКОЙ БЕРЕМЕННОСТИ ПОСЛЕ ЭКСТРАКОРПОРАЛЬНОГО ОПЛОДОТВОРЕНИЯ

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Ectopic pregnancy occupies a significant place in the structure of causes of maternal mortality. Timely diagnosis is even more complicated when there is a combination of both uterine and ectopic localization of the ovum. The article describes the clinical observation of heterotopic pregnancy, features of the clinical picture, diagnostic search and treatment strategy. The possibility of preservation of intrauterine pregnancy after surgical removal of a pathologically located second fertilized ovum has been shown. The patient was admitted to the gynecological department with complaints of bleeding from the genital tract against the background of delayed menstruation. An ultrasound examination revealed the presence of dichorionic diamniotic twins, with one fertilized egg localized in the interstitial part of the fallopian tube stump. Surgical removal of the stump with the fertilized egg was performed. The intrauterine pregnancy was preserved. Thus, with timely diagnosis of heterotopic pregnancy and adequate tactics, it is possible to maintain intrauterine pregnancy.
Keywords. Heterotopic pregnancy, surgical treatment, prolongation of intrauterine pregnancy, in vitro fertilization.

Приведено клиническое наблюдение сочетания маточной и внематочной беременности после экстракорпорального оплодотворения. Было проведено оперативное удаление культи маточной трубы с беременностью в истмическом отделе с сохранением маточной беременности у пациентки, перенесшей тубэктомию слева по поводу непроходимости маточной трубы при подготовке к программе ВРТ и ту-

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бэктомию справа в связи с последующей трубной беременностью. Показано, что при динамическом наблюдении возможно родоразрешение при доношенном сроке гестации. Использованы данные медицинских документов наблюдения пациентки в амбулаторных и стационарных условиях, в том числе результаты лабораторных, инструментальных, гистологических методов исследования. Получено информированное согласие пациентки для публикации результатов наблюдения.
Ключевые слова. Гетеротопическая беременность, оперативное лечение, пролонгирование маточной беременности, экстракорпоральное оплодотворение.

INTRODUCTION

Ectopic pregnancy (EP) continues to be an important issue in obstetrics and gynecology. The etiological factors of abnormal nidation of the fertilized egg are diverse. EP occurs in 1–2 % of total pregnancies and causes up to 10 % of maternal mortality [1; 2]. Risk factors for ectopic pregnancy include inflammatory diseases of the internal genital organs, operations on the fallopian tubes and uterus, hormonal disorders, endometriosis, advanced reproductive age, use of intrauterine contraceptive devices, endocrine diseases, and sexual infantilism [3; 4]. A special place is given to the use of assisted reproductive technologies (ART). [5; 6]. Currently, clinical data is accumulating on the combination of intrauterine and ectopic pregnancy when transferring several embryos in ART programs for patients with a history of tubectomy, i.e., pregnancy develops in the uterine tube stump together with intrauterine pregnancy [7]. The study of risk factors for retrograde embryo migration, in addition to those mentioned, revealed the following: a history of ectopic pregnancy, reconstructive surgery on the fallopian tubes, congenital anomalies of the uterus development, uterine fibroids; the use of gonadotropin-releasing hormone agonists in the ovulation stimulation protocol; ovarian hyperstimulation; intensive progesterone support of the luteal phase; assisted hatching of the embryo, transfer technique and embryo quality, smoking; patient's age [3; 8; 9].

There are rare forms of ectopic pregnancy: multiple, persistent, combination of uterine and extrauterine, which cause additional difficulties in diagnosis [10; 11]. In heterotopic pregnancy, the attachment of the fertilized egg is more often observed in the fallopian tubes (97.7 %), while isthmic localization is less common than others. It is precisely the rarity of pregnancy in the interstitial part of the fallopian tube, the peculiarities of the ultrasound picture that lead to some difficulties in differential diagnosis of uterine and ectopic pregnancies. With this localization, pregnancy develops quite successfully. Its growth is facilitated by good blood supply to this area of the uterus and the development of collaterals during pregnancy.

Of particular interest is the development of an ectopic pregnancy in the stump of the fallopian tube. Usually, tubectomy is performed due to an ectopic pregnancy, as well as the presence of sactosalpinx in preparation for ART programs. At the same time, surgical removal of an extrauterine pregnancy is a necessary condition for treatment. There are cases described in the literature of spontaneous rupture of the uterus along the scar after removal of pregnancy of this localization [12–14]. It is logical to assume a complicated course of preserved uterine pregnancy, the need for high-quality dynamic observation to achieve a positive result.

The aim of the study is to present a clinical case of a combination of intrauterine and ectopic pregnancies with a successful outcome after surgical removal of the fertilized egg located in the interstitial part of the fallopian tube stump in a patient after bilateral tubectomy and pregnancy in an ART program.

MATERIALS AND METHODS

The analysis of the clinical observation of a patient who had a combination of intrauterine and ectopic pregnancy after in vitro fertilization was carried out. Data from medical documents were used: medical records of an inpatient, dispensary card of a pregnant woman, birth history. To diagnose the presence and localization of pregnancy, an ultrasound examination of the pelvic organs was performed upon admission to the gynecological department at 8–9 weeks, determination of β-hCG was carried out. The material removed intraoperatively (fallopian tube stump, elements of the fertilized egg) was sent for histological examination. The excised pieces were fixed in 10 % neutral formalin, after standard processing, paraffin sections were stained with hematoxylin and eosin. Microscopic examination was performed on a Primo Star Carl Zeiss microscope at magnifications x4, x10. Further studies were carried out as part of monitoring the pregnant woman in an out-patients department.

The patient's informed consent was obtained for publication of the results of observation.

CLINICAL CASE

Patient K., 28-year-old, applied to the gynecology department on June 5 2023 with complaints of bright, spotting bloody discharge from the genital tract and dull pain in the lower abdomen against the background of menstrual delay. A β-hCG test was performed, and a positive result was obtained. An ultrasound examination revealed a dichorionic diamniotic twin pregnancy with one fertilized egg localized in the fallopian tube stump. The patient was hospitalized. Medical history: the patient considers herself ill for two weeks, when dark, spotting, bloody discharge from the genital tract first appeared 6 weeks after the transfer of two embryos under the ART program. The patient has a normosthenic physique, body mass index is 24.7 kg/m^2. The general condition is satisfactory. Heart rate is 74 bpm, blood pressure is 109/71 mmHg, body temperature is 36.2 °C. There are no concomitant diseases. The patient experienced menarche at the age of 13, with regular menstruation lasting 7 days every 28 days, which is moderate and painless. She has been sexually active since the age of 15 and has not used protection against pregnancy. The patient is currently married. In 2018, she was examined for primary infertility, due to obstruction of the fallopian tube, laparoscopic tubectomy was performed on the left side. In 2019, the first tubal pregnancy occurred, which ended in laparoscopic tubectomy on the right side. The second pregnancy in 2021 ended in incomplete miscarriage at 7–8 weeks after in vitro fertilization (IVF), complicated by acute endometritis. The current pregnancy is the third one, induced by IVF, transfer of two embryos was performed.

The result of pelvic ultrasound examination on June 5 2023 was the following: two

fetal eggs were detected in the uterine cavity. The first fetal egg was 38 mm in diameter. The embryo was visualized, its length was 22 mm, which corresponded to a gestational age of 8 weeks and 6 days. The heart beat was positive. The yolk sac was visualized with a diameter of 3.9 mm. The predominant localization of the villous chorion was on the posterior wall, closer to the fundus of the uterus. The structure of the chorion had not changed. The second fetal egg, 21 mm in diameter, was visualized in the stump of the fallopian tube on the right side. The embryo was visualized, its length was 20 mm, corresponding to a gestational age of 8 weeks and 4 days. The heart beat was also positive. The yolk sac had a diameter of 4.1 mm. There were no peculiarities in the right and left ovaries. The conclusion indicated an 8–9 week pregnancy with dichorionic diamniotic twins and an ectopic pregnancy on the right. On June 6 2023, a telemedicine consultation was held with the National Medical Research Center for Obstetrics, Gynecology and Perinatology named after academician V.I.Kulakov, Ministry of Health of the Russian Federation. Given the presence of tubal pregnancy, it was recommended to perform a tubectomy while preserving uterine pregnancy.

The surgery on June 8 2023 revealed that the uterus was up to 9 weeks of gestation of soft consistency. There was a rounded thin-walled formation measuring 6x7 cm in the area of the uterine tube stump. The left fallopian tube wasn't visualized as it had been removed. The ovaries weren't visually changed. A section was made in the thin part of the right uterine tube stump formation. An embryo 4 cm long and chorionic tissue were removed from the cavity. The uterine tube stump was removed. The abdominal cavity was dried. Napkins and instruments were checked. The abdominal cavity was closed tightly. A cosmetic suture was applied to the skin. An aseptic bandage was placed. Blood loss was 50 ml.

Gross specimen included embryo, chorion, uterine tube tissue. Pregnancy was confirmed histologically. On the 7th day after the operation, the patient was discharged in satisfactory condition under observation of the gynecologist in an outpatients department. The following discharge recommendations were given: to appear at the antenatal clinic on June 16 2023; to treat the postoperative wound for a month; to wear a bandage for up to three months; to avoid physical exertion; to avoid heat treatments for two months; to abstain from sexual intercourse for two months; to consult a gynecologist at the patient's medical facility with the results of histology.

Further dynamic observation was carried out on an outpatient basis in accordance with the clinical protocol "Normal pregnancy". Ultrasound examination was performed at 12 weeks, fetal heart rate was 155 beats per minute, crown-rump length was 56 mm, nuchal translucency thickness was 1.7 mm. The nasal bone was visualized. Dopplerometry of the tricuspid valve was normal. Dopplerometry of the venous duct was 1.05. Fetal dimensions corresponded to the gestational age. The results of maternal serum biochemistry were the following: free β-hCG subunit 68.28 IU/L (1.327 MoM); PAPP-A: 6.115 IU/L (1.458 MoM).

"The calculated risks were as follows: trisomy 2 – 1 in 5,621, trisomy 18 – 1 in 13,134, trisomy 13 – less than 1 in 20,000, preeclampsia before 37 weeks of pregnancy – 1 in 1,856, fetal growth restriction before

37 weeks – 1 in 395, spontaneous delivery before 34 weeks – 1 in 1,659. Considering the anamnestic data, cervical measurement was performed at 16 weeks of gestation, the length of the closed part of the cervical canal was 39 mm. Further repeated examinations with an interval of two weeks did not reveal shortening of the cervix until 24 weeks.

Until 34 weeks, the patient received micronized progesterone 200 mg per day vaginally. Then, at 19 weeks of pregnancy, a second screening ultrasound examination was performed. There was one fetus in the uterine cavity in cephalic presentation, according to fetometry data, it corresponded to 19 weeks of gestation. The placenta was on the back wall of the uterus, closer to the fundus, its thickness was 22 mm, maturity degree was 0. The amount of amniotic fluid was normal. The umbilical cord had three vessels, central attachment to the placenta. The length of the closed part of the cervical canal was 38 mm, the internal os was closed. Dynamic monitoring showed no pathology. Dopplerometry of blood flow velocity in the "mother – placenta – fetus" system revealed no abnormalities. Similar studies at 32–34 weeks also indicated the normal development of pregnancy, absence of fetal malformations and signs of placental insufficiency. Cardiotocography was regularly performed from 32 weeks of pregnancy every two weeks and also indicated a satisfactory condition of the fetus. At 38–39 weeks of gestation, the patient was hospitalized in an obstetric hospital for delivery. The condition was satisfactory. Abdominal circumference was 98 cm, height of uterine fundus was 37 cm, head presentation of the fetus. Pelvic dimensions were 24–27–29–18.5 cm, which corresponded to a generally uniformly narrowed pelvis of the 1st degree of narrowing according to the classification of A.F. Palmov. Solovyov index was 1.5. Estimated fetal weight was 3580 g according to ultrasound examination results. The main factor determining the delivery tactics was surgical intervention in the first trimester of pregnancy in the amount of removal of the isthmic portion of the fallopian tube, combined with anatomically narrow pelvis and reproductive history of the woman. It was collectively decided to proceed with a planned operative delivery by caesarean section. A male fetus weighing 3,510 g and 52 cm long was delivered, Apgar score was 8/8 points. A scar was noted in the area of the right uterine corner during the surgery, without penetration into the uterine cavity. The blood loss amounted to 680 ml.

RESULTS AND DISCUSSION

Both domestic and foreign literature emphasize the increasing incidence of rare forms of ectopic pregnancy. Combinations of uterine and ectopic pregnancies occur on average once in 30,000 pregnancies. More often than not, abnormal attachment of the fertilized egg occurs in different parts of the fallopian tube. When the location of the fertilized egg is in the intramural or isthmic portion of the tube, the ultrasound picture may mimic a uterine pregnancy. Literature data show that even indications of voluntary sterilization or tubectomy do not exclude the development of an ectopic pregnancy in the future [5; 7]. Special attention should be paid to the patients who have undergone removal of the fallopian tubes and transfer of several embryos in ART programs [8; 9]. It is these women who are at high risk of

heterotopic pregnancy. A concerning point is the localization of the fertilized egg in one of the corners of the uterus detected by ultrasound. The appearance of complaints about pain in the lower abdomen and spotting, bloody discharge from the genital tract should prompt a differential diagnosis between threatened miscarriage and heterotopic pregnancy. The uniqueness of the described case lies in the fact that an ectopic pregnancy developed in the isthmic part of the uterine tube stump up to 8–9 weeks.

Thus, women with a history of surgery on the fallopian tubes, including tubectomy, are at risk of developing heterotopic pregnancy. These factors play a significant role in the retrograde migration of the fetal egg. Ultrasound examination greatly facilitates determining the localization of the fetal egg and conducting differential diagnosis between uterine and ectopic (isthmic) pregnancy. Timely removal of an abnormally localized fetal egg increases the likelihood of carrying a uterine pregnancy to term. At the same time, a complicated course of pregnancy is expected, primarily miscarriage and premature birth. When planning observation in an out-patients department conditions, it is necessary:

1) to perform cervical measurement at 16–24 weeks;

2) in special cases, to provide progesterone support;

3) to carry out delivery in accordance with the obstetric situation and the extent of surgical intervention performed during this pregnancy.

Conclusions

In the presented clinical case, risk factors for ectopic pregnancy were a history of ectopic pregnancy, operations on the fallopian tubes (bilateral tubectomy), and in vitro fertilization.

Early diagnosis of this pathology using ultrasound examination allowed timely removal of the ectopic fetal egg with further carrying a uterine pregnancy to term and delivery at full-term pregnancy.

References

1. *Mullany K., Minneci M., Monjazeb R., C Coiado O.* Overview of ectopic pregnancy diagnosis, management, and innovation. Womens Health (Lond). 2023; 19: 17455057231160349. DOI: 10.1177/17455057231160349. PMID: 36999281; PMCID: PMC10071153.

2. *Tonick S., Conageski C.* Ectopic Pregnancy. ObstetGynecolClin North Am. 2022; 49 (3): 537–549. DOI: 10.1016/j.ogc.2022.02.018. PMID: 36122984.

3. *Dunphy L., Boyle S., Cassim N., Swaminathan A.* Abdominal ectopic pregnancy. BMJ Case Rep. 2023; 16 (9): e252960. DOI: 10.1136/bcr-2022-252960.

4. *Jeon J.H., Hwang Y.I., Shin I.H., Park C.W., Yang K.M., Kim H.O.* The risk factors and pregnancy outcomes of 48 cases of heterotopic pregnancy from a single center. J Korean Med Sci. 2016; 31: 1094–1099. DOI: 10.3346/jkms.2016.31.7.1094

5. *Dukembaeva A., Kaldyybekova A., Omar M., Sarykova N., Tanabaeva Sh* Clinical case of a combination of uterine and tubal pregnancy. *Vestnyk KazNMU* 2017; 1: 88–90 (in Russian).

6. *Lv S., Wang Z., Liu H., Peng J., Song J., Liu W., Yan L.* Management strategies of heterotopic pregnancy following in vitro fertilization-embryo transfer. Taiwan J

Obstet Gynecol. 2020; 59 (1): 67–72. DOI: 10.1016/j.tjog.2019.11.010

7. *Wu Z., Zhang X., Xu P., Huang X.* Clinical analysis of 50 patients with heterotopic pregnancy after ovulation induction or embryo transfer. Eur J Med Res. 2018; 23: 17. DOI: 10.1186/s40001-018-0316-y

8. *Aryan Maleki, Noorulain, Khalid Chandni, Rajesh Patel, Essam El-Mahdi* The rising incidence of heterotopic pregnancy: Current perspectives and associations with in-vitro fertilization. Eur J Obstet Gynecol Reprod Biol 2021; 266: 138–144. DOI: 10.1016/j.ejogrb.2021.09.0

9. *Kuznecova E.P., Talabadze A.S.* Ectopic pregnancy as a complication of ART programs. *Farmateka* 2017; 12 (345): 37–39 (in Russian).

10. *Pi R., Liu Y., Zhao X., Liu P., Qi X.* Tubal infertility and pelvic adhesion increase risk of heterotopic pregnancy after in vitro fertilization: A retrospective study. Medicine (Baltimore). 2020; 99 (46): e23250. DOI: 10.1097/MD.0000000000023250

11. *Baranovskaja E.Y., Fedoseenko A.V., Krasnyckyj A.V.* Heterotopic pregnancy with natural conception and pregnancy. *Rossyjskyj vestnyk akushera-gynekologa* 2018; 18 (6): 70 72. DOI: 10.17116/rosakush 20181806170 (in Russian).

12. *Zhukovskaja Y.G., Sandakova E.A., Semenova M.V.* Assessing the effectiveness of preconception training for women with chronic inflammatory diseases of the genital organs based on an in-depth study of the health status of married couples. *Lechenye y profylaktyka* 2017; 2: 38–42 (in Russian).

13. *Tskhai V.B., Domracheva M.Y., Grebennikova E.K., Brekhova I.S., Ryazankin A.A.* A case of successful delivery after resection of the isthmus for ectopic pregnancy after in vitro fertilization in a patient with twins. *Problemy reproduktsii* 2021; 27 (4): 156–159. DOI: 10.17116/repro202127041156 (in Russian).

14. *Davydov A.I., Rubina E.V., Shablamova M.N.* Ektopicheskaia beremennost posle ekstrakorporalnogo oplodotvoreniia: faktory riska i patofiziologicheskie mekhanizmy. *Voprosy ginekologii, akusherstva i perinatologii* 2017; 16 (2): 50–8. DOI: 10.20953/1726-1678-2017-2-50-58 (in Russian).

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Naumova V.Ya., Semyonova M.V., Mukhametgalimova A.R. – research concept and design.

Naumova V.Ya., Semyonova M.V., Mukhametgalimova A.R. – data collection and processing.

Naumova V.Ya., Semyonova M.V., Mukhametgalimova A.R. – text writing.

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CLINICAL CASE OF STAGE COMBINED TREATMENT OF A PATIENT WITH INFECTED PANCREONECROSIS AND ITS EARLY AND LATE COMPLICATIONS

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КЛИНИЧЕСКИЙ СЛУЧАЙ ЭТАПНОГО КОМБИНИРОВАННОГО ЛЕЧЕНИЯ ПАЦИЕНТА С ИНФИЦИРОВАННЫМ ПАНКРЕОНЕКРОЗОМ И ЕГО РАННИМИ И ПОЗДНИМИ ОСЛОЖНЕНИЯМИ

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Acute pancreatitis is the 3rd most common abdominal pathology after acute appendicitis and acute cholecystitis occurring in 10 to 25 % of patients. The lethality in acute pancreatitis, according to different data, varies from 15 to 25 %. We presented the results of minimally invasive stage combined endovideosurgical and X-ray

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vascular treatment of the patient with infected subtotal mixed pancreonecrosis complicated by pseudocyst formation of pancreatic tail, recurrent arrosive hemorrhage, formation of external gastric and incomplete external pancreatic fistula in the late postoperative period.
Keywords. Acute pancreatitis, pancreonecrosis, minimally invasive surgical technologies, arrosive bleeding, X-ray endovascular methods of hemostasis, external fistula.

Острый панкреатит по распространенности занимает 3-е место среди всех патологий органов брюшной полости, уступая только острому аппендициту и острому холециститу, его доля составляет от 10 до 25 %. Летальность при остром панкреатите, по разным данным, варьируется от 15 до 25 %.
Представлены результаты мини-инвазивного этапного комбинированного эндовидеохирургического и рентгеноваскулярного лечения пациента с инфицированным субтотальным смешанным панкреонекрозом, осложненным формированием псевдокисты хвоста поджелудочной железы, рецидивирующим аррозивным кровотечением, образованием наружного желудочного и неполного наружного панкреатического свищей в позднем послеоперационном периоде.
Ключевые слова. Острый панкреатит, панкреонекроз, мини-инвазивные хирургические технологии, аррозивное кровотечение, рентгеноэндоваскулярные методы гемостаза, наружный свищ.

INTRODUCTION

Among abdominal surgical emergencies, acute pancreatitis accounts for 10 to 25 % of the total number of patients with surgical pathology of the abdominal organs and ranks third, second only to acute appendicitis and acute cholecystitis [1]. In recent years, lethality from acute pancreatitis in the Russian Federation has ranged from 15 to 25 % [2–4].

Acute pancreatitis is a polyetiological disease. The most common cause of pancreatitis is alcoholic-alimentary, accounting for up to 55 % of cases, followed by acute biliary pancreatitis, which accounts for up to 35 % [5]. Post-manipulation pancreatitis deserves attention due to the increasing number of minimally invasive surgical and endoscopic methods for treating pathologies of the pancreaticobiliary system. According to various authors, acute pancreatitis after a diagnostic study develops in 3.5–8.6 % of cases, and after therapeutic manipulations on the major duodenal papilla in 4.5–9.6 % of observations [6].

Due to the general trend towards an increase in the number of patients with acute pancreatitis, there is a constant increase in destructive forms of the disease, which account for up to 20–44 % [7].

Pancreonecrosis is an aseptic demarcation type inflammation based on necrobiosis of pancreatocytes and enzymatic autoaggression, followed by subcapsular breakthrough of pancreatic secretions, necrosis and dystrophy of the gland, further spread of pancreatogenic aggression to surrounding tissues [8]. Lethality from aseptic pancreatic necrosis over the past 30 years ranges from 15 to 20 %, and from 30 to 39 % if infection occurs [9]. On the one hand, constantly improving methods of prevention, diagnosis and treatment of acute pancreatitis, and on the other hand, an increase in cases of severe course of the disease contribute to an increase in the

number of patients with late post-necrotic complications [7]. According to the literature, external pancreatic fistulas (EPF), cicatricial strictures of the main pancreatic duct and pancreatic pseudocysts occur in 9.5–87 %, 47–50 % and 5–10 %, respectively; less frequently, calculi of the pancreatic ductal system are formed – 18 % [10; 11]. About 20 % of patients with chronic post-necrotic pancreatitis die from its complications within the first 10 years and more than 50 % after 20 years [12].

Thus, despite a large number of studies, constantly improving methods of diagnosis and treatment of acute necrotizing pancreatitis, it is not possible to significantly reduce lethality rates in the early and late postoperative period, prevent the development of complications in the long-term period, or improve the quality of life.

The analysis of the clinical case of stage combined treatment of a patient, based on the surgical department of State Autonomous Healthcare Institution of Perm Krai City Clinical Hospital No. 4, Perm, with infected pancreonecrosis, pseudocyst formation of pancreatic tail, complicated by recurrent arrosive hemorrhage, formation of external gastric and incomplete external pancreatic fistula in the late postoperative period.

Clinical case

Patient F., 45-year-old, was admitted to the emergency room of the State Autonomous Healthcare Institution of Perm Krai «City Clinical Hospital No. 4» (CHB No. 4) in Perm with complaints of acute, intense pain (according to the visual analogue scale (VAS) is 7–8 points) in the epigastric region and left hypochondrium, anuria. It was known from the anamnesis that the patient had been consuming alcohol up to 1 liter per day for six days. He considered himself sick for three days before going to the emergency room, when abdominal pain began to bother him. The patient independently took antispasmodics without effect. Against the background of increasing pain syndrome, he called an ambulance and was taken to the emergency room of City Clinical Hospital No. 4.

On admission the condition was severe, due to pain syndrome, endotoxicosis, multiple organ dysfunction syndrome (MODS). The skin was pale. Skin turgor was reduced. Body temperature was 37.6 °C. Peripheral lymph nodes weren't palpable. The patient was breathing spontaneously. Lung breathing was harsh, conducted in all departments. There were no rales. The patient had respiratory rate of 23 per minute. Pulse was 90 per minute, rhythmic, he had blood pressure of 90/60 mmHg. The patient had anuria. Local status: the abdomen was swollen, didn't participate in the act of breathing. There were no postoperative scars, hernial defects, infiltrates on the anterior abdominal wall upon examination. Upon superficial palpation, the abdomen was tense, painful in all sections. Peritoneal symptoms were positive. In the lumbar region there was no

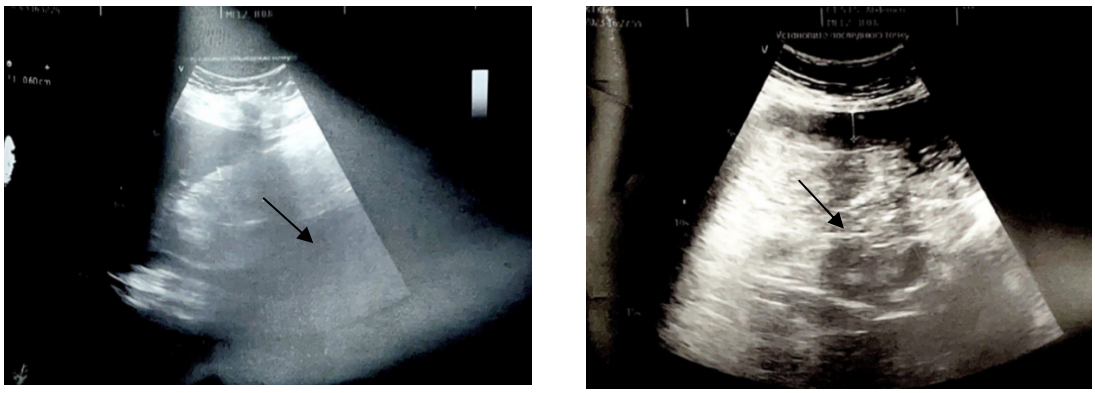
infiltration, bulging, or other pathological changes. Auscultatively, peristalsis was heard, weakened. There had been no stool. Gases were released. *Per rectum*: the sphincter was toned, there were traces of brown-colored feces without pathological impurities in the ampoule. The patient underwent a standard set of diagnostic tests and procedures in the emergency room according to the current national clinical guidelines of the Russian Society of Surgeons «Acute Pancreatitis» (2020). According to the complete blood test, leukocytosis was noted ($23.9 \cdot 10^9$/L). In the biochemical blood analysis there was an increase in AST up to 95.7 U/L; ALT up to 49.6 U/L, blood amylase up to 614.5 U/L; alkaline phosphatase up to 146.6 U/L, urea up to 12.1 mmol/L; total bilirubin up to 32.8 μmol/L; indirect bilirubin up to 23.5 μmol/L; direct bilirubin up to 9.3 μmol/L. A urine test was not performed due to anuria. On an overview X-ray of the abdominal cavity in direct projection, no free gas under the diaphragm was detected, There was gas and fecal matter in the large intestine, moderate aerocolia was presented, horizontal levels were not determined, structures of the abdominal cavity were leveled.

According to the abdominal ultrasound, there were signs of limited accumulations of anechoic content in the left flank and left hypochondrium (Fig. 1).

Based on the patient's complaints, medical history, objective examination results, and laboratory and instrumental studies, a diagnosis of severe acute pancreatitis complicated by widespread enzymatic peritonitis and multiple organ dysfunction syndrome (MODS) with predominant hepatic and renal failure (qSOFA score of 2) was made. The concomitant disease was an exacerbation of chronic gastroduodenitis. It was decided that emergency surgical intervention was necessary due to vital indications. The patient underwent diagnostic and therapeutic laparoscopy, omentobursostomy, lavage and drainage of the abdominal cavity, blockade of the round ligament of the liver and the root of the mesentery with a solution of 0.5 % novocaine (60 ml).

After surgery the patient was diagnosed with severe acute pancreatitis (Atlanta, 2012) complicated by mixed subtotal pancreatic necrosis, dense parapancreatic infiltrate, widespread enzymatic serous-hemorrhagic peritonitis, multiple organ dysfunction syndrome (MODS) with predominant hepatic and renal failure (qSOFA score of 2)). toxic hepatitis. The concomitant disease was an exacerbation of chronic gastroduodenitis.

In the postoperative period, in the intensive care unit (ICU), infusion, anti-inflammatory, antibacterial, and symptomatic therapy were performed, as well as dynamic observation. On the second day of the postoperative period, against the background of resolution of anuria, marked amylasuria (up to 1740.3 U/L) and amylasemia (up to 144.5 U/L) were noted, as well as a decrease in hemoglobin levels to 81 g/L and red blood cells to $2.5 \cdot 10^{12}$/L.



a *b*

Fig. 1. Ultrasound signs of the presence of limited accumulations of anechoic content: a – in the left flank region; b – in the left hypochondrium

Up to 500 ml of serous-hemorrhagic discharge was obtained from the abdominal cavity through the tubular drains. Considering the increasing anemia, it was decided to perform a diagnostic relaparoscopy in order to identify the source of hemorrhage and determine further treatment tactics.

During relaparoscopy, no signs of ongoing intra-abdominal hemorrhage were found. There was up to 200 ml of serous hemorrhagic exudate in the abdominal cavity. The abdominal exudate was evacuated, the abdominal cavity was drained and dried.

Within the first day after relaparoscopy against the background of complex symptomatic therapy and blood transfusion, there was a negative trend in the complete blood test. Hemoglobin (HGB) decreased to 71 g/L; hematocrit (HCT) to 21.2 %; red blood cells (RBC) to $2.25 \cdot 10^{12}$/L. There was hemorrhagic discharge up to 150 ml from the drains in the abdominal cavity.

Based on the clinical picture of ongoing intra-abdominal hemorrhage, it was decided to perform surgical treatment, specifically an upper midline laparotomy and revision of the abdominal cavity. Intraoperatively, up to 500 ml of fresh blood and clots were found in the abdominal cavity. The contents were taken for bacteriological examination. During the revision of the omental bursa, a blood clot was found in the area of the tail of the pancreas with a volume of up to 400 ml. Massive diffuse hemorrhage developed when it was removed from the tail of the pancreas. The hemorrhage was stopped using irrigation with the local hemostatic drug «Hemoblock». The abdominal cavity was sanitized and redrained.

The patient was treated in the intensive care unit (ICU) for 9 days, where laboratory and instrumental parameters were monitored, symptomatic therapy was performed, including infusion, antispasmodic, analgesic, antibacterial, hemostatic, and blood transfusion therapy. Intra-abdominal pressure was monitored using the Iberti–Kron method. On the first day after surgery, intra-abdo-

minal hypertension (IAH) corresponded to grade II (19 mmHg). To prevent postoperative intestinal paresis, a saline enteral solution (SES) was administered through a gastric tube. By the third day after the operation, a significant reduction in IAH was achieved (13 mmHg). According to the results of microbiological testing for aerobic and facultative anaerobic microorganisms, the following were detected: Escherichia coli 10^5 CFU/g; Klebsiella pneumoniae 10^5 CFU/g; Corynebacterium xerosis 10^5 CFU/g. Specific complex antibacterial therapy was prescribed: linezolid 0.2 % – 300 ml, once a day + cefotaxime 1.0 twice a day intramuscularly.

On the 10th day of the postoperative period, according to CT scans of the abdominal cavity, there was a picture of acute pancreatitis with pronounced infiltrative changes in the parapancreatic tissue. A pseudocyst of the tail of the pancreas was formed (Fig. 2).

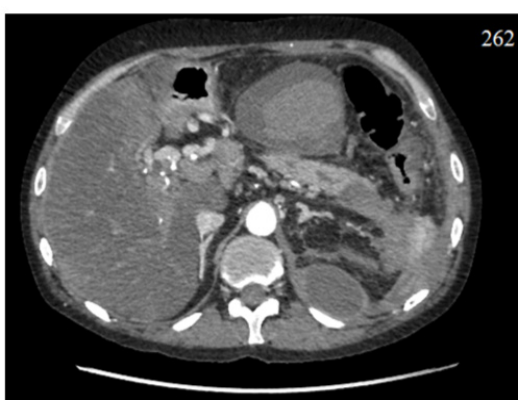
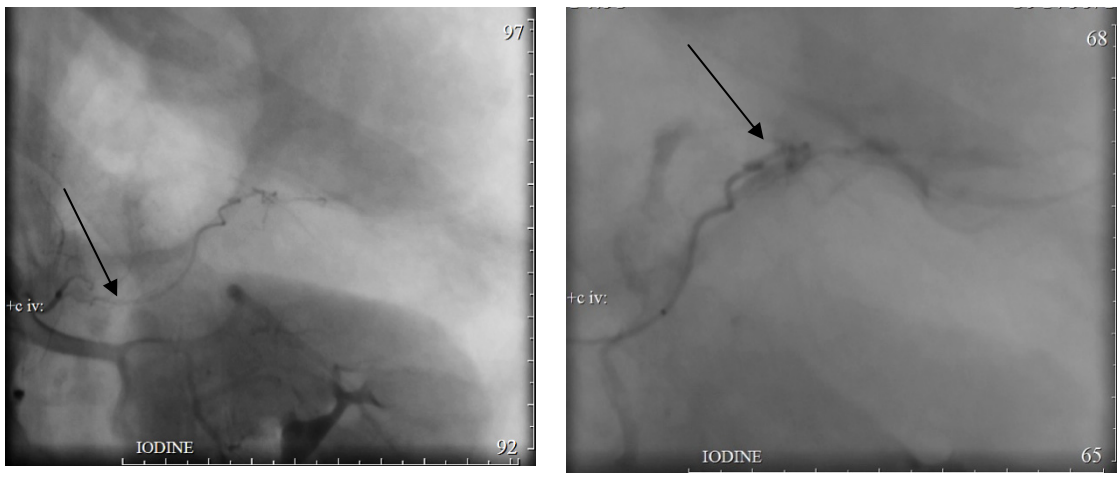


Fig. 2. CT scan of acute pancreatitis with infiltrative changes in the parapancreatic tissue. Pseudocyst of the tail of the pancreas (indicated by arrows)

In the postoperative period, there was a positive trend in the patient's condition and normalization of laboratory parameters. On the 28th day after surgery there was a decrease in blood amylase to 24.8 U/L and urea to 1.5 mmol/L; increase in CRP level up to 125 mg/L; slight increase in hemoglobin (HGB) up to 86 g/L, hematocrit (HCT) up to 26.6 %, red blood cells (RBC) up to $3.1 \cdot 10^{12}$/L; increased ESR up to 67 mm/h. All other indicators were within normal limits.

On the 30th day after surgery, there was a deterioration in the patient's condition. According to the complete blood test, hemoglobin levels decreased to 63 g/L, hematocrit to 17.9 %, red blood cells to $2.18 \cdot 10^{12}$/L. To exclude repeated arrosive hemorrhage from the pancreas parenchyma, angiography was performed. The study revealed an aberrant branch of the celiac trunk that departed 0.3 cm above the left renal artery and hypervascularization in the spleen gate projection (in the area of the pancreatic tail pseudocyst). The hemorrhage was stopped by X-ray endovascular embolization of the aberrant artery lumen using a Merit Maestro 2.4F microcatheter and ASAHI Fielder conductor with PVA particles (45–150 microns – Boston Scientific) (Fig. 3).

On the 34th day, an abscess of the omental bursa formed. The patient underwent relaparotomy, omentobursostomy, drainage of the omental bursa, redraining of the abdominal cavity. An abscess was found in the omental bursa, opened, about 100 ml of thick creamy pus with old blood



a *b*

Fig. 3. X-ray endovascular embolization of the aberrant artery lumen:
a – pathological branch of the splenic artery feeding the area of the formed pseudocyst;
b – embolization of the artery with PVA particles

clots was obtained. Purulent discharge was taken for bacteriological examination. The abdominal cavity was sanitized and drained with tubular and glove drains.

In the postoperative period, symptomatic therapy, monitoring of laboratory parameters, and dressing of postoperative wounds were performed.

According to the results of microbiological testing for aerobic and facultative anaerobic microorganisms, Enterococcus faecalis 10^4 CFU/ml was detected. Ciprofloxacin was additionally prescribed at a dosage of 500 mg twice a day.

On the 42nd day after surgery, gastric contents were noted through the drainage tube installed in the omental bursa. Diagnostic fibrogastroscopy was performed. Necrosis of the stomach wall with perforation and a 10 mm drainage tube inside were detected in the subcardial region, upper third of the body of the stomach, along the greater curvature; the free edge of the tube was directed towards the bottom of the stomach. A microirrigator was installed in the duodenum to prevent food from entering through the perforation hole in the stomach wall and enteral feeding was started. Then all tubular drains from the omental bursa and the stomach cavity were removed, only glove drains remained.

For the next 15 days, the patient continued conservative therapy with constant monitoring of laboratory parameters, daily dressing of postoperative wounds, and flushing of the omentobursostomy. Laboratory test results showed a tendency towards normalization.

On the 57th day after surgery, the gastric fistula closed. According to the results of X-ray examination of the stomach with a water-soluble contrast agent, no extra con-

tours of the contrast substance were detected. The contrast entered the duodenum in small portions (Fig. 4).

By the 63rd day after the operation, the pain syndrome was stopped. The pancreatic fistula closed during conservative treatment. There was no negative trend in laboratory or instrumental parameters.

Postoperative wounds healed by primary/secondary intention, without signs of inflammation. The patient was discharged for outpatient treatment at the local clinic. Recommendations were given on treatment, including therapy, diet, and care of postoperative wounds.

The final clinical diagnosis was severe acute alcoholic pancreatitis complicated by mixed subtotal pancreonecrosis, dense parapancreatic infiltrate, widespread enzymatic serous-hemorrhagic peritonitis, multiple organ dysfunction syndrome (MODS) with predominant hepatic and renal failure (qSOFA score of 2), toxic hepatitis. The first operation involved diagnostic and therapeutic laparoscopy, omentobursostomy, sanitation, drainage of the abdominal cavity, blockade of the circular ligament of the liver and the root of the mesentery with a solution of 0.5 % novocaine in amount of 60 ml, postoperative sluggish peritonitis. The second operation was a relaparoscopy with revision of the abdominal cavity, sanitation, and redraining of the abdominal cavity, addressing arrosive diffuse hemorrhage from the pancreatic parenchyma tissue into the abdominal cavity, and hemoperitoneum. The third operation was an upper midline laparotomy, abdominal cavity revision, stopping the hemorrhage from the pancreatic tissue, sanitation, and redraining of the abdominal cavity, due to arrosive hemorrhage from an aberrant branch of the celiac trunk. The fourth operation involved stopping the hemorrhage from the aberrant

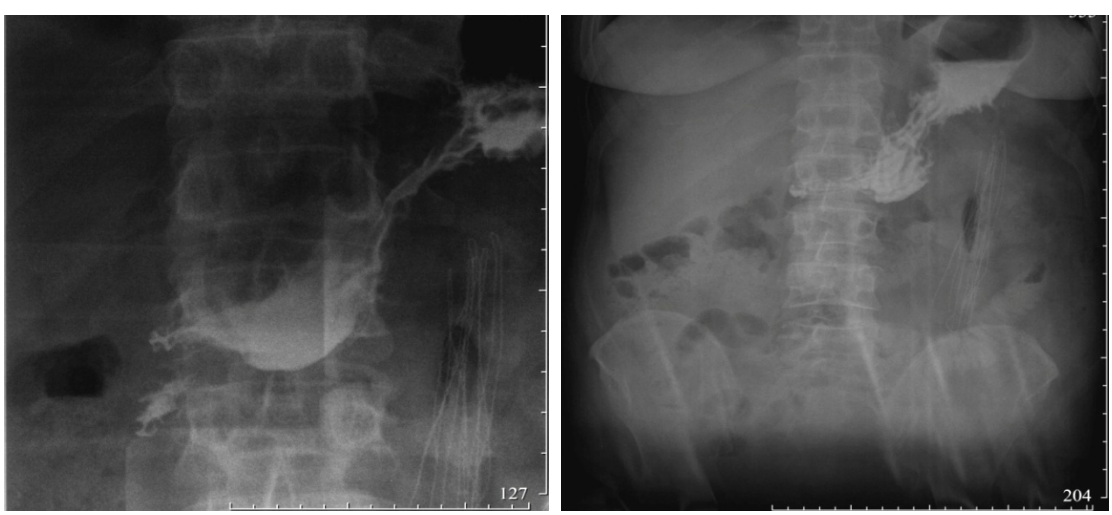


Fig. 4. X-ray of the stomach and duodenum with a water-soluble contrast agent

artery of the celiac trunk by X-ray endovascular embolization, addressing a pancreatic pseudocyst in the tail, and arrosive hemorrhage into the pseudocyst cavity in the pancreatic tail that had already occurred, as well as an abscess of the omental bursa. The fifth operation included a relaparotomy, opening and drainage of the abscess of the omental bursa, and omentobursostomy, resulting in a closed external gastric incomplete pancreatic fistula and severe posthemorrhagic anemia. The concomitant disease was an exacerbation of chronic gastroduodenitis.

The given clinical observation presents a case of treating a patient with infected subtotal pancreonecrosis complicated by massive arrosive hemorrhage from the tail of the pancreas in the early postoperative period, hemorrhage into the cavity of the formed pseudocyst of the pancreatic tail, abscess of the omental bursa, formation of an external gastric, incomplete pancreatic fistula in the late postoperative period..

Conclusions

It is particularly important to use the full range of modern diagnostic and treatment technologies in order to achieve positive results in the treatment of patients with pancreatic necrosis. These technologies allow for reliable stratification of perioperative risks of complications, as well as prompt selection of the optimal and individualized extent of surgical intervention. The stage implementation of minimally invasive surgical interventions using a combination of surgical approaches is key to successful treatment for this group of patients.

References

1. *Kulikov D.V., Korolkov A.Y., Morozov V.P., Vaganov A.A.* Unresolved issues of treatment of acute destructive pancreatitis. *Bulletin of experimental and clinical surgery* 2019; 12 (2): 134–140 (in Russian).

2. *Chyngysheva J.A., Niyazov B.S., Rasul N., Adylbaeva V.A., Dinlosan O.R., Abdullaev J.S.* Modern view on the diagnosis and treatment of acute intestinal obstruction in gerontological patients (literature review). *Bulletin of Science and Practice* 2022; 8 (7): 261–292 (in Russian).

3. *Zhukembaeva A.M., Kaparova K.M., Serkbaev E.A., Toretaev E.N., Aitzhanov D.M.* Features of intestinal dysfunction after operations on abdominal cavity organs. *Eurasian Scientific Association* 2021; 2–3: 146–148 (in Russian).

4. *Mikhailichenko V.Yu, Trofimov P.S., Samarin S.A.* Algorithm of diagnostics and treatment of early adhesion postoperative obstruction. A. Algorithm of diagnostics and treatment of early adhesion postoperative obstruction. *Tavricheskiy medico-biological bulletin* 2018; 21 (2): 57–64 (in Russian).

5. *Menshikova, I.L.* Prevention of acute pancreatitis during endoscopic endobiliary interventions. *Bulletin of the Kyrgyz-Russian Slavic University* 2013; 13 (6): 162–165 (in Russian).

6. *Dronov A.I., Kovalskaya I.A., Gorlach A.I.* Postnecrotic complications of acute

pancreatitis and their surgical correction. Surgery. *Eastern Europe* 2015; 2 (14): 90–95 (in Russian).

7. *Maltseva L.A., Mishchenko E.A., Kutovoy A.B., Mosentsev N.F., Lisnichaya V.N., Kazimirova N.A.* Enteral tolerance in critical patients (literature review). *Emergency Medicine* 2020; 16 (1): 36–44 (in Russian).

8. *Bagnenko S.F., Goltsov V.R., Savello V.E., Vachetko R.V.* Classification of acute pancreatitis: current state of the problem. *Bulletin of Surgery named after I.I. Grekov* 2015; 174 (5): 86–92 (in Russian).

9. *Stepan E.V., Rogal M.L., Ozova Z.M., Ivanov P.A.* External pancreatic fistulas – diagnosis and treatment. *Bulletin of surgical gastroenterology* 2017; 1: 3–9 (in Russian).

10. *Budzinsky S.A., Shapovalyants S.G., Fedorov E.D.* Endoscopic retrograde pancreatic stenting in chronic pancreatitis – possibilities, limitations, complications. *Experimental and clinical gastroenterology* 2014; 3 (103): 72–80 (in Russian).

11. *Natalskiy A.A., Tarasenko S.V., Zaitsev O.V., Peskov O.D., Bogomolov A.Y., Kadykova O.A., Bakonina I.V.* Chronic pancreatitis as a multidisciplinary medical and social problem. *EiCG* 2017; 6 (142) (in Russian).

12. *Samartsev V.A., Gavrilov V.A., Podtaev S.Y.* Diagnostics and correction of microcirculation disorders and endothelial dysfunction in complex therapy of acute pancreatitis with antioxidant drugs. *Perm Medical Journal* 2022; 39 (3): 63–72 (in Russian).

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THE CASE OF DEVELOPMENT OF HIV-ASSOCIATED KAPOSI'S SARCOMA WITH SKIN AND LUNG LESIONS

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СЛУЧАЙ РАЗВИТИЯ ВИЧ-АССОЦИИРОВАННОЙ САРКОМЫ КАПОШИ С ПОРАЖЕНИЕМ КОЖИ И ЛЕГКИХ

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A clinical case of HIV-associated Kaposi's sarcoma with skin and lung lesions is presented. A patient referred to the Perm Regional Center for the Prevention and Control of AIDS and Infectious Diseases complaining of rash on the skin of the right wing of the nose, forehead, in the right axillary and right inguinal areas, on the shins. The first skin changes occurred in December 2020 on the right wing of the nose, later the pathological process spread to other areas of the skin. HIV was revealed in 2009 and the patient had not received specialized medical care until 2022 as he had been in prison. Since March 2022, the patient has been registered at the dispensary and regularly receives antiretroviral therapy. In April 2022, PET/CT tests and histological examination of a biopsy of skin rashes were performed. On the basis of these findings the diagnosis of Kaposi's sarcoma with skin and lungs lesions was made.

HIV-associated Kaposi's sarcoma is accompanied by lesions of the skin and internal organs. Skin changes in Kaposi's sarcoma are characterized by the primary localization of foci on the face and upper extremities, and without anti-

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retroviral therapy, by rapid progression and generalization of the pathological process. Visceral lesions worsen the course of the disease and complicate its prognosis. Patients with HIV-associated Kaposi's sarcoma need dynamic monitoring and complex therapy from infectious diseases specialists, dermatovenerologists, oncologists.
Keywords. Kaposi's sarcoma, HIV infection, skin lesions, lungs.

Представлен клинический случай ВИЧ-ассоциированной саркомы Капоши с поражением кожи и легких. В Пермский краевой центр по профилактике и борьбе со СПИД и инфекционными заболеваниями обратился пациент с жалобами на высыпания на коже правого крыла носа, лба, в правой подмышечной и правой паховой областях, на голенях. Первые кожные изменения возникли в декабре 2020 г. на правом крыле носа, в дальнейшем патологический процесс распространился на другие участки кожного покрова. ВИЧ-инфекция с 2009 г., до 2022 г. пациенту не оказывалась специализированная медицинская помощь, поскольку он находился в местах лишения свободы. С марта 2022 г. пациент находится на диспансерном учете и регулярно получает антиретровирусную терапию. В апреле 2022 г. были выполнены ПЭТ/КТ и гистологическое исследование биоптата кожных высыпаний, по результатам которых установлен диагноз саркомы Капоши с поражением кожных покровов и легких. ВИЧ-ассоциированная саркома Капоши сопровождается поражением кожи и внутренних органов. Кожные изменения при саркоме Капоши характеризуются первичной локализацией очагов на лице и верхних конечностях, а при отсутствии антиретровирусной терапии – быстрым прогрессированием и генерализацией патологического процесса. Висцеральные поражения усугубляют течение заболевания и осложняют его прогноз. Пациенты с ВИЧ-ассоциированной саркомой Капоши нуждаются в динамическом наблюдении и комплексной терапии у инфекционистов, дерматовенерологов, онкологов.
Ключевые слова. Саркома Капоши, ВИЧ-инфекция, поражения кожи, легкие.

INTRODUCTION

The continuous improvement of methods for working with patients infected with the human immunodeficiency virus (HIV), combining timely diagnosis and administration of antiretroviral therapy (ART), has led to an increase in the length and quality of life of these patients [1]. However, the incidence rates of HIV infection in the Russian Federation and the Perm region remain high, ranging from 43.2 to 89.2 per 100,000 population, respectively*. Against the background of this trend, there are patients who do not seek medical help and do not receive antiretroviral therapy (ART). This leads to an increase in secondary viral and bacterial diseases recorded in this nosology, as well as the number of cancer patients among these individuals [1–3]. Disseminated Kaposi's sarcoma, a rarely recorded secondary disease in patients with HIV infection, is an indicator of oncological pathology. It is a tumorous, multi-focal disease of vascular origin that affects the skin, lymph nodes, and internal organs. It is known that the first description of this pathology was made in 1872 by the Hungarian dermatologist Moritz Kaposi. The development of sarcoma is based on immunosuppression with a pronounced violation of antitumor immunity and subsequent neoangiogenesis: the formation of spindle-

* Federal Service for Supervision of Consumer Rights Protection and Human Welfare, available at: https://www.rospotrebnadzor.ru/deyatelnost/epidemiological-surveillance; Federal Service for Supervision of Consumer Rights Protection and Human Welfare in the Perm Territory, available at https://59.ru/text/health/2023/07/28/72544472.

shaped cells lining the walls of new vessels, capillaries, the formation of anastomoses between adjacent blood vessels. [4; 5]. Kaposi's sarcoma occurs when the number of CD_4+ T-lymphocytes in the blood is less than 500/mm^3, dissemination is recorded in patients with a level of CD_4+ T-lymphocytes less than 200/mm^3 [1; 6].

In view of the above, we present the clinical case of a patient with the development of Kaposi's sarcoma against the background of HIV infection.

CLINICAL CASE

Patient Ch., born in 1981, applied to the Perm Regional Center for AIDS and Infectious Diseases on December 12, 2023, complaining of skin rash on the right wing of his nose, forehead, in the right axillary and right inguinal areas, on the shins, which were not accompanied by subjective sensations.

According to his medical history, the patient first noticed changes in the skin of the right wing of his nose in December 2020. In 2021, the pathological process spread to the right frontal region and shin. In April 2022, the patient was referred to the Perm Regional Oncology Dispensary for a more accurate diagnosis. A positron emission tomography combined with X-ray computed tomography (PET/CT) was performed, and surgical excision of efflorescences on the right wing of the nose followed by histological examination was carried out. Based on the results of the studies, the diagnosis was established: Kaposi's sarcoma of the skin affecting the right wing of the nose, right frontal region, shin skin, lungs. Subsequently, in 2022, similar rashes were also noted in the right armpit and groin areas.

From the patient's life history, it was known that he had five criminal records, incomplete secondary education, was single, and had a son born in 2007.

Past medical history included chronic cytomegalovirus infection since 2005, intravenous drug use since 2007, HIV infection since 2009 (ART has been administered since March 2022), chronic viral hepatitis C since 2009, mild cytolysis syndrome, oral candidiasis.

The patient denied any occupational hazards.

Allergological anamnesis revealed a urticaria-type reaction to the administration of penicillin antibiotics.

No family history of cancer.

Objectively, the patient's condition is satisfactory, body temperature is 36.5 °C. Height is 170 cm, weight is 86 kg, BMI is 30. The musculoskeletal system is proportionally formed. The tongue is moist, there is a curdled coating on the back of the tongue and gums. Breathing through the nose is free, vesicular breathing in the lungs is carried out to all parts, no wheezing, respiratory rate is 18 per minute. Heart sounds are clear, rhythmic, heart rate is 74 beats per minute, blood pressure is 120/80 mmHg. The abdomen is soft, painless, the liver is 1.0 cm below the edge of the costal arch, the spleen is not palpable. The symptom of shaking the lumbar region is negative on both sides. Submandibular lymph

nodes of 1.0 cm, anterior cervical lymph nodes of 0.5 cm, axillary and inguinal lymph nodes of 0.5 cm are palpated, elastic consistency, mobile, not soldered with surrounding tissues and among themselves, the skin above them is of physiological color.

Status localis: the skin pathological process is widespread, asymmetric, located on the face in the forehead and right wing of the nose, in the right axillary and right inguinal areas, on the shins. It is represented by polymorphic rashes in the form of purple-brown hemorrhagic spots of round and elongated shape, 2.5–3.0 cm in diameter, with clear borders and smooth surface, as well as single lenticular reddish-brown rounded papules of dense elastic consistency (Fig. 1). An atrophic scar of irregular white shape is determined in the area of the right wing of the nose (Fig. 2).

Laboratory and instrumental studies were performed: the complete blood test showed an increase in hemoglobin levels – 165 g/L, eosinophils – 5.5 %, lymphocytes – 52.9 %, a decrease in segmented neutrophils to 35.6 %. The urine test was unchanged.

The biochemical blood test revealed an increase in AST – 51.7 U/L, ALT – 43.0 U/L, glucose – 6.27 mmol/L. The immunogram showed an increase in the number of T-lymphocytes – 2232/mm^3 (82 %), CD_8^+ – 2024 cells/ mm^3 (74 %), a significant decrease in CD_4^+ – 197 cells/ mm^3 (7 %), a change in the ratio $CD_4^+ / CD_8^+ = 0.10$.

When examining the patient for viral hepatitis, serological markers for hepatitis B were not detected. Antibodies to HCV (IgM and IgG) and anamnestic antibodies to cytomegalovirus were found. Quantitative determination of HIV-1 RNA by PCR was 240 copies/ml.

PET/CT scans performed in dynamics revealed a neoplastic lesion of the right wing of the nose with increased metabolic activity, focal soft tissue thickening in the right frontal region with low metabolic activity (metastases?), focal changes in the lungs, the largest ones with low fixation of fluorodeoxyglucose, probably metastases, multiple foci of fluorodeoxyglucose fixation in the shin skin.

Pathohistological examination of the skin biopsy specimen from the right wing of the nose revealed the following: the epidermis is slightly thinned, in the dermis

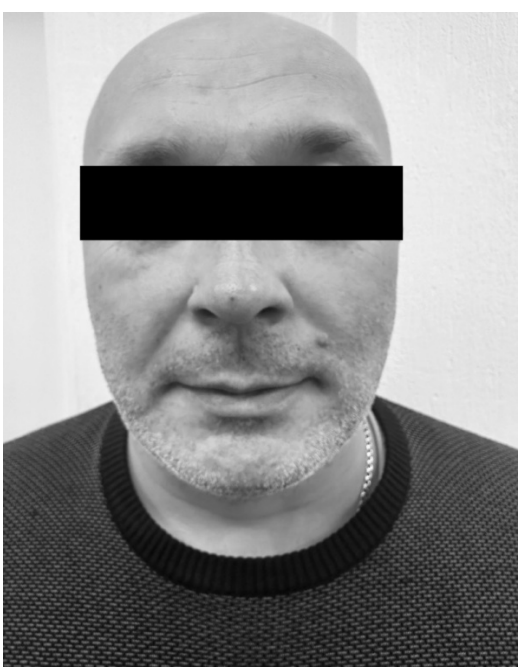

Fig. 1. Lesion of the nose in HIV-associated Kaposi's sarcoma

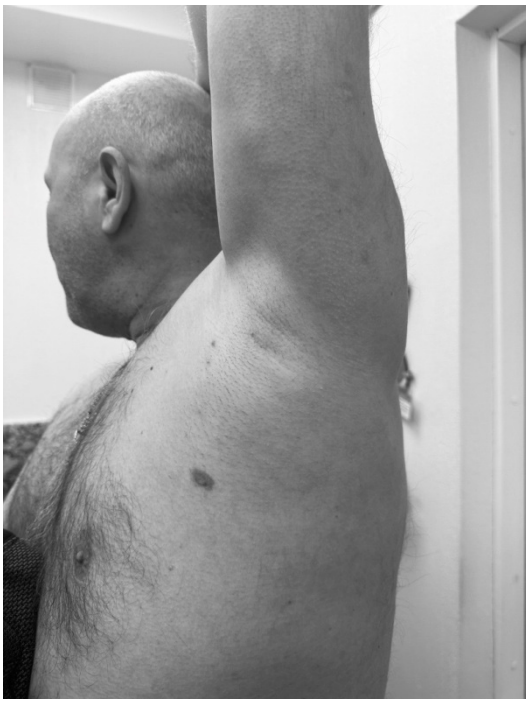

Fig. 2. Purple-brown spots and papules in in the right axillary area

there are proliferates of round and spindle-shaped cells around the vessels, the vessels are dilated, hemorrhages, hemosiderin deposits, foci of hyalinosis, infiltration by lymphocytes and plasma cells are determined. Conclusion: the morphological picture corresponds to Kaposi's sarcoma.

Diagnosis: HIV infection, stage 4B, remission against the background of antiretroviral therapy. Chronic hepatitis C, mild cytolysis syndrome. Kaposi's sarcoma of the skin and lungs. Oral candidiasis.

RESULTS AND DISCUSSION

It should be noted that clinical types of sarcomas are divided into four varieties – classical, occurring in elderly people, immunosuppressive, endemic (African) and HIV-associated [7]. The case described by us belongs to the latter type. According to literature data, HIV-associated Kaposi's sarcoma develops at the age of 40, more often in men, and in 95 % of cases is accompanied by skin manifestations, with the clinical picture beginning with lesions of the face skin, upper extremities and mucous membranes, where small pinkish-red spots similar to insect bites form, which was also recorded in this patient [8; 9]. Foreign researchers note that as the disease progresses, the spots that have appeared increase to 3–4 cm, transforming into nodes and plaques of cherry-violet-brown color, spreading to other areas of the skin, and the elements acquire a yellow halo, which indicates tumor growth [10]. In addition to the skin, internal organs can be involved in the process, more often lymph nodes, stomach, duodenum and lungs. Visceral lesions worsen the course and prognosis of the disease [11]. Thus, the clinical picture of the disease developed in this patient according to the noted studies with a level of CD_4^+ T-lymphocytes less than 200/mm^3 of blood.

The diagnosis was established for the patient based on the characteristic clinical picture and histological examination data, which revealed proliferations of spindle-shaped cells around newly formed vessels, lymphocytic infiltration, diapedesis of red blood cells, and hemosiderin deposits [12].

Healthcare practitioners should remember that if HIV-associated Kaposi's sarcoma is

suspected, a comprehensive examination of patients should be performed to assess the prevalence of the tumor process: a complete medical examination of the oral and genital mucous membranes, abdominal ultrasound, and, if necessary, computed tomography or magnetic resonance imaging [13].

It is also necessary to conduct differential diagnosis of the disease with pseudosarcomas (Mali type and Stewart–Bluefarb type), bacillary angiomatosis, pyogenic granuloma, glomus tumor, sarcoidosis, hematomas, pigmentary urticaria, lichen planus, cutaneous B-cell lymphoma [14].

It should be noted that treatment of HIV-associated Kaposi's sarcoma begins with antiretroviral therapy; if the effect is insufficient, it is advisable to add chemotherapy. At the same time, it must be remembered that all known methods of therapy do not lead to a complete cure, but only provide temporary suppression of the pathological process [15].

Conclusions

1. Long-term HIV infection without antiretroviral therapy contributes to the development of tumor processes, primarily Kaposi's sarcoma.

2. Kaposi's sarcoma against the background of HIV infection is characterized by primary facial lesions; the pathological process is widespread and rapidly progressive, affecting internal organs.

3. HIV-associated Kaposi's sarcoma is a multidisciplinary disease that requires complex therapy from infectious disease specialists, dermatologists, venereologists, and oncologists.

References

1. HIV infection and AIDS: national guidelines: 2nd edition. Ed. V.V. Pokrovsky. M.: GEOTAR-Media, 2020; 686 (in Russian).

2. *Nikolenko V.V., Nikolenko A.V., Minikeyeva M.R.* Study of changes in nutritional status in HIV-positive patients with pneumonia caused by *Streptococcus pneumoniae*. *Perm Medical Journal* 2018; 4: 14–19. DOI: 10.17816/pmj35414-19 (in Russian).

3. *Koshkin S.V., Evseeva A.P., Ryabova V.V., Kovrova O.S.* Features of the course of syphilis in HIV-infected patients: a clinical case. *Bulletin of Dermatology and Venereology.* 2020; 96 (1): 52–57. DOI: 10.25208/vdv553-2020-96-1-52-57 (in Russian).

4. *Cesarman E., Damania B., Krown S.E.* Kaposi Sarcoma. Nat. Rev. Dis. Primers. 2019; 5 (1): 9. DOI: 10.1038/s41572-019-0060-9

5. *Debordes P.A., Hamoudi C., Di Marco A.* Metastatic Kaposi sarcoma in a non-HIV patient leading to metacarpal lysis then upper-limb amputation: a case report. Case Reports. Plast. Surg. Hand. Surg. 2023; 10 (1): 2251581. DOI: 10.1080/23320885.2023.2251581

6. *Openshaw M.R., Gervasi E., Fulgenzi C.A., Pinato D.J., Dalla Pria A., Bower M.* Taxonomic reclassification of Kaposi Sarcoma identifies disease entities with distinct immunopathogenesis. J. Transl. Med. 2023; 21 (1): 283. DOI: 10.1186/s12967-023-04130-6

7. *Shiels M.S., Engels E.A.* Evolving epidemiology of HIV-associated malignancies. Curr. Opin. HIV AIDS. 2017; 12 (1): 6–11. DOI: 10.1097/COH.0000000000000327

8. *El'kin V.D., Kobernik M.Yu., Mikova O.E.* AIDS is an indicator dermatological syndrome in an HIV-infected patient. *Perm Medical Journal* 2022; 32 (1): 131–134 (in Russian).

9. *Koshkin S.V., Evseeva A.P., Ryabova V.V., Kovrova O.S.* Clinical observation of secondary syphilis in an HIV-infected patient. *Russian Medical Inquiry* 2021; 5 (11): 778–781. DOI: 10.32364/2587-6821-2021-5-11-778-781 (in Russian).

10. *Vangipuram R., Tyring S.K.* Epidemiology of Kaposi sarcoma: review and description of the nonepidemic variant. Int. J. Dermatol. 2019; 58 (5): 538–542. DOI: 10.1111/ijd.14080

11. *Tekcan Sanli D.E., Kiziltas S.* Gastrointestinal Kaposi's Sarcoma. N. Engl. J. Med. 2023; 388 (13): e45. DOI: 10.1056/NEJMicm2102502

12. *Vally F., Selvaraj W., Ngalamika O.* Admitted AIDS-associated Kaposi sarcoma patients. Indications for admission and predictors of mortality. Medicine (Baltimore). 2020; 99 (39): e22415. DOI: 10.1097/MD.0000000000022415

13. *Nwabudike S.M., Hemmings S., Paul Y.* Pulmonary Kaposi Sarcoma: an uncommon cause of respiratory failure in the era of highly active antiretroviral therapy – case report and review of the literature. Case Rep. Infect. Dis. 2016; 2016: 9354136. DOI: 10.1155/2016/9354136

14. *Radu O., Pantanowitz L.* Kaposi sarcoma. Arch. Pathol. Lab. Med. 2013; 137 (2): 289–294. DOI: 10.5858/arpa.2012-0101-RS

15. *Dupin N.* Update on oncogenesis and therapy for Kaposi sarcoma. Curr. Opin. Oncol. 2020; 32 (2): 122–128. DOI: 10.1097/CCO.0000000000000601

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Kobernik M.Yu. – contributed to the concept and design of the study; prepared the first version of the article.

Nikolenko V.V. – edited and finally approved the manuscript sent to the editorial office.

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Zavyalova A.A. – collected main information.

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