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IMPROVEMENT OF THE PROCESS OF PRODUCTION OF POLYSACCHARIDE POLYRIBOSYL RIBITOL PHOSPHATE USED IN THE *HAEMOPHILUS INFLUENZAE* VACCINES

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The production of vaccines requires constant improvement of methods and tools, revision and modernization of the current technology with the aim to improve quality of the product made for the benefit of public health. The purposяe of this work was to improve the process of production of polysaccharide polyribosyl ribitol phosphate (PRP), which is the active agent of *Haemophilus influenzae* type b (Hib) vaccines. We investigated how PRP yield depends on the following factors: concentration of dissolved oxygen in the culture liquid, glucose concentration control method applied in cultivation, source of protein for the producer microorganism, stability of the polysaccharide at the culture liquid inactivation stage. As a result, we managed to increase the PRP yield in the culture liquid by 10%, ensured a 25% boost of the biomass accumulation rate during cultivation in the fermenter and reduced the cultivation time by 6.5 hours. The PRP loss rate at the culture liquid inactivation stage was reduced by 80%. Relying on the patented composition, we invented a new composition of the nutrient medium that meets the current regulatory requirements.

Keywords: *Haemophilus influenzae* type b, polyribosyl ribitol phosphate, nutrient medium, vaccine, cultivation, peptone, hemin, protoporphyrin

Author contribution: Belyankin AA — collection of information, experimental work and processing of their results; Salimova EL, Konon AD — scientific and technical consulting; Trukhin VP — general management.

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УСОВЕРШЕНСТВОВАНИЕ ПРОЦЕССА ПОЛУЧЕНИЯ ПОЛИСАХАРИДА ПОЛИРИБОЗИЛРИБИТОЛФОСФАТА, ИСПОЛЬЗУЕМОГО В ПРОИЗВОДСТВЕ ВАКЦИН ПРОТИВ ГЕМОФИЛЬНОЙ ИНФЕКЦИИ

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Производство вакцин требует постоянного усовершенствования методов и инструментов, пересмотра и модернизации существующих технологий, позволяющих получать качественный продукт для обеспечения здоровья населения. Целью работы было усовершенствование стадии получения полисахарида полирибозилрибитолфосфата (PRP) — активного компонента вакцин для профилактики гемофильной инфекции. Изучено влияние на выход PRP следующих факторов: концентрации растворенного кислорода в культуральной жидкости, способа регулирования концентрации глюкозы во время культивирования, источников белкового питания микроорганизма-продуцента, стабильности полисахарида на стадии инактивации культуральной жидкости в процессе получения полисахаридной вакцины для профилактики гемофильной инфекции. Выход PRP в культуральной жидкости увеличен на 10%, скорость накопления биомассы во время культивирования в ферментере — на 25%, время культивирования сокращено на 6,5 ч. Потери PRP на стадии инактивации культуральной жидкости сокращены на 80%. Предложен новый состав питательной среды на основе запатентованного состава, соответствующий актуальным требованиям нормативной документации.

Ключевые слова: *Haemophilus influenzae* тип b, полирибозилрибитолфосфат, питательная среда, вакцина, культивирование, пептон, гемин, протопорфирин

Вклад авторов: А. А. Белянкин — сбор информации, проведение экспериментальных работ и обработка их результатов; Е. Л. Салимова, А. Д. Конон — научное и техническое консультирование; В. П. Трухин — общее руководство.

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Haemophilus influenzae type b causes severe meningitis and pneumonia in children. Before the widespread vaccination, *Haemophilus influenzae* type b (Hib) was behind 8.13 million cases of invasive diseases among children under 5 years of age and 371 thousand deaths. Vaccination campaigns in 136 brought down the associated mortality by 45.28% [1]. The risk of complications (severe deafness in children, 10% of cases) makes Hib especially dangerous [2]. Haemophilus influenzae is highly resistant to antibiotics, which makes anti-infective chemotherapy less effective against the disease associated therewith [3, 4].

The vaccines used for prevention of the *Haemophilus influenzae* disease are of the combined type. There are three such vaccines registered in Russia: Infanrix Hexa, aAPDT-HEP B+Hib, Pentaxim. However, there are no monovalent Hib vaccines registered in the country, which can be used for patients intolerant to any of the components of the combined vaccines. The current scale of Hib vaccination in Russia is insufficient [5], therefore, to secure reliable availability of the Hib prevention preparations, it is necessary to set up domestic production of such vaccines relying on the current advancements in biotechnology.

Optimization of biotechnological production means increasing the amount of the product yielded from one batch without compromising its quality, as well as making the production time shorter. Polysaccharide polyribosyl ribitol phosphate (PRP) is the active component of the vaccine used to prevent *Haemophilus influenzae* disease in children [6–8]. It induces an effective immune response upon conjugation with the carrier protein. PRP is a microbial synthesis product made at biotechnological facilities. The production technology used by a facility directly determines the amount of polysaccharide produced, with the key production stages affecting the yield being fermentation, which is expected to deliver the maximum

amount of PRP, and isolation and purification, which minimize losses.

Designing solutions, a drug developer should rely on regulations: WHO requirements and recommendations [9], GMP system, and pharmacopoeial monographs [10, 11]. The XIVth edition of the State Pharmacopoeia of the Russian Federation contains the first-ever monograph regulating production and control of quality of the Hib vaccine [11]. The quality of production of the *Haemophilus influenzae* disease vaccine depends on the biotechnological stage thereof: cultivation of the producer culture in a fermenter in order to synthesize PRP. The main task at this stage is to produce the maximum amount of polysaccharide that meets the requirements of the specification.

There are many factors that influence quantity and quality of the produced PRP: concentration of oxygen dissolved in the culture liquid during cultivation; concentration of glucose and method of introduction of additional nutrients to the culture fluid during cultivation; source of nitrogen nutrition and growth factors in the nutrient medium; conditions of cultivation and inactivation of the culture liquid to stabilize the end product.

The purpose of this work was to improve the PRP production technology by optimizing the stage of cultivation of the producer culture in a fermenter.

METHODS

Estimation of the amount of polysaccharide

The quantitative content of PRP was determined with the help of the orcinol method (ribose identification) [12]. The samples were appropriately prepared before polysaccharide quantity assessment: it was precipitated in the culture liquid with a cetyltrimethylammonium bromide (CTAB) solution, the samples were centrifuged, upper layer removed and the PRP-containing precipitate dissolved subsequently [13, 14].

Producer microorganism

Haemophilus influenzae type b, a naturally occurring agent, is used in polysaccharide production. It is a gram-negative coccobacillus, auxotroph (requires growth factors in the medium, hemin and nicotinamide adenine dinucleotide (NAD)), facultative anaerobe. We used the *Haemophilus influenzae* SPB type b strain deposited in the State Collection of Pathogenic Microorganisms and Cell Cultures of the GNCPMB under the number B-7884 [15].

Cultivation

To prepare the inoculum for cultivation in a laboratory fermenter, we added 1 ml of thawed culture from a cryovial (working inoculum) to 150 ml of a synthetic liquid nutrient medium poured into flasks. The seeded nutrient medium was kept on a Unimax 1010 incubator shaker (Heidolph; Germany) for 6 h with temperature and rpm controlled. Optical density and microbiological purity were the controlled properties of the inoculum. The entire 150 ml of inoculum were subcultured into a Biostat A laboratory fermenter (Sartorius Stedim Biotech; Germany). Cultivation lasted 18 hours and was carried out in a 2.0 L laboratory fermenter, with ceaseless stirring and oxygen supply and controlled pH at 7.2±0.2. With the aim to investigate how oxygen concentration in the culture liquid affects the yield, we maintained its level at 10, 30 and 60% during cultivation. The fermenter consisted of a borosilicate glass flask (UniVessel), a stand and a lid made of AISI 304 stainless steel, a six-blade two-tier stirrer agitating the culture liquid, a bubbler supplying sterile compressed air to the culture liquid. During cultivation, the temperature of the culture liquid was controlled with the help of a heat exchanger made of AISI 304 stainless steel complete with a heating plate mounted on the outer surface of the fermenter flask. To maintain pH at the required level, we delivered 2.0 M NaOH and 1.0 M HCl (titrating solutions) in the automatic mode. Glucose concentration was controlled manually, by introduction of a feed solution of dissolved glucose and yeast extract. A sampler mounted into the lid of the fermenter allowed taking samples during cultivation.

Nutrient medium

For the study part, we used a semi-synthetic liquid nutrient medium [16] containing saline solutions, sources of nitrogen and carbon nutrition, and growth factors. For the experiments designed to investigate the impact of nitrogen nutrition sources and growth factors, we changed the patent composition of the nutrient medium: animal peptone was replaced by vegetable (soy) peptone (Sigma-Aldrich, P6463; Germany); pork hemin — by protoporphyrin IX.

RESULTS

Haemophilus influenzae type b is a facultative anaerobe, therefore, it is possible to influence its growth and biosynthesis of the target product by controlling aeration during cultivation. In this context, at the first stage we studied the impact of aeration on the accumulation of biomass and synthesis of the target product, PRP. It was assumed that by changing the oxygen concentration in the culture liquid, it would be possible to regulate the biochemical processes of the producer microorganism and stimulate it to accumulate biomass (the target product is a polysaccharide, which is the outer protective shell of the bacterium) or accelerate synthesis of the target product when the producer is under stressful conditions.

Culture liquid was saturated with oxygen by bubbling it with sterile compressed air and stirring with a two-tier six-blade stirrer (Biostat A fermenter design). Table 1 presents the results of the experiment designed to investigate the impact of the culture liquid oxygen concentration in cultivation.

With aeration increased by early intensive stirring and bubbled supply of compressed sterile air (to maintain the oxygen concentration at 60%), biomass accumulation grows up 1.3 times, which is significant, but synthesis of the target

Table 1. Impact of aeration on *Haemophilus influenzae* type b biomass growth and synthesis of the target product during the preparation of inoculum

Concentration of oxygen dissolved oxygen in the culture liquid, %	Culture liquid optical density*	Concentration of PRP, μg/ml*
10	3,232 ± 0,109	350 ± 23
30	4,101 ± 0,095	423 ± 27
60	5,634 ± 0,145	450 ± 21

Note: PRP — polyribosylribitolphosphate; * — the table shows standard deviation.

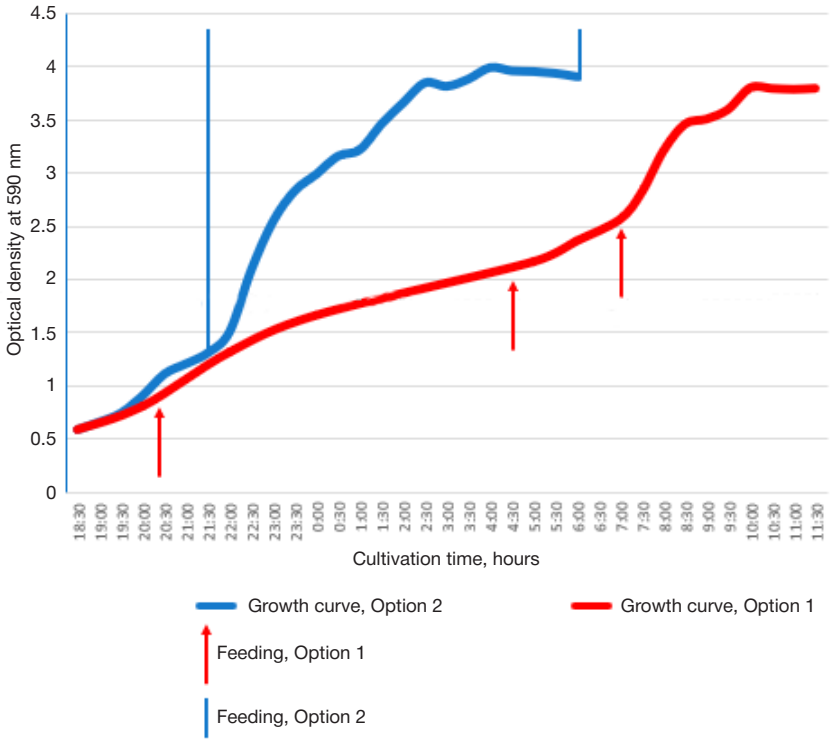

Fig. 1. Growth curves describing cultivation of *Haemophilus influenzae* type b

product increased insignificantly (maximum by 10%) (see Table 1).

The next step was to study the impact of the culture liquid glucose concentration on PRP yield during cultivation of *Haemophilus influenzae* type b.

We used a solution of glucose and yeast extract as a feed in cultivation of *Haemophilus influenzae* SPB type b B-7884. Glucose acts as a carbon source, and yeast extract is the source of nitrogen, vitamins and microelements. It is assumed that introduction of a large volume of feed, for example, at the beginning of the exponential phase, can significantly accelerate the formation of biomass due to the high concentration of nutrients in the culture liquid. Controlled feeding throughout the cultivation process allows responding to the microorganism's need for glucose at a given moment and adding the nutrients to the culture liquid gradually.

To study the impact of the feeding method, we compared two options: option 1, introduction of large volumes at certain stages of cultivation (upon reaching a certain optical density value), and option 2, introduction of small volumes throughout the entire cultivation, seeking to maintain glucose concentration within the range from 12 to 34 mmol/L. Figures 1 and 2 show the results of this com comparison.

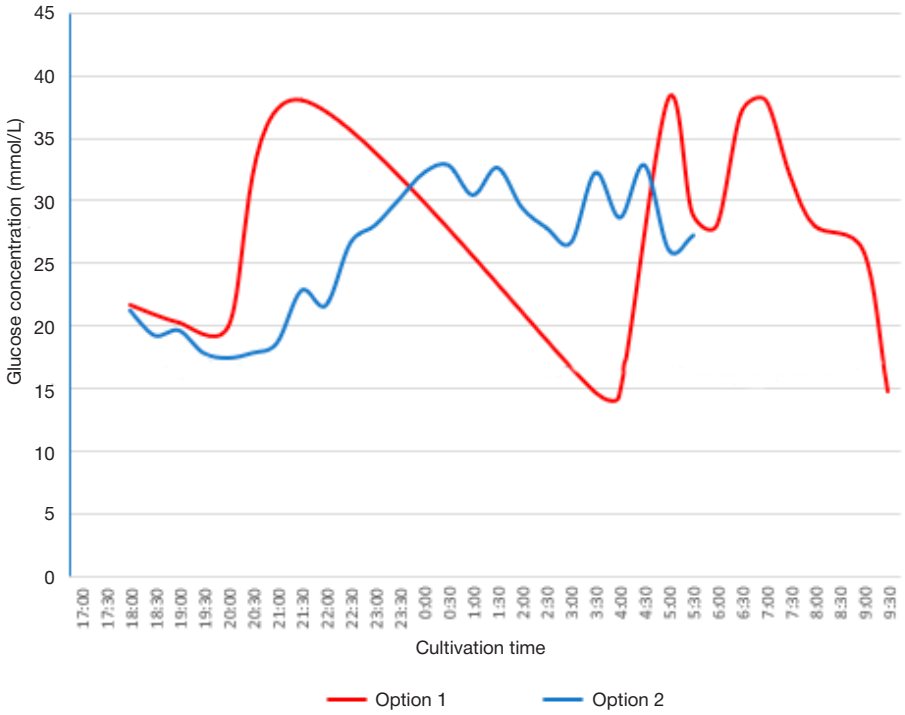

Fig. 2. Glucose concentration in cultivation of *Haemophilus influenzae* type b

Table 2. The results of cultivation of *Haemophilus influenzae* type b in nutrient media containing different sources of protein nitrogen

Peptone	OD* before cultivation	OD* after cultivation	OD* difference	Concentration of PRP, μg/ml	Percentage of PRP
From animal raw materials	0,245 ± 0,034	1,150 ± 0,097	0,905 ± 0,063	307,5 ± 5,3	100
Soy	1,213 ± 0,085	2,092 ± 0,102	0,879 ± 0,017	288,2 ± 7,4	93

Note: * — optical density

With the first feeding method, it took 16 hours to achieve the culture liquid optical density of 3.8 ± 0.2, which was maintained for 1 hour of cultivation. The reached optical density of 3.8 ± 0.2 and its persistence at this level indicate onset of the stationary phase. The second feeding method allowed reaching the optical density value marking transition to the stationary phase faster, in 12.5 hours.

The next step was to investigate how various sources of nitrogen and growth factors affect PRP biosynthesis.

The pharmacopoeia monograph regulating production and control of quality of the Hib vaccine sets out the requirements for PRP quality indicators and PRP production recommendations, including composition of the nutrient media used for cultivation. One of them is to use the media free from animal products with the aim to eliminate the risk of prion infection. The nutrient media used for cultivation of *Haemophilus influenzae* type b B-7884 contains some animal products. One of them is peptone, made from meat, another is hemin, the X-growth factor produced, in most cases, from pork or beef material. To ensure conformity to the regulatory requirements, it is necessary to study how the origin of nitrogen sources and growth factors in the nutrient medium influences growth of biomass and biosynthesis of the target product. Peptones from animal raw materials can be replaced with peptones derived from plants: pea, wheat, soy and proteose peptones. These peptones can differ significantly in chemical composition, and since biomass growth and synthesis of PRP depend on the amino acid composition of the medium [17–19], the chemical composition of peptones can have a significant effect on the production of the target product.

It is also important to evaluate how the origin of source of the X factor in the nutrient medium influences growth of the *Haemophilus influenzae* type b biomass and PRP biosynthesis. The X factor is involved in the synthesis of cytochrome C and other iron-containing respiratory enzymes. *Haemophilus influenzae* type b has an enzyme called ferrochelatase, which converts protoporphyrin IX to hemin [20]. Thus, hemin can be replaced with protoporphyrin IX in the nutrient media used to cultivate *Haemophilus influenzae* type b [20]. Traditionally, the X factor used for the purpose is hemin derived from the blood of cattle. This is a potentially dangerous raw material that presents the risk of prion contamination. Using pig blood as the source of hemin is one approach to mitigation of the said prion infection risk [21], but some countries outlaw pig products, which hinders imports of the vaccine and makes replacement of hemin with protoporphyrin promising.

We conducted a number of experiments to assess the possibility of replacement of animal peptone with plant peptone. The control medium was a nutrient medium containing peptone from animal raw materials and yeast extract as prescribed by the patent [16] in a ratio of 15 : 2. The peptone-to-yeast ratio in the experimental culture media with plant peptone was the same. The cultivation was done in shaking flasks on an incubator shaker; it lasted for 6 hours at a temperature of (35 ± 2) C°, with the shaking flasks constantly stirred at 150 rpm. Table 2 shows the results of the experiment designed to evaluate the possibility of replacing animal peptone with plant peptone.

The results of cultivation in the nutrient medium based on soy peptone were similar to the results peculiar to cultivation in the animal peptone nutrient medium.

Next, we experimented with replacing hemin (the X factor substance) with protoporphyrin IX. The cultivation was done in shaking flasks on an incubator shaker; it lasted for 6 hours at a temperature of (35 ± 2) C°, with the shaking flasks constantly stirred at 150 rpm.

Table 3 shows how the source of the X factor affects the biomass growth.

Culture medium with protoporphyrin IX as the X factor gave a yield resembling that produced by the medium with hemin (patent medium).

The experiments allowed suggesting a new composition of the nutrient medium that accords with recommendations set out in the regulations. This new composition has different sources of nitrogen nutrition and the X factor. Table 4 shows the results of comparison of the two media.

Experimentally, we discovered that a nutrient medium without components of animal origin insignificantly slows productivity of *Haemophilus influenzae* type b (by 8%).

The next step was to investigate the possibility to reduce PRP losses at the culture liquid inactivation stage.

Fermentation is followed by purification allowing to isolate the target product. Purification may be chemical (precipitation, extraction) and mechanical (filtration); regardless, this process implies unrecoverable losses of the target product since the stage of biological transformations (biosynthesis) is over by that time. According to the requirements for products made with the involvement of pathogenic microorganisms, the end product should contain no living pathogenic microorganisms. To eliminate the risk of such contamination, vaccine producers typically resort to inactivation, which completely kills all living microorganisms in the culture medium after cultivation. Inactivation, regardless of the method of implementation (chemically or thermally), is inevitably associated with the loss of the target product. During inactivation, exposed to high temperatures, PRP can depolymerize and degrade. It is known that the PRP polysaccharide is more stable in an acidic medium

Table 3. The results of cultivation with various substances acting as X factors

Nutrient medium	OD[1] before cultivation	OD[1] after cultivation	OD[1] difference	PRP content, μg/ml	Percentage of PRP
Hemin environment[2]	0,343 ± 0,024	1,649 ± 0,101	1,306 ± 0,077	307,5 ± 10,5	100
Protoporphyrin medium[3]	1,015 ± 0,092	1,757 ± 0,145	0,742 ± 0,053	300,1 ± 11,3	98

Note: [1] — optical density; [2] — patent composition medium; [3] — medium of patent composition, that contains same concentration of protoporphyrin instead of hemin

Table 4. Comparison of the two *Haemophilus influenzae* type b cultivation nutrient media by productivity and biomass accumulation

Nutrient medium	Optical density before cultivation	Optical density after cultivation	Optical density gain	PRP content, μg/ml	Percentage of PRP
Patent composition	0,352 ± 0,023	1,767 ± 0,125	1,41 ± 0,102	448,5	100%
No components of animal origin[1]	3,064 ± 0,164	4,456 ± 0,312	1,39 ± 0,148	427,2	92,25%

Note: [1] — patent composition medium with meat peptone replaced with soy and pork hemin with protoporphyrin IX.

(pH 6.5 and below), where, according to the mathematical model, it virtually does not depolymerize [22].

When the cultivation process in the fermenter was complete, we lowered the pH of the culture liquid to 6.5 by introducing titrating agents. Then the culture liquid was transferred to the inactivation stage. For the purpose of control, we relied on the cultivation data that had the pH unchanged until its completion (pH 7.2 ± 0.2). The results are shown in Table 5.

Lowering the pH during inactivation allowed to reduce the losses at this stage by 80%.

DISCUSSION

Investigation of the impact of the culture liquid oxygen concentration in cultivation

As shown by the experiments (see Table 1), the dependence of biomass growth and PRP synthesis may be associated with the fact that the culture of Haemophilus influenzae SPB type b B-7884 actively consumes oxygen to oxidize nutrients used in the anabolic processes of formation of the new cells, which slows down the synthesis of the target product. In addition, the increased amount of biomass can affect the parameters of the subsequent stages of isolation and purification, significantly complicating them due to the increased load on equipment and materials, which boosts the loss of the target product at these stages.

With culture liquid oxygen concentration decreased to 30%, biomass growth went down by 27% and the synthesis of the target product slowed down insignificantly (by up to 6%), allowed producing a sufficient amount of PRP, isolating and purifying it. An experiment with the culture liquid oxygen concentration at 10% ended in a significant decrease in the level of both biomass and PRP.

These results indicate that oxygen concentration in the culture liquid affects cultivation, which can be used to optimize the process of production to ensure the maximum possible yield of the PRP while keeping the subsequent isolation and purification stages as simple as possible in the view of the increased amount of biomass.

Study of the impact of the culture liquid glucose concentration on PRP yield during cultivation of *Haemophilus influenzae* type b

The second feed introduction method tested enabled rapid transition to the stationary phase (Fig. 1), which is associated with maintaining a certain concentration of glucose in the culture fluid (Fig. 2). The first feeding method option implied introduction of large amounts of glucose and subsequent spike in its concentration, which can inhibit growth of the culture. With the glucose level kept constant, as the feeding option 2 allows, there are no sharp increases in glucose concentration, and, consequently, no inhibition of culture growth. The PRP yield in the experiment that tested option 1 was 403.2 μg/ml, and that for option 2 was 443.5 μg/ml. These results enable optimization of the glucose delivery strategy during cultivation.

Investigation of how various sources of nitrogen and growth factors affect PRP biosynthesis

As shown experimentally (Table 2, 3, 4), replacement of animal components with plant components in the *Haemophilus influenzae* type b cultivation medium led to an insignificant (less than 9%) decrease in the amount of the produced PRP. Despite this, it was shown that it is possible to replace some animal components of the nutrient medium with components of non-animal origin, which will ensure conformity of the Hib vaccine production facilities to the latest regulatory requirements.

Investigation of the possibility to reduce PRP losses at the culture liquid inactivation stage

Based on the results of the experiment (Table 5), it is possible to offer a fundamental possibility of reducing the loss of PRP at the inactivation stage by lowering the pH of the culture liquid to 6.5 ± 0.1 once cultivation is complete. But, regardless, it should be noted that direct cultivation at such pH values is impractical, since accumulation of the polysaccharide under such conditions is slower [23].

CONCLUSIONS

In the course of this work, we suggested several methods of optimization of the process of producing PRP through cultivation of *Haemophilus influenzae* SPB type b B-7884. The results of this study allow optimizing a PRP production facility to ensure conformity to the regulatory requirements. The yield of PRP from the culture liquid was increased by 10%. The rate of biomass growth during cultivation in a fermenter was increased by 25%, the cultivation time is reduced by 6.5 hours. The PRP loss rate at the culture liquid inactivation stage was reduced by 80%. We also suggested a composition of a new culture medium is proposed that meets the latest requirements of regulatory documents. The results of this study allow improving the production process of PRP, which is the active component of Hib vaccines.

Table 5. Study of the influence of culture liquid pH of inactivation

pH at inactivation	PRP before inactivation, μg/ml	PRP after inactivation, μg/ml	Loss of PRP during inactivation
7,2 ± 0,2	405,6 ± 12,6	305,2 ± 10,3	100,4 ± 11,3 μg/ml
6,5 ± 0,1	407,4 ± 14,1	388,6 ± 9,4	18,8 ± 12,7 μg/ml

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SURGICAL CORRECTION OF POSTTRAUMATIC NASAL DEFORMITIES IN ADOLESCENT ATHLETES

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Nasal breathing is of great importance for professional athletes because of the peculiarities of carbon dioxide metabolism in the body. Problems with nasal breathing caused by post-traumatic deformities of the nose can be successfully corrected with the help of rhinoseptoplasty, but the possibility of performing this surgery on patients under 18 years of age is a discussed matter. This study aimed to analyze the results of the effect functional rhinoseptoplasty has on nasal breathing, consider rhinoseptoplasty as the preferred method of treatment for adolescents with post-traumatic deformities of the structures of the nose. The study involved 15 professional athletes aged 15–18 years with post-traumatic deformities of the external nose and troubled nasal breathing. Five of them (33.3%) were female, 10 (66.7%) were male; all underwent open rhinoseptoplasty. The NOSE and SCHNOS questionnaires were used to assess the symptoms of nasal obstruction before and after surgery. Post-surgery, all patients subjectively noted that their nasal breathing improved, which was confirmed by the filled questionnaires. There were no significant complications registered during the follow-up period. Functional rhinoseptoplasty is a viable surgical option for adolescents under 18 years of age.

Keywords: rhinoseptoplasty, septoplasty, rhinoplasty, adolescents, nasal breathing, pediatric rhinoseptoplasty

Author contribution: Zyabkin IV, Grachev NS, Frolov SV — study concept and design; Ataeva DM, Galkina TA — collection and processing of material; Magomedova AM — statistical data processing; Frolov SV, Magomedova AM — text authoring; Polev GA — editing; Frolov SV, Grachev NS — surgical treatment.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Federal Research and Clinical Center for Children and Adolescents of the Federal Medical Biological Agency of Russia (Minutes #1 of January 18, 2021), conducted in accordance with the principles of biomedical ethics formulated in the 1964 Declaration of Helsinki and its subsequent updates. All study participants signed informed voluntary consent.

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ХИРУРГИЧЕСКАЯ КОРРЕКЦИЯ ПОСТТРАВМАТИЧЕСКИХ ДЕФОРМАЦИЙ НОСОВЫХ СТРУКТУР У ПОДРОСТКОВ-СПОРТСМЕНОВ

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Носовое дыхание имеет большую значимость для профессиональных спортсменов в связи с особенностями метаболизма углекислого газа в организме. Затруднения носового дыхания, обусловленные посттравматическими деформациями носа, можно успешно корректировать с помощью риносептопластики, однако возможность ее проведения до 18 лет на сегодняшний день обсуждается. Целью исследования было изучить результаты влияния функциональной риносептопластики на носовое дыхание, рассмотреть возможность проведения риносептопластики в качестве предпочтительного метода лечения подростков с посттравматическими деформациями носовых структур. В исследовании участвовало 15 профессиональных спортсменов 15–18 лет с посттравматическими деформациями наружного носа и затруднением носового дыхания, из них 5 пациентов (33,3%) — женского пола, 10 (66,7%) — мужского пола, перенесшие риносептопластику открытым доступом. Для оценки симптомов назальной обструкции до и после операции использовали стандартизированные опросники NOSE и SCHNOS. Все пациенты, перенесшие хирургическое лечение, субъективно отмечают улучшение носового дыхания, что подтверждают результаты опросников. За период наблюдения не отмечено значимых осложнений. Функциональную риносептопластику можно рассматривать в качестве метода хирургического лечения у подростков младше 18 лет.

Ключевые слова: риносептопластика, септопластика, ринопластика, подростки, носовое дыхание, детская риносептопластика

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Соблюдение этических стандартов: исследование одобрено этическим комитетом ФНКЦ детей и подростков ФМБА России (протокол № 1 от 18 января 2021 г.), проведено в соответствии с принципами биомедицинской этики, сформулированными в Хельсинкской декларации 1964 г. и ее последующих обновлениях. Все участники исследования подписали информированное добровольное согласие.

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Troubled nasal breathing contributes to the development of many pathological changes in the upper respiratory tract: vasomotor rhinitis, sinusitis, dysfunction of the auditory tube, retraction of the tympanic membrane, etc. [1]. Children and adolescents that chronically cannot breathe well through the nose have the respiratory tract diseases accompanied with disorders of formation of facial structures, which entail various diseases of the entire dental-jaw system: hypoplasia of the middle third of the face, malocclusion, retrognathia, temporomandibular joint dysfunction, xerostomia etc. [2].

With mouth breathing, the level of aerodynamic resistance is lower and the volume of emitted carbon dioxide is higher This, in turn, leads to vasoconstriction, more frequent inhales that bring in more air, with subsequent hyperventilation, which has a negative effect on the functional parameters of the body. During physical activity, nasal breathing significantly reduces hyperventilation [3, 4].

The low sensitivity of chemoreceptors to carbon dioxide is one of the factors characterizing stamina during prolonged intense physical activity [5, 6].

There are many anatomical and functional disorders that can make nasal breathing inadequate: inferior turbinates enlarged by vasomotor rhinitis, bullous middle turbinates, adenoid hypertrophy, etc. However, both for adolescents and adults, the most common reasons behind impeded nasal breathing are septal deviation and nasal valve insufficiency [1, 2].

Septoplasty is the well-known method of surgical treatment of deviations of nasal septum. However, in some cases, the results of classical septoplasty are unsatisfactory and the patient that underwent it does not have the ability to breathe through the nose restored. The protocol of this operation does not imply access large enough to reach all the nasal structures that were deformed. Septal deviations in the upper sections require other types of surgery, same as cicatricial and anatomical nasal valve stenosis, caudal septal deviations, pronounced post-traumatic deviations of the entire nasal pyramid with nasal septum deformations (Figure).

Whether it is possible and feasible to do rhinoseptoplasty on patients under 18 years of age is a matter of debate. For a long time, specialists did not consider rhinoseptoplasty an option for such patients due to the lack of convincing data on changes in the facial skeleton after surgery and popularity of the opinion that interventions into nasal structures have negative impact [7].

Initially, children and adolescents under 18 years of age were also not recommended to undergo septoplasty. However, in 1980 there were published the first studies the authors of which reported positive results of septoplasty in children and absence of post-surgery disturbances of growth of the nasal structures and the face. After that, the number of such studies has been growing steadily. Many functional and anthropometric indicators of facial structures were assessed, which allowed formulating the basic principles of the nasal structures growth and development in children and adolescents.

As of today, there are no exact data on the age at which nasal structures finally complete their formation and dimensional growth. According to some researchers, cartilage tissue continues to grow throughout life [9]. However, according to the data published by many authors who studied anthropometric characteristics of faces of children and adolescents, there are certain periods during which nasal structures, both bone and cartilage, complete their active and rapid growth and acquire the size and morphological outlook of an "adult" nose. According to the review, the so-called peak periods of growth occur at 13 ± 1 years in girls and 14 ± 1 years in boys [10].

To date, septoplasty has been proven safe for children from 6 years of age. As for rhinoseptoplasty, the respective research is in progress. The available data shows that surgical interventions associated with rhinoplasty do not lead to further changes in the facial skeleton, which allows considering rhinoplasty a surgery option for adolescents [8–10].

There has been published studies that describe large samples of patients under 18 years of age who underwent rhinoseptoplasty. One of them, published in 2011, covered cases of 202 patients (124 (61.4%) male and 78 (38.6%) female) aged 4–16 years (median age — 11 years) who underwent rhinoplasty and/or septoplasty between 1994 and 2010. Septoplasty was done in 157 (77.7%) cases, rhinoseptoplasty — in 23 (11.4%) cases, rhinoplasty — in 22 cases (10.9%). Complications were observed in 15.3% of patients: the largest number (14%) was associated with recurring nasal septum deflection; 4.45% of patients has to have receptoplasty (3.5); in isolated cases, there were perforation (0.5%) and synechiae (0.5) registered [11].

Another study described a cohort of 64 patients 4–17 years old who underwent rhinoseptoplasty from 2003 to 2011. The researchers assessed anthropometric parameters before, immediately after and long after the operation, and noted lack of growth retardation or developmental disorders [12]. In such works, all authors note the absence of negative effects of rhinoseptoplasty on the ongoing growth of facial structures and suggest that girls have their nasal structures fully formed by the age of 13–14 years, boys — by the age of 15–16 years [13–15].

METHODS

This study included 15 patients aged 15–17 years, with the average age being 16.07 years. Five of them (33.3%) were female, 10 (66.7%) were male. All had post-traumatic deformities of the nasal septum and external nose and troubled nasal breathing. The participants underwent surgery in the period from January to October 2021 in the head and neck pathology surgical department of the Federal Research and Clinical Center for Children and Adolescents of the Federal Medical Biological Agency of Russia.

The degree of surgical intervention varied depending on the concomitant pathologies of the paranasal structures. The type of rhinoseptoplasty for all patients was open access; inferior turbinates were wave disintegrated.

Three participants also underwent simultaneous plastic closure of the nasal septum perforation. Two patients with severe external nose saddle deformity and perforation of the nasal septum had rhinoseptoplasty done with costal cartilage autograft.

All operations were performed under general anesthesia by one surgical team. All patients are professional athletes, 11 of them practicing contact sports: boxing, judo, Greco-Roman wrestling, etc.

The Nasal Obstruction Symptom Evaluation (NOSE) (Table 1) scale/questionnaire and the Russian-language adapted version of the Standardized Cosmesis and Health Nasal Outcomes Survey (SCHNOS) (Table 2) were used to assess the efficacy of surgical treatment. Both scales have high internal consistency with Cronbach's alpha [16, 17]. The patients filled out the questionnaires before surgery and one month after it.

The NOSE scale offered to patients contains five main criteria: "nasal breathing difficulties", "nasal congestion", "nasal obstruction", "sleep problems", "nasal breathing

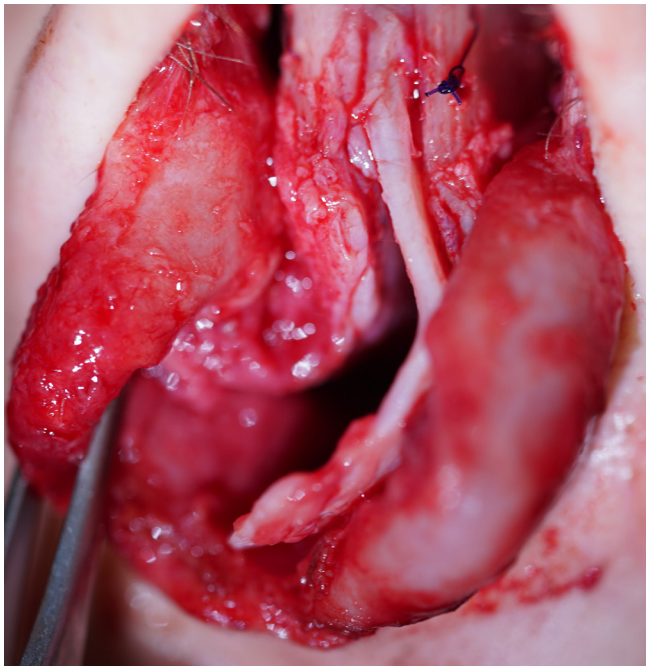

Fig. Severe deviation of the nasal septum (intraoperatively)

Table 1. NOSE scale

Symptom	No problem				No problem
Nasal congestion	0	1	2	3	4
Nasal breathing difficulties	0	1	2	3	4
Nasal obstruction	0	1	2	3	4
Sleep problems	0	1	2	3	4
Nasal breathing insufficiency/inadequacy during exercise	0	1	2	3	4

insufficiency during exercise." The severity of manifestation corresponds to the number of points: 0 points — no problem, 1 point — a minor problem, 2 points — a moderate problem, 3 points — a significant problem, 4 points — a very pronounced problem. Each patient assessed the criteria suggested in points from 0 to 4 before and one month after the operation. The score was calculated as the sum of the points multiplied by 5. The SCHNOS scale follows the same principle: it relies on the Likert scale, however, it enables assessment of not only functional but also aesthetic criteria. For this purpose, the scale has two parts, items 1 through 4 for the functional criteria, 5 through 10 for aesthetic.

We used SPSS Statistics 23.0 software package (IBM; USA) with nonparametric methods to process the data statistically. The level of 0.05 was used as the critical level of reliability of the null statistical hypothesis of the absence of differences and influences.

DISCUSSION

All patients who underwent surgical treatment subjectively noted a significant improvement in nasal breathing.

The significance shown by the statistical analysis of the NOSE points given before and after the operation was 0.002, which, at $p < 0.05$, confirms that the number of points decreased and, accordingly, the quality of nasal breathing improved. The median before and after treatment was 50.00 and 5.00, respectively. The mean for the sample before treatment was 53.3, after treatment it was 8.3.

Statistical analysis of the SCHNOS scale data yielded the significance of 0.001, which, at $p < 0.05$, also confirms the decrease in the number of points. The median before and after surgical treatment was 70.0 and 5.0, respectively, mean — 61.0 and 6.6.

Thus, according to the analyzed data obtained with the help of NOSE and SCHNOS questionnaires, one month after the treatment the number of points decreases significantly, which indicates an improvement in nasal breathing.

Postoperative complications occurred in three cases out of 15 (20%); they were synechia of the nasal cavity; episode of nosebleeds in the early postoperative period; recurrence of vasomotor rhinitis. All complications were promptly arrested, no further relapse was observed.

CONCLUSIONS

During physical exercising of moderate and high intensity, nasal breathing allows achieving better functional results, which is especially important for professional athletes. For adolescents, rhinoseptoplasty may be the surgery of choice when there are specific deformities: nasal septum deflection in the upper sections, pronounced deviation in the caudal section, saddle nose deformity with insufficient nasal tissues, columella retraction; deformities of the nasal septum in combination with massive perforations; pronounced C-shaped post-traumatic deflection of the nasal pyramid with collapse of the nasal valves. According to the data published by foreign researchers and our own observations, rinoseptoplasty in female adolescents over 13 years old and male adolescents over 15 years old does not affect the further growth of facial structures.

Table 2. SCHNOS scale

	Symptom	No problem					No problem
Functional	Troubled or fully obstructed nasal breathing	0	1	2	3	4	5
	Nasal breathing during exercise	0	1	2	3	4	5
	Nasal congestion	0	1	2	3	4	5
	Nasal breathing during sleep	0	1	2	3	4	5
Aesthetic criteria	Impaired mood and self-esteem because of the nose	0	1	2	3	4	5
	Nose tip shape	0	1	2	3	4	5
	Straightness of the nose	0	1	2	3	4	5
	Profile nose shape	0	1	2	3	4	5
	Nose-and-face overall harmony	0	1	2	3	4	5
	General symmetry of the nose	0	1	2	3	4	5

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COMPARATIVE ANALYSIS OF POPULATION MORTALITY IN THE CITIES OF SEVERODVINSK AND ARKHANGELSK

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Increasing use of ionizing radiation sources in different spheres of human life dictates the need for investigating the effects of low-dose radiation on mortality and morbidity. The aim of this study was to compare mortality from the most common non-communicable diseases in the cities of Severodvinsk and Arkhangelsk. We analyzed the rates of age- and sex-specific mortality from circulatory system diseases (CSD), malignancies, digestive system disorders, respiratory system diseases, and external causes. CSD-related mortality among men and women past working age was higher in Severodvinsk than in Arkhangelsk (median (Q_1; Q_3): 3,349 (3,271; 3,458) vs 2,651 (2,618; 2,756), $p < 0.012$; 1,947 (1,890; 2,022) vs 1,753 (1,727; 1,809), $p < 0.012$; 292 (281; 342) vs 265 (253; 274), $p < 0.025$, respectively). For other causes of death, mortality rates in Severodvinsk did not exceed those in Arkhangelsk. Increased mortality from CSD in Severodvinsk cannot be linked to socioeconomic conditions or chemical air pollution because the standard of living is higher in Severodvinsk than in Arkhangelsk, whereas the level of chemical pollution is lower. At the same time, the presence of the nuclear shipyard and radioactive waste repository in Severodvinsk could cause chronic exposure to low-dose radiation. It is important to expand preventive measures aimed at early detection of vascular damage in nuclear workers and general groups of population residing in the vicinity of hazardous radiation sites.

Keywords: circulatory system diseases, risk factors, mortality

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СРАВНИТЕЛЬНЫЙ АНАЛИЗ СМЕРТНОСТИ НАСЕЛЕНИЯ В ГОРОДАХ СЕВЕРОДВИНСКЕ И АРХАНГЕЛЬСКЕ

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В связи с широким использованием источников ионизирующего излучения в разных сферах деятельности человека увеличивается число исследований, изучающих влияние облучения в малых дозах на заболеваемость и смертность населения. Целью данного исследования было провести сравнительный анализ смертности от основных неинфекционных заболеваний в городах Северодвинске и Архангельске. В анализ включили данные о возрастных коэффициентах смертности от болезней системы кровообращения (БСК), злокачественных новообразований, болезней органов пищеварения, болезней органов дыхания, а также от внешних причин. Показано, что в Северодвинске выше, чем в Архангельске, смертность от БСК мужчин и женщин в возрасте старше трудоспособного и мужчин в трудоспособном возрасте (медиана (Q_1; Q_3): 3349 (3271; 3458) против 2651 (2618; 2756), $p < 0,012$; 1947 (1890; 2022) против 1753 (1727; 1809), $p < 0,012$; 292 (281; 342) против 265 (253; 274), $p < 0,025$ соответственно). Смертность в Северодвинске от других причин не превосходила соответствующие показатели в Архангельске. Повышенная смертность от БСК в Северодвинске не могла быть обусловлена социально-экономическими условиями или химическим загрязнением атмосферного воздуха, поскольку уровень жизни в Северодвинске выше, чем в Архангельске, а уровень химического загрязнения ниже. Вместе с тем, расположение в Северодвинске предприятий атомного судостроения и хранилища радиоактивных отходов потенциально могло обуславливать хроническое облучение в малых дозах части населения этого города. Необходимо расширение профилактических мероприятий, направленных на раннее выявление поражения кровеносных сосудов у лиц, работающих и проживающих в районах расположения радиационно-опасных объектов.

Ключевые слова: болезни системы кровообращения, факторы риска, смертность

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Wide use of ionizing radiation sources in various industries and fields of human life dictates the need to research the effects of low-dose radiation on the risk of cardiovascular diseases, their exacerbation and the associated mortality [1–8]. The primary sources of ionizing radiation with the most significant effect on the human body include naturally occurring background radiation (cosmic rays from space, radionuclides in the Earth's crust and ambient air, etc.) and man-made radionuclides. Besides, medical equipment has made a considerable contribution to the total public exposure to radiation in the past decades. It is assumed that exposure to medical diagnostic and therapeutic technologies and modern nuclear technologies will be low-dose [4–8].

Today, the level of radiation safety at nuclear fuel cycle enterprices facilities satisfactory [9, 10]. However, only a few decades ago, communities residing in their vicinity could have been exposed to low doses of radiation over long periods of time. At the same time, organ damage is not directly caused

Table 1. The level of chemical air pollution in Arkhangelsk and Severodvinsk in 2010–2018

	2010	2011	2012	2013	2014	2015	2016	2017	2018
AArkhangelsk	H	H	H	H	I	I	I	L	I
Severodvinsk	I	L	I	I	L	L	L	L	L

Note. H — high (API: 7–13), I — increased (API: 5–6), L — low (API <5).

by ionizing radiation but is induced by free radicals generated by it [11–13].

The biological effects of such radiation are far milder than those associated with acute exposure owing to the compensatory mechanisms maintaining body functions under such conditions; diseases caused by ionizing radiation can manifest many years after exposure [6]. This raises the need for improved methodological approaches to health surveillance in the areas where hazardous radiation sites are located. Stratification by age will help to account for the impact of increased radioactive pollution in previous years or decades. One of the ways to make public health assessment more objective is to conduct comparative studies using data on mortality rates in cities with and without nuclear fuel cycle industries. The pairs of cities should be selected in such a way so as to exclude the confounding effects of environmental and socioeconomic factors.

The aim of this study was to compare mortality rate from the most common non-communicable diseases in Severodvinsk (population: 183,255 in 2018) and Arkhangelsk (population: 349, 742 in 2018). Severodvinsk is a monocity with a nuclear shipyard. Arkhangelsk is located in similar climatic conditions, 30 km away from Severodvinsk, and was chosen for comparison.

METHODS

We analyzed mortality rates from circulatory system diseases (CSD), malignant neoplasms (MN), digestive system diseases (DSD), respiratory system diseases (RSD), and external causes (EC) in different age groups using reports from 2011–2018 provided by the Federal State Statistics Service (Rosstat). The mortality rate was defined as the number of deaths per 100,000 population in a specified age and sex group. The analysis was done by quinary age groups (30–85 years), larger working-age groups (18–55 years for women and 18–60 yeas for men) and the group of individuals past working age.

In addition, we analyzed the Air Pollution Index (API), which characterizes ambient air pollution, using data from the Federal Service for Hydrometeorology and Environmental Monitoring (Gidromet) [14, 15], as well as migration data and socioeconomic indicators in the two cities using Rosstat data. The economic index (EI) was calculated based on Rosstat data to estimate the standard of living [16, 17]. EI was calculated as a mean ratio of the average monthly salary in each of the studied cities (this parameter is the most resistant to the impact of economic inequality [18]) to the subsistence minimum. To estimate population migration, the migration rate was calculated as a ratio of net migration to the average annual population size in each of the cities using Rosstat data [16].

Statistical analysis was performed in STATISTICA 10.0 (StatSoft Inc.; USA). Median values were used as an indicator of the center of distribution for annual mortality values and other studied parameters; the lower and upper quartiles (Q1 and Q3) were used as a measure of intragroup spread. The two-sided Wilcoxon rank-sum test was performed to assess the statistical significance of differences in the studied parameters between the two cities. Differences were considered significant at p (type I error rate) < 0.05.

RESULTS

Table 1 illustrates the level of chemical air pollution in Arkhangelsk and Severodvinsk. In 2010-2018, the level of air pollution in Severodvinsk was lower than in Arkhangelsk. At the same time, the standard of living (EI) was higher in Severodvinsk (3.95 (3.7–4.2) vs 3.3 (3.1–3.8) in Arkhangelsk).

The analysis of migration rates revealed the following patterns. For individuals over 6o years of age, the migration rate (per 10,000 of population in the analyzed age group) was significantly lower in Severodvinsk than in Arkhangelsk (–93 (–108; –77) vs –36 (–44; –26) for women, p = 0.018; –104 (–123; –71) vs –56 (–60; –46) for men, p = 0.018). No differences were observed in the migration rate for the individuals aged 20–59 years (women: –75 (–90; –32) in Severodvinsk vs –29 (–47; –16) in Arkhangelsk, p = 0.176; men: –46 (–53; –40) in Severodvinsk vs –36 (–53; –26) in Arkhangelsk, p = 0.612). The negative migration rate suggests that more people were leaving both cities than coming to live in them.

Tables 2 and 4 show mortality rates for men; Tables 3 and 5 show mortality rates for women. Tables 2 and 3 contain data on different working-age groups. Tables 4 and 5 provide information on men and women past working age. Mortality was significantly higher in Severodvinsk for CSD only. Specifically, it was higher for working-age men and past working age men and women. A more detailed analysis of the quinary age groups revealed that mortality from CSD was significantly higher for both men and women over 65 years residing in Severodvinsk. At the same time, no significant differences in mortality rates were detected between the quinary age groups of working-age men and women: although median CSD mortality in the quinary age groups of working-age individuals was higher in Severodvinsk than in Arkhangelsk, the observed differences were insignificant due to interannual differences and small sample sizes (8 years,

Table 2. Rates of mortality from the leading causes of death among working-age men (per 100,000 population)

	Mortality rates in Arkhangelsk Median (Q_1; Q_3)	Mortality rates in Severodvinsk Median (Q_1; Q_3)	p
CSD	265 (253; 274)	292 (281; 342)	0,025
MN	104 (97; 108)	101 (95; 111)	0,999
DSD	52 (48; 58)	43 (40; 50)	0,207
RSD	40 (35; 44)	29 (27; 30)	0,012
EC	232 (211; 251)	202 (199; 221)	0,036

Note. Q_1 and Q_3 are the lower and upper quartiles.

Table 3. Rates of mortality from the leading causes of death among working-age women (per 100,000 population)

	Mortality rates in Arkhangelsk Median (Q_1; Q_3)	Mortality rates in Severodvinsk (Q_1; Q_3)	*p*
CSD	51 (46; 55)	63 (55; 70)	0,208
MN	45 (43; 49)	48 (45; 56)	0,263
DSD	21 (20; 23)	23 (21; 29)	0,400
RSD	9 (7; 14)	7 (5; 8)	0,575
EC	47 (45; 52)	43 (37; 44)	0,123

2011–2018). Differences in CSD mortality were significant only when all age subgroups of working-age men were pooled.

The analysis of mortality in the working-age population associated with other causes of death (Tables 2 and 3) demonstrated that male mortality from RSD and external causes was significantly lower in Severodvinsk; no significant differences in cancer-related and DS-related male mortality were observed between the cities. Besides, no significant differences were found in the rates of mortality from the leading causes of death among working-age women.

The analysis of mortality among individuals past working age (Tables 4 and 5) showed that unlike CSD mortality, which was higher in Severodvinsk, both male and female mortality rate from the leading causes of death was significantly higher in Arkhangelsk. The exception was male mortality from DSD, for which no significant differences were observed. The analysis of mortality associated with cancer, DSD, RSD, and EC in quinary age groups revealed no stable patterns.

DISCUSSION

The analysis revealed that mortality from CSD among working-age men and past working age women and men was higher in Severodvinsk; for other causes of death, either no significant differences between the cities were established, or the mortality rate was higher in Arkhangelsk (specifically, mortality from other causes among men and women past working age, except for male mortality from DSD, and mortality from RSD and EC for working-age men).

Because the standard of living was higher and the outward migration of the population past working age was greater in Severodvinsk than in Arkhangelsk (it is only logical that people with chronic deseases will be among the first to leave cold climate regions), differences in the socioeconomic conditions could not be the underlying cause of increased mortality from CSD in Severodvinsk.

The fact that CSD-related mortality was higher in Severodvinsk for both men and women past working age suggests the important role of environmental as opposed to occupational health factors because there are more men working in hazardous industries than women. The level of chemical air pollution in Severodvinsk was lower than in Arkhangelsk but the environmental conditions and climate in these cities are the same. This leads us to hypothesize that increased mortality from CSD in individuals past working age residing in Severodvinsk may be associated with increased background radiation in the last decades of the 20th century and the first years of the 21st century due to environmental pollution with radioactive waste: at that time, Mironov mountain (JSC PO Sevmash), the repository for solid radioactive waste, could not provide the sufficient level of radiation safety [19].

This study demonstrates significant differences in CSD-related mortality among working-age men between the two cities in the absence of differences in female mortality. This may indirectly indicate the role of occupational exposure to radiation. The absence of radiation emergencies at Severodvinsk nuclear facilities suggests that its nuclear workers and city dwellers were exposed to only low doses of ionizing radiation in the past. However, there are no published data on radiation monitoring in Russia before 2000, so it is impossible to infer the doses the population was exposed to at that time.

At the same time, our findings are consistent with the results of other studies. The prevalence of arterial hypertension and cerebrovascular diseases among nuclear workers is higher than across Russia in general [20, 21], whereas cancer prevalence and cancer mortality are lower. Besides, the risk of hypertension (one of the main risk factors for CSD) is heightened in people occupationally exposed to ionizing radiation. A meta-analysis of studies investigating the effect of low radiation doses on mortality conducted in 9 industrially developed countries from 1990 to 2010 revealed that the main contribution to mortality associated with prolonged exposure to low-dose radiation is made by cancer and CSD, in equal proportions [22].

Table 4. Rates of mortality from the leading causes of death among men past working age (per 100,000 population)

	Mortality rates in Arkhangelsk Median (Q_1; Q_3)	Mortality rates in Severodvinsk Median (Q_1; Q_3)	*p*
CSD	2651 (2618; 2756)	3349 (3271; 3458)	0,012
MN	1458 (1432; 1510)	1333 (1181; 1377)	0,025
DSD	227 (202; 267)	243 (234; 258)	0,779
RSD	328 (266; 393)	194 (171; 213)	0,012
EC	370 (350; 408)	274 (260; 303)	0,017

Table 5. Rates of mortality from the leading causes of death among women past working age (per 100,000 population)

	Mortality rates in Arkhangelsk Median (Q_1; Q_3)	Mortality rates in Severodvinsk Median (Q_1; Q_3)	*p*
CSD	1753 (1727; 1809)	1947 (1890; 2022)	0,012
MN	610 (598; 647)	497 (471; 515)	0,012
DSD	165 (154; 169)	121 (118; 134)	0,017
RSD	98 (90; 127)	46 (40; 49)	0,012
EC	116 (110; 128)	76 (74; 81)	0,012

As demonstrated by multiple studies, low doses of radiation received over a long time period cause oxidative and nitrosative stress accompanied by increased lipid peroxidation [11–13]. Low-dose radiation does not cause specific radiation-induced disorders but instead stimulates non-cancer non-communicable diseases, including cardiovascular disorders, that can manifest years after the exposure [6, 23, 24].

The main mechanism underlying CSD development following exposure to ionizing radiation involves damage to the blood vessel wall. Its inner layer, endothelium, participates in the regulation of vascular tone through synthesis and release of vasoactive compounds and is the most sensitive to radiation [11–13].

CONCLUSIONS

Experimental and epidemiological studies conducted in the past decades have shown that prolonged exposure to low-dose ionizing radiation induces CSD; the main mechanisms underlying the detrimental effect of radiation on the cardiovascular system is oxidative and nitrosative stress, which leads to endothelial dysfunction, arterial hypertension and atherosclerosis. These pathological processes may be implicated in high mortality from CSD in Severodvinsk. It is important to continue research into the causes of increased morbidity and mortality from CSD (which is the leading cause of death in Russia) and the effects of low-dose radiation on the health of nuclear workers and other populations residing in the vicinity of hazardous radiation sites. In order to prevent premature deaths and improve the quality of life, it would be helpful to expand prevention measures aimed at timely detection of vascular damage in individuals exposed to low doses of ionizing radiation over long periods of time or those living near hazardous radiation sites and to elucidate the potential routes of entry of radionuclides into the human body.

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LONG-TERM IMMUNITY ALTERATIONS IN THE EMPLOYEES OF THE HIGH HYDROGEN SULFIDE CONTENT GAS CONDENSATE PROCESSING FACILITY

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The current measures for protection of the gas processing plant employees cannot fully prevent the impact of pollutants. Evaluation of the immune system is one of the methods for monitoring of the employees' health, and testing the system of measures used to improve the working conditions. The study was aimed to identify alterations in the immune status of the employees at the gas processing and high hydrogen sulfide content condensate processing facility depending on their working experience. The working environment and the employees' immune system were evaluated by standard methods. Pollutants were detected with the Bruel & Kjaer 1302 Multi-Gas Monitor, and the Tsvet-550 gas chromatographer. A total of 160 employees and 81 controls (blood donors of the regional blood transfusion station) were surveyed. The immune system was evaluated using the System 9000 Plus hematological analyser, Cyto FLEX LX flow cytometer, UNICO 2100UV specrophotometer, and KFK-3-03-ZOM3 photometer. It was concluded that the existing complex of occupational and industrial hazards affects the immune status of the main production unit employees, which is reflected in the decreased CD20 levels and increased CD8 levels along with the constant levels of CD4. Correlations were revealed between the immuniglobuline level alterations, decrease in the phagocytic index and phagocytic number, as well in lysozyme activity, and the working experience. Pollutant exposure results in altered immunity of the employees, which could be considered the adaptation mechanism.

Keywords: production factors, pollutants, immunological indicators

Author contribution: Boiko OV — study concept and design, data acquisition and processing; Dotsenko Yul — data acquisition and processing; all the authors — approval of the final version of the article, responsibility for integrity of all article sections.

Compliance with ethical standards: the study was approved by the Ethics Commitee of the municipal outpatient clinic № 8 (protocol № 15 dated November 21, 2020); the informed consent was submitted by all study participants.

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СТАЖЕВЫЕ ИЗМЕНЕНИЯ ИММУНИТЕТА РАБОЧИХ ПРЕДПРИЯТИЯ ПО ПЕРЕРАБОТКЕ ГАЗОКОНДЕНСАТА С ВЫСОКИМ СОДЕРЖАНИЕМ СЕРОВОДОРОДА

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Существующие меры защиты сотрудников газоперерабатывающих заводов не могут полностью предотвратить воздействие на них поллютантов. Одним из методов мониторинга здоровья рабочих и системы мероприятий по нормализации условий труда является исследование иммунной системы. Целью работы было выявить изменения в иммунном статусе рабочих, занятых на предприятии по переработке газа и конденсата с высоким содержанием сероводорода в зависимости от их стажа. Использовали стандартные методы для характеристики производственной среды и оценки состояния иммунной системы работающих. Для индикации поллютантов применяли универсальный газовый монитор 1302 Bruel & Kjaer, газовый хроматограф Цвет-550. Были обследованы 160 рабочих, а также 81 человек контрольной группы (доноры областной станции переливания крови). Исследования иммунной системы проводили на гематологическом анализаторе Sistem 9000 Plus, цитофлуориметре Cyto FLEX LX, спектрофотометре UNICO 2100UV, фотометре фотоэлектрическом КФК-3-03-ЗОМ3. Сделаны выводы, что комплекс существующих профессионально-производственных вредностей оказывает влияние на состояние иммунитета рабочих основных производств, которое проявляется в снижении содержания CD20 и увеличении содержания CD8 при почти неизменном содержании CD4. Выявлена взаимосвязь изменения концентрации иммуноглобулинов, снижения фагоцитарного индекса и фагоцитарного числа, а также активности лизоцима с увеличением производственного стажа. Воздействие поллютантов вызывает изменения состояния иммунитета рабочих, что может быть расценено как приспособительный механизм.

Ключевые слова: производственные факторы, поллютанты, иммунологические показатели

Вклад авторов: О. В. Бойко — концепция и дизайн исследования, сбор и обработка материала, статистическая обработка, написание текста; Ю. И. Доценко — сбор и обработка материала; все соавторы — утверждение окончательного варианта статьи, ответственность за целостность всех частей статьи.

Соблюдение этических стандартов: исследование одобрено этическим комитетом Городской поликлиники № 8 (протокол № 15 от 21 ноября 2020 г.); все участники исследования подписали добровольное согласие на участие в исследовании.

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Air pollution with harmful chemicals inside the gas processing plants remains the major hygiene factor that might have some influence on the employees' health [1–6]. Gas from the Astrakhan field, having the unique natural composition, has a certain impact both on the environment and the human body. It is distinguished by high hydrogen sulfide content (up to 25%), along with hydrocarbons (2.84%), carbon oxides (14–20%), nitrogen oxides (2.45%), mercaptans (0.03–0.22%), and carbonyl sulphide (0.02–0.42%) [3]. The current measures for protection of the gas processing plant employees cannot fully prevent the impact of harmful factors.

In this regard, there is a scientific and practical interest in the qualitative and quantitative assessment of the changing immunological parameters, which reflect the essence of the emloyee's body alteration and make it possible to monitor the employees' health in a timely manner in order to prevent

the risk of developing a disease [7–8]. Immune system is one of the body systems, being the most responsive to pollutant exposure; immunological tests may be regarded as the most reliable tests for establishing the causal relationship between the disease and the hazardous working conditions. However, there are just a few papers on this issue [8–11]. The data on the immune system sensitivity to the long-term exposure to production factors is also insufficiently represented in literature [9–16].

METHODS

The workplace hygiene certification involved assessing the concentrations of air pollutants in the working area based on legislative requirements.

Determination of SO_2 in air was performed using the Bruel & Kjaer 1302 Multi-Gas Monitor (Bruel & Kjaer; Denmark). The H2S concentrations were assessed by photometric method based on the interaction of hydrogen sulfide with sodium arsenite and silver nitrate. Alkanes (C1–C10), alkenes (C2–C5), and aromatic hydrocarbons (benzene, toluene, xylenes and ethylbenzene) were assessed by gas chromatography. These substances were detected using the Tsvet-550 gas chromatographer (Rospribor; Russia). Along with the listed above methods, hydrocarbons (total) were assessed with the Bruel & Kjaer 1302 Multi-Gas Monitor. The concentration of nitrogen oxides was measured by photometry. Determination of methanol in air in the working areas was performed by gas chromatography, and carbon monoxide was assessed by the reaction gas chromatography. The Bruel & Kjaer 1302 Multi-Gas Monitor was also used for this purpose.

A total of 160 employees (operators, engine drivers) of the main and auxiliary facilities of the gas processing plant were surveyed. Inclusion criteria: males; age 30–40 years (the average age was 36.4 years). A total of 81 controls (blood donors of the regional blood transfusion station) were also surveyed. The control group inclusion criteria were as follows: individuals matching the facility employees in gender and age (comparing the groups by age revealed no significant differences ($p > 0.05$)); exclusion criteria: professional experience in the gas processing, petroleum or chemical industry; exposure to any chemical process hazard.

The studied group was surveyed during the routine medical examination with the use of the standard assessment methods. All the participants were divided into groups based on their length of service with the plant: 1–3 years, 3–5 years, 5–10 years, 10 years or more.

Hematological tests were performed using the System 9000 Plus automatic hematological analyser (Serono; Switzerland). Samples were analyzed with the Cyto FLEX LX flow cytometer (Beckman Coulter; USA) in order to determine the lymphocyte subpopulations. Phagocytic cells were examined by the direct morphological method. Classes of immunoglobulins were determined by a turbidimetric assay; concentrations of the circulating immune complexes (CIC) were defined by precipitation with polyethylene glycol (PEG-6000) and registered at 280 nm with the UNICO 2100UV spectrophotometer (United Products & Instruments, Inc.; USA). Lysozyme activity was detected by turbidity assay based on measuring the changes in the turbidity of the Micrococcus lysodeikticus suspension with the KFK-3-03-ZOM3 photometer (Zagorsk Optical-Mechanical Plant; Russia).

Statistical analysis of the results was performed using the Statistica 12 software (StatSoft; USA) and the analysis of variance. Previously the descriptive statistics data were assessed: number of observations that constituted the sample (n), arithmetic mean of the data obtained (M), standard deviation (m), standard error of the mean (т), minimum (min) and maximum (max) values of the studied parameter, as well as the relative values (%) and the corresponding errors. The quantitative data distribution was assessed using the Shapiro–Wilk test. In case of compliance with the normal distribution law, the method of statistical analysis was selected (parametric or nonparametric). When the quantitative variables were distributed normally, central tendencies and dispersion were described using mean values (M) and standard deviations (m). Significance of the differences was defined with the use of the Wilcoxon test and the Mann–Whitney U test; the differences were considered significant when $p < 0.05$.

RESULTS

The findings demonstrate the presence of significant air concentrations of numerous harmful substances in the working area. Despite the fact that almost all of these substances are involved in the technological processes and are almost completely converted to sulfur compounds (patricularly, to sulfur dioxide) or removed through the chimneys of the facility (carbon oxides), the constant presence of pollutants in the working area is observed. The presence of those is characteristic not only of the purely production areas (pump rooms, engine rooms), but also of the soundproof compartments with no production machinery installed (Table 1).

The impact of production factors on the employees' health is confirmed by the correlation between the detected changes in immune status and the working experience. It was found that with an increase in the working experience, there were trends towards the increase in white blood cell and lymphocyte counts, decrease in the levels of CD20, and progressive increase in the levels of CD8 along with the constant levels of CD4 (Table 2).

Correlations between the alterations of the cellular and humoral factors and the employees' working experience. The indicators of phagocytosis were characterized by progressive decrease in the phagocytic index and phagocytic number with the increase in the working experience, which was to some extent offset by the increase in the total number of phagocytic cells. However, such a compensatory capacity started to decline in individuals with working experience exceeding 10 years.

The humoral factors of nonspecific resistance demonstrate a greater diversity of the correlations with working experience. Thus, lysozyme activity in employees progressively decreases with the increase in their working experience, and the classes of immunoglobulins show a variety of responses. The trend towards the decrease in concentrations is characteristic of IgG, and the trend towards the increase is characteristic of IgA and IgM.

Thus, the correlation between the changes in the majority of the immune status indicators and the employees' working experience and, therefore, their working conditions, has been shown, which confirms the professional etiology of these alterations. However, the changes are phase-type, which makes it possible to treat the alterations as different stages of the adaptation process.

To identify the possible correlations between the serum and saliva levels of certain humoral resistance factors, we assessed lysozyme activity in the saliva obtained from different groups of employees. It was found that the changes of this indicator in blood and saliva of the employees were almost exactly the same both in terms of tendencies and intensity. Moreover, the discovered similarities have been found in all groups of employees, which makes it possible to use lysozyme levels for

Table 1. Concentrations of harmful substances in the air of the working areas

Air sampling site	Pollutants	Number of tests	Pollutant concentrations, mg/m³			MPC, mg/m³
			min	max	mean M ± *m*	
Engine rooms	Hydrogen sulfide	25	1.3	8.1	5.4 ± 0.8	3.0
	Sulphur dioxide	25	1.3	45.3	23.1 ± 2.6	10.0
	Nitrogen dioxide	22	0.9	4.1	2.1 ± 0.3	2.0
	Carbon monoxide	16	3.9	53.1	29.1 ± 6.0	20.0
	Hydrocarbons	25	1.5	80.0	43.1 ± 4.6	300.0
	Mercaptans	15	0.3	2.2	1.24 ± 0.2	0.8
Pump rooms	Hydrogen sulfide	25	1.1	7.7	5.1 ± 0.8	3.0
	Sulphur dioxide	25	2.5	54.6	27.4 ± 4.5	10.0
	Nitrogen oxides	22	1.4	3.7	3.0 ± 0.6	2.0
	Carbon monoxide	16	3.2	49.7	25.1 ± 5.6	20.0
	Hydrocarbons	25	2.7	63.8	38.3 ± 3.9	300.0
	Mercaptans	15	0.2	2.1	1.07 ± 0.25	0.8
Soundproof compartments in engine rooms	Hydrogen sulfide	23	1.0	7.4	5.0 ± 0.7	3.0
	Sulphur dioxide	25	0.6	32.2	12.6 ± 3.4	10.0
	Nitrogen dioxide	22	1.7	3.8	3.01 ± 0.09	2.0
	Carbon monoxide	16	3.6	49.4	25.3 ± 6.0	20.0
	Hydrocarbons	25	1.8	72.8	30.6 ± 2.6	300.0
	Mercaptans	15	0.2	2.0	1.7 ± 0.3	0.8
Soundproof compartments in pump rooms	Hydrogen sulfide	23	1.0	6.2	4.8 ± 0.6	3.0
	Sulphur dioxide	25	3.3	31.4	14.3 ± 5.9	10.0
	Nitrogen oxides	22	1.3	3.0	1.9 ±0.2	2.0
	Carbon monoxide	16	3.1	41.6	24.3 ± 5.9	20.0
	Hydrocarbons	25	18.2	88.6	45.2 ± 9.2	300.0
	Mercaptans	15	0.2	1.4	0.7 ± 0.21	0.8
Compressor house	Hydrogen sulfide	24	0.6	1.8	1.1 ± 0.2	3.0
	Sulphur dioxide	24	3.8	22.6	16.6 ± 2.4	10.0
	Nitrogen oxides	23	0.8	3.8	2.2 ± 0.2	2.0
	Carbon monoxide	15	3.3	33.3	17.2 ± 1.6	20.0
	Hydrocarbons	25	3.0	38.6	23.2 ± 5.8	300.0
	Mercaptans	14	0.2	1.4	0.8 ± 0.31	0.8
Rack for manual loading of sulfur and trucking area for solid and granulated sulfur	Hydrogen sulfide	50	1.3	66.5	29.8 ± 6.8	3.0
	Sulphur dioxide	53	7.4	360.0	57.2 ± 9.6	10.0
	Nitrogen oxides	28	0.6	3.4	1.8 ± 0.2	2.0
	Carbon monoxide	62	3.8	47.5	22.9 ± 5.1	20.0
	Hydrocarbons	54	1.7	12.2	7.9 ± 0.9	300.0
	Sulphur dust	42	8.4	21.4	13.7 ± 1.4	6.0

noninvasive diagnosis. Serum lysozyme levels in employees reached 5.43 ± 0.29 μg/mL, and serum lysozyme levels in controls were 6.48 ± 1.42 μg/mL. Saliva lysozyme levels in employees were 8.82 ± 0.49 μg/mL, and in controls these were 10.41 ± 0.65 μg/mL.

DISCUSSION

Research has shown that the complex of occupational and industrial hazards specific to the enterprises that process gas condensate with high hydrogen sulfide content has a certain impact on the immune system of the employees. The accompanying bodily processes are directly related to the duration of exposure to the production factors, i.e. depend on the working experience in the gas industry.

The decrease in the phagocytic activity of peripheral blood neutrophils we have identified is very much in line with the existing literature data, and can be interpreted as a consequence of the employees' intoxication with air pollutants present in the factory premises. The groundwork is thus being laid for inefficient elimination of the infectious causative agents, and, consequently, for chronic infections, to the extent of becoming the resident bacteria carrier. This assumption could be supported by the elevated levels of IgA found in the factory employees. It is known that it is IgA which is responsible for the mucous membrane resistance to pathogens, and the IgA concentration increase is associated with inflammation in the area of the entrance gate of infection. Taking into account the decrease in lysozyme activity observed both in blood serum and saliva of the employees compared to controls, there is a theoretical possibility of the chronic infectious disease.

The long-term persistence of an infectious agent in the human body may, among other things, result in the autoimmune disorder development. An example is the autoantibody against the TSH receptor gangliosid region, which is responsible for

Table 2. Immune status indicators in employees of the Astrakhan Gas Processing Plant with different working experience

Indicators	Mean values by groups, M ± *m*				
	Group 1	Group 2	Group 3	Group 4	Control group
White blood cells, × 10^9	7.35 ± 0.37	7.88 ± 0.33	8.35 ± 0.26**	7.35 ± 0.32	5.27 ± 0.36
Lymphocytes, %	36.8 ± 1.87	37.2 ± 0.83	38.9 ± 1.46	38.3 ± 1.42	34.23 ± 1.88
CD3, %	56.6 ± 1.54	58.0 ± 1.76	57.5 ± 1.76	57.3 ± 1.6	56.38 ± 2.12
CD4, %	36.1 ± 1.31	36.1 ± 1.49	38.0 ± 0.67	38.7 ± 1.6	38.69 ± 1.98
CD8, %	19.5 ± 0.73	20.5 ± 1.37	21.9 ± 1.35	18.6 ± 1.8	17.69 ± 0.88
CD4/CD8	2.32 ± 0.12	2.06 ± 0.19	1.83 ± 0.15**	2.42 ± 0.3	2.25 ± 0.17
CD20, %	14.7 ± 0.72	13.9 ± 0.38	13.5 ± 0.69	14.2 ± 0.6	14.64 ± 0.85
IgG, g/L	9.21 ± 0.12	9.04 ± 0.19	9.03 ± 0.2	9.11 ± 0.2	9.45 ± 0.33
IgA, g/L	1.81 ± 0.07	1.84 ± 0.08	1.84 ± 0.04	1.86 ± 0.06	1.87 ± 0.08
IgM, g/L	1.24 ± 0.07	1.28 ± 0.06	1.28 ± 0.04	1.29 ± 0.07	1.33 ± 0.11
CIC, AU	4.77 ± 0.41	5.01 ± 0.44	5.83 ± 0.27	5.45 ± 0.47	2.49 ±0.5
Phagocytic index, %	72.1 ± 2.51	70.7 ± 0.75*	66.4 ± 0.16**	67.1 ± 3.0	73.64 ± 2.3
Phagocytic number,	5.73 ± 0.27	5.65 ± 0.2*	5.08 ± 0.11**	5.36 ± 0.32	6.98 ± 0.39
Phagocytic activity per 1 μL	3033 ± 239	2961 ± 231	3183 ± 143	2609 ± 202	2345 ± 232
Lysozyme, μg/mL	5.67 ± 0.48	4.86 ± 0.64	4.17 ± 0.54**	6.16 ± 1.29	6.48 ± 1.42

Note. * — significant differences ($p < 0.05$) between groups 2 and 3; ** — significant differences ($p < 0.05$) between groups 1 and 3; group 1 — working experience 1–3 years, group 2 — working experience 3–5 years, group 3 — working experience 5–10 years, group 4 — working experience exceeding 10 years.

the development of hyperthyroidism associated with Graves' disease. Certain bacterial infections trigger the development of such autoimmune disorders, since glycosphingolipids of bacterial antigens often cause cross-reactivity. In Graves' disease, this role is played by Yersinia enterocolitica.

Considering the fact that IgM is capable of complement activation and playing a part of the mediator in the cytotoxic reactions, that we and other researchers define as the increased IgM levels in the employees of the chemical production facilities, IgM is capable of facilitating the employees' predisposition to autoimmune disorders.

CONCLUSIONS

Maximum consumption of raw material and all intermediate products used in the the natural sulfur containing gas and condensate processing, achieved by highly efficient operation of the major production objects (Claus process and Sulfreen), is of primary importance in terms of improving working conditions in the studied industries. This would make it possible to minimize the overall air pollution and the pollution of air specifically inside the premises of the Astrakhan Gas Processing Plant. High level of sealing for the technological equipment, installed in the engine room (pumps, compressors, valves), is required, as well as organization of automated control of the components in the flow. Both direct and indirect impact of the Astrakhan Gas Processing Plant prodiction factors causes the noticeable changes in the immune status of the employees, which could be considered the adaptation mechanism. The identified changes in the immune status could be one of the factors, contributing to the rising morbidity rate in the facility employees, being the most susceptible to the damaging effects of specific factors of the working environment. This suggests that it is appropriate to include immunological tests in the routine hygienic assessment of the working conditions at the gas production facilities. Taking into account the strength of the used laboratory methods, these methods can be recommended for the inclusive health check-ups of employees. The results obtained may be used as criteria for distinguishing the risk groups for rehabilitation, as well as for occupational selection of new personnel.

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CLINICAL AND RADIOLOGICAL ASSESSMENT OF THE CONDITION OF IMPLANTS WITH FIXED STRUCTURES IN THE DYNAMICS OF 20-YEAR FOLLOW-UP

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The statistically significant long-term results of the implant survival and the effectiveness of prostheses are inadequately represented in scientific literature. The study was aimed to assess the effectiveness of prosthetics with fixed structures on the intraosseous dental implants for the replacement of partially absent dentition in the dynamics of the 20-year follow-up. A total of 671 patients with partially missing teeth were examined at the Clinical Center of Dentistry of the FMBA of Russia, who were fitted with 1,700 intraosseous titanium dental implants with the terms from the moment of completion of prosthetics on implants of 5, 10, 15 or 20 years. The criteria for clinical and radiological evaluation of the implant condition were as follows: no complications affecting the condition of periimplant tissues (normal), mucositis, periimplantitis with bone resorption at 1/3 or 1/2 of the implant height, implant removal. Based on 20 years of experience, prosthetics with fixed structures on implants is highly effective in replacing the partial defects of dentition. In total, 62.2% of implants remain functional for 20 years. The average life of implant-supported fixed prostheses is 15 years for bridges, and 20 years for single and combined implant-supported crowns. The most effective are single implant-supported crowns, and the least effective are prostheses supported by implants and teeth. The significantly preserved implant-supported prostheses make it possible to support the concept of the long-term implant installation with respect to the implant-supported non-removable prostheses. The view is thus confirmed that the effectiveness of the implant-supported prosthetics is reduced with the inclusion of teeth in the bridge support, along with implants.

Keywords: dental implants, fixed prostheses, efficiency, 20-year follow-up

Author contribution: Olesov EE, Ivanov AS — clinical data collection and processing; Zaslavskiy RS, Ragulin AV — statistical analysis; Romanov AS — illustrations.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Clinical Center of Dentistry of the Federal Medical Biological Agency (protocol № 12 dated December 4, 2020). The informed consent was submitted by all study participants.

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КЛИНИКО-РЕНТГЕНОЛОГИЧЕСКАЯ ОЦЕНКА СОСТОЯНИЯ ИМПЛАНТАТОВ С НЕСЪЕМНЫМИ КОНСТРУКЦИЯМИ В ДИНАМИКЕ ЗА 20 ЛЕТ

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Статистически значимые результаты выживаемости имплантатов и эффективности протезов на имплантатах в отдаленные сроки недостаточно представлены в научной литературе. Целью исследования было изучить эффективность протезирования несъемными конструкциями на внутрикостных дентальных имплантатах при замещении частичных дефектов зубных рядов в динамике за 20 лет. В Клиническом центре стоматологии ФМБА России обследованы 671 пациент с частичным отсутствием зубов, которым были установлены 1700 внутрикостных титановых дентальных имплантатов со сроками с момента завершения протезирования на имплантатах 5, 10, 15 и 20 лет. Критериями клинико-рентгенологической оценки состояния имплантатов были состояние периимплантатных тканей без осложнений (нормальное), мукозит, периимплантит с резорбцией костной ткани на 1/3 или 1/2 высоты имплантата, удаление имплантата. Протезирование несъемными конструкциями на имплантатах, согласно 20-летнему опыту замещения частичных дефектов зубных рядов, характеризуется высокой эффективностью. В общей сложности 62,2% имплантатов сохраняют функциональность в течение 20 лет. Средний срок функционирования несъемных протезов на имплантатах составляет 15 лет для мостовидных протезов и 20 лет — для одиночных и объединенных коронок на имплантатах. Наиболее эффективны одиночные коронки на имплантатах, наименее — протезы с опорой на имплантаты и на зубы. Значительная сохранность протезов на имплантатах позволяет поддержать концепцию долгосрочной установки имплантатов относительно несъемных протезов на имплантатах. Подтверждается мнение о снижении эффективности протезирования на имплантатах при включении в опору мостовидных протезов зубов, наряду с имплантатами.

Ключевые слова: дентальные имплантаты, несъемные протезы, эффективность, 20-летняя динамика

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Соблюдение этических стандартов: исследование одобрено этическим комитетом ФГБУЗ «Клинический центр стоматологии» ФМБА России (протокол № 12 от 4 декабря 2020 г.). Все участники подписали добровольное информированное согласие на участие в исследовании.

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The dental implant treatment method is being actively introduced into dental practice in the Russian regions, particularly in the sectoral healthcare institutions [1–4]. The experience of using the dental implants as the intraosseous support for dental prostheses in Russia dates back several decades, however, the statistically significant long-term results of the implant survival and the effectiveness of the implant-supported prostheses are inadequately represented in scientific literature. This leads to discrepancies in advising the patients with indications for dental implant treatment, provided by different dentists, as well as in teaching the clinical residents, and advanced training of dentists.

The efficiency of prosthetics on implants depends on the clinical settings, especially on the full or partial absence of dentition, the prosthesis design (including the number of supporting implants), and the prosthesis lifespan [5–13].

In practice, the implant removal due to mobility, resulting from the surrounding bone tissue resorption, is the main criterion for evaluating the implant condition, however, the timely prevention of periimplant inflammation and the implant overloading requires a more detailed evaluation of periimplant tissue.

In the Clinical Center of Dentistry of the FMBA, the dental implant treatment has been used as the main method for the complex dental rehabilitation of patients with partially missing teeth for 20 years. A wealth of experience has been gained in the dynamic analysis of longitudinal data on the dental implant condition depending on the prosthetic method in acordance with the international assessment criteria.

The study was aimed to assess the effectiveness of prosthetics with fixed structures on the intraosseous dental implants for the replacement of partially absent dentition in the dynamics of the 20-year follow-up.

METHODS

A total of 671 patients were examined, who were fitted with 1,700 intraosseous titanium dental implants. Among the patients there were 379 females and 292 males, and the average age of the patients was 26–81 years (149 individuals under the age of 40, 318 individuals aged 40–60, 204 individuals over the age of 60). Inclusion criteria: non-removable prostheses on implants, the term from the moment of the implant installation and prosthetics completion exceeding 5 years. Exclusion criteria: the presence of dental implants and removable prostheses; the service life of implant-supported prostheses of less than 5 years; the implants istalled in different healthcare provider organizations; the refusal of clinical and radiological examination. Based on the terms from the moment of the completion of prosthetics on implants, the patients were divided in the following way: 5 years — 120 individuals, 10 years — 130 individuals, 15 years — 180 individuals, 20 years — 241 individuals (the number of implants installed was 319, 405, 453, and 52, respectively).

In terms of the design, the fixed prostheses (number of individuals and supporting implants) were represented by single crowns (201 individuals, 501 implants), combined crowns (132 individuals, 321 implants), implant-supported bridges (285 individuals, 725 implants), bridges supported by implants and teeth (53 individuals, 153 implants).

The standard two-stage titanium intraosseous implant installation technique and the generally accepted method of fabricating the metal ceramic implant-supported fixed prostheses were used [14–15].

The majority of patients hardly ever contacted the dentist for professional oral hygiene or other follow-up care.

In accordance with the aim of the study, the criteria for evaluation of the implant condition were as follows: no complications affecting the condition of periimplant tissues (normal), mucositis, periimplantitis with bone resorption at 1/3 or 1/2 of the implant height, implant removal [16–18]. That is why the patients underwent orthopantomography in addition to the standard clinical examination of the teeth, periodontium, and implants.

Statistical processing of the results was performed by standard methods with the use of the Microsoft Excel software (Microsoft; USA).

RESULTS

After 5 years of functioning, the clinical and radiological assessment of the implant condition in the partial fixed dental prostheses revealed that normal condition, mucositis, periimplantitis with bone resorption at 1/3 or 1/2 of the implant height, and implant removal were found in 103, 76, 86, 33, and 21 implants, respectively, which accounted for 32.3%, 23.8%, 27.0%, 10.4%, and 6.6% of all the implants installed in this clinical settings (Table 1). In patients with single crowns on implants, the 5-year period of functioning was characterized by 40.0% of implants with no complications (56 implants), mucositis in 20.0% of implants (28 implants), periimplantitis with bone resorption at 1/3 of the implant height in 23.6% (33 implants), and at 1/2 of the implant height in 10.7% (15 implants), as well as by 5.7% of implants removed (8 implants). Based on the listed above criteria, the efficiency of the combined crowns was as follows: 31.0% (18 implants), 22.4% (13 implants), 32.8% (19 implants), 6.9% (4 implants), 6.9% (4 implants). After 5 years of loading, the implant-supported bridges showed no changes in the state of gums or bone tissue in 24.0% of observations (29 implants), mucositis was found in 28.9% (35 implants), periimplantitis with bone resorption at 1/3 was found in 28.1% (34 implants), periimplantitis with bone resorption at 1/2 of the implant height was found in 11.6% (14 implants), and 7.4% of implants were removed (9 implants). Bridges supported by teeth and implants were no longer used 5 years ago.

After 10 years, the listed above indicators of the implant condition in partial fixed dental prostheses (normal condition, mucositis, periimplantitis with bone resorption at 1/3 or 1/2 of the implant height, and implant removal) accounted for 15.1% (61 implants), 23.2% (94 implants), 25.2% (102 implants), 12.6% (51 implants), and 24.0% (97 implants), respectively.

Table 1. Clinical and radiological dental implant assessment results based on the prosthesis design and the term from the moment of installation (quantity, %)

Characteristics	No complications				Mucositis				Resorption at 1/3				Resorption at 1/2				Removed			
Term (years)	5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20
Single crowns	56 40.0	27 15.3	–	–	28 20.0	25 14.2	10 13.2	4 3.7	33 23.6	61 34.7	27 35.5	29 26.6	15 10.7	23 13.1	7 9.2	20 18.4	8 5.7	40 22.7	29 38.2	56 51.4
Combined crowns	18 31.0	15 18.5	–	–	13 22.4	24 29.6	16 17.8	2 2.2	19 32.8	10 12.4	29 32.2	27 29.4	4 6.9	13 16.1	9 10.0	15 16.3	4 6.9	19 23.5	36 40.0	48 52.2
Bridges	29 24.0	17 15.6	–	–	35 28.9	35 32.1	50 21.9	24 9.0	34 28.1	23 21.1	56 24.5	42 15.7	14 11.6	12 11.0	24 10.5	30 11.2	9 7.4	22 20.2	107 46.9	171 64.1
Combined with teeth	–	2 5.1	–	–	–	10 25.6	10 17.0	–	–	8 20.5	8 13.5	–	–	3 7.7	12 20.3	–	–	16 41.0	23 39.0	55 100
Partially abscent dentition	103 32.3	61 15.1	–	–	76 23.8	94 23.2	86 19.0	30 5.7	86 27.0	102 25.2	120 26.5	98 18.7	33 10.4	51 12.6	52 11.5	65 12.4	21 6.6	97 24.0	195 43.1	330 63.1

Table 2. Clinical and radiological dental implant assessment results based on the prosthesis design (quantity, %)

Characteristics	No complications	Mucositis	Resorption at 1/3	Resorption at 1/2	Removed
Single crowns	83 16.6	68 13.4	150 29.9	66 13.0	133 26.5
Combined crowns	33 10.3	55 17.1	85 26.5	41 12.8	107 33.3
Bridges	46 6.3	144 19.9	155 21.4	80 11.0	309 42.6
Combined with teeth	2 1.3	20 13.1	16 10.4	15 9.8	94 61.4
Partially abscent dentition	164 9.6	286 16.9	406 23.9	201 11.9	643 37.8

The number of implants supporting the single crowns, being in the same condition as when installed 10 years before, was 27 (15.3% of the implants installed); mucositis was found in 25 implants (14.2%), bone resorption at 1/3 or 1/2 of the implant height was observed in 61 and 23 implants (34.7% and 13.1%), respectively, a total of 40 implants were removed (22.7%). The combined implant-supported crowns showed the following figures: 18.5% (15 implants), 29.6% (24 implants), 12.4% (10 implants), 16.1% (13 implants), 23.5% (19 implants). After 10 years, 15.6% of implants in the implant-supported bridges remained unchanged (17 implants), mucositis was observed in 32.1% of implants (35 implants), periimplantitis (bone resorption at 1/3 or 1/2 of the implant height) in 21.1% and 11.0% (23 and 12 implants), respectively, 22 implants were removed (20.2%). In patients with bridges supported by implants and teeth, normal tissue condition was found in 5.1% of implants (2 implants), the listed above complications were revealed in 25.6% (mucositis in 10 implants), 20.5% and 7.7% (periimplantitis at 1/3 or 1/2 of the implant height in 8 and 3 implants), 41.0% of implants were removed (16 implants).

After 15 years, the implant-supported partial fixed dental prostheses showed the following characteristics: no complications in 0% of implants, mucositis in 19.0% of implants (86 implants), п periimplantitis with bone resorption at 1/3 of the implant height in 26.5% (120 implants), with bone resorption at 1/2 in 11.5% (52 implants), 43.1% of implants were removed (195 implants). The listed above indicators in the implant-supported single crowns were 0%, 13.2% (10 implants), 35.5% (27 implants), 9.2% (7 implants), 38.2% (29 implants); in the combined implant-supported crowns these were 0%, 17.8% (16 implants), 32.2% (29 implants), 10.0% (9 implants), 40.0% (36 implants), respectively. After the 15-year loading, no implant-supported bridges preserved intact the periimplant tissue; mucositis was observed in 21.9% of implants (50 implants), periimplantitis with bone resorption at 1/3 or 1/2 of the implant height in 24.5% and 10.5% of implants (56 and 24 implants), 107 implants were removed (46.9%). When combining the implant abutments and the natural teeth in bridges, the listed above characteristics were as follows: 0%, 17.0% (10 implants), 13.5% (8 implants), 20.3% (12 implants), 39.0% (23 implants), respectively.

After 20 years of follow-up, no implants with intact periimplant tissues were found in partial fixed dental prostheses; mucositis was found in 5.7% of implants (30 implants), periimplantitis with bone resorption at 1/3 or ½ of the implant height in 18.7% and 12.4% (98 и 65 implants), 63.1% of implants were removed (330 implants). Single and combined implant-supported crowns had the following characteristics: no complications in 0% of implants, mucositis in 3.7% and 2.2% (4 and 2 implants), respectively, periimplantitis with bone resorption at 1/3 of the implant height in 26.6% and 29.4% (29 and 27 implants), with bone resorption at 1/2 of the implant height in 18.4% and 16.3% (20 and 15 implants), 51.4% and 52.2% of implants were removed (56 and 48 implants). After the 20-year follow-up, the implant-supported bridges together with bridges, supported by implants and teeth, showed no unchanged periimplant tissues; mucositis was observed in 9.0% and 0% of implants (24 and 0 implants), respectively, periimplantitis at 1/3 of the implant height in 15.7% and 0% (42 and 0 implants), periimplantitis at 1/2 of the implant height in 11.2% and 0% (30 and 0 implants), 64.1% and 100% of implants were removed (171 and 55 implants).

Summarizing the data on the condition of periimplant tissue obtained during the 20-year follow-up period regardless of the specific lifespan of the fixed prosthesis, it must be stated that no complications were observed in 9.6% of implants, mucositis in 16.8% of implants, periimplantitis with bone resorption at 1/3 of the implant height in 23.9% of implants, and with bone

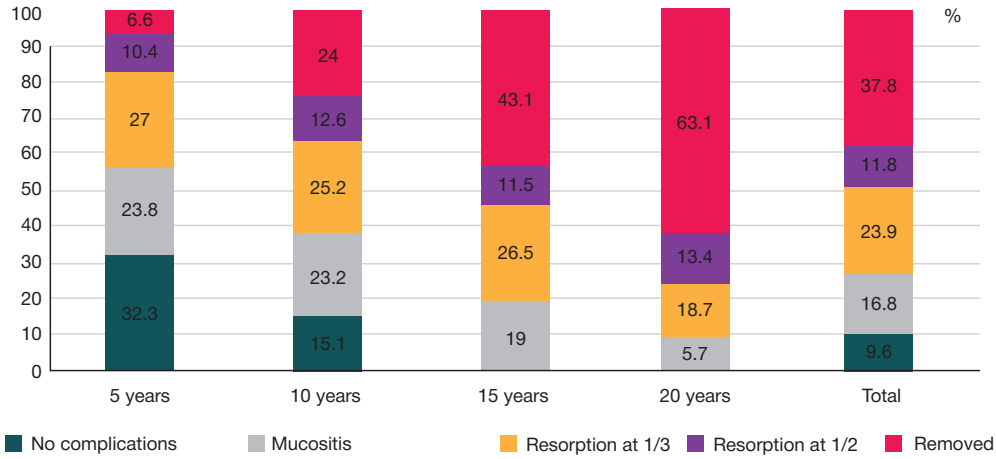

Fig. 1. Comparison of clinical and radiological dental implant assessment results for different terms from the moment of prosthetics completion

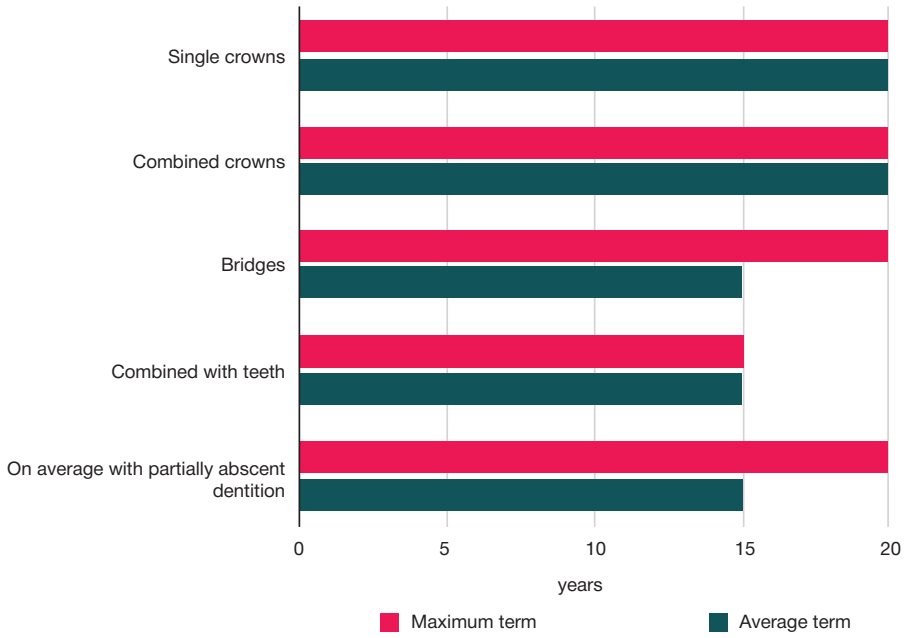

Fig. 2. Maximum and average service life of non-removable implant-based prostheses (years)

resorption at 1/2 of the implant height in 11.8% (164, 286, 406, 201 implants, respectively); 643 implants were removed (37.8%) (Fig. 1).

Summarizing the correlations between the periimplant tissue condition and the type of the fixed prosthesis, revealed during the whole 20-year follow-up period, it must be stated that the most effective are the implant-supported single crowns, and the least effective are the prostheses supported by implants and natural teeth (removals accounted for 26.6% and 61.4%, respectively). Based on their efficiency, the implant-supported crowns and bridges are in between (33.3% and 42.6% removed during the 20-year period, respectively) (Table 2).

The average lifespan of the implants is defined by the time, when the patients have more than a half of implants removed. Based on the examination results, the average lifespan of the implant-supported fixed prostheses was as follows: 20 years for single and combined crowns when teeth are partially missing, and 15 years for bridges (including those supported by implants and natural teeth) (Fig. 2).

DISCUSSION

The results, obtained by assessing the large amount of clinical material, elaborate on the conflicting data on the time limits of functioning for the intraosseous implants supporting the dental prostheses. The current knowledge about the rate of implant removal, limited due to the follow-up period not exceeding 10 years, has been supplemented by the implant survival data obtained during 15–20 years of service life [6, 7, 9, 10, 13]. The significantly preserved implant-supported prostheses make it possible to support the concept of the long-term implant installation with respect to the non-removable implant-supported prostheses. The view is thus confirmed that the effectiveness of the implant-supported prosthetics is reduced with the inclusion of teeth in the bridge support, along with implants.

CONCLUSIONS

The non-removable dental prosthetics on implants used with partially abscent dentition showed high efficiency during 20 years of the partial dentition defects replacement. Regardless of the low patient compliance with the follow-up visits for professional oral hygiene or bite correction, 62.2% of implants remain functional for 20 years. The average lifespan of the implant-supported fixed prostheses is 15 years for bridges, and 20 years for single and combined crowns. Among the non-removable prostheses, the most effective are the implant-supported single crowns, and the least effective are the prostheses supported by implants and natural teeth. High rate of chronic inflammation in the periimplant zone at every stage of the prosthesis life explain the need for the strict compliance of the patients, having the implant-based prostheses installed, with the follow-up dental care.

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RECOMBINANT ADENO-ASSOCIATED VIRUSES AS A GENE DELIVERY VEHICLE FOR THE USE IN MOLECULAR MEDICINE

AV Blagov ✉

Prospects of using oncolytic viruses in breast cancer therapy

Breast cancer (BC) is a cancer with a high prevalence and mortality among women worldwide. With the current diagnostics methods, BC may remain undetected at its early stages, and the therapies developed for the disease are associated with severe side effects. Oncolytic viruses can be the basis of the new, effective BC treatment approaches. The viruses destroy tumor cells directly and launch the antitumor immune response; this dual action supports their efficacy. It is possible to make the oncolytic virus therapy more effective by designing genetically modified viruses that can target BC cells better and/or induce a stronger antitumor immune response. This review outlines the directions of development of oncolytic viruses in BC treatment, covers the optimal ways of delivering viruses to the tumor and the efficacy of their use in combination with other therapeutic agents (methods) and presents the prospects of using oncolytic viruses in antitumor vaccines.

Keywords: oncolytic viruses, breast cancer, viral vector, chemotherapy, estrogen receptors

Author contribution: Blagov AV — analysis of scientific literature, review authoring.

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ПЕРСПЕКТИВЫ ТЕРАПИИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ С ИСПОЛЬЗОВАНИЕМ ОНКОЛИТИЧЕСКИХ ВИРУСОВ

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Рак молочной железы (РМЖ) — онкологическое заболевание с высокой распространенностью и смертностью среди женщин во всем мире. Диагностика РМЖ не столь эффективна для выявления заболевания на ранних стадиях, а терапевтические методы связаны с тяжелыми побочными эффектами. Онколитические вирусы могут стать новым эффективным средством в терапии РМЖ. Их эффективность обусловлена двумя типами воздействия на раковую опухоль: непосредственным уничтожением опухолевых клеток и запуском противоопухолевого иммунного ответа. Повысить эффективность терапии онколитическими вирусами можно путем конструирования генетически-модифицированных вирусов, обладающих лучшей селективностью к опухолевым клеткам молочной железы и (или) способных к большему усилению противоопухолевого иммунного ответа. Представлены дальнейшие направления применения онколитических вирусов в терапии РМЖ, оптимальные пути доставки вирусов в опухоль и эффективность их использования в комбинации с другими терапевтическими средствами (методами), а также перспектива использования онколитических вирусов в качестве противоопухолевых вакцин.

Ключевые слова: онколитические вирусы, рак молочной железы, вирусный вектор, химиотерапия, эстрогеновые рецепторы

Вклад авторов: А. В. Благов — анализ научной литературы по данной теме, написание обзора.

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Breast cancer (BC) is the most common type of malignancy in women [1]. In Russia, the incidence of breast cancer has doubled over 15 years; about 50 thousand new patients with this diagnosis are registered annually [2]. Over 40% of women are diagnosed with BC when the tumor is already at its later stages of development, which adds to the complexity of treatment of this disease [2]. It should also be noted that BC is a group of heterogeneous diseases with different molecular mechanisms of development and cellular origins, which further complicates its diagnosing and treatment [3]. Breast cancer is distinguished by high mortality rates: in 2020, 685 BC fatalities were recorded in the world [4].

The main types of treatment for breast cancer are surgery, chemotherapy, radiation, hormonal and targeted therapies [5]. Hormonal and targeted therapy drugs have better safety profiles, but they are also not without side effects and cannot be used as the only BC treatment method. The effects of other anticancer therapies on the body are more severe. For example, radiation can damage lymphatic vessels close to the chest, causing lymphedema [6]. Breast removal surgery (mastectomy) can adversely affect mental and emotional state of the patients [7]. Chemotherapeutic drugs cause the most massive negative consequences: they are systemic and have effect not only on the cancer cells but also on the rapidly dividing normal cells of the body [8].

Severity and prevalence of the disease, as well as the negative side effects of the existing types of treatment, make the task of developing new groups of anti-BC drugs urgent. Drugs based on oncolytic viruses can form one of such groups. Both naturally occurring and genetically engineered, these viruses can specifically target tumors without harming healthy cells [9]. The investigation of possibilities of using oncolytic viruses as therapeutic agents is a fairly new field of research, yet it is already an intensively developing one. The amount of research and development efforts in this sphere has increased noticeably: from 2015 to 2020, the number of publications returned by PubMed for the "oncolytic viruses" query has grown from 276 to 457, that for the "oncolytic viruses for breast cancer" query — from 11 to 28. Every year, there are more papers published on the subject. This review presents an analysis of the possibilities of using oncolytic viruses as a platform for drugs against BC. The review describes the mechanisms of action of oncolytic

viruses, approaches to increasing the selectivity of their action and enhancing the antitumor effects they trigger. The directions of development of oncolytic therapy are also outlined.

Breast cancer subtypes and their pathogenesis mechanisms

Breast cancers constitute a group of diseases heterogeneous by both phenotypic and genetic characteristics [10]. BC is classified by histological origins, stages of development, properties of pathological lesions and types of oncogenic markers [10, 11]. Based on the expression of such dominant oncogenes as estrogen receptor (ER), progesterone receptor (PR), epidermal growth factor receptor 2 (HER2) and ki 67 proliferation marker, there are four molecular subtypes of breast cancer distinguished: luminal A, luminal B, HER2 positive and triple negative (Table 1) [10].

Using the statistical data from different countries, we will consider the incidence and mortality rate for each subtype of BC. The most common subtype of BC is luminal A. Its incidence is 50–60%, and it is the most survivable BC subtype: within 3 years from the diagnosis, 95–100% of luminal A BC patients survive the disease [12, 13]. Other subtypes of cancer have a more even incidence of 10–15% [14]. The most dangerous subtype is the triple negative BC: within 3-4 years from the diagnosis, the average patient survival rate is 75–80% [13].

Oncological diseases develop against the background of proliferation, apoptosis, and cell migration mechanisms malfunctioning on the epigenetic and genetic levels [10]. Identification of the signaling pathways that determine pathogenesis of specific cancer subtypes enables deduction of new targets for targeted therapy.

One of the main mechanisms of BC development that is registered in about 70% of cases has estrogen receptors involved in the signaling pathway [15]. It should be noted that there are two types of estrogen receptors: ERα and ERβ. With BC, the expression of ERα is often increased and that of ERβ, contrarily, decreased [10]. Typically, when this pathway is activated, after ERα and estrogen binding the resulting complex dimerizes and interacts with coregulator proteins and specific regions of DNA, the estrogen response elements (ERE). These interactions shape the transcription of a number of genes that regulate the cell cycle, apoptosis, DNA replication, cell differentiation and angiogenesis [15]. Thus, additional activation of the ER pathway stimulates transcription of the cyclin D1 gene, which supports subsequent activation of the CDK 4/6 kinase and transition of the cell from G1 phase to S phase [15]. Increased expression of cyclin D1 is one of the signs of the early pathogenesis of BC and some other malignant tumors [15].

Another important mechanism in the BC pathogenesis is the signaling pathway through HER2, which is a tyrosine kinase [16]. After HER2 and ligand binding and dimerization of the resulting complex there occurs phosphorylation of tyrosine residues of the enzyme's intracellular domain, which leads to the activation of several signaling pathways, such as Ras/MAPK and PI3K/AKT, that triggers cell proliferation acceleration [10].

Cancer treatment with oncolytic viruses: the underlying mechanism

Cancer therapy relying on oncolytic viruses is a fairly new field of research. To date, only one drug based on an oncolytic virus has been made commercially available: Talimogene laherparepvec, which is used to treat melanoma [17]. Some similar drugs are at the clinical trials stage currently. If they are successfully through these trials, there will appear a new niche of anticancer drugs. According to clinicaltrials.gov [18], 12 anti-BC drugs based on oncolytic viruses are undergoing clinical trials today (Table 2). The priority subtype for the researchers is the triple negative BC, the choice probably supported by its high molecular heterogeneity, lack key receptors that can be used in targeted therapy, and the highest mortality among the molecular subtypes of BC. It is also worth noting that most clinical trials have the oncolytic viruses combined with other anticancer therapy options in order to increase treatment efficacy. In addition, many oncolytic viruses are genetically engineered for the same purpose of increasing their efficacy (see Table 2); such efforts are described in the next section.

Oncolytic viruses have a number of useful traits: the resistance to drugs based on them is typically low, they are highly selective in targeting tumor cells, relatively non-pathogenic, capable of replicating in the tumor and thus increasing the dose in action [19]. The viruses used in oncology are those with the efficacy proven in vector vaccines and easily modified genetically [20]. The list of such viruses includes double-stranded DNA viruses (adenoviruses, herpes simplex virus, vaccinia virus), double-stranded RNA viruses (reoviruses), single-stranded (+)-RNA viruses (picornaviruses), single-stranded (-)-RNA viruses (measles virus, viscular stomatitis virus, Maraba virus) [20].

From the point of view of action, oncolytic viruses can selectively damage cancer cells and foster development of antitumor immunity [21]. The overall therapeutic effect depends on the interaction of the virus, the immune system, and the tumor [21]. It is important that the immune response is triggered after the virus enters cancer cells and replicates: in this case, the virus has time to destroy the infected population of cancer cells and cause inflammation in the tumor microenvironment. When the immune cells bind to the virions before interaction with the tumor, therapy fails. Cell carriers and pegylated nanoparticles can help protect the virus from premature neutralization by the immune system [22, 23]. In addition to the time of activation of the immune response, efficacy of oncolytic virus therapy also depends on the type of cancer cells, their sensitivity to the given virus and the structure of the tumor, including the degree of its vascularization that determines the rate of leukocyte inflow, as well as the presence of resident macrophages and the level of expression of tumor markers [19].

There are several factors that influence selective damage to the tumor cells. The first and the most important one is the enhanced tropism of a specific virus to a specific type of tumor cell, which is determined by the affinity of the cell receptor and the virus surface antigen [21]. As a result of the receptor-mediated interaction, the virus enters the cell. Engineered

Table 1. Classification of BC subtypes by molecular oncogenes

Type	Oncogenes
Luminal A	ER^+, PR^+, $HER2^-$, low Ki67
Luminal B	ER^+, PR^+, $HER2^±$, high Ki67
HER2	ER^-, PR^-, $HER2^+$
Triple negative	ER^-, PR^-, $HER2^-$

Table 2. Current clinical trials of drugs based on oncolytic viruses and designed for BC treatment

Drug, therapy	Molecular biological subtype of BC	Stage	ClinicalTrials.gov identifier
Radiation therapy and adenoviral vector expressing herpes simplex virus thymidine kinase	Triple negative	2	NCT03004183
Pelareorep (unmodified human reovirus)	Triple negative	2	NCT04445844
Talimogene laherparepvec (modified herpes simplex virus) and paclitaxel (chemotherapy)	Triple negative	1, 2	NCT02779855
Talimogene laherparepvec in combination with monoclonal antibodies	HER2– and triple negative	1	NCT04185311
Vaccinia virus and pembrolizumab	Triple negative	1, 2	NCT04301011
Pelareorep in combination with paclitaxel and avelumab	Luminal A	2	NCT04215146
Pelareorep in combination with letrozole, atezolizumab, and trastuzumab	All types	1	NCT04102618
HER2-specific CAR-T cells combined with CAdVEC (genetically engineered adenovirus carrying genes of immunity modulating proteins)	HER2	1	NCT03740256
Modified measles virus MV-s-NAP expressing neutrophil activating protein (NAP) Helicobacter pylori (MV-s-NAP)	Not specified	1	NCT04521764
Edmonston strain measles virus genetically modified to express human thyroid sodium iodide symporter (NIS)	$HER2^-$, $HER2^+$	1	NCT01846091
Vaccinia virus encoding human CTLA4-specific antibody 4-E03 IgG1 in combination with pembrolizumab	Triple negative	1, 2	NCT04725331
Recombinant herpes simplex virus in combination with pembrolizumab	Triple negative	1	NCT04348916

pseudotyped viruses have the selectivity enhanced even further: they carry surface antigens of another virus or non-viral ligands with increased affinity to tumor-specific receptors [24]. Besides, the rapid division and accelerated metabolism of tumor cells allows the virus to replicate actively [21]. An additional factor is the disruption of the type I interferon signaling process, which has an antiviral effect. This disruption protects the virus from premature clearance by immune cells [9]. The efficacy can also be increased through direct intratumoral administration of high concentrations of oncolytic viruses [21].

As indicated above, drugs based on oncolytic viruses do not only damage tumor cells directly but also activate the body's antitumor response. In the bloodstream, viral particles can be captured by antibodies and antigen-presenting cells (APCs) before penetrating the tumor cells, which translates into higher antiviral immunity but inhibited antitumor immune response [25]. After the oncolytic virus enters the tumor cell, the viral cycle starts. The final stage of this cycle involves formation of many copies of the virions that, through lysis, leave the cell and thus destroy it and infect the nearby cells. The damaged cells fill the intercellular environment with a large number of DAMP (damage-associated molecular pattern) molecules, which trigger non-infectious inflammation and, consequently, an inflammatory reaction that involves attraction of NK cells and macrophages into the tumor microenvironment. Capture of a tumor-associated antigen (TAA) and its presentation to the lymphocytes by APCs triggers adaptive immunity, predominantly - cytotoxic immune response. The development of the antitumor response is further stimulated by the secretion of viral proteins released into the focus of inflammation [19].

Approaches to using oncolytic viruses in breast cancer therapy

Enhanced selectivity of oncolytic viruses for breast cancer cells

To make oncolytic therapy more safe and effective, it is necessary to enhance viral vector's selectivity for cancer cells, breast tumor cells in particular. There are two ways to achieve this goal: through inducing specific binding of the virus surface antigen to the tumor cell receptor and through enabling selective replication of the virus only in tumor cells by extending the genome with a promoter vector that activates upon binding to specific tumor markers [26]. Both approaches had the Ad5 adenoviral vector with chimeric fiber surface protein derived from serotypes Ad5 and Ad3, which improved its tropism, and tissue-specific promoters regulating the expression of protein E1A, which enables viral replication, so that the virus replicated in $CD44^+$ $CD24^-$ /low cell population, the BC stem cells [27].

Viral antigen may be modified not only through insertion of the antigen of another virus with a greater affinity for tumor cells but also by introduction of other ligands for the receptors of tumor cells. For example, the adenovirus fiber protein was modified by insertion of the Lyp-1 peptide, the receptor of which, the p32 protein, is overexpressed in BC cells [28]. The thus engineered oncolytic virus was injected into immunocompetent mice and suppressed tumor growth and slowed down metastasis in them. Another noteworthy effort had the herpes simplex virus tropism genetically altered, retargeting it to $HER2^+$ cells through insertion of a synthetic single-chain anti-HER2 antibody (which served as a ligand) into the gD domain of the herpes simplex virus glycoprotein [29].

It seems promising to modify oncolytic viruses by introducing tumor suppressor sequences or their binding sites into the viral vector genome, thus not only improving selectivity but also enhancing the antitumor effect. In such a way, Ad5 was genetically engineered to enable its selective replication in breast tumor cells: the modification involved introduction of binding sites for miR-145, a tumor suppressor the concentration of which is reduced in tumor cells, into the adenoviral vector genome [30]. As a result, high titers of the virus were registered in the breast tumor cell lines MDA-MB-453, BT-20, and MCF-7, while the normal mammary epithelial cells exhibited a decreased level of HMEpC lines. In another study, a tumor suppressor sequence of the KISS1 gene was inserted into the adenoviral vector genome [31]. The expression of KISS1 resulted in a stronger cytotoxic effect of the virus on breast

tumor cells in combination with the lytic effect of the adenoviral vector.

Antitumor response enhancing through modification of oncolytic viruses

In addition to the direct destruction of cancer cells, oncolytic viruses promote development of the antitumor immune response. This response, as manifesting in the tumor microenvironment in particular, can be further enhanced through introduction of the immunomodulatory proteins into the gene sequences of the virus. In this case, the virus itself acts as a kind of "leukocyte." There are several studies that prove efficacy of this technique. One of them employed mice; the researchers have shown that herpes simplex virus and Newcastle disease virus extended with the IL12 transgene, a proinflammatory cytokine that plays an important role in initiating the antitumor response, can inhibit growth of the tumor [32]. A recombinant adenovirus carrying the IL15 gene, which encodes the cytokine activating proliferation of the natural killer cells and CD8+ T lymphocytes, was also shown to possess the capacity to inhibit BC cells [33]. Antitumor efficacy was also revealed in the oncolytic vaccinia virus the genome of which was extended with the GM-CSF cytokine gene. Analysis of the immune profile of a mouse model showed an increased infiltration of CD8+ T-lymphocytes into the tumor microenvironment, which proves the immunomodulatory effect of this oncolytic virus [34].

In addition to the general inflammation induction through cytokine synthesis, oncolytic viruses, through production of antibodies, can be given specific targets that enable tumor development. Thus, there was engineered an adenoviral vector that contains the sequence of a full-length anti-HER2 antibody [35]. The virus has shown high antitumor efficacy against HER2-positive BC in cell and mouse models. Adenovirus produced antibodies to the HER2 tumor marker, thus reinforcing antibody-dependent cellular cytotoxicity and making the destruction of cancer cells more effective. In another work, the vaccinia virus was modified with a gene encoding the antibody against vascular endothelial growth factor, VEGF (an angiogenesis regulator that promotes tumor growth) [36]. The engineered virus showed oncolytic and antiangiogenic activity in the triple negative BC xenografts implanted in mice.

BC oncolytic therapy: further development directions

Delivery of viral vectors

To prevent neutralization by antibodies, accumulation in other organs and premature elimination of viral particles, it is important to find the optimal method of delivery of oncolytic viruses to the tumor. The simplest one that mitigates these problems is direct intratumoral injection [37]. For localized and initially local forms of BC, this is the presumably preferred delivery method since the tumor is accessible for injection. However, if there are metastatic lesions, more complex methods of delivery may be required: administration of the viruses together with immunomodulators, use of liposomes and cells as carriers [37]. In a mouse model study, researchers have shown that oncolytic therapy is highly effective when viral vectors are delivered to BC metastatic lesions with the help of dendritic cells [38].

Oncolytic viruses as vaccines

Oncolytic viruses themselves can act as immunomodulatory agents that enhance antitumor immunity. One of the possible strategies is to use an oncolytic virus as a vaccine: a tumor antigen gene is inserted into the virus genome, and when the virus enters the cell, it boosts antigen expression, which increases the likelihood of initiation and enhancement of the antitumor response [26]. This approach has the oncolytic virus acting as a kind of bait for immune cells. In a mouse with ovarian cancer, it was shown that administration of the Maraba virus carrying a tumor antigen caused an increase in the $CD8^+$ antitumor immune response [39]. Accordingly, it is possible to design viral vectors carrying ER, PR and HER2 tumor markers, which will allow targeting the immune response to a specific subtype of BC. Triple negative BC requires special attention as the subtype for which specific tumor markers need to be found. An even more specific triggering of the antitumor immune response is possible with a combination of CAR-T cell therapy (using T-cells carrying chimeric receptors for tumor antigens) and oncolytic viruses delivering the antigenic target for CAR-T lymphocytes [26].

Combination with other therapies

Potentially, the use of oncolytic viruses in combination with other BC treatments may have a synergistic effect. In addition, oncolytic viruses administered as part of a chemotherapeutic protocol often allow reducing the dose of the chemotherapeutic agent, which helps alleviate the severe side effects peculiar to chemotherapy [40]. Most likely, chemotherapy drugs do not have a negative effect on the virus itself. In a mouse model study, it was shown that paclitaxel does not affect the infectious and replicative abilities of the oncolytic virus, and their combined antitumor effect on BC cells was synergistic [41]. According to the results of the second phase of clinical trials, the combined oncolytic reovirus and paclitaxel therapy increased the overall life expectancy in patients with metastatic BC compared to the group taking only paclitaxel [42]. Viruses may also have a synergistic effect with radiation therapy, as was shown in a preclinical study dedicated to the development of a melanoma treatment protocol [43]. Unfortunately, there are no similar studies assessing the effect on BC, but it is assumed that the efficacy of such therapy will be comparable to the results of treatment of other types of tumors. The mechanism underlying the effect has not been identified, however, viruses can interfere with DNA repair after radiation therapy thus promoting a more rapid death of tumor cells [44]. The current direction of therapy is the use of oncolytic viruses in conjunction with monoclonal antibodies. In a phase one clinical trial, some patients exhibited a clinical response with the formation of a pool of reactive $CD8^+$ T cells when solid tumors were treated with vaccinia virus p53MVA in combination with pembrolizumab [45]. In a phase two clinical trial, a combination of Talimogen Lagerparepvec and pembrolizumab proved to have antitumor properties in treatment of sarcoma [46].

CONCLUSION

Oncolytic viruses are a promising platform for BC drugs. Their efficacy is backed by the dual effect they have on a tumor: the lysis of tumor cells — the effector action and the launch (enhancement) of the antitumor immune response — the immunomodulatory action. The effector action can be enhanced by improving the selectivity of the oncolytic virus to BC tumor cells. The immunomodulatory action of the virus can also be enhanced by introducing genes of the immune system proteins into the genome of the virus. Further considerations about the use of oncolytic viruses in the treatment of BC are

related to the methods of delivery of viral particles into the tumor, viral vectors as carriers of tumor antigens accelerating initiation of the antitumor response, and the use of oncolytic viruses in combination with other methods of treatment. However, making the developments in this field practical still requires a significant amount of time, since it is necessary to accumulate a certain amount of evidence on the effectiveness of this approach. Thus, oncolytic viruses are potentially effective and flexible therapeutic tools that may become the basis for a new group of anticancer drugs in the future.

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ISSUES OF CLIMATIC AND GEOGRAPHICAL ADAPTATION OF ATHLETES

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The problem of optimizing the functional state of an athlete, who often travels to the training venues and competition sites, is an integral part of the system for ensuring the maximum efficiency of his professional activity. An athlete, who lives and trains in central Russia, the next day may find himself at the competition halfway around the world, in any climatic zone or time zone. This review details the stages and terms of the adaptation of athletes; criteria of the athlete's adaptation to the new climatic conditions and geographical settings are provided. The existing adaptation models are presented, together with the recommended method for diagnosis and control of climatic and geographic adaptation in athletes.

Keywords: climatic and geographical adaptation, jetlag, professional athletes, pharmacological support, physiotherapy

Author contribution: Samoilov AS — study concept, final editing; Petrova VV — raw data analysis, manuscript writing and editing.

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ПРОБЛЕМЫ КЛИМАТОГЕОГРАФИЧЕСКОЙ АДАПТАЦИИ СПОРТСМЕНОВ

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Проблема оптимизации функционального состояния спортсмена при частых переездах в места тренировок и проведения соревнований является неотъемлемым звеном системы обеспечения максимальной результативности его профессиональной деятельности. Спортсмен, живущий и тренирующийся в средней полосе России, на следующий день может оказаться на соревнованиях в другом полушарии Земли в любой климатической зоне и любом часовом поясе. В обзоре детально рассмотрены этапы и сроки адаптации спортсменов, приведены критерии адаптированности спортсмена к новым климатогеографическим условиям. Представлены существующие модели адаптации и рекомендуемая методика диагностики и контроля климатогеографической адаптации у спортсменов.

Ключевые слова: климатогеографическая адаптация, десинхроноз, профессиональные спортсмены, фармакологическая коррекция, физиотерапия

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International competitions, such as the Olympic Games or the World Cups, are conducted anywhere on the globe. That is why the issues of the athletes' adaptation are the pressing issues of the sports medicine, which in turn determine the relevance of the physiological and hygienic substantiation for optimization of the athletes' adaptation both to the climatic conditions and to the jet lag.

The issues of the athletes' adaptation to the changing climatic conditions and geographical settings were studied by many eminent specialists in sports medicine. Their papers present theoretical aspects of the effects of the climate loads and the mechanisms, underlying adaptation to the changing environmental conditions, provide a list of various groups of remedies (pedagogical, hygienic, biomedical, and psychological). However, no specific schemes for their use by athletes during the acclimatization period are reported.

Adaptation phases and terms

Adaptive responses of the human body may be roughly divided into three groups:

a) general adaptive physiological responses related to the basic functions, which make it possible to live and work in changing environment;

b) specific morphofunctional, physiological, and psychological changes based on the genotype-phenotype features;

c) adaptative behavioral responses (water drinking schedule, diet, clothing, and the facilities equipped with air conditioning or heating systems) [1].

Based on the above classification, we believe that behavioral aspects of adaptation are of particular importance, since their realization is up to the athlete, and these aspects contribute greatly to the success of both general physiological responses and specific responses to the changing environment.

The period of the athlete's body acclimatization (adaptive reorganization) may vary considerably. The period and nature of the acclimatization response are influenced by both environmental factors (contrasting climate zones change, daily and seasonal changes in weather patterns) and the athlete's condition (individual characteristics, age, acute and chronic disorders, state of the central nervous system, respiratory system, and other systems, weather sensitivity, etc.) [2].

Adaptive capacity of the body (adaptivity, plasticity of regulatory systems) enables the athlete to adjust to a changing environment within a short time.

High levels of physical performance increase the body's capability of adaptation to environmental factors. This is because physical exercise improves cardiovascular health (in particular, heart rate is lowered, stroke volume and cardiac output are increased, etc.) [3].

Sufficient mental capacity makes it possible to successfully endure the exposure to environmental factors. Emotional management skills allow one to ensure the individual's optimal activity and adaptation to the changing environment.

The contrasting changes in climatic conditions and geographical settings determine the physiological loads the body is exposed to, i.e. the intensity of the body's mechanisms of adaptation, related to the impact of the climate change. The more contrasting are the climate changes, the larger is the amount of information brought by the climate change, the more severe is the stress to adaptive mechanisms, and the higher is the risk of adverse effects during acclimatization (disadaptation). Travel speed when changing the climatic conditions has a certain impact [4].

The main risk factors for disadaptation in athletes are as follows: history of injuries, acute disorders, and the extent to which the chronic disorder is compensated.

The following factors and types of reserve contribute to the body's adaptive capacity: biological reserve (genetically determined), professional training, biochemical reserve.

The majority of adaptive responses occur in two phases: initial adaptation (short-term, imperfective) and subsequent adaptation with the formation of structural trace (long-term, perfective) [5].

The adaptive response short-term phase starts immediately after exposure to the stimulus and could be realized based on the previously shaped physiological mechanisms only. The long-term phase of adaptation develops gradually with the prolonged or repeated exposure to environmental factors [6].

A the same time, a thorough approach to the athlete's condition assessment during the acclimatization period shows that the period from days 1–3 to days 7–8 after the journey is the worst (Fig. 1) [7].

During the first three days after the journey, the “stress cap” is developed in the athlete being pressurized by the changes in climatic conditions and geographical settings, high social responsibility, psycho-emotional stress, and competition loads. During this period, the athlete demonstrates the emotional uplift, accompanied by the stress hormones release and the body functional reserve mobilization. Regardless of the numerous literary sources suggesting the opposite, any environmental stimuli, including the competitive activity, are well tolerated during this period.

Since day 7–8 of exposure to a new environment, the athlete enters the phase of developing the long-term adaptation (structural trace). During this period, the body's resistance is close to baseline, and subsequently the functional reserve capacity is increased.

From day 3 to day 7, within the period between “taking off the stress cap” and the beginning of the structural trace formation, the athlete's body becomes the most vulnerable. During this period, the risk of the reduced athlete's resistance to environmental factors is the most probable.

The discussed adaptation phases suggest that the option of performing within the first three days after the journey to the competition venue (the phase characterized by the development of “stress cap”) is most appropriate for sports where the competitions are carried out for 1–3 days. In our opinion, in case of performance on day 4 of adaptation or later, it is advisable to focus on addressing the combination of bio-psycho-social issues, which determines both successful adaptation and successful competitive activity. For more details, see below.

Criteria for athlete's adaptation to new climatic conditions and geographical settings

The criteria for the athlete's body adaptation are roughly divided into non-specific (integral) and specific (Fig. 2). The non-specific criteria reflect the athlete's body functional state when exposed to any factor; specific criteria reflect the typical alterations evolving under the influence of one or another damaging factor [8].

In case of favorable adaptation, there are minor deviations of the non-specific and specific indicators, which finally equate the normative values, typical for the population in a certain location. This state is regarded to as the “person's environmental portrait” [9].

Acceleration or facilitation (optimization) of adaptation to the changing environment is one of the ways to improve the efficiency of the athlete's competitive activity. Optimization of the adaptation processes results in the improved overall athlete's body resistance and body defences, as well as in the reduced impact of the disease pathogenic mechanisms, and in mitigating the lack of external (natural) stimuli.

In order to define the criteria for the adaptive capabilities and the integrated assessment of the athlete's body functional reserve capacity, the following formula was developed:

$$BAC = \frac{PP \times HT \times PT \times MC}{HI \times ChD \times \Delta CCC \times TZ \times V_{tr}},$$

where BAC — body's adaptive capacity (adaptivity, plasticity); PP — physical performance; HT — heat tolerance; PT — professional training; MC — mental capacity; HI — history of injuries; ChD — chronic disorders; ΔCCC — contrast between

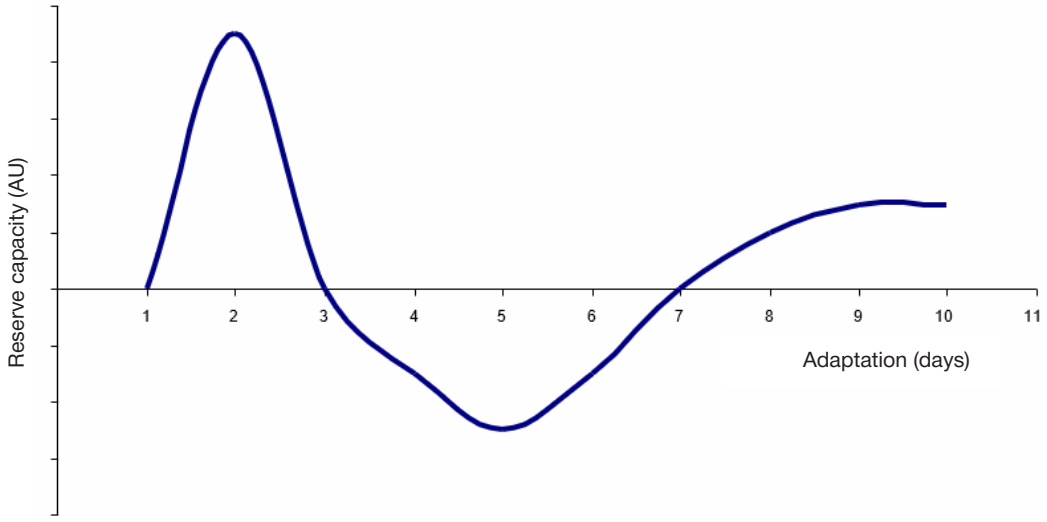

Fig. 1. Dynamic changes in body's reserve capacity when exposed to environmental factors [7]

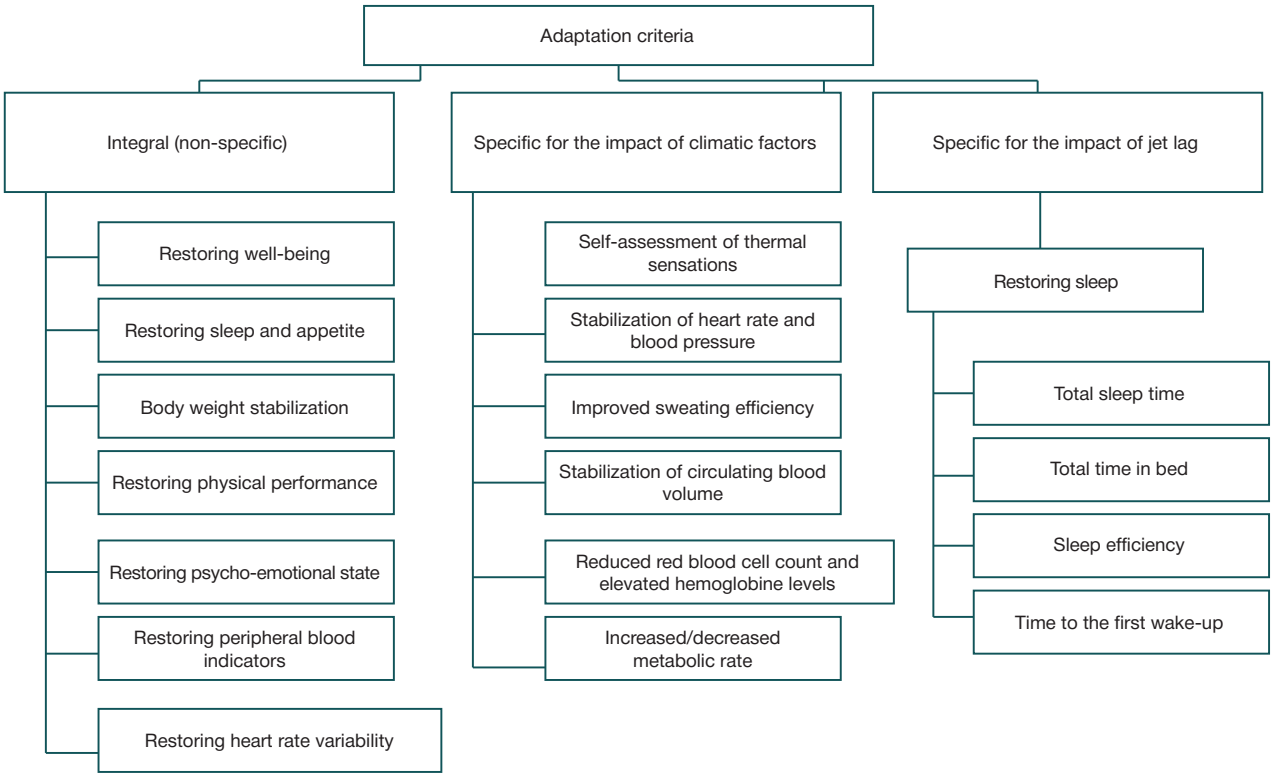

Fig. 2. Criteria for adaptation to hot climate

climatic conditions; TZ — number of time zones crossed; V_{tr} — athlete's speed of travel.

The closer to one is the BAC value, the larger is the athlete's adaptive capacity and the higher is his functional readiness.

The groups of individuals with four types of response are distinguished based on their functional systems' response to the changing environment. The first type consists of individuals unable to adapt to the changing environmental conditions; such individuals constitute only 5–7%, i.e. this group is the smallest one.

The second, "flexible", type constitutes 20–30% of the population. It consists of individuals with the pronounced deviations of homeostatic indicators (heart rate, blood pressure, T °C, etc.) due to exposure to environmental factors, and the rapid recovery of the body's functional state after the end of exposure. These individuals are characterized by high quality performance in the changing environment along with the pronounced cardiorespiratory response and the lack of thermal stability.

The third, "passive", type constitutes 20–30% of the population. This group demonstrates stable homeostasis (stabilization) of the adjustable parameters when exposed to the factor, and the prominent deviation of the parameter after the end of exposure. The athletes in this group are characterized by decreased performance and inactive decision-making style before adjusting to the changed climatic conditions.

The fourth, "mixed", type constitutes about 40%. This type integrates the features of responses typical for individuals of the second and third types, as well as of the types with the modest predominance of one of those. Such individuals have a stable, albeit slightly decreased, level of maintaining their functional state and performance when operating in the changed environment.

Apart from the individuals not capable of the climate change adaptation, the listed above three types of response to environmental stimuli are divided in literature into the following types: hyperergic–normoergic–hypoergic types, or sprinter–mixed–stayer. Individuals of the "mixed" type are considered normoergic [10].

The athetes with hyperergic type of response are able to compete since the first day after their arrival in the different climate zone. However, it should be pointed out that their performance would be at the expense of the enormous physiological loads.

The athetes with hypoergic type of response have a poor prognosis of performing after changing the climate zone. They need to be adapted to the environment, in which they have to perform, for a long period.

Thus, after defining the type of the athlete's body response, we can assume the athlete's individual response to the changed climatic conditions, and plan the biomedical support activities.

Rationale for the models of the Russian national team athletes' adaptation to the new climatic conditions and geographical settings

In view of the foregoing, we have proposed seven models of adaptation to climate for the athletes performing in the open areas. The essence of the model, the summary, the sports a model is relevant for, and the time frame are presented in Table 1.

In our opinion, the model of "readaptation" is the more preferable one among the listed above models. In this case, the athlete's adaptation to climatic loads is formed naturally during the repeated appearances on the competitions, carried out in various climatic conditions and time zones. Readaptation is accompanied by the formation of "vegetative memory", triggering the sequence of adaptive responses, which, consequently, reduces the adaptation time. This model is appropriate for athletes from all sports.

The option of "no need for adaptation" is the most appropriate for sports, where the competitions last for 1–2 days [11]. During the first three days after arrival, the athlete

Table 1. Models and strategies of adaptation for the highly qualified athletes performing in the open areas

Adaptation model	Adaptation strategy			
	Days between arrival and the start of competition	Essence of strategy	Summary	Sports the model is relevant for
1. No need for adaptation	1–2 days	"Stress cap"	Emotional tension and the new environment cause the release of stress hormones and body functional reserve mobilization	Short-term competitions (sprint, all types of jumping, throwing, etc.)
2. Long-term adaptation	10–14 days	The long-term adaptation structural trace formation by day 10–14	Capacity of all specific adaptation systems is increased	Long-term activities (marathon, bicycle racing, triathlon, etc.), and sports where the competitions are carried out for a few days (football, beach volleyball, etc.)
3. Preliminary adaptation (preconditioning)	10–14 days (up to 21 days)	Preliminary adaptation in places with a similar climate within the same time zone	Long-term adaptation is formed. Readaptation is required after arrival to the competition venue	Long-term activities (marathon, bicycle racing, triathlon, etc.), and sports where the competitions are carried out for a few days (football, beach volleyball, etc.)
4. Readaptation	1–2 days	Multiple appearances of the athlete on the competitions carried out in the same climatic conditions within the same time zone	"Vegetative memory" is formed, triggering the sequence of adaptive responses. This occurs in a natural way when the athlete takes part in various competitions	All sports
5. Cross-adaptation	10–14 days	Adaptation to one factor improves adaptation to another factor	Hypoxic hypoxia demonstrates the broadest range of cross-adaptation	All sports (especially those that require physical endurance)
6. Engineered adaptation with the use of technical means	5–7 days	Simulation of the conditions for adaptation, (Environmental chambers, equipment for artificially induced hypoxia, etc.)	Arises from the body's non-specific response to the effects of various environmental factors, the body has to adjust to	All sports
7. Preliminary self-adaptation	5–7 days	Applying the simple techniques to boost the reserve capacity of the body (cold exposure training, sauna, contrast bath therapy, etc.)	Partial adaptation in response to the exposure to various environmental factors	All sports

demonstrates the emotional uplift, accompanied by the stress hormones release and the body functional reserve mobilization, i.e. the "stress cap" is being formed [12].

The models of "cross-adaptation" and "preliminary self-adaptation" may be used in athletes from all sports. It should be noted that hypoxic hypoxia demonstrates the broadest range of cross-adaptation, and is the most appropriate for the representatives of cyclic sports. Cross-adaptation is based on the fact that adaptation to one factor improves adaptation to another factor.

It is assumed that preliminary self-adaptation involves the use of simple techniques for boosting the reserve capacity of the body by the athlete (cold exposure training, sauna, contrast bath therapy, etc.).

In our opinion, the use of the "long-term", "preliminary" and "engineered" adaptation in athletes is socially and economically unreasonable.

When using the selected stratedy, and in order to correctly assess the integral adaptation criteria, it is recommended to analyze the pooled data, obtained with the use of the following generally accepted methods:

– supervision of the sport physician or coach;
– heart rate variability;
– WAM questionnaire (Well-being, Activity, Mood);
– daily weight control;
– athlete's self-esteem journal;
– assesment of physical well-being by the coach (training tests);
– analysis of the peripheral blood indicators (whenever possible).

Table 2 presents the recommended method for the diagnosis and control of the climatic and geographical adaptation in athletes taking into account both non-specific and specific adaptation criteria.

It is recommended to use fitness trackers, which track sleep quality and are capable of tracking such parameters as total sleep time, total time in bed, sleep efficiency (sleep phases analysis), and time to the first wake-up, for the mobile diagnosis of a number of specific adaptation criteria, namely the normal sleep restoration.

In addition to the analysis of sleep, fitness trackers allow the athlete to pursue a strategy of maintaining the "domestic routine" after moving to the competition venue by crossing more that three time zones.

CONCLUSION

In order to minimize the effects of negative factors, resulting from the athletes' climatic and geographical adaptation, special attention should be paid to the following aspects: preliminary assessment of the althlete's health and performance when taking part in the competitions; in-depth study of physiological and hygienic features of adaptation in athletes from various

Table 2. Method for diagnosis and control of climatic and geographical adaptation in athletes

Diagnostic methods	Day after the journey													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Supervision of the sport physician or coach	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Heart rate variability	+++	+++	+++	+++	+++	+++	+++	–	–	–	–	–	–	–
WAM questionnaire	+++	+++	+++	+++	+++	+++	+++	–	–	–	–	–	–	–
Weight control	+++	+++	+++	+++	+++	+++	+++	–	–	–	–	–	–	–
Athlete's self-esteem journal	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
Monitoring the dynamic changes in physical condition	+++	+++	+++	+++	+++	+++	+++	–	–	–	–	–	–	–
Analysis of the peripheral blood indicators	+	+	+	+	+	+	+	–	–	–	–	–	–	–
Fitness tracker or smartwatches	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++

Note: +++ — strongly recommended; ++ — recommended; + — at the discretion of the athlete, the coach or the team physician; – — avoid using.

sports at the various stages of training and competitive activity; continuous pursuit and improvement of the means for the athlete's performance optimization, particularly in the context of long-distance flights and extreme climatic conditions; developing the new methods for adjustment and improvement of the athlete's heat tolerance; accelerated adaptation to the adverse effects of the chronobiological rhythms desynchronization.

The use of the recommended adaptation strategies together with the diagnosis and control methods, allowing one to monitor both non-specific and specific adaptation criteria, would make it possible to not to miss disadaptation in athletes, as well as to properly plan the adjustment and adjust the pathological manifestations, resulting from the impact of the negative climatic and geographical factors.

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CARDIOVASCULAR COMORBIDITY IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

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Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide. It is characterized by hepatic steatosis and stetohepatitis and in some cases can progress to cirrhosis with or without hepatic failure and hepatocellular carcinoma. At present, NAFLD is deemed a predictor of cardiovascular risk. Besides, it can aggravate pre-existing cardiovascular conditions. Structural and functional changes in the heart, liver and blood vessels are interdependent and mutually aggravating. Metabolic factors (dyslipidemia, hyperglycemia and insulin resistance) contribute to hepatic, cardiac and vascular damage, and NAFLD and comorbid cardiovascular disorders together can activate fibrogenesis in the heart, blood vessels and liver.

Keywords: nonalcoholic fatty liver disease, fatty steatosis, nonalcoholic steatohepatitis, liver fibrosis, endothelial dysfunction

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КАРДИОВАСКУЛЯРНАЯ КОМОРБИДНОСТЬ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Неалкогольная жировая болезнь печени (НАЖБП) занимает первое место в мире среди болезней печени. Заболевание характеризуется развитием стеатоза и стеатогепатита, в некоторых случаях прогрессирует до цирроза с или без развития печеночной недостаточности и гепатоцеллюлярной карциномы у части пациентов. В настоящее время НАЖБП рассматривают как маркер сердечно-сосудистого риска. Кроме того, она может усугублять течение уже имеющихся сердечно-сосудистых заболеваний. Известно, что развитие структурно-функциональных изменений сердца, печени и сосудов взаимообусловлены и носят взаимоотягощающий характер. Изучено и отрицательное влияние метаболических факторов (дислипидемии, гипергликемии, инсулинорезистентности) на формирование поражения печени, сердца и сосудов, а сочетание НАЖБП и сердечно-сосудистых заболеваний может оказывать влияние на активацию фиброгенеза как в сердце и сосудах, так и в печени.

Ключевые слова: неалкогольная жировая болезнь печени, жировой стеатоз, неалкогольный стеатогепатит, фиброз печени, эндотелиальная дисфункция

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Nonalcoholic fatty liver disease (NAFLD) is a chronic metabolic disorder developing in the absence of exogenous hepatotoxicity-inducing factors (e.g. exogenous ethanol) and characterized by excess accumulation of lipids in the cells constituting the hepatic lobule. Morphological findings confirming NAFLD include steatosis, steatohepatitis, fibrosis, cirrhosis, and adenocarcinoma. The diagnosis is considered verified if triglycerides (TG, a type of lipids) make up over 5–10% of the liver's weight or if lipid deposits are observed in over 5% of hepatocytes [1].

At present, NAFLD is the most common chronic liver condition worldwide, affecting on average 25% of the population in high-income countries [2]. Although the majority of patients with NAFLD have moderate steatosis, 20 to 30% develop steatohepatitis with progressive fibrosis. Of them, about 20% will eventually progress to liver cirrhosis and thus be at increased risk for hepatocellular carcinoma [3, 4]

In 2007, the DIREG-1 screening study was conducted to estimate the prevalence of NAFLD in the Russian population. Of 30,750 participants included in the study 27% were diagnosed with NAFLD. Of them, 80.3% had steatosis, 16.8% had steatohepatitis and 2.9% had liver cirrhosis [5]. According to DIREG-2 estimates, the prevalence of NAFLD in the Russian population has been growing steadily in the past years, reaching 37% in 2015 [6]. In the majority of patients, NAFLD is associated with such metabolic comorbidities as obesity, type 2 diabetes mellitus and/or dyslipidemia [7].

NAFLD is deemed a predictor of cardiovascular diseases (CVD). The risk of CVD in patients with NAFLD is 4.12 times higher than in those without NAFLD; notably, women with NAFLD are at higher risk for CVD than men [8]. Insulin resistance, dyslipidemia and obesity contribute to NAFLD progression, extrahepatic complications and overall poor prognosis. NAFLD is recognized as a hepatic manifestation of metabolic syndrome. Metabolic risk factors like overeating, a sedentary lifestyle and genetic predisposition cause visceral adipose dysfunction, i.e. overproduction of free fatty acids (FFA) and proinflammatory

cytokines and underproduction of adiponectin. This leads to insulin resistance, dyslipidemia, thrombophilia, and progressive liver cirrhosis. NAFLD causes systemic buildup of TG in various organs, including the myocardium, and induces oxidative stress, which in turn results in cardiomyocyte dysmetabolism and dysfunction provoking ventricular and supraventricular arrhythmias, coronary artery disease and aortic valve sclerosis. Inflammation and metabolic disorders lead to hepatic steatosis, steatohepatitis, liver fibrosis, and heart pathology (atherosclerosis and myocardial dysmetabolism); the latter manifests as subclinical atherosclerosis, arterial hypertension, coronary artery disease (CAD), arrythmias, myocardial infarction, chronic heart failure and eventually death [9].

Notably, patients with progressive fibrosis and advanced steatosis (F > 3) are at the highest risk for death from liver disease, and CVD are very common in patients with early-stage fibrosis (F < 3) associated with NAFLD [10–12].

Possible mechanisms underlying cardiac complications in patients with NAFLD [13] are shown in the Figure.

Patients with NAFLD present with pronounced cardiac remodeling: heart chambers are significantly enlarged and their walls are thickened, epicardial fat thickness and myocardial mass are increased [14]. Myocardial fibrosis during myocardial remodeling leads to electrophysiological disorders and secondary ischemia. The loss of cardiomyocytes is accompanied by an increase in adipocytes. Adipose tissue is an active endocrine organ that synthesizes and secretes large amounts of bioactive substances, including interleukin 6, renin, angiotensin I and II, tumor necrosis factor α, resistin, adiponectin, and leptin [15–17]. Visceral adipose tissue lipolysis results in increased secretion of FFA, which, on the one hand, become a substrate for atherogenic lipoproteins and, on the other hand, potentiate IR at the liver level, reducing plasma membrane permeability to glucose [16]. The severity of visceral obesity and adipose tissue dysfunction in patients with NAFLD has been shown to reliably correlate with the severity of the cytolysis syndrome and cholestasis [18]. Thus, progression of visceral obesity in patients with NAFLD is accompanied by progressive structural and functional liver damage [18]. Notably, secretion of proinflammatory cytokines by epicardial adipose tissue into the bloodstream enhances systemic inflammation, which in turn aggravates cardiometabolic dysfunction promoting buildup of epicardial fat [19]. The latter is a source of FFA, especially in the setting of increased myocardial energy demand observed in many conditions, including ischemia [20, 21]. FFA produced by epicardial adipose tissue are taken up by the myocardium, where they fuel myocardial steatosis, inducing structural and functional changes in the heart (heart enlargement, left ventricular hypertrophy and left ventricular diastolic disfunction) [22].

In patients with NAFLD, the risk of death from CVD is determined by the stage of NAFLD and other cardiometabolic risk factors [23]. As a rule, the severity of fibrosis becomes the defining factor for CVD development and death from CVD in patients with NAFLD. Non-alcoholic steatohepatitis increases mortality by 70%, mostly due to an increase in CVD-related mortality [24]. Patients with steatohepatitis and patients with NAFLD and co-existing type 2 DM constitute a special risk group for CVD and cardiovascular events.

It has been demonstrated that patients with NAFLD are at higher risk for cardiovascular pathology on the SCORE scale than those without NAFLD [25]. Moreover, the study has established an association between the severity of NAFLD and the high risk of poor cardiovascular outcomes. These findings are consistent with the results of another study in which NAFLD confirmed by ultrasonography was strongly associated with non-fatal cardiovascular events [26].

Arterial hypertension is the most common risk factor for CVD. According to WHO's estimates, 54% of all strokes and 47% of all CAD cases are direct consequences of elevated blood pressure [27, 28]. Patients with NAFLD and arterial hypertension make up 40–70% of the general population. NAFLD is also associated with heightened risk of prehypertension [29].

The Finnish OPERA study conducted in hypertensive patients revealed that the average diurnal blood pressure values were higher in patients diagnosed with liver steatosis (30.9% vs 24.6%; p = 0,057) [30]. In another study, blood pressure variability was greater in patients with arterial hypertension and NAFLD than in those with isolated hypertension [31]. It is reported that the high 10-year risk of cardiovascular events is more frequent among patients with hypertension and NAFLD than among patients with isolated hypertension [32].

Systemic inflammation associated with NAFLD can stimulate activation of the sympathetic nervous system, promoting hypertension. Another mechanism implicated in elevated blood pressure is IR: it leads to overproduction of free fatty acids and increased oxidative stress [33].

NAFLD is associated with a high risk of coronary atherosclerosis [34, 35], impaired myocardial perfusion and poor outcomes of coronary artery stenting due to the high risk of restenosis [36, 37]. These impairments are predominantly associated with abnormal vasodilatory response, increased coronary intima-media thickness and atherosclerosis. According to the meta-analysis of 6 studies with a total sample of 25,837 participants, patients with NAFLD were at higher risk of clinical CAD than patients without NAFLD (CI 1.04–4.92; p < 0.001) [38]. Another study conducted in 360 patients with a past history of ST-segment elevation myocardial infarction found that nonalcoholic liver steatosis was an independent predictor of plaque formation in coronary arteries, revealing higher hospitalization and 3-year mortality rates among patients with NAFLD than in the control group [39].

Atrial fibrillation (AF) is a common type of arrythmia; due to the global population ageing, its incidence has been on the rise over the past decades [40]. According to the study of NAFLD effects on the risk of paroxysmal AF, patients with type 2 DM and co-existing NAFLD have more frequent episodes of paroxysmal or permanent AF than those without NAFLD [41, 42]. It is known that intra-atrial conduction delay underlies the pathophysiology of AF. It is reported that NAFLD patients without DM, clinically confirmed hypertension or CVD have significantly longer inter-atrial and intra-atrial electromechanical delay intervals than the control group. This is associated with reduced electrophysiological potential of the myocardium, when cardiac conduction velocity is reduced due to fibrosis, causing cardiac rhythm disturbances and especially high-risk arrythmias. It has been demonstrated that NAFLD is an independent predictor of such electrophysiological disorders of the heart [43].

Being the risk markers of ventricular arrythmia, heart rate variability and prolonged QT intervals are associated with a higher risk of death from cardiovascular disorders [33]. In a study conducted in NAFLD patients with type 2 DM without preexisting heart conditions, NAFLD severity was associated with prolonged QT intervals regardless of the patient's age, sex, the presence of hypertension or type 2 DM. The analysis confirmed the association between the severity of NAFLD and the probability of prolonged QT regardless of the presence of cardiometabolic risk factors [44]. Indeed, the role of NAFLD in the development of ventricular arrythmia still remains understudied

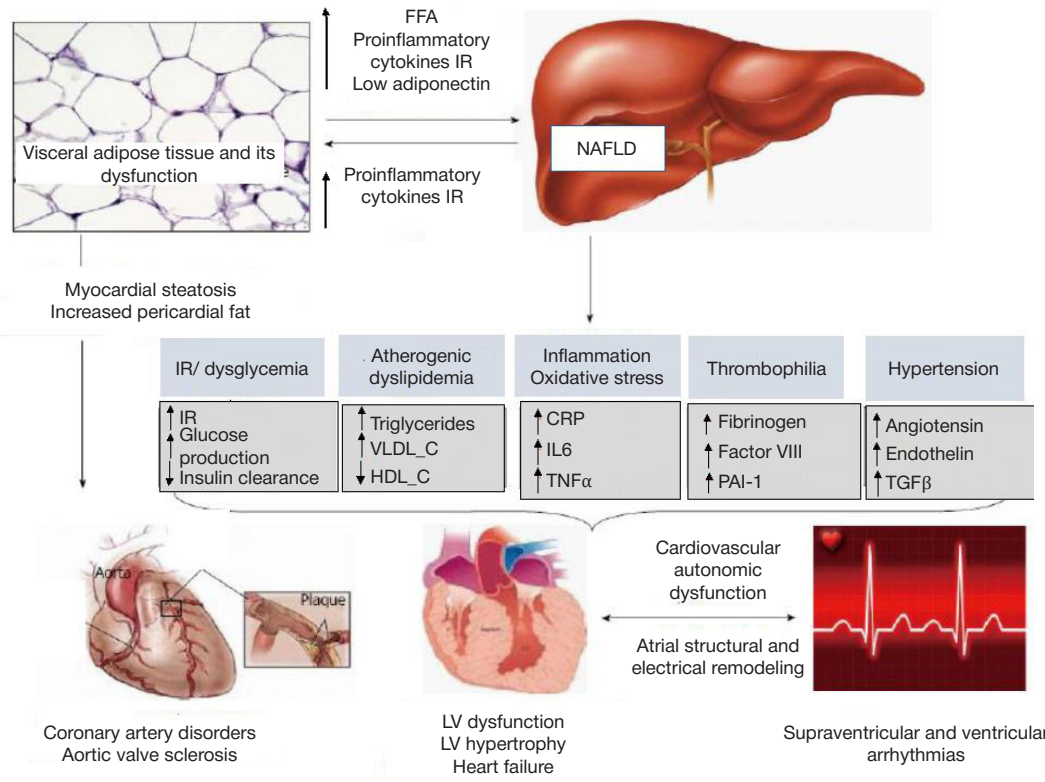

Fig. Possible mechanisms underlying cardiovascular complications in patients with NAFLD. PAI-1 — plasminogen activator inhibitor-1; TGFβ — transforming growth factor β; IL6 — interleukin 6; IR — insulin resistance; FFA — free fatty acids; LV — left ventricle; VLDL_C — very-low-density lipoprotein cholesterol, HDL_C — high-density lipoprotein cholesterol, CRP — C-reactive protein

but the implication of pathophysiological mechanisms typically underlying NAFLD (chronic inflammation and insulin resistance) in electrophysiological myocardial dysfunction is undeniable.

Chronic heart failure (CHF) is an extremely severe complication of CVD characterized by poor outcomes. In addition, it poses a diagnostic difficulty and its therapy and prevention required special approaches. It has been established that NAFLD aggravates the course of CHF. One of CHF manifestations is left ventricular diastolic dysfunction. NAFLD is associated with left ventricular diastolic dysfunction regardless of the presence of other cardiovascular risk factors and metabolic syndrome [45, 46]. In a multicenter study conducted in 2,713 patients with cardiovascular pathology, NAFLD patients had elevated left ventricular filling pressure, increased left atrial volume, reduced ejection fraction, and reduced diastolic function in comparison with patients who had no history of NAFLD [47]. Other studies report an association between NAFLD and diastolic dysfunction of the left ventricle in patients with type 2 DM [48, 49].

Moreover, patients with NAFLD develop early left ventricular diastolic dysfunction more frequently [50]. Diastolic dysfunction is indicative of myocardial stiffness and fibrosis. These changes are manifestations of systemic fibrosis. In addition, our study conducted in patients with chronic heart failure and nonalcoholic fatty liver disease revealed that changes in vascular wall stiffness and microcirculation disorders (pathological hemodynamic types of microcirculation with predominance of shunt blood flow, nutritional insufficiency) correlated with changes in the structural and functional state of the liver [51].

CONCLUSION

Patients with NAFLD can progress from steatosis (fatty infiltration of over 5% of hepatocytes) to nonalcoholic steatohepatitis (fatty infiltration with necroinflammation) to liver fibrosis, cirrhosis and hepatocellular carcinoma. NAFLD is a risk factor for cardiovascular comorbidities, predictor of CVD and death. Patients with NAFLD should undergo screening for cardiovascular pathology and NAFLD-associated risk factors without delay. Timely therapy commenced at the stage of liver steatosis will prevent progression of the disease and poor cardiovascular outcomes in NAFLD patients.

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MEDICAL REHABILITATION AND INFECTIOUS DISEASES IN CHILDREN

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Today, medical rehabilitation is undergoing significant transformation. The new system built around the biopsychosocial model includes assessment of physical constraints and rehabilitation diagnosis, determination of rehabilitation potential, formulation of goals and objectives of individual interventions, development of rehabilitation plans, and progress evaluation. All of these rehabilitation components can be implemented using a personalized, problem-oriented, multidisciplinary approach, which is now being actively introduced into clinical practice. The current pandemic of the novel coronavirus infection has demonstrated that medical rehabilitation is crucial for convalescents. However, its principles and techniques have not been fully elaborated yet. This review describes the current state of medical rehabilitation of children with or after infectious diseases and identifies its avenues and prospects.

Keywords: children, rehabilitation, infectious diseases, ICF, telemedicine, biopsychosocial model, personalized approach, COVID-19

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МЕДИЦИНСКАЯ РЕАБИЛИТАЦИЯ И ИНФЕКЦИОННЫЕ БОЛЕЗНИ У ДЕТЕЙ

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Медицинская реабилитация в наши дни претерпевает существенные изменения. Эта новая, выстраиваемая на основе биопсихосоциальной модели, система, включает в себя оценку ограничений жизнедеятельности, определение реабилитационного диагноза и реабилитационного потенциала, формирование цели и отдельных задач реабилитационных вмешательств, построение и осуществление плана реабилитационных интервенций с последующей оценкой достигнутых результатов. Все эти действия возможны в условиях реализации персонифицированного, проблемно-ориентированного и мультидисциплинарного подходов, которые сейчас активно внедряются в клиническую практику. Пандемия новой коронавирусной инфекции определила жизненную необходимость медицинской реабилитации реконвалесцентов инфекционных болезней, принципы и технологии которой не отработаны до настоящего времени. В обзоре представлено состояние современной медицинской реабилитации в детской инфектологии, специфика медицинской реабилитации у детей в условиях инфекционного процесса и после его завершения. Определены основные направления медицинской реабилитации детей с инфекционными болезнями и перспективы ее развития.

Ключевые слова: дети, реабилитация, инфекционные заболевания, МКФ, телемедицина, биопсихосоциальная модель, персонифицированный подход, COVID-19

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The conventional approaches to medical rehabilitation adopted in Russia are undergoing significant transformation toward the biopsychosocial model of disease that public healthcare is yet to fully incorporate. Unlike the classical biomedical model, the biopsychosocial model is not constrained by the nosological approach and sees disease as a complex of biological, psychological and social processes [1]. Apart from focusing on the biological factors implicated in disease, biopsychosocial rehabilitation actively exploits psychological and social approaches to recovery and thus can exert broader effects on sanogenesis.

In the past decade, this new model of medical rehabilitation has been actively implemented in Russia. New rehabilitation specialties have emerged, including physical medicine and rehabilitation doctors and rehabilitation nurses indispensable to the multidisciplinary rehabilitation team. Professional standards have been elaborated for healthcare workers engaged in ergotherapy (ergotherapists, ergospecialists), physical therapy (physical therapists, kinesiotherapists), speech therapy, and medical psychology [2, 3].

According to the now effective legislation on medical rehabilitation, the latter must be multidisciplinary in nature and utilize the International Classification of Functioning, Disability and Health (ICF) [4].

Being a representation of the biopsychosocial disease model, ICF provides a framework for rehabilitation: based on

the ICF-coded diagnosis, the ultimate goal of rehabilitation and its smaller objectives are identified, the rehabilitation plan is designed (considering the rehabilitation potential) and rehabilitation outcomes are evaluated [5].

Developmental issues are a serious ramification of childhood diseases; therefore, a series of consecutive rehabilitation courses may be needed for children with a past history of disease, each course being a continuation of the previous one. Children may develop concurrent debilitating conditions that together produce a devastating effect. Establishing a good rapport with children and their parents is critical for successful pediatric rehabilitation. Immediate family (ICF code e310) is an environmental factor that has a tremendous impact on the child's health. Many problems experienced by the child may be linked to the individual attitudes perpetuated in the family (ICF code e410). Another important contributor is physical environment (Products and Technology, ICF code e1): skills and activities are learnt through the interaction with the environment, which is ideally fosters development and is a powerful rehabilitation tool. Restricting children in their basic activities, including mobility, may preclude other activities and cause secondary damage to cognitive development.

The medical rehabilitation of today is very much different from what it was in the past. Its concept raises the need for rethinking and refining rehabilitation strategies and techniques. Approaches to rehabilitation are changing in every medical field, including the domain of pediatric infectious diseases.

Pediatric infectious diseases are very common, making up 90% of childhood diseases [6, 7]. The most prevalent are acute respiratory infections: their incidence among children is 2.5–2.9 times higher than among adults [8]. The impact of pediatric infections on child health and development is difficult to underestimate, considering current trends in their incidence and the spread of the novel coronavirus infection, which has convincingly shown that infections are still one of the primary threats to mankind. Today, old infections are resurfacing and novel infections are emerging. Antimicrobial resistance, human microbiome transformation and herd immunity fluctuations remain a serious challenge. The economic burden of infections is growing [9, 10].

This review covers Pubmed, e-library and Cochrane library publications of the past decade focusing on the medical rehabilitation of children with a history of infectious diseases.

Neuroinfections

Neuroinfections are among the leading contributors to pediatric morbidity from infectious diseases. Half of pediatric patients with neuroinfections develop disabilities with persistent organic symptoms in the residual period [11, 12]. Poor outcomes may be associated with the child's age, the corresponding stage of brain development and vulnerability of some CNS structures. Pre-existing pathology of the nervous system can aggravate the damage [11].

High demand for rehabilitation is associated with severe sequelae of neuroinfectious diseases; some authors emphasize the importance of starting rehabilitation in the acute stage of the disease because the early commencement of rehabilitation therapy may determine rehabilitation potential and prevent complications or disability [13].

According to publications investigating the outcomes of neuroinfections, mechanisms underlying neurological deficit and cognitive disorders remain understudied, meta-analyses are scarce and there are certain difficulties in formulating conclusions [14–17]. The long-term neurological consequences of neuroinfections that reduce the quality of the patient's life are observed in 25–63% of cases [17, 18]. While studying the outcomes of neuroinfections, many authors focus on immunization, premorbidities, length of hospital stay, timeframe and choice of antibacterial or glucocorticoid therapy, nutritional status, and dehydration [14, 19–22]. Unfortunately, the effects of rehabilitation on the outcomes of neuroinfection are barely discussed.

Children with a past history of neuroinfection experience a variety of health problems differing in form and severity. Those include cognitive impairment, autonomic disorders, attention deficit/hyperactivity disorder, central or peripheral paresis, coordination disorders and speech impairment, epilepsy, etc. [6]. The meta-analysis of 868 meningococcal meningitis cases [17] revealed the presence of residual symptoms in 18% of the patients manifesting as hearing loss (5.4%), skin scarring (5.4%), renal dysfunction (2.6%) or seizures (2.5%). Cerebrasthenia was observed in 40–85% of convalescent children with aseptic meningitis, whereas reduced working memory was reported in 24% of cases; these conditions persisted for up to 6 months in 20–40% of the patients [23]. Among other neuroinfection sequelae reported in the literature are increased intracranial pressure (13%), diencephalic (16%) and focal (10%) manifestations. Neurasthenia (35%), increased intracranial pressure (19%) and symptomatic epilepsy (3%) can last for over a year following the infection [6]. Significant functional decline is observed after infectious encephalitis [24, 25]. Almost 80% of patients with encephalitis suffer from neuropsychological impairment. There are reports of attention and behavioral deficits and emotional impairment continuing for 3 years after the acute phase of the disease [26, 25].

According to an American study, 37 of 55 children infected with tick-borne encephalitis in 2004–2008 had cognitive deficit, headaches, fatigue and irritability 2–5 years after the infection. Parent and teacher surveys revealed that over one-third of the affected children had behavioral problems, motivational deficiency and reduced working memory [27]. Similar findings were reported by Swedish, Chinese and Russian researchers. Attention deficit/hyperactivity disorder was diagnosed in 50% of children with a past history of tick-borne encephalitis in both early and late postinfectious periods [27–29]. Another concern is postinfectious epilepsy. Over half of children infected with encephalitis develop seizures in the acute stage of the disease [30]. Besides, patients with postinfectious epilepsy are at increased risk for depression and anxiety [31].

According to the nationwide population-based cohort study that relied on the data from Danish registries collected in 1980–2008, adults with a past history of childhood neuroinfection are less educated, less financially secure, less involved socially and are dependent on disability payments [32].

Canadian researchers attempted to conduct a meta-analysis of 20 studies on rehabilitation after infectious encephalitis extracted from 12,737 sources. Nine of the included studies investigated the effects of cognitive therapy, 5 looked at behavioral therapy, 2 focused on physical therapy and 4 on complex rehabilitation involving 2 or more types of therapy. Unfortunately, due to small sample size (no more than 25 patients in each case) and clinical and methodological heterogeneity, the meta-analysis failed [33, 34].

Another study demonstrated a reduced quality of life 6 months after encephalitis for both children and adults [35, 36].

The following conditions are reported in children with a medical history of herpes simplex encephalitis: diverse neurological symptoms (tetraparesis, hydrocephalus, symptomatic epilepsy, developmental delay) in the first year of

Table. Domains of functional and structural damage in convalescent children after infectious disease (from [64], printed by permission of the authors)

Clinical examples (diagnoses)	Domains and functional/structural damage categories	
	Code	Domains and categories
Prolonged neonatal jaundice	b 598.1	Mild disorders of the digestive, metabolic and endocrine systems, other specified
Hepatitis B	b 515.1 b 525.1 b 535.1 s560.17	Mild disorders of digestive functions Mild disorders of defecation functions Mild disorders of sensations associated with the digestive system Mild changes to liver structure
Chronic CMV hepatitis resulting in fibrosis	b 515.2 b 525.2 b 535.2 s560.27	Moderate disorders of digestive functions Moderate disorders of defecation functions Moderate disorders of sensations associated with the digestive system Moderate changes to liver structure
Highly active autoimmune hepatitis, developing cirrhosis	b 515.3 b 520.3 b 525.2 b 530.3 b 535.3 b 550.2 b 430.3 b 435.3 s560.37	Severe disorders of digestive functions Severe disorders of assimilation functions Severe disorders of defecation functions Severe disorders of weight maintenance functions Severe disorders of sensations associated with the digestive system Moderate disorders of thermoregulatory functions Severe disorders of hematological system functions Severe disorders of immunological system functions Severe changes to liver structure
TTV hepatitis in the presence of hepatic steatosis, metabolic syndrome, asthma	b 515.3 b 520.3 b 540.3 b 545.2 b 555.2 b 440.1 b 455.2 b 460.2 s560.37	Severe disorders of digestive functions Severe disorders of assimilation functions Severe disorders of general metabolic functions Moderate disorders of water, mineral and electrolyte balance functions Moderate disorders of endocrine gland functions Mild disorders of respiration functions Moderate disorders of exercise tolerance functions Moderate disorders of sensations associated with cardiovascular and respiratory functions Severe changes to liver structure
Salmonella-induced dysbiosis	b 515.2 b 520.2 b 525.2 b 530.2 b 535.2 b 540.2	Moderate disorders of digestive functions Moderate disorders of assimilation functions Moderate disorders of defecation functions Moderate disorders of weight maintenance functions Moderate disorders of sensations associated with the digestive system Moderate disorders of general metabolic functions
Enteroviral meningitis	b 126.1 b 130.1 b 134.1 b 147.1	Mild disorders of temperament and personality functions Mild disorders of energy and drive functions Mild disorders of sleep functions Mild disorders of psychomotor functions
Haemophilus meningitis	b 126.3 b 130.3 b 134.3 b 147.3 s130.27	Severe disorders of temperament and personality functions Severe disorders of energy and drive functions Severe disorders of sleep functions Severe disorders of psychomotor functions Moderate changes to the structure of meninges
Obstructive bronchitis	b 440.1 b 435.1	Mild disorders of respiration functions Mild disorders of immunological system functions
Chronic bronchiolitis, diffuse bronchiectasis, stage 1 chronic respiratory failure	b 410.2 b 440.2 b 435.2 b 455.2 b 460.2 s410.27 s430.273	Moderate disorders of heart functions Moderate disorders of respiration functions Moderate disorders of immunological system functions Moderate disorders of exercise tolerance functions Moderate disorders of sensations associated with cardiovascular and respiratory functions Moderate changes to the structure of cardiovascular system. Moderate bilateral changes to the structure of respiratory system

life; motor skills disorder and a speech and language delay in children aged 1-3 years; ataxia, neurosis, neurosis-like states in preschoolers; emotional, volition and hypothalamus disorders, and intellectual disability in school children [6].

Focal demyelination caused by infection can result in residual neurologic deficit in 30% of children or have a progressive course leading to severe polysyndromic neurologic deficit in 20% of cases. Spinal cord and peripheral nervous system infections often manifest as myelopathy, myelopolyneuropathy, polyneuropathy, facial neuropathy, and polyradiculopathy [6].

Rehabilitation after neuroinfection includes early mobilization, physical exercise, massage, speech therapy, psychotherapy, body positioning, prophylaxis of pressure ulcers, contractures, pneumonia, and thrombotic complications. Motor rehabilitation should be step-wise and include training of movement components, proprioception enhancement, simple associated movements, joints, and motor skills. Children with peripheral paresis associated with myelitis or poliomyelitis should undergo therapy with electrical stimulation, paraffin or ozokerite applications, general fitness physical and respiratory exercise, special exercises for the affected limb, and hydrokinesiotherapy. To relieve pain, alleviate autonomic and trophic disturbances and regain motor function, a variety of interventions are recommended, including two or four-cell tub baths, diadynamic, sinusoidal modulated and interferential currents, ultrasound therapy and phonophoresis, therapy with alternating magnetic fields, ozokerite applications, and a combination of magnet and laser therapy. Other options include kinesiotherapy, robotic therapy for motor function recovery, standing and walking frames, dynamic proprioceptive correction, speech therapy, and biolfeedback therapy [6].

Complex rehabilitation and follow-up care are crucial for achieving complete recovery, especially when it comes to infants, whose immunity is underdeveloped and who are at risk for serious complications [13].

Acute gastrointestinal infections

Acute gastrointestinal infections are leading in incidence, both in Russa and worldwide [37, 38]. In 20–30% of cases, acute gastrointestinal infections provoke functional gastrointestinal disorders [13]. It is known that acute intestinal infections cause dysbiosis and allergies, change the reactivity of the immune system, triggering autoimmune disorders, promote gastrointestinal pathology, have an adverse effect on the physical and mental development of the child [39]. In up to 30% of cases, children develop irritable bowel syndrome following acute intestinal infection. There is evidence that 25% of children with acute infectious diarrhea are at high risk of gallbladder, pancreas and bowel dysfunction 6 months after the infection [39]. There are reports of exacerbations of atopic dermatitis and developmental delay in children recovering from intestinal infections, suggesting that rehabilitation should start as early as the subacute stage of infection [13].

The primary objectives of rehabilitation at each of its stages are as follows: treatment of intestinal dysbiosis using galvanic therapy of the abdomen with topically applied microelements or microwave diathermy [40–42]; correction of functional and morphologic changes of intestinal mucosa (ultrahigh-frequency therapy, low-energy laser irradiation [43]), restoration of colon motility and normal evacuation (amplipulse therapy, interferential therapy, diadynamic therapy, localized cryotherapy, massage [40]); management of asthenia and autonomic disorders (magnet therapy, resonance frequency therapy [44]); hydrotherapy [40].

There is a paucity of studies focusing on the rehabilitation of pediatric patients with postinfectious cardiovascular disorders although their incidence is quite high [45]. Cardiac pathology associated with infection poses a high risk of complications, raising the need for timely diagnosis and adequate rehabilitation [46, 47].

Novel coronavirus disease COVID-19

This infection typically has respiratory and gastrointestinal presentations in children and adolescents [48–50]. Respiratory viral coinfection is diagnosed in 11–46% of patients with COVID-19 [51]. Severe COVID-19 is often observed in very young children or those who have preexisting cardiovascular disorders, chronic pulmonary conditions, compromised immunity, etc. [51–54].

Rehabilitation is needed for children with COVID-19 who develop lung damage [55, 56], cardiovascular complications [49], neurologic [57] and gastrointestinal [58, 59] disorders. The broad spectrum of neurologic sequelae of COVID-19 comprises anosmia, ageusia/dysgeusia, acute Guillain-Barr– syndrome, cerebral and spinal damage [57]. Follow-up care and rehabilitation are required for children with postinfectious asthenia persisting for 1–2 months in 30% of patients. Clinically, it is manifested as increased fatiguability, malaise, mental and physical exhaustion [60, 61]. Regardless of the underlying mechanisms, forms and severity, damage to the nervous system that requires further rehabilitation manifests as asthenia, autonomic dysfunction, central or peripheral paresis, coordination impairment, seizures, and speech impairment.

Recent research has demonstrated that children with a past history of COVID-19 need rehabilitation regardless of the severity of disease (even when the disease is asymptomatic or mild). This is associated with the risk of functional impairment of respiratory and other systems. Rehabilitation includes physiotherapy, balneotherapy (pelotherapy), physical exercise, reflexotherapy, manual therapy, psychotherapy, etc. [62]. The principles of medical rehabilitation for children with COVID-19 are the same as for adults and account for small age and exercise tolerance [63].

Similar to other types of pediatric rehabilitation, medical rehabilitation of children with COVID-19 follows certain guidelines. Rehabilitation of children with COVID-19 is aimed at training and recovery of compensatory capacity of the bronchopulmonary and cardiovascular systems.

Rehabilitation for bronchopulmonary pathology associated with COVID-19 should include respiratory and psychological rehabilitation, nutritional support, and physical methods for managing bronchial obstruction syndrome (inhalation therapy, halotherapy) [50]. Respiratory muscle function can be supported through transcutaneous electrical stimulation of the diaphragm, mucostasis inhibition, huffing, and autogenic drainage. Rehabilitation techniques used in pediatric patients with COVID-19-associated neurological disorders depend on the child's age, the leading pathological syndrome, severity of respiratory disorders and can include muscle relaxation, motor skills training required for self-care, electrical muscle stimulation, motor correction, and therapy for neurasthenia. To restore bowel motility in children with COVID-19-associated intestinal disorders, amplipulse therapy, interferential therapy, localized cryotherapy, diadynamic therapy, massage, pine baths, and microwave diathermy (for children over 2 years of age) are recommended.

Is pediatric medical rehabilitation for infectious diseases sufficiently elaborated? Literature analysis reveals a dearth of publications on the effectiveness of both individual rehabilitation methods and complex approaches, as well as the almost complete absence of guidelines for load tolerance control. ICF is rarely used; there is no information about activity constraints and patient involvement; the impact of the environment, including parents and family, is not analyzed. There are no publications on the effectiveness of early rehabilitation in the intensive care setting. Obviously, medical rehabilitation of children with infectious diseases is still based on outdated biomedical approaches. The long overdue transition to the new model is mentioned in by a handful of authors, who provide rationale for personalized, problem-oriented and multidisciplinary approaches.

Special attention should be paid to the arguments advocating a personalized approach to the rehabilitation of children with infectious diseases that involves assessment of structural and functional damage using ICF categories [64]. The authors of the cited study conducted health assessment of 103 children discharged from the departments of respiratory, intestinal, neurological infections and hepatitis (see Table). Using ICF criteria, 5 patient groups were identified based on the severity of functional damage. Over 36% of the patients needed medical rehabilitation. The authors concluded that ICF had good potential as a tool for designing individual rehabilitation plans and controlling their implementation and effectiveness.

The cited publication was a pioneer study. It did not attempt to analyze factors limiting patient activity, patient involvement or the effects of the environment on patient progress.

The use of ICF in the therapy of children with mental conditions and hearing and speech disorders [65] and in designing rehabilitation plans for children with speech impairments [66] was discussed in earlier publications.

Some authors highlight the economic benefits of rehabilitation [67], which can significantly improve social adaptation and daily performance of children with a past history of neuroinfection [68]. It is believed that continuity, diversity and order of rehabilitation procedures at different stages of rehabilitation is key to successful recovery. It is also important to adjust the rehabilitation plan to the patient's condition and monitor their health throughout the rehabilitation process [69].

Recently, nutritional support has been recognized as an essential rehabilitation tool complementing physical therapy and psychotherapy in the hospital setting [70].

Parents and other family members play a tremendous role in the successful rehabilitation of the child; parents should be encouraged to get more involved in order to ensure a gradual, long-lasting positive effect of rehabilitation procedures [71].

There is a pressing need for an agency that would ensure effective patient routing based on the severity of their condition. Some authors stress that rehabilitation should be started as early as possible and be patient- and problem-oriented [72–75]. Recently, telerehabilitation has been actively discussed in the literature, including its potential as a method for controlling adherence and evaluating patient performance and general health [76–78].

New software for designing rehabilitation plans is emerging. A decision support system may be helpful in deciding on the extent of interventions for pediatric rehabilitation [79]. A good example here is a guidance and a parent's diary developed by British researchers for parents whose children had a history of meningitis [80]. Development of such rehabilitation tools for basic pediatric infections is a critical milestone in the adoption of the biopsychosocial approach to patient and their family.

CONCLUSION

There is a paucity of fresh systematic reviews and original research studies on the rehabilitation of children with infectious diseases. The majority of the identified publications only describe methods of pediatric rehabilitation after infection, which raises the need for high-quality research into this problem.

Still, studies of the biomedical approach to pediatric rehabilitation will not be of much help. Earlier, an unsuccessful attempt was made to conduct a meta-analysis of studies focusing on the rehabilitation of children after infectious encephalitis [34]. Approaches to rehabilitation can be systematized by using ICF as a classification system and the basis for formulating a rehabilitation diagnosis. It will be necessary to adopt a multidisciplinary approach to the diagnostic process (to assess physical activity constraints, patient involvement and the impact of environmental factors), set the goals and objectives of interventions and elaborate the plan for their implementation.

We hope that in the nearest future medical rehabilitation of children with infectious diseases will be systematized and assimilate new methodological approaches, thereby becoming more effective, improving the quality of life of patients and their parents, and creating economic benefits for the state by maintaining health of its citizens.

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PROTON THERAPY FOR RE-IRRADIATION OF PEDIATRIC DIFFUSE BRAIN STEM TUMORS

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Currently, there is no cure for pediatric diffuse brain stem (BS) tumors. Radiotherapy, including proton therapy, is an important component of combination treatment for this cancer, especially in children with a complicated medical history. The article addresses the issues of therapy for pediatric BS tumors and reports the use of proton re-irradiation in a 9-year-old boy with unverified diffuse BS tumor. Proton re-irradiation is an effective treatment option that can sustain and improve the quality of life and prolong survival in children with diffuse BS tumors.

Keywords: diffuse brainstem tumor, re-irradiation, proton therapy

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ВОЗМОЖНОСТИ ПРОТОННОЙ ТЕРАПИИ ПРИ ПОВТОРНОМ ОБЛУЧЕНИИ ДИФФУЗНОЙ ОПУХОЛИ СТВОЛА МОЗГА У ДЕТЕЙ

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В настоящее время полное и стойкое излечение диффузных опухолей ствола мозга (СМ) у детей невозможно. Современная лучевая терапия диффузных опухолей СМ, включая терапию протонами, является важным элементом комплексного лечения, особенно у пациентов детского возраста с отягощенным анамнезом. В статье обсуждены вопросы специального противоопухолевого лечения диффузных опухолей ствола мозга у детей и представлен сложный клинический случай повторной лучевой терапии рецидива неверифицированной диффузной опухоли СМ у девятилетнего мальчика с применением протонной терапии (ПТ). Проведение повторной лучевой терапии протонами при диффузных опухолях СМ является эффективным методом сохранения, а иногда улучшения качества жизни у детей и увеличения ее продолжительности.

Ключевые слова: диффузная опухоль ствола головного мозга, повторная лучевая терапия, протонная терапия

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Pediatric diffuse brain stem (BS) tumors remain an unsolved therapeutic challenge. Their radical surgical resection is impossible due to the unique anatomy of this brain structure that controls vital body functions. According to autopsy reports, most of BS tumors are ependymomas and astrocytomas of different grades of malignancy [1]. Currently there are no effective medication therapies against childhood BS tumors [2–6]. The main treatment option is radiotherapy (RT): it temporarily delays tumor progression, sustains or improves the patient's quality of life and neurological status, and prolongs survival [7, 8]. However, RT offers no cure despite the advanced instrumentation, the vast variety of radiation sources and the ongoing development of new treatment planning techniques and therapeutic strategies guided by radiobiological and molecular prognostic factors [8–12]. Therapy for childhood BS tumors provides a temporary effect which depends on the degree of malignancy and the aggressiveness of the tumor. In light of this, development of novel therapies targeting the genetic machinery of the tumor, as well as cancer vaccines, holds promise for the therapy of BS tumors [13]. Local recurrence and, less frequently, metastatic spread are the primary obstacles to treatment success. Re-irradiation is one of

the very few therapeutic options for progressive or recurrent BS tumors [14–16]. Therapy against childhood BS tumors seeks to sustain or improve the quality of life and prolong survival. This goal can be achieved through using state-of-the-art RT, including proton RT [17, 18].

Clinical case

Below we report a clinical case of a pediatric patient with a recurrent diffuse BS tumor treated with re-irradiation (proton therapy) at the Federal Research and Clinical Center for Medical Radiology and Oncology (FMBA, Dimitrovgrad, Russia) [19].

Patient G, 9 years, was first diagnosed with unverified diffuse BS glioma (C71.7) in July, 2019. The patient suffered a relapse in December 2020. Stabilization was achieved till September 2021. The patient's condition was complicated by obstructive hydrocephalus.

At the age of 9 (prior to diagnosis), the patient started complaining of headaches, gait disturbance, squinting, and morning vomiting. Brain MRI performed on July 10, 2019 was suggestive of a diffuse BS neoplasm 58 × 34 × 40 mm in size spreading to the right pons, the right peduncle and the hemisphere of the cerebellum (Fig. 1).

On July 24, 2019, the patient received a ventriculoperitoneal shunt (VPS).

From August 2 to September 12, 2019, the patient was undergoing 3D conformal photon RT at the total dose of 54 Gy delivered in 1.8 Gy per fraction (Fig. 2).

Two months after the initial RT course, brain MRI performed on October 31, 2019 showed no contrast enhancement, suggesting tumor regression (Fig. 3).

^{11}C-methionine PET/CT conducted on November 5, 2019 detected no signs of metabolic tumor activity in the brain structures.

The patient was followed up for 15 months.

Then, brain MRI (December 8, 2020) and ^{11}C-methionine PET/CT (January 11, 2021) were suggestive of diffuse changes in BS and increased radiopharmaceutical uptake in the pons (uptake ratio: 2.2); the lesion size on PET/CT was 21 × 15 × 22 mm, which was consistent with MRI findings (Fig. 4).

Considering the medical history of the patient, time elapsed from the first RT course and the fact of tumor recurrence, proton re-irradiation was recommended by the case conference panel.

Optimized intensity-modulated proton therapy [17] for the metabolically active recurrent lesion was delivered to the patient at the Federal Research and Clinical Center for Medical Radiology and Oncology from January 26, 2021 to March 5, 2021. Dose planning was based on ^{11}C-methionine PET/CT findings. A ProteusPlus 235 system (IBA; Belgium) was used for irradiation. Therapy was delivered in 28 daily fractions (1.8 Gy or per fraction); the total dose was 50.4 Gy. Glucocorticoids were administered concomitantly to reduce cerebral edema. PTV dose coverage D98% was 98% Gy of the prescription dose (Fig. 5). No adverse effects were observed. By the end of the treatment course, the tumor had regressed completely.

The patient was discharged home. Further follow-up with a local pediatric oncologist and other involved specialists was recommended. As of September 2021 (6 months after re-irradiation), there had been no signs of recurrent tumor growth, neurologic deficit or VPS dysfunction.

Discussion

Diffuse intrinsic pontine glioma (DIPG) is the primary cause of pediatric mortality from CNS malignancies. This aggressive tumor makes up 75–80% of pediatric BS malignancies and 10% of all pediatric CNS tumors [20–22]. Prognosis for DIPG is much poorer than for other BS tumors and malignant gliomas because the pons contains structures that control vital body functions like breathing, heart rate and arterial pressure [22]. Despite countless clinical trials of chemotherapy drugs and biological response modifiers, children with BS tumors still die, typically within 1 year after diagnosis [16, 20–24]. There is no effective treatment for recurrent/progressive BS tumors after initial RT. The average time to death after tumor recurrence is 3 months [25]. Various approaches, including RT and systemic drug therapy, tried for refractory and recurrent pediatric BS tumors are not standardized. RT is the only treatment option that has been shown to prolong survival in patients with recurrent/progressive DIPG [26, 27]. As more evidence is being accumulated about the safety of this approach for treating pediatric CNS tumors, re-irradiation is being increasingly used to manage recurrent/progressive DIPG in children [28–30].

RT is an important component of therapy for many pediatric CNS tumors, including DIPG. Re-irradiation is a safe option for managing recurrent ependymomas and medulloblastomas. It prolongs progression-free survival and, although there has been only 1 non-randomized phase 2 trial of this method, it has been shown to be a safe therapy for progressive DIPG [26, 29, 30]. Currently there are no treatment standards for re-

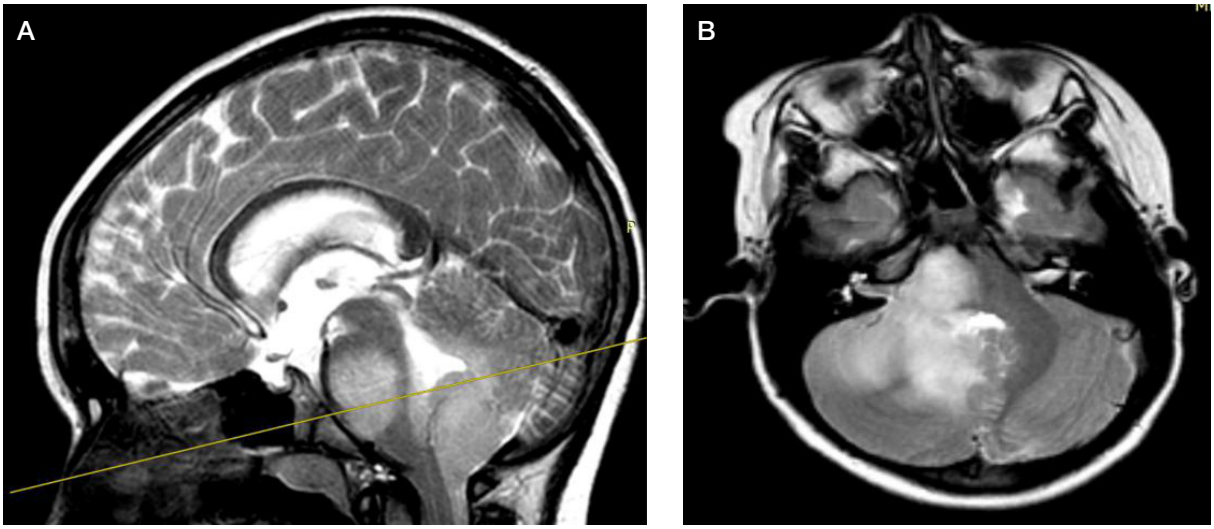

Fig. 1. Sagittal (**A**) and axial (**B**) MRI images of the patient's brain performed on July 10, 2019 before commencing RT

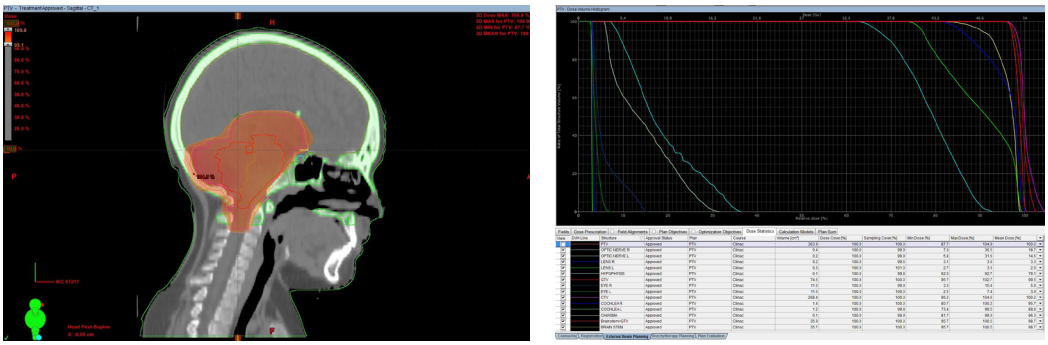

Fig. 2. Sagittal dose distribution of 3D conformal RT for the diffuse BS and a dose-volume histogram (DVH)

irradiation for pediatric CNS tumors. Most radiotherapists and pediatric oncologists consider a total dose of 20–36 Gy to be a therapeutic dose for children with BS tumors undergoing re-irradiation, but the number of sessions, the use of systemic drugs as a concomitant therapy and indications/contraindications vary.

A few retrospective studies of re-irradiation have been conducted in small cohorts of pediatric patients with recurrent/progressive DIPG.

In one of such studies, 5 children underwent re-irradiation and concomitant chemotherapy for progressive DIPG at the University of Texas MD Anderson Cancer Center. The following regimens were applied: 18 Gy in 1.8 Gy per fraction for 1 patient and 20 Gy in 2 Gy per fraction for 4 patients. Adverse events were minimal (≤ grade 2 RTOG). The median time to progression was 5 months [31].

An Italian research team studied the effects of radiation and concomitant therapy with nimotuzumab and vinorelbine in a phase 2 trial which included first-time patients with DIPG; relapsing patients were treated with re-irradiation. Tumor progression occurred in 20 patients; of them, 16 had a local recurrence. Focal re-irradiation of the locally progressing lesion (total dose of 19.8 Gy delivered in 1.8 Gy per fraction) was performed on 11 patients. Four of 5 other relapsing patients with metastatic tumor spread received focal re-irradiation for the primary lesion and its metastases. This approach was well tolerated, no unexpected adverse events or neurological status deterioration were observed. Survival after re-irradiation ranged from 6 weeks to 14 months and was 6 months on average [32].

Another European research team conducted a retrospective analysis of DIPG cases, including 31 patients who had received re-irradiation for the first tumor progression (total dose: 30 Gy delivered in 1.8 Gy per fraction); in addition to RT, some patients had received chemotherapy. Clinical improvement was observed in 77% patients, no life-threatening radiation toxicity was reported after re-irradiation. However, the study underscores that a combination of repeat RT and chemotherapy can produce lethal toxicity. Average survival in the study was 6.4 months after re-irradiation vs 3 months in the historical control group (no re-irradiation therapy) [15].

In another retrospective review published by Canadian researchers, re-irradiation was used on 16 patients with progressive DIPG. Focal re-irradiation therapy was delivered to 14 patients (total dose: 21.6–36 Gy). Two patients had to undergo whole-brain radiotherapy (total dose: 30.6 Gy) due to of metastasis. The applied RT doses varied, the total dose ranged from 12 to 36 Gy and was 24 Gy on average. The average re-irradiation dose per fraction was 2 Gy (1–9 Gy). The average time to progression after diagnosis was 10.5 months (4–37 months). One patient relapsed 6 months after re-irradiation and had to undergo one more course of re-irradiation therapy (total dose: 21.6 Gy). One patient received concomitant therapy with bevacizumab. The rest were treated with RT only. Following the course of re-irradiation, 7 patients were prescribed chemotherapy with temozolomide, valproic acid, nimotuzumab, or bevacizumab. Re-irradiation was mostly well tolerated except for one patient who developed necrosis of the pons which caused cerebellar dysfunction and tetraparesis after exposure to the total dose of 30 Gy delivered in 3 Gy per fraction. Six patients did not require steroids; 4 patients discontinued steroids at the end of the re-irradiation course. The median follow-up time from diagnosis was 19.2 months; all

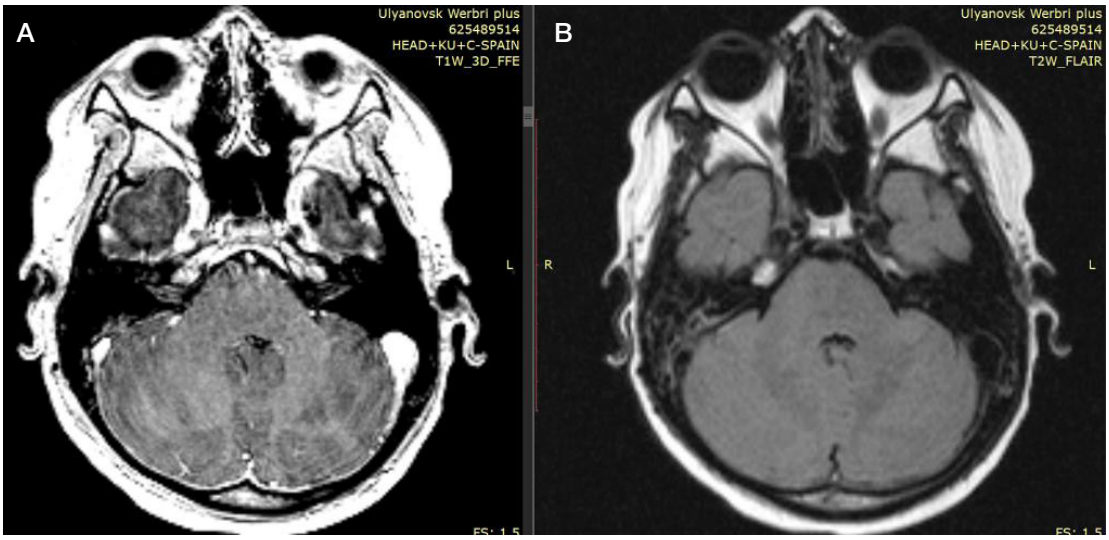

Fig. 3. Axial MRI images 1.5 months after RT completion (October 31, 2019): T1W (**A**) and T2W FLAIR (**B**)

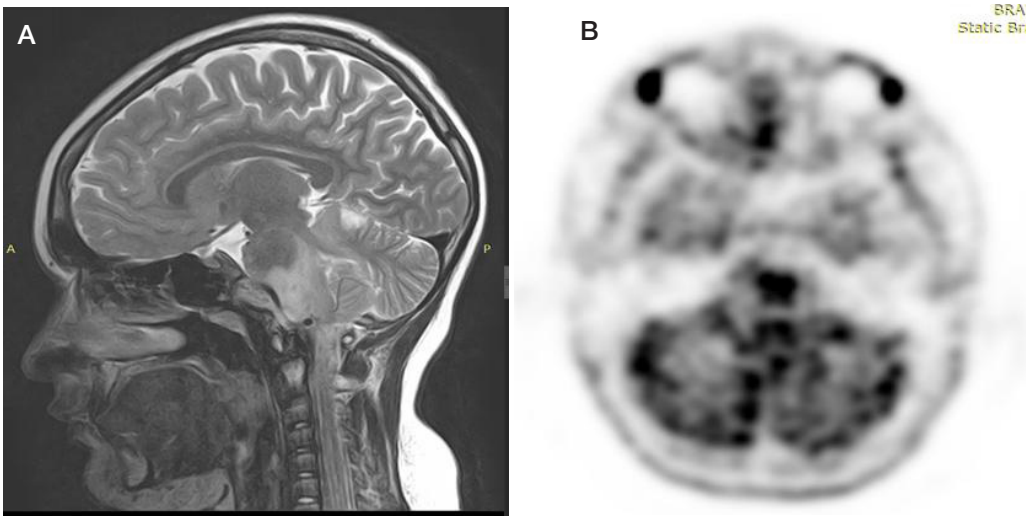

Fig. 4. A. Sagittal brain MRI image (December 8, 2020). **B**. Axial 11C-methionine PET/CT image (January 11, 2021)

the patients included in the study died. The median time from re-irradiation to death was 6.48 months (3.8-13.3 months) vs 3 months (3.8–13.9 months) in the historical control group of 46 patients with progressive DIPG (no re-irradiation; $p = 0.0001$) [16].

Russian researchers have retrospectively analyzed the outcomes of re-irradiation among 20 children with different BS tumors undergoing treatment between 2001 and 2011. All of the children received re-irradiation after the initial RT (total dose: 50–55 Gy) course (combined with temozolomide in 7 cases). Re-irradiation was prescribed for clinically and radiographically confirmed tumor progression. Time between the end of the initial treatment and the beginning of re-irradiation therapy ranged from 5 to 32 months and was 12 months on average. Re-irradiation was delivered in combination with adjuvant systemic chemotherapy: temozolomide (10 patients) and bevacizumab (3 patients). The total re-irradiation dose was < 30 Gy for 10 patients, 31–45 Gy for 9 patients and 50 Gy for 1 patient. While in treatment, 5 patients with radiographic signs of tumor destruction deteriorated and their therapy was terminated. The average survival time for those patients was 3.5 months. Other patients did not have signs of tumor destruction on MRI and their condition was improving. They were able to achieve complete or partial regression of neurological symptoms. In this subgroup, 93% survived 6 months after re-irradiation, 53% survived 1 year, 40% survived 1.5 years, and 20% survived 2 years. One patient stayed alive for 5 years after re-irradiation and died at the age of 13. Another patient developed symmetric necrotic lesions in the cerebellar hemispheres in the setting of persistent tumor growth detected on MRI 5 months after re-irradiation (total dose: 50 Gy) [2, 3, 8, 14].

Literature analysis and clinical experience show that pediatric diffuse BS tumors are currently incurable. The best effect that a combination of RT and chemotherapy can achieve is stabilization of tumor growth. Although there are no treatment standards regulating the use of re-irradiation therapy for pediatric CNS tumors, re-irradiation is an effective option that can sustain or improve the quality of life and prolong survival in children with diffuse BS tumors [34].

CONCLUSION

Modern RT, including proton re-irradiation, is an important component of combination therapy for diffuse BS tumor, especially in pediatric patients with complicated medical history.

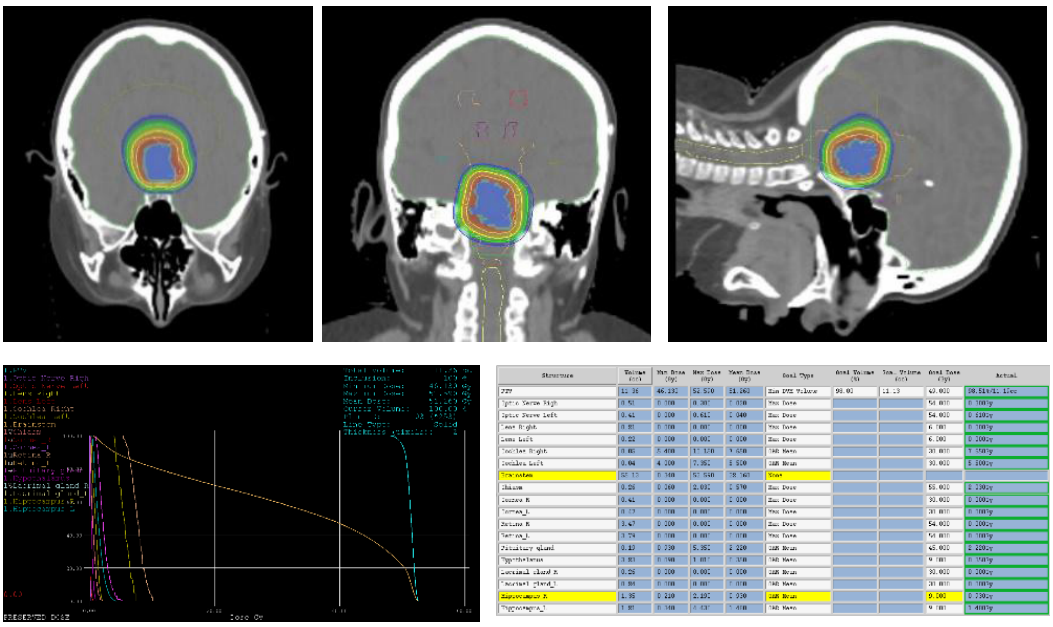

Fig. 5. Proton therapy dose distribution for the recurrent diffuse BS tumor and a dose-volume histogram

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SIMULTANEOUS REPAIR OF THE SKULL BASE AND THE FRONTAL LOBE DEFECT USING CAD-CAM TECHNOLOGY

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Many patients with traumatic brain injury develop complications in the postoperative period. The article describes a case of revision surgery in a female patient with cerebrospinal fluid rhinorrhea following a severe car accident. During one surgery, the skull base and the frontal bone defect were repaired and a lumboperitoneal shunt was placed. The skull base was repaired using an autologous musculoaponeurotic graft. For a better cosmetic effect, the implant was designed using CAD-CAM technologies. The patient had a relapse of the leak in the postoperative period, which required revision surgery (multilayer reconstruction using a fibrin-thrombin sponge). The patient was followed up for 2 years, with no relapse. The desired clinical and cosmetic effects were successfully achieved.

Keywords: cranial bone defect, reconstructive surgery, CAD-CAM technology, CSF leak, fibrin glue

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Compliance with ethical standards: the patient gave her informed consent to participate in the study

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СИМУЛЬТАННАЯ РЕКОНСТРУКЦИЯ ОСНОВАНИЯ ЧЕРЕПА И ДЕФЕКТА ЛОБНОЙ КОСТИ С ИСПОЛЬЗОВАНИЕМ CAD-CAM-ТЕХНОЛОГИЙ

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После черепно-мозговой травмы в послеоперационный период у пациентов нередко возникают осложнения. Представлен случай ревизионной операции по поводу назальной ликвореи после тяжелой автодорожной травмы. Пациентке в ходе одной операции провели реконструкцию основания черепа, дефекта лобной кости и люмбоперитонеальное шунтирование. Реконструкцию основания черепа выполнили мышечно-апоневротическим аутотрансплантатом, для лучшего косметического эффекта использовали имплант, изготовленный с использованием CAD-CAM-технологий. В послеоперационном периоде возник рецидив назоликвореи, потребовавший повторной многослойной пластической операции на основании черепа с использованием фибрин-тромбиновой клеевой композиции. Послеоперационное наблюдение составило более двух лет, рецидива ликвореи не отмечено, достигнут желаемый клинический и косметический результат.

Ключевые слова: дефекты костей черепа, реконструктивно-пластическая операция, CAD-CAM-технологии, назоликворея, фибрин-тромбиновый клей

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Финансирование: субсидия на выполнение государственного задания ФМБА по теме «Замещение дефектов костей черепа с применением материалов с памятью формы».

Соблюдение этических стандартов: пациентка подписала добровольное информированное согласие на исследование.

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The first description of cranioplasty dates back to 1505, when it appeared in the surgery textbook Alâ'im-i Cerrâhîn (Wonders of Surgeons) written by Ibrahim ben Abdullah [1]. Later on, the Italian physician Fallopius Gabriele (1523–1562) described a method for closing cranial defects with a gold plate. A similar method was documented by Petronius in 1565. In 1668, Van Meekeren reported a case of cranioplasty with a canine bone graft performed in a Russian nobleman who had sustained a sword injury to the head [2]. In 1965, D. Simpson proposed titanium as a material for reconstructive surgery. Since then, titanium and its alloys have been widely adopted in surgical practice. Craniofacial injury poses a serious diagnostic and therapeutic challenge to modern neurotraumatology. Conventionally, such type of injury is managed in two steps. First, surgical debridement is performed: crushed fragments of the frontal bone, including the superior margin of the orbital rim, the roof of the orbit and frontal sinus tables, are removed while trying to preserve as much of the bone as possible, and then primary reconstruction of the skull and facial skeleton defects is carried out. A few months later, reconstructive surgery is performed.

Possible causes of craniofacial injury include road accidents (51.3%), blows to the head or face (31.8%), penetrating skull, orbital or brain injuries (10.4%), falls from height (5.4%), and other causes (1.1%) [3]. Craniofacial injury makes up 6–9% of all traumatic brain injuries (TBI) and amounts to 34–52.9% among all concomitant injuries. Moderate and severe brain injuries are reported in 7% patients with facial trauma [4, 5]. Injuries to the central part of the face can be disfiguring. Basilar fractures of the skull involving the frontal sinus, ethmoid labyrinth and sphenoid sinus are a common cause of cerebrospinal fluid (CSF) leaks. Fractures at the interface between the posterior table of the frontal sinus and the lamina cribosa pose a risk for CSF fistulas, which require surgical management [5].

Below we describe how one surgical intervention can solve a number of important tasks and report the use of CAD-CAM technology in revision surgery for cranio-orbital traumatic injury [6, 7].

Clinical case

Female patient U aged 32 years presented with posttraumatic CSF rhinorrhea. 5 months ago after the accident, the patient had been transported to the City Hospital and diagnosed with an open penetrating TBI, severe brain contusion, comminuted depressed penetrating fracture of the frontal bone, contusion of bilateral frontal lobes, and displaced fracture of the right zygomatic bone.

Following the accident, the patient's wound was debrided, broken fragments of the posterior frontal sinus wall and the frontal bone were removed, osteosynthesis of the affected zygomatic bone was performed (Fig. 1, 2). Two weeks later, the patient underwent cranioplasty: the frontal bone defect was repaired, the frontal sinus was cranialized and the skull base was reconstructed. Postoperatively, the patient developed CSF rhinorrhea. Lumbar puncture and lumbar drain placement produced no positive effect.

The cosmetic effect of the initial surgery was satisfactory. However, due to the complex geometry of the lost bone fragment, the sustained defect was noticeable (Fig. 3) and the patient had to change her hairstyle to conceal it. Generally, to achieve good outcomes, frontal bone reconstruction should be done with custom-made implants or the plate should be thoroughly modelled.

We were faced with 2 main challenges: perform cranial base plasty and frontal sinuplasty to stop the CSF leak and restore the geometry of the patient's skull.

To identify the source of the CSF leak, CT cisternography was performed (Fig. 4). The scans showed the absence of the posterior frontal sinus wall and the presence of the contrast agent in the frontal sinuses.

A decision was made to repair the anterior cranial fossa to stop the CSF leak, perform frontal bone plasty and install a ventriculoperitoneal shunt during one surgery. The shunt was necessary because the leak had been continuing for 5 months and the risk of damage to the basal cisterns was very high.

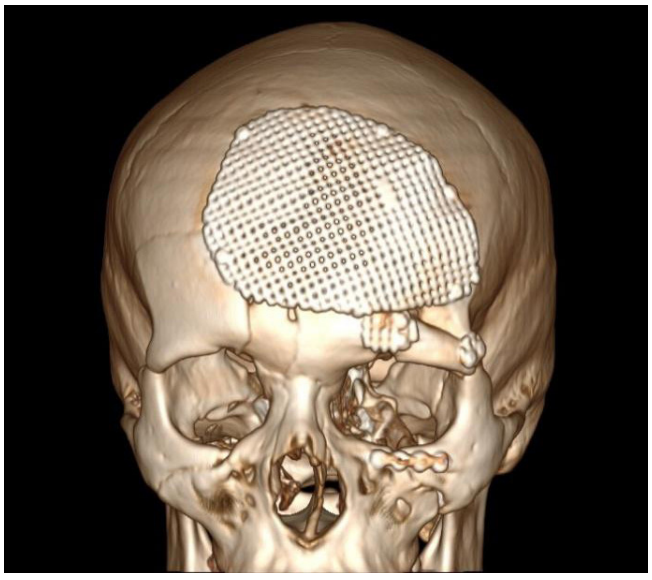

Fig. 1. Computed tomography: 3D skull reconstruction, frontal view. A titanium mesh is visualized in the projection of the frontal bone defect. The image shows frontal lobe fragments forming the superior orbital wall after osteosynthesis

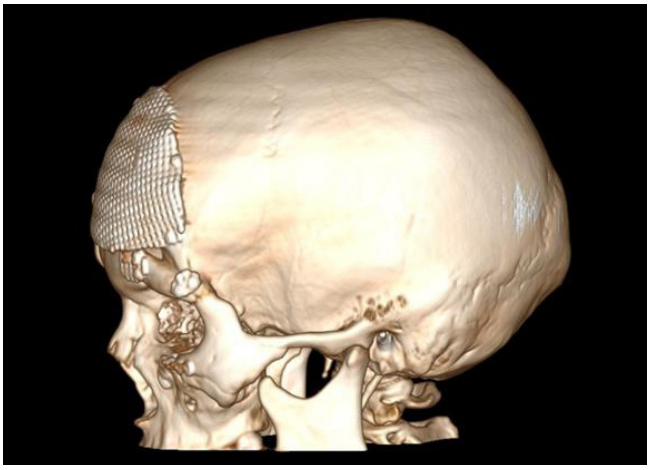

Fig. 2. Computed tomography: 3D skull reconstruction (*side view*)

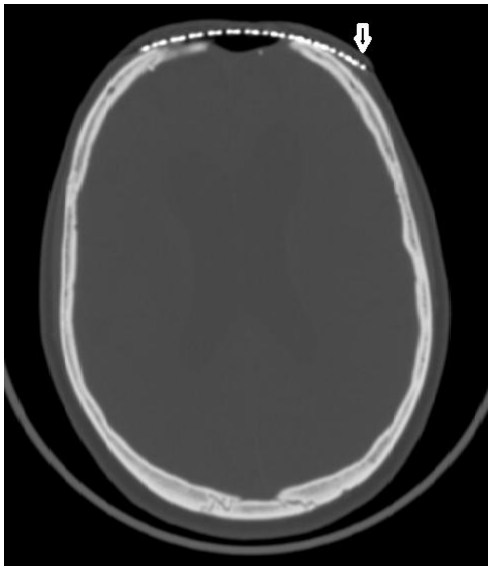

Fig. 3. An axial CT image. The arrow points to the edge of the plate that deforms the cranial contour. The image shows the difference in geometry between the cranial vault and the implant

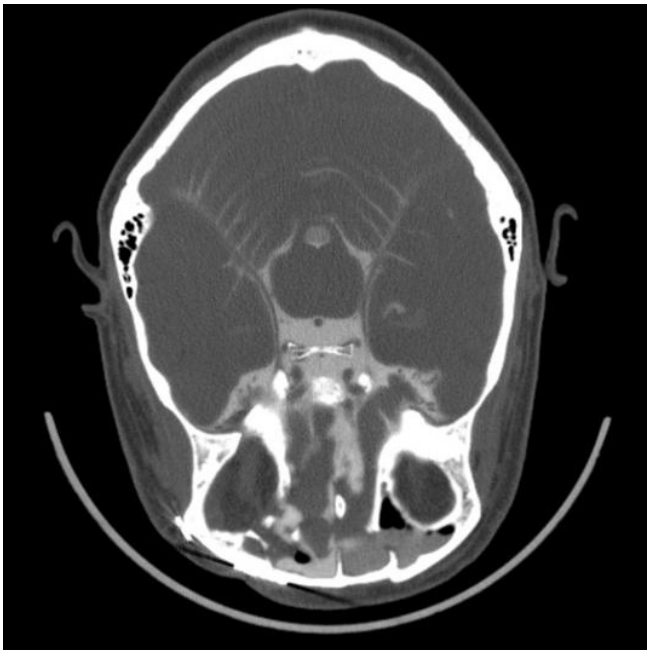

Fig. 4. An axial CT cisternography image

The implant was designed by Logeeks Medical Systems. Since the defect was already closed with a titanium mesh, there was a need for non-standard design tools, which made the task even more complicated. Using the CAD software, the mesh was visually "removed": normally, a defect has to be open to perform the planning step. The implant was printed from a VT6 alloy (vanadium + titanium + aluminum) on a 3D EOS M 290 printer (EOS GmbH; Germany) using direct metal laser sintering (DMLS). Fig. 1, 4 show multiple lines of displaced fractures (one bone width displacement). Mesh fragments used for osteosynthesis of the superior orbital wall were preserved during the surgery. Prior to the intervention, the patient underwent lumbar puncture and her CSF was collected for analysis. The test revealed no signs of meningitis. Figure 5 and 6 demonstrate stages of the design process in CAD. CAD allowed us to accurately recover the geometry of the skull.

In June 2019, the patient received extradural repair of the skull base with an autologous musculoaponeurotic graft; the donor site was the quadriceps femoris muscle with a fragment of broad fascia and subcutaneous adipose tissue. The complex defect of the frontal bone was closed with the 3D implant. The dural defect was closed with a fibrin-coated thrombin-containing collagen sponge. As an alternative to the external ventricular drain, a lumboperitoneal shunt was installed to reduce intracranial pressure in the postoperative period. The shunt was introduced at the L3–L4 level using a 16-gauge Tuohy needle, passed under the skin and brought to the surface 1.5 cm below the umbilicus. Then, the shunt was placed into the peritoneum through a paracentesis trocar port.

The implant was installed at the defect site and then adjusted. Due to multiple linear displaced fractures, the patient had developed calluses, which were removed with a high-speed rotating diamond cutter. The implant was fixed with self-tapping screws.

Postoperatively, the patient's condition was satisfactory. A follow-up CT scan was performed (Fig. 7). On day 3, she started complaining of dripping in the throat. Nose blowing caused a headache. Another brain CT scan was ordered.

The scan revealed the presence of pneumocephalus (Fig. 8; red arrow). Revision surgery (repeated reconstruction of the anterior cranial fossa) was performed 5 days after the first intervention. During the surgery, a sandwich technique was used which consisted in multilayered closure of the anterior cranial fossa defect using a musculofascial autologous flap, a synthetic dural substitute and a fibrin-thrombin sponge.

After the intervention, the patient was stable although she had moderate headaches. Her condition was gradually

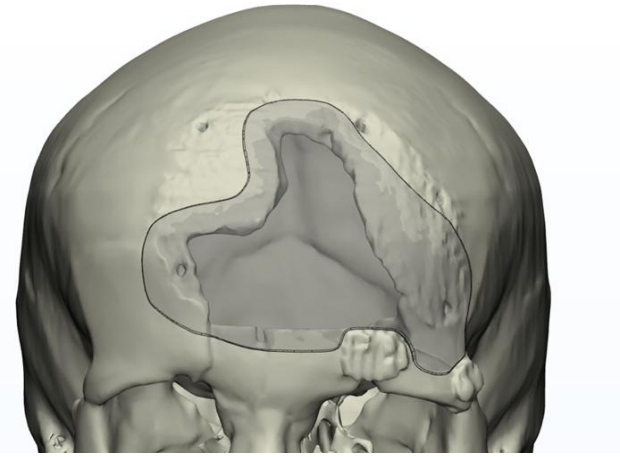

Fig. 5. 3D reconstruction of the skull: CAD planning. The implant is larger than the defect size, which is necessary for more accurate restoration of the frontal bone shape at the planning stage

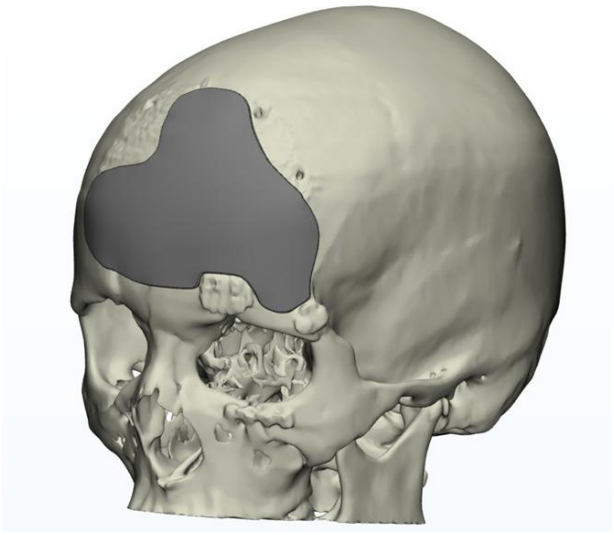

Fig. 6. 3D reconstruction of the skull, CAD planning. The final version of the implant

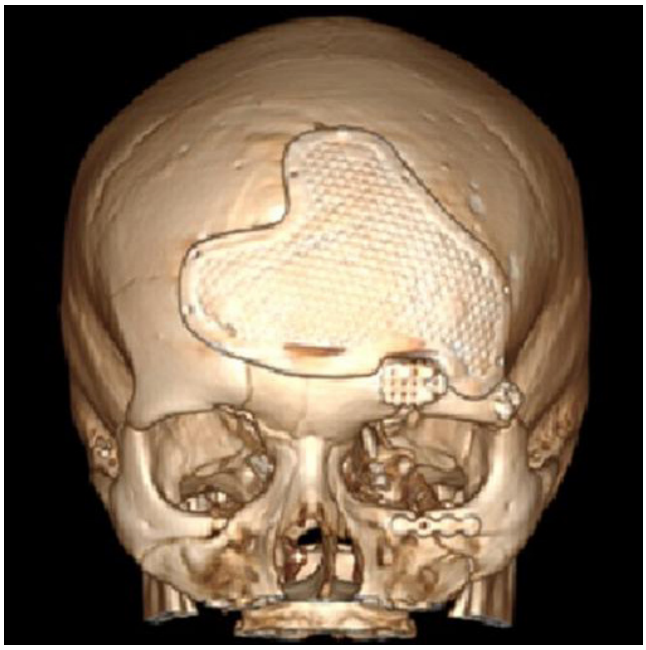

Fig. 7. 3D reconstruction of the skull after the surgery (*frontal view*)

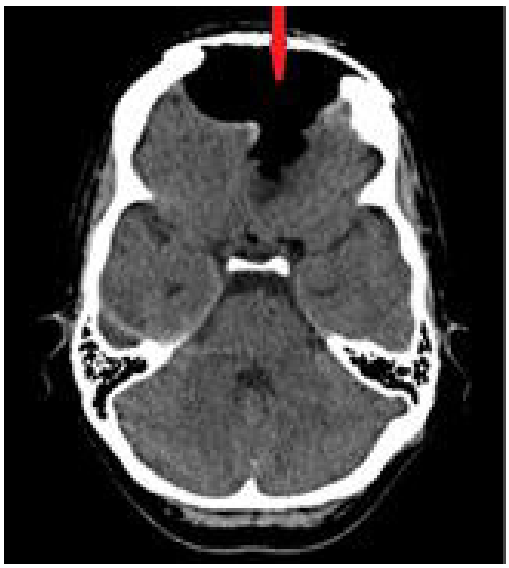

Fig. 8. The axial CT image after the surgical intervention

improving, the surgical wound was healing by first intention, the cosmetic effect was excellent. There were signs of intracranial hypotension (headaches, vertical dizziness). The shunt was removed 2 weeks after the intervention.

The follow-up CT scan performed after shunt removal demonstrated that the amount of gas had significantly decreased (Fig. 9). On discharge, the patient's condition was satisfactory. So far, CSF leak has not recurred.

DISCUSSION

CSF leaks after neurosurgery are reported in 0.9–42% of cases [8]; the risk is determined by a number of factors, including the surgical site, the surgical technique, the patient's general health (compromised immunity, therapy with corticosteroids, uncontrolled diabetes, renal failure, hepatic failure, etc.) In patients with basilar injuries, CSF leaks are hard to control with conservative therapy like lumbar drains; the condition can cause serious complications and increase the risk of death [9]. Repair of skull base defects is required to seal the subdural space and isolate it from the nasal cavity and paranasal sinuses to prevent such complications as pneumocephalus, meningocele, encephalocele, meningitis, meningoencephalitis [10].

The applied repair strategy depends on the location, size, shape of the defect, and proximity of the subarachnoid cisterns [10]. Autologous grafts should be preferred because they do not cause a biological reaction [9, 11].

When planning the surgical intervention, it is important to know whether CSF leak pressure is high or low [10, 12]. A lumbar drain or a shunt is placed only if CSF leak pressure is high. As a rule, lumbar drains are placed for 3-5 days. The rate of complications in patients with external lumbar drains can be as high as 12.5% [9]; the complications include infection, headaches, nerve root irritation, pneumocephalus in the presence of hyperdrainage, etc. During the initial surgery, we used a musculoaponeurotic autologous flap, subcutaneous fat and a fibrin-thrombin sponge [13]. Some authors point to the efficacy of fibrin sealants as a cranioplasty material [14]. In our case, no allografts were used. Multilayer cranioplasty should be a preferred technique in patients at high risk of postoperative CSF leaks [15]. Comminuted frontal bone fractures involving the anterior cranial fossa affect the basal cisternae, so we decided to place a lumboperitoneal shunt. We did not use fibrin glue because multilayer cranioplasty with autologous grafts and a fibrin-thrombin sponge ensure that the defect of the skull base is reliably sealed [13, 14]. Some authors think that thrombin-fibrin sealants do not affect the outcome but simplify the applied surgical technique [16]. After the first intervention, the patient was recommended to temporarily refrain from blowing her nose. Poor adherence led to tension pneumocephalus. During the subsequent revision surgery, the multilayer cranioplasty technique was applied: we used a musculoaponeurotic autologous graft with subcutaneous fat, an allograft (synthetic dural substitute) and fibrin glue. No recurrent CSF leaks were observed in the follow-up period.

CONCLUSION

It is always preferable to perform a few procedures during one surgery since it can reduce the length of treatment and the level of stress. However, the reported clinical case shows that simultaneous surgeries are not always justifiable despite their advantages. A persistent preoperative CSF leak and conventional therapy failure indicate a possible risk of leak recurrence in the postoperative period. With recurred CSF leaks, operative time for revision surgery is increased because the implant has to be removed first. Besides, there is an increased risk of meningitis and meningoencephalitis due to the presence of a foreign body (an implant) in the setting of persistent CSF leak. Therefore, it is important to consider the duration of the leak, the type of CSF leak pressure (high or low), the tried treatment options, and the outcomes. If external drains do not produce any positive effect and the leak is continuing for over 2 months, the surgical treatment should be split in 2 phases. First, the skull base should be repaired and then (2 months later) the frontal bone defect can be finally closed. Although the resulting cosmetic effect may not be satisfactory, this approach is safer. It is still debatable whether lumbar puncture and shunting should be used as auxiliary techniques for reducing intracranial pressure.

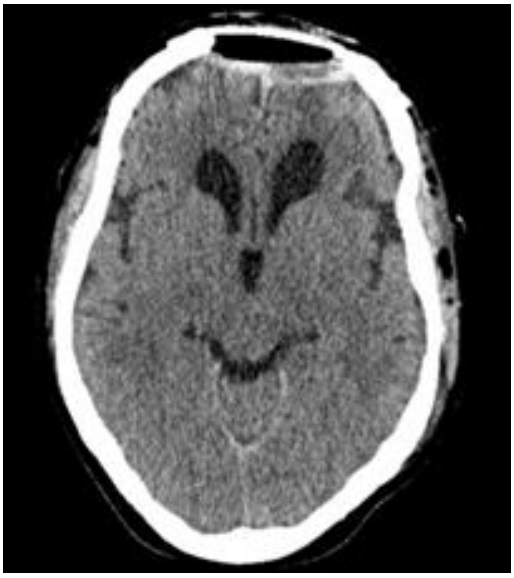

Fig. 9. Postoperative follow-up CT images

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