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STUDY OF NEUROTROPIC EFFECTS OF SEX STEROIDS ON AN EXPERIMENTAL MODEL OF ACUTE STRESS

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Abstract. ***Introduction.*** Mental disorders associated with the consequences of stressors represent a serious healthcare problem. Neurosteroids, including progesterone and its metabolite allopregnanolone, play an important role in regulating emotions and stress responses. This suggests their therapeutic potential in correcting post-stress anxiety and depressive disorders. ***The aim*** of this study was to investigate the stress-protective effects of progesterone in an animal model of post-traumatic stress disorder (PTSD) induced by predator exposure. ***Materials and methods.*** Forty male rats were randomly divided into four groups: control, predator stress, predator stress + progesterone, and predator stress + sulpiride (an antipsychotic). The animals' behavior was tested using a battery of behavioral tests including the elevated plus maze, the open field test, and the forced swim test. ***Results.*** The results demonstrated that the administration of progesterone significantly reduced anxiety and depressive-like behavior compared to the group exposed to predator stress. Rats treated with progesterone showed increased locomotor and exploratory activity in the open field test, spent more time in the open arms of the elevated plus maze, and exhibited decreased immobility time in the forced swim test. These effects were comparable to those observed with sulpiride, highlighting the anxiolytic and antidepressant properties of progesterone. ***Conclusion.*** The results confirm the potential use of progesterone as a therapeutic agent in the treatment of stress-related disorders and emphasize its modulatory influence on the brain's GABAergic system. Further research is necessary to elucidate the underlying mechanisms and to optimize treatment protocols.

Keywords: post-traumatic stress disorder, progesterone, neurosteroids

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ИЗУЧЕНИЕ НЕЙРОТРОПНЫХ ЭФФЕКТОВ ПОЛОВЫХ СТЕРОИДОВ НА ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ ОСТРОГО СТРЕССА

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Резюме. ***Введение.*** Психические расстройства, связанные с последствиями стрессоров, представляют собой серьезную проблему для здравоохранения. Нейростероиды, в том числе прогестерон и его метаболит аллопрегнанолон, играют важную роль в регуляции эмоций и стрессовых реакций, что позволяет предположить их терапевтический потенциал в коррекции постстрессовых тревожных и депрессивных расстройств. ***Целью*** данного исследования было изучение стресс-протекторного действия прогестерона в животной модели посттравматического стрессового расстройства (ПТСР), вызванного воздействием хищника. ***Материалы и методы.*** Сорок крыс-самцов были случайным образом разделены на четыре группы: контроль, стресс от хищника, стресс от хищника + прогестерон и стресс от хищника + сульпирид (антипсихотик). Поведение животных тестировалось в батарее поведенческих тестов с использованием «приподнятого крестообразного лабиринта», теста «открытое поле» и теста на принудительное плавание. ***Результаты*** показали, что введение прогестерона значительно снижало тревожность и депрессивно-подобное поведение по сравнению с группой переживших стресс предъявления хищника. Животные, получавшие прогестерон, демонстрировали повышенную локомоцию и исследовательское поведение в тесте «открытое поле», большее время нахождения в открытых руках в «приподнятом крестообразном лабиринте» и уменьшение времени неподвижности в тесте на принудительное плавание. Эти эффекты были сопоставимы с теми, что наблюдались при использовании сульпирида, что подчеркивает анксиолитические и антидепрессивные свойства прогестерона. ***Заключение.*** Полученные результаты подтверждают возможность использования прогестерона в качестве терапевтического средства для лечения расстройств, связанных со стрессом, и подчеркивают его модулирующее воздействие на ГАМК-эргическую систему мозга. Необходимы дальнейшие исследования для выяснения основных механизмов и оптимизации протоколов лечения.

Ключевые слова: посттравматическое стрессовое расстройство, прогестерон, нейростероиды

INTRODUCTION

Psychogenic disorders, widespread in modern society, prove to become a significant burden on healthcare system, especially if people are present in dangerous zones of war action, local conflicts, natural and manmade disasters [1]. Meanwhile health conditions associated with psychological trauma, stress and anxiety are included in the number of the most prevalent mental disorders which result in a significant economic burden for the system of healthcare. WHO-sponsored studies have demonstrated that the spread of mood disorders has dramatically increased over the past decade: patients diagnosed with depression and anxiety account for 4.4% and 3.6% of the adult population [2]. Modern therapeutic approaches, including medication, are effective in relieving the symptoms of anxiety disorders and manifestations of post-traumatic stress disorder (PTSD) in a large proportion of patients [2]. However, the main problem of modern pharmacological correction of these disorders, alongside a significant number of side effects, is a marked reduce of the severity of special individual symptoms and of the clinical picture of a disease in general, but not the elimination of the cause of the disease [3]. With the awareness of the multidimensional and comorbid nature of mental illness it becomes evident that anxiety-phobic spectrum disorders are phenomena that exceed modern diagnostic potential and known pathophysiological mechanisms [4].

Sex steroid hormones play a basic role not only in reproductive biology, but also participate in maintaining the homeostasis of the nervous system, while many steroid hormones are also synthesized de novo in the central and peripheral nervous system out of cholesterol molecules by means of neuronal cells [5]. In the central nervous system, neurosteroids perform various functions: regulation and metabolism of GABA, glutamate and other mediators, certain stages of neurogenesis such as neuronal growth, formation and growth of dendrites, myelination, synapse formation and neurones survival. Thus, sex steroids are involved not only in the coordination of reproductive health, but also in the regulation of emotions, mood and social behavior [6].

Progesterone and its neuroactive metabolite allopregnanolone ((3α,5α)-3-hydroxypregnan-20-one or 3α,5α-THP) play a key role in the response to stress action [7]. Several studies have demonstrated that depressive and anxious behavior is associated with changes in progesterone and/or allopregnanolone levels, with stated normalization of these neurosteroid levels when treated with anxiolytics or antidepressants [8]. The data obtained serve as the pathogenetic basis for the use of progesterone and its metabolites in the treatment of anxiety spectrum disorders. For example, brexanolone, being an analogue of endogenous allopregnanolone, was approved by the FDA in 2019 as a medication for the treatment of severe post-partum depression. However, it is suggested that the use of progesterone and its neuroactive metabolites has therapeutic potential and may be effective in the treatment of other mental disorders, regardless of gender [9].

THE AIM OF THE STUDY

To analyze the stress-protective properties of progesterone in an animal model of post-traumatic stress disorder.

MATERIALS AND METHODS

General experimental design

An experimental investigation was conducted to study the stress-protective effect of progesterone. To simulate a traumatic event, the classical method of imaging a predator was implemented. In our study, the tiger python (*Python molurus*) was used as a predator (stressor). Based on behavioral tests, a pronounced change in behavioral patterns was recorded in rats of each group: freezing, huddling, prolonged and altered grooming.

Maintenance of animals, formation of experimental groups and randomization

40 white mongrel male rats weighing 240–250 grams, from the Rappolovo laboratory animal nursery (Leningrad Region) were taken for the study. The animals were kept under standard

Table 1

Description of experimental groups

Group name	Group Description	Number of laboratory animals, n	Study drug/placebo
Con	Group of animals receiving intraperitoneal injection of solvent	10	0.9% NaCl
PS	Group of animals exposed to vital stress	10	0.9% NaCl
PS+P	Group of animals exposed to vital stress receiving progesterone	10	progesterone
PS+S	Group of animals exposed to vital stress receiving an antipsychotic drug	10	sulpiride

Table 2

Pharmacological agents used in the study

INN	Trade name, dosage form (manufacturer, country)	Method of administration, dose	
Progesterone	Prolutex, oil solution (Angelini, Switzerland)	Subcutaneously, 8 mg/kg	Within 10 days before the day of stress exposure
Sulpiride	Egnonyl, solution for injection (Sanofi-Aventis, France)	Intraperitoneal, 10 mg/kg	Once every 30 minutes. before stress

Table 3

Behavior of animals in the "Open field" test after exposure to vital stress

Index		Con	PS	PS+P	PS+S
Locomotion	n	20.5±3.5	16.40±4.2 *	21.2±3.2#	12.5±1.3 #
Sniffing	n	2.4±1.67	6.9±0.59*	3.3±0.9#	2.1±0.9
Movement in place	n	4.8±1.2	2.20±0.6*	3.4±1.2	2.6±1.2*
Grooming	n	2.9±1.5	5.5±1.9*	6.43±2.8*	1.9±0.9*#
Vertical racks	n	1.51±0.77	1.71±0.87	1.8±0.8	0.5±0.1*#
Racks With emphasis	n	7.00±0.7	6.2±1.87	8.1±1.5#	4.4±1.2*#
Mink research	n	7.60±1.45	16.40±1.3*	15.2±2.1*#	2.3±1.5 * #

Note. * p ≤0.05 — significant differences compared to the control group; # p ≤0.05 — significant differences compared to animals that experienced a traumatic event; n — number of acts, M±m.

vivarium conditions, 5 animals were placed in plastic cages with free access to water and granulated food. After a 14-day quarantine, the experimental animals were divided using a random number generator into 4 equal experimental equal groups (Table 1, 2):

Model of vital stress

Modeling of the stress effect was carried out by placing a group of rodents (n=10) into a transparent plastic container with a perforated cover this container was placed opposite the terrarium in which a food object (rat) was placed next to the tiger python; the process of the attack and consumption of the food object was observed by rats from the plastic container [1].

Behavioral tests

To record changes in emotional-motor patterns of the control and experimental groups, a battery of behavioral tests was used.

The "Elevated Crucified Maze" installation is designed to study the behavior of rodents under the conditions of variable stress (with a free choice of comfortable conditions) and allows to assess the level of anxiety of the animal (by preference for darkness/light, fear of highness, severity and dynamics of "peeking out" behavior).

Open field test. The technique makes it possible to record a whole range of behavioral components: the motor activity of rodents, level of anxiety, the degree of expression of indicative and exploratory behavior.

Forced swimming (behavioural despair, Porsolt test) is a universally recognized test for assessing depressive behavior in rodents. Mice or rats are used as experimental animals. Each animal, one at a time, is placed in a cylinder with water, with a diameter of 18 to 38 cm, 40 cm high, i.e. large enough for rats or mice to swim freely in it. The water temperature is maintained within 22–23 °C. The time during which the animal hangs motionless in the water, i.e., demonstrates symptoms of depression, the duration of the first episode of active swimming, the total swimming time, and the number of dives are recorded. The longer time of immobility, the shorter the total swimming time and the duration of the first episode of active swimming, the higher the level of depression, and vice versa. Testing time is 6 minutes.

Ethical rules and regulations

The work was carried out in accordance with the ethical principles established by the Basel Declaration (signed in Basel on November 30, 2010), the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (adopted in Strasbourg on March 18, 1986 and confirmed in Strasbourg on June 15, 2006), and approved by the Local ethical committee.

Statistical data processing

Descriptive statistics methods for quantitative characteristics included estimation of the mean (x), standard error of the mean (SE) and root mean square error (m), median

Table 4

Behavior of animals in the elevated plus maze test and the Porsolt test after exposure to vital stress

Index		Experimental group			
		Con	PS	PS+P	PS+S
Behavior of animals in the elevated plus maze test after exposure to vital stress					
Time is up your sleeve	t	87.86±3.12	10.14±0.93*	26.57±0.71 #	22.57±1.28 #
Time on your sleeve	t	202.3±3.04	286.7±0.86 *	268.4±0.71 #	273.6±1.67 #
Behavior of animals in the Porsolt test after exposure to vital stress					
Active swimming	t	242.8±6.21	201.3±9.39*	251.5±5.93 #	190.8±6.70
Passive swimming	t	72.33±0.98	91.83±1.74*	76.17±2.78 #	64.17±1.40 #
Immobilization	t	44.33±5.64	67.00±8.72*	36.67±5.36 #	105.0±6.39 #

Note. * p ≤0.05 — significant differences compared to the control group; # p ≤0.05 — significant differences compared to animals that experienced a traumatic event; t — time of act (seconds); M±m.

(Me), and confidence interval boundaries. Data are presented as arithmetic mean ± standard error of the mean or median with confidence interval boundaries. The distribution of the trait in the group was performed based on Monte Carlo methods. To compare the control and experimental groups with a regular distribution, the student's test was used. The statistical significance of differences was assessed using the GraphPad Prism 8.0 software package. Of the nonparametric tests, the Kruskal–Wallis's test was also used to compare the groups. The critical level of significance of the null statistical hypothesis (about the absence of significant differences or factor influences) was taken equal to 0.05.

RESULTS

Our study was carried out in two stages: at the first stage, changes in emotional and exploratory behavior were recorded between intact control (n=10) and animals that were exposed to vital stress; at the second stage, the influence of pharmacological agents on emotional — exploratory behavior and on animals that had experienced the effects of vital stress was analysed.

After exposure to vital stress, a number of patterns of emotional, exploratory and motor behavior was recorded in the Open Field test. The behavior of the studied animals was characterized by a significant (p ≤0.05) decrease in the number of sniffs in animals that had experienced vital stress, which is assessed as a manifestation of exploratory behavior and a decrease in the negative emotionality of the "novelty" of the open field (Table 3). In animals of the experimental group, the "Open Field" test recorded a significant decrease in locomotion time (p ≤0.05) relative to the control group of animals, which was assessed as a decrease in locomotor behavior. However, in animals that survived the effect of a vital stress, a significant increase of acts of grooming and exploration of minks, which characterizes an increase of exploratory behavior was observed.

Important data were obtained after administering progesterone and sulpiride to animals that had survived a traumatic event. Intraperitoneal administration of sulpiride significantly reduced the following behavioral acts: locomotion and movement on a place, as well as the number of acts of grooming and exploration of minks, both in the control group and in the group of animals that survived exposure to vital stress (p ≤0.05). Changes in behavioral patterns were also observed after intraperitoneal administration of progesterone to animals that had experienced a traumatic event. A positive effect on the "emotionality" zone was characterized by a significant increase in sniffing (p ≤0.05), an increase in locomotor activity was also observed (p ≤0.05). Also attracts attention that a simultaneous increase in the reaction of exploration of minks, both relative to the control and relative to animals that experienced a traumatic event, and a decrease in acts of grooming, may indicate the controversial effect of intraperitoneal administration of progesterone on the areas of "exploratory" behavior.

When analyzing the influence of a traumatic event in the "Elevated Cruciform Maze" test, experimental animals showed a significant increase (p ≤0.05) in the time spent in the closed arm of the device, which indicates an increase in the level of anxiety in comparison with the control group of animals.

Intraperitoneal administration of the studied pharmacological agents demonstrated the tranquilizing (anxiolytic) effect of both the oil solution of progesterone and the reference drug, sulpiride. The tranquilizing effect consisted of reducing the time the experimental animals spent in the closed arm of the installation and, accordingly, increasing the time the animals spent in the open arm, which may indicate a decrease in the level of anxiety (Table 4).

When analyzing the influence of a traumatic event by the Porsolt test, experimental animals showed increased depres-

sion compared to animals in the control group. In animals that survived an encounter with a predator, there was a statistically significant increase in the time of immobilization ($p \leq 0.05$) compared to the control group.

THE DISCUSSION OF THE RESULTS

The antidepressant effect of progesterone is to normalize the time of behavioral patterns in animals that have experienced stressors, while the use of the drug compared has shown its more pronounced tranquilizing effect, since the time of immobilization, i.e., immobility of animals increased 2 times relative to intact control and 1.5 times relative to animals that experienced stress ($p \leq 0.05$). The introduction of progesterone had a milder effect (Table 4).

Progesterone and its metabolites act on target cells through 2 signaling pathways: classical (canonical, genomic pathway) and non-classical (non-canonical, non-genomic pathway). In the classical signaling pathway, both progesterone and 5α-dihydroprogesterone (5α-DHP) bind with intracellular progesterone receptors (PR), which dimerize and translocate to the nucleus, where they regulate the expression of certain genes [10]. Non-genomic pathway regulation involves activation of membrane progesterone, G protein-coupled receptors (mPR) and membrane progesterone receptor component 1 (PGRMC1), which leads to activation of the MAPK signaling pathway, protein kinase C (PKC) pathway and PI3K/Akt. Unlike other progesterone metabolites, allopregnanolone is a positive modulator of γ-aminobutyric acid type A (GABAA) receptors and is also a ligand for mPR [11].

Due to its small size and lipid solubility, circulating progesterone easily crosses the blood-brain barrier (BBB) by free transmembrane transport and diffuses throughout the nervous tissue. The work of Pardridge W.M., Mietus L.J. demonstrated that 83% of 3 h — labeled progesterone was found in the ipsilateral hemisphere of the rat brain 15 seconds after its administration in an aqueous solution into the common carotid artery. These data serve as justification for the intraperitoneal method of administering progesterone [12].

Progesterone is a neurosteroid because it can be synthesized locally in the nervous system by almost all types of neuronal cells [13]. Also, progesterone received from the systemic circulation can be sequentially metabolized into its neuroactive 5α-reduced metabolites: 5α-reductase metabolizes to 5α-dihydroprogesterone (5α-DHPROG), 3α-hydroxysteroid dehydrogenase (3α-HSD) to 3α-5α-THPROG. Thus, the pool of progesterone and its metabolites in the central nervous system depends on (1) its peripheral synthesis, absorption and accumulation in the brain; (2) its local synthesis; and (3) metabolic features [5].

Depending on its level of concentration in the brain, progesterone can differently activate certain receptors: higher doses of progesterone can saturate nuclear receptors (PRs) while activating membrane mPRs. However, high doses may also cause receptor desensitization or decrease in their expression, saturation of pathways leading to neuroactive metabolites, or induction of inactivating metabolic pathways.

Progesterone and its metabolites are involved in neurohumoral regulation during the body's response to acute stress. Droogleever Fortuyn et al demonstrated that in situations of acute stress the adrenal glands secrete much more allopregnanolone, while its synthesis in brain structures also increases [14].

Currently, accurate data on the mechanism of the neuroprotective action of progestogens are at the stage of accumulating scientific knowledge. Data on the systemic anti-inflammatory effect of progestogens, for example, in patients with rheumatoid arthritis have been accumulated. It has been stated that long-term administration of progesterone leads to activation of the expression of some tissue-specific anti-inflammatory genes. An increase in BDNF expression in the hippocampus in response to allopregnanolone administration has also been described. However, most likely the main contribution to the neuro- and stress-protective effects of progestogens is realized through non-genomic mediated actions [10]. Neurosteroids affect the excitability of nerve cells by increasing the permeability of ion channels through membrane ionotropic receptors such as $GABA_A$ and NMDA receptors, and the stereoselectivity of steroids plays a decisive role in binding with both receptors [15].

Thus, progestogens primarily exert proGABAergic effects with insignificant involvement in the metabolic process of other neurotransmitters and demonstrate sedative, hypnotic, anesthetic, anxiolytic and anticonvulsant properties [3]. We obtained similar pharmacological effects in the results of our work in the model of acute stress of predator presentation. The neuroprotective effects of progesterone have also been studied in models of traumatic brain injury, the therapeutic effects being a reduction in cerebral edema, neuroinflammation and BBB dysfunction, which promoted neuronal survival and functional recovery [16]. An effective cerebroprotective dose of progesterone (8 mg/kg) used in rodent models of both traumatic brain injury and stroke results in plasma progesterone concentrations of 150 nM, a similar dose that we have used in our work [17]. In experimental models of stroke, progesterone levels in brain structures reached 100 nM 2 hours after the last administration of progesterone; these levels are compatible with the activation of progesterone receptors. In our future work, we also plan to determine the levels of progesterone and its metabolites in brain structures (Kd=1 nM) [18, 19].

The neuroprotective effects of progesterone and its derivatives have been studied in various experimental models of neurodegenerative diseases. Brinton laboratory et al Researchers from Briton laboratory treated ovariectomized female 3xTg-AD

mice (a model of Alzheimer's disease) with progesterone alone or in combination with estradiol for 3 months, which specifically attenuated Tau hyperphosphorylation [20–22]. Researchers have demonstrated that neuroactive progesterone derivatives enhance neurogenesis, improve cognitive functions and memory, reduce neuroinflammation and levels of beta-amyloid accumulation in 3xTgAD mice. However, an increasing number of publications demonstrate great importance of allopregnanolone in the processes of neurogenesis [23]. At the cellular level, allopregnanolone reduced the severity of NMDA-mediated excitotoxicity and, in general, reduced presynaptic glutamate release and Ca^{2+} influx through activation of GABA receptors in response to activating stimuli. At the tissue level, this progesterone metabolite activated the induction of proliferation of neural progenitor cells, increasing the survival of newly formed neurons; decreased amyloid generation and microglial activation, increased oligodendrogenesis [24].

Thus, our data confirm that despite the evidence for the neuroprotective effects of allopregnanolone, our experimental findings support the possibility of using progesterone as a stress-preventive drug. Subsequent clinical tasks include specifying the indications, determining the dose, duration and timing of progesterone administration.

CONCLUSIONS

1. Long-term introduction of progesterone (8 mg/kg) for 10 days before exposure to stressor has pronounced anxiolytic, antidepressant effects according to the results of a series of behavioral tests in the predator presentation stress model.

2. These effects appear to be associated with the action of progesterone and its neuroactive metabolites on the GABA system of brain of the experimental animals.

3. Progesterone and its metabolites may provide an alternative direction of research to explore potential methods of treatments of anxiety and depression in patients who had experienced psychotraumatic events.

ADDITIONAL INFORMATION

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

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

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

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

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SOMATOTYPE PROFILE OF YOUNG MEN LIVING IN DIFFERENT REGIONS OF THE REPUBLIC OF TAJIKISTAN

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Abstract. ***Introduction.*** Determination of somatotype opens up the possibility of creating approaches to personalized monitoring of health status of various population groups. The aim of this work is a comparative analysis and determination of prevalence of ecto-, meso- and endomorphic somatotypes in residents of regions of Tajikistan with different environmental conditions. ***Materials and methods.*** The study involved 701 male volunteers aged 19 to 22 years, 400 subjects lived in Dushanbe, 301 students — in Gorno-Badakhshan Autonomous Oblast (GBAO). Somatotyping was carried out using the Heath–Carter method. All volunteers were determined by body length and weight, knee and elbow breadth, shoulder and calf circumference, triceps, subscapular, suprailiac, calf skinfolds were measured. Based on the measured anthropometric parameters, the ecto-, meso- and endomorphic components of the somatotype were calculated using a Heath–Carter formula. The obtained data were compared using the Mann–Whitney U-test and the Pearson χ^2 test. ***Results.*** Young men who have lived in Dushanbe since birth surpass their peers from GBAO in having greater body length and weight, massive bones determined by the breadth of large joints, and the thickness of the skinfat folds. 72% of the capital's residents had a high contribution of endomorphic and a low contribution of meso- (4%) and ectomorphic (2%) components of the somatotype. Subjects from GBAO were distinguished by a high contribution of meso- (36%), ectomorphic (15%), and endomorphic (16%) body types. Overweight was determined in 35% of volunteers from Dushanbe and only 2% of subjects from GBAO. Underweight was detected in only 11% of volunteers from Dushanbe and 61% of subjects from GBAO. ***Conclusions.*** The anthropometric profile and constitutional diversity of young male residents of the Republic of Tajikistan depends on the region of their permanent residence and environmental conditions.

Keywords: anthropometric profile, somatotype, Heath–Carter, Tajikistan, Dushanbe, Gorno-Badakhshan Autonomous Oblast

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ПРОФИЛЬ СОМАТОТИПА У МОЛОДЫХ МУЖЧИН, ПРОЖИВАЮЩИХ В РАЗЛИЧНЫХ РЕГИОНАХ РЕСПУБЛИКИ ТАДЖИКИСТАН

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Резюме. ***Введение.*** Определение типа телосложения открывает возможность создания подходов к персонифицированному мониторингу состояния здоровья различных групп населения. ***Цель работы*** — провести сравнительный анализ и определить распространенность экзо-, мезо- и эндоморфных соматотипов у жителей регионов Таджикистана с различными условиями окружающей среды. ***Материалы и методы.*** В исследовании приняли участие 701 мужчина-доброволец в возрасте от 19 до 22 лет, 400 субъектов проживали в г. Душанбе, 301 студент — в Горно-Бадахшанской автономной области (ГБАО). Для определения соматотипа по методу Хит–Картер всем добровольцам измеряли длину и массу тела, ширину колена и локтя, окружность плеча и голени и кожно-жировые складки на плече, спине, животе, голени. На основании этих антропометрических параметров производили расчет экто-, мезо- и эндоморфного компонента соматотипа, используя общеизвестную формулу. Для сравнения полученных данных использовали U-критерий Манна–Уитни и тест χ^2 Пирсона. ***Результаты.*** Молодые мужчины, с рождения проживающие в г. Душанбе, превосходят своих сверстников из ГБАО, имеют бóльшую длину и массу тела, массивность костей, определяемую по ширине крупных суставов, толщину кожно-жировой складки. У 72% жителей столицы имел место высокий вклад эндоморфного и низкий — мезо- (4%) и эктоморфного (2%) компонентов соматотипа. Субъекты из ГБАО отличались высоким вкладом мезо- (36%), экто- (15%) и эндоморфного (16%) типов телосложения. У 35% добровольцев из Душанбе и всего у 2% испытуемых из ГБАО определен избыток массы тела. Дефицит массы тела выявлен всего у 11% добровольцев из Душанбе и у 61% испытуемых из ГБАО. ***Выводы.*** Антропометрический профиль и конституциональное разнообразие молодых мужчин — жителей Республики Таджикистан зависит от региона их постоянного проживания и условий окружающей среды.

Ключевые слова: антропометрический профиль, соматотип, Хит–Картер, Таджикистан, Душанбе, Горно-Бадахшанская автономная область

INTRODUCTION

Body type is a stable anthropometric indicator in adults associated with muscle strength and endurance [1–4], motor skills [5, 6], and athletic performance [7, 8] in both athletes of various specializations and non-athletes. Assessment of somatotypes is used in the complex evaluation of anthropometric features, their connection with motor skills and muscle work in children [9, 10]. A candidate's belonging to the "dominant" somatotype in a given sport increases the chance of being selected for elite teams [4, 11]. Body type may be a predictor both of insufficient weight [12, 13] and obesity [14–19], and also outcome of different diseases [20–23]. Moreover, body type can be related to some morphological and functional features of the body, for example, to the size of organs [12, 15], blood cell content [24–26], vegetative status [27, 28]. Information about the constitutional characteristics of patients helps in the implementation of approaches to organizing proper nutrition [29] and prescribing adaptive physical education programs [30].

Due to the above, including differentiation of body types in objective examination of healthy athletes, children and adults, and also sick people gives up the possibility of implementing approaches to personalized monitoring of their health. The scientific literature has documented population studies to determine the prevalence of somatotypes in Russian [15, 31–33], Polish [34], Portuguese [35], Chinese [18, 36], Korean [37], Japanese [19], and Chilean [38] cohorts. At the same time, there is a lack of studies involving subjects from Central Asia. There is a limited number of publications describing the constitutional characteristics of residents of Uzbekistan [39–41], Kazakhstan [42], Kyrgyzstan [43, 44], and Tajikistan [45–47].

AIM

The aim of the study is to conduct a comparative analysis and determine the prevalence of exo-, meso- and endomorphic somatotypes determined by the Heath–Carter method in residents of two regions of Tajikistan with different environmental conditions: Dushanbe and the Gorno-Badakhshan Autonomous Region (GBAO). This work is necessary to expand our understanding of the constitutional characteristics of residents of Central Asia.

MATERIALS AND METHODS

The study included data on 701 healthy men aged 19–22 years. All of them were students of the Tajik State Medical University named after Abu Ali Ibni Sino. Of these,

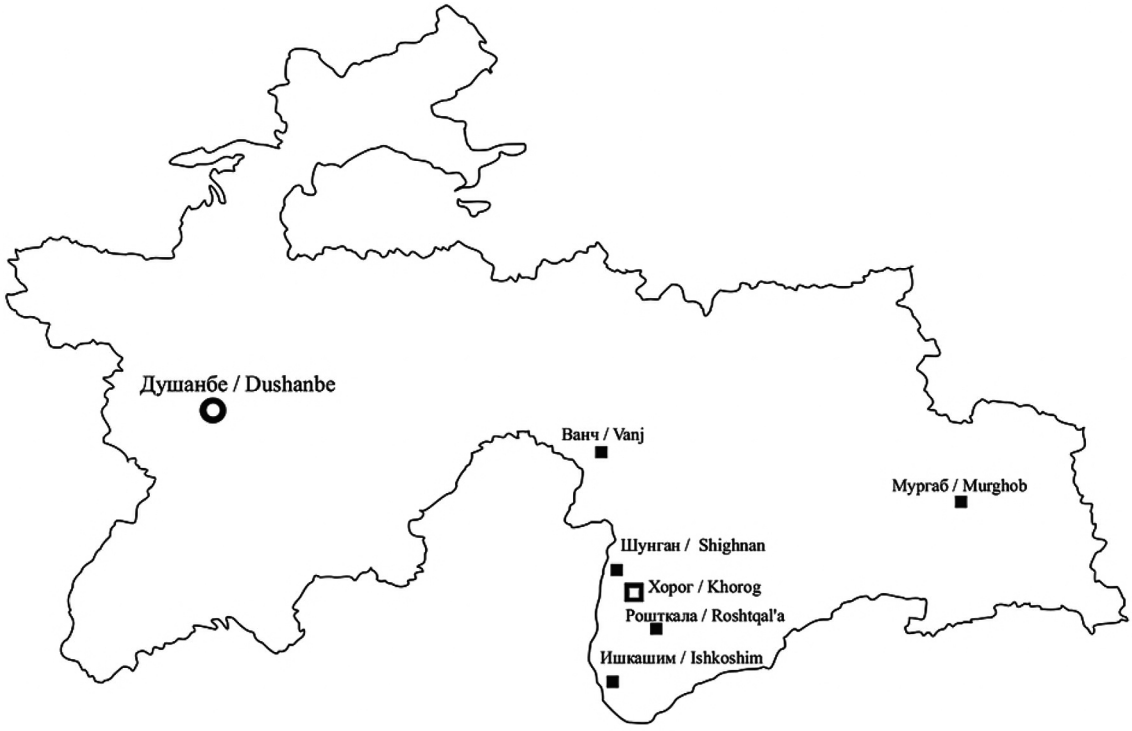


Fig. 1. Study area. ○ — capital of the Republic of Tajikistan; □ — administrative center of Gorno-Badakhshan Autonomous Oblast; ■ — settlements of Gorno-Badakhshan Autonomous Oblast

Рис. 1. Область исследования. ○ — столица Республики Таджикистан; □ — административный центр Горно-Бадахшанской автономной области; ■ — населенные пункты Горно-Бадахшанской автономной области

400 subjects lived in Dushanbe, the capital of the republic, from birth, and 301 students lived in the Gorno-Badakhshan Autonomous Region (GBAO): the villages of Vanch, Ishkashim, Roshtkala, Shugnan, Murghab, and the city of Khorog (Fig. 1). To assess somatotype due to the Heath–Carter method, the subjects had their apical body length (ABL) measured using a medical stadiometer MP-01/S (Moscow Weighing Plant MIDL), and their body mass (BM) measured using medical scales VMEN-150-50/100-I-D1-A (JSC Tulinovsky Instrument-Making Plant TVES). Also, the knee width (KW) and elbow width (EW) were measured using a sliding caliper ("KAFA", Russia). A non-elastic ergonomic tape measure (SECA 203, Germany) was used to measure the upper arm circumference (UA) and lower leg circumference (LLC) with an accuracy of 0.01 cm. The thickness of the skin-fat folds (SFF) was measured using a professional caliper ET MEASURE model SK-101 (China), with a spring calibrated to create the same pressure (0.01 kg/mm^2) on both sides of the fold, the measurement accuracy was 0.2 mm. SFF was measured in four places: on the back of the shoulder in the triceps area (SFF triceps), on the back in the scapula area (SFF back), on the abdomen above the iliac crest (SFF supraspinatus) and on the back of the shin (SFF shin). All anthropometric measurements were made according to modern recommendations [48].

In 1960, Barbara Heath and Lindsay Carter proposed an approach based on a series of equations requiring the above measurements of anthropometric parameters, which allows calculating the degree of expression of the ectomorphic (ECTO (1)), mesomorphic (MESO (2)) and endomorphic (ENDO (3)) components in the somatotype of a particular subject [49].

$$\text{ECTO (BL/BM, body length/body weight ratio)} = \frac{\text{BL, sm}}{\sqrt[3]{\text{BM, kg}}}; \quad (1)$$

If BL/BM ≥40,75, so ECTO = 0,732 · BL/BM – 28,58.

If BL/BM 38,25 to 40,75, so ECTO = = 0,463 · BL/BM – 17,63.

If BL/BM ≤38,25, so ECTO = 0,5.

$$\text{MESO} = (0{,}858 \cdot \text{EW, cm} + 0{,}601 \cdot \text{KW, cm} + 0{,}188 \cdot (\text{UA, cm} - \frac{\text{SFF triceps, mm}}{10}) + 0{,}161 \cdot (\text{CC, cm} - \frac{\text{SFF shin, mm}}{10}) - (0{,}131 \cdot \text{BL, cm}) + 4{,}5; \quad (2)$$

$$\text{ENDO} = -0{,}7182 + 0{,}1451 \cdot X - 0{,}00068 \cdot X^2 + 0{,}0000014 \cdot X^3. \quad (3)$$

$$X = (\text{SFF triceps, mm} + \text{SFF back, mm} + \text{SFF supraspinatus, mm}) \cdot (\frac{170{,}18}{\text{BL, sm}})$$

Assessment of each component was done due to recommendations published by J.E.L. Carter, B.H. Heath [49]. The ECTO, MESO and ENDO values from 0.5 to 2.5 were considered as low contribution; from 2.6 to 5.5 as moderate, from 5.6 to 7 as high, 7.1 and above as very high contribution.

Body mass index was calculated using Kettle formula (4). Body weight deviations were assessed taking into account the 1995 World Health Organization (WHO) recommendation for the Asian cohort of subjects [50]: BMI <18.5 — underweight; BMI 18.6 to 22.9 — normal body weight; BMI 23.0 to 27.4 — overweight; >27.5 — obesity.

$$\text{BMI} = \frac{\text{BM, kg}}{\text{BL}^2\text{, m}}. \quad (4)$$

Comparison of anthropometric parameters and quantitative contribution of ecto-, meso- and endomorphic body type in residents of Dushanbe and GBAO was performed using the Mann–Whitney U-test. The decision to use a nonparametric test was made after checking the data using the Shapiro–Wilk test, which indicated a deviation from the normal distribution. Categorical variables, the numerical ratio of the distribution of the contribution of various components of somatotypes and body weight deviations were analyzed using the Pearson χ^2 test for 4×2 conjugation tables.

Calculations were performed using the statistical software Past version 2.17, Norway, Oslo (2012), the statistical algorithm StatXact-8 with the Cytel Studio software package version 8.0.0. Results were considered significant at $p < 0.05$. All continuous data are presented as arithmetic means and 95% confidence intervals (CI). Categorical data are presented as proportions with 95% CI.

RESULTS

As shown in Table 1, residents of Dushanbe, compared to their peers from GBAO, had statistically significantly higher values of body length and weight, width of large joints, sizes of all skin-fat pads and endomorphy in combination with lower values of meso- and ectomorphy. The values of shin and shoulder circumferences were not statistically significant (Table 1).

Data analysis showed that the distribution of contributions of ecto-, meso- and endomorphism of varying degrees (low, moderate, high, very high) is heterogeneous and statistically significantly differs in volunteers from Dushanbe and GBAO (Table 2, Fig. 2). Consequently, the degree of ecto-, meso- and endomorphism depends on the region of residence.

The distribution of weight deviations determined by BMI is heterogeneous and statistically significantly different in young men living in Dushanbe and GBAO (Table 3). Thus, the presence of underweight, normal or overweight, and obesity depends on the region of residence.

Table 1

Comparison of anthropometric parameters and ecto-, endo- and mesomorphic somatotype components contributions in young men living in different regions of the Republic of Tajikistan

Таблица 1

Сопоставление антропометрических параметров и вклада экто-, эндо- и мезоморфного компонента соматотипа у молодых мужчин, проживающих в различных регионах Республики Таджикистан

Параметр / Parameter	Душанбе / Dushanbe	ГБАО / GBAO	p-значения / p-value
Длина тела, см / Height, cm	171,18 (170,32; 172,04)	156,45 (155,31; 157,60)	$1{,}19\times10^{-61}$
Масса тела, кг / Body mass, kg	64,88 (63,75; 65,97)	44,23 (43,45; 45,02)	$1{,}87\times10^{-94}$
Индекс массы тела, кг/м^2 / Body mass index, kg/m^2	22,08 (21,76; 22,39)	18,04 (17,80; 18,28)	$1{,}47\times10^{-61}$
Ширина колена, см / Knee breadth, cm	6,38 (6,32; 6,45)	7,04 (6,91; 7,16)	$3{,}27\times10^{-15}$
Ширина локтя, см / Elbow breadth, cm	5,44 (5,40; 5,48)	5,74 (5,67; 5,82)	$1{,}10\times10^{-8}$
Окружность голени, см / Calf circumference, cm	36,88 (36,46; 37,30)	37,16 (36,67; 37,66)	0,409
Окружность плеча, см / Upper arm circumference, cm	32,40 (31,94; 32,87)	31,92 (31,40; 32,44)	0,1868
Кожно-жировая складка плечо, см / Upper arm skinfold, cm	3,09 (2,99; 3,18)	1,28 (1,23; 1,33)	$3{,}49\times10^{-99}$
Кожно-жировая складка под лопаткой, см / Subscapular skinfold, cm	2,55 (2,44; 2,69)	1,72 (1,66; 1,78)	$1{,}71\times10^{-19}$
Кожно-жировая складка голени, см / Calf skinfold, cm	0,67 (0,65; 0,68)	0,16 (0,16; 0,16)	$5{,}54\times10^{-114}$
Кожно-жировая складка надостная, см / Suprailiac skinfold, cm	1,87 (1,76; 1,98)	1,41 (1,35; 1,47)	$1{,}51\times10^{-6}$
Эктоморфия, усл. ед. / Ectomorphy, conv. units	2,76 (2,61; 2,91)	3,91 (3,74; 4,08)	$7{,}64\times10^{-19}$
Мезоморфия, усл. ед / Mesomorphy, conv. units	1,92 (1,75; 2,10)	4,88 (4,64; 5,11)	$1{,}86\times10^{-58}$
Эндоморфия, усл. ед / Endomorphy, conv. units	6,69 (6,51; 6,85)	4,42 (4,31; 4,54)	$3{,}06\times10^{-60}$

Table 2

Prevalence of various components of somatotypes contributions in young men living in Dushanbe and Gorno-Badakhshan Autonomous Oblast

Таблица 2

Распределение вкладов различных компонентов соматотипов у молодых мужчин, проживающих в г. Душанбе и Горно-Бадахшанской автономной области

Вклад / Contribution	Душанбе / Dushanbe	ГБАО / GBAO
Эктоморфия / Ectomorphy*		
Низкий / Low	0,42 (0,36; 0,48)	0,23 (0,17; 0,29)
Умеренный / Moderate	0,56 (0,50; 0,62)	0,62 (0,55; 0,69)
Высокий / High	0,02 (0,01; 0,04)	0,14 (0,10; 0,20)
Очень высокий / Very high	0 (0; 0,01)	0,01 (0,002; 0,03)
Мезоморфия / Mesomorphy**		
Низкий / Low	0,65 (0,59; 0,71)	0,13 (0,09; 0,18)
Умеренный / Moderate	0,32 (0,26; 0,38)	0,52 (0,44; 0,59)
Высокий / High	0,03 (0,01; 0,05)	0,23 (0,17; 0,29)
Очень высокий / Very high	0,01 (0,0004; 0,02)	0,13 (0,09; 0,18)
Эндоморфия / Endomorphy***		
Низкий / Low	0 (0; 0,01)	0,01 (0,002; 0,03)
Умеренный / Moderate	0,29 (0,23; 0,35)	0,83 (0,77; 0,88)
Высокий / High	0,31 (0,25; 0,37)	0,15 (0,10; 0,21)
Очень высокий / Very high	0,41 (0,34; 0,47)	0,01 (0,001; 0,03)

Note: / Примечание: *p=$3{,}69\times10^{-55}$; **p=$1{,}13\times10^{-53}$; ***p=$2{,}76\times10^{-14}$.

Table 3

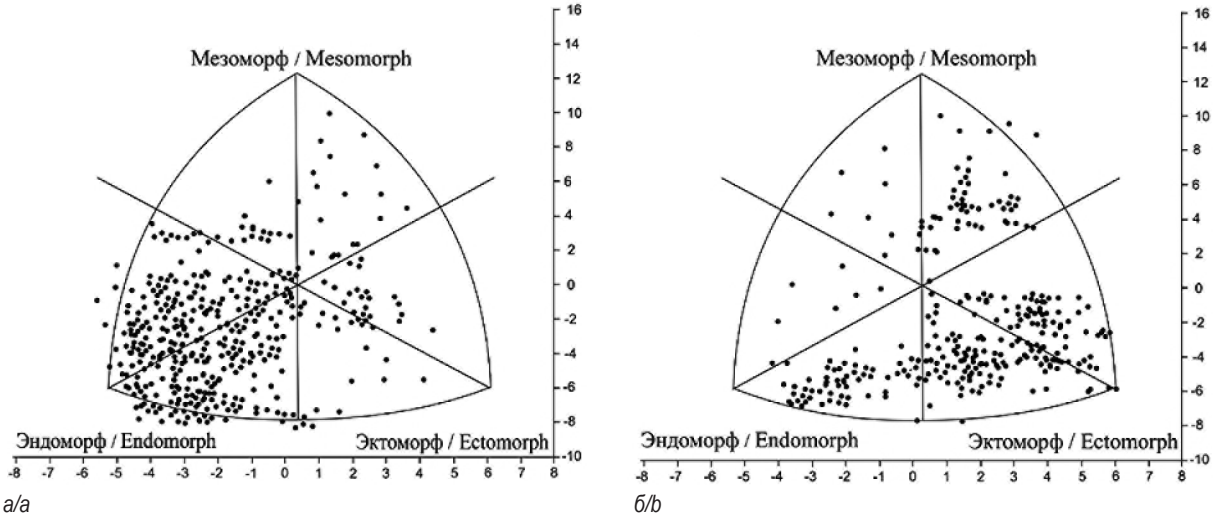
Distribution of body weight deviations in young men living in Dushanbe and Gorno-Badakhshan Autonomous Oblast

Таблица 3

Распределение отклонений массы тела у молодых мужчин, проживающих в г. Душанбе и Горно-Бадахшанской автономной области

Вклад / Contribution	Душанбе / Dushanbe	ГБАО / GBAO
Дефицит массы тела / Underweight	0,11 (0,07; 0,15)	0,61 (0,54; 0,68)
Нормальная масса тела / Normal body weight	0,55 (0,48; 0,61)	0,37 (0,30; 0,44)
Избыточная масса тела / Overweight	0,28 (0,22; 0,34)	0,02 (0,01; 0,05)
Ожирение / Obesity	0,07 (0,04; 0,10)	0,00 (0,00; 0,02)

Note: / ***Примечание:*** $p=1{,}607\times10^{-9}$.



а/a *б/b*

Fig. 2. Distribution of somatotype profiles in young men living in Dushanbe (*a*) and Gorno-Badakhshan Autonomous Oblast (*b*)

Рис. 2. Распределение профиля соматотипов у молодых мужчин, проживающих в г. Душанбе (*а*) и Горно-Бадахшанской автономной области (*б*)

DISCUSSION

To our knowledge, this is the first study to compare constitutional and anthropometric characteristics of young men living in Dushanbe and GBAO. The other studies with the similar aim were conducted in children, young women and did not take into account the territorial distribution of subjects [45, 47, 51]. Persons from Dushanbe surpassed their peers from GBAO in almost all anthropometric parameters: they are tall, heavy, with a large amount of subcutaneous fat and high bone mass (Table 1). Also, 72% of the capital's residents demonstrate a high and very high contribution of the endomorphic component of somatotype (Table 2, Fig. 2). In 35% of them, overweight and obesity were identified (Table 3). At the same time, subjects from GBAO were distinguished by a high and very high contribution of the mesomorphic (36%) component of somatotype in combination with underweight in 61% of subjects. For residents of Dushanbe, these indicators were recorded at the level of 4, 2 and 11%, respectively (Tables 2, 3, Fig. 2). The high and very high contribution of the ecto- and endomorphic somatotype among residents of GBAO was approximately equivalent — 15 and 16%, respectively.

In recent studies, examining more than 1000 subjects of different sexes and ages, it was found that the prevalence of overweight and obesity among residents of the capital of Tajikistan is 20–25% [52, 53]. This generally corresponds to the 35% prevalence of these disorders obtained in our work and the results of other studies involving adults [54] and children [55].

It is noted that the main reason for the increase in metabolic disorders is the formation of incorrect eating patterns and motor behavior in the population [51]. Recent surveys have shown an increase in the total volume of food consumed in combination with a decrease in physical activity in urban residents of Tajikistan [51, 53, 54]. More than 95% of respondents regularly consumed flour products, up to 30%

of respondents indicated a preference for fast food and its regular consumption 1–2 times a week [51, 53], while 63% of respondents did not eat enough vegetables and fruits [56]. Only 8% of 1000 participants said about regular physical activity in their life [51]. It is also assumed that leptin resistance [57] and insulin resistance [58, 59] play a significant role in the development of metabolic disorders in residents of Tajikistan. Despite the innate determination of body types [60], environmental factors and lifestyle can influence the expression of one or another component of the somatotype [40, 61]. For example, endomorphic body type shows a strong positive correlation with the thickness of skin and fat folds [62]. Thus, the endomorphization of body type in Dushanbe residents can be explained by the prevalence of excess body weight, which is also shown in this work. Dushanbe is the largest city, the capital of Tajikistan, with a widespread network of public catering establishments providing high-calorie food with fast service and a developed network of public transport, eliminating the need for walking long distances [63]. GBAO, on the contrary, is a rural region, the economy of households of which is based exclusively on the agricultural sector, which forces more than 70% of its residents to work daily on their own plots, consuming large amounts of energy [53]. Fast food establishments are not widespread in this region, and the socioeconomic conditions of the population are also low [63]. In this work we identified underweight in 60% of examined men living in GBAO. Thus, we assume that intensive physical activity in combination with a negative energy balance in the majority of GBAO residents may be the reason for the increase in ecto- and mesomorphic components of body type (Table 2, Fig. 2). It should be noted, that the obtained results partially contradict the literature, which reports that the prevalence of overweight among residents of GBAO is high. According to our data, only 2% of men from GBAO had overweight (Table 3), and at the same time 16% of them had endomorphic body type (Table 2). This can most likely be explained by the wide range of ages of the subjects and the limited scope of observations [56]. Our results partially coincide with the data published on the results of studies conducted in 2000–2008 involving newborn children from GBAO [64]. It should be emphasized that the age of participants in this study suggests that they were born in 2000–2002.

The article compared anthropometric parameters of residents of flat areas from the city of Dushanbe (706 m above sea level) and volunteers who have lived in high-altitude conditions since birth — the urban-type settlements of Vanch (1722 m above sea level), Roshtkala (2696 m above sea level), Ishkashim (3037 m above sea level), Shugnan (2287 m above sea level), Murghab (3618 m above sea level), the city of Khorog (2123 m), located in GBAO. Numerous studies have documented the impact of high altitude living conditions on the physical development of adults and children. Andrade et al. (2023) reported a dominant mesomorphic body type in prepubertal children living in high altitude areas of Argentina [65], which is consistent with the results of the survey of GBAO residents in this work. Observational studies conducted with the participation of Nepalese [66], Ethiopian [67], Tibetan [68], Sri Lankan [69], Peruvian [70, 71], Colombian [72, 78], Indian [36] cohorts revealed a deficit in linear growth in children living in high altitude conditions. In our study, residents of high-mountain regions also lagged behind their peers from Dushanbe in terms of apical body length (Table 1). Some authors believe that intrauterine hypoxia can cause growth retardation in fetuses and newborns from high-mountain regions [73]. Anthropometric deficiency and small lung size [74], as well as genetic polymorphism of cell cycle regulators and signalling molecules involved in the transduction of the key mechanism of bone lengthening [75], insulin-like growth factor 1 [76], are likely to be mechanisms limiting the rate of “catch-up” growth during the pubertal spurt [72, 77] in children with short stature due to the influence of high altitude. According to J.I. Martínez et al. (2021), maternal short stature caused by high altitude and hypoxia can be transmitted to the next generations [78]. It should also be noted that ectomorphic body type is positively associated with the polymorphism of the adrenoreceptor gene *ADRB3* rs4994 genotype Trp64Arg [79], the alpha-actinin-3 gene *ACTN3* RX [80], the brain-derived neurotrophic factor *BDNF* variant rs925946, neurexin-3-alpha NRXN3 variant rs10146997, the obesity-associated gene FTO variant rs9939609 and the protein kinase gene *MAP2K5* rs4776970 [17]. Mesomorphic type is associated with *NRXN3* variant rs10146997, *FTO* variant rs9939609 [17]. Endomorphic type is associated with *ADRB3* rs4994 genotype Trp64Trp [79], KLF14 polymorphism [81], *BDNF* variant rs925946, *NRXN3* variant rs10146997 [17]. Identification of genetic determination of body shape and its influence on motor functions and endurance in GBAO residents may become the subject of future research.

The high prevalence of underweight combined with meso- and ectomorphic components in residents of high-altitude regions of Tajikistan identified in the article also corresponds to literature data. Several independent studies have confirmed a reduced risk of overweight and obesity in residents of highland regions of Nepal [81], Tibet [82], and the United States [83].

The high prevalence of underweight in combination with meso- and ectomorphic components in high-altitude populations revealed in the article is a strong point of this work is the attempt to create a prognostic model of a personalized approach to monitoring the health status of residents of the

Republic of Tajikistan in connection with the territory of their residence and environmental features. Thus, the endomorphic somatotype revealed in men from Dushanbe, in case of their failure to comply with the principles of healthy nutrition and lifestyle, can be a predictor of metabolic disorders and associated functional disorders. In patients from Tajikistan suffering from obesity, a high levels of oxidative stress [84], insulin resistance [58, 59], and thyroid dysfunction [85] were revealed.

Ecto- and mesomorphic body types, found in residents of mountainous regions of the republic, can explain the development of underweight with improper nutrition and gastrointestinal tract disorders. Malnutrition and growth retardation are risk factors for the development of cognitive impairment [86, 87], decreased motor functions [88], micronutrient deficiency [89], and increased susceptibility to infectious diseases due to decreased immunity [90, 91]. However, the literature does not report the prevalence of diseases associated with growth retardation and low weight in residents of GBAO. Based on this, it can be assumed that young men have a compensated form of body weight deficiency. The prevalence of meso- and ectomophic body types has a “positive” side. As mentioned earlier, these somatotype variants are positively associated with the development of motor skills and endurance in athletes [9, 10, 92, 93]. Thus, healthy male athletes from GBAO may gain a biological advantage to achieve maximum efficiency of sports training and the likelihood of selection into professional teams [4, 11, 94].

The described patterns are the result of the implementation of a pilot project, so this study has a number of limitations. Firstly, the work did not involve determining the functional, hematological, genetic, biochemical characteristics of residents of Tajikistan and their correlation with the somatotype. Secondly, these results require reproducibility in other comparison groups (women, children). Thirdly, it is necessary to examine a sample from other areas, focusing on the influence of environmental factors, highlands, living in rural and urban regions of Tajikistan on the anthropometric characteristics of residents of the republic.

CONCLUSION

1. The anthropometric profile and constitutional diversity of young male residents of the Republic of Tajikistan depend on the region of their permanent residence.

2. The city of Dushanbe, the capital of the republic, is characterized by high urbanization, which has led to the creation of conditions that have affected the level of physical activity and nutrition of young people. Subjects from Dushanbe are distinguished by tall stature, high thickness of subcutaneous fat, massive bones, endomorphic body type, as well as the prevalence of overweight and obesity.

3. Their peers from GBAO, a region with an agrarian economy of households requiring energy-intensive manual work, were characterized by anthropometric deficits in linear growth, weight, bone mass, subcutaneous fat thickness in combination with a predominantly mesomorphic somatotype and a high prevalence of nutritional deficiencies.

The obtained results open up the possibility of introducing elements of a personalized approach to monitoring the health of residents of Tajikistan, expressed in the creation of prognostic models of nutritional status disorders and related pathologies. They can also be useful for the implementation of sports selection programs based on the analysis of physical development.

ADDITIONAL INFORMATION

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

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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MORPHOMETRIC AND HISTOCHEMICAL CHARACTERISTICS OF THE ESOPHAGEAL EPITHELIUM AFTER ADMINISTRATION OF MORPHOGEN AND CYTOSTATIC DRUG

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Abstract. ***Introduction.*** Esophagitis of various etiologies, metaplasia (Barrett's disease) and cancer are a serious problem at the current stage of medical development. Understanding the regulation of esophageal epithelial proliferation and differentiation is crucial for developing effective therapeutic strategies. ***The aim of the study*** was to conduct a comparative analysis of the effects of the peptide morphogen hydra and the cytostatic drug cyclophosphamide on the morphometric and histochemical parameters of the esophageal epithelium in mice, with special attention to changes in tissue organization characterized as heteromorphism. For the first time, a comprehensive approach combining morphometric, histochemical, and immunohistochemical methods is presented to assess the effect of these drugs on epithelial cell proliferation and metabolism. ***Materials and methods.*** 45 white mongrel mice were used in the experiment. Groups of animals were injected intraperitoneally with the peptide morphogen hydra (PMG) (100 mcg/kg) or cyclophosphamide (CF) (400 mg/kg) for 5 days, the control group received saline solution. Histological analysis, morphometry, histochemistry (NADH-diaphorase and succinate dehydrogenase activity), and immunohistochemistry (detection of nuclear antigen of proliferating PCNA cells) were performed 24 hours after the last injection. ***The results*** showed that the peptide morphogen of hydra induces epithelial hyperplasia, mainly due to the spiny layer, and increases the activity of NADH-diaphorase and succinate dehydrogenase, as well as the proliferative index. Cyclophosphamide causes hyperkeratosis, impaired differentiation, and decreased enzyme activity, with a paradoxical initial increase and then decrease in proliferative activity. ***Conclusions.*** The peptide morphogen of hydra and cyclophosphamide cause opposite changes in the epithelium of the esophagus, enhancing its heteromorphism. The data obtained are important for understanding the pathogenesis of chemotherapy complications and developing new strategies for the treatment of esophageal diseases.

Keywords: esophageal epithelium, heteromorphy, cyclophosphamide, morphogen

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ВЛИЯНИЕ ПЕПТИДОГО МОРФОГЕНА ГИДРЫ И ЦИКЛОФОСФАНА НА МОРФОМЕТРИЧЕСКИЕ И ГИСТОХИМИЧЕСКИЕ ПАРАМЕТРЫ ЭПИТЕЛИЯ ПИЩЕВОДА МЫШЕЙ

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Резюме. ***Введение.*** Эзофагиты различной этиологии, метаплазия (болезнь Барретта) и рак представляют серьезную проблему на современном этапе развития медицины. Понимание регуляции пролиферации и дифференцировки эпителия пищевода критически важно для разработки эффективных терапевтических стратегий. ***Цель исследования*** — провести сравнительный анализ воздействия пептидного морфогена гидры и цитостатического препарата циклофосфана на морфометрические и гистохимические параметры эпителия пищевода у мышей, с особым вниманием к изменениям тканевой организации, характеризующимся как гетероморфия. Впервые представлен комплексный подход, объединяющий морфометрические, гистохимические и иммуногистохимические методы для оценки влияния этих препаратов на пролиферацию и метаболизм эпителиальных клеток. ***Материалы и методы.*** В эксперименте использовали 45 белых беспородных мышей. Группам животных вводили внутрибрюшинно пептидный морфоген гидры (ПМГ) (100 мкг/кг) или циклофосфана (ЦФ) (400 мг/кг) в течение 5 дней, контрольная группа, получала физиологический раствор. Гистологический анализ, морфометрия, гистохимия (активность НАДН-диафоразы и сукцинатдегидрогеназы) и иммуногистохимия (выявление ядерного антигена пролиферирующих клеток PCNA) проводились через 24 часа после последней инъекции. ***Результаты*** показали, что пептидный морфоген гидры индуцирует гиперплазию эпителия, преимущественно за счет шиповатого слоя, и повышает активность НАДН-диафоразы и сукцинатдегидрогеназы, а также пролиферативный индекс. Циклофосфан вызывает гиперкератоз, нарушение дифференцировки и снижение активности ферментов с парадоксальным начальным увеличением, а затем снижением пролиферативной активности. ***Выводы.*** Пептидный морфоген гидры и циклофосфан вызывают противоположные изменения в эпителии пищевода, усиливая его гетероморфию. Полученные данные важны для понимания патогенеза осложнений химиотерапии и разработки новых стратегий лечения заболеваний пищевода.

Ключевые слова: эпителий пищевода, гетероморфия, циклофосфан, пептидный морфоген гидры

INTRODUCTION

Diseases of the esophagus, including esophagitis of various etiologies, metaplasia (Barrett's disease) and cancer, represent a serious medical problem [7, 9, 14]. Understanding the regulation of esophageal epithelial proliferation and differentiation is critical for the development of effective therapeutic strategies [10, 11, 15]. In this study, we compared the influence of two agents with opposite mechanisms of action on esophageal epithelium: peptide morphogen hydra (PMG), known for its regenerative properties, and cyclophosphamide (CPh), a cytostatic drug widely used in oncology. The study hypothesis was that these agents would induce opposite changes in epithelial morphometry and histochemistry.

AIM

The aim of the study is to conduct a comparative experimental investigation of changes in the histological structure of the esophageal mucosal epithelium, its proliferative and metabolic activity under the influence of a cytostatic agent and a morphogen, taking into account the heteromorphism of this tissue

MATERIALS AND METHODS

The experiment was conducted on 45 adult outbred white male mice (23–25 g), randomly divided into three groups of 15 animals each: control (intraperitoneal administration of physiological NaCl solution), PMG group (intraperitoneal administration of PMG at a dose of 100 μg/kg body weight), CPh group (intraperitoneal administration of CPh, LENS-Pharm, Russia, 400 mg/kg body weight). Daily intraperitoneal administration of the drugs was carried out for 5 days. 24 hours after the last injection, the animals were euthanized [2]. Esophageal samples were fixed in Carnoy's fluid, histological sections were prepared, and hematoxylin and eosin staining was performed. Morphometric analysis (thickness of the epithelial layer and its parts) was performed using an ocular micrometer (×280). Proliferative activity was assessed by counting mitoses in the basal layer (≥3000 cells per animal, ×900). NADH diaphorase (NADH-d) and succinate dehydrogenase (SDH) activities were determined histochemically on cryostat sections (tetrazolium method) with quantitative assessment on a spectrophotometer (×280, λ=545 nm) [6]. Immunohistochemical detection of the nuclear antigen of proliferating cells PCNA (DAKO A/S, Denmark, dilution 1:100) was performed on paraffin sections. Statistical data processing was performed using Student's t-test (Statistica for Windows v.6.0). The significance of differences was accepted at $p < 0.05$. The work was carried out in accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (adopted in Strasbourg on 18.03.1986 and confirmed in Strasbourg on 15.06.2006) and approved by the Local Ethics Committee.

RESULTS

In the control group, the stratified squamous non-keratinizing epithelium of the esophagus demonstrated typical architecture: clear stratification into basal, spinous, granular and horny layers, as well as characteristic vertical cellular polarization. Basal cells had a cuboidal or low prismatic shape, basophilic cytoplasm, and an approximately equal ratio of eu- and heterochromatin in the nuclei. Mitotic activity was predominantly localized in the basal layer, appearing as individual foci. The spinous layer was formed by 2–4 rows of polygonal cells with predominance of euchromatin in the nuclei and intense basophilic colour of the cytoplasm. The granular layer consisted of 1–2 rows of flattened cells with pronounced heterochromatin in the nuclei and a large number of basophilic keratohyaline granules in the cytoplasm. The stratum corneum was represented by densely packed horny scales with acidophilic cytoplasm.

Peptide morphogen hydra group

Histological study. In animals receiving PMG, the general structure of the esophageal epithelium was preserved, but statistically significant hyperplasia was observed ($p < 0.001$), mainly due to an increase in the thickness of the spinous layer. The morphology of cells in different layers, including the size of nuclei and the distribution of chromatin, did not visually differ from the control group. At the same time, an increase in the number of mitoses in the basal layer was noted.

Morphometric study. Quantitative morphometric analysis showed an increase in the total thickness of the epithelial layer by 1.4 times ($p < 0.001$) compared to the control group. This increase was mainly due to an increase in the thickness of the spinous layer (1.7 times, $p < 0.001$) and, to a lesser extent, the basal layer (1.3 times, ($p < 0.05$)). The thickness of the stratum corneum did not differ statistically significantly from the controls. Mitotic activity in the basal layer increased by 1.4 times ($p < 0.01$) compared to the controls (Fig. 1). The proliferative index also demonstrated a reliable increase ($p < 0.05$).

*Histochemical study. I*n the control group, NADH-d activity was recorded in all layers of the epithelium, except for the stratum corneum, with uniform distribution of the reaction

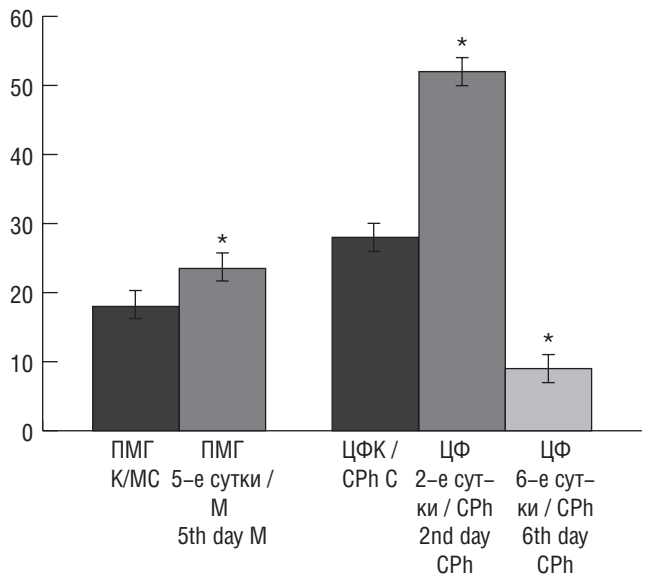

Fig. 1. Mitotic activity in the basal layer of the esophageal epithelium after administration of morphogen (M) and cyclophosphamide (CPh). Ordinate axis: mitotic activity (in ‰). Abscissa axis here and in Figs. 2 — index values: C — control group, 2, 5, 6 — days of the experiment. * Difference from control is significant (p <0,05)

Рис. 1. Митотическая активность в базальном слое эпителия пищевода при введении пептидного морфогена гидры (ПМГ) и циклофосфана (ЦФ). По оси ординат: митотическая активность (в ‰). По оси абсцисс здесь и на рис. 2 — значения показателя: К — контрольная группа, 2, 5, 6 — сутки эксперимента. * Отличие от контроля значимо (p <0,05)

product in the cell cytoplasm. Enzyme activity was higher in the basal layer than in the spinous layer. The introduction of PMG did not change the localization of enzymatic activity, but an increase in the reaction in the basal and spinous layers was visually observed. No significant changes were detected in the stratum corneum and granular layers. Quantitative assessment showed a 1.6-fold increase in NADH-d activity in the basal layer and 1.3-fold in the spinous layer (p <0.01) (Fig. 2). SDH activity also increased significantly (p <0.01) — 1.4 times in the basal layer and 1.5 times in the spinous layer.

Cyclophosphamide group

Histological study. Short-term exposure to high doses of CPh resulted in significant thickening of the epithelial layer already by the second day of the experiment, accompanied by uneven thickening and looseness of the stratum corneum. The overall thickening of the epithelium was statistically significant (p <0.001) and was primarily due to hyperkeratosis. Impaired stratification and differentiation of epithelial cells were observed, with dyskeratosis. Altered relief of the epithelial surface and interstitial edema were observed. Basal cells were randomly located, forming a multi-row layer with variability of basophilic cytoplasm. An increase in the number of cell rows and the volume of epit helial cell cytoplasm were observed in the spinous layer. The size of keratohyaline granules increased in the cells of the granular layer.

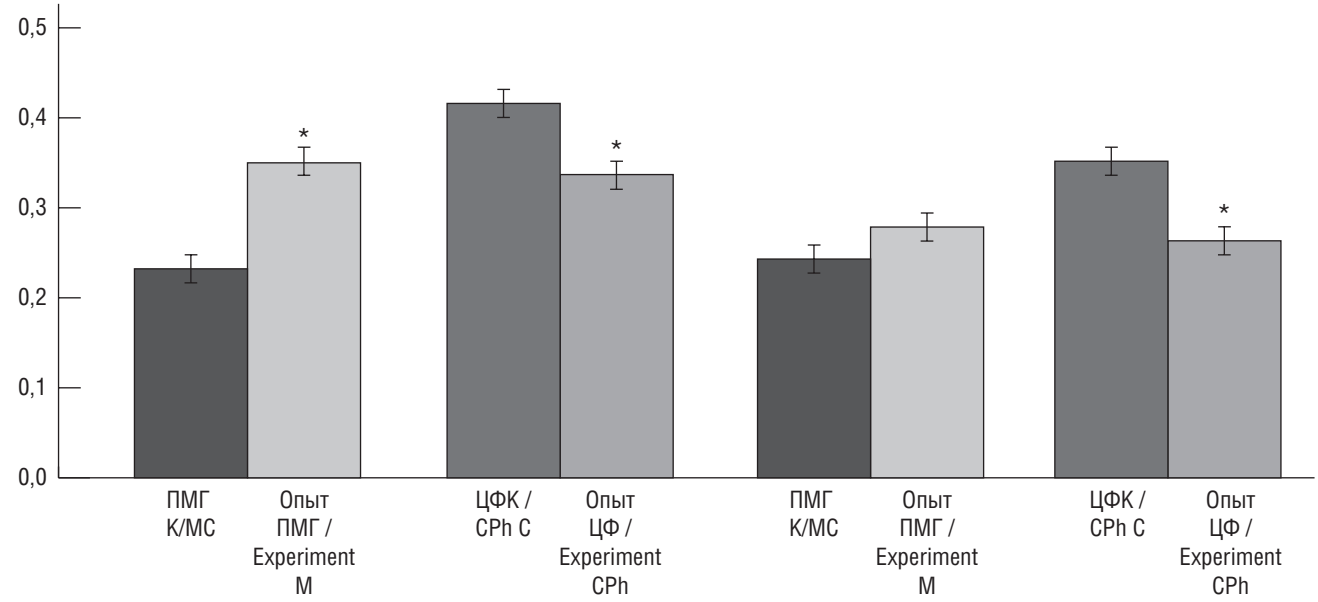

Fig. 2. Activity of NADH diaphorase in the basal (I) and spinous (II) layers of the esophageal epithelium after administration of morphogen (M) and cyclophosphamide (CPh). Ordinate axis: enzyme activity (relative units)

Рис. 2. Активность НАДН-диафоразы в базальном (I) и шиповатом (II) слоях эпителия пищевода при введении пептидного морфогена гидры (ПМГ) и циклофосфана (ЦФ). По оси ординат: активность фермента (отн. ед.)

Morphometric study. The maximum increase in the thickness of the epithelial layer (by 1.7 times) and the thickness of the stratum corneum (by 2.3 times) (Fig. 1) was recorded on the 6th day of the experiment. Mitotic activity after the first injection of CPh increased by 3 times, but by the 8th day it decreased by 1.3 times relative to the control (Fig. 1). The proliferative index showed paradoxical dynamics: the initial increase was replaced by a significant decrease by the end of the experiment ($p < 0.05$).

Histochemical study. NADH-d activity remained relatively stable at the beginning of the experiment, but by the 6th day it decreased by 1.2 times in the basal and spinous layers ($p < 0.01$) (Fig. 2). Similarly, SDH activity in the cytoplasm of spinous cells decreased on average by 1.5 times ($p < 0.01$), which correlates with the suppression of mitochondrial activity under the influence of CPh. *Immunohistochemical study.* Detection of PCNA showed an initial decrease in the number of PCNA-positive cells by 27% relative to the control, followed by an increase of 23% in the basal layer and 99% in the spinous layer on the 6th day.

DISCUSSION

The results demonstrate the antagonistic effect of PMG and CPh on the esophageal epithelium. Since PMG belongs to the class of regulatory neuropeptides [1, 13], it can be assumed that, like other representatives of this class, it is one of the elements of a complex neuropeptide regulatory system that controls various functions of esophageal epithelial cells — proliferation, differentiation, functional activity. This study confirms that PMG induces stimulation of proliferation and metabolism, leading to hyperplasia predominantly in the spinous layer.

The increase in NADH-d activity in the esophageal epithelium after the administration of PMG and the early identified stimulating effect of PMG on SDH activity [3] corresponds to an increase in oxidative metabolism of the tissue.

In general, histological, morphometric and quantitative histochemical data provide grounds to speak about the stimulating effect of PMG on the esophageal epithelium, which is manifested by increased proliferation, general thickening, an increase in the pool of differentiating cells and metabolic activation.

With short-term administration of high doses of CPh, pronounced disturbances in the processes of differentiation and keratinization are observed in the esophageal mucosal epithelium: thickening of the epithelial layer, especially pronounced in the stratum corneum, hyperkeratosis, disturbance of vertical anisomorphism and cytoarchitectonics, such as multi-row arrangement of cells in the basal layer, an increase in the number of rows of epithelial cells in the spinous layer, the appearance of cells with atypical nuclei, an increase in the size of keratohyalin granules in the epithelial cells of the granular layer, loosening of the stratum corneum and its disintegration into complexes of scales, widening of intercellular spaces and interstitial edema. Similar changes have been described in various forms of esophagitis, as well as in foci of esophageal epithelial dysplasia [11, 15]. Morphological changes are accompanied by a decrease in the activity of mitochondrial enzymes NADH-d and SDH, which is consistent with information on the suppression of mitochondrial enzyme activity by cytostatics and the damaging effect of CPh on mitochondria [3–5].

Since CPh is a cytostatic, it could be assumed that its administration would inhibit cell proliferation. However, after the first injection, we, on the contrary, observed a sharp increase in mitotic activity, which can probably be explained by the synchronous completion of mitoses by cells that had already entered the G1 period before the administration of CPh. Perhaps this was also a consequence of the long-term delay of epithelial cells in the S-phase, associated with the alkylating effect of CPh, as well as the processes of reparation of DNA damaged by the cytostatic. This can also explain the decrease in the proportion of PCNA+ cells during this period, since PCNA marks cells in the early S phase and is also a marker of neoplastic transformation of the esophageal epithelium [12]. Decrease of mitotic activity is led by DNA damage of epithelial cells. CPh has cytostatic influence, characterised by hyperkeratosis, impaired differentiation and decreased metabolic activity [8], probably due to mitochondrial dysfunction. The biphasic change in the proliferative response to CPh may be associated with cell cycle synchronization and subsequent cell death.

The obtained results confirm opposite influence of PMG and CPh on epithelial cells of the esophagus. PMG increases proliferation and metabolic function of epithelial cells leading to hyperplasia, predominantly in the spinous layer. This effect is due to the data about regenerative function of PMG. In contrast, CPh causes cytotoxic action, accompanied by hyperkeratosis, differentiation impairment and suppression of metabolic activity, which is probably associated with mitochondrial dysfunction. The initial increase in the proliferative index in the CPh group may be associated with cell cycle synchronization and subsequent cell death.

CONCLUSION

1. The obtained data indicate the opposite effect of PMG and CPh on the morphofunctional characteristics of the esophageal epithelium: PMG stimulates regeneration, while CPh causes damage.

2. The effect of PMG and CPh leads to a pronounced increase in the heteromorphism of the esophageal epithelium.

ADDITIONAL INFORMATION

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

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

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Experiments with animals. The work was carried out in accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (adopted in Strasbourg on March 18, 1986 and confirmed in Strasbourg on June 15, 2006), and approved by the Local Ethics Committee.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

Эксперименты с животными. Работа проведена в соответствии с этическими принципами, установленными Европейской конвенцией по защите позвоночных животных, используемых для экспериментальных и других научных целей (принятой в Страсбурге 18.03.1986 г. и подтверждённой в Страсбурге 15.06.2006 г.) и одобрена Локальным этическим комитетом.

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MORPHOFUNCTIONAL CHARACTERISTICS OF THE GLANDULAR EPITHELIUM OF THE ORAL MUCOSA DURING CYTOSTATIC THERAPY

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Abstract. ***Introduction.*** Cytostatic drugs used in oncological practice have a systemic effect on the body, including on the mucous membranes of the gastrointestinal tract, the side effects of which are stomatitis and mucositis, which complicate treatment. ***Objective*** — experimental study of the damaging effect of cytostatic drugs on the glandular epithelium of the oral mucosa and assessment of the reversibility of these changes. ***Materials and methods.*** The epithelium of the minor salivary glands of the tongue was studied on 20 mature white outbred mice after intraperitoneal administration of the cytostatic drug cyclophosphamide at a dose of 400 mg/kg body weight for 5 days. Animals in the control group (20 mice) were injected with isotonic sodium chloride solution at the same frequency. The material was obtained 24 hours and 20 days after the last injection of the drug. Histological and histochemical methods were used. Histochemical studies revealed the activity of the enzyme succinate dehydrogenase in the epithelial cells of the secretory portions of the minor salivary glands, the content of total proteins in serocytes, and the content of glycoproteins and glucosaminoglycans in mucocytes. ***Results.*** Exposure to cyclophosphamide led to a decrease in the activity of cyclophosphamide in serocytes and mucocytes, a decrease in the concentration of proteins in serocytes, and inhibition of the synthesis of glycoproteins and glucosaminoglycans in mucocytes. The changes were reversible. ***Conclusions.*** Cytostatic therapy causes damage to the glandular epithelium of the oral mucosa, which is expressed in the suppression of metabolic and synthetic processes. Serocytes are more sensitive to cytotoxic action than mucocytes. There was a high degree of regeneration of the glandular epithelium of the oral mucosa after the withdrawal of the cytostatic drug.

Keywords: oral cavity, mucous membrane, glandular epithelium, minor salivary glands, cyclophosphamide

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МОРФОФУНКЦИОНАЛЬНАЯ ХАРАКТЕРИСТИКА ЖЕЛЕЗИСТОГО ЭПИТЕЛИЯ СЛИЗИСТОЙ ОБОЛОЧКИ ПОЛОСТИ РТА ПРИ ВВЕДЕНИИ ЦИТОСТАТИКА

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Резюме. ***Введение.*** Цитостатические препараты, применяемые в онкологической практике, оказывают системное воздействие на организм, в том числе и на слизистые оболочки желудочно-кишечного тракта, побочными эффектами которых являются стоматит и мукозит, затрудняющие проведение лечения. ***Цель исследования*** — экспериментальное изучение повреждающего действия цитостатических препаратов на железистый эпителий слизистой оболочки полости рта и оценка обратимости этих изменений. ***Материалы и методы.*** Эпителий малых слюнных желез языка исследовали у 20 половозрелых белых мышей после внутрибрюшинного введения цитостатического препарата циклофосфана в дозе 400 мг/кг массы тела течение 5 дней. Животным контрольной группы (20 животных) через те же промежутки времени вводили изотонический раствор натрия хлорида. Материал получали через 24 часа после последнего введения препарата, а также с целью изучения обратимости изменений, через 20 суток. Применяли гистологический и гистохимический методы. Гистохимические исследования выявляли активность фермента сукцинатдегидрогеназы (СДГ) в эпителиоцитах концевых отделов малых слюнных желез, содержание суммарных белков в сероцитах, а также содержание гликопротеинов и глюкозаминогликанов в мукоцитах. ***Результаты.*** Воздействие циклофосфана приводило к снижению активности СДГ в сероцитах и мукоцитах, уменьшению концентрации белков в сероцитах, угнетению синтеза гликопротеинов и глюкозаминогликанов в мукоцитах. Нарушения были обратимыми, и показатели вернулись к контрольным значениям в конце эксперимента. ***Выводы.*** Терапия цитостатиками вызывает повреждение железистого эпителия слизистой оболочки полости рта, которое выражается в угнетении метаболических и синтетических процессов. Сероциты более чувствительны к цитотоксическому действию, чем мукоциты. На фоне прекращения терапии наблюдалась высокая степень регенерации железистого эпителия слизистой оболочки полости рта.

Ключевые слова: полость рта, слизистая оболочка, железистый эпителий, малые слюнные железы, циклофосфан

INTRODUCTION

Cytostatic drugs used in oncological practice [1, 2] exert a systemic effect on the body, including the mucous membranes of the gastrointestinal tract [3–5]. Side effects such as stomatitis and mucositis are common complications of chemotherapy, significantly impairing patients' quality of life and complicating treatment regimens. Damage to the oral mucosa leads to xerostomia, which causes significant physical discomfort and compromises the suprapepithelial protective mechanisms of the oral mucosa (OM), thereby predisposing patients to infectious complications. The minor salivary glands of the oral cavity are primarily located in the submucosa. They are classified into three types: serous, mucous, and mixed. The secretory end pieces of serous glands consist of serous cells (serocytes), those of mucous glands are composed of mucous cells (mucocytes), while mixed glands contain both cell types [6].

AIM

The aim of this study was to experimentally investigate the damaging effect of cytostatic drugs on the glandular epithelium of the oral mucosa (OM) and assess the reversibility of these changes.

MATERIALS AND METHODS

The study utilized 40 female outbred white mice weighing 23–25 g. Animals in the experimental group (n=20) received intraperitoneal injections of the alkylating cytostatic agent cyclophosphamide (CF, LENS-Pharm, Russia) at a dose of 400 mg/kg body weight every 48 hours for 5 days. Control group animals (n=20) were administered isotonic sodium chloride solution following the same schedule. The investigation focused on the minor salivary glands of the tongue. Tissue samples (tongue) were collected 24 hours after the third CF injection. To assess the reversibility of CF-induced changes, additional samples were obtained 20 days following the final drug administration.

The study targeted the ventral tongue mucosa. *Conventional histological analysis* was carried out on transverse sections stained with hematoxylin and eosin. *Histochemical and cytophotometric analyses* included the detection of total proteins using tetrazolium reactions for histidine, tyrosine, and tryptophan (Burstone's method), glycosaminoglycans with Alcian blue (pH 2.7), and glycoproteins via the periodic acid-Schiff (PAS) reaction in paraffin-embedded sections. Succinate dehydrogenase (SDH) activity was determined in cryostat sections using Lloyd's tetrazolium method. Quantitative cytophotometric analysis of histochemical reactions was performed using a plug-in spectrophotometer, with results expressed as relative optical density units. Statistical analysis was conducted using Statistica for Windows v6.0. Intergroup differences were assessed by Student's t-test, with $p < 0.05$ considered statistically significant. The study complied with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, March 18, 1986; revised June 15, 2006) and was approved by the Local Ethics Committee.

RESULTS

Histological analysis demonstrated a reduction in the volume of secretory end pieces in both serous and mucous glands of the tongue, along with decreased size of their constituent serocytes and mucocytes. These findings were supported by quantitative histochemical data, which revealed: a reduction in total protein content within serous cells (from 0.32±0.02 to 0.21±0.03 relative units, RU; Fig. 1), along with suppressed glycoprotein synthesis (Fig. 2) and decreased glycosaminoglycan levels in mucous cells (from 0.55±0.05 to 0.42 ± 0.02 RU and from 0.30±0.02 to 0.22±0.02 RU, respectively). SDH activity decreased from 0.32±0.02 to 0.21±0.02 RU in serocytes (Fig. 3) and from 0.41±0.02 to 0.36±0.01 RU in mucocytes.

By day 20 after treatment cessation, total protein concentration, glycoprotein and glycosaminoglycan levels, and SDH activity in both serous and mucous cells had returned to baseline control values.

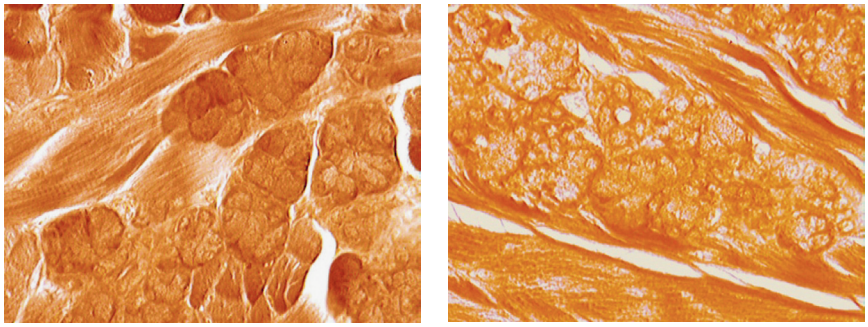
DISCUSSION

Structural changes in the minor salivary gland epithelium accompanied by suppressed synthetic and metabolic activity were observed, indicating high susceptibility to cytotoxic damage from chemotherapeutic agents. These findings correlated with reported data on major salivary gland damage during cytostatic therapy [7, 8]. The resulting xerostomia compromises the protective mechanisms of the OM. Our data revealed more pronounced structural and functional impairment in serocytes than in mucocytes, consistent with the previously reported preferential damage to serous cells in major salivary glands during chemotherapy [8]. Comparative analysis of metabolic and synthetic process disturbances in glandular epithelium versus previously identified disturbances in the surface epithelium of the OM [9] demonstrated that changes in the surface epithelium were less pronounced than in glandular epithelium.

The post-treatment recovery period showed normalization of morphofunctional parameters in the glandular epithelium of the OM, indicating its high regenerative capacity.

CONCLUSION

1. Our findings demonstrate that cytostatic therapy induces damage to the glandular epithelium of the OM, manifesting as suppression of both metabolic and synthetic processes.



а/a *б/b*

Fig. 1. **Secretory portions of protein salivary glands of the tongue: *a* — control group; *b* — after three injections of cyclophosphamide. Reduction of protein content in serocytes. Histochemical detection of total proteins, ×400**

Рис. 1. **Концевые отделы белковых слюнных желез языка: *а* — контрольная группа; *б* — после трех инъекций циклофосфана. Снижение содержания белков в сероцитах. Гистохимическое выявление суммарных белков, ×400**

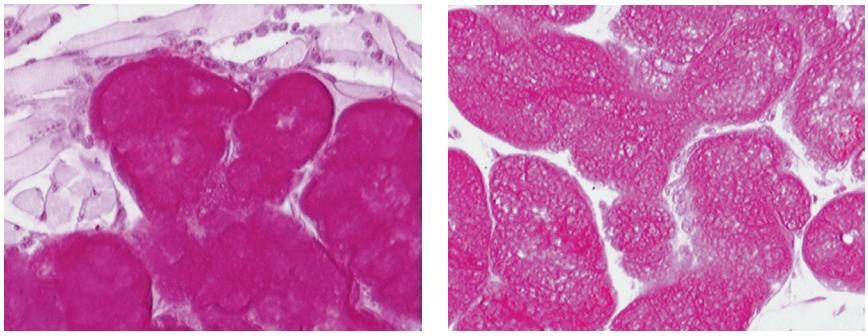


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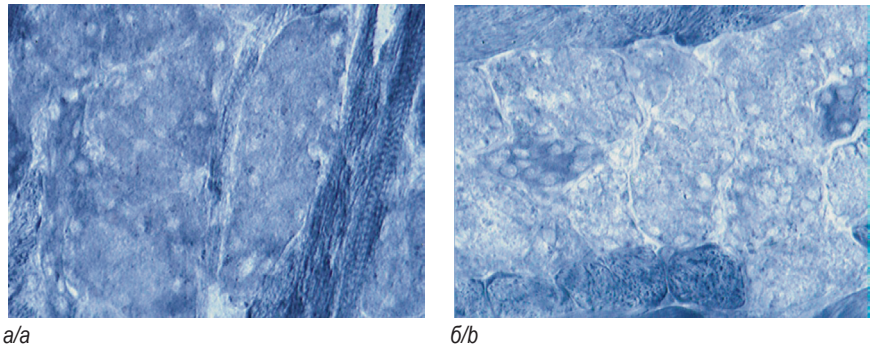
Fig. 2. **Secretory portions of mucous salivary glands of the tongue: *a* — control group; *b* — after three injections of cyclophosphamide. Reduction in the content of glycoproteins in mucocytes. PAS reaction, ×400**

Рис. 2. **Концевые отделы слизистых оболочек слюнных желез языка: *а* — контрольная группа; *б* — после трех инъекций циклофосфана. Снижение содержания гликопротеинов в мукоцитах. ШИК-реакция, ×400**



а/a *б/b*

Fig. 3. **Secretory portions of protein salivary glands of the tongue: *a* — control group; *b* — after three injections of cyclophosphamide. Decreased cyclophosphamide activity in serocytes. Histochemical detection of cyclophosphamide, ×400**

Рис. 3. **Концевые отделы белковых слюнных желез языка: *а* — контрольная группа; *б* — после трех инъекций циклофосфана. Снижение активности сукцинатдегидрогеназы в сероцитах. Гистохимическое выявление сукцинатдегидрогеназы, ×400**

2. Serous cells show significantly greater sensitivity to cytotoxic effects compared to mucous cells.

3. There was a high degree of regeneration of the glandular epithelium of the OM after the withdrawal of the cytostatic drug.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

Эксперименты с животными. Работа проведена в соответствии с этическими принципами, установленными Европейской конвенцией по защите позвоночных животных, используемых для экспериментальных и других научных целей (принятой в Страсбурге 18.03.1986 г. и подтверждённой в Страсбурге 15.06.2006 г.) и одобрена Локальным этическим комитетом.

ADDITIONAL INFORMATION

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

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

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Experiments with animals. The work was carried out in accordance with the ethical principles established by the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (adopted in Strasbourg on March 18, 1986 and confirmed in Strasbourg on June 15, 2006), and approved by the Local Ethics Committee.

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DOI: 10.56871/RBR.2025.17.33.005

FETOMETRY PARAMETERS IN PREGNANCY AFTER *IN VITRO* FERTILIZATION

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Abstract. ***Introduction.*** Current research supports the efficacy and safety of in vitro fertilization (IVF), but questions about pregnancy and fetal development after their use continue to be relevant. Early sources claim that there is a relationship between IVF and low birth weight, premature birth, placental abruption, congenital malformations, and perinatal mortality. More recent data show that the incidence of perinatal complications is higher in women after IVF. ***The aim of the study*** was to evaluate fetometric parameters in pregnancies resulting from in vitro fertilization in the Orenburg region. ***Material and method.*** Retrospectively we studied 1333 ultrasound protocols at 11–14, 20–22, 30–34 weeks in 462 pregnant women of the first (343) and second (119) gestational periods after IVF. When analyzing screening at 11–14 weeks, we compared the crown-rump length (CRL) and nuchal translucency (NT) of fetuses in women of two age groups. The second and third screens looked at averages the mean biparietal diameter (BPD), occipitofrontal diameter (OFD), head circumference (HC) and abdominal circumference (AC) and femur length (FL) in fetuses from women of the two age periods and according to sex were compared, as well as the growth intensity of the above parameters depending on the sex of the fetus and the age period of the mother. ***Results.*** The study showed that at the first screening, the mean CRL of the fetus was not statistically significantly different between the two groups, while the mean value of the nuchal NT was significantly higher in fetuses of second gestational age women. When comparing the fetometric parameters obtained at the second screening, there was a significant difference in OFD in fetuses of women of the two age periods. When comparing the studied fetometric parameters depending on the sex of the fetus, significant differences were found in a greater direction for male fetuses. ***Conclusion.*** Thus, fetometry revealed uneven growth of the studied parameters from the intermediate to late fetal period, including depending on the sex of the fetus and the age of the mother.

Keywords: fetus, fetometry, *in vitro* fertilization, growth intensity

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ПОКАЗАТЕЛИ ФЕТОМЕТРИИ ПРИ БЕРЕМЕННОСТИ ПОСЛЕ ЭКСТРАКОРПОРАЛЬНОГО ОПЛОДОТВОРЕНИЯ

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Резюме. ***Введение.*** Современные исследования подтверждают эффективность и безопасность экстракорпорального оплодотворения (ЭКО), однако продолжают оставаться актуальными вопросы о течении беременности и развитии плода после их применения. Ранние источники утверждают о существовании взаимосвязи между процедурой ЭКО и низким весом при рождении, преждевременными родами, отслойкой плаценты, врожденными аномалиями развития, перинатальной смертностью. Поздние данные показывают, что частота перинатальных осложнений выше у женщин после ЭКО. ***Цель исследования*** — дать оценку фетометрическим показателям при беременности, наступившей в результате экстракорпорального оплодотворения, в Оренбургской области. ***Материалы и методы.*** Ретроспективно были изучены 1333 протокола ультразвукового исследования в сроки 11–14, 20–22, 30–34 недели у 462 беременных первого (343) и второго (119) периодов зрелого возраста после применения вспомогательных репродуктивных технологий (ВРТ). При анализе скрининга в 11–14 недель сравнивали копчико-теменной размер (КТР) и толщину воротникового пространства (ТВП) плодов у женщин двух возрастных групп. Во втором и третьем скрининге сравнили средние значения бипариетального (БПР), лобно-затылочного размеров (ЛЗР), окружности головы (ОГ) и живота (ОЖ) и длины бедра (ДБ) у плодов от женщин двух возрастных периодов и в зависимости от пола, а также интенсивность роста вышеперечисленных параметров в зависимости от пола плода и возрастного периода матери. ***Результаты.*** Исследование показало, что при первом скрининге среднее значение КТР плода не имело статистически значимых различий у женщин двух групп, а среднее значение ТВП у плодов женщин второго периода зрелого возраста было значимо больше. При сравнении фетометрических показателей, полученных при втором скрининге, выявлено значимое различие ЛЗР у плодов женщин двух возрастных периодов. При сравнении исследуемых фетометрических параметров в зависимости от пола плода выявлены значимые различия в большую сторону для плодов мужского пола. ***Заключение.*** Таким образом, фетометрия выявила неравномерный рост исследуемых параметров от промежуточного к позднему плодному периоду, в том числе в зависимости от пола плода и возраста матери.

Ключевые слова: плод, фетометрия, экстракорпоральное оплодотворение, интенсивность роста

INTRODUCTION

Since the first in vitro fertilization (IVF) procedure was performed, extensive experience has been accumulated in the use of assisted reproductive technologies (ART). Numerous randomized controlled trials have demonstrated the efficacy and safety of ART [1]. However, the study of pregnancy outcomes following IVF, including fetal development, remains relevant. The fundamental question remains unresolved: whether to consider IVF-conceived pregnancy as physiological (i.e., identical to spontaneous conception) or to regard it as a pregnancy with an inherently higher risk of perinatal complications [2].

On one hand, IVF success is conventionally determined by ultrasound-confirmed intrauterine pregnancy.

On the other hand, current practice places greater importance on evaluating outcomes through the birth of a healthy term infant with preserved maternal health.

Early studies suggested an association between IVF procedures and adverse perinatal outcomes, including low birth weight, preterm delivery, placental abruption, congenital anomalies, and perinatal mortality [3]. More recent data indicate that women who conceive through IVF experience higher rates of perinatal complications compared to the general population [4]. Currently, IVF is increasingly being utilized by women of advanced maternal age.

Consequently, a critical priority for obstetric-gynecologic care is to enhance the quality and efficacy of medical management during pregnancy, delivery, and the postpartum period [3], as well as to optimize prenatal fetal diagnostics — particularly standard ultrasound fetal biometry [5].

Fetal ultrasound screening holds a pivotal position in prenatal diagnostics [6]. Standard screening examinations were traditionally performed at 11–14, 18–21, and 30–34 gestational weeks. Retrospective analysis demonstrates the feasibility of fetal assessment in women with IVF-conceived pregnancies during intermediate and late fetal development stages.

AIM

The aim of the study was to evaluate fetometric parameters in pregnancies resulting from in vitro fertilization in the Orenburg region.

MATERIALS AND METHODS

The study sample comprised 462 electronic pregnancy and delivery records following IVF between 2016–2022. All cases were stratified by maternal age: first period of mature age (FPA, 20–34 years) and second period of mature age (SPA, 35–45 years) — 343 and 119 cases, respectively. For the second and third trimester screenings, the sample was equally divided by fetal sex (50% male and 50% female). Inclusion criteria were: women with singleton IVF pregnancies, term deliveries, and without severe extragenital pathology.

Using retrospective analysis of electronic pregnancy and delivery records, we analyzed standardized fetal biometry data obtained during routine ultrasound screenings at 11–14, 18–22, and 30–34 gestational weeks[1]. It should be noted that the third (mandatory) screening was discontinued as of January 1, 2021[2].

We analyzed 1,333 ultrasound examination protocols across different pregnancy trimesters. For first-trimester screening (450 scans), we measured crown-rump length (CRL) and nuchal translucency (NT). Second-trimester screening (456 scans) included assessment of biparietal diameter (BPD), occipitofrontal diameter (OFD), head circumference (HC), abdominal circumference (AC), and femur length (FL). The same parameters as the second trimester (BPD, OFD, HC, AC, FL) were evaluated in third-trimester scans (427 examinations).

All ultrasounds were performed using Voluson S10 systems with RAB6-RS transducers alongside Samsung HS70(A) machines equipped with 5–9 MHz microconvex transducers.

The study was conducted at the Medical-Genetic Counseling Center of Orenburg Regional Clinical Hospital No. 2 and the Department of Human Anatomy, Orenburg State Medical University (Ministry of Health of Russian Federation. The research protocol was approved by the Local Ethics Committee of Orenburg State Medical University (Protocol No. 308, dated November 28, 2022).

For Groups 1 and 2, as well as for male and female fetuses, growth intensity rates for the aforementioned fetometric parameters were calculated from intermediate to late fetal periods using the formula (Sokolov V.V. et al., 2005):

$$GI = \frac{(D_2 - D_1)}{0{,}5 \cdot (D_1 + D_2)} \cdot 100\%.$$

where D_2 represents the parameter value in the late fetal period and D_1 and epresents the value in the intermediate fetal period.

All morphometric data underwent variation-statistical processing using MS Excel and IBM SPSS Statistics soft-

[1] Prikaz Ministerstva zdravookhraneniya Rossiyskoy Federatsii ot 28 dekabrya 2000 goda № 457 “O sovershenstvovanii prenatal’noy diagnostiki v profilaktike nasledstvennykh i vrozhdennykh zabolevaniy u detey”. Available at: https://base.garant.ru/4177325/ (accessed: 16.03.2025).

[2] Prikaz Ministerstva zdravookhraneniya Rossiyskoy Federatsii ot 20 oktyabrya 2020 goda № 1130n “Ob utverzhdenii Poryadka okazaniya meditsinskoy pomoshchi po profilyu «akusherstvo i ginekologiya»”.Available at: https://base.garant.ru/74840123/ (accessed: 16.03.2025).

ware, version 20.0. We determined the mean value (X), standard deviation (Sx), minimum (min) and maximum (max) values. The significance of differences between compared parameters was assessed using Student's t-test, with the statistical significance level (p) set at 0.05 as the critical threshold in our study.

RESULTS

Ultrasound scanning provides detailed images of nearly all fetal structures and enables their qualitative and quantitative assessment. Ultrasound fetometry serves as a prenatal diagnostic method that forms the basis for establishing regional standards of fetal growth evaluation.

Fetometry data at different gestational timepoints in IVF-conceived pregnancies are presented in Table 1.

During first-trimester screening, analysis of women in first and second mature age periods revealed mean CRL values of 63.6±6.6 mm (FPA group) and 64.7±7.8 mm (SPA group). These measurements showed no statistically significant intergroup difference (p=0.246).

Mean NT measurements were 1.6±0.3 mm in the FPA group compared to 1.7±0.3 mm in the SPA group, demonstrating statistically significant differences (p=0.045), with higher values observed in women of SPA.

During second-trimester screening (without accounting for fetal sex), women in first and second mature age periods following IVF demonstrated the following mean fetal biometry values in the intermediate fetal period. For pregnant women of FPA biparietal diameter, occipitofrontal diameter, head circumference, abdominal circumference, and femur length measured 48.7±3.5 mm, 64.1±3.9 mm, 181.9±10 mm, 156.2±9.6 mm, and 33.7±2.5 mm, respectively. For pregnant women of SPA, these parameters were 48.8±2.8 mm, 65.1±3.8 mm, 183.7±9.2 mm, 157.4±10.5 mm, and 34.1±3.1 mm, respectively.

Comparative analysis revealed no significant differences in BPD, HC, AC, or FL between age groups, while

Table 1

Fetal parameters in pregnancy after in vitro fertilization

Таблица 1

Фетометрические параметры при беременности после экстракорпорального оплодотворения

Первый скрининг / First screening (n=450)			
Параметр / Parameter	X±Sx	min	max
КТР, мм / CRL, mm	63,9±6,9	48	83
ТВП, мм / NT, mm	1,6±0,3	0,8	3,2
Срок беременности, недель / Gestational age, weeks	12,6±0,5	11	14
Второй скрининг / Second screening (n=456)			
БПР, мм / BPD, mm	49±3,3	43	54
ЛЗР, мм / OFD, mm	65±3,9	56	73
ОГ, мм / HC, mm	183,3±9,9	160	205
ОЖ, мм / AC, mm	158,1±9,9	134	178
ДБ, мм / FL, mm	34±2,6	30	41
Срок беременности, недель / Gestational age, weeks	20,7±0,8	19,1	22,6
Третий скрининг / Third screening (n=427)			
БПР, мм / BPD, mm	80,2±3,7	74	89
ЛЗР, мм / OFD, mm	99,8±4,8	87	111
ОГ, мм / HC, mm	287±12,3	256	315
ОЖ, мм / AC, mm	272±14,3	228	296
ДБ, мм / FL, mm	60,5±4	53	66
Срок беременности, недель / Gestational age, weeks	31,3±1,1	29	33,6

Note: BPD — biparietal diameter of the head; FL — femur length; CRL — coccygeal-parietal size; NT — nuchal translucency thickness; OFD — occipitofrontal diameter; HC — head circumference; AC — abdominal circumference.

Примечание: БПР — бипариетальный размер головы; ДБ — длина бедренной кости; КТР — копчико-теменной размер; ТВП — толщина воротникового пространства; ЛЗР — лобно-затылочный размер; ОГ — окружность головы; ОЖ — окружность живота.

OFD showed statistically significant greater values in the advanced maternal age cohort.

Evaluation of biparietal diameter, occipitofrontal diameter, head circumference, abdominal circumference, and femur length during third-trimester screening in the late fetal period revealed the following mean values for women of FPA: 79.4±3.7 mm, 100.2±4.8 mm, 287.3±12.3 mm, 270.1±14.3 mm, and 59.4±4 mm, respectively. For women of SPA, the corresponding fetal parameters were 79.2±3.7 mm, 100.6±4.8 mm, 287.2±12 mm, 270.2±14.9 mm, and 59.7±2.8 mm, respectively.

The results of screening examinations performed at established gestational timepoints, showing fetal size variations by maternal age and fetal sex, are presented in Table 2.

Table 2

Size of male and female fetuses

Таблица 2

Размеры плодов мужского и женского пола

Параметр / Parameter	Срок беременности, недель / Gestational age, weeks	Мужской пол / Male gender, n=231	Женский пол / Female gender, n=231	Значимость различий / Significance of differences, p
		X±Sx	X±Sx	
18–22 недели / 18–22 weeks				
ППЗВ / FPA, n=343				
БПР, мм / BPD, mm	20,8±0,8	49,7±3,7	47,7±3	<0,001
ЛЗР, мм / OFD, mm		65,2±4	63±3,5	<0,001
ОГ, мм / HC, mm		185,1±10,1	178,8±8,9	<0,001
ОЖ, мм / AC, mm		159±9	153,5±9,3	<0,001
ДБ, мм / FL, mm		34,2±2,6	33,3±2,2	0,002
ВПЗВ / SPA, n=119				
БПР, мм / BPD, mm	20,6±0,8	48,8±3,2	48,9±2,4	0,945
ЛЗР, мм / OFD, mm		65,9±4,5	64,2±2,8	0,02
ОГ, мм / HC, mm		185,1±10,5	182,2±7,2	0,099
ОЖ, мм / AC, mm		158,9±11,7	155,6±8,5	0,09
ДБ, мм / FL, mm		34±3	34,2±3,1	0,72
30–34 недели / 30–34 weeks				
ППЗВ / FPA, n=343				
БПР, мм / BPD, mm	31,6±1	80,3±3,7	78,4±3,5	<0,001
ЛЗР, мм / OFD, mm		100,6±5	99,8±4,5	0,172
ОГ, мм / HC, mm		289,8±12,7	284,9±11,4	0,001
ОЖ, мм / AC, mm		272±14,4	268,3±14	0,02
ДБ, мм / FL, mm		59,5±4,3	59,2±3,6	0,55
ВПЗВ / SPA, n=119				
БПР, мм / BPD, mm	31,1±1,2	79,8±3,9	78,5±3,1	0,05
ЛЗР, мм / OFD, mm		101,4±4,9	99,7±4,7	0,07
ОГ, мм / HC, mm		290±12,5	283,9±10,6	0,009
ОЖ, мм / AC, mm		271,8±14,5	268,2±15,4	0,2
ДБ, мм / FL, mm		59,7±3	59,8±2,6	0,79

Note: BPD — biparietal diameter of the head; SPA — second period of mature age; FL — femur length; OFD — occipitofrontal diameter; HC — head circumference; AC — abdominal circumference; FPA — first period of adulthood.

Примечание: БПР — бипариетальный размер головы; ВПЗВ — второй период зрелого возраста; ДБ — длина бедренной кости; ЛЗР — лобно-затылочный размер; ОГ — окружность головы; ОЖ — окружность живота; ППЗВ — первый период зрелого возраста.

Table 2 demonstrates that during 18–22-week screening, women of FPA showed significantly greater mean values for all measured parameters in male fetuses compared to female fetuses. In contrast, at 30–34-week screening during the late fetal period, no statistically significant differences were observed in mean BPD, OFD, HC, AC, or FL values between male and female fetuses across both maternal age groups.

Growth intensity analysis of fetal biometric parameters was conducted between the second and third trimester screenings.

The study revealed non-uniform changes in fetal biometric parameters during transition from intermediate to late fetal periods. Growth rates varied significantly across measured parameters, between the two maternal age groups undergoing IVF, and between fetal sexes.

The highest growth intensity was observed in FL and AC, while the lowest rates occurred in OFD and HC, with an 11.8% difference between maximum and minimum values. These findings indicate that during the intermediate fetal period, the most pronounced growth occurs in lower body segments and free lower extremities (thighs).

Growth rates (BPD, OFD, HC, AC, FL) in both maternal age groups were as follows: FPA — 48.2%, 43.4%, 44.5%, 53.4%, 55.2% and SPA — 47.7%, 43.0%, 44.0%, 52.6%, 54.7%, respectively. Comparative analysis revealed consistently higher growth intensity across all parameters in women of FPA, with the most pronounced difference observed in biparietal diameter and the smallest difference in occipitofrontal diameter.

Growth rates for BPD, OFD, HC, AC, and FL from intermediate to late fetal periods in **male fetuses** of women of **FPA** were 47.1%, 42.7%, 44.1%, 52.4%, and 54.0%, respectively (Figure 1). The highest growth intensity was recorded for femur length and abdominal circumference, while the lowest rates were observed for occipitofrontal diameter. The difference between the highest and lowest values values was 11.3%.

Growth rates for BPD, OFD, HC, AC, and FL from intermediate to late fetal periods in **female fetuses** of women of **FPA** were 48.7%, 45.2%, 45.8%, 54.4%, and 56.0%, respectively. The highest growth intensity was observed in femur length, while the lowest rates were recorded for occipitofrontal diameter. The difference between maximum and minimum values was 10.8%.

Comparative analysis between male and female fetuses of women of FPA revealed consistently higher growth rates across all parameters in female fetuses.

Growth rates for BPD, OFD, HC, AC, and FL from intermediate to late fetal periods in **male fetuses** of women of **SPA** were 48.2%, 42.4%, 44.2%, 52.4%, and 54.9%, respectively. The highest growth intensity was observed in femur length, while the lowest rates were recorded for

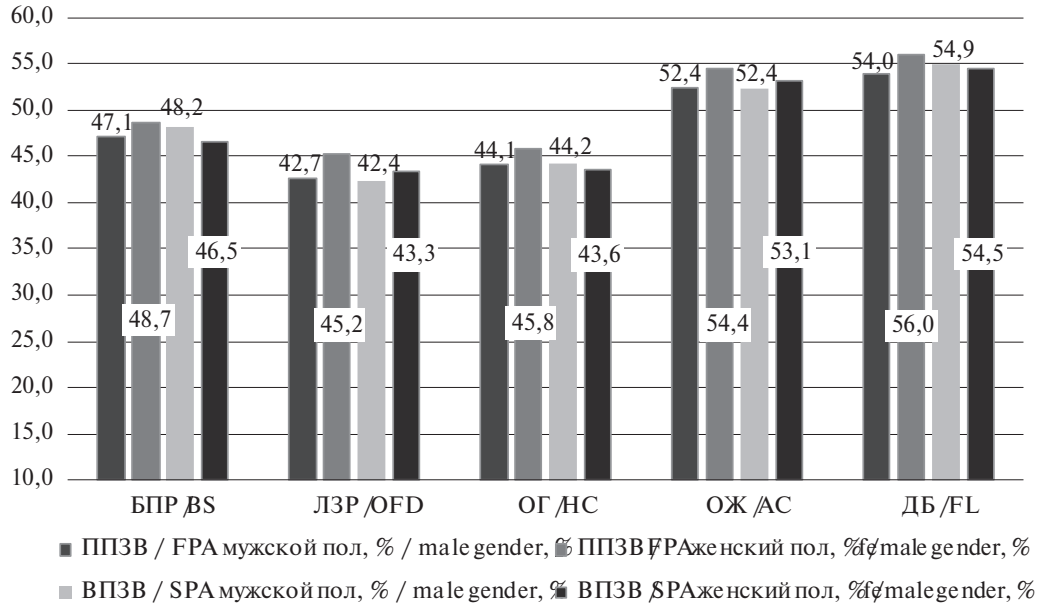

Fig. 1. Growth intensity of the main fetal parameters in first period of adulthood (FPA) and second period of mature age (SPA) women depending on the sex of the fetus (%). BPD — biparietal diameter; FL — femur length; OFD — occipitofrontal diameter; HC — head circumference; AC — abdominal circumference

Рис. 1. Интенсивность роста основных параметров плода у женщин первого периода зрелого возраста (ППЗВ) и второго периода зрелого возраста (ВПЗВ) в зависимости от пола плода (%). БПР — бипариетальный размер головы; ДБ — длина бедренной кости; ЛЗР — лобно-затылочный размер; ОГ — окружность головы; ОЖ — окружность живота

occipitofrontal diameter. The difference between the highest and lowest values was 12.5%.

Growth rates for BPD, OFD, HC, AC, and FL from intermediate to late fetal periods in **female fetuses** of women of **SPA** were 46.5%, 43.3%, 43.6%, 53.1%, and 54.5%, respectively. The highest growth intensity was observed in femur length, while the lowest rates were recorded for occipitofrontal diameter. The difference between maximum and minimum values was 11.2%.

DISCUSSION

This study demonstrated no significant differences in crown-rump length between fetuses of the two maternal age groups, with all mean values falling within the normal reference range at 12.6±0.5 weeks of gestation [7]. In contrast, nuchal translucency measurements showed statistically significant differences between first and second mature age period groups, being greater in the latter, though still remaining within normal physiological ranges [7, 8].

Analysis of fetal biometric parameters at 18–22 and 30–34 weeks of gestation revealed no significant differences in mean values of biparietal diameter, occipitofrontal diameter, head circumference, abdominal circumference, and femur length when compared to regional fetal growth standards [9, 10]. These findings underscore the importance of using region-specific reference norms for ultrasound assessment of fetal growth [11, 12]. Sex-based comparison demonstrated significantly larger mean biometric measurements in male fetuses, consistent with data from the population-based prospective birth cohort study (2016), which confirmed that from the second trimester onward, head circumference and abdominal circumference were consistently greater in male fetuses than in female [13].

The highest growth rates were observed for femur length and abdominal circumference, while the lowest rates were recorded for occipitofrontal diameter and head circumference. The difference between the highest and lowest values was 11.8%. These findings support our data demonstrating that "...the segments of the free lower extremity (thigh and shin) show maximal longitudinal growth during the intermediate fetal period" [14]. Growth patterns also differed significantly between sexes, corroborating findings by Z.A. Broere-Brown et al. that in singleton pregnancies, male fetuses exhibit distinct growth dynamics compared to females [13].

CONCLUSION

1. During first-trimester screening, crown-rump length and nuchal translucency measurements in IVF-conceived fetuses were within normal reference ranges.

2. Second- and third-trimester evaluations demonstrated that biparietal diameter, occipitofrontal diameter, head circumference, abdominal circumference, and femur length in IVF pregnancies conformed to both standard norms and regional nomograms. Sex-based comparisons revealed systematically larger biometric values in male fetuses.

3. Fetal biometry revealed non-uniform growth across all studied parameters from intermediate to late fetal periods, with sex-specific growth rate variations characteristic of IVF-conceived fetuses.

ADDITIONAL INFORMATION

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

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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ASSESSMENT OF HEMODYNAMIC STATUS IN ANIMALS WITH BURN SHOCK AND PROLONGED TISSUE COMPRESSION SYNDROME AGAINST THE BACKGROUND OF ANTIHYPOXANT APPLICATION

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Abstract. ***Introduction.*** Burn disease and compartment syndrome, despite differences in etiological factors, have similar pathogenesis links that determine the severity of the patient's condition and high mortality rates. In this regard, the study of their mutual aggravation and possible ways to correct developing disorders is relevant. ***Purpose of the study*** — to study the functional state of the cardiovascular system in animals with burn disease and compartment syndrome against the background of the use of antihypoxants. ***Materials and methods of the study.*** The study included 180 small laboratory animals (rats), which modeled extensive deep skin burns and compartment syndrome. All rodents were divided into three equal groups taking into account the composition of infusion therapy: saline (0.9% NaCl), antihypoxants mufasol and polyoxyfumarin. In the course of the work, stroke volume and minute blood volume, as well as the effectiveness of succinate dehydrogenase, were studied. Statistical data processing was performed using generally accepted methods of variation statistics. The alternative hypothesis was accepted at $p < 0.05$. ***Research results and discussion.*** It was found that when using polyoxyfumarin, the stroke volume and minute blood volume were higher by 25% ($p < 0.05$) and 21.4% ($p < 0.05$) relative to the use of mufasol and by 67% ($p < 0.05$) and 40% ($p < 0.05$) relative to the introduction of sodium chloride. The use of the Parkland formula + 40% made it possible to increase the overall effectiveness of infusion therapy by 39% regardless of its composition. The effect of polyoxyfumarin and mufasol on the activity of succinate dehydrogenase was established. On the second day after the injury, the analyzed indicator was 32.1 and 34.2, respectively, which is 54.7% ($p < 0.05$) and 71.4% ($p < 0.05$) relative to the introduction of sodium chloride. ***Conclusion.*** The use of antihypoxants as part of anti-shock infusion therapy for extensive burns and prolonged tissue compression syndrome improves the condition of the cardiovascular system and myocardium.

Keywords: skin burn, deep burns, burn disease, prolonged tissue compression syndrome, crush syndrome, antihypoxants, infusion therapy, hemodynamics

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ОЦЕНКА СОСТОЯНИЯ ГЕМОДИНАМИКИ У ЖИВОТНЫХ С ОЖОГОВЫМ ШОКОМ И СИНДРОМОМ ДЛИТЕЛЬНОГО СДАВЛЕНИЯ ТКАНЕЙ НА ФОНЕ ПРИМЕНЕНИЯ АНТИГИПОКСАНТОВ

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Резюме. ***Введение.*** Ожоговая болезнь и синдром длительного сдавления тканей, несмотря на различия в этиологических факторах, обладают схожими звеньями патогенеза, определяющими тяжесть состояния пациента и высокие показатели летальности. В связи с чем изучение вопросов их взаимного отягощения и возможных путей коррекции развивающихся нарушений является актуальным. ***Цель исследования*** — изучить функциональное состояние сердечно-сосудистой системы у животных с ожоговой болезнью и синдромом длительного сдавления тканей на фоне применения антигипоксантов. ***Материалы и методы исследования.*** В исследование включено 180 мелких лабораторных животных (крыс), которым моделировались обширные глубокие ожоги кожи и синдром длительного сдавления тканей. Все грызуны были разделены на три равные группы с учетом состава инфузионной терапии: физиологический раствор (0,9% NaCl), антигипоксанты муфасол и полиоксифумарин. В ходе работы изучались ударный объем и минутный объем крови, а также эффективность сукцинатдегидрогеназы. Статистическая обработка данных осуществлялась общепринятыми методами вариационной статистики. Альтернативная гипотеза принималась при $p < 0,05$. ***Результаты исследования и обсуждения.*** Установлено, что при использовании полиоксифумарина показатели ударного объема и минутного объема крови оказались выше на 25% ($p < 0,05$) и 21,4% ($p < 0,05$) относительно применения муфасола и на 67% ($p < 0,05$) и 40% ($p < 0,05$) относительно введения натрия хлорида. Использование формулы Паркланда + 40% позволило увеличить общую эффективность инфузионной терапии на 39% независимо от ее состава. Констатировано влияние полиоксифумарина и муфасола на активность сукцинатдегидрогеназы. На вторые сутки после травмы анализируемый показатель составил, соответственно, 32,1 и 34,2, что на 54,7% ($p < 0,05$) и 71,4% ($p < 0,05$) больше относительно введения натрия хлорида. ***Заключение.*** Назначение антигипоксантов в составе противошоковой инфузионной терапии при обширных ожогах и синдроме длительного сдавления тканей улучшает состояние сердечно-сосудистой системы и миокарда.

Ключевые слова: ожог кожи, глубокие ожоги, ожоговая болезнь, синдром длительного сдавления тканей, краш-синдром, антигипоксанты, инфузионная терапия, гемодинамика

INTRODUCTION

Burn injuries represent a major medical, social, and economic challenge [1]. This is evidenced by their high incidence in domestic, occupational, and military settings. Globally, over 180,000 fatal burn injury cases are reported annually [2].

Extensive high-temperature injuries are accompanied by disturbances in the homeostasis system. A complex set of interrelated pathophysiological changes occurring in the body leads to the development of burn disease, which is characterized by severe hypovolemia, endotoxemia and exotoxemia, progressing to sepsis [3].

Modern combat trauma is characterized by a high frequency of not only thermal but also mechanical injuries. The destruction of fortifications and damage to equipment often lead to compression of distal limb segments with subsequent development of crush syndrome, tissue ischemia, and severe endotoxicosis. The latter ultimately determines the high mortality rate in this type of injury [4].

The simultaneous development of burn disease and crush syndrome contributes to the formation of intersecting vicious cycles of pathogenesis, significantly increasing the likelihood of an unfavorable treatment outcome for the victim [5]. Disruption of respiratory chains has the most profound effect on energy-dependent tissues of the body, particularly the myocardium. Maintaining the contractile function of the heart muscle is impossible without adequate supply of metabolites and oxygen. Changes in their concentrations contribute to the development of not only functional but also structural disorders [6]. Meanwhile, existing intensive care protocols fail to account for the developing syndrome of mutual aggravation of mechanical and burn shock, as well as pronounced processes of tissue hypoxia and ischemia.

Currently, specialists have access to various metabolic drugs that optimize respiratory chain function. However, despite their high efficacy demonstrated in certain studies, these groups of medications have not gained widespread clinical use due to insufficient evidence base [7]. Consequently, the present study holds significant relevance and importance for the healthcare system.

AIM

The aim of this study was to assess the functional state of the cardiovascular system in animals with burn disease and crush syndrome during administration of antihypoxants..

MATERIALS AND METHODS

The experimental study was conducted at the Department of Pathological Physiology (Head — Professor V.N. Tsygan), the Clinic of Experimental and Biological Models, and the Research Laboratory of Military Surgery at the Research Center (Director — Professor K.P. Golovko) of the S.M. Kirov Military Medical Academy. The study included 180 small adult white outbred rats of both sexes weighing 240–250 g. All animals were divided into three equal groups according to the composition of infusion therapy: sodium chloride, and the antihypoxants mufasol and polyoxufumarin. All animal experiments were performed in strict compliance with Directive 2010/63/EU of the European Parliament and of the Council (22 September 2010) on the protection of animals used for scientific purposes and Federal Law No. 498-FZ of the Russian Federation (27 December 2018, as amended 27 December 2019) “On Responsible Treatment of Animals and Amendments to Certain Legislative Acts.”

For analgesia prior to inducing extensive burns and crush syndrome, animals received a 2% xylazine solution at a dose of 20 mg/kg. Crush syndrome in rats was reproduced by compressing the soft tissues of either right or left thigh for 4 hours using specialized metal clamps applying 8–10 kg/cm² pressure over a 5 cm² area. Dorsal skin burns were modeled using thermal radiation from a KDB-22 light lamp (500 W power output). The lamp was positioned 2.5 cm from the body surface with an exposure duration of 20 seconds.

Shock therapy was administered through infusion of sodium chloride, mufasol, and polyoxufumarin. The needle was inserted intraperitoneally via a parenteral access in the thigh region. Fluid volumes were calculated using the Parkland formula:

$$V\ (inf)\ (mL) = 4 \cdot M \cdot \%,$$

where M — animal body weight (kg); % — burn surface area (absolute units).

The effectiveness of treatment methods was analyzed using the following parameters: stroke volume and minute blood volume, along with succinate dehydrogenase enzyme activity efficiency. Database processing followed conventional methods of variation statistics in three stages: research model development and study design, implementation and data collection, and statistical processing using MS Excel and SPSS Statistics 17.0 software. Quantitative parameters were assessed using the nonparametric Mann–Whitney U-test. The alternative hypothesis was accepted at a significance level of $p < 0.05$.

RESULTS AND DISCUSSION

The results of hemodynamic parameter studies in small laboratory animals with burn disease and crush syndrome, receiving Parkland formula-calculated infusion therapy, are presented in Table 1.

As shown in Table 1, no statistically significant differences in the analyzed parameter were observed between different treatment groups at 15 minutes post-infusion initiation. After one hour of observation, the polyoxufumarin-treated animal group maintained a stroke volume of 0.05±0.003 mL, representing a 25% ($p < 0.05$) increase compared to mufasol treatment and a 66% ($p < 0.05$) increase versus normal saline administration.

The study of minute blood volume revealed no statistically significant differences between the analyzed groups after 15 minutes of infusion therapy. Extending the treatment duration to 60 minutes demonstrated the greatest efficacy of polyoxufumarin infusion. In this animal group, the minute blood volume reached 81.5±6.9 mL/kg/min, which was 21.4% greater ($p < 0.05$) compared to mufasol and 37.9% higher ($p < 0.05$) than normal saline infusion.

At the second stage, we evaluated the efficacy of shock therapy using different pharmacological agents, with infusion volumes calculated according to the Parkland formula + 40% (Table 2).

The results presented in Table 2 indicate that stroke volume during high-volume infusion therapy showed no statistically significant differences between study groups during the first 15 minutes post-trauma. However, one-hour administration of polyoxufumarin maintained this parameter at 0.08±0.003 mL. In animals receiving mufasol and sodium chloride, stroke volume was 37.5% ($p < 0.05$) and 50% ($p < 0.05$) lower, respectively.

Evaluation of minute blood volume revealed comparable findings. During the first 15 minutes of infusion therapy, no statistically significant differences were observed among the study groups. After 60 minutes of observation, the highest minute blood volume (81.6±6.8 mL/kg/min) was recorded in the polyoxufumarin group — representing an 18% ($p < 0.05$) increase compared to mufasol and a 29.3% ($p < 0.05$) increase compared to sodium chloride administration.

Analysis of succinate dehydrogenase activity in cardiomyocytes of rats with burn disease and crush syndrome receiving Parkland formula +40% calculated infusion therapy is presented in Table 3.

Data from Table 3 demonstrate that during the first 24 hours post-resuscitation for burn shock and crush syndrome, polyoxufumarin administration achieved the highest succinate dehydrogenase activity in rat cardiomyocytes (38.7±3.2 U/mg). This corresponded to a 6% increase over mufasol ($p > 0.05$) and a 71.2% elevation compared to sodium chloride ($p < 0.05$). At the 48-hour post-administration timepoint, the observed trend persisted. The highest enzyme activity was recorded with polyoxufumarin administration (34.2±4.2 U/mg), representing a 6.5% increase compared to mufasol ($p > 0.05$). Sodium chloride infusion showed the lowest values (12.6±1.2 U/mg).

Table 1

Hemodynamic parameters in animals with burn disease and crush syndrome depending on the composition of infusion therapy, calculated using the Parkland formula

Таблица 1

Параметры гемодинамики у животных с ожоговой болезнью и синдромом длительного сдавления в зависимости от состава инфузионной терапии, рассчитанной по формуле Паркланда

Анализируемые параметры / Analyzed parameters	Группы наблюдения / Observation groups	После травмы, перед началом инфузии / After injury, before starting infusion	После начала инфузии, через / After the start of the infusion, after	
			15 минут / 15 min	1 час / 1 hour
Ударный объем, мл / Stroke volume, ml	Натрия хлорид / Sodium chloride	0,06±0,01	0,06±0,01	0,03±0,006
	Мафусол / Mafusol	0,06±0,01	0,06±0,01 [1]	0,04±0,005
	Полиоксифумарин / Polyoxyfumarin	0,07±0,01	0,05±0,01	0,05±0,003 [1, 2]
Минутный объем крови, мл/кг/мин / Minutes volume, ml/kg/min	Натрия хлорид / Sodium chloride	114,2±9,1	93,6±7,2	59,1±6,3
	Мафусол / Mafusol	107,1±6,9	92,2±8,8	67,1±7,1
	Полиоксифумарин / Polyoxyfumarin	106,1±8,3	100,5±6,2	81,5±6,9 [1,2]

Note. Mann–Whitney U-test: [1] — $p < 0.05$ compared to the group receiving sodium chloride solution; [2] — $p < 0.05$ compared to the group receiving mufasol.
Примечание. U-критерий Манна–Уитни: [1] — $p < 0,05$ по сравнению с группой, получавшей раствор натрия хлорида; [2] — $p < 0,05$ по сравнению с группой, получавшей муфасол.

Table 2

Hemodynamic parameters in animals with burn disease and crush syndrome depending on the composition of infusion therapy, calculated using the Parkland formula + 40%

Таблица 2

Параметры гемодинамики у животных с ожоговой болезнью и синдромом длительного сдавления в зависимости от состава инфузионной терапии, рассчитанной по формуле Паркланда + 40%

Анализируемые параметры / Analyzed parameters	Группы наблюдения / Observation groups	После травмы, перед началом инфузии / After injury, before starting infusion	После начала инфузии, через / After the start of the infusion, after	
			15 минут / 15 min	1 час / 1 hour
Ударный объем, мл / Stroke volume, ml	Натрия хлорид / Sodium chloride	0,07±0,01	0,06±0,01	0,04±0,004
	Мафусол / Mafusol	0,06±0,01	0,06±0,01	0,05±0,006
	Полиоксифумарин / Polyoxyfumarin	0,07±0,01	0,06±0,01	0,08±0,003[1, 2]
Минутный объем крови, мл/кг/мин / Minutes volume, ml/kg/min	Натрия хлорид / Sodium chloride	114,1±8,2	94,5±7,9	63,1±5,8
	Мафусол / Mafusol	108,3±7,1	101,8±8,4	69,1±6,3
	Полиоксифумарин / Polyoxyfumarin	107,2±7,9	90,3±9,1	81,6±6,8[1, 2]

Note. Mann–Whitney U-test: [1] — p <0.05 compared to the group receiving sodium chloride solution; [2] — p <0.05 compared to the group receiving mufasol.
Примечание. U-критерий Манна–Уитни: [1] — p <0,05 по сравнению с группой, получавшей раствор натрия хлорида; [2] — p <0,05 по сравнению с группой, получавшей муфасол.

Table 3

Activity of the enzyme succinate dehydrogenase in animals with burn disease and crush syndrome depending on the composition of infusion therapy, calculated using the Parkland formula + 40%

Таблица 3

Активность фермента сукцинатдегидрогеназы у животных с ожоговой болезнью и синдромом длительного сдавления в зависимости от состава инфузионной терапии, рассчитанной по формуле Паркланда + 40%

После травмы, час / After the injury, an hour	Активность фермента (M±m) после введения / Enzyme activity (M±m) after injection		
	натрия хлорида / sodium chloride	мафусола / mufasol	полиоксифумарина / polyoxyfumarin
24	22,6±2,4	36,5±4,4 [1]	38,7±3,2[1]
48	12,6±1,2	32,1±5,2 [1]	34,2±4,2[1]

Note. Mann–Whitney U-test: [1] — p <0.05 compared to the group receiving sodium chloride solution.
Примечание. U-критерий Манна–Уитни: [1] — p <0,05 по сравнению с группой, получавшей раствор натрия хлорида.

CONCLUSION

1. Incorporation of antihypoxants into shock infusion therapy for burn shock and crush syndrome helps maintain systemic hemodynamic parameters.

2. The conventional Parkland formula-calculated volume of antihypoxant infusion for burn shock and crush syndrome proves insufficient to compensate for systemic pathophysiological disturbances.

Our findings demonstrate the therapeutic potential of including antihypoxants in intensive care protocols for patients with mechano-thermal shock. However, despite their proven efficacy, this therapeutic approach requires further in-depth investigation.

ADDITIONAL INFORMATION

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

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

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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OSTEOSARCOMA OF THE SPINE — MODERN CLASSIFICATION, THE ROLE OF THE mTOR SIGNALING PATHWAY, PROSPECTS FOR THERAPY (LITERATURE REVIEW)

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Abstract. Despite their rare occurrence, spinal tumors pose a serious problem for public health due to the difficulty of their diagnosis and treatment. Neoplasms of the spine are divided into primary and secondary tumors (metastases) by origin. Osteosarcoma is of great interest among primary tumors. Osteosarcoma is a malignant osteogenic tumor consisting of neoplastic cells that produce osteoid. Osteosarcoma of the spine develops quite rarely, however, it is characterized by a high degree of malignancy, local aggressiveness, a tendency to metastasis, as well as a long asymptomatic course. The prognosis for osteosarcoma of the spine remains extremely unfavorable. All this indicates the need to develop new methods and treatment regimens for osteosarcoma. One of the promising areas is the development of drugs that affect the intracellular signaling pathway mTOR. mTOR is a serine/threonine protein kinase that forms a catalytic subunit of two different protein complexes: mTORC1 and mTORC2. It has been established that this signaling pathway regulates the processes of vital activity of the cell and the entire organism at the deepest level. Its hyperactivation plays an important role in carcinogenesis, including in the pathogenesis of osteosarcoma. In this regard, it was proposed to use drugs that affect the mTOR signaling pathway for its therapy. Such drugs include: rapamycin, everolimus, temsirolimus, catalytic inhibitors of mTOR (MLN0128 and PP242), micro-RNA (miR-223 and miR-101), oleanolic acid, spautin-1, metformin and so on. It is proposed to combine these drugs with classical chemotherapy to achieve better results in the treatment of osteosarcoma. At the moment, it is necessary to select rational combinations and dosages of drugs.

Keywords: osteosarcoma of the spine, mTOR signaling pathway, mTORC1, mTORC2, rapamycin, autophagy inhibitors, metformin, catalytic inhibitors of mTOR, PP242, classification of spinal neoplasms

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ОСТЕОСАРКОМА ПОЗВОНОЧНИКА — СОВРЕМЕННАЯ КЛАССИФИКАЦИЯ, РОЛЬ СИГНАЛЬНОГО ПУТИ mTOR, ПЕРСПЕКТИВЫ ТЕРАПИИ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме. Несмотря на редкую встречаемость, опухоли позвоночника представляют серьезную проблему для здравоохранения по причине сложности их диагностики и лечения. Новообразования позвоночного столба в зависимости от происхождения подразделяются на первичные и вторичные опухоли, или метастазы. Среди первичных опухолей большой интерес вызывает остеосаркома, которая представляет собой злокачественную остеогенную опухоль, состоящую из неопластических клеток, которые продуцируют остеоид. Остеосаркома позвоночника развивается довольно редко, однако характеризуется высокой степенью злокачественности, местной агрессивностью, склонностью к метастазированию, а также длительным асимптомным течением. Прогноз при остеосаркоме позвоночника остается крайне неблагоприятным. Все это говорит о необходимости разработки новых методов и схем терапии остеосаркомы. Одним из перспективных направлений является разработка препаратов, воздействующих на внутриклеточный сигнальный путь mTOR. mTOR представляет собой серин / треониновую протеинкиназу, которая образует каталитическую субъединицу двух различных белковых комплексов: mTORC1 и mTORC2. Установлено, что данный сигнальный путь регулирует процессы жизнедеятельности клетки и всего организма на глубочайшем уровне. Его гиперактивация играет большую роль в канцерогенезе, в том числе в патогенезе остеосаркомы. В связи с этим было предложено использовать препараты, влияющие на сигнальный путь mTOR, для ее терапии. К таким препаратам относятся: рапамицин, эверолимус, темсиролимус, каталитические ингибиторы mTOR (MLN0128 и PP242), микро-РНК (miR-223 и miR-101), олеаноловая кислота, спаутин-1, метформин и т.д. Предлагается комбинировать данные препараты с классической химиотерапией для достижения лучших результатов в лечении остеосаркомы. В настоящий момент необходим подбор рациональных сочетаний и дозировок препаратов.

Ключевые слова: остеосаркома позвоночника, сигнальный путь mTOR, mTORC1, mTORC2, рапамицин, ингибиторы аутофагии, метформин, каталитические ингибиторы mTOR, PP242, классификация новообразований позвоночника

BACKGROUND

Spinal tumors remain a serious problem for public health care, which, despite their rare occurrence, are characterized by extreme complexity of their diagnosis and treatment. Thus, vertebral column neoplasms are diagnosed annually in 2.5–8.5 cases per 100,000 population, which is naturally much less frequent than degenerative-dystrophic diseases and traumas [1, 2]. In this regard, specialists often do not consider them as a possible reason for a patient's treatment. This lack of oncological caution may lead to delayed correct diagnosis and, consequently, to a later start of therapy [1].

The main method of treatment of spinal neoplasms remains surgical intervention, supplemented with chemotherapy and radiation therapy if the malignancy of the tumor is confirmed [3, 4]. The complex anatomical structure of this region requires the surgeon to have knowledge not only in traumatology and orthopedics, but also in neurosurgery, neurology, oncology, etc. A related issue is spinal cord tumors [5].

All the above-mentioned points to the significance and relevance of this problem, as well as the need to search for new methods of therapy of spinal neoplasms.

CLASSIFICATION

Spinal neoplasms are subdivided by origin into primary and metastatic (secondary neoplasms). Primary non-lymphoproliferative neoplasms of the spine account for about 5% of all bone tumors (excluding hemangiomas) [4, 6], and in turn are subdivided into benign and malignant neoplasms.

Benign neoplasms of the spine include enostosis, osteoid osteoma, osteoblastoma, aneurysmal bone cyst, osteochondroma, giant cell tumor (osteoblastoclastoma), vertebral hemangioma, notochord cell tumor, pneumatocyst, and Schmorl's cystic nodule [1, 7].

Enneking staging characterizes the activity of benign neoplasms. Stage 1 — latent, stage 2 — active and stage 3 — aggressive [8].

Malignant neoplasms of the spine are divided into nonmyeloproliferative — chondrosarcoma (7–12% of the total number of malignant neoplasms of the spine), Ewing sarcoma (8%), osteosarcoma (3–14%), chordoma (20%), and myeloproliferative — multiple myeloma, solitary plasmacytoma, lymphoma [4, 9].

The degree of malignancy, spread and presence of metastases determines the stage of malignant neoplasms according to Enneking. According to the stage, the type and volume of treatment are chosen [1, 8].

Secondary neoplasms account for about 96% of the total number of spinal tumors. The incidence of metastatic lesions of the spine in disseminated malignant neoplasms is very high. For breast cancer it is 68–74%, for prostate cancer it is 60–68%, for lung cancer it is 40–50%, for thyroid cancer it is 36–42%, for kidney cancer it is 35%, for salivary glands and ENT organs it is 12–22%, for bladder cancer it is 16%, for esophagus and stomach cancer it is 13%, for pancreas cancer it is 6–12%, for colon cancer it is 9%, for cervix and uterine body cancer it is 9%. Melanomas, lymphomas, and sarcomas metastasize to the spine less frequently [10, 11].

Classification of spinal neoplasms by origin and their Enneking staging are presented in Figure 1.

The localization and degree of tumor spread are described by the "Weinstein-Boriani-Biagini surgical staging system" [12], as well as the "surgical classification of spinal tumor lesions according to K. Tomita" [13] (Fig. 2).

Spinal cord tumors deserve special attention. In relation to the spinal cord and its membranes, tumors are divided into three groups:

- intradural intramedullary - those located in the thickness of the spinal cord;
- intradural extramedullary tumors, which lie outside the spinal cord and inside the dura mater;
- extradural tumors located outside the dura mater [14].

Sometimes tumors growing from vertebral column masses or surrounding tissues, when they penetrate the spinal canal and compress the spinal cord, are also referred to as extradural spinal cord tumors [5].

In relation to the length of the spinal cord, neoplasms of the cervical, thoracic, lumbar, and sacrococcygeal sections are distinguished. Craniospinal tumors and cauda equina tumors are distinguished separately [5] (Fig. 3).

PRIMARY NEOPLASMS OF THE SPINE

Primary neoplasms of the spine have different histogenesis. There are tumors of bone, fat, fibrous, nervous tissue, nerve sheaths, adjacent paravertebral soft tissues, and lymphatic vessels [4, 15].

As mentioned above, primary spinal neoplasms are quite rare compared to secondary neoplasms and account for only 4% of the total number of spinal tumors, but benign primary tumors are often asymptomatic, so their true prevalence is unknown. Malignant primary neoplasms are characterized by high local aggressiveness and have the potential to metastasize, which further emphasizes the relevance of the problem [1, 4, 10, 11].

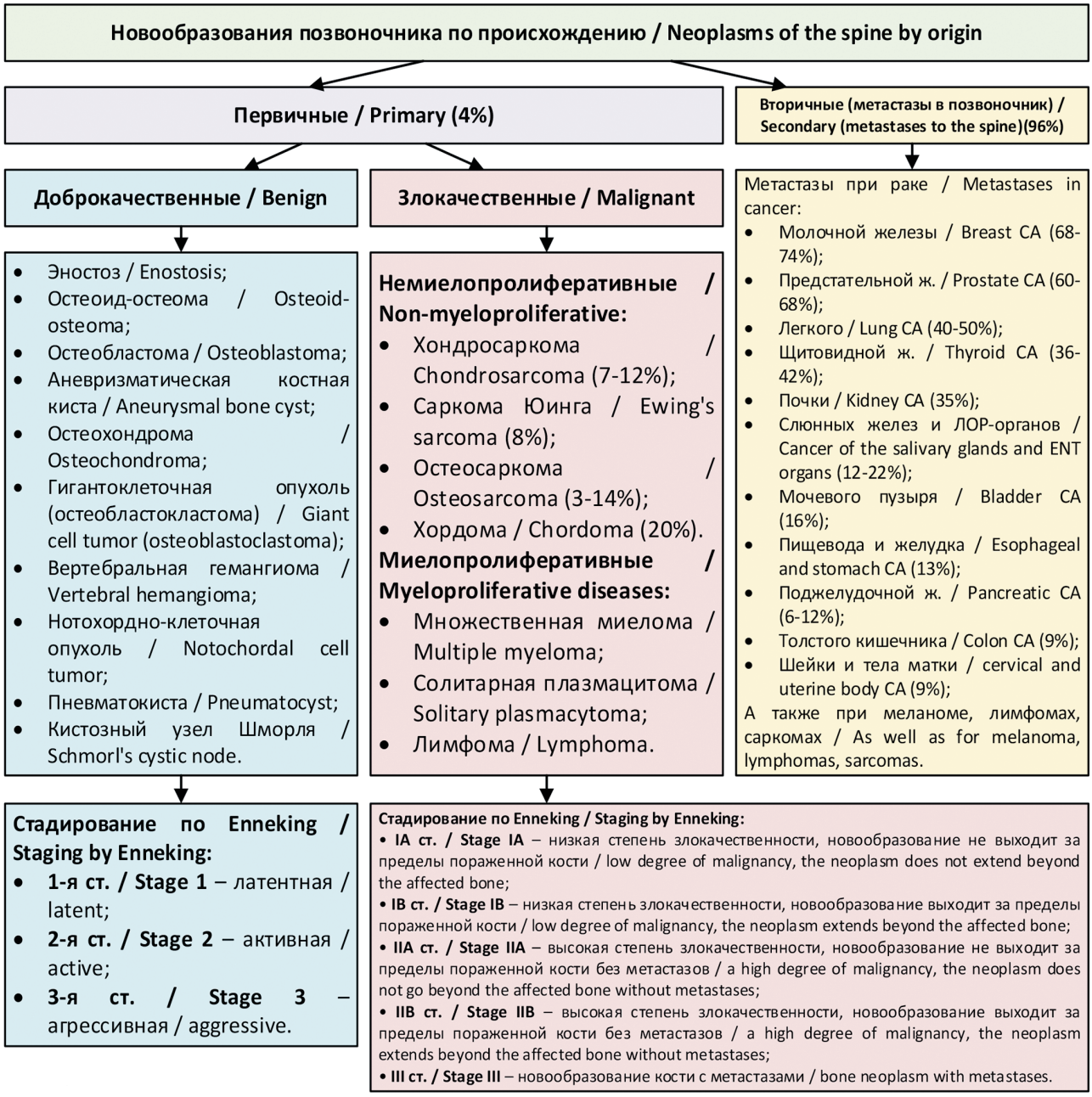

Fig. 1. Classification of spinal neoplasms by origin. CA — cancer

Рис. 1. Классификация новообразований позвоночника по происхождению

Nevertheless, the improvement of imaging techniques and the development of surgical technologies have made it possible to achieve significant progress in their diagnosis and treatment [16, 17]. In particular, surgical interventions on the spine, whether radical tumor removal or palliative surgeries, reliably reduce the severity of pain syndrome and neurological deficit caused by compression of the spinal cord and spinal nerve roots, which significantly improves the quality of life of patients. In addition, the mandatory task of surgeons is to restore the stability of the affected spinal-motor segments [18].

OSTEOSARCOMA

Osteosarcoma is a malignant osteogenic tumor consisting of neoplastic cells that produce osteoid or a substance histologically indistinguishable from it in at least one field of view [19].

The morphologic classification of osteosarcomas according to the “International Classification of Diseases — Oncology (WHO, 2017)” is quite complex and is presented in Table 1 [20].

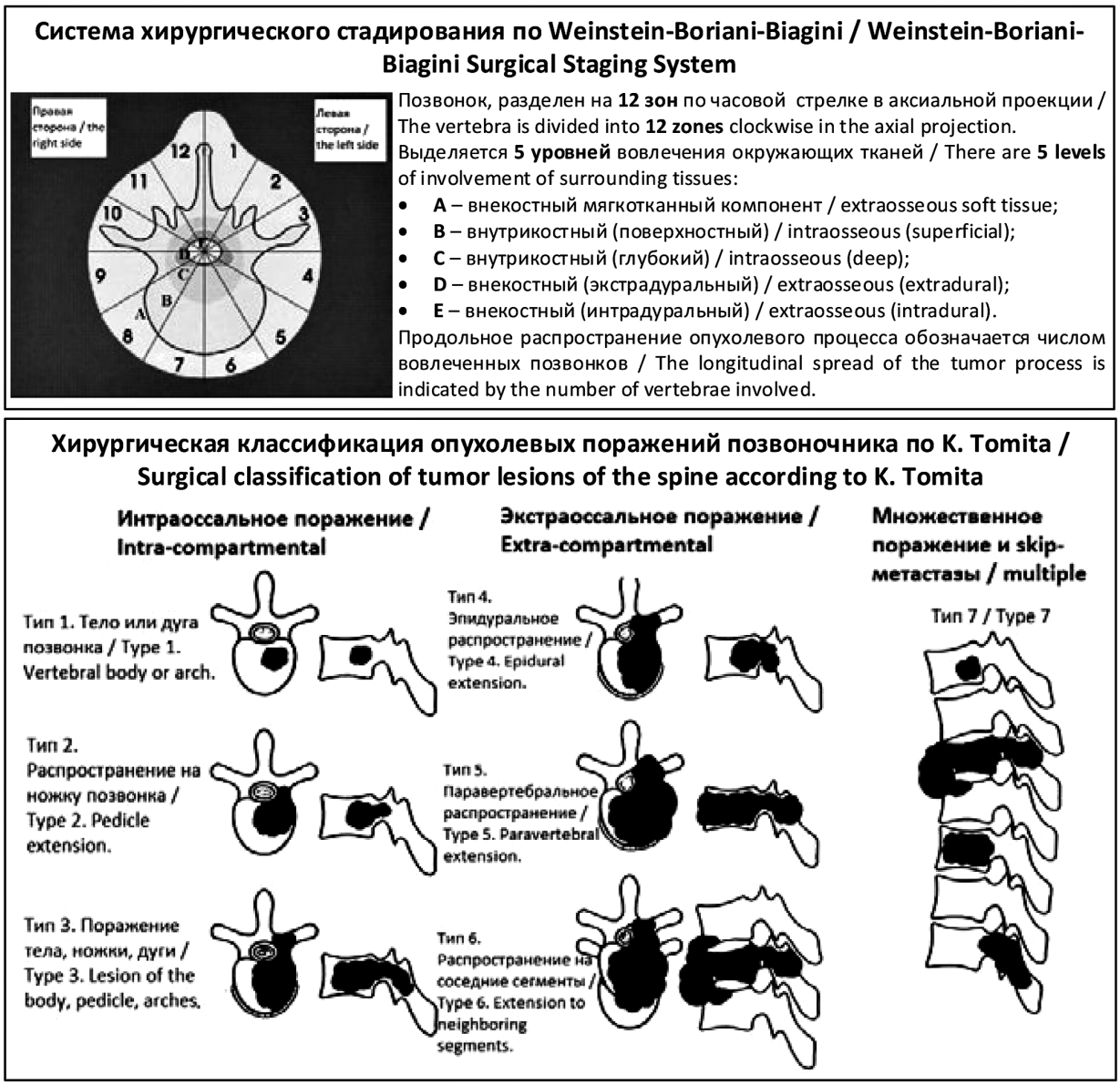

Fig. 2. Classification of spinal neoplasms by localization and degree of spread

Рис. 2. Классификация новообразований позвоночника по локализации и степени распространения

In accordance with the International Classification of Diseases — Oncology (ICD-O), each neoplasm is also assigned a topographic index, and two indices are used for osteosarcomas: C40 - bones and articular cartilage of limbs and C41 — bone and articular cartilage of other and unspecified sites. For example, a neoplasm of the tibia corresponds to the index C40.2.

More convenient for clinicians is the classification given in his works by Dr. E.R. Musaev, corresponding member of the Russian Academy of Sciences. According to this classification, the following subvariants of osteosarcomas are distinguished: by the degree of malignancy — high and low; by localization — central, para-osteal and periosteal; by cell type — osteoblastic, chondroblastic, fibroblastic and so on; by etiology, radioinduced osteo-sarcomas, osteosarcomas on the background of Paget's disease, as well as osteosarcomas of unidentified etiology are distinguished [4] (Fig. 4).

Osteosarcoma is characterized by a high degree of malignancy and unfavorable prognosis, but it develops quite rarely. In the structure of all malignant neoplasms developing in the population, osteosarcoma of any localization accounts for less than 0.001% [19, 21]. Osteosarcoma of the spine, in turn, accounts for about 2% of all osteosarcomas and from 3 to 14% of malignant tumors of the spine [1, 4].

More often this tumor localizes in the lumbosacral region and involves the vertebral body in 90% [22]. Osteosarcoma

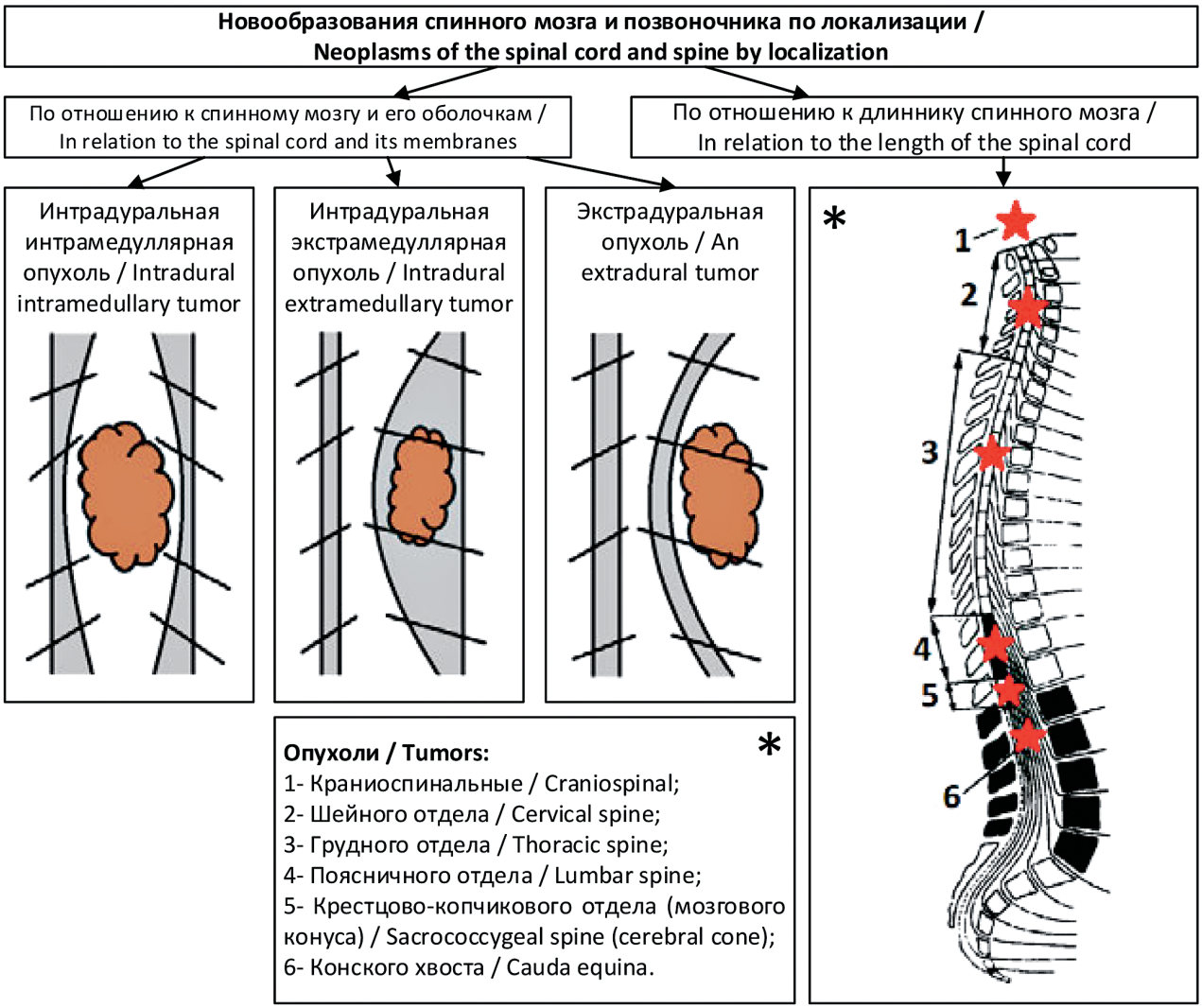

Fig. 3. Classification of tumors of the spinal cord and spine by their localization

Рис. 3. Классификация новообразований спинного мозга и позвоночника по их локализации

generally has a bimodal age distribution. The first peak is seen in the age group of 10–14 years and the second peak is seen above the age of 40 years [19]. However, unlike osteosarcoma of the extremities, osteosarcoma of the spine occurs at older ages [4].

Due to the high degree of malignancy, the generally accepted standard of surgical treatment of osteosarcoma is considered to be its radical removal *en bloc*, which provides significantly better local control compared to intratumoral removal [23].

Preoperative chemotherapy is a mandatory component of treatment [24]. Osteosarcoma is considered a tumor conditionally sensitive to chemotherapy [25]. Radiosensitivity of the tumor is low, but radiation therapy may be administered in case of incomplete removal or lump removal of the tumor [4, 23].

The prognosis of osteosarcoma depends on a large number of factors, including the patient's age and gender, tumor size, presence of metastases, radicality of surgery, stage, levels of alkaline phosphatase and lactate dehydrogenase enzymes, tumor response to preoperative chemotherapy, etc. [19, 24].

To a large extent, the prognosis depends on the localization of the tumor; thus, while in localized distal lesions of long tubular bones in combination with radical resection the 5-year survival rate is more than 80% [19], in osteosarcoma of the spine the prognosis remains extremely negative due to the complexity of radical intervention. According to some data, in a group of 22 patients with osteosarcoma of the spine, the median survival rate was only 23 months [4, 19, 24].

Therefore, there is a need to develop new drugs and treatment regimens for osteosarcoma that would improve the prognosis and increase the survival rate of patients. One of the promising directions is the development of drugs that affect the intracellular mTOR signaling pathway.

Table 1

Morphological variants of ostesarkom in accordance with the International Classification of Diseases — Oncology (WHO, 2017) [20]

Таблица 1

Морфологические варианты остесарком в соответствии с Международной классификации болезней — онкология (ВОЗ, 2017) [20]

Новообразование / Neoplasm	Морфологический индекс / Morphological index
Остеосаркома, БДУ / Osteosarcoma, NOS Остеогенная саркома, БДУ / Osteogenic sarcoma, NOS Остеобластическая саркома / Osteoblastic sarcoma Остеохондросаркома / Osteochondrosarcoma	9180/3
Хондробластическая остеосаркома / Chondroblastic osteosarcoma	9181/3
Фибробластическая остеосаркома / Fibroblastic osteosarcoma Остеофибросаркома / Osteofibrosarcoma	9182/3
Телеангиэктатическая остеосаркома / Telangiectatic osteosarcoma	9183/3
Остеосаркома при болезни Педжета костей / Osteosarcoma in Paget's disease of bones	9184/3
Мелкоклеточная остеосаркома / Small cell osteosarcoma Круглоклеточная остеосаркома / Round-cell osteosarcoma	9185/3
Центральная остеосаркома / Central osteosarcoma Обычная центральная остеосаркома / Common central osteosarcoma Медуллярная остеосаркома / Medullary osteosarcoma	9186/3
Внутрикостная высокодифференцированная остеосаркома / Intraosseous highly differentiated osteosarcoma Внутрикостная остеосаркома низкой степени злокачественности / Low grade intraosseous osteosarcoma	9187/3
Паростальная остеосаркома / Parosteal osteosarcoma Юкстакортикальная остеосаркома / Juxtacortical osteosarcoma	9192/3
Периостальная остеосаркома / Periosteal osteosarcoma	9193/3
Поверхностная остеосаркома высокой степени злокачественности / Superficial osteosarcoma of high malignancy	9194/3
Интракортикальная остеосаркома / Intracortical osteosarcoma	9195/3

Note: NOS — not otherwise specified.
Примечание: БДУ — без дополнительных уточнений.

mTOR SIGNALING PATHWAY

mTOR (Mechanistic, formerly mammalian, target of rapamycin), as the name suggests, is the direct target of rapamycin action. Rapamycin (sirolimus) is a substance first obtained from the culture of bacteria of the *Streptomyces hygroscopicus* species found on Easter Island (Rapa Nui). Rapamycin, by inhibiting the mTOR signaling pathway, was found to exhibit unique anti-fungal, immunosuppressive and antitumor properties [26–28].

mTOR is a serine / threonine protein kinase of the PI3K-related kinase family that forms the catalytic subunit of two different protein complexes: mTORC1 and mTORC2 [26, 28].

It has been found that mTORC1 plays a central role in controlling the balance between anabolism and catabolism in response to environmental conditions, regulates the relationship between nutrition and cell growth, and mTORC2 in turn is responsible for cell survival and tissue proliferation. Thus, it is obvious that mTOR regulates the processes of cell and whole organism life activity at the deepest level [26, 29, 30].

Researchers have suggested that hyperactivation of this signaling pathway may lead to the development of a large number of aging-associated diseases, including stimulation of carcinogenesis. This hypothesis was confirmed experimentally [26, 31, 32].

Let us elaborate on the relationship between mTOR hyperactivation and the pathogenesis of osteoarcoma.

Fig. 4. Subtypes of osteosarcomas (according to Musaev E.R.)

Рис. 4. Подтипы остеосарком (по Мусаеву Э.Р.)

ROLE OF mTOR SIGNALING PATHWAY IN THE PATHOGENESIS OF OSTEOSARCOMA

It has been found that mTORC1 activates the enzyme S6K (ribosomal protein kinase), which in turn phosphorylates and activates several substrates that promote mRNA translation, including eIF4B (a positive regulator of 5'cap complex binding). S6K also enhances the translation efficiency of spliced mRNA (EJK) through its interaction with SKAR (a component of exon-junction complexes) [33]. In addition, S6K suppresses the action of programmed cell death protein (PDCD4 — eIF4B inhibitor) [34]. On top of that, mTORC1 itself inhibits the action of the 4EBP complex (eukaryotic translation initiation factor eIF4E binding protein) [35]. All of the above induces protein synthesis and tumor cell growth.

In addition, mTORC1 suppresses the action of MGMT methyltransferase and NDRG1 regulatory protein, which promotes the accumulation of errors in the genome and also contributes to carcinogenesis [36].

Autophagy is a physiological process by which cytoplasmic material is delivered to the lysosome to provide energy and nutrients to the cell. It is a strategic cell survival mechanism that allows cells to reuse energy and nutrients under extreme conditions. In addition, the process of autophagy recycles damaged organelles and proteins. This enables the cells of the whole organism in general and bone tissue cells in particular to cope with oxidative stress, which has an anticarcinogenic effect [37, 38].

mTORC1 blocks this process. It suppresses the action of such important activators of autophagy as ULK1 (kinase) and ATG14L complex [37], as well as the transcription factor of lysosomal hydrolases and membrane proteins (TFEB) [38].

Thus, drugs inhibiting mTORC1 in this respect have a complex dose-dependent effect. Under physiological conditions, autophagy activation prevents carcinogenesis, but it can also improve the survival of osteosarcoma cells under conditions of nutrient deficiency and chemotherapy with other cytostatics. This phenomenon can be leveled by combining rapalogs with autophagy inhibitors, which will be mentioned later [28, 30, 31].

At the same time, hyperactivated mTORC2 complex promotes carcinogenesis. It activates SGK (kinase), a FoxO1/3a substrate inhibitor, which prevents apoptosis of osteosarcoma cells [39–41]. Along with this, mTORC2 activates Akt (a key effector of insulin signaling), which further inhibits FoxO1/3a substrate and also stimulates proliferation [39, 41, 42]. In addition, mTORC2 promotes the secretion of interleukin-1 (IL-1), which activates angiogenesis in growing tumors [39, 41, 43]. Hyperactivation of mTOR may also indirectly contribute to osteosarcoma metastasis [39, 41].

It should be noted that mTORC1 and mTORC2 are in a complex inter-regulatory relationship. Thus, mTORC1 phosphorylates S6K, which suppresses mTORC2 activity, while mTORC2 in turn stimulates mTORC1 via the Akt-TSC-Rheb pathway [28, 30].

All the above-mentioned interrelationships are clearly represented in the summarizing scheme (Fig. 5).

DRUGS AFFECTING THE mTOR SIGNALING PATHWAY IN THE THERAPY OF OSTEOSARCOMA

The use of rapamycin and its derivatives, such as everolimus and temsirolimus, for the treatment of tumors, including osteosarcoma, has been proposed for quite some time. However, despite good in vitro results, no significant improvement in patient survival has been achieved. As mentioned above, this is largely due to the fact that rapalogs, by activating autophagy in tumor cells, increase their survival under extreme conditions. In addition, this group of drugs has been

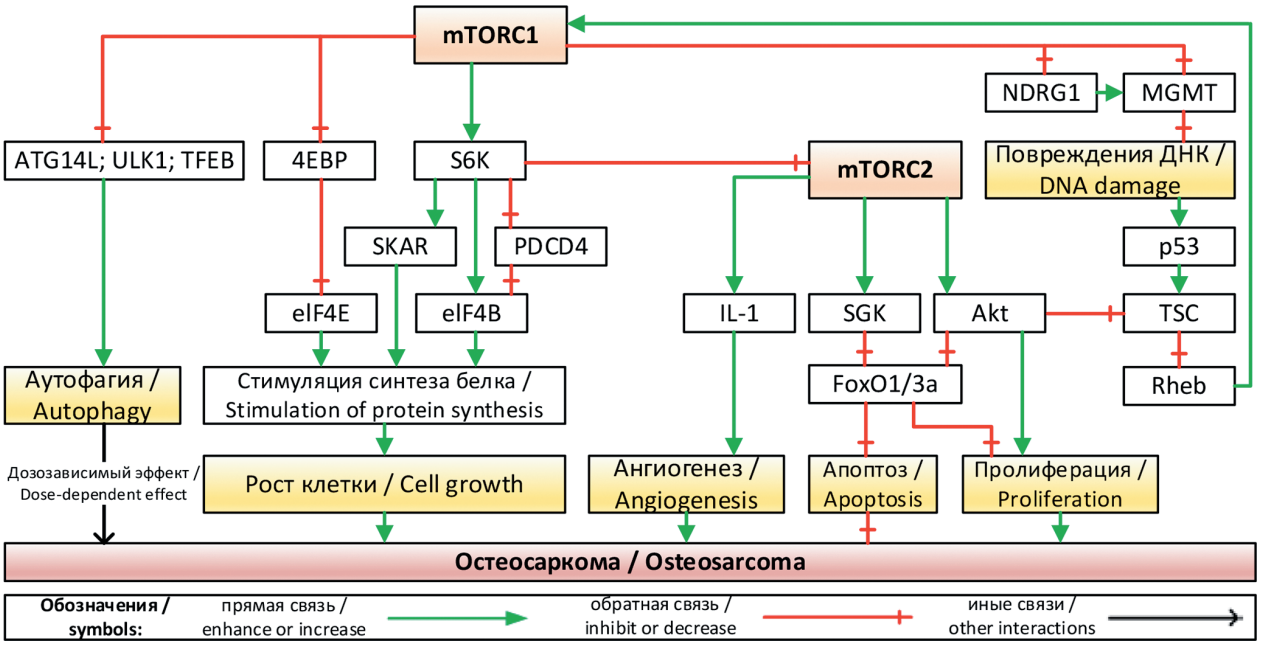

Fig. 5 **The role of hyperactivation of the mTOR signaling pathway in the development of osteosarcoma: mTORC1 — mammalian target of rapamycin complex 1; mTORC2 — mammalian target of rapamycin complex 2; S6K — ribosomal S6 Kinase; 4EBP — eukaryotic translation initiation factor 4E binding protein; SKAR — a component of exon-junction complexes; PDCD4 — programmed cell death protein 4; eIF4B — eukaryotic translation initiation factor 4B; eIF4E — eukaryotic translation initiation factor 4E; ATG14L — autophagy related 14; ULK1 — unc-51 like autophagy activating kinase 1; TFEB — transcription factor EB; MGMT — O6-alkylguanine DNA alkyltransferase; NDRG1 — N-myc downstream regulated 1; p53 — transformation-related protein 53; TSC — tuberous sclerosis complex; Rheb — Ras homolog enriched in brain; IL-1 — interleukin-1; SGK — serum/glucocorticoid regulated kinase; Akt — RAC-alpha serine/threonine-protein kinase; FoxO1/3a — forkhead box protein O1/3a**

Рис. 5. **Роль гиперактивации сигнального пути mTOR в процессе развития остеосаркомы: mTORC1 — мишень рапамицина млекопитающих комплекс 1; mTORC2 — мишень рапамицина млекопитающих комплекс 2; S6K — рибосомальная S6-киназа; 4EBP — белок, связывающий фактор инициации трансляции эукариот 4E; SKAR — компонент экзон-переходных комплексов; PDCD4 — белок программируемой клеточной гибели 4; eIF4B — фактор инициации трансляции эукариот 4B; eIF4E — фактор инициации трансляции эукариот 4E; ATG14L — связанный с аутофагией комплекс 14; ULK1 — unc-51-подобная киназа, активирующая аутофагию 1; TFEB — фактор транскрипции EB; MGMT — O6-алкилгуаниновая ДНК-алкилтрансфераза; NDRG1 — N-myc, регулируемый ниже по течению 1; p53 — связанный с трансформацией белок 53; TSC — комплекс туберозного склероза; Rheb — гомолог Ras, обогащенный в мозге; IL-1 — интерлейкин-1; SGK — киназа, регулируемая сывороткой/глюкокортикоидами; Akt — RAC-альфа серин/треонин-протеинкиназа; FoxO1/3a — раздвоенный блок O1/3a**

shown to inhibit the mTORC1 complex but not mTORC2, which also limits their therapeutic effect [28, 31, 39, 41].

Therefore, new drugs inhibiting both complexes have been developed. These include catalytic inhibitors of mTOR, such as MLN0128 [44] and PP242 [45], an ATP-competitive inhibitor of mTOR kinase; microRNAs (miR-101 [46] and miR-223 [47]), a promising class of drugs that affect the genetic apparatus of the cell and inhibit mTOR protein expression, and several others. Activity against both complexes was also shown for oleanolic acid [48].

These drugs, in turn, were proposed to be combined with autophagy inhibitors such as spautin-1. This combination was able to significantly enhance apoptosis of osteosarcoma cells [49].

In addition, metformin, which activates TSC, the most important inhibitor of mTORC1, has been proposed for the treatment and prevention of malignant neoplasms, including osteosarcoma [50]. The drug is economically advantageous; moreover, its ability to overcome the negative effect of high glucose concentration on osteogenesis is of great interest [51].

The points of action of the described drugs are presented in the summarizing scheme (Fig. 6).

It should be noted that most of these drugs are an addition to classical chemotherapy. They are proposed to be combined, in particular, with doxorubicin, cisplatin, adriamycin, high doses of methotrexate with leucovorin, etc. [39, 41]

Such combinations as temsirolimus and cisplatin; temsirolimus and bevacizumab; mTOR catalytic inhibitors (PP242 or microRNA) in combination with cisplatin; cucurbitacin B (ERK, Akt and mTOR inhibitor) in combination with low doses of methotrexate have already demonstrated their efficacy in osteosarcoma models [39, 41].

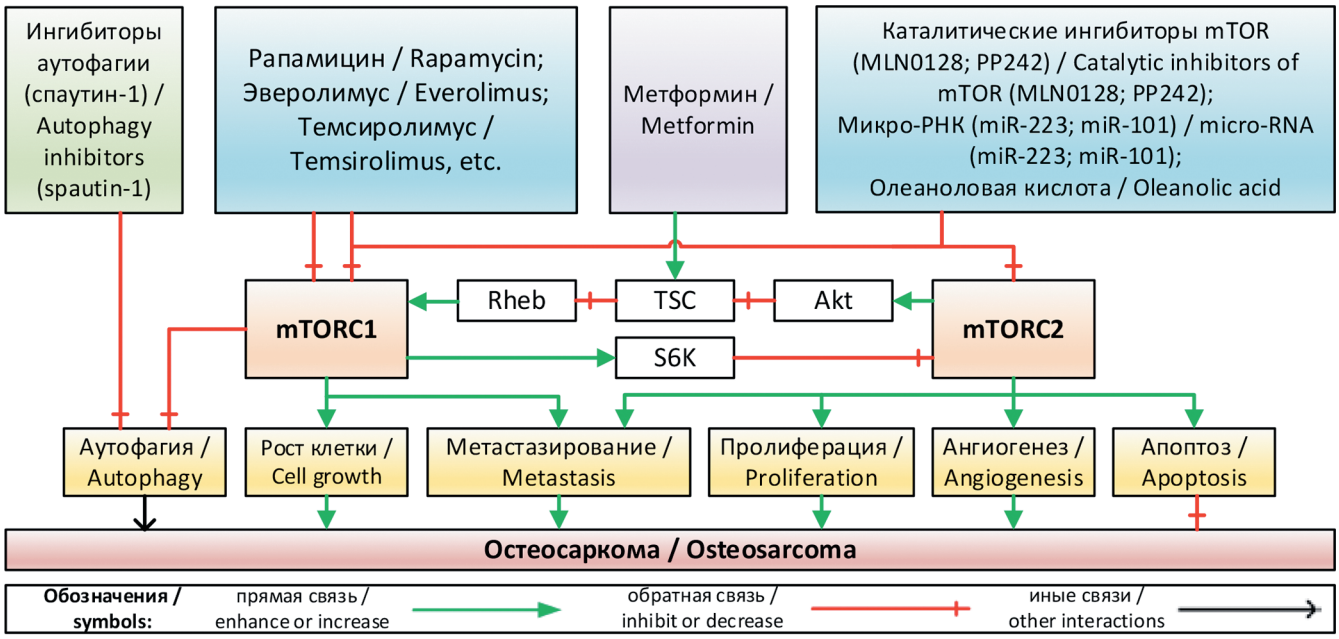

Fig. 6. **Drugs affecting the mTOR signaling pathway in the treatment of osteosarcoma: mTORC1 — mammalian target of rapamycin complex 1; mTORC2 — mammalian target of rapamycin complex 2; Rheb — Ras homolog enriched in brain; TSC — tuberous sclerosis complex; Akt — RAC-alpha serine/threonine-protein kinase; S6K — ribosomal S6 Kinase; PP242 — selective mTORC2 inhibitor**

Рис. 6. **Препараты, влияющие на сигнальный путь mTOR, в терапии остеосаркомы: mTORC1 — мишень рапамицина млекопитающих комплекс 1; mTORC2 — мишень рапамицина млекопитающих комплекс 2; Rheb — гомолог Ras, обогащенный в мозге; TSC — комплекс туберозного склероза; Akt — RAC-альфа серин/треонин-протеинкиназа; S6K — рибосомальная S6-киназа; PP242 – селективный ингибитор mTORC2**

CONCLUSION

Thus, despite the significant development of surgical and conservative treatment methods, osteosarcoma, and in particular osteosarcoma of the spine, remains a threatening nosology with an unfavorable prognosis. Studies of the mTOR signaling pathway not only shed light on aspects of the pathogenesis of this disease, but also contribute to the development of completely new therapeutic regimens. It is possible that in the near future any of the drug combinations described above will be approved for the treatment of patients with osteosarcoma.

ADDITIONAL INFORMATION

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

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

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NEUROPLASTICITY OF LIMBIC STRUCTURES: CRITICAL PERIODS FOR THE FORMATION OF COGNITIVE FUNCTIONS IN ONTOGENESIS

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Abstract. Living organisms have a unique ability to adapt to constantly changing environmental conditions. There are critical periods, also called time windows, when different areas of the brain become most sensitive to the effects of environmental factors that affect the formation of strong bonds. Mammalian neurogenesis is a lifelong process limited to certain areas of the brain, namely the subgranular zone, part of the dentate gyrus of the hippocampus, and the subventricular zone. Also, an important role in neurogenesis in primates and rodents is played by “neurogenic niches”, which are microenvironments for neuronal precursor cells and their descendants. Depending on the area of the brain, the process of neurogenesis is carried out through different mechanisms, for example, the main molecular factors of neurogenesis are the Notch and Sonic hedgehog pathways, extracellular signaling molecule and bone morphogenetic protein. The functioning of the blood-brain barrier maintains a certain chemical homeostasis and level of metabolic activity of brain tissues, which are necessary for neurogenesis. However, a number of brain structures, known as circumventricular organs, are characterized by the absence of a blood-brain barrier and a unique composition of the microenvironment, in particular the presence of chronically activated microglia in the environment, which probably affects neuro- and angiogenesis. The study of the effects of stress on the body during critical periods of neurogenesis, depending on gender, age and type of organism, duration of stress exposure, will expand the understanding of the formation of the nervous system during early ontogenesis and pathogenetic mechanisms of the development of mental disorders. In turn, the information obtained will increase the possibilities of prevention and treatment of this group of diseases.

Keywords: neuroplasticity, neurogenesis, limbic system, critical periods

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НЕЙРОПЛАСТИЧНОСТЬ ЛИМБИЧЕСКИХ СТРУКТУР: КРИТИЧЕСКИЕ ПЕРИОДЫ ДЛЯ ФОРМИРОВАНИЯ КОГНИТИВНЫХ ФУНКЦИЙ В ОНТОГЕНЕЗЕ

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Резюме. Живые организмы обладают уникальной способностью адаптироваться к постоянно изменяющимся условиям окружающей среды. Существуют критические периоды, то есть временные окна, когда различные области мозга становятся наиболее чувствительными к воздействию окружающих факторов, влияющих на формирование прочных связей. Нейрогенез млекопитающих — процесс, протекающий на протяжении всей жизни, ограниченный определенными зонами мозга, а именно: субгранулярной зоной, частью зубчатой извилины гиппокампа и субвентрикулярной зоной. Важную роль в нейрогенезе у приматов и грызунов выполняют также «нейрогенные ниши», представляющие собой микросреды для клеток-предшественников нейронов и их потомков. В зависимости от области головного мозга процесс нейрогенеза осуществляется за счет разных механизмов. Так, основными молекулярными факторами нейрогенеза являются пути Notch и Sonic hedgehog, внеклеточная сигнальная молекула и костный морфогенетический белок. Благодаря функционированию гематоэнцефалического барьера поддерживаются определенный химический гомеостаз и уровень активности метаболизма тканей головного мозга, необходимые для нейрогенеза. Однако для ряда структур головного мозга, известных как циркумвентрикулярные органы, характерны отсутствие гематоэнцефалического барьера и уникальный состав микроокружения, в частности наличие в окружении хронически активированной микроглии, которая, вероятно, влияет на нейро- и ангиогенез. Изучение влияния стресса на организм в критические периоды нейрогенеза в зависимости от пола, возраста и вида организма, продолжительности стрессового воздействия позволит расширить представление о формировании нервной системы в период раннего онтогенеза и патогенетических механизмах развития психических расстройств. В свою очередь, полученные сведения увеличат возможности профилактики и лечения данной группы заболеваний.

Ключевые слова: нейропластичность, нейрогенез, лимбическая система, критические периоды

INTRODUCTION

Living organisms have a unique ability to adapt to constantly changing environmental conditions. There are critical periods, time windows, when different brain regions become the most sensitive to the influence of environmental factors affecting the formation of strong connections [1].

Maternal deprivation as a model of acute stress in early ontogenesis was used as an example to demonstrate its effect on biochemical parameters in cerebral structures [2]. As a result, there was a decrease in dopamine and dopamine D-1 receptor mRNA expression levels in the prefrontal cortex and amygdala, and a decrease in neuropeptide Y (NPY) levels in the basolateral amygdala and dorsal part of the hippocampus [3, 4].

Studying stress during critical periods of neurogenesis in relation to sex, age and type of the organism, as well as duration of stress exposure will allow us to expand our understanding of nervous system formation during early ontogenesis and pathogenetic mechanisms of mental disorders [5]. In turn, the obtained information will increase opportunities for prevention and treatment of this group of diseases [6].

Our review focuses on critical periods of neurogenesis, as well as on the factors that influence the development of different brain structures, including different time periods. The role of the blood-brain barrier and microglia in neurogenesis is also described. The main objective of this review is to combine and systematize data on the structures involved in neurogenesis and the factors regulating this complex process.

MECHANISMS OF REGULATION OF NEUROGENESIS IN THE POSTNATAL PERIOD

Neurogenesis is one of the key and most important and complex processes, consisting of many sequential steps, responsible for brain adaptation and repair. Local cell microenvironment, which determines further formation of neuronal networks, is considered to play a key role in the molecular mechanism controlling neurogenesis [7]. The local microenvironment triggers many processes in the so-called neurogenic niches, where successive processes of neural stem cells (NSCs) and neural progenitor cells (NPCs) transformation, migration, selection and differentiation take place.

Neurogenesis in mammals is a process that exceeds the limits of embryonic period of development. It continues throughout life but is restricted to specific brain areas such as the subgranular zone, part of the gyrus dentatus of the hippocampus and the subventricular zone located in the lateral ventricles of the brain [8].

When discussing neurogenesis and mechanisms of its regulation, it is necessary to dwell separately on the area of the infundibular recess located in the lower part of the third brain ventricle. Lining of the infundibular recess is formed by tanycytes, highly specialized bipolar cells with a long basal outgrowth [9].

Tanicites with basal outgrowths passing through the neural tissue and ending at blood vessels are represented by a specialized population of glial cells [10, 11].

Extended ends of basal outgrowths of tanycytes also end on the portal system of the pituitary gland with fenestrated capillaries, thus participating in the formation of hematoliquor and liquor-encephalic barriers [12].

Tanycytes are able to differentiate into neurons and glia and participate in the regulation of the ventromedial and arcuate nuclei. In total, four types of tanycytes are distinguished, which are different in structure, cytochemical and functional features and their location in the infundibular recess (α1-, α2-, β1- and β2-) [11, 13, 14].

Neurogenesis in adult primates and rodents is active in the olfactory bulb, where there are special areas called “neurogenic niches”. These niches are microenvironments that contain neuronal progenitor cells and their progeny. Astrocytes, oligodendrocytes, ependymal cells, capillary endothelial cells and already mature neurons surround these cells [15].

The subventricular zone (SVZ) is another brain region where neurogenesis occurs in adult animals. This zone consists of several layers (2 to 5), each containing different cell types, labeled A, B, C, and E.

Type A cells are immature neurons, neuroblasts, capable of migration. They move along the SVZ, contacting astrocytes and forming clusters near the surface of the ventricle. These cells have a specific marker, PSA-NCAM (Polysialylated-neural cell adhesion molecule), which is involved in cell adhesion, and a membrane marker, doublecortin (DCX, doublecortin).

Type B cells contain many intermediate filaments in their structure and contact the ventricular ependyma.

Type E cells (ependymal cells) are localized in the cavity of lateral ventricles, express vimentin, CD-24 (cluster definition) and S-100 protein. Due to their ability to differentiate, they are considered neuronal progenitor cells.

Type C cells are transitional cells, a transitional stage between types A and B. They have similarities with both types, making them difficult to recognize. Closely related to type A cells, however, they do not have the PSA-NCAM marker peculiar to neuroblasts, they express the transcription factor Dlx2 (Distal-Less Homeo Box 2), EGFR (epidermal growth factor receptor), Mash1 (mammalian achaete — scute homologue) [16, 17].

Three main types of cells involved in neurogenesis are distinguished in the hippocampus:

- type I cells (neuronal progenitor cells) are descendants of radial glia cells, which explains that they share common

markers such as nestin, aromatase B, Sox 1, Sox 2, BLBP (brain lipid binding protein), GLAST (glutamate/aspartate transporter), and are pluripotent (multipotent), capable of proliferation into astro- and oligodendrocytes [18];
- type II cells (intermediates) are capable of neuronal differentiation and are divided into subtypes IIa and IIb, have specific markers of neuronal differentiation — DCX, PSA-NCAM;
- type III cells (neuroblasts) become mature granular cells after migration into the gyrus dentatus; the differentiation process takes 4–7 weeks; the outgrowths of granular cells are located in the molecular layer (dendrites) and in the CA3 zone of the hippocampus (axons).

Neuroblasts migrate in chains along glial tubes, which are located along blood vessels. The endothelium of blood vessels synthesizes signaling molecules, such as BDNF (brain-derived neurotrophic factor), which stimulate migration [19].

The existence of newly differentiated cells is maintained by previously formed connections. In order to maintain a constant number of neuronal cells in the olfactory bulb, there is a mechanism for screening new cells.

The process of neurogenesis includes proliferation, differentiation, migration, and other stages regulated by multiple factors: hormones, cytokines, growth factors, and electrophysiological activity [20].

The persistence of newly formed neurons depends on the animal species and brain area. In adult Wistar line rats, neurogenesis occurs in the fascia dentata, CA1-CA4 fields of the hippocampus, cerebellar worm, and various cortical areas, but proliferation, apoptosis, and differentiation of new neurons differ in these areas. Although there is evidence of incorporation of new neurons into existing networks, their functionality is not yet fully understood [21].

FACTORS AFFECTING NEUROGENESIS IN RATS

Winstar rats demonstrated that the intensity of neurogenesis varied depending on brain areas. Certain areas, such as different parts of the cerebral cortex, cerebellar worm and CA1-CA4 fields of the hippocampus, show more active proliferation, differentiation and apoptosis of new neurons, while in other areas these processes are less pronounced [22].

At the same time, there are significant differences regarding degree and magnitude of neurogenesis between rat and human brains. Neurogenesis is essential in the gyrus dentatus of humans, as well as in the subventricular zone, where neural stem cells (progenitor cells) retain their neurogenic potential, generating a subset of interneurons of the striatum. This pathway of neurogenesis is absent in the subventricular zone in rats [23].

Rats also have a neurogenic niche formed by the NSC and its microenvironment formed by various cells: oligo- and astrocytes, capillary endothelial cells.

The process of further transformation of progenitor cells is controlled by humoral and biochemical compounds. It has been shown that administration of nitric oxide synthase inhibitor leading to inhibition of nitric oxide synthesis in the olfactory bulb, SVZ zone, and rostral migratory pathway leads to an increase in cell proliferation in these zones.

The microcirculatory system plays an important role in the paracrine regulation of neurogenesis, acting as a conductor for signaling molecules. As the brain blood vessel network ages and shrinks, the level of VEGF (vascular endothelial growth factor) decreases, which may have a negative impact on neurogenesis.

Another biochemical factor that stimulates cell proliferation and differentiation in the hippocampus is insulin growth factor (IGF-I). It is expressed in the postnatal period with a further decrease in its level during aging [24].

Thus, three main factors of age-related neurogenesis can be identified: reduction of VEGF, impaired angiogenesis, and further reduction of blood flow in cerebral vessels [22].

One of the key roles in aging process is assigned to microglia as a structure that supports apoptotic processes in the neurogenic niche as it contains factors that activate oxidase damage. Proinflammatory cytokines, in particular IL-1β and TNFα (tumor necrosis factor α), activate microglial cells, which has a negative effect on neurogenesis [22]. At the same time, microglia cells are both sources of IGF-1 and BDNF, which promote neurogenesis; their decreased activity leads to dysregulation of progenitor cell transformation in the hippocampus [25].

Hippocampus

The dentate gyrus of the hippocampus is one of the brain regions responsible for the process of neurogenesis. With the development of astrocytes followed by oligodendrocytes in the brain, neuronal activation becomes a critical factor determining synaptogenesis. Synaptic connections formed between cells can either stabilize (with sequential stimulation) or completely disappear (in the absence of stimuli).

Specifically, neurons in rodents develop from neural epithelial cells, which are considered early neural stem cells (SCs) at approximately day 9–9.5 of embryonic development and are finally formed by 15–17.5 weeks of age. The dentate gyrus of the hippocampus develops from a distinct source of progenitor cells (dentate neuroepithelium), which may have important consequences in the postnatal period [26, 27].

Hippocampal neurons develop from dentate neuro-epithelium at 13.5–17.5 weeks with the formation of the hippocampal fissure. Subsequently, the dentate progenitor cells, accumulating within the fissure, will form the future neural stem cell

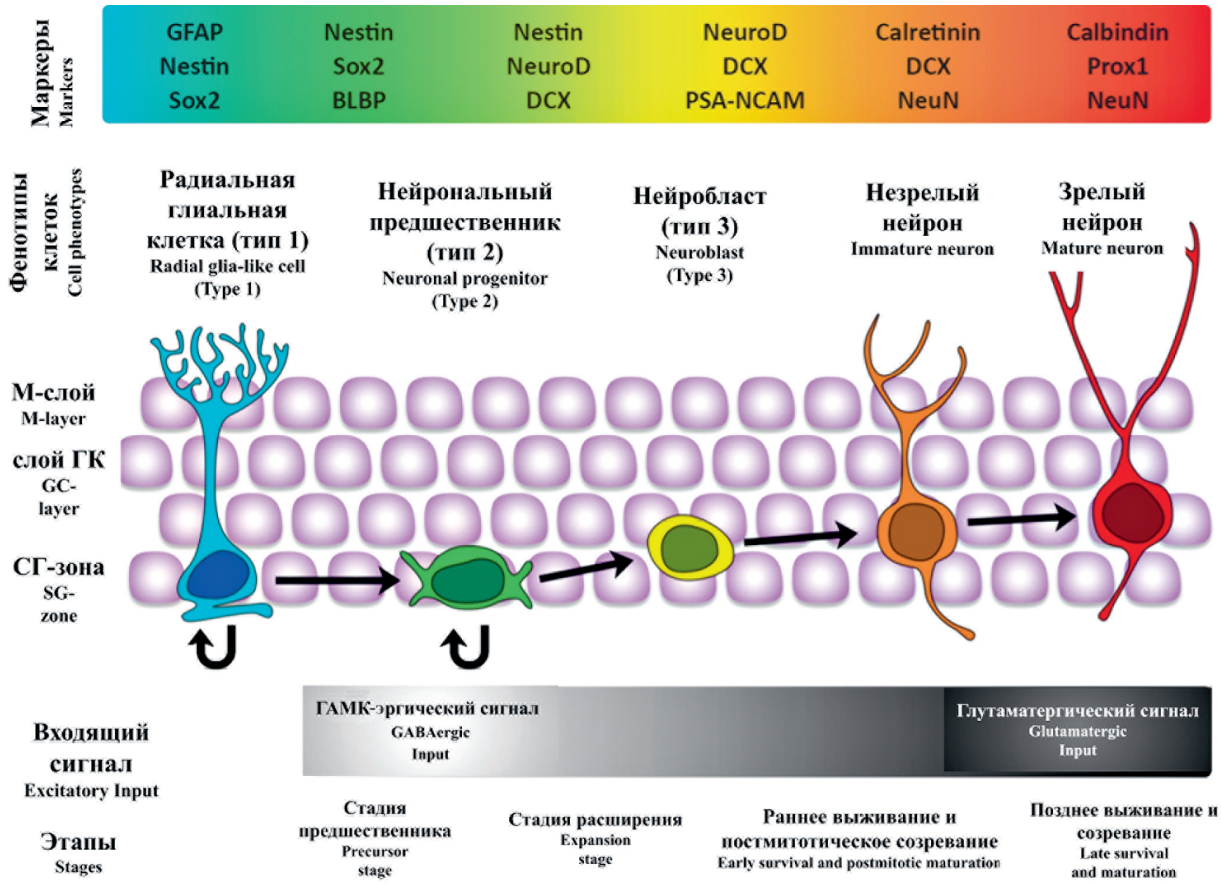


Fig. 1. Stages of hippocampal neurogenesis. Stem cells, radial glia-like (type 1; blue) maintain their pool through self-renewal and give rise to progenitor cells expressing markers with different morphologies (type 2 (A and B); green), which undergo rapid proliferation and begin to express markers necessary for subsequent cells. Type 2 cells differentiate into neuroblasts (type 3; yellow). Neuroblasts enter the early survival stage (orange cells) and extend their processes into the molecular layer. At the late stage of survival, only those neurons remain that have formed functional connections and matured morphologically (red cells). Granule neurons somata is represented in purple. The color bar at the top illustrates the gradual transition of marker expression as cells progress through different stages of neurogenesis. The gray gradient bar at the bottom indicates the switching of neurons from GABA-ergic to glutamatergic signals [26]. *Note:* M-layer — molecular layer; GC-layer — granule cell layer; SG-zone — subgranular zone; GFAP — glial fibrillary acidic protein; *Sox2* — gene *Sox2*; BLBP — brain lipid-binding protein; NeuroD — gene NeuroD (Neurogenic differentiation 1); DCX — doublecortin; PSA-NCAM — Polysialylated-neural cell adhesion molecule; NeuN — neuronal nuclei; Prox1 — Prospero homeobox protein 1

Рис. 1. Стадии гиппокампального нейрогенеза. Стволовые клетки, подобные радиальной глии (тип 1; синий), поддерживают свой пул посредством самообновления и дают начало клеткам-предшественникам, экспрессирующим маркеры различной морфологией (тип 2 (A и B); зеленый), которые подвергаются быстрой пролиферации и начинают экспрессировать маркеры, необходимые для последующих клеток. Клетки 2-го типа дифференцируются в нейробласты (тип 3; желтый). Нейробласты переходят на раннюю стадию выживания (оранжевые клетки) и распространяют свои отростки в молекулярный слой. На поздней стадии выживания остаются только те нейроны, которые сформировали функциональные связи и созрели морфологически (красные клетки). Тела гранулярных нейронов представлены фиолетовым цветом. Цветная полоса сверху иллюстрирует постепенный переход экспрессии маркеров по мере прохождения клетками различных стадий нейрогенеза. Серая градиентная полоса снизу указывает на переключение нейронов с ГАМК-эргических (ГАМК — гамма-аминомасляная кислота) на глутаматергические сигналы [26]. *Примечание:* М-слой — молекулярный слой; слой ГК — слой гранулярных клеток; СГ-зона — субгранулярная зона; GFAP — глиальный фибриллярный кислый белок (glial fibrillary acidic protein); nestin — нестин; *Sox2* — ген *Sox2*; BLBP— жиросвязывающий белок мозга (brain lipid-binding protein); *NeuroD* — ген *NeuroD* (Neurogenic differentiation 1); DCX — даблкортин (doublecortin); PSA-NCAM — молекула адгезии полисиалированных нейронных клеток (polysialylated-neural cell adhesion molecule); NeuN —нейронные ядра (neuronal nuclei); Prox1 — гомеобоксный белок 1 Просперо (Prospero homeobox protein 1); calretinin — кальретинин; calbindin — кальбиндин

layer of the adult subgranular zone or become neurons that will form the granular cell layer (Fig. 1) [28]. It is assumed that hippocampal neurogenesis can continue its development throughout life due to its increased plasticity [29, 30].

The structure of the hippocampus is heterogeneous. The dorsal hippocampus (DH) is connected to the neocortex and is mainly involved in cognitive processes, memory and learning, whereas the ventral hippocampus (VH) is connected to the amygdala and hypothalamus, playing an important role in the emotional and stress response of the organism. Inflammation in hippocampal structures can affect the functional state of neurons by modulating their synaptic plasticity. Inflammation in the structures of the central nervous system (CNS) develops faster in the DH, whereas corticosterone accumulation progresses faster in the VH and neocortex, and the DH is affected functionally (by the state of synaptic plasticity in the phenomenon of prolonged potentialization *in vivo*), and then the disorder spreads to the VH [31, 32].

There is strong evidence that neurogenesis in the adult hippocampus plays an important role in regulating memory and mood. Alterations in hippocampal neurogenesis are associated with a variety of neurological and psychiatric disorders [33, 34]. It has been shown that the period in which neurons were exposed to environmental factors (e.g., stress) will determine their further vulnerability and risk of disease [35].

Neurogenesis in the cerebral cortex

Radial glial cell (RGC) division in the cerebral cortex is regulated by the intracellular distribution of cell polarity determinants of PAR (protease-activated receptors; PAR3 and PAR6) family proteins and their regulator CDC42, which are localized at the ventricular ends of the cell pedicles.

However, these cells mainly undergo asymmetric divisions to generate a differentiated daughter cell while simultaneously renewing their pool. This process is considered as direct neurogenesis. RGCs in the forebrain undergo changes by a more complex mechanism by generating intermediate progenitor cells called basal progenitor cells (BPCs) [36]. These cells subsequently differentiate into postmitotic cells. This process is referred to as indirect neurogenesis.

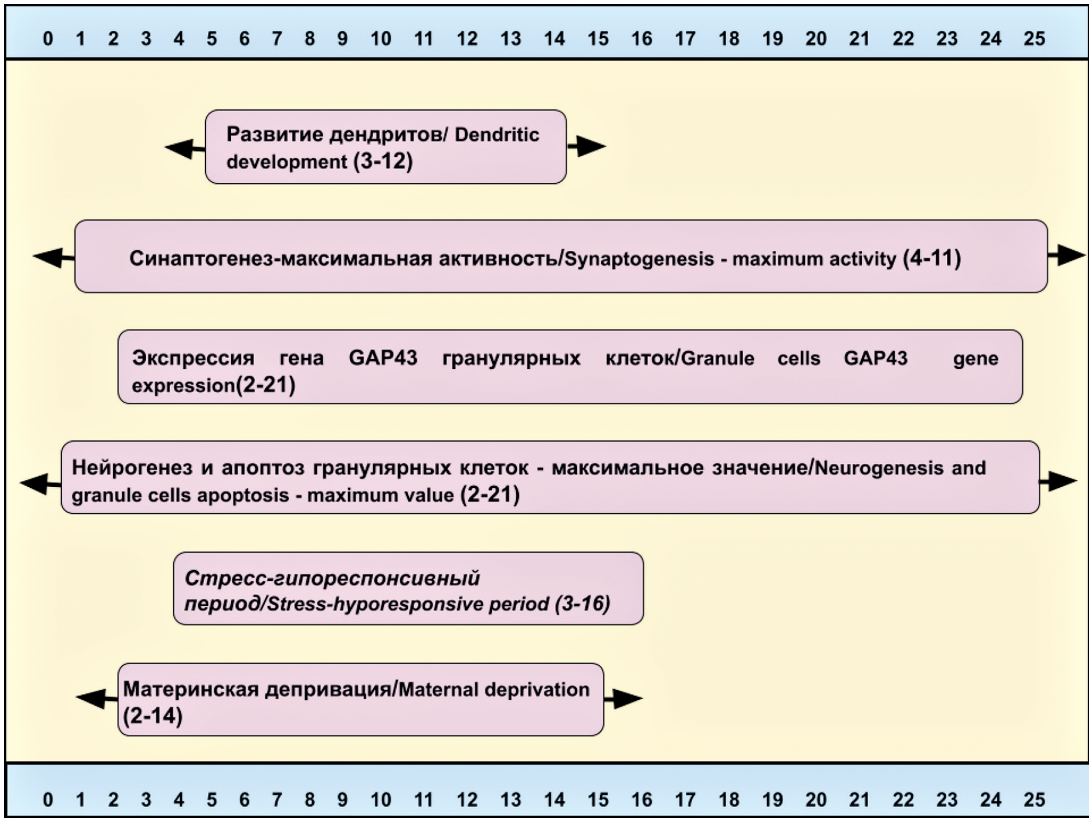


Fig. 2. **The process of neurogenesis in the postnatal period in rodents. During the newborn period, neurogenesis, myelination, apoptosis occur, as well as the processes of synaptogenesis and synaptic pruning. All these mechanisms are targets for further epigenetic modifications and the influence of environmental factors on the formation of the central nervous system [39]**

Рис. 2. **Процесс нейрогенеза в постнатальный период у грызунов. На протяжении периода новорожденности происходят нейрогенез, миелинизация, апоптоз, равно как и процессы синаптогенеза и синаптической обрезки. Все эти механизмы являются мишенями для дальнейших эпигенетических модификаций, влияния факторов окружающей среды на формирование центральной нервной системы [39]**

Neurogenesis in the brain proceeds through several stages generating different neurons. Disturbances at any stages of neurogenesis and neuronal migration can lead to impaired brain development (Figure 2). Premature transition of proliferative divisions of RGCs to the neurogenic stage can lead to their insufficient number and heterogeneity of neurons in the brain leading to microcephaly, and impaired neuronal migration can further condition lissencephaly [37, 38].

The main molecular factors of neurogenesis include:

1. Notch pathway, premature activation of which will lead to an increase in RG cell markers in the forebrain. Notch signaling promotes proliferative signaling during neurogenesis, facilitating nerve differentiation.
2. Sonic hedgehog (Shh) pathway. Shh promotes generation of oligodendrocytes and GABAergic interneurons in the ventral terminal medulla, which later infiltrate into the cortical lamina. In contrast to the ventral terminal brain, the developing cortex undergoes limited Shh signaling, the physiological role of which remains poorly understood. Reduced Shh signaling transmission in RGCs impairs their proliferation and ability to generate intermediate progenitor cells, outer RGCs, and, consequently, projection neurons. This impairment of Shh signaling causes a reduction in neuronal output, which is responsible for reducing the size of the dorsal endbrain, which may contribute to microcephaly [40].
3. Another extracellular signaling molecule, WNT, promotes the proliferative capacity of RGCs in the developing cortex. WNT has also been shown to induce neuronal differentiation of basal precursor cells, thereby providing a dual level of neurogenesis regulation.
4. In addition to WNT, bone morphogenetic protein also regulates brain cytogenesis at early stages of cortical development (12th–13th weeks of embryogenesis) and astrocytogenesis do so in later periods (14th week and afterwards) [41, 42].

Amygdala

The amygdala is part of the limbic system, responsible for expressing aggression, fear, and defensive behavior. It plays an important role in forming and retrieving emotional memories. The neural network of the amygdala is closely interconnected with other cortical areas and receives input from the thalamus, hypothalamus, and hippocampus.

The prefrontal cortex, hippocampus, amygdala, and anterior cingulate gyrus influence fear formation and are key in the development of anxiety-associated disorders. Studies show increased amygdala volume in children (age group 7–9 years) with generalized anxiety disorders, which aggravated the clinical picture [43, 44].

It has been shown that the amygdala plays the most significant role in forming emotional and social behavior in the early postnatal period. The sensitive period for the amygdala begins on postnatal day 21 and continues through childhood [45, 46].

The critical period for amygdala activity is 20–30 minutes immediately after psychotrauma, during the same period the formation of emotional memory takes place. The central region of the amygdala can inhibit GABAergic neurons, indirectly affecting the activity of the hypothalamic-pituitary-adrenal axis (HPA axis) [47, 48].

Studies by M.M. Sidor et al. showed that proinflammatory stress at an early age leads to impaired functioning of the serotonin system in young rats. It is manifested by changes in the expression of serotonin receptors and enzymes involved in its synthesis and metabolism in the neocortex, amygdala and hippocampus [49].

The amygdala, the brain region responsible for emotion processing, is also the site of corticoliberin (CL) synthesis. Corticosteroids have been found to stimulate CL production in the central nucleus of the amygdala, thus participating in regulating the effects of stress on memory [50].

Neurons of the amygdala expressing CL participate in realization of the stress response. Activation of these neurons in the central nucleus of the amygdala increases anxiety and simultaneously decreases the number of hippocampus-dependent behaviors [51]. However, a model of anhedonia induced by early stress resulted in a decrease in CL expression in the central nucleus of the amygdala by RNA interference leading to increased sucrose consumption. Thus, we can suggest a possible role for CL in the regulation of mood and motivation [5].

In summary, most anxiety disorders develop during childhood and adolescence, which is an important developmental period. They are often characterized by dynamic changes in the frontolimbic nervous system. The frontolimbic system plays a vital role in fear learning and understanding the neurobiological mechanisms associated with anxiety disorders throughout development [52, 53].

Maturation of the blood-brain barrier and its role in neurogenesis

The blood-brain barrier (BBB) is a structural and functional element of the neurovascular unit (NVU), which includes neuronal, glial, and endothelial cells. The main tasks of NVU functioning include maintaining the control of metabolism and chemical homeostasis in brain tissue, ensuring adequate blood flow in active regions, regulation of neuroplasticity processes. These tasks are reflected in a complex set of intercellular interactions in norm, stress, neurodegeneration, neuroinfection, and brain development disorders [54, 55].

The BBB development in rodents starts by E10–17, controlled permeability is formed by E21, but the development of dense contacts continues in the postnatal period as well.

Human BBB markers appear at the 8th week of embryogenesis, and intensive angiogenesis in brain tissue continues until 2–3 weeks of postnatal development [56].

It is noteworthy that the formation of barrier structures begins only after the formation of the NSC/NPC (neural stem cells/neural progenitor cells) pool and always proceeds in parallel with synaptogenesis and induction of synaptic activity in brain tissue. The formation of barrier structures also occurs in the adult brain. An integral part of this process is the formation of new microvessels with actively proliferating and differentiating endothelial progenitor cells, as well as effects of various regulatory molecules and components of cell signaling pathways (Notch, FOX (forkhead box protein), HIF-1, GSK-3 (glycogen synthase kinase 3)). In general, the association between neurogenesis and angiogenesis has been sufficiently characterized, and its disorders are recognized as a probable cause of neurogenesis suppression in the aging brain [57].

Contribution of controlled and selective permeability of the BBB in order to maintain local microenvironment in neurogenic niches is not fully understood. Currently, the effect of paracrine effector molecules produced by BBB cells on NSCs/NPCs (neural stem cells/neural progenitor cells) has been proved. Such factors include vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (FGF2, Fibroblast growth factor 2), brain-derived neurotrophic factor (BDNF), and pigment epithelium-derived factor (PEDF) [7].

The permeability of the BBB, including those in microvessels of neurogenic niches, is determined by the following factors:

1) expression of intercellular contact proteins;
2) expression of transporter and channel proteins;
3) metabolism of cerebral endotheliocytes and other NVU cells;
4) signal transduction and intercellular communication;
5) the state of the basal membrane;
6) the degree of maturity of the BBB.

In most brain regions, the BBB is formed by endotheliocytes, pericytes, and astrocytes.

Endotheliocytes are an important structure of the brain NVU and form the basis of the BBB [58]. Endothelial cells in brain microvessels are controlled by perivascular astroglia, provide selective transport of substances, sequester prothrombogenic factors and control blood rheological properties, as well as implement mechanisms of microcirculation control, and participate in the regulation of neurogenesis. They also interact with leukocytes and microglia, participating in local immune response and inflammation, and are capable of producing cytokines, metabolites, and growth factors [25, 59].

Endotheliocytes, which are part of the BBB, form barrier structures in the early period of development and participate in restoring the barrier after damage.

The features of cerebral endothelial cells are:

1) low fenestration and reduced pinocytosis;
2) high expression of intercellular contact proteins (tight junctions, adherence junctions);
3) relatively high content of mitochondria in cells;
4) close interaction with pericytes and perivascular astroglia;
5) expression of transferrin receptors, insulin receptors, and a large spectrum of transporter proteins.

All these properties provide high selectivity of the BBB, which is important for chemical homeostasis in the central nervous system. These properties help to maintain the level of glucose and other energy substrates, excretion of metabolic products, regulation of cytokine and growth factor concentrations, etc. [60, 61].

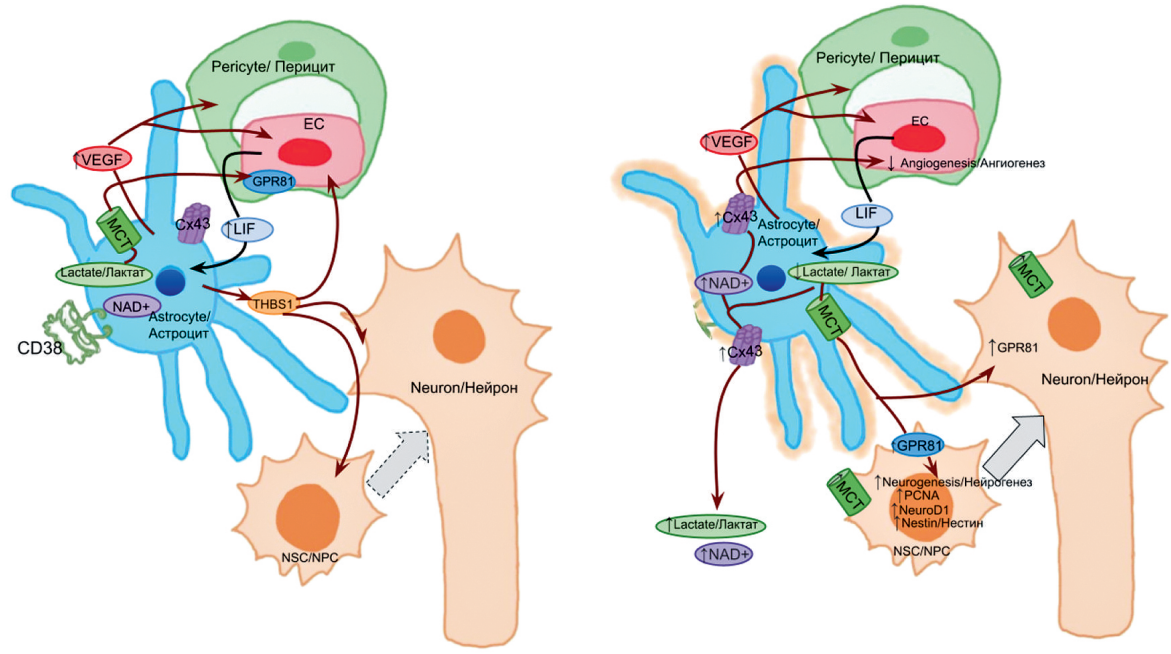
In addition to endothelial cells, neurogenesis is also controlled by perivascular astrocytes. Astrocytes also affect brain microvascular cells, for example, by causing vasodilation and stimulating angiogenesis through calcium-induced glycolysis and lactate production or generation of arachidonic acid metabolites, while astrocyte-expressed thrombospondin-1 downregulates the angiogenic potential of endothelial progenitor cells [62]. In addition, the formation of astroglial network connected via connexin channels forms a local microenvironment favorable for proliferative processes in neurogenic niches (Fig. 3).

Astrocytes in the SGZ of the hippocampus are tightly surrounded by the endothelial layer of cells, so the local microenvironment is formed mainly due to the local secretion of neuro- and gliotransmitters and growth factors, whereas in the SVZ astrocytes are loosely adjoined to the layer of endothelium and pericytes, which ensures the entry of regulatory molecules from the blood into the niche [63, 64].

Brain cell death activates the process of reparative neurogenesis in SVZ with subsequent migration of new neuroblasts to the area of damage [65].

Studies of cortical ischemia in mice have shown that this stress effect causes changes in cell proliferation in the SVZ, in which three stages can be distinguished. The first stage is an acute decrease in proliferation during the first day after cortical ischemia, then, in the second stage, the proliferation level starts to recover with reaching a maximum by day 14. The third stage is a decrease in cell proliferation by day 28 after ischemia, reaching a minimum on day 1 after ischemia. Probably, each peak in proliferation, due to increased cell division and neurogenesis, is followed by a decrease in these parameters as a result of depletion of the neurogenic niche. The decrease in cell proliferation at the first stage is probably due to increased cell migration from the SVZ to the olfactory bulb region [66].

These same events are accompanied by activation of cerebral angiogenesis, probably as a compensatory mechanism in



а / a *б / b*

Fig. 3. Scheme of neuron-glial coupling and interaction of astrocytes with other cells of the blood-brain barrier under normal conditions (*a*) and during activation of astrocytes (*b*). Brown arrows show the influence of astrocytes on other types of cells, the black arrow shows the influence of endothelial cells on astrocytes [7]. *Note:* EC — endothelial cells; MCT — monocarboxylate transporter; VEGF — vascular endothelial growth factor; LIF — leukemia inhibitory factor; Cx43 — connexin 43; CD38 —claster definition 38; GPR81 — hydroxycarboxylic acid receptor 1 (HCA1), G protein-coupled receptor 81; THBS1 — thrombospondin 1; NSC/NPC — Neural stem / neural progenitor cell; PCNA — proliferating cell nuclear antigen; NeuroD1 — neurogenic differentiation 1; NAD+ — nicotinamide adenine dinucleotide

Рис. 3. Схема нейрон-глиального сопряжения и взаимодействия астроцитов с другими клетками гематоэнцефалического барьера в обычных условиях (*а*) и при активации астроцитов (*б*). Коричневые стрелки отображают влияние астроцитов на другие виды клеток, черная стрелка показывает влияние эндотелиоцитов на астроциты [7]. *Примечание:* EC — эндотелиальные клетки (endothelial cells); MCT — монокарбоксилатный транспортер (monocarboxylate transporter); VEGF — сосудисто-эндотелиальный фактор роста (vascular endothelial growth factor); LIF — лейкемия-ингибирующий фактор (leukemia inhibitory factor); Cx43 — коннексин 43; CD38 — кластер дифференцировки 38 (claster definition 38); GPR81 — рецептор лактата 81, рецептор, связанный с G-белком 81 (hydroxycarboxylic acid receptor 1 (HCA1), G protein-coupled receptor 81); THBS1 — тромбоспондин 1 (thrombospondin 1); NSC/NPC — нормальные промежуточные клетки/нормальные стволовые клетки (neural stem/neural progenitor cell); PCNA — маркер пролиферирующих клеток (proliferating cell nuclear antigen); NeuroD1 — фактор нейрогенной дифференцировки-1 (neurogenic differentiation 1); NAD+ — никотинамидадениндинуклеотид (nicotinamide adenine dinucleotide)

response to tissue damage and reduced perfusion, for example, after ischemic brain injury or in slowly progressive degenerative diseases of the nervous system. The permeability of new vessels is increased in these situations and this is probably related to both neuroinflammation and the need to create new areas of neurogenesis in the damaged brain. The Notch signaling pathway conversion is one of the mechanisms, whereby endothelium and pericytes of cerebral microvessels are able to express the Notch receptor ligand Delta-like ligand-4 (DLL4) in response to high local production of VEGF [67]. This mechanism stimulates Notch proliferation and initiates the formation of additional neurogenic niches in the brain ventricular walls.

It is interesting to note that a number of brain structures are characterized by the absence of the BBB. These areas, known as circumventricular organs, contain highly permeable fenestrated capillaries. Circumventricular organs include the medial eminence, subfornical organ, vascular plexus, etc. For some circumventricular organs, the presence of neural stem cell niches has been suggested [15]. From this point of view, it seems important to note some features of the microenvironment characteristic of circumventricular organs that may influence the process of neurogenesis. One of such features is the presence of chronically activated microglia in circumventricular organs. Thus, it has been demonstrated that microglia of the medial eminence are characterized by morphological signs of activation throughout postnatal ontogenesis, despite the absence of pathology [17].

The presence of highly activated microglia in circumventricular organs in the mouse has been demonstrated under physiologi-

cal conditions [68]. It is important to note that microglia express high levels of CD16/32, CD86 — markers of M1 phenotype of macrophages responsible for proinflammatory response, endotoxicity and activation of phagocytosis, as well as CD206 — markers of M2 phenotype of macrophages regulating the phases of resolution of inflammation and repair of damaged tissues.

Reasons for this state of microglia are not fully understood, but studies performed on adult mice emphasize the importance of these markers for neurogenesis: microglia activated by endotoxins block neuro- and oligodendrocytogenesis, while microglia activated by such cytokines as interleukin-4 and interferon-γ stimulate neurogenesis, further emphasizing the influence of microglial phenotype on NSC/NPC renewal [68].

In this case, microglia activation is represented by the fact that the total length and number of outgrowths of microglial cells are significantly shorter than in other brain regions, and on the contrary, the expression level of activation marker molecules is elevated. Presumably, this is due to specific features of the structural and functional organization of these organs. In particular, this is due to the constant contact of microglia in circumventricular organs with molecules circulating in blood [36]. A probable function of microglia may be phagocytosis of neurotoxic molecules coming from the bloodstream in order to maintain a normal microenvironment in circumventricular organs.

Another possible function of activated microglia is regulating blood vessel permeability and angiogenesis [68, 69]. Intensive angiogenesis accompanied by constant proliferation and apoptosis of endothelial cells in blood vessels is carried out in circumventricular organs. In turn, the ability to regulate the proliferative activity of endothelium, as well as to participate in the removal of apoptotic cells remaining from dead endothelial cells has been indicated for activated microglia [58].

Finally, microglia can be involved in neurogenesis and acquire an activated morphotype [70–73]. Thus, it allows us to suggest a possible contribution of activated microglia to form neurogenic niches in this organ. This was previously observed in subventricular zone of the lateral ventricles and subgranular zone of the dentate gyrus of the hippocampus [74].

CONCLUSION

Mechanisms of neurogenesis in the postnatal period, as well as the processes of neuronal differentiation and migration are extremely important. The features of neurogenesis processes in different brain regions, using the hippocampus, cerebral cortex, and amygdala as examples, are interesting during critical periods of neurogenesis, the so-called time windows, both in intrauterine and postnatal periods. There is no doubt that the blood-brain barrier and microglia cells play a special role in forming microenvironment as well as influence neurogenesis in future.

Studying stress effect during critical periods of neurogenesis is promising both in theoretical and applied direction in order to develop methods of prevention and therapy of mental diseases, including neurodegenerative diseases.

ADDITIONAL INFORMATION

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

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

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CLAUDICATION AND IT'S APPROACH TO PRIMARY MANAGEMENT

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Abstract. Peripheral artery disease (PAD) is common and associated with significant morbidity and mortality. PAD occurs in about 18 percent of persons over 70 years of age. Usually, patients who have PAD present with intermittent claudication with pain in the calf, thigh or buttock that is elicited by exertion and relieved with a few minutes of rest. The disease may also present in a subacute or acute fashion. Symptoms of ischemic rest pain, ulceration or gangrene may be present at the most advanced stage of the disease. In caring for these patients, the primary care physician should focus on evaluation, risk factor modification and exercise. Optimal primary medical management of PAD is required for each patient, irrespective of the decision regarding lower extremity revascularization. The goals include reducing cardiovascular morbidity and mortality and improving quality of life. The approach should consist of aggressive and individualized risk factor modification including smoking cessation, antiplatelet therapy, a statin, and an angiotensin-converting enzyme inhibitor. Exercise is critical for cardiovascular health and highly effective for improving claudication symptoms. Cilostazol may be considered for symptomatic treatment in certain patients. Arterial occlusive diseases, such as coronary artery disease, cerebrovascular disease and peripheral arterial disease (PAD), are common in the primary care setting. These diseases often coexist in the same patient. Treatment of these diseases, which typically affect older adults, will consume a greater percentage of health care costs as the elderly population in the Russian Federation increases.

Keywords: peripheral arterial disease, atherosclerosis, claudication, primary management

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ХРОМОТА И ПОДХОД К ЕЕ ПЕРВИЧНОМУ ЛЕЧЕНИЮ

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Резюме. Заболевания периферических артерий (ЗПА) широко распространены и связаны со значительной заболеваемостью и смертностью. ЗПА встречается примерно у 18% лиц старше 70 лет. Обычно у пациентов с ЗПА отмечается перемежающаяся хромота с болью в икре, бедре или ягодице, которая возникает при нагрузке и проходит через несколько минут отдыха. Заболевание может протекать как подостро, так и остро. Симптомы ишемической боли в покое, язвы или гангрены могут проявляться на самой поздней стадии заболевания. При уходе за такими пациентами врач первичного звена должен сосредоточиться на оценке, изменении факторов риска и физических упражнениях. Оптимальное первичное медицинское ведение ЗПА необходимо для каждого пациента, независимо от решения о реваскуляризации нижних конечностей. Цели включают снижение сердечно-сосудистой заболеваемости и смертности и улучшение качества жизни. Подход должен включать агрессивную и индивидуальную модификацию факторов риска, в том числе отказ от курения, антитромбоцитарную терапию, статины и ингибиторы ангиотензин-превращающего фермента. Физические упражнения имеют решающее значение для здоровья сердечно-сосудистой системы и высокоэффективны для улучшения симптомов хромоты. Цилостазол может быть рассмотрен для симптоматического лечения у некоторых пациентов. Окклюзионные заболевания артерий, такие как ишемическая болезнь сердца, цереброваскулярные заболевания и ЗПА, часто встречаются в первичном звене медицинской помощи. Эти заболевания часто сосуществуют у одного и того же пациента. Лечение этих заболеваний, которые обычно поражают пожилых людей, будет занимать все большую долю расходов здравоохранения по мере увеличения численности пожилого населения в Российской Федерации.

Ключевые слова: заболевания периферических артерий, атеросклероз, хромота, первичное ведение

INTRODUCTION

Peripheral artery disease (PAD) is a common manifestation of the progressive stenosis of peripheral arteries (Fig. 4). More than 200 million people have PAD worldwide, and the prevalence of PAD is ≥20% in individuals over the age of 80 years [1]. Approximately 30% of patients with PAD experience intermittent claudication, a walking-induced muscle pain primarily affecting the calves that is relieved only by rest [2]. Patients experiencing claudication generally have sedentary lifestyles and poor health-related quality of life [2, 3]. PAD negatively affects the quality and length of life among those affected. The prognosis of the diseased extremity is generally favorable. Without specific therapy, the distance that affected persons are able to walk generally remains stable, worsening in 26 percent of persons and improving in 27 percent [4, 5]. Over five years, approximately 4 to 8 percent of affected persons require arterial reconstruction, and 2 to 4 percent require amputation [4, 6, 7]. The goals of the primary medical management of PAD focus on two areas: helping patients "live longer" by reducing cardiovascular morbidity and mortality and helping patients "feel better" by improving quality of life. However, patients with PAD are at risk for other atherosclerotic diseases. Up to 20 percent of asymptomatic patients may have carotid artery stenosis greater than 50 percent, and 12 to 17 percent have stenosis greater than 75 percent [8, 9]. The cornerstones of the primary medical management of PAD include risk factor modification, medications, such as statins and antiplatelet therapy, and exercise. PAD is associated with a significant increase in mortality [10–14]; a major contributor to this is cardiac death. In the Bypass Angioplasty Revascularization Investigation Trial [13, 14], the five-year survival rate was 77 percent in patients with coronary artery disease and PAD, compared with 90 percent in patients who had isolated coronary disease. Other studies have demonstrated a cumulative mortality of approximately 30 percent at five years and 47 to 61 percent at 10 years [10, 11, 14]. Given these associated risks, it would seem reasonable for asymptomatic patients with PAD to be screened for coronary artery disease and carotid artery stenosis; however, the most appropriate and cost-effective course of action remains unclear. In addition, cilostazol may be considered for treatment of claudication symptoms, although adverse side effects can be limiting.

EVALUATION

It is important to take a complete history that identifies symptoms of and risk factors for systemic atherosclerosis. Patients usually inform physicians of the signs and symptoms of coronary artery disease or cerebrovascular disease, but the presentation of PAD may be subtle, particularly in sedentary patients. The most common complaint is intermittent claudication with pain of the calf, thigh or buttock occurring with exertion and relieved after several minutes of rest. Other conditions that may need to be distinguished from PAD are listed in Table I.

Examination of the patient with PAD may reveal bruits over the abdominal aorta, iliac, femoral, carotid or subclavian arteries, and absent or decreased peripheral pulses. Physical findings that further support the diagnosis of PAD include decreased skin temperature, shiny, hairless skin over the lower extremities, dystrophic toenails, pallor on elevation of the extremity and rubor when the limb is dependent (Fig. 1).

PAD is classified by using the A.V. Pokrovsky, Fontaine Staging System and Rutherford category system (Table 2). The initial claudication distance (distance at which the patient first experiences pain with exertion) and the absolute claudication distance (distance at which the patient can no longer ambulate) are usually constant. With advancing disease or acute ischemia, patients may complain of a sudden decrease in the initial claudication distance, disabling claudication, or rest pain, or on examination may be found to have ulceration or tissue loss. Any of these complaints or findings warrants immediate referral to a vascular subspecialist.

The ankle-brachial index is an effective screening tool. The tools required to obtain an ankle-brachial index include a blood pressure cuff and a continuous wave Doppler. Blood pressure is measured in both upper extremities, and the highest systolic reading — the first return of Doppler sound as the cuff is deflated — is recorded. The ankle systolic pressure is similarly measured using the

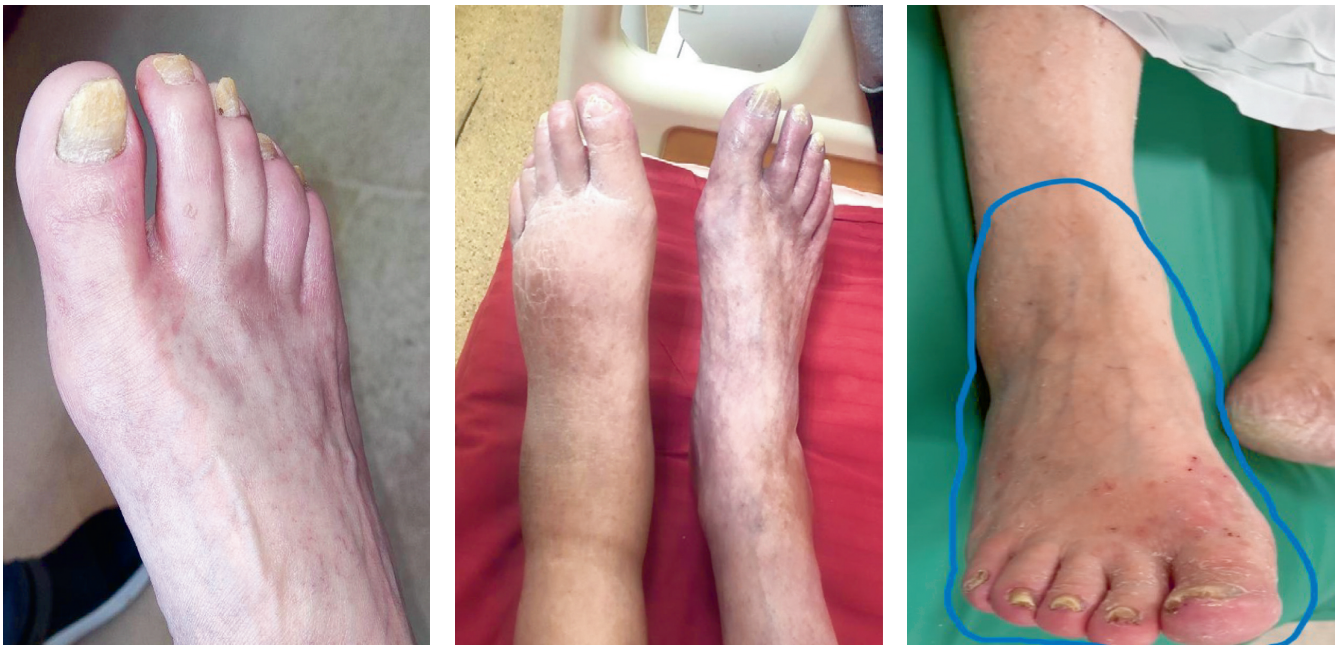
Table 1

Differential diagnosis of lower extremity pain

Таблица 1

Дифференциальная диагностика боли в нижних конечностях

Neurologic	Musculoskeletal	Vascular
• Lumbar canal stenosis (pseudoclaudication). • Radiculopathy/plexopathy. • Peripheral neuropathy	• Baker's cyst. • Muscle strain. • Ligament/tendon injury. • Arthritis/connective tissue disorder	• Intermittent claudication/ischemia. • Arterial thromboembolism. • Cholesterol embolism. • Deep venous thrombosis, vasculitis



а/a *б/b* *в/c*

Fig. 1. Shiny, hairless skin (*a*), dystrophic nail changes (*b*) and dependent rubor associated (*c*) with peripheral arterial occlusive disease of the different patient's right and left foot

Рис. 1. Сияющая, безволосая кожа (*а*), дистрофические изменения ногтей (*б*) и зависимый рубец (*в*), связанные с окклюзионным заболеванием периферических артерий правой и левой стопы у разных пациентов

Table 2

A.V. Pokrovsky, Fontaine and Rutherford peripheral artery disease classification

Таблица 2

Классификация заболеваний периферических артерий по А.В. Покровскому, Фонтейну и Рутерфорду

A.V. Pokrovsky classification	Fontaine classification
• Stage I — Asymptomatic or pain in calf muscles (>1 km). • Stage IIA — Intermittent claudication (>200 meters). • Stage IIB — Intermittent claudication (<200 meters). • Stage III — Intermittent claudication, rest pain. • Stage IV — Ulceration or gangrene	• Stage I — Asymptomatic, decreased pulses, ABI <0.9. • Stage II — Intermittent claudication. • Stage III — Daily rest pain. • Stage IV — Focal tissue necrosis
Rutherford classification	
• Category 0 — Asymptomatic. • Category 1 — Mild claudication (completes treadmill test/ankle pressures >50 mm Hg post treadmill test. • Category 2 — Moderate claudication (between category 1 and 3). • Category 3 — Severe claudication (unable to complete treadmill test/ankle pressures <50 mmHg post treadmill test). • Category 4 — Ischemia rest pain. • Category 5 — Minor tissue loss. • Category 6 — Major tissue loss	

dorsalis pedis or posterior tibial arteries. The ankle-brachial index is calculated by dividing the ankle pressure (the higher of the posterior tibial artery pressures) by the brachial systolic pressure (the higher of the two arm pressures). An ankle-brachial index below 0.95 at rest or following exercise is considered abnormal. An ankle-brachial index between 0.8 and 0.5 is consistent with intermittent claudication, and an index of less than 0.5 indicates severe disease [15]. In patients with an abnormal ankle-brachial index, testing with segmental arterial pressures and a pulse volume recording before and after exercising to the point of absolute claudication are indicated.

Pulse volume recording demonstrating bilateral segmental pressure decrease across the superficial femoral arteries, significantly worse on the left side than on the right side (Fig. 2). Note the mild dampening of the arterial wave form on the left, compared with the right. The ABI is consistent with mild disease on the right and moderate to severe disease on the left. Note the significant decrease following exercise. The resting ABI is calculated

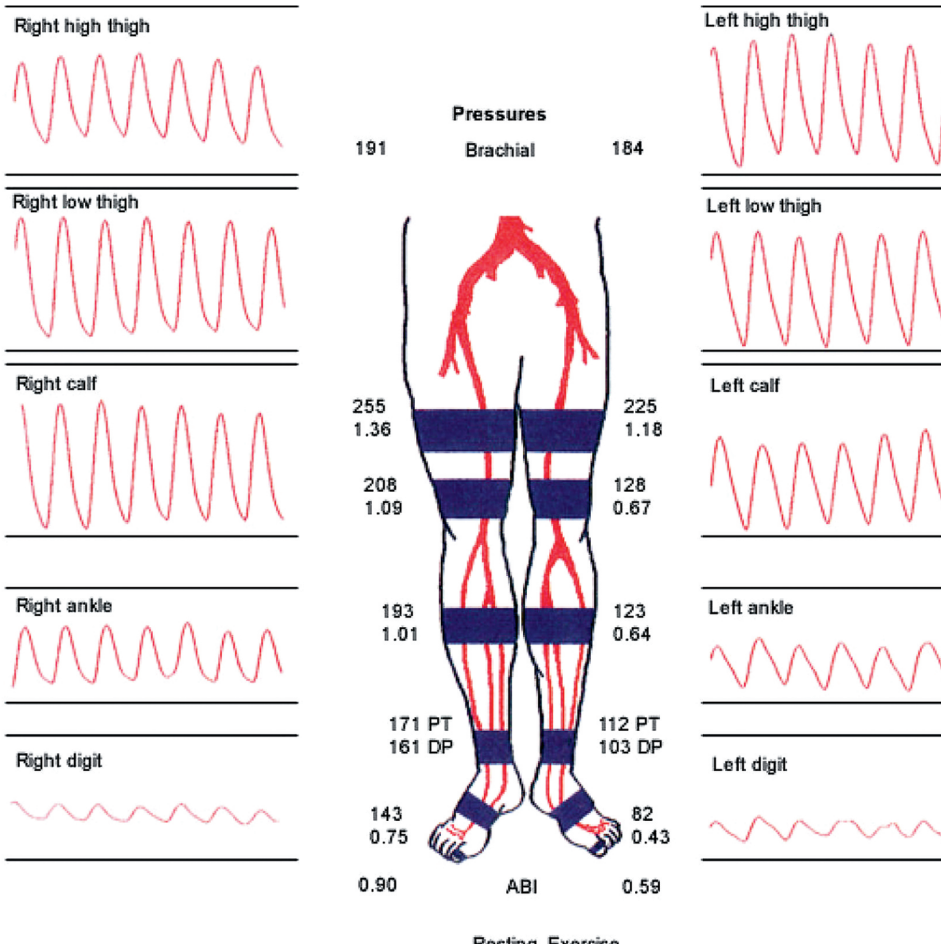


Fig. 2. Pulse Volume Recording (Source: https://doi.org/10.1177/154431671403800306)

Рис. 2. Запись объема пульса (Источник: https://doi.org/10.1177/154431671403800306)

as 171/191=0.90 (right) and 112/191=0.59 (left). All calculations are based on the higher brachial systolic reading, which in this case is 191. The ankle systolic reading is based on the higher of the posterior tibial and dorsalis pedis systolic readings. (ABI=ankle-brachial index; PT=posterior tibial; DP=dorsalis pedis.)

Management. Patients with intermittent claudication should receive conservative treatment. Aggressive risk factor modification, smoking cessation, antiplatelet therapy and a walking program are essential. In addition, medical treatment of the symptoms of claudication may benefit some patients.

RISK FACTOR MODIFICATION

The aim of risk factor modification in patients with PAD are the same as those in patients with coronary artery disease. Unfortunately, many patients with PAD are undertreated [16, 17]. All classes of antihypertensive agents are suitable in the treatment of PAD; the type of therapy is influenced by coexisting disease. Vasodilators provide no symptomatic relief and are not indicated over other agents. Historically, beta blockers have been avoided; however, the literature does not support worsening of symptoms with their use [18]. Many patients may have underlying coronary artery disease and could benefit from treatment with beta blockers.

Lipid abnormalities must be recognized and treated. High levels of low-density lipoprotein (LDL) cholesterol, low levels of high-density lipoprotein (HDL) cholesterol and high levels of triglycerides are associated with the development and progression of atherosclerosis. Patients should be treated in accordance with the guidelines of the National Cholesterol Education Program [19], which recommend a target LDL cholesterol level of less than 100 mg per dL (2.60 mmol per L) in patients with symptomatic vascular disease.

Tobacco is directly toxic to the vascular endothelium and is implicated in initiating and perpetuating atherosclerosis [20]. All patients must be strongly encouraged to abstain from tobacco use.

Smoking cessation. The effect of smoking in PAD is enormous, both in scope and effect. Up to 80% of patients with PAD

Table 3

Approach to smoking cessation: The 5 A's[a]

Таблица 3

Подход к отказу от курения: 5 A's[a]

The 5 A's	Explanation	Example
Ask	Ask every patient at every single visit if he or she uses any tobacco products (including electronic cigarettes or smokeless tobacco). Implement a system in the office for universal identification.	Do you smoke? Do you use smokeless tobacco like snuff or chew? Do you use electronic cigarettes (vaping)?
Advise	Advise every patient to quit at every visit. Use clear, strong, and personalized advice	You need to quit smoking as soon as possible to help keep your leg arteries open.
Assess	Assess the patient's willingness to quit.	Do you want to quit? Are you ready to quit?
Assist	Assist the patient by helping to set a quit date and providing medication and counseling and resources. For patients who have recently quit, discuss any challenges and the importance of preventing relapse.	What quit date would work for you? (Suggest an upcoming holiday or birthday or anniversary). Prescribe varenicline. Provide hotline information such as 1-800 QUIT NOW and the Smoking Cessation Patient Page from Vascular Medicine [23].
Arrange	Arrange for follow-up contact (office visit or phone call or email), ideally within the first week after the quit date.	Call the patient to check in. Set a delayed message in MyChart reminding the patient of the quit date.

[a] The entire office staff or treatment team can be engaged to help support the smoking cessation efforts [26].

are current or former smokers [21]. The risk of death, myocardial infarction (MI), and amputation is reported to be higher with continued smoking. Smoking cessation in PAD patients may reduce disease progression and may increase walking distance. Smoking after lower extremity bypass increases the risk of graft failure by at least threefold; however, smoking cessation may restore the patency rates to the level of nonsmokers [22]. The patient with claudication is often uniquely motivated to quit smoking after learning that (1) the leg symptoms could improve with smoking cessation, and (2) the disease will worsen with continued smoking. If the symptoms can improve with simply quitting smoking without any further medical or surgical intervention, then smoking cessation should always be the first step [23].

Varenicline is the most effective medication on the market for smoking cessation. It is a partial agonist (it both agonizes and blocks) α-4-β-2 nicotinic acetylcholine receptors, and by doing so, relieves withdrawal symptoms and simultaneously prevents further nicotine binding, which then partially blocks the reinforcing effects of nicotine [24]. Varenicline is more effective than bupropion and more effective than nicotine replacement therapy. Originally, practitioners would tend not to prescribe varenicline until patients were "ready to quit," partly because the medication is to be started ~1 week before the patient's proposed quit date. More recent evidence suggests that perhaps patients should be prescribed varenicline even if they are not immediately ready to quit because it will still increase smoking cessation rates [25]. Table 3 offers a basic approach to smoking cessation in the vascular patient [26]. The five "A's" of smoking cessation are Ask, Advise, Assess, Assist, and Arrange. For providers who prefer not to provide pharmacologic treatment or counseling, another approach is Ask, Advise, and Refer. Partnerships between vascular surgery and vascular medicine can help to achieve this goal. The most important message is that the benefits of smoking cessation greatly exceed any risks associated with pharmacologic treatment [26].

Hypertension. Hypertension should be treated according to current published guidelines to lower the risk of cardiovascular events. Guidelines from the Eighth Joint National Committee advised a target blood pressure of <140/90 mm Hg if the patient has diabetes or chronic kidney disease or is aged <60 years [27]. Otherwise, the target from the Eighth Joint National Committee was <150/90 mm Hg. The more recent SPRINT (Systolic Blood Pressure Intervention Trial) study has led to a more aggressive approach to blood pressure lowering [28]. SPRINT compared the benefit of treatment of systolic blood pressure to a target of <120 mm Hg with treatment of <140 mm Hg among patients at high risk for cardiovascular events but without diabetes. The lower target resulted in lower rates of major cardiovascular events and death from any cause, although with an increased risk of adverse events [28]. The ideal target blood pressure for patients with atherosclerotic vascular disease remains an active topic of debate.

Angiotensin-converting enzyme (ACE) inhibitors are an excellent choice for the treatment of hypertension in the setting of PAD and reduce cardiovascular risk beyond simply lowering blood pressure. The current guidelines support the use of ACE inhibitors or ARBs to reduce the risk of cardiovascular events in patients with lower extremity PAD.

Of note, b-blockers are not contraindicated in PAD patients. A meta-analysis of 11 randomized trials showed that β-blockers do not adversely affect walking capacity or claudication symptoms [29]. However, β-blockers are not first-line for treatment of hypertension but are commonly used for other indications such as heart failure, atrial fibrillation, or secondary prevention after MI.

Diabetes. Diabetes is a major risk factor for PAD and increases the risk of poor outcomes among PAD patients [30]. Patients with diabetes and PAD require a comprehensive and multidisciplinary care plan to include nutrition, weight management, podiatry, ophthalmology, endocrinology, and medications for glycemic control. For many years, the accepted target hemoglobin A_{1c} was <7%. Recently, the trend has shifted to a more individualized approach to glycemic control. For example, a more relaxed goal may be safer in older patients on insulin. Glycemic control has more effect on microvascular complications than on macrovascular complications and is particularly vital among patients with critical limb ischemia.

Body mass index. Body mass index (BMI) is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). The BMI should be calculated at each visit. Being overweight or obese is associated with increased all-cause mortality; all-cause mortality is lowest with a BMI of 20.0 to 24.9 kg/m^2 [31]. The association of obesity as a risk factor for PAD is controversial. However, among patients who already have PAD, weight loss can potentially improve claudication symptoms by reducing workload on the lower extremities. One study found that obesity decreased the time to claudication and delayed postexercise hemodynamic recovery [32]. PAD patients should be encouraged to lose weight if overweight or obese, with the goals of reducing mortality, reducing the risk of developing diabetes and metabolic syndrome, and, potentially, improving claudication symptoms.

MEDICATION

Statin therapy. All patients with PAD should be taking a statin, regardless of cholesterol levels. This recommendation is based on the Heart Protection Study (n 1/4 20,536, of whom 6748 had PAD), which demonstrated a 22% relative risk reduction in the first major vascular event among PAD patients randomized to simvastatin (40 mg) vs placebo [33]. Patients with PAD qualify for high-intensity statin treatment based on current cholesterol guidelines, which means that the goal is lowering the low-density lipoprotein cholesterol (LDL-C) by at least 50% [34]. To achieve this degree of LDL-C lowering, the best options based on clinical trial data are atorvastatin (40 mg or 80 mg) or rosuvastatin (20 mg or 40 mg). Atorvastatin and rosuvastatin are similar. One study found that rosuvastatin (40 mg) had a more favorable effect on the lipid profile (with lower LDL-C and higher high-density lipoprotein cholesterol levels) compared with atorvastatin (80 mg), but a similar degree of regression of percent atheroma volume was seen in the coronary arteries [35]. Atorvastatin and rosuvastatin are generic; however, the cost to the patient may differ by formulary or prescription plan. Of note, the maximum daily dose of rosuvastatin is 10 mg if the creatinine clearance is <30 mL/min.

Moderate-intensity statin treatment (lowering the LDL-C by ~30% to <50%) can be considered for patients who are aged >75 years (eg, atorvastatin at 10 mg or 20 mg; rosuvastatin at 5 mg or 10 mg) [34, 35]. Simvastatin (20–40 mg) is another moderate-intensity option, but the FDA has issued restrictions. Simvastatin at 80 mg should be avoided altogether due to the risk of myopathy. Furthermore, the maximum daily dose of simvastatin is 20 mg when combined with amiodarone or with amlodipine, which is commonly prescribed for hypertension. In addition to reducing cardiovascular risk, a few small studies have reported that statins may also improve claudication symptoms. In one study (n 1/4 69), simvastatin (40 mg) increased pain-free treadmill walking time at 6 and 12 months compared with placebo [36]. In a larger study (n 1/4 354), atorvastatin (80 mg) also improved pain-free walking time at 12 months compared with placebo [37]. Statins also improve outcomes in patients with critical limb ischemia [38]. Statins receive considerable attention in the media, with various reports of increased risk of diabetes, muscle issues, and liver toxicity. Much of the current controversy surrounds the use of statins in primary prevention, which is not relevant to PAD patients. Patients with PAD are high risk and have established atherosclerotic vascular disease, in which case there is no debate about the statin benefits, which are enormous regardless of the cholesterol levels.

Given that PAD patients usually already have leg pain, the question of myalgias or statin-induced myopathy often arises among PAD patients. Adverse effects of statins are typically mild and reversible. Efficacy and adverse effects vary among all statins because of their different pharmacokinetic and pharmacodynamics properties [39]. Thus, if a patient reports muscle pains from one statin, then a lower dose of the same statin or an alternative statin should be prescribed. The cardiovascular benefits of statins greatly outweigh any risks in the PAD population.

Antiplatelet therapy. Three antiplatelet agents are available for use in patients with vascular disease. Aspirin should be considered for use in any patient with coronary artery disease, cerebrovascular disease or PAD. In the Physicians' Health Study [40], patients who were randomized to receive aspirin therapy had a relative risk of 0.54 for peripheral arterial surgery when compared with patients who received placebo [40]. The Antiplatelet Trialists' Collaboration Study [41] demonstrated that patients with intermittent

claudication who were treated with antiplatelet therapy had a 17.8 percent relative reduction in the incidence of myocardial infarction, stroke and vascular death.

Treatment with ticlopidine (Ticlid) or clopidogrel (Plavix) should be considered in patients who are intolerant of aspirin therapy. In the Swedish Ticlopidine Multicentre Study [42], the group treated with ticlopidine had an incidence of myocardial infarction, stroke and transient ischemic attack of 13.8 percent versus an incidence of 22.4 percent in the group taking placebo. A lower rate of mortality from all causes was also demonstrated — 18.7 percent of the ticlopidine group compared with 26.1 percent of the placebo group.

The mechanism of action of clopidogrel is similar to that of ticlopidine, with fewer hematologic side effects. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial [43], patients with recent ischemic stroke, recent myocardial infarction or symptomatic PAD were evaluated. Patients who were treated with clopidogrel for the combined end points of ischemic stroke, myocardial infarction and vascular death demonstrated an overall relative risk reduction of 8.7 percent compared with patients who were treated with aspirin without a significant reduction in overall mortality. In the subgroup analysis, patients with PAD had a relative risk reduction of 23.8 percent for the combined end points.

Aspirin (typically 81 mg/d; range, 75–325 mg/d) is recommended for the reduction of the risk of MI, ischemic stroke, and vascular death among patients with symptomatic PAD (Table 4). The data supporting this recommendation are derived from the Antiplatelet Trialists' Collaboration, a meta-analysis of 287 studies of 135,000 patients with cardiovascular disease, including 9214 patients with PAD [44]. In the PAD subgroup, there was a 23% odds reduction for serious vascular events. Subsequent studies have suggested that the benefits of antiplatelet therapy are greater among patients with symptomatic PAD and are somewhat controversial among patients with asymptomatic PAD. In general, aspirin is under prescribed in PAD patients compared with patients with coronary artery disease (CAD). Clopidogrel (75 mg/d) is an alternative to aspirin. It may be marginally more effective than aspirin based on the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial, although it is more costly [45].

CAPRIE randomized 19,185 patients with recent MI, ischemic stroke, or symptomatic PAD to clopidogrel vs aspirin (325 mg). In the PAD subgroup (n 1/4 6452), a 23.8% relative risk reduction for vascular events was seen with clopidogrel compared with those treated with aspirin; however, the absolute risk reduction was small (1.15%). Dual antiplatelet therapy (aspirin plus clopidogrel) is generally not needed in PAD patients, although it may be considered in patients who are extremely high risk [46]. For example, dual antiplatelet therapy may be reasonable for a high-risk patient with diabetes who smokes and has PAD with concomitant CAD, particularly for as long as the patient continues to smoke. Ticagrelor is an oral, reversible inhibitor of P2Y12 with faster onset/offset than clopidogrel and more predictable inhibition of adenosine 50-diphosphate-induced platelet aggregation. The recent EUCLID (A Study Comparing Cardiovascular Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease) trial found that ticagrelor (90 mg twice daily) was not superior to clopidogrel for the reduction of cardiovascular events among patients with symptomatic PAD and that major bleeding rates were similar [47]. In the WAVE (Warfarin Antiplatelet Vascular Evaluation) trial, the combination of anticoagulation with warfarin plus antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing cardiovascular events; the combination was associated with an increase in life threatening bleeding [48]. Thus, there is no role for anticoagulation for PAD.

Table 4

Quick reference to assess optimal medical management in patients with peripheral artery disease[a]

Таблица 4

Краткие рекомендации по оценке оптимального медицинского ведения пациентов с заболеваниями периферических артерий[a]

Question to ask	Possible next steps
Is the patient on antiplatelet therapy?	Add aspirin, 81mg daily
Is the patient on a statin?	Add atorvastatin, 40 mg daily (or 10-20 mg if aged >75)
Is the patient currently smoking?	Consider varenicline
Is the blood pressure above goal?	Add ramipril
Is the hemoglobin A_{1c} >7%?	Refer to primary care, nutrition, comprehensive diabetes center, and/or endocrinology
Is BMI >25 kg/m2?	Set appropriate weight loss goals

BMI — Body mass index.
[a]Consider referral to vascular medicine if any of the goals are not met.

EXERCISE

Exercise plays a fundamental role in the treatment of PAD. It has been shown since the 1960s to be an effective treatment for claudication, leading to improvement in both pain-free and maximal walking distance. The CLEVER (Claudication: Exercise Vs Endoluminal Revascularization) trial found that a supervised exercise program improved treadmill walking performance more than endovascular revascularization for patients with aortoiliac disease [49]. A detailed discussion of exercise for PAD is provided in this supplement.

Current guidelines indicate that all patients should achieve 30 minutes of brisk exercise daily for overall cardiovascular health. This recommendation is especially important for PAD patients. Generally, patients should walk until they have moderate pain or discomfort (4 on a scale of 1 to 5), stop and rest until the pain subsides, and then start walking again [49]. Patients should aim to reach this moderate level of pain within the first 5 to 7 minutes of walking. Over time, they will need to walk uphill or more quickly, or both, to bring on the pain within this timeframe. These intermittent bouts of rest and exercise are thought to improve oxygen extraction by the muscles; claudication symptoms improve through a variety of mechanisms [50]. Exercise has tremendous benefits that extend far beyond the improvement in claudication symptoms and functional capacity and include improving endothelial function, blood pressure, cholesterol, glycemic control, and systemic cardiovascular health [50].

Walking improves the symptoms of claudication in several ways. The muscle can better adapt to anaerobic metabolism with repeated exposure to an ischemic environment. Oxidative metabolism and the overall number of available mitochondria increase. A meta-analysis [51] showed an increase of 179 percent in the initial claudication distance and 122 percent in the absolute claudication distance in patients who followed a walking program. Five components of a successful program were also identified. Walking is the preferred mode of exercise. Patients should walk at least three times per week for at least 30 minutes at each session. Near-maximal claudication pain (absolute claudication distance) should be the resting point, and the patients should follow the program for at least six months [51]. A supervised program is superior to a home-based exercise program [52]. A walking program can increase the objective distance that the patient with claudication can ambulate. This may result in subjective improvement and lead to an enhanced quality of life.

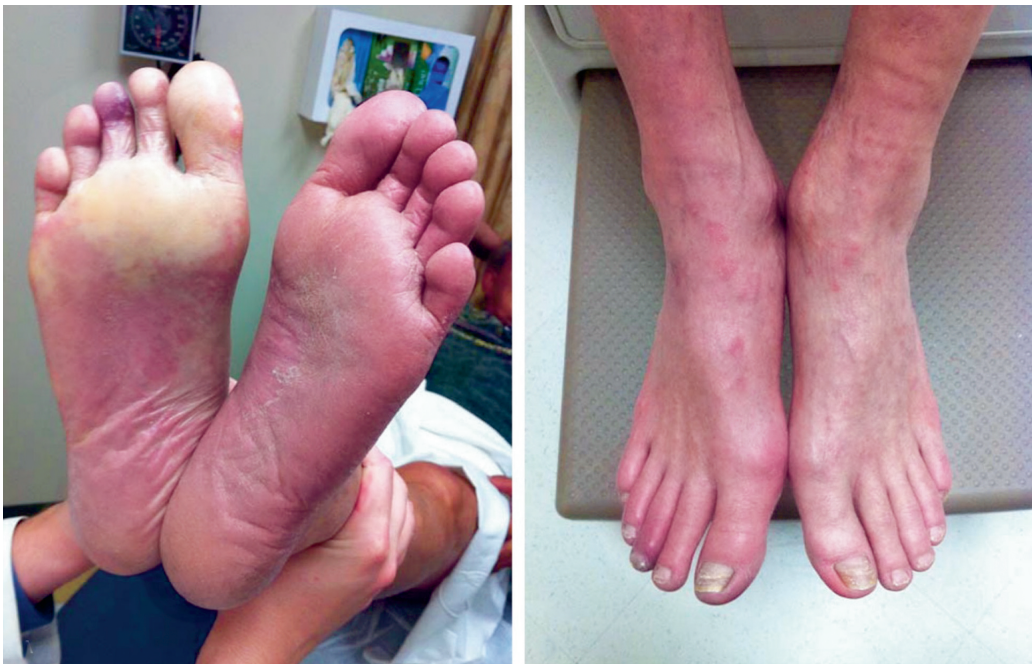
PHARMACOLOGIC TREATMENT OF CLAUDICATION SYMPTOMS

Options are limited in the medications directed at ameliorating claudication symptoms. The first such medication was Pentoxifylline (Trental) (400 mg thrice daily with meals), which was approved by the FDA in 1984 based on small studies. Pentoxifylline is thought to reduce viscosity and improve erythrocyte flexibility; unfortunately, subsequent studies have shown that it is no different from placebo in treating claudication [53]. While the overall efficacy of pentoxifylline has been questioned [54], a recent meta-analysis [55] of patients treated with pentoxifylline demonstrated small improvements in the initial claudication distance and absolute claudication distance. Pentoxifylline is thus not recommended for PAD patients.

The newest agent for treating intermittent claudication is cilostazol. Cilostazol is a phosphodiesterase III inhibitor that suppresses platelet aggregation and acts as a direct arterial vasodilator [56–58], inhibitor and is more effective than pentoxifylline. In one study [58], the patients who received cilostazol had a 35 percent increase in the distance they could walk before claudication and a 41 percent increase in absolute claudication distance when compared with the subjects who received placebo. One half of the patients treated with cilostazol judged their walking to be “better” or “much better”; 84 percent of patients taking placebo felt that their symptoms were unchanged or worse [58]. Other patients taking cilostazol documented improvement in the absolute claudication distance and ankle-brachial index, along with similar subjective improvements in quality of life and walking ability [59].

A Cochrane review of 15 double-blind, randomized controlled trials (n 1/4 3718) concluded that cilostazol improves walking distance among patients with claudication. Cilostazol is a vasodilator that inhibits vascular smooth muscle cell proliferation and prevents platelet aggregation. Its mechanism for improving claudication symptoms is not clear and is probably multifactorial. The dose is 100 mg twice daily and should be taken at least 30 minutes before or 2 hours after breakfast and dinner. Adverse effects can be limiting and include headache, palpitations, dizziness, and gastrointestinal complaints. Cilostazol is contraindicated in heart failure. The dose should be reduced to 50 mg twice daily in patients with hepatic dysfunction or when given with cytochrome P450 enzyme inhibitors, such as azole antifungals, macrolide antibiotics, or proton pump inhibitors; grapefruit juice should be avoided. The dose may also be reduced if adverse effects are an issue.

In clinical practice, patients with PAD are often taking many medications. For example, a typical ideal regimen may include aspirin (81 mg/d), atorvastatin (40 mg/d), and ramipril (10 mg/d). These three medications are aimed at reducing cardiovascular morbidity and mortality, or to achieve the “live longer” goal. Given the high prevalence of diabetes and hypertension, the same PAD patient may also take other medications such as metformin, gabapentin, amlodipine, or hydrochlorothiazide. With this extensive medication list, the patient and the practitioner may be hesitant to add cilostazol



a/a *б/b*

Fig. 3. Critical limb ischemia: *a* — elevation pallor; *b* — dependent rubor

Рис. 3. Критическая ишемия конечностей: *а* — бледность при подъеме; *б* — зависимый рубец

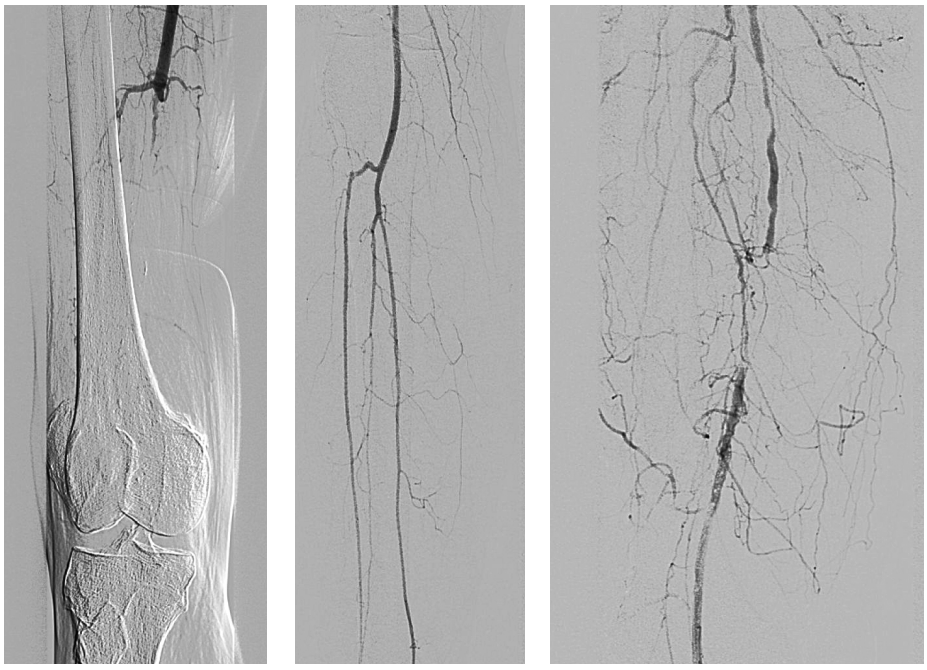


Fig. 4. Angiograms of atherosclerosis in lower limb arteries (peripheral artery disease)

Рис. 4. Ангиограммы атеросклероза артерий нижних конечностей (заболевания периферических артерий)

considering its adverse effect profile and suboptimal efficacy. A 3-month course of medical management, including an exercise program, is a reasonable approach before adding cilostazol, which can be seen as an intermediate step before endovascular or surgical revascularization.

Clinical Presentation. Intermittent claudication is the hallmark of PAD and is defined as fatigue, discomfort, cramping, or pain of vascular origin in the calf muscles of the lower extremities that is consistently induced by exercise and consistently relieved within 10 minutes by rest. In the

general population, only about 10% of persons with known PAD have the classic symptom of intermittent claudication. Approximately 40% do not complain of leg symptoms at all, and 50% have a variety of leg symptoms different from classic claudication, such as exertional pain that does not stop the individual from walking, does not involve the calves, or does not resolve within 10 minutes of rest [60–71]. The 2016 American Heart Association/American College of Cardiology (AHA/ACC) guideline on the management of patients with lower extremity PAD recommends patients at increased risk of PAD should be assessed for exertional leg symptoms, ischemic rest pain, and nonhealing wounds. Other common lower extremity findings include hair loss, shiny skin, and muscle atrophy. Arterial ulcerations are characterized by well-demarcated, "punched-out" lesions. Dependent rubor and elevation pallor may be present in advanced disease and result from impaired autoregulation in the dermal arterioles and capillaries (Fig. 3, 4).

CONCLUSIONS

The primary medical management of PAD clearly demonstrates the benefits of cholesterol lowering statin therapy, smoking cessation, antiplatelet therapy and physical exercises, safely producing highly significant reductions in cardiovascular morbidity and mortality. The medical management is aimed at the two goals of feeling better and living longer. For the "live longer" goal, compulsory medications include antiplatelet therapy, a statin, and an ACE inhibitor, as summarized in Table 4. For the "feel better" goal, the main pharmacologic treatment is cilostazol. Fortunately, smoking cessation, exercise are safe and low-cost treatment option's that achieves both aims.

ADDITIONAL INFORMATION

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

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

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EOSINOPHILIC ESOPHAGITIS AS A RARE COMPLICATION OF SUBLINGUAL ALLERGEN-SPECIFIC ALLERGEN IMMUNOTHERAPY. CLINICAL CASE

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Abstract. Allergen-specific immunotherapy (ASIT) is the only disease-modifying method of allergy treatment that allows the development of long-term tolerance to an allergen. The therapy is that after confirmation of IgE-dependent sensitization to a particular allergen, the patient can receive treatment with a preparation of this allergen. The most common and effective ASIT for respiratory forms of allergy — rhinitis and bronchial asthma — is allergen therapy with pollen and house dust mite allergens. There is still insufficient data on the effectiveness of animal allergens. For vital indications, ASIT is performed with allergenic venoms of webworms and, in some countries, with food allergens. The duration of therapy is from 3 to 5 years, except for therapy with insect venoms and food allergens, when it is recommended to take the allergen for life to maintain tolerance. Tolerance itself is formed after 4–6 months from the start of treatment and is maintained for years. The safest in terms of anaphylactic reactions is sublingual allergen-specific immunotherapy (SLIT). However, cases of eosinophilic esophagitis (EoE), a rare complication of SLIT, have been described. The present case report describes the development of EoE in a 27-year-old man 4 weeks after starting SLIT with a tablet preparation of meadow grass allergens. The symptoms of EoE resolved rapidly within a few days of SLIT withdrawal. Possible options for continuing ASIT in the development of EoE and specifically in this patient are described.

Keywords: allergen immunotherapy (AIT), eosinophilic esophagitis (EoE), sublingual immunotherapy (SLIT), pollinosis

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ЭОЗИНОФИЛЬНЫЙ ЭЗОФАГИТ КАК РЕДКОЕ ОСЛОЖНЕНИЕ СУБЛИНГВАЛЬНОЙ АЛЛЕРГЕН-СПЕЦИФИЧЕСКОЙ ИММУНОТЕРАПИИ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Резюме. Аллерген-специфическая иммунотерапия (АСИТ) — единственный болезнь-модифицирующий метод лечения аллергии, который позволяет выработать долгосрочную толерантность к аллергену. Терапия заключается в том, что после подтверждения IgE-зависимой сенсибилизации к конкретному аллергену пациент может получать лечение препаратом этого аллергена. Терапия может проводиться препаратами для сублингвального применения либо подкожными инъекциями. Наиболее распространена и эффективна АСИТ при респираторных формах аллергии — рините и бронхиальной астме аллергенами пыльцы и клещей домашней пыли. Об эффективности применения аллергенов животных данных пока недостаточно. По жизненным показаниям проводится АСИТ ядами перепончатокрылых, и в некоторых странах — пищевыми аллергенами. Длительность терапии — от 3 до 5 лет, за исключением терапии ядами насекомых и аллергенами пищи, когда аллерген рекомендуется принимать пожизненно для поддержания толерантности. Сама толерантность формируется уже через 4–6 месяцев от начала лечения и сохраняется годами. Наиболее безопасная в плане развития анафилактических реакций — сублингвальная аллерген-специфическая иммунотерапия (СЛИТ). Тем не менее описаны случаи развития редкого осложнения СЛИТ — эозинофильного эзофагита (ЭоЭ). В данном клиническом случае приводится пример развития ЭоЭ у 27-летнего мужчины через 4 недели от старта СЛИТ таблетированным препаратом аллергенов луговых трав. Симптомы ЭоЭ быстро разрешились в течение нескольких дней после отмены СЛИТ. Описаны возможные варианты продолжения АСИТ при развитии ЭоЭ и конкретно у этого пациента.

Ключевые слова: аллерген-специфическая иммунотерапия (АСИТ), эозинофильный эзофагит (ЭоЭ), сублингвальная иммунотерапия (СЛИТ), поллиноз

INTRODUCTION

Allergen-specific immunotherapy (ASIT) is the only disease-modifying method of allergy treatment that allows the development of long-term tolerance to an allergen. The essence of therapy is that after confirmation of IgE-dependent sensitization to a particular allergen, the patient can be treated with a preparation of this allergen. The formation of tolerance is based on the induction of allergen-specific T-regulatory cells (T-reg), which, with the help of suppressor cytokines, modulate the specific T- and B-cell response [1]. This leads to increased production of specific IgG4, blocking the action of IgE, functional restriction of mast cells, basophils and eosinophils and the formation of long-term tolerance to the allergen. Therapy can be carried out with sublingual drugs or subcutaneous injections. Each method has its own advantages and disadvantages. The most common and effective ASIT for respiratory forms of allergy — rhinitis and bronchial asthma caused by pollen and house dust mite allergens. There is still insufficient data on the effectiveness of animal allergens. For vital indications, ASIT is performed with venoms of webworms and, in some countries, with food allergens. The duration of therapy is 3 to 5 years, with the exception of insect venom and food allergen therapy, where it is recommended to take the allergen for life to maintain tolerance. Tolerance is formed in 4–6 months from the beginning of treatment and lasts for years. The method is more than 100 years old, its founders — Leonard Noon and John Freeman — first published the results of their work — therapy of hay fever by subcutaneous injections of aqueous pollen extracts — in The Lancet in 1911 [2]. Over the years, the ASIT methodology has been improved, and effective and standardized preparations with a high safety profile have appeared.

(СЛSublingual allergen-specific immunotherapy (SLIT) is the safest in terms of systemic allergic reactions (there is no cases requiring epinephrine administration have been reported) and is often the method of choice [3]. However, cases of eosinophilic esophagitis (EoE), a rare complication of SLIT, have been described [4–6].

Typical adverse reactions when using SLIT are localized (burning under the tongue) and moderate aggravation of allergic rhinoconjunctivitis at the beginning of therapy. These phenomena are successfully controlled with antihistamines and, if necessary, topical steroids without discontinuation of ASIT. These symptoms usually disappear within 2–4 weeks.

Eosinophilic esophagitis is a rare (less than 1% of cases according to the ASIT product instructions) complication of sublingual allergen-specific immunotherapy. EoE is a chronic, immune/antigen-mediated esophageal disease clinically characterized by symptoms associated with esophageal dysfunction and histologically by eosinophil-dominated inflammation [7–13].

The pathogenesis is based on genetically determined disruption of esophageal epithelial function, which leads to failure of its barrier function and development of Th2 inflammation. The triggers are mainly food allergens. Much less frequent are cases of provocation by aeroallergens — seasonal exacerbations of EoE in patients with allergic rhinitis against the background of flowering of significant plants. SLIT with pollen allergens can also be a trigger and, as a rule, it is a contraindication for continuing SLIT [3, 4].

EoE was previously classified as an allergic disease with a mixed mechanism: type I, IgE-dependent, and type IV, delayed-type hypersensitivity. Modern classification categorizes EoE as type IVb allergic reactions, which are based on Th2 inflammation. Th2 produce a variety of cytokines — interleukin-4 (IL-4), IL-5, IL-9, IL-13, IL-31 and eotaxins I-III. IL-4 and IL-13 play a key role in inducing a switch of B-lymphocytes to synthesize IgE. IL-13 is also responsible for tissue remodeling involved in chronic inflammation. IL-5 ensures the recruitment of eosinophils from the bone marrow and their persistence in the focus of inflammation. Degranulation of eosinophils and release of their endogenous proteases contributes to further tissue damage, inflammation chronization, and aggravation of the defect in the barrier function of the epithelium [14].

EoE was previously considered a rare disease. However, nowadays, there is an increasing number of publications and a growing incidence, which is probably due to the introduction of knowledge into practice and continued study of this pathology.

The first publications on esophageal eosinophilia appeared in the 70s of the XX century. In the Russian Federation, recommendations on the diagnosis and treatment of EoE were first published in 2013 [9].

CLINICAL CASE

A 27-year-old male patient with seasonal allergic rhinitis and conjunctivitis, sensitization to meadow grasses. His complaints have been present for several years, with clinical manifestations increasing in dynamics. Sensitization to meadow grasses was confirmed by prick tests.

The first course of SLIT was started in February 2022. According to the drug instructions, the patient swallowed saliva after dissolving the tablet. In the first week of therapy, a moderate local reaction (burning of the mucous membrane under the tongue) was noted, which is common with SLIT and expected at the initial stages of therapy. Against the background of antihistamines, these symptoms decreased and later did not bother even without medication support.

Approximately one month after the start of therapy, the patient first developed symptoms of dysphagia, which he did not pay attention to and did not connect with SLIT. The patient did not report his symptoms until 2 weeks later, as they became daily and there was a very intense pain when swallowing,

according to the patient, “to the point of tears”. There were also complaints of intermittent nasopharyngeal discomfort, a feeling of shortness of breath, and an intractable cough lasting up to several minutes after meals, mostly during the day.

EoE was clinically suspected, and immediately after the patient reported the side effect of the drug SLIT was interrupted, leading to a rapid resolution of the clinical picture. The patient was examined by an otorhinolaryngologist (ENT), no pathology from the ENT organs was found.

In the next few days, an endoscopic examination (esophagogastroduodenoscopy — EGDS) was performed. Due to the short time of SLIT administration, the macroscopic picture was not convincing and was regarded only as a suspicion of EoE. Histologic examination of six biopsy specimens of esophageal mucosa revealed up to 50 eosinophils in the field of view at ×400 magnification with acceptable values for esophagus up to 15, which confirmed the diagnosis of EoE.

Since after the drug withdrawal the symptoms of dysphagia completely resolved within 1–2 days, drug therapy for esophagitis was not prescribed. On re-endoscopy performed 10 months later, a normal mucosal picture was observed. The biopsy showed no evidence of esophagitis.

Despite the development of a serious complication of SLIT, the patient was determined to continue ASIT in the next season (each season SLIT with pollen allergens begins 4 months before the onset of flowering and lasts until the end of flowering), because the symptoms of pollinosis severely impaired the quality of life. The possibility of continuing SLIT against the background of standard therapy of EoE (proton pump inhibitors (PPIs), budesonide or fluticasone) was considered, which would not exclude a possible exacerbation. The possibility of continuing SLIT “under cover” with Dupilumab for the treatment of EoE was considered. However, given the normal results of repeat endoscopy with biopsy, receipt of this therapy within the framework of compulsory medical insurance was excluded. Switching to subcutaneous immunotherapy (SCIT) was also undesirable due to the lack of standardized drugs for SCIT.

There are studies confirming the possibility of continuing SLIT if saliva is spit out after sublingual exposure to the drug [5]. Before resuming SLIT, the patient underwent endoscopic examination with biopsy, which showed the absence of eosinophilic inflammation in the esophagus. Therapy was continued. With this method of SLIT, the patient in 2023 successfully completed the entire first preseasonal-seasonal course of therapy without side effects and with positive results in the form of reduction of pollinosis symptoms. The treatment is currently ongoing (the 2nd course out of the required three), indicating that continuation of SLIT is possible and effective.

CONCLUSION

This example demonstrates that in case of EoE development on the background of SLIT, continuation of SLIT with the causative allergen is possible. For successful continuation of therapy, certain conditions must be met: achievement of complete remission of EoE before returning to SLIT, saliva spitting after sublingual exposure to the allergen.

In our case, the continuation of SLIT was carried out after a year, which was dictated by the peculiarities of SLIT with pollen allergens — a preseasonal-seasonal protocol, when treatment begins 4 months before flowering and continues throughout the flowering period. This long interval ensured complete remission of EoE in the patient. A repeat endoscopy with biopsy was performed immediately before the planned continuation of SLIT.

In case of using SLIT with year-round protocol it is necessary to be guided by the terms of standard remission of EoE. In most cases, repeated esophageal endoscopy with biopsy after 2 months of elimination of the causative allergen reveals complete resolution of esophageal eosinophilia [8].

ADDITIONAL INFORMATION

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

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

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

The manufacturer was informed about the complication that had arisen.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

Компании-производителю о возникшем осложнении было сообщено.

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ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом и.о. ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 05.04.24

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

Условия настоящего Договора (далее «Договор») являются публичной офертой в соответствии с п. 2 ст. 437 Гражданского кодекса Российской Федерации. Данный Договор определяет взаимоотношения между редакцией журнала «**Russian Biomedical Research»** (далее по тексту «Журнал»), зарегистрированного Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР), свидетельство: ПИ № ФС77-74228 от 02 ноября 2018 г. (ранее ПИ № ТУ78-01869 от 17 мая 2016 г.), именуемой в дальнейшем «Редакция» и являющейся структурным подразделением ФГБОУ ВО СПбГПМУ Минздрава России, и автором и/или авторским коллективом (или иным правообладателем), именуемым в дальнейшем «Автор», принявшим публичное предложение (оферту) о заключении Договора.

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Файл статьи называется по Фамилии первого автора, например, Иванов.doc или Petrov.doc. Никаких других слов в названии не должно быть!

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

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

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- Текст статьи может быть написан либо на русском, либо на английском языке, также возможна публикация статьи с полным переводом. На русском и английском языках необходимо предоставить все рисунки и таблицы (заголовки, все надписи, а также текст таблиц должны иметь перевод).

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

  Таблицы и рисунки приводятся непосредственно в теле статьи, каждый из которых имеет номер и название с обязательными ссылками на них в тексте статьи — в контексте предложения (например: «…как показано на рисунке 1…») или в конце предложения в круглых скобках (например: «...выявлена положительная корреляционная связь умеренной степени (r=0,41) между уровнем ТТГ матери и новорожденного (рис. 2)»; просьба учитывать, что в печатной версии журнала рисунки будут воспроизводиться в черно-белом варианте.
- Список литературы обязательно приводится в порядке упоминания.

Текст статьи должен быть подготовлен в строгом соответствии с настоящими правилами и тщательно выверен автором. В случае обнаружения значительного количества опечаток, небрежностей, пунктуационных и орфографических ошибок, нерасшифрованных сокращений, отсутствия основных компонентов, переводов заголовков таблиц, подрисуночных подписей, надписей на рисунках,

текста таблиц и других технических дефектов оформления статей редакция возвращает статью автору для доработки. Небольшие погрешности редакция может исправить сама без согласования с автором. Редакция оставляет за собой право осуществления литературного и технического редактирования статей.

Сокращений, кроме общеупотребительных, следует избегать. Сокращения в названии статьи, названиях таблиц и рисунков, в выводах недопустимы. Если аббревиатуры используются, то все они должны быть непременно расшифрованы полностью при первом их упоминании в тексте (например: «Наряду с данными о РОН (резидуально-органической недостаточности), обусловливающей развитие ГКС (гиперкинетического синдрома), расширен диапазон исследований по эндогенной природе данного синдрома».

Все цитирования производятся следующим образом:

ФИО автора, год издания и прочая информация не упоминаются в тексте. Вместо этого указывается ссылка на источник литературы в виде номера в квадратных скобках (пример: «Ряд исследователей отмечает различные нарушения речевых функций при эпилепсии в детском возрасте [17, 21, 22].»), который включен в расставленный в порядке упоминания (1, 2, 3 и т.д.) список источников в конце статьи.

Все ссылки должны иметь соответствующий источник в списке, а каждый источник в списке — ссылку в тексте.

В виде исключения в тексте могут приводиться ФИО конкретных авторов в формате И.О. Фамилия, год и даже название источника, но при этом все равно обязательна ссылка (в квадратных скобках в конце предложения) на источник, включенный в список литературы. (Например: «В 1892 году великий Эраст Гамильтонский описал в своем бессмертном труде «Об открытии третьего уха у человека» третье (непарное) ухо» [34].)

Литература (References)

Учитывая требования международных систем цитирования, список литературы приводится не только в обычном виде, но также и дополнительно в переведенном на английский язык (References).

В статье приводятся ссылки на все упоминаемые в тексте источники.

Фамилии и инициалы авторов в пристатейном списке приводятся в порядке упоминания.

В описании указываются все авторы публикации.

Библиографические ссылки в тексте статьи даются в квадратных скобках.

Ссылки на неопубликованные работы не допускаются.

Список литературы комплектуется в следующем порядке:

Нормативные акты

Приказы, нормативные акты, методические письма и прочие законные акты, патенты, полезные модели не вносятся в список литературы, оформляются в виде сносок. Сноска — примечание, помещаемое внизу страницы (постраничная сноска). Знак сноски ставят цифрой после фрагмента основного текста, где есть упоминание об этих источниках. Рекомендуется сквозная нумерация сносок по тексту.

Интернет-ресурс

1. Интернет-ресурс, где есть название источника, автор, вносится в список литературы (в порядке алфавита) с указанием даты обращения (см. ниже пример оформления).

2. Если есть только ссылка на сайт, оформляется подстрочное примечание (сноска), с указанием даты обращения.

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

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

Примеры оформления литературы

Книга:

Юрьев В.К., Моисеева К.Е., Глущенко В.А. Основы общественного здоровья и здравоохранения. Учебник. СПб.: СпецЛит; 2019.

Никифоров О.Н., ред. Санкт-Петербург в 2021 году. СПб.: Петростат; 2022.

Brandenburg J.H., Ponti G.S., Worring A.F. eds. Vocal cord injection with autogenous fat. 3 rd ed. NY:Mosby; 1998.

Domeika M. Diagnosis of genital chlamydial infection in humans as well as in cattle. Uppsala; 1994.

Глава из книги:

Тутельян В.А., Никитюк Д.Б., Шарафетдинов Х.Х. Здоровое питание — основа здорового образа жизни и профилактики хронических неинфекционных заболеваний. В кн.: Здоровье молодежи: новые вызовы и перспективы. Т. 3. М.; 2019: 203–227.

Статья из журнала:

Карсанов А.М., Полунина Н.В., Гогичаев Т.К. Безопасность пациентов в хирургии. Часть 2: Программа менеджмента качества хирургического лечения. Медицинские технологии. Оценка и выбор. 2019;1(35):56–65. DOI: 10.31556/2219-0678.2019.35.1.056-065.

Brandenburg J.H., Ponti G.S., Worring A.F. Vocal cord injection with autogenous fat: a long-term magnetic resona. Laryngoscope. 1996;l06(2,pt l):174–80.

Deb S., Campbell B.K., Pincott-Allen C. et al. Quantifying effect of combined oral contraceptive pill on functional ovarian reserve as measured by serum anti-Müllerian hormone and small antral follicle count using three-dimensional ultrasound. Ultrasound Obstet Gynecol. 2012;39(5):574–580.

Тезисы докладов, материалы научных конференций:

Марковская И.Н., Завьялова А.Н., Кузнецова Ю.В. Микробный пейзаж пациента первого года жизни с дисфагией, длительно находящегося в ОРИТ. XXX Конгресс детских гастроэнтерологов России и стран СНГ: тез. докл. М.; 2023: 29–31.

Салов И.А., Маринушкин Д.Н. Акушерская тактика при внутриутробной гибели плода. В кн.: Материалы IV Российского форума «Мать и дитя». Ч. 1. М.; 2000; 516–519.

Авторефераты:

Авилов А.Ю. Девиации полоролевой идентичности мужчин с умственной отсталостью в условиях психоневрологического интерната. Автореф. дис. … канд. психол. наук. СПб.; 2021.

Описание интернет-ресурса:

Естественное движение населения. Москва: Росстат. Доступен по: https://rosstat.gov.ru/folder/12781 (дата обращения: 23.10.2023).

World Health Organization. Prevalence and incidence of selected sexually transmitted infections — 2008. Geneva: World Health Organization; 2012. Available at: https://aefsg.ch/wp-content/uploads/who-9789241503839_eng.pdf (accessed^ 11.04.2024)

Перевод и транслитерация

В зависимости от ситуации следует либо проводить транслитерацию (писать исходные неанглоязычные слова буквами романского алфавита), либо указывать перевод неанглоязычной информации о первоисточниках в References.

Если цитируемая статья написана **на латинице** (на английском, немецком, испанском, итальянском, финском, датском и других языках, использующих романский алфавит), ссылку на нее следует привести на оригинальном языке опубликования. Пример (статья в норвежском журнале на норвежском языке):

Ellingsen A.E., Wilhelmsen I. Sykdomsangst blant medisinog jusstudenter. Tidsskr Nor Laegeforen. 2002;122(8):785–787. (In Norwegian).

Если статья написана **не на латинице** (на кириллице, в том числе на русском), нужно привести официальный перевод или выполнить транслитерацию в романский алфавит. Для книг необходимо в этом случае привести транслитерацию на латиницу. В конце описания в скобках указать язык издания.

Ссылка на источник литературы в References может состоять одновременно и из транслитерированных элементов (например, ФИО авторов, названия журналов), и из переводных (название публикации).

Стандарт транслитерации. При транслитерации рекомендуется использовать стандарт BSI (British Standard Institute, UK). Для транслитерации текста в соответствии со стандартом BSI можно воспользоваться ссылкой http://ru.translit.ru/?account=bsi.

ФИО авторов, редакторов. Фамилии и инициалы всех авторов на латинице следует приводить в ссылке так, как они даны в оригинальной публикации. Если в оригинальной публикации уже были приведены на латинице ФИО авторов, в ссылке на статью следует указывать именно этот вариант (независимо от использованной системы транслитерации в первоисточнике). Если в официальных источниках (на сайте журнала, в базах данных, в том числе в eLIBRARY) ФИО авторов на латинице не приведены, следует транслитерировать их самостоятельно по стандарту BSI.

Название публикации. Если у цитируемой Вами работы существует официальный перевод на английский язык или англоязычный вариант названия (его следует искать на сайте журнала, в базах данных, в том числе в eLIBRARY), следует указать именно его. Если в официальных источниках название публикации на латинице не приведено, следует выполнить транслитерацию в романский алфавит по стандарту BSI.

Название издания (журнала). Некоторые не англоязычные научные издания (журналы) имеют кроме названия на родном языке официальное «параллельное» название на английском (например, у журнала «Сахарный диабет» есть официальное англоязычное название «Diabetes Mellitus»). Таким образом, для списка References в ссылке на статью из русскоязычного журнала следует указать либо транслитерированное название журнала, либо переводное. Переводное название журнала можно взять либо с официального сайта журнала (или использовать данные о правильном написании англоязычного названия из цитируемой статьи), либо проверить его наличие в базе данных, например в CAS Source Index, библиотеке WorldCat или каталоге Web of Science (ISI), каталоге названий базы данных MedLine (NLM Catalog). В случае, когда у журнала нет официального названия на английском языке, в References нужно приводить транслитерацию по системе BSI. Не следует самостоятельно переводить названия журналов.

Место издания. Место издания в ссылках всегда следует указывать на английском языке и полностью — не в транслитерации и без сокращений. То есть Moscow, а не «Moskva» и не «M.:», Saint Petersburg, а не «Sankt Peterburg» и не «SPb».

Название издательства/издателя. В отличие от места издания, название издательства для ссылок в References следует только транслитерировать (за исключением крайне редких случаев наличия у издателя параллельного официального англоязычного названия).

Примеры перевода русскоязычных источников литературы для англоязычного блока статьи

Книга:

Yuriev V.K., Moiseeva K.E., Glushchenko V.A. Fundamentals of public health and healthcare. Textbook. Saint Petersburg: SpetsLit; 2019. (In Russian).

Nikiforov O.N., ed. Saint Petersburg in 2021. Saint Petersburg: Petrostat; 2022. (In Russian).

Глава из книги:

Tutelyan V.A., Nikityuk D.B., Sharafetdinov Kh.Kh. Healthy nutrition is the basis of a healthy lifestyle and the prevention of chronic non-communicable diseases. In: Youth health: new challenges and prospects. T. 3. Moscow; 2019: 203–227. (In Russian).

Статья из журнала:

Karsanov A.M., Polunina N.V., Gogichaev T.K. Patient safety in surgery. Part 2: Quality management program for surgical treatment. Medical technologies. Evaluation and selection. 2019;1(35):56–65. DOI: 10.31556/2219-0678.2019.35.1.056-065. (In Russian).

Тезисы докладов, материалы научных конференций:

Markovskaya I.N., Zavyalova A.N., Kuznetsova Yu.V. Microbial landscape of a patient in the first year of life with dysphagia who has been in the ICU for a long time. XXX Congress of pediatric gastroenterologists of Russia and the CIS countries: abstract. report. Moscow; 2023: 29–31.

Salov I.A., Marinushkin D.N. Obstetric tactics in intrauterine fetal death. In: Materialy IV Rossiyskogo foruma “Mat’ i ditya”. Part 1: Moscow; 2000; 516–519. (In Russian).

Авторефераты:

Avilov A.Yu. Deviations of gender role identity of men with mental retardation in a psychoneurological boarding school. PhD thesis. Saint Petersburg; 2021. (In Russian).

Описание интернет-ресурса:

Natural population movement. Moscow: Rosstat. Available at: https://rosstat.gov.ru/folder/12781 (accessed: 10/23/2023). (In Russian).

Kealy M.A., Small R.E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women’s accounts in Victoria,

Australia. BMC Pregnancy and Childbirth. 2010. Available at: http://www.biomedcentral.com/1471-2393/10/47/ (accessed: 11.09.2013).

Пример списка литературы (References):

ЛИТЕРАТУРА

1. Криворученко В.К. Жестокое обращение с ребенком. Проявление и меры предотвращения. Информационный гуманитарный портал Знание. Понимание. Умение. 2012; 3. Доступен по: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (дата обращения: 27.12.2023).
2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231-239. DOI: 10.3238/arztebl.2010.0231.

REFERENCES

1. Krivoruchenko V.K. Child abuse. Manifestation and prevention measures. Informatsionnyy gumanitarnyy portal Znaniye. Ponimaniye. Umeniye. 2012; 3. Available at: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (accessed: 27.12.2023) (In Russian).
2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231-239. DOI: 10.3238/arztebl.2010.0231.

Для всех статей необходимо указывать индекс DOI в конце библиографического описания, а также EDN при его наличии.

Примеры:

Саттаров А.Э., Карелина Н.Р. Особенности ростовых процессов у мальчиков и юношей различных пропорций и телосложения, проживающих в южной части Кыргызстана. Педиатр. 2018;9(5):47–52. DOI: 10.17816/PED9547-52. EDN: YRAEPZ.

Voropaeva E.E., Khaidukova Yu.V., Kazachkova E.A., et al. Perinatal outcomes and morphological examination of placentas in pregnant women with critical lung lesions in new COVID-19 coronavirus infection. Ural Medical Journal. 2023;22(2):109–121. DOI: 10.52420/2071-5943-2023-22-2-109-121. EDN: CXRCMN. (In Russian).

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

АВТОРСКОЕ ПРАВО

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

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2) территория, на которой разрешается использовать авторский материал, — Российская Федерация и сеть Интернет;
3) срок действия Договора — 5 лет. По истечении указанного срока Редакция оставляет за собой, а Автор подтверждает бессрочное право Редакции на продолжение размещения авторского материала в сети Интернет;
4) Редакция вправе по своему усмотрению без каких-либо согласований с Автором заключать договоры и соглашения с третьими лицами, направленные на дополнительные меры по защите авторских и издательских прав;
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6) Автор оставляет за собой право использовать предоставленный по настоящему Договору авторский материал самостоятельно, передавать права на него по договору третьим лицам, если это не противоречит настоящему Договору;
7) Редакция предоставляет Автору возможность безвозмездного получения справки с электронными адресами его официальной публикации в сети Интернет;
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ПОРЯДОК ЗАКЛЮЧЕНИЯ ДОГОВОРА

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