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РОССИЙСКИЕ БИОМЕДИЦИНСКИЕ ИССЛЕДОВАНИЯ

СОДЕРЖАНИЕ CONTENTS

ОРИГИНАЛЬНЫЕ СТАТЬИ

О.О. Исмати, Е.В. Зиновьев, Д.В. Костяков, Е.В. Ермилова, Т.З. Гогохия, В.О. Сидельников фон Ессен, А.В. Костякова, А.Г. Васильева

Патогенетическое обоснование физиотерапевтических методик обезболивания после эндопротезирования молочных желез 5

Д.С. Шилин, Н.Н. Кошовкина, К.Г. Шаповалов

Изменения гемодинамики при развитии дыхательной недостаточности у пациентов с тяжелыми формами COVID-19 13

О.С. Чепуряева

Определение эффективности авторского способа получения идентичных растровых изображений окклюзограмм 19

К.А. Бельская, С.А. Лытаев

Электроэнцефалографическая оценка нейродинамических компонентов деятельности мозга при психопатологии и их возможной роли в развитии нейрокогнитивного дефицита 24

А.А. Кучай, А.Н. Липин, Н.Н. Груздев, А.Г. Борисов, И.С. Кашапов

Критическая ишемия нижних конечностей и ее лечение 34

ОБЗОРЫ

А.Т. Марьянович, Д.Ю. Кормилец

Белки SARS CoV-2 и белки человеческого организма 48

Д.Ф. де Карвальо, Т. Скаре, А.А. Басина, Н.Ю. Гаврилова, Л.П. Чурилов

5-гидрокситриптофан при ревматологических заболеваниях: систематический обзор 59

ORIGINAL PAPERS

O.O. Ismati, E.V. Zinoviev, D.V. Kostyakov, E.V. Ermilova, T.Z. Gogokhiya, V.O. Sidelnikov von Essen, A.V. Kostyakova, A.G. Vasilyeva

Pathogenetic rationale for physiotherapeutic methods for pain relief after breast endoprosthetics 5

D.S. Shilin, N.N. Koshovkina, K.G. Shapovalov

Changes of hemodynamics during the development of respiratory failure in patients with severe forms of COVID-19 13

O.S. Chepuryaeva

Determination of the effectiveness of the author's method of obtaining identical raster images of occlusiograms 19

K.A. Belskaya, S.A. Lytaev

Electroencephalographic assessment of cerebral activity neurodynamic components and their possible role in the development of neurocognitive deficiency 24

A.A. Kuchay, A.N. Lipin, N.N. Gruzdev, A.G. Borisov, I.S. Kashapov

Critical limb threatening ischemia and its management 34

REVIEWS

A.T. Maryanovich, D.Yu. Kormilets

SARS CoV-2 proteins and human proteins 48

J.F. de Carvalho, T. Skare, A.A. Basina, N.Yu. Gavrilova, L.P. Churilov

5-hydroxytriptophan in rheumatological diseases: a systematic review 59

И.А. Баранов, Д.П. Гладин, Н.С. Козлова

Рациональное сочетание онколитических вирусов и аналогов рапамицина в терапии рака (литературный обзор)..... 65

А.А. Басина, А. Ахметова, Н.Ю. Гаврилова, Л.А. Сопрун, В.А. Воловникова, В.И. Утехин, Л.П. Чурилов

Нейропатия малых волокон в патогенезе постковидного синдрома 78

ЛЕКЦИИ

Н.С. Козлова, Д.П. Гладин, А.М. Королюк, И.А. Баранов

Сибирская язва: далекая и близкая..... 88

ИНФОРМАЦИЯ

Правила для авторов 100

I.A. Baranov, D.P. Gladin, N.S. Kozlova

Rational combination of oncolytic viruses and rapamycin analogues in cancer therapy (literature review)..... 65

A.A. Basina, A. Akhmetova, N.Yu. Gavrilova, L.A. Soprun, V.A. Volovnikova, V.I. Utekhin, L.P. Churilov

Small fiber neuropathy in the pathogenesis of post-covid syndrome 78

LECTURES

N.S. Kozlova, D.P. Gladin, A.M. Korolyuk, I.A. Baranov

Anthrax: near and far..... 88

INFORMATION

Rules for authors 100

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PATHOGENETIC RATIONALE FOR PHYSIOTHERAPEUTIC METHODS FOR PAIN RELIEF AFTER BREAST ENDOPROSTHETICS

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Abstract. ***Introduction.*** Breast augmentation is the most common aesthetic surgical intervention. However, endoprosthetics using silicone implants is often accompanied by a number of negative consequences in the postoperative period, including severe pain. One of the possible ways to solve this problem is the intramuscular injection of botulinum toxin followed by the use of electromagnetic influence in the field of endoprosthetics. ***Purpose of the study:*** to evaluate the effectiveness of the combined use of intramuscular injection of butolotoxin followed by the use of electromagnetic influence in order to reduce the severity of pain in patients after breast augmentation. ***Materials and methods.*** The study is based on the results of a survey of 89 females who underwent breast replacement with silicone implants. All women were divided into 4 groups, taking into account the approach to the use of botulinum toxin type A and an electromagnetic field with a frequency of 448 kHz. During the observation, the intensity of the pain syndrome was assessed intraoperatively, as well as in the early and late postoperative periods. ***Results of the study.*** It was found that a course of electrophysiological effects with INDIBA, carried out in the first week after aesthetic endoprosthetics of the mammary glands, significantly increases the effectiveness of the analgesic effect of botulinum toxin. The frequency and severity of mild pain in this subgroup of patients on days 1 and 2 is less by 51.7% ($p < 0.01$) and 41.8% ($p < 0.01$) compared to the results using only botulinum toxin. Statistical calculations revealed a strong connection between the course of use of the electrophysiological effect of INDIBA after the administration of botulinum toxin with the severity of pain on the 1st, 2nd and 7th day of the rehabilitation period after breast replacement ($p < 0,01$). ***Conclusion.*** The proposed set of rehabilitation measures after aesthetic endoprosthetics of the mammary glands has a statistically significant, pathogenetically substantiated, pronounced and long-lasting analgesic effect in the postoperative period.

Keywords: mammary gland augmentation, endoprosthetics, pain syndrome, butolotoxin, electrophysiological effect

ПАТОГЕНЕТИЧЕСКОЕ ОБОСНОВАНИЕ ФИЗИОТЕРАПЕВТИЧЕСКИХ МЕТОДИК ОБЕЗБОЛИВАНИЯ ПОСЛЕ ЭНДОПРОТЕЗИРОВАНИЯ МОЛОЧНЫХ ЖЕЛЕЗ

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Резюме. ***Введение.*** Аугментация молочных желез является наиболее частым эстетическим хирургическим вмешательством. Однако эндопротезирование с использованием силиконовых имплантов зачастую сопровождается рядом негативных последствий в послеоперационном периоде, связанных в том числе с выраженным болевым синдромом. Одним из возможных путей решения данной проблемы является внутримышечное введение ботулотоксина с последующим использованием электромагнитного воздействия в области эндопротезирования. ***Цель исследования*** — оценить эффективность комбинированного применения внутримышечного введения ботулотоксина с последующим использованием электромагнитного воздействия с целью снижения выраженности болевого синдрома у пациенток после аугментации молочных желез. ***Материалы и методы.*** Исследование основано на результатах обследования 89 лиц женского пола, перенесших эндопротезирование молочных желез силиконовыми имплантами. Все женщины были разделены на 4 группы с учетом подхода к использованию ботулотоксина типа А и электромагнитного поля с частотой 448 кГЦ. В ходе наблюдения оценивали интенсивность болевого синдрома интраоперационно, а также в раннем и позднем послеоперационных периодах. ***Результаты исследования.*** Установлено, что курс электрофизиологического воздействия препаратом INDIBA, проводимый в первую неделю после эстетического эндопротезирования молочных желез, существенно повышает эффективность обезболивающего действия ботулотоксина. Частота и выраженность легкого болевого синдрома в этой подгруппе пациенток на 1-е и 2-е сутки оказывается меньше на 51,7% ($p < 0,01$) и на 41,8% ($p < 0,01$) по сравнению с результатами использования лишь ботулотоксина. Статистический расчет позволил выявить сильную связь между курсовым использованием электрофизиологического воздействия INDIBA после введения ботулотоксина с выраженностью болевого синдрома на 1-е, 2-е и 7-е сутки реабилитационного периода после эндопротезирования молочных желез ($p < 0,01$). ***Заключение.*** Предложенный комплекс реабилитационных мероприятий после эстетического эндопротезирования молочных желез оказывает статистически значимый патогенетически обоснованный выраженный и длительный обезболивающий эффект в послеоперационном периоде.

Ключевые слова: аугментация молочных желез, эндопротезирование, болевой синдром, ботулотоксин, электрофизиологическое воздействие

NTRODUCTION

Surgery involving the placement of silicone implants in breast and mammary gland tissues in order to increase their volume and improve shape is considered one of the most frequently performed by plastic surgeons [9]. Medical devices in the form of silicone gel-filled breast implants have become a routine practice for surgeons and are currently most often used in women for augmentation mammoplasty [13].

There is accumulating evidence that breast endoprosthetics with silicone implants is associated with a number of negative consequences in the postoperative period, up to the development of complications [4].

There is also information that in the postoperative period after breast augmentation using silicone implants,

women experience the pain of varying severity, which is related to the volume of implants placed and patients' age. It is natural that clinical manifestations of pain after breast surgery are accompanied by fear, feeling of shortness of breath, inability to breathe deeply, dyspnea, tachycardia, increased blood pressure, and various vegetative symptoms [3].

Pain syndrome is a typical companion of the postoperative period after breast augmentation. Its manifestations significantly impair the quality of life and reduce the positive perception of even an excellent aesthetic effect, and satisfaction of women after this type of intervention [14].

In a focused assessment of the intensity and severity of pain in postoperative period after various breast surgeries, it was found that after reduction mammoplasty and classical mastectomy, their frequency corresponds to 20 and 30%, respectively. In cases of mastectomy with subsequent reconstruction using an implant, prevalence of pain was up to 52% of observations [1].

Direct trauma to nerve trunks (during tissue incisions, application of nodal sutures) localized in immediate vicinity of the operating field, taking into account the surgical access, leads to postoperative breast pain. Such pain can also be caused by secondary trauma to nerve trunks during the formation of edema, inflammatory reaction in the area of intervention. As a result, persistent pain syndrome occurs in the zone of corresponding innervation within 1–7 days after surgery [10, 15].

In-depth studies have shown that intense acute pain after breast surgery and implant placement is an obligatory factor in the development of chronic pain in postoperative period [11, 12]. To prevent such a vicious path and reduce acute pain after mammoplasty, it is advisable to use the entire arsenal of pain relief methods during this period [2, 7].

The development of pain syndrome in postoperative period after augmentation mammoplasty is detected in two out of three women who underwent the intervention. In this case, pain significantly reduces the quality of life of convalescents and their satisfaction with the operation. Obviously, measures aimed at reducing pain intensity have a pathogenetic focus and are very important in the list of rehabilitation activities.

After aesthetic endoprosthetics of mammary glands with silicone implants, the aim of rehabilitation measures is recognized as the fastest possible labor and social adaptation, improving the quality of life of convalescents.

An important role in the list of methods and techniques of rehabilitation after surgical endoprosthetics of mammary glands belongs to complete analgesia and complete pain relief in postoperative period after such breast surgeries [2]. It is comprehensive postoperative analgesia that stops the typical pathological process — stress response to surgical trauma. As a result, this significantly reduces the incidence of inflammatory complications, hematomas and seromas, respiratory disorders and other complications. Listed pathological conditions substantially impair the quality of life and satisfaction with aesthetic intervention performed.

In order to provide rehabilitation activities in postoperative period, prevention and relief of pain syndrome after breast augmentation with silicone implants, it is advisable to use physiotherapy techniques, in particular microcurrent. It has been shown that microcurrent therapy improves intracellular processes, has an anti-inflammatory effect, normalizes hydrobalance, increases the synthesis and accumulation of macroergic compounds. This is explained by the fact that pain in the area where surgical operation was performed is mediated by the development of an inflammatory reaction. In ideal conditions, this is a sterile aseptic inflammation caused by inevitable destruction of cellular compartments and membranes. It is these products containing arachidonic acid and its phospholipid metabolites, along with mediators of inflammation, that lead to an inevitable inflammatory reaction, edema and typical microcirculation disorders. Microcurrent therapy in these cases has a pronounced pathogenetic significance, exerting an anti-inflammatory effect, stopping microcirculation disorders in tissues in the area of surgery performed [5, 6].

In recent years, electromagnetic field exposure to 448 kHz electric stimulus has been proposed for accelerated relief of inflammatory tissue changes and pain syndrome in postoperative period. It activates ion exchange, as a result of which natural regenerative processes in cells proceed much more effectively. Such physiotherapeutic devices ensure restoration of electrical potential of the cell membrane in postoperative period, improve its permeability, activate collagen production, improve microcirculation and tissue trophism, have anti-edematous effect, promote the reorganization of hematoma areas, as well as stem cell proliferation [8]. These properties seem to be very important for achieving the aims of rehabilitation after breast endoprosthetics and need to be studied.

AIM

The aim of the study is to evaluate the effectiveness of the combined use of intramuscular botulinum toxin injections followed by use of electromagnetic field therapy in order to reduce the severity of pain in patients after breast augmentation.

MATERIALS AND METHODS

The scientific work within the framework of this thesis is planned and completed in the period 2023–2024 at the Department of Surgical Diseases No. 2 of the Faculty of Medicine of the Samarkand State Medical University.

Collection of material for the formation of clinical observation groups was carried out in the period 2021–2024 in the plastic surgery department of the Relax Med Servis clinic, Samarkand, Republic of Uzbekistan.

Observation groups included 89 females who underwent aesthetic endoprosthetics of mammary glands with silicone implants.

Conditions (criteria) for inclusion in this study were: age from 25 to 50 years, presence of clinically significant hypomastia, breast asymmetry, no previous operations in chest and mammary glands area. Voluntary consent of the patient to participate in a scientific study to assess the effectiveness of rehabilitation measures in postoperative period was also required.

Conditions (criteria) for exclusion from the study were: age under 25 and over 50 years, presence of chronic infectious diseases, as well as their exacerbation, coronary heart disease, chronic obstructive pulmonary diseases, respiratory failure of any type, skin infectious and noncommunicable diseases in chest area, hyper- and hypocoagulability, HIV, history of hepatitis B, C, tuberculosis, pregnancy at any stage, lactation, use of pacemakers, thrombophlebitis. Also excluded from the study were patients who signed refusal to voluntarily to participate in a scientific study to assess the effectiveness of rehabilitation measures in postoperative period.

The group of clinical observations No. 1 included 23 women (25.8%) who underwent breast endoprosthetics with silicone implants. They were administered botulinum toxin type A into *musculus pectoralis major* 14 days before intervention to achieve its denervation and prevent pain syndrome after surgery.

The group of clinical observations No. 2 included 24 females (26.9%) who also underwent breast augmentation using silicone implants. They were administered botulinum toxin type A into *musculus pectoralis major* 14 days before intervention to achieve its denervation and prevent pain. Moreover, in this group, during the 1, 2, 3, 4, 5, 6, and 7th days of postoperative period, additional physiotherapeutic treatment was performed. It was carried out using INDIBA — a device that has an electromagnetic field with a frequency of 448 kHz.

The group of clinical observations No. 3 included 22 women (24.7%) who also underwent endoprosthetics of mammary glands with silicone implants. They were administered equivalent volume of placebo (0.9% sodium chloride solution) into *musculus pectoralis major* 14 days before intervention. Also, in the period of 1, 2, 3, 4, 5, 6, 7th days of postoperative period they underwent physiotherapy with the INDIBA — an electromagnetic field with a frequency of 448 kHz.

The group of clinical observations No. 4 included 20 females (22.4%) who also underwent breast augmentation with silicone implants. They were administered equivalent volume of placebo (0.9% sodium chloride solution) into *musculus pectoralis major* 14 days before surgery. Physiotherapeutic treatment with the INDIBA — an electromagnetic field with a frequency of 448 kHz was not performed for organizational reasons.

The group of clinical observations No. 1 was considered control.

In order to achieve denervation and immobilization of *musculus pectoralis major* and reduce the intensity of pain, botulinum toxin type A “Botox” was administered at 200 U (100 U on the right and left) at a concentration of 1:25 (1 ml of the drug in 25 ml of 0.9% sodium chloride) no more than 2.5 ml at one injection point (according to Ermilova E.V. et al., 2022). It was administered in the early stages after augmentation of mammary glands 14 days before intervention to patients of the 1st and 2nd groups (a total of 47 observations) intramuscularly into specified muscle, in ten conditional sectors of muscle corresponding to injection points. Patients in groups 3 and 4 (42 observations in total) were administered equivalent volume of placebo (0.9% sodium chloride) according to the same regimen.

During postoperative period, patients of the 3rd and 4th groups (42 observations in total) underwent physiotherapeutic treatment with the INDIBA active 801 (Spain) for accelerated rehabilitation and tissue restoration. It is aimed to affect the skin and muscle fibers. It is recommended for working with superficial tissues abundantly supplied with vessels. Device ensures recovery of membrane potential, improvement of membrane permeability, restoration and maintenance of normal cellular physiology, activation of collagen production, improvement of microcirculation and tissue trophism. The use of appliance had three contraindications: pregnancy, use of pacemakers, thrombophlebitis, which were included in exclusion criteria.

The mode of operation of device used in women in postoperative period after breast endoprosthetics provides exposure to the method of radio frequency cellular electrotherapy at a frequency of 448 kHz. It was used in the first week after surgery, daily, on chest area, exposure was 15 minutes.

After surgery, in the first week daily, in the second week every other day, as well as on the 15th and 30th day, and 3, 6, 9, 12 months later during control check-ups and examinations, general condition of convalescents, intensity of pain,

presence and severity of respiratory disorders, possibility of activation, ability to work and performance were analyzed.

In order to assess the intensity of pain syndrome intraoperatively (anamnestically) and in postoperative period at 1, 2, 3, 7, 14 days, 1, 3 and 6 months after intervention, a questionnaire of the Numeric Pain Rating Scale (Numeric Pain Scale) was used. It was proposed by McCaffery M. and Beebe A. in 1993, and allowed to assess the intensity of pain sensations from 0 to 10 scores. The score of 1–3 was considered as a mild pain syndrome (unpleasant pain sensations), 4–6 were considered as a moderate syndrome (moderate pain); 7–10 scores corresponded to a high degree of pain syndrome, severe pain.

The results obtained were processed by generally accepted methods of variation statistics.

RESULTS AND DISCUSSION

The intensity of pain syndrome in analyzed subgroups, as well as in the control subgroup of patients during the month after aesthetic endoprosthetics of mammary glands with silicone implants is shown in Table 1. The data of the table allow us to conclude that among the subgroup of women in whom administration of botulinum toxin type A was combined with the course of electrophysiological effect, by the end of the first day of postoperative period, pain syndrome of mild and moderate severity prevailed — in 76.4 and 11.3% of observations. Simultaneously, during the same period, among patients who received only botulinum toxin, frequency of mild and moderate pain syndrome was 51.7% lower ($p < 0.01$) and 25.4% higher ($p < 0.05$), respectively. In the control group, where botulinum toxin was not administered, there was no electrophysiological exposure, and severe and moderate pain syndrome predominated — in 45.7 and 36.8% of clinical observations, respectively (Table 1).

In the meantime, in the same array of clinical observations, on the 2nd day after aesthetic breast endoprosthetics, in the subgroup of observations where rehabilitation measures included the introduction of botulinum toxin and electrophysiological effects, absence of pain syndrome was recorded in 11.3% of cases. Moreover, pain of mild or moderate intensity was observed in 74.5 and 11.1% of patients, respectively. Within the same period, in the comparison group, where only botulinum toxin was used, frequency of mild pain syndrome was 41.8% lower ($p < 0.01$), and moderate pain was 28.2% higher ($p < 0.05$). As on the first day, by the end of the second day in the control group, where only placebo was used without electrophysiological exposure, severe and moderate pain syndromes prevailed — in 32.6 and 43.6% of cases, respectively.

One week after surgery, pain syndrome in analyzed group of patients, whose rehabilitation activities included administration of botulinum toxin and course of electrophysiological treatment, was practically absent — 78.2% of observations. Low intensity was found in 21.8% of cases. During the same period, in the subgroup of patients who received only botulinum toxin before surgery, cases of absence of pain syndrome were detected 21.9% less frequently ($p < 0.05$). Moreover, in 6.1% of cases, pain syndrome of moderate intensity was noted.

By the end of the second and fourth weeks of postoperative period, in the subgroup of women who received botulinum toxin preparation and course of electrophysiological treatment, complete absence of pain syndrome was noted in 89.2 and 94.5% of cases, respectively. This was 10.7 and 9.1% ($p > 0.05$) more, respectively, than in the same periods in the subgroup of females who received only botulinum toxin. Statistical differences in frequency and severity of mild pain syndrome in these two subgroups of patients on the 14th and 30th days after surgery also reached 10.7% (parameter values 21.5 and 10.8%) and 9.4% (parameter values 14.9 and 5.5%), respectively. However, differences were also statistically insignificant ($p > 0.05$).

The results of conducted studies lead to the conclusion that course of electrophysiological treatment using INDIBA, carried out daily during the first week, i.e. seven procedures after aesthetic endoprosthetics of mammary glands, significantly increases the effectiveness of analgesic effect of administration of botulinum toxin type A 14 days before surgery. It was found that with their combined use, frequency and severity of mild pain syndrome on the 1st and 2nd days are lower by 51.7% ($p < 0.01$) and 41.8% ($p < 0.01$), respectively, compared to results of using botulinum toxin alone.

Pathogenetically conditioned factor providing anti-inflammatory and analgesic action, early rehabilitation is electrophysiological effect of electromagnetic field of the INDIBA used by us. It was found that among women in whom administration of botulinum toxin was combined with the course of electrophysiological exposure, by the end of the first day, pain syndrome of mild and moderate intensity prevailed — in 76.4 and 11.3% of observations. On the second day after aesthetic breast endoprosthetics in the same array of patients, absence of pain syndrome was noted in 11.3% of cases. At the same time, pain of mild or moderate intensity was detected in 74.5 and 11.1% of patients, respectively.

After a week, in analyzed group of patients, whose rehabilitation measures included administration of botulinum toxin and course of electrophysiological treatment, pain was practically absent in 78.2% of observations. In addition, mild pain syndrome was detected in 21.8% of cases. By the end of the second and fourth weeks of postoperative period, in the subgroup of women who received botulinum toxin

Table 1

Dynamics of pain after breast augmentation, taking into account electrophysiological therapy in the postoperative period

Таблица 1

Динамика болевого синдрома после аугментации груди с учетом электрофизиологической терапии в послеоперационном периоде

Срок, сут. Duration, days	Курс процедур INDIBA / INDIBA treatment course	Частота выявления болевого синдрома, % / Frequency of detection of pain syndrome, %			
		нет / no	легкого / slight	умеренного / moderate	выраженного / severe
1	Есть, без ботулотоксина / Yes, without botulinum toxin	5,8	24,7	36,7	32,8
	Есть, на фоне ботулотоксина / Yes, with botulinum toxin	4,6	76,4	11,3	7,7
	Нет / No	0	17,5	36,8	45,7
2	Есть, без ботулотоксина / Yes, without botulinum toxin	8,9	32,7	39,3	19,1
	Есть, на фоне ботулотоксина / Yes, with botulinum toxin	11,3	74,5	11,1	3,1
	Нет / No	0	23,8	43,6	32,6
7	Есть, без ботулотоксина / Yes, without botulinum toxin	56,3	37,6	6,1	0
	Есть, на фоне ботулотоксина / Yes, with botulinum toxin	78,2	21,8	0	0
	Нет / No	34,7	38,4	26,9	0
14	Есть, без ботулотоксина / Yes, without botulinum toxin	78,5	21,5	0	0
	Есть, на фоне ботулотоксина / Yes, with botulinum toxin	89,2	10,8	0	0
	Нет / No	61,2	38,8	0	0
30	Есть, без ботулотоксина / Yes, without botulinum toxin	85,1	14,9	0	0
	Есть, на фоне ботулотоксина / Yes, with botulinum toxin	94,5	5,5	0	0
	Нет / No	67,9	32,1	0	0

preparation and course of electrophysiological exposure, complete absence of pain syndrome was noted in 89.2 and 94.5% of cases, respectively.

The results of the conducted studies lead to the conclusion that the course of electrophysiological treatment using INDIBA, carried out in the first week after aesthetic endoprosthetics of mammary glands, significantly increases the effectiveness of analgesic action of botulinum toxin. When combining these methods, frequency and severity of mild pain on the 1st and 2nd day are lower by 51.7% ($p < 0.01$) and by 41.8% ($p < 0.01$) compared to results of using only botulinum toxin. Statistical calculation revealed a strong connection between course use of electrophysiological treatment with INDIBA after administration of botulinum toxin with the severity of pain on the 1st, 2nd and 7th days of rehabilitation period after breast augmentation using silicone implants ($p < 0.01$).

FINDINGS

1. Adequate analgesia in the early and late postoperative periods after breast endoprosthetics is the main task of aesthetic surgery, ensuring the fastest possible labor and social adaptation of patients.

2. When combining the injection of botulinum toxin and the electromagnetic field expusure of INDIBA, the intensity of the pain syndrome during the first month of observation in more than 90% of cases was mild. This indicates complete denervation of musculus pectoralis major, accompanied by pronounced analgesic effect.

CONCLUSION

Thus, presented results of the study of methods for reducing the severity of pain in patients after aesthetic endoprosthetics of mammary glands turned out to be convincing. The proposed set of rehabilitation measures after surgery in the form of parenteral intramuscular administration of botulinum toxin with course of electrophysiological exposure to an electromagnetic field has a pronounced and long-term analgesic effect in postoperative period.

ADDITIONAL INFORMATION

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

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

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

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CHANGES OF HEMODYNAMICS DURING THE DEVELOPMENT OF RESPIRATORY FAILURE IN PATIENTS WITH SEVERE FORMS OF COVID-19

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Abstract. ***Background.*** The search for effective predictors of the severity of COVID-19 is an important problem in medical science at the present stage. In the pathogenesis of the severe course of a new coronavirus infection, changes in the state of hemodynamics are essential. ***Aim:*** to identify hemodynamic predictors of decompensated respiratory failure in patients with COVID-19. ***Materials and methods.*** The study was carried out on 100 patients of both sexes with community-acquired polysegmental viral-bacterial pneumonia against the background of COVID-19. Next, the patients were divided into 2 groups based on the development of severe respiratory failure. The 1st group included 50 patients who did not require mechanical ventilation, the second included patients who were either undergoing mechanical ventilation at the time of the study or will be undergoing it in the future. The studies were carried out using a complex of hardware-software non-invasive study of central hemodynamics using volumetric compression oscillometry. ***Results.*** In patients with progression of respiratory failure against the background of the new coronavirus infection COVID-19, the value of stroke volume and index is 1.27 and 1.16 times less before the prone position, as well as 1.3 and 1.23 times after the prone position according to compared with patients in the favorable group. In addition, in group 2, the volumetric ejection velocity in the supine position was 1.26 times less, and in the stomach position it was 1.22 times less. The compliance of the vascular wall and the reaction of precapillaries in patients who required mechanical ventilation were lower by 1.19 and 1.81 times before proning, and by 1.28 and 2.04 times after proning. ***Conclusions.*** In patients with progression of severe respiratory failure against the background of the new coronavirus infection COVID-19, changes in stroke volume and index, volumetric ejection velocity, and vascular wall compliance were identified.

Keywords: predictors, respiratory failure, prone position, COVID-19, hemodynamics

ИЗМЕНЕНИЯ ГЕМОДИНАМИКИ ПРИ РАЗВИТИИ ДЫХАТЕЛЬНОЙ НЕДОСТАТОЧНОСТИ У ПАЦИЕНТОВ С ТЯЖЕЛЫМИ ФОРМАМИ COVID-19

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Резюме. ***Актуальность.*** Поиск эффективных предикторов тяжести течения COVID-19 является важной проблемой медицинской науки на современном этапе. В патогенезе тяжелого течения новой коронавирусной

инфекции существенное значение имеют изменения состояния гемодинамики. ***Цель исследования*** — выявить изменения гемодинамики у пациентов с COVID-19 при прогрессирующей дыхательной недостаточности. ***Материалы и методы.*** Исследование выполнили у 100 пациентов обоего пола с внебольничной полисегментарной вирусно-бактериальной пневмонией на фоне COVID-19. Проспективно пациенты были разделены на 2 группы с учетом развития тяжелой дыхательной недостаточности. В 1-ю группу вошли 50 пациентов, которым не потребовалась механическая вентиляция, во 2-ю вошли пациенты, которым либо проводилась на момент исследования механическая вентиляция, либо потребуется в будущем. Наблюдение осуществляли с помощью комплекса аппаратно-программного неинвазивного исследования центральной гемодинамики методом объемной компрессионной осциллометрии. ***Результаты.*** У пациентов с прогрессированием дыхательной недостаточности на фоне новой коронавирусной инфекции COVID-19 меньше значение ударного объема и индекса в 1,27 и 1,16 раз соответственно до прон-позиции, а также в 1,3 и 1,23 раза после прон-позиции соответственно по сравнению с больными группы благоприятного течения. Помимо этого, во 2-й группе показатель объемной скорости выброса в положении на спине меньше в 1,26, на животе в 1,22 раза. Податливость сосудистой стенки и реакция прекапилляров у пациентов, которым потребовалась механическая вентиляция легких, ниже в 1,19 и 1,81 раз соответственно до прон-позиции, а также в 1,28 и 2,04 раза соответственно после пронирования. ***Выводы.*** У пациентов с прогрессированием тяжелой дыхательной недостаточности на фоне новой коронавирусной инфекции COVID-19 выявлены изменения ударного объема и индекса, объемной скорости выброса, податливости сосудистой стенки.

Ключевые слова: предикторы, дыхательная недостаточность, прон-позиция, COVID-19, гемодинамика

BACKGROUND

Coronavirus disease 2019 (COVID-19) is an extremely contagious disease produced in humans by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [15]. Due to mild symptoms and high contagiousness, the infection quickly spread throughout the world [14]. 81 percent of COVID-19 patients had cold-like symptoms and moderate pneumonia, 14 percent had severe respiratory syndrome, and 5 percent had critical respiratory failure, septic shock, and/or multiple organ dysfunction or failure; the overall fatality rate was 1%. [18]. Approximately 17 to 35% of hospitalized patients with COVID-19 are treated in the intensive care unit, most often due to hypoxemic respiratory failure and the development of ARDS, and between 29 and 91% of patients in intensive care units require invasive ventilation. [7]. More than 75% of patients hospitalized with COVID-19 require supplemental oxygen. [12, 17]. A number of risk factors for severe COVID-19 have been identified, among which the patient's age and comorbidity are of leading importance — factors that determine the prognosis of in-hospital mortality of hospitalized patients [2, 6]. Therefore, it is extremely important to research the pathophysiological features of patients, identify risk factors of disease progression, prognosticate severity for clinical diagnosis and early initiation of adequate treatment, which is crucial to improve the survival of critically ill patients.

AIM OF THE STUDY

To identify changes in hemodynamics in patients with COVID-19 with progressive respiratory failure.

MATERIALS AND METHODS

A prospective non-randomized study was performed in 100 patients. The study was performed in the City Clinical Hospital № 1 in Chita, Russian Federation. The investigation was carried out after approval by the local ethical committee of Chita State Medical Academy (protocol N 102 of 15.05.2020) according to the local treatment protocols.

The study was carried out in two stages. First, a hemodynamic study was performed in patients of both sexes with community-acquired polysegmental viral-bacterial pneumonia against the background of COVID-19, aged from 35 to 87 years, in intensive care units, with various types of respiratory support. The diagnosis was made according to the temporary methodological recommendations of the Provisional Guidelines of the Russian Ministry of Health on prevention, diagnosis, and treatment of novel coronavirus infection COVID-19. The patients were diagnosed with at least 50% viral-induced involvement of lungs using chest computed tomography. The patients were prescribed the standard treatment according to the current version of the Provisional Guidelines of the Russian Ministry of Health on prevention, diagnosis, and treatment of novel coronavirus infection

COVID-19. During the study, patients at various stages of respiratory support were randomly recruited. Respiratory support through a face mask with a flow of 5–7 liters was provided for 40 patients, death was recorded in 8 of them. Non-invasive artificial pulmonary ventilation was performed in 41 patients, of which 23 died.Mechanical pulmonary ventilation was performed in 19 patients who subsequently died.

Next, the patients were divided into 2 groups based on the dynamics of respiratory failure (Table 1). The first group included 50 patients who did not require mechanical ventilation, the second group included patients who were either undergoing mechanical ventilation at the time of the study or would be undergoing it in the future. The need for mechanical ventilation during hospitalization was a sign of decompensation.

The non-inclusion criteria included neoplastic diseases, severe immunodeficiency, unstable hemodynamics, vasopressor infusion, signs of hypovolemia, uncontrolled hypertension (SBP above 200 mm Hg).

Hemodynamic studies of two groups of patients were performed using the integrated hard- and software system for noninvasive central hemodynamic study by volumetric compression oscillometry “KAP TsG Osm-Globus” (Russia).

The following sets of parameters were recorded: blood pressure, cardiac activity and vascular parameters. The first block included data on systolic (SBP), diastolic (DBP), mean (SBP), oscillometric “true” systolic (OTSBP), pulse (pBP) and stroke (StBP) blood pressure, pulse blood pressure velocity (PBPV). The second set consisted of indicators of pulse, cardiac output (CO) and cardiac index (CI), stroke volume (SV) and stroke index (SI), volume ejection rate (VER), left ventricular contractile power (LVCP) and energy expenditure (EE) per 1 liter of cardiac output per minute. The third block was presented by the linear blood flow rate (LBFR) and pulse wave velosity (PWV), vascular compliance (VC), total peripheral resistance (TPR) and normalized peripheral resistance (NPR) as well as NPR actual/NPR estimated ratio (FS). All parameters were obtained from the software and hardware readings and calculated according to the instructions. The indicators recorded in patients in the laying position belong to the 1st group of parameters, the data recorded on the stomach belong to the 2nd group.

The authors followed the International Committee of Medical Journal Editors (IC MJE) guidelines and the Statistical Analysis and Methods in the Published Literature (SAMPL) guidelines when conducting statistical analyses. The normality of the distribution of characteristics was assessed using the Kolmogorov–Smirnov test. Taking into account the distribution of characteristics that differed from normal in all studied groups, the data obtained were presented as the median, first and third quartiles: Me (Q1; Q3). To compare two independent groups on one quantitative characteristic, the Mann–Whitney test (U) was used. Nominal data were described with absolute values and percentages. Comparisons of nominal study data were made using Pearson’s χ^2 test. For small samples, preference was given to the Pearson chi-square test with likelihood adjustment. If the number of expected observations in at least one cell of the four-field table was less than 10, the chi-square test with Yates’ correction for continuity was used to compare two independent groups of nominal data. If the number of expected observations in at least one of the cells of the four-field table was less than 5, Fisher’s exact test is used to compare two independent groups of nominal data. The prognostic model was built using logistic regression [3]. To establish the diagnostic value of the prognostic model, ROC analysis was used. Statistical processing of the study results was carried out using the IBM SPSS Statistics Version 25.0 software package (International Business Machines Corporation, license No. Z125-3301-14, USA).

RESULTS

When comparing the indicators recorded before the prone position, it was found that in patients of the 1st group, systolic and pulse blood pressure was higher than in patients of the 2nd group by 1.04 times at p=0.05, 1.13 times at p=0.023. The values of stroke volume and stroke index are also higher

Table 1

Characteristics of patient groups (M[25;75])

Parameter	Group 1, n =50	Group 2, n= 50	Statistical significance
Age, years	63,00 [58,19;62,70]	68,00 [64,05;67,46]	**p=0,049**
Height, m	1,67 [1,66;1,70]	1,67 [1,66;1,69]	**p=0,812**
Weight, kg	80,00 [82,26;88,84]	80,00 [79,19;85,46]	**p=0,364**
BMI, kg/m²	30,04 [29,25;30,97]	29,24 [28,38;30,33]	**p=0,266**
Hypertension	36/50 (72%)	36/50 (72%)	p=0,87
CHD	21/50 (42%)	33/50 (67,3%)	p=0,011
Chronic heart failure	16/50 (32,7%)	30/50 (61,2%)	p=0,005
Chronic obstructive pulmonary disease	6/50 (12%)	8/50 (16,3%)	p=0,742
Diabetes mellitus	8/50 (16%)	12/50 (24,5%)	p=0,423
Chronic kidney disease	4/50 (8%)	8/50 (16,3%)	p=0,336
Neurological diseases	6/50 (12%)	16/50 (33,3%)	p=0,011

p — statistical significance of indicators.

Table 2

Comparison of vascular and cardiac performance indicators in patients with critical respiratory failure

Parameter	Group 1, n =50	Group 2, n= 50	p
Systolic blood pressure, mm Hg. Art.	128,00 [126,35;131,73]	123,00 [117,54;123,73]	**p=0,050**
Pulse blood pressure-1, mm Hg. Art.	52,00 [51,49;56,59]	46,00 [44,20;48,90]	**p=0,023**
Pulse-1, beats/min	69,00 [68,70; 73,83]	84,00 [84,73;91,44]	**p <0,005**
Pulse-2, beats/min	73,00 [73,70;78,26]	88,00 [86,57;94,20]	**p=0,001**
Stroke volume-1, ml	89,00 [85,43;93,10]	70,00 [64,67;71,00]	**p <0,005**
Stroke volume-2, ml	86,00 [78,07;84,66]	66,00 [65,83;74,70]	**p=0,007**
Stroke index-1, ml/m^2	44,00 [44,67;48,96]	38,00 [34,81;38,13]	**p <0,005**
Stroke index-2, ml/m^2	43,00 [40,72;44,22]	35,00 [35,14;40,00]	**p=0,022**

p — statistical significance of indicators.

Table 3

Comparison of vascular and cardiac activity parameters in patients with critical respiratory failure

Parameter	Group 1, n=50	Group 2, n=50	p
Volumetric ejection velocity — 1, ml/s	272,00 [277,56;309,86]	215,00 [203,44;221,13]	**p <0,005**
Volumetric ejection velocity — 2, ml/s	244,00 [243,81;267,70]	200,00 [207,31;232,89]	**p=0,016**
Left ventricular contraction power — 1, W	3,20 [3,38;3,86]	2,60 [2,36;2,64]	**p <0,005**
Compliance of the vascular wall — 1. ml/mm Hg. Art.	1,52 [1,51;1,63]	1,28 [1,24;1,36]	**p <0,005**
Compliance of the vascular wall — 2. ml/mm Hg. Art.	1,47 [1,42;1,53]	1,15 [1,19;1,32]	**p <0,005**
FS - 1	0,58 [0,51;0,60]	0,32 [0,21;0,32]	**p <0,005**
FS - 2	0,55 [0,45;0,53]	0,27 [0,17;0,30]	**p <0,005**

p — statistical significance of indicators.

in patients who did not require mechanical ventilation, 1.27 times at p <0.005 and 1.16 times at p <0.005 (Table 2 and 3).

The parameters of the volumetric cardiac output velocity and left ventricular power are greater in group 1 by 1.26 times at p <0.005 and 1.23 times at p <0.005 than in group 2. The compliance of the vascular wall and the FS coefficient in the group where respiratory failure did not progress were 1.19 times higher at p <0.005 and 1.81 times higher at p <0.005, respectively.

When comparing the pulse rate measured before the prone position maneuver, the indicators were 1.2 times lower in patients of the 1st group than in the 2nd group with p <0.005.

When comparing the group of indicators recorded after the prone position maneuver, stroke volume and stroke index were higher in patients of the 1st group by 1.30 times at p=0.007 and 1.23 times at p=0.022 than in the 2nd group.

The value of the volumetric cardiac output rate and vascular wall compliance was greater in the group where respiratory failure did not progress, by 1.22 times at p=0.016 and 1.28 times at p <0.005. We also found that in patients where mechanical ventilation was not required, the FS coefficient was 2.04 times higher with p <0.005.

When comparing the pulse rate measured after the prone position maneuver, the indicators were lower in patients of the 1st group than in the 2nd group by 1.21 times with p <0.005.

When comparing the group of indicators recorded after the prone position maneuver, stroke volume and stroke index were higher in patients of the 1st group by 1.30 times at p=0.007 and 1.23 times at p=0.022 than in the 2nd group.

The value of volumetric cardiac output velocity and vascular wall compliance was greater in the group where respiratory failure did not progress by 1.22 times at p=0.016 and 1.28 times at p <0.005. It was also found that in patients where mechanical ventilation was not required, the FS coefficient was 2.04 times higher at p <0.005.

When comparing the pulse rate measured after the prone position maneuver, the indicators were lower in patients of the 1st group than in the 2nd group by 1.21 times with p <0.005.

DISCUSSIONS OF THE RESULTS

Previous studies have placed [8] importance on identifying and confirming factors that predict COVID-19 progression. Factors including age, comorbidities, immune response, radiographic data, laboratory markers, and indices of organ dysfunction may individually or collectively predict worse outcomes. Not all facts studied are conclusive evidence predicting severe disease, some are presumptive, and others are still preliminary and need further study. However, the difficulty of predicting the severity of COVID-19 disease is underscored by the fact that SARS-CoV-2 appears to have tropism for several tissues, including primarily the respiratory tract [9].

SARS-CoV-2 affects multiple organ systems, including the respiratory, cardiovascular and urinary systems, causing pneumonia and respiratory failure in patients [9, 11, 16].

Considering the fact that the treatment of respiratory failure is closely related to the use of prone position, we decided to study the hemodynamic state before and after proning of patients. Any change in the position of a patient in critical condition can cause different responses, which indicate a breakdown of adaptive mechanisms.

Patients whose respiratory failure did not progress had lower systolic blood pressure, pulse blood pressure, and pulse. This is probably due to changes in the block of cardiovascular parameters. Placing patients in a prone position caused an increase in intrathoracic and intra-abdominal pressure, which interferes with venous return and likely reduces ejection volume flow (EVF) [5].

Changes in stroke volume and index, the volumetric velocity of ejection, were observed both before and after the prone position. Probably, a significant decrease in the indicators of this block is due to the fact that patients in group 2 had more significant changes in the lungs (Tables 2 and 3). Extensive pneumonia caused by the new coronavirus infection COVID-19 led to damage to many alveolar units and disturbances in micro- and macrocirculation. A common complication in such patients is the development of pulmonary embolism [10, 13]. Often against this background, indicators of pulmonary hypertension increased [4], which in turn affected the speed and indicators of stroke volume. Also, against the background of a new coronavirus infection, ischemic and inflammatory processes occurred in the myocardium, which could also affect the indicators of cardiac block.

Compliance decreased statistically significantly both before and after the prone position. SARS-CoV-2 has a destructive effect on the cardiovascular system, which can be explained by both a direct cytotoxic effect on the endothelium and immune-mediated damage to endothelial cells. Angiotensin-converting enzyme 2, expressed on the endothelium, serves as a receptor for viral entry into the cell. The result of this interaction is an imbalance in the functioning of the renin-angiotensin system, which disrupts the regulation of vascular tone, stimulates proliferation and has a pro-inflammatory effect. Interleukin 6, which plays a key role in the development of cytokine storm, mediates a wide range of inflammatory changes that cause disturbances in the structural and functional organization of blood vessels [1]. An indirect sign of changes in hemodynamics in group 2 is reflected by the FS coefficient; it indicates the reaction of precapillaries to changes in cardiac output.

CONCLUSIONS

1. In patients with progression of respiratory failure against the background of the new coronavirus infection COVID-19, the value of stroke volume and index is 1.27 and 1.16 times less before the prone position, as well as 1.3 and 1.23 times after the prone position according to compared with patients in the favorable group.

2. In addition, in group 2, the volumetric ejection velocity in the supine position was 1.26 times less, and in the stomach position it was 1.22 times less.

3. The compliance of the vascular wall and the reaction of precapillaries in patients who required mechanical ventilation were lower by 1.19 and 1.81 times before proning, and by 1.28 and 2.04 times after proning.

ADDITIONAL INFORMATION

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

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

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

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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

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

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

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

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DETERMINATION OF THE EFFECTIVENESS OF THE AUTHOR'S METHOD OF OBTAINING IDENTICAL RASTER IMAGES OF OCCLUSIOGRAMS

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Abstract. Dentists attach great importance to the diagnosis of occlusive contacts, as well as their reproduction. The quality of the treatment depends on the accuracy of the restoration of occlusal contacts. To date, there is no way that would guarantee an accurate, fast, effective result. Therefore, we have developed and patented an author's method for obtaining bitmap images of occlusograms. We conducted a patent search for all similar methods of assessing occlusion and occlusive relationships in the literature sources available to us. Next, we compared our author's method of obtaining bitmap images of occlusograms with other known methods. And as a result of the conducted research, we have proved the effectiveness of the author's method of obtaining raster images of occlusograms in clinical dental practice.

Keywords: occlusography, area of occlusal contacts, flatbed scanner, diagnostics, occlusal fingerprint

ОПРЕДЕЛЕНИЕ ЭФФЕКТИВНОСТИ АВТОРСКОГО СПОСОБА ПОЛУЧЕНИЯ ИДЕНТИЧНЫХ РАСТРОВЫХ ИЗОБРАЖЕНИЙ ОККЛЮЗОГРАММ

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Резюме. Диагностике окклюзионных контактов, а также их воспроизведению стоматологи придают большое значение. Именно от точности восстановления окклюзионных контактов зависит качество проведенного лечения. В настоящее время нет способа, который бы гарантировал точный, быстрый, эффективный результат, поэтому мы разработали и запатентовали авторский способ получения растровых изображений окклюзограмм. Мы провели патентный поиск всех похожих способов оценки окклюзии и окклюзионных взаимоотношений в доступных нам источниках литературы. Далее мы сравнили наш авторский способ получения растровых изображений окклюзограмм с другими известными методами. В результате проведенного исследования нами была доказана эффективность применения авторского способа получения растровых изображений окклюзограмм в клинической стоматологической практике.

Ключевые слова: окклюзография, площадь окклюзионных контактов, планшетный сканер, диагностика, окклюзионный отпечаток

INTRODUCTION

Diagnosis of occlusal contacts, analysis of various lower jaw positions, examination of the condition of muscles and temporomandibular joint are important in dental practice. At stages of examining patients before and after dental treatment, dentists attach great importance to reproduction of occlusal contacts. The quality of treatment depends on the accuracy of the restoration of occlusal contacts [1–3].

Physiological occlusion is provided by occlusal contacts of posterior teeth, which are characterized by the presence of upper and lower fissures and tubercles on chewing surface of the teeth [2, 4].

Restoration of chewing function is one of the main results of high-quality dental treatment, be it orthopedic, orthodontic or, to a lesser extent, therapeutic treatment [1, 7, 13]. Violation or incorrect restoration of occlusal landscape relief [11] leads to increased patient anxiety due to the disruption of vital chewing function [4]. Despite the variety of possible modern dental studies currently available [8, 14], methods for determining chewing efficiency remain the most informative and fully characterize the quality of restoration of chewing function [5, 6, 12]. Accurate restoration of occlusal contacts and near-contact areas during dental treatment is one of the most difficult tasks in dentist's job. To solve it, various devices have been developed that reproduce the movements of lower jaw, as well as various methods for determining and fixing the relationship of jaws have been proposed. There are many ways to record occlusion, there are also several ways to transfer occlusal surface relief to a personal computer and then to a program for determining the area of occlusal surface. However, the problem is still not solved. A.V. Mashkov proposed a method for obtaining bitmap images using a negatoscope, camera and tripod. Occlusogram image was placed on the negatoscope, then photographed and transferred to a personal computer for later analysis [2, 9]. In our opinion, this is inconvenient, requires additional equipment in the form of a negatoscope and high-quality camera and still does not guarantee receiving identical images.

A method of creating occlusal contacts and dentures is known from the literature, using an occlusogram obtained in the oral cavity. According to it, a plane is formed on a plaster model in which contact points lie perpendicular to tooth axis, and the areas of occlusal contacts are created depending on the degree of jaw bone atrophy. In accordance with it, occlusal contacts, their location and the area of occlusal surface of artificial teeth are restored [10, 11]. The disadvantage of this technique is the occlusogram method of determining the location of occlusal contacts when transferring to a plaster model, which is used to obtain a conditional plane with location of contact points. This does not ensure accurate reproduction of occlusal surfaces of artificial teeth and determination of the parameters of interocclusal space of a pair of antagonist teeth. In addition, this method does not allow obtaining accurate parameters of artificial relief of occlusal surfaces of antagonist teeth.

Due to the need for accurate diagnosis and receiving high-quality bitmap images of occlusograms, the author considered that it was necessary to develop a new "Method of obtaining identical bitmap images of occlusograms" [12].

AIM

The aim of the study is to determine the effectiveness of the author's method of obtaining identical bitmap images of occlusograms.

MATERIALS AND METHODS

At the Department of Orthopedic Dentistry with the course in clinical Dentistry of the Volgograd State Medical University, studies were conducted aimed at assessing the efficiency of the "Method of obtaining identical bitmap images of occlusograms" developed by the author of this article [10]. The purpose of these researches was also to test the possibility of using obtained images in the "Program for measuring areas of occlusal contacts using a bitmap image" [12] developed by Mashkov A.V., Chepuryaeva O.S., Shemonaev V.I. and others [12].

Initial data for working in the "Program for measuring areas of occlusal contacts using a bitmap image" are scanned images of patient's occlusograms in centric occlusion. We obtained the occlusogram using a method developed at the Department of Orthopedic Dentistry with a course in clinical Dentistry [2]. Then, in accordance with developed "Method for obtaining identical bitmap images of occlusograms" to identify occlusal contacts, an occlusogram of contact points of the teeth was previously received in the oral cavity. The material used to record occlusal contacts was base wax with thickness of 2.0±0.2 mm in the form of a pink plate with dimensions of 180×90×1.8 mm. Color and optical properties of selected wax made it possible to achieve accurate calibration of plate thickness according to changes in accordance with occlusal surfaces. They also helped to obtain color characteristics for variety of thicknesses on relief imprint of occlusal surfaces of antagonist teeth. To give rigidity, wax plate was fixed on a wire frame bent to the shape of dentition, pressing tightly along edges of wire frame. This structure was then heated in a water bath to an oral temperature of 35.5–37.5 °C, ensuring production of an easily deformable imprint of occlusal surface of antagonist teeth.

The framework with wax plate was inserted into the oral cavity and positioned relative to upper jaw dentition. Then the patient closed the teeth with maximum force in centric occlusion position, in which maximum contraction of masticatory muscles is possible. Resulting occlusogram was removed from the oral cavity, cooled and received a fixed imprint of occlusal surfaces and occlusal contacts of antagonist teeth.

Further operations to fix and study occlusal contacts of antagonist teeth were performed outside the oral cavity, without patient's participation.

You need to create a template to obtain "Identical bitmap images of occlusograms". This is easy to do even at home. You should take a sheet of thick white A4 paper, determine the center of the sheet and draw a cross. Lines must be strictly perpendicular to each other, that is, angles between lines are strictly 90 °. After this, you need to draw a horizontal and vertical line through the center to the edge of the sheet, then step back 50 mm from the center and put dots on horizontal and vertical. Next, you should connect 4 points and get a square with a side of 100 mm.

Then, you need to place previously obtained occlusogram in this square and fix it with transparent adhesive tape. After that, you should place this structure on the glass of flatbed desktop scanner for scanning documents with occlusogram down on glass, and the sheet of white paper should be on top. Then you need to open image scanning software on a personal computer. In our case, we used a Kyocera ECOSYS M2530dn KX flatbed desktop document scanner and ABBYY FineReader 14/FineReader.exe image scanning software, or you can use any available image scanning software. You need to select "Full-color", "Photo" in settings. Next, select "Scan" command and get a "Bitmap identical image of occlusogram" on personal computer screen. Resulting images can be used to diagnose the condition of the teeth and dentitions before, during and after treatment. Wax plate is scanned against the light, as a result of which occlusal contacts on scanned image differ in brightness, which depends on the density of occlusion of antagonist teeth.

The study involved 50 patients of both genders aged 18–35 with intact dentitions, healthy periodontium and proper occlusion. 150 occlusograms were obtained. The average time from the moment of making occlusogram until occlusal imprint was received on personal computer monitor, suitable for analysis in program we developed to determine the area of occlusal surface. Then data were entered into tables and analyzed. Statistical processing of study results was performed using the Statistica and Microsoft Office software packages. Digital data were processed on a personal computer using variation statistics method. We used Student's t-test and Pearson's correlation coefficient (r). The confidence interval with random deviation was no more than 5% ($p < 0.05$). Principles of evidence-based medicine were used in studying research results [2, 6].

RESULTS AND DISCUSSION

When receiving occlusograms during the study conducted using the author's technique and further processing using the "Method of obtaining identical bitmap images of occlusograms", and subsequent transfer of images obtained to the "Program for measuring areas of occlusal contacts using a bitmap image" [12], an average of 155 seconds were spent. While working according to approach proposed by A.V. Mashkov, an average of 725 seconds were spent on the same work, which is 570 seconds more than obtaining bitmap images of occlusograms using the author's method. At higher speed of work, quality of bitmap images did not suffer and repeatability increased. That is, receiving images using the author's "Method of obtaining identical bitmap images of occlusograms" can increase productivity by 4.7 times compared to other techniques used previously ($p < 0.001$). These include, for example, the method of Associate Professor of the Department of Orthopedic Dentistry with the course in clinical Dentistry of Volgograd State Medical University A.V. Mashkov.

CONCLUSION

As a result of study conducted, the effectiveness of the author's "Method of obtaining bitmap images of occlusograms" for diagnosis of chewing efficiency was proven. Thus, when receiving bitmap images of occlusograms using the technique proposed by the author of this article, time for transferring from a wax reproduction of occlusal surface relief to a digital model is reduced by 570 seconds. This is 4.7 times faster than previously used method. Thus, application of this author's approach increases efficiency of the dentist, reduces time costs. Thanks to this method, work as a whole can become more convenient, cheaper, simpler, more effective, more accessible. In this regard, this "Method of obtaining identical bitmap images of occlusograms" can be recommended for diagnosis of chewing efficiency and use in clinical dental practice.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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

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ELECTROENCEPHALOGRAPHIC ASSESSMENT OF CEREBRAL ACTIVITY NEURODYNAMIC COMPONENTS AND THEIR POSSIBLE ROLE IN THE DEVELOPMENT OF NEUROCOGNITIVE DEFICIENCY

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Abstract. ***The relevance*** of this article is due to the variability of scientific ideas about the mechanisms of development of neurocognitive deficit associated with a line of psychopathological conditions. Many questions remain about the functions of individual brain structures and systems, as well as central neurodynamics in the development of cognitive defects. The question of the influence of the disorganization of vertically oriented structures of the first brain functional block (BFB) on the formation of neurocognitive deficit in mental pathology of the schizophrenic spectrum remains the least studied in modern neuroscience. ***The present research was aimed*** to assess the functional state of the first brain energy block and to determine the role of disorders in the neurodynamic components of activity in the development of neurocognitive deficit in psychopathology. ***Materials and methods.*** 40 patients with paranoid schizophrenia and 38 healthy subjects matched in age, gender ratio and educational level were examined. EEG by monopolar according to the international system 10/20 using a 21-channel system "Telepat-1" was registered. With the help of visual and spectral methods of analysis, both nonspecific physical parameters of the α-rhythm — index, frequency and amplitude, and physiological features of α-oscillations — reactivity, regularity, autorhythm (modulation) and stability of the α-rhythm were studied. The functional state of the RF was determined by the parameters of the latent periods of synchronization, desynchronization, and the depth of desynchronization in the eye opening/closing test. The tonus of the cortex by the ratio of the values of the indices of alpha- and delta-rhythms was determined. The threshold of convulsive readiness of the brain was calculated from the number of recorded flashes in the background EEG. Fluctuations in the frequency of the basic alpha rhythm exceeding 0.5 Hz were regarded as a sign of instability in the oscillatory activity of the brain. ***Results.*** It has been established that impairment of cognitive functions in schizophrenia is associated not only with cortical dysfunction (II and III BFB), but also with disorganization of vertically oriented structures of the I BFB. Revealed disorganization of the reticular formation and alpha-regulating system, decreased tone and activation of the cerebral cortex. The possible pathogenetic influence of these pathophysiological factors on the formation of neurocognitive deficit has been substantiated. The most informative diagnostic EEG-signs of disorders in the neurodynamic components of brain activity were determined.

Keywords: paranoid schizophrenia, EEG, spectral analysis, brain functional block, neurocognitive deficit

ЭЛЕКТРОЭНЦЕФАЛОГРАФИЧЕСКАЯ ОЦЕНКА НЕЙРОДИНАМИЧЕСКИХ КОМПОНЕНТОВ ДЕЯТЕЛЬНОСТИ МОЗГА ПРИ ПСИХОПАТОЛОГИИ И ИХ ВОЗМОЖНОЙ РОЛИ В РАЗВИТИИ НЕЙРОКОГНИТИВНОГО ДЕФИЦИТА

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Резюме. ***Актуальность*** работы обусловлена вариабельностью научных представлений о механизмах развития нейрокогнитивного дефицита, ассоциированного с рядом психопатологических состояний. Остается много вопросов о функциях отдельных структур и систем мозга, а также центральной нейродинамики в развитии когнитивного снижения. Наименее изученным в современной нейронауке остается вопрос о влиянии дезорганизации вертикально ориентированных структур I функционального блока мозга (ФБМ) на формирование нейрокогнитивного дефицита при психической патологии шизофренического спектра. ***Цель исследования*** заключалась в оценке функционального состояния первого энергетического блока мозга и определении роли нарушений нейродинамических компонентов деятельности в развитии нейрокогнитивного дефицита при психопатологии. ***Материалы и методы.*** Обследовано 40 пациентов, страдающих хронической параноидной шизофренией, и 38 здоровых испытуемых, сопоставимых по возрасту, гендерному соотношению и образовательному уровню. Регистрация ЭЭГ осуществлялась монополярно по международной системе 10/20 с помощью 21-канального аппаратно-программного комплекса «Телепат-1». С помощью визуального и спектрального методов анализа изучались как неспецифические физические параметры α-ритма — индекс, частота и амплитуда, так и физиологические особенности α-осцилляций — регулярность, авторитмичность (модуляции) и стабильность α-ритма. Функциональное состояние ретикулярной формации (РФ) определяли по параметрам латентных периодов синхронизации, десинхронизации и глубины десинхронизации в пробе с открытием/закрытием глаз. Тонус коры определяли по соотношению значений индексов альфа- и дельта-ритмов. Порог судорожной готовности мозга рассчитывали по количеству зарегистрированных вспышек в фоновой ЭЭГ. Колебания частоты базового альфа-ритма, превышающие 0,5 Гц, расценивались как признак нестабильности осцилляторной активности мозга. ***Результаты.*** Установлено, что нарушения познавательных функций при шизофрении связаны не только с дисфункцией коры (II и III ФБМ), но также с дезорганизацией вертикально ориентированных структур I ФБМ. Выявлена дезорганизация ретикулярной формации и альфа-регулирующей системы, снижение тонуса и активации коры мозга. Обосновано возможное патогенетическое влияние этих патофизиологических факторов на формирование нейрокогнитивного дефицита. Определены наиболее информативные диагностические ЭЭГ-признаки нарушения нейродинамических компонентов деятельности мозга.

Ключевые слова: параноидная шизофрения, электроэнцефалография, спектральный анализ, нейродинамика, нейрокогнитивный дефицит

INTRODUCTION

Modern civilization is based on the knowledge and processing of significant amounts of information. At the same time, the volume and speed of accumulation of new information necessary for successful functioning of society and activities of an individual are growing exponentially. That is why a modern person in order to remain professionally competent and develop his intelligence and innovative thinking, needs to acquire ever greater amounts of knowledge throughout his life [1, 10, 11].

Meanwhile, modern education system is acquiring the character of personality-oriented learning, in which cognitive development is aimed at qualitative transformation of all cognitive processes. In the age of information technology, it is not enough for a person to possess the only knowledge and skill. It is also necessary to possess such qualities of higher nervous activity as flexibility in thinking,

high adaptability to changing conditions, desire to self-education and volitional qualities in achieving the goal [17].

However, literature analysis shows that cognitive impairment is associated with a significant number of neurological, mental and psychosomatic disorders. Their prevalence is increasing due to population aging. Many forms of psychopathology related to the sphere of so-called major psychiatry are in most cases also associated with neurocognitive deficit. It has often had chronic disabling nature and leads to pronounced occupational and social maladjustment. The most common disease in this category is schizophrenia.

Currently, there are about 50 million people in the world suffering from various types of dementia. The number of patients with severe cognitive disorders doubles every ten years, and by 2050 their total number in all countries of the world will reach 130 million [13]. Cognitive disorders occur in 20% of children and adolescents. This leads to learning difficulties, deviant behavior, psychoemotional disorders and, as a consequence, to social maladjustment [2, 3, 14].

In this regard, there is growing interest in cognitive psychophysiology in studying the mechanisms of cognitive dysfunction, as well as their role in the development of learning difficulties and mechanisms of neurocognitive deficit. The problem of studying the biological basis of cognitive dysfunction (especially in severe forms of psychopathology) has become one of the most pressing issues in neuroscience [10, 11]. The formation of neurocognitive deficit that occurs during the development of the schizophrenic process is one of the most complex and poorly understood problems of modern neurobiology.

According to DSM-V criteria, cognitive disorders include a decrease, compared to premorbid level, in one or more higher brain functions that ensure the processes of attention, perception, storage, transformation and transmission of information [27].

From the standpoint of the concept of three functional units of the brain according to A.R. Luria, structures of all blocks of the brain are of interest in formation of neurocognitive deficit. However, specifics and mechanisms of disorders at the level of each of them remain poorly studied [14, 19]. For this reason, establishing patterns and deciphering the mechanisms of cognitive disorganization, participation in their pathogenesis of vertically (Unit I) and horizontally (Unit II and III) oriented parts of the brain is one of the most complex and interesting issues of neuropsychology, which has both theoretical and practical significance.

An analysis of the available neuropsychological literature shows that pathogenetic significance of disorganization of central neurodynamics, which is carried out by Unit 1, in mechanisms of development of neurocognitive deficit in schizophrenia and other psychopathological conditions is also a poorly studied problem. There are few publications in literature devoted to the study of neurodynamics in cognitive dysfunction [2, 18].

The paradigm of “neurocognitive deficit” proposed at the end of the 20th century by A. Breier considers cognitive impairment as the “third key group of symptoms” of schizophrenia, along with positive and negative clinical symptoms [26]. Recently, it has been established that neurocognitive deficit in schizophrenia is observed in 94% of patients, manifests itself in the early stages, persists throughout the entire period of disease and remains in remission [13].

In clinical neuropsychology, the study of mechanisms of neurocognitive decline and, in particular, the role of neurodynamic aspects of cognitive impairment in patients with psychopathology is given undeservedly little attention. Objective neuropsychological research on brain function based on the systemic neurodynamic approach, the founder of which in the field of psychophysiology was A.A. Ukhtomsky, remains unreasonably little in demand by modern researchers. In addition, the term “neurodynamics” itself is used less and less in neuroscientific literature.

Productivity of studies of cerebral dysfunctions in neuropsychology is associated with a systemic approach. Its essence consists in constructing a holistic picture of the object of study based on the proposed systemic principle and conducting research based on this principle. Beginning with the classical works of A.A. Ukhtomsky, it was shown that brain is a complex neurodynamic system, constantly striving for integration and stereotype of unified activity [6, 24].

According to modern concepts, brain is considered as a complex computer information system with a large number of equilibrium, but variable states. Brain stability within certain functional level is a neurodynamic process that maintains physiological parameters through homeostatic regulation. Homeostatic regulation processes correct all internal fluctuations in state of the central nervous system (CNS) around the average levels [9].

The theoretical framework of this study of neuropsychological mechanisms of neurocognitive deficit was: A.R. Luria’s concept of three functional units of the brain [14, 19], I.P. Pavlov’s teaching on the major neurodynamic laws [23], and A.A. Ukhtomsky’s theory of dominance [24].

According to the concept of A.R. Luria, all mental processes and various types of conscious human activity in normal and pathological conditions should be considered from the standpoint of functional role of three functional units or blocks of the brain. Unit I is a unit that ensures the regulation of tone and level of wakefulness. Unit II is a block for receiving, processing and storing information.

Unit III is a unit for programming, regulation and control of mental activity.

Optimal cortex tone and adequate level of wakefulness are necessary to ensure the normal speed and quality of neurocognitive processes. The brain can best receive and process information, recall necessary selective systems of connections and associations, and program activities only in such a neurodynamic state.

The fact that optimal tone of the cortex is necessary for implementation of organized and effective cognitive activity was already indicated by I.P. Pavlov, who described major neurodynamic laws. Thus, according to the neurodynamic "law of force", in a state of reduced tone of the cortex, normal ratio of excitatory and inhibitory processes. Their mobility, necessary for implementation of organized course of mental activity, is also disrupted [23].

The first energy block of the brain includes structures of the brainstem, parts of the diencephalon and mediobasal regions of the frontal and temporal lobes (Fig. 1).

At different levels of Unit I of the brain, there are three main energy sources, which provide regulatory influences on the cerebral cortex, maintenance of working tone and level of wakefulness.

The main source of maintaining tone and activation of the cerebral cortex is the brainstem reticular formation (RF). The ascending and descending reticular systems of the brainstem constitute a single self-regulating apparatus. It ensures the redistribution of tone and activation of the cerebral cortex depending on the level of its functional activity in a certain period of time. At the same time, activating and inhibitory effects of the RF affect all sensory, motor, verbal thinking, and other functions of the brain.

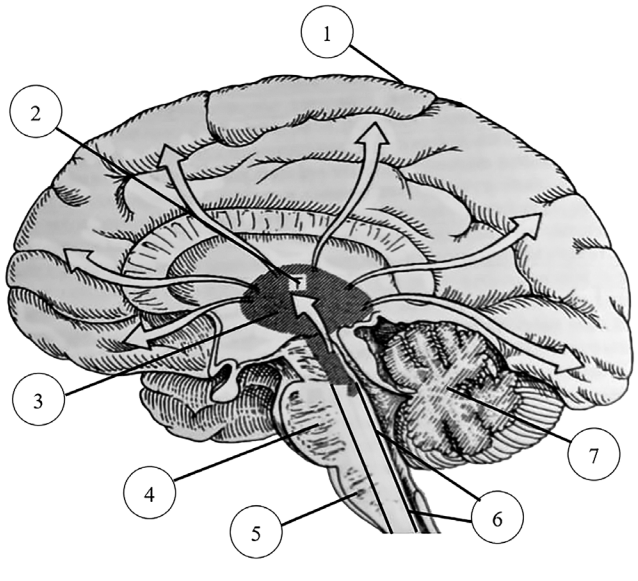

Fig. 1. The first functional block of the brain: 1 — cerebral cortex; 2 — visual tubercle; 3 — hypothalamus; 4 — brainstem; 5 — medulla oblongata; 6 — ascending brainstem RF; 7 — cerebellum

Рис. 1. Первый функциональный блок мозга: 1 — кора головного мозга; 2 — зрительный бугор; 3 — гипоталамус; 4 — мост; 5 — продолговатый мозг; 6 — восходящая РФ ствола мозга; 7 — мозжечок

The second key structure of Unit I of the brain, responsible for maintaining brain energy status, tone and activation of the cortex, is neural apparatus of the hypothalamus, which regulates the body's metabolic processes.

The third energy source is associated with thalamic system, which controls the entry of polymodal information into the brain. Firstly, sensory streams of verbal and non-verbal information support activation processes and tone of the cortex. Secondly, the thalamus is morphofunctionally closely connected with the Peipets' limbic circle, through which energy impulses associated with the cerebral cortex circulate [19, 25].

Perception of any information causes a reaction in the form of an orienting reflex. According to I.P. Pavlov, it is the most important factor of cognitive activity, closely connected with the work of both the RF and thalamic system of the brain. A significant source of activation and maintenance of tone of the cerebral cortex is also the verbal thinking activity of a person, his mental plans and understanding of perspective, which are formed in the process of purposeful cognitive activity.

In this way, normally all levels of the first functional block of the brain and all its energy sources are closely interconnected and work in interaction with the higher areas of the cortex. They not only tone the cortex, but also experience modulating influences from cortical regions of the brain, thus ensuring an adequate level of cognitive functioning.

Cognitive resource is considered in psychophysiology as a general factor of successful solution of cognitive tasks. It ensures the perception of verbal and non-verbal verbal imaginative information, analysis and correlation of perceived information with that stored in long-term memory and decision-making [6, 8, 9, 20]. According to Hans Eysenck's activation theory, the level of tone and activation of the brain is the central explanatory point of the influence of individual differences on the efficiency of cognitive activity [4, 25]. The Yerkes-Dodson law establishes an inverted U-shaped relationship between the success of completing a cognitive task and level of tone and activation of the brain. Optimal condition for cognitive success is a certain average level of tone and activation of the cerebral cortex, which was confirmed in our previous studies of efficiency of perception of non-verbal auditory information [7].

According to G. Eysenck, with insufficient activation of the cerebral cortex, the number of errors in subjects when

presented with cognitive tasks increases by 3 times compared to patients with an optimal level of tone and activation [4].

It is known that the world around us, as we know it, is based on our cognitive structures. They are nonspecific, but ordered representations of previous experience. Cognitive structures formed during individual development support the processes of cognitive self-regulation and internal mechanisms of self-control. The process of cognitive self-regulation involves the development and improvement of cognitive structures and concepts, which are the product of learning. The functional role of cognitive self-regulation system lies in its ability to ensure purposeful activity in the direction that we consider correct in specific conditions. That is, we behave as our cognitive structures prescribe. At the same time, cognitive skills of a mentally healthy person give us opportunity to manage our own behavior and ensure a variety of interpersonal interactions and correction of ineffective cognitive schemas [5].

In schizophrenia and other forms of psychopathology, as a result of disorganization of physiological mechanisms of neurocognitive self-control, the ability for cognitive self-regulation is reduced. The cognitive system formed during the development of the schizophrenic process becomes invariant, often acts automatically. It is not very dynamic and is unable to perceive experience and adapt to changing circumstances. The ability to adhere to standards of behavior is lost, patient's actions are subordinated, rather, to external stimuli than to the mechanisms of cognitive self-regulation [12].

AIM

The aim of the study was to conduct an EEG assessment of functional state of the main structures of brain's energy block and to substantiate the pathogenetic significance of disturbances in neurodynamic components of activity in the development of cognitive deficit in psychopathology.

MATERIALS AND METHODS

A total of 78 people were examined, including 40 patients suffering from chronic paranoid schizophrenia associated with neurocognitive deficit and 38 healthy subjects. The average age of the main group was 37.7±3.3 years, average duration of disease was 13.4 years. Women accounted for 55%, men — 45%. The control group consisted of 38 healthy subjects, matched by age, gender ratio and social status: the average age of subjects was 38.6±3.7 years, men accounted for 52.6%, women — 47.4%.

Computer-based electroencephalography was used as the main method for studying central neurodynamics and local dynamic cerebral systems. EEG was recorded using a 21-channel system "Telepat-1" of national production with a sampling frequency of 400 Hz. EEG was recorded monopolarly according to the international system "10%–20%" from the frontal (F3–F4), central (C3–C4), parietal (P3–P4), occipital (O1–O2), anterior temporal (F7–F8), middle temporal (T3–T4) and posterior temporal (T5–T6) cortical regions. Combined ear clips served as the reference electrode.

In the post-real period, visual and spectral analysis of artifact-free EEG sections was performed, duration of which was established experimentally. A detailed analysis of alpha-frequency range parameters as one of the basic brain regulatory systems was carried out taking into account exceptional role of alpha rhythm in information and analytical activities of the brain. Attention was also paid to the fact of its close morphofunctional connection with fronto-thalamic system, which is the key structure of Unit I of the brain. Both nonspecific physical parameters of alpha wave process (index, frequency and amplitude) and physiological features of alpha oscillations (regularity, autorhythmicity (modulations) and stability of alpha rhythm) were analyzed.

Functional state of the RF was determined by parameters of latent periods of synchronization (normally 0.4–1.0 s), desynchronization (normally 0.01–0.03) and depth of desynchronization (normally 5–6 times) in the "open eyes — close eyes" test.

Tone of cerebral cortex was determined by ratio of frequency indices of alpha and delta rhythms. Normally, values of cerebral cortex tone vary in the range of 12–15. The paroxysmal index was estimated by the number of flashes in background EEG. More than two flashes in a minute segment of EEG recording are usually considered a sign of an increase in the degree of paroxysmal activity or lowering seizure threshold of the brain. Functional stability of brain oscillatory activity was evaluated by the degree of stability of background frequency of alpha rhythm. In this case, alpha frequency fluctuations exceeding 0.5 Hz are regarded as a sign of instability of brain's oscillatory activity [15, 16, 21, 22]. The WIN-EEG software, version 1.3, developed at the Institute of Human Brain of the Russian Academy of Sciences, was used to process EEG data. Statistical analysis of all data obtained was performed using the STATISTICA package, version 6.0. The reliability of results was assessed using Student's t-test.

RESULTS

Functional state of key vertically oriented structures of Unit I was assessed differentially taking into account their physiological role in maintaining cortex tone and wakefulness level. Comparative assessment of neurodynamics of the brain in main and control groups was carried out on

the basis of computer-based EEG as a systemic method of studying the brain. The results of EEG study of functional state of non-specific systems, cortex tone and seizure threshold of the brain are presented in Table 1.

In subjects of the main sample, the latent period of desynchronization exceeded normative values by 2.3 times ($p < 0.05$), and latent period of synchronization was higher than normative values by 1.6 times ($p < 0.05$). At the same time, depth of synchronization in patients with schizophrenia was 1.22 times lower than normal. The totality of obtained data indicates a violation of functional state of ascending activating and ascending inhibitory systems of the brainstem.

Based on average normative values of the alpha index in healthy subjects of 50–60% and normative values of the delta index of 4–5%, value of the coefficient of tone and activation of cerebral cortex is normally 12.2. In our studies, average values of the coefficient of tone and activation of the cerebral cortex in subjects of the control group were 12.5, which corresponds to physiological norm. In subjects of the main group, values of the coefficient of tone of the cerebral cortex were 4.5, which is significantly lower than normative values by 2.3 times ($p < 0.001$). A decrease in basic values of tone of the cerebral cortex creates the prerequisites for disorganization of neurophysiological mechanisms of information and analytical activity of the brain.

Functional state of ponto-hypothalamic region of the brain was assessed by the number of flashes recorded in background EEG. Normally, number of flashes on electroencephalogram does not exceed 2 per 1 minute of recording. In patients with psychopathology, the average number of flashes was 5.1 per minute, which exceeded normal values of the control group by 2.5 times ($p < 0.04$). This indicated a tendency toward a moderate but reliable increase in the degree of paroxysmal activity of the brain.

A detailed analysis of alpha-frequency range parameters as one of the basic brain regulatory systems was carried out taking into account exceptional role of alpha rhythm in information and analytical activities of the brain. Attention was also paid to the fact of its close morphofunctional connection with fronto-thalamic system, which is the key structure of Unit I of the brain.

Both nonspecific physical parameters of alpha wave process (index, frequency and amplitude) and physiological features of alpha oscillations (regularity, autorhythmicity (modulations) and stability of alpha rhythm) were analyzed.

The functional status of thalamic system of the brain was determined based on analysis of the main parameters of the alpha-frequency regulatory system of the brain: the alpha index (%), average frequency (Hz) and amplitude (μV) of alpha rhythm, width of alpha range (Hz), depth of EEG desynchronization, regularity, modulations and stability of alpha rhythm.

Comparative analysis of parameters of alpha rhythm, presented in Table 2, reflects functional state of key cognitive areas of the brain in norm and in pathology.

In individuals with psychopathology all parameters of alpha activity are significantly changed. Zonal decrease in frequency of alpha rhythm below 9.15 indirectly demonstrates disintegration of neurofunctional structures that play a key role in the functioning of the brain. Fluctuations in frequency of basic alpha rhythm exceeding 0.5 Hz indicate instability of oscillatory activity that ensures the most important regulatory processes in the brain.

At the same time, EEG showed a 2.5-fold increase ($p < 0.04$) in the number of flashes, which indicates an upward trend in the degree of paroxysmal activity of the brain in schizophrenia.

Table 1

Comparative analysis of key parameters of neurodynamics in persons of the main and control groups

Таблица 1

Сравнительный анализ ключевых параметров нейродинамики у лиц основной и контрольной групп

Показатели нейродинамики / Indicators of neurodynamics	Нормативные значения / Normative values	Основная группа / The main group	Контрольная группа / The control group
ЛП десинхронизации / LP desynchronization	0,01–0,03 с	0,07±0,002	0,02±0,012
ЛП синхронизации / LP synchronization	0,4–1,0 с	1,61±0,009	0,75±0,03
Коэффициент глубины десинхронизации / Depth factor desynchronization	5–6-кратное снижение / 5–6-times reducing	3–4-кратное снижение / 3-4-times reducing	5–6-кратное снижение / 5–6- times reducing
Коэффициент тонуса и активации коры мозга / The coefficient of tone and activation of the cerebral cortex	12,2	4,50±2,58	12,50±2,15
Вспышки / Flashes	Не более 2 с / No more 2 sec	5,1±0,85	1,8±0,25

Table 2

Comparative analysis of background parameters of the EEG alpha rhythm in individuals of the main and control groups

Таблица 2

Сравнительный анализ фоновых параметров ЭЭГ альфа-ритма у лиц основной и контрольной групп

Параметры α-ритма / α-rhythm parameters	Основная группа / The main group	Контрольная группа / The control group
Индекс, % / Index, %	38,6±6,6	65,7
Частота, Гц / Frequency, Hz	8,8	10,1
Ширина альфа-диапазона, Гц / The width of the alpha range, Hz	7,2–12,1	8–13
Амплитуда, мкВ / Amplitude, uV	49,8	62,2
Регулярность, Гц / Regularity, Hz	1,9	0,47
Модуляции / Modulations	– –	+++
Стабильность / Stability	– –	+++

DISCUSSION

In modern neuropsychology, the strategy for studying mental resources of a person is based on understanding the brain as a global neurodynamic system consisting of many neural networks whose operating modes are modulated by structures of Unit I. Anatomically, neural networks consist of many neurons of different brain modules. In addition, they interact in such a way that as a result of their functioning, an optimal cognitive reserve is created. It, in turn, ensures targeted cognitive and behavioral activity of the individual. That is why neurodynamic system is the basis for studying disorders of mental processes, mechanisms of development of cognitive deficit, negative and positive symptoms. All this is observed within the framework of formation of schizophrenic process and other psychopathological conditions [20].

According to the two-component model, total EEG is considered as the result of interaction of synchronizing and desynchronizing systems of the brain. Electroencephalogram reflects the activity of neurons of the cortex, which are under the constant influence of these regulatory systems of the brain.

Functional state of the cerebral cortex is determined by the balance of reciprocally interacting desynchronizing and synchronizing subcortical structures. The speed of interaction of activating and inhibitory effects of the RF on cortical horizontally oriented structures of the brain (Unit II and III), determined by latent periods of synchronization and desynchronization of alpha rhythm, was significantly reduced. When performing the test of opening and closing eyes, a reliable increase in latent periods was revealed. This, combined with incomplete suppression of alpha rhythm in patients with schizophrenia, indicates a violation of functional balance of desynchronizing (activating) and synchronizing (inhibitory) systems of the brainstem. A decrease in functional state of these basic modulating systems creates prerequisites for a slowdown in the speed of mental processes.

In 10 subjects of the main sample (25%), EEG showed dysrhythmia patterns, which were characterized by a non-dominant combination of waves of different frequency ranges. Dysrhythmia patterns are caused by a simultaneous increase in activity of synchronizing and desynchronizing systems. Such neurodynamic states are usually manifested by a pronounced cognitive decline.

Average values of the alpha index in control group subjects were within the range of normal values — 65.7%. In main sample subjects, average values of the alpha-index did not exceed 38.6%, which is 1.7 times lower than in the group of healthy subjects.

A decrease in representation of dominant alpha rhythm in EEG as a functional core of oscillatory activity of the brain can be rightfully interpreted as a factor that negatively affects cognitive functions. Any morphological or functional disorders in the brain lead primarily to a decrease in the alpha index, usually below 50%, or its complete reduction.

It is known that frequency of alpha rhythm is a neurophysiological condition and prerequisite for the effectiveness of cognitive activity. At the same time, its slowdown is due to disorganization of thalamic system of the brain and disruption of corticothalamic interactions.

Indicators of width of alpha range and variability of its amplitude are markers of neurodynamic plasticity, and therefore, the effectiveness of cognitive activity. In the group of patients suffering from schizophrenia, these indicators differ significantly from normative values towards slowing down and a left-sided frequency shift of alpha rhythm.

Modulations of alpha rhythm are the most important qualitative criterion of electroencephalograms related to

organized alpha type. The presence of modulations in relative resting state indicates the optimal interaction of three regulatory systems of the brain: activating desynchronizing system of the brainstem, synchronizing inhibitory system of the thalamus and lower parts of the pons, as well as system of neocortical control of desynchronization and synchronization processes [14].

This EEG parameter subtly reflects the dynamics of ensemble organization of cortical neural activity, volume and "lifetime" of the neuronal ensemble, which is an important prerequisite for normal cognitive functioning of the brain. In EEG studies we conducted, all subjects in the main sample either had no alpha rhythm modulations at all, or they were intermittent and fragmentary.

Consequently, the decrease in frequency, regularity, absence of modulations, disruption of synchronization-desynchronization processes of alpha rhythm indicates disorganization of alpha regulatory system of the brain. This system is closely connected with the first functional block of the brain. The multi-vector disorganization of alpha rhythm that we have identified is of unconditional importance in mechanisms of development of cognitive decline in schizophrenia, as well as in other psychopathological conditions.

An increase in the number of flashes on EEG by 2.5 times above normal values indicates dysfunction of the brainstem-thalamic regions of Unit I. According to modern concepts, the neurodynamic structure that causes flashes is formed as a result of a decrease in functional state of posterior hypothalamus and brainstem structures and hyperactivation of nonspecific and specific nuclei of the thalamus [6, 25].

In this way, the results of studies we have presented show that patients suffering from schizophrenia have a functional decline in key areas of the first block of the brain, which provide activation-energy functions in brain activity. Structures of Unit I determine the function of attention, individual perceptual capabilities, memory and access to cognitive resources through the regulation of tone and activation of the cerebral cortex. Thus, they determine the efficiency of cognitive functioning. Therefore, disorganization of these brain regions creates the preconditions for a decline in cognitive resources.

Experience with patients of neuropsychiatric spectrum shows that they are characterized by intellectual passivity, inability to "mental stress", lack of motives and goals in behavior, "atony" of psyche, complacency, aspontaneity, attention disorder. These qualities combine with the manifestation of inertia, tendency to stereotypes, fantasizing and reasoning. Along with this, patients suffering from schizophrenia clearly demonstrate oddities of thought and behavior, inadequacy of speech and actions.

Pathophysiology of these psychopathological phenomena remains insufficiently studied. The results of our studies allow us to conclude that indicated disorders are largely determined by the primary defect of subcortical systems that form energy basis of mental activity. In terms of neuropsychology, the set of these signs characterizes a neurocognitive deficit associated with functional decline in energy block of the brain and decrease in the level of wakefulness.

CONCLUSION

Our studies have revealed previously unknown information about the significance of disturbances in neurodynamic components of activity in the development of cognitive deficit in paranoid schizophrenia, which have not only theoretical but also practical importance. It has been established that psychopathology involves multilevel disorganization of Unit I, which provides the entire spectrum of basic neurodynamic processes. A decrease in activation-energy and other neurodynamic components of brain function creates prerequisites for impaired concentration, perception of information, memory loss, and slowed mental processing speed. Disorganization of these components of cognitive reserve inevitably leads to the formation of profound cognitive deficits.

FINDINGS

1. Reliable signs of disorganization of nonspecific brain systems were revealed: the latent period of desynchronization increased by 2.33 times; latent period of transition to synchronization register increased by 2.14 times, and depth factor desynchronization decreased by 1.22 times, which indicates a significant violation of activation processes of the cerebral cortex.

2. The indicators of tone and energy of the cerebral cortex in the main sample were 2.8 times lower than normative values, which is an objective sign of a decrease in wakefulness level.

3. In patients with psychopathology, a moderate but reliable tendency to increase paroxysmal activity was revealed. The number of EEG flashes exceeded normal values by 2.5 times, which indicates a decrease in functional state of the posterior hypothalamus and lower brainstem during activation of nonspecific and specific nuclei of the thalamus.

Thus, EEG study of the main neurodynamic components of brain activity that determine the cognitive resource and mental performance of an individual may be very useful in objectifying functional cognitive disorders. It can also be important in choosing pathogenetic treatment of psychopathological disorders.

ADDITIONAL INFORMATION

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

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CRITICAL LIMB THREATENING ISCHEMIA AND ITS MANAGEMENT

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Abstract. Critical limb threatening ischemia (CLTI), the most advanced form of peripheral artery disease, is associated with significant morbidity, mortality, and health care resource utilization. It is a clinical syndrome of ischemic pain at rest or tissue loss, such as non-healing ulcers or gangrene, related to peripheral artery disease. CLTI has a high short-term risk of limb loss and cardiovascular events. Non-invasive or invasive angiography helps determine the feasibility and approach to arterial revascularization. An “endovascular-first” approach is often advocated based on a lower procedural risk; however, specific patterns of disease may be best treated by open surgical revascularization. Balloon angioplasty and stenting form the backbone of endovascular techniques, with drug-eluting stents and drug-coated balloons offering low rates of repeat revascularization. Combined antegrade and retrograde approaches can increase success in long total occlusions. Below the knee, angiosome-directed angioplasty may lead to greater wound healing, but failing this, any straight line flow into the foot is pursued. Hybrid surgical techniques such as iliac stenting and common femoral endarterectomy are commonly used to reduce operative risk. Lower extremity bypass grafting is most successful with a good quality, long, single-segment autogenous vein of at least 3.5 mm diameter. Minor amputations are often required for tissue loss as part of the treatment strategy. Major amputations (at or above the ankle) limit functional independence and their prevention is a key goal of CLTI therapy. Medical therapy after revascularization targets risk factors for atherosclerosis and assesses wound healing and new or recurrent flow limiting disease.

Keywords: peripheral artery disease, endovascular, vascular intervention, vascular disease extremities, vascular surgery, critical limb threatening ischemia, drug coated balloons, drug-eluting stent

КРИТИЧЕСКАЯ ИШЕМИЯ НИЖНИХ КОНЕЧНОСТЕЙ И ЕЕ ЛЕЧЕНИЕ

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Резюме. Критическая ишемия, угрожающая конечностям, — наиболее распространенная форма заболевания периферических артерий, которая связана со значительной заболеваемостью, смертностью и использованием ресурсов здравоохранения. Это клинический синдром ишемической боли в покое или потери тканей, например незаживающих язв или гангрена, связанный с заболеванием периферических артерий. Хроническая ишемия

угрожающей потери конечности (ХИУПК) имеет высокий краткосрочный риск потери конечностей и сердечно-сосудистых событий. Неинвазивная или инвазивная ангиография помогает определить возможность и подход к артериальной реваскуляризации. Часто предлагается подход «сначала эндоваскулярный», основанный на более низком риске процедуры, однако при определенных формах заболевания лучше всего лечить открытую хирургическую реваскуляризацию. Баллонная ангиопластика и стентирование составляют основу эндоваскулярных методов, при этом стенты с лекарственным покрытием и баллоны с лекарственным покрытием обеспечивают низкую вероятность повторной реваскуляризации. Комбинация антеградного и ретроградного подходов может повысить успех при протяженной тотальной окклюзии. Ангиопластика ниже колена, направленная на ангиосомы, может привести к более быстрому заживлению ран, но если это не удалось, то сохраняется любой прямой поток крови в стопу. Гибридные хирургические методы, такие как стентирование подвздошной артерии и бедренная эндартерэктомия, обычно используются для снижения операционного риска. Шунтирование нижних конечностей наиболее эффективно при использовании длинной односегментарной аутогенной вены хорошего качества диаметром не менее 3,5 мм. Небольшие ампутации часто требуются из-за потери тканей в рамках стратегии лечения. Большие ампутации (на уровне лодыжки или выше) ограничивают функциональную независимость, и их предотвращение является ключевой целью терапии критической ишемии нижних конечностей (КИНК)/ХИУПК. Медикаментозная терапия после реваскуляризации нацелена на факторы риска атеросклероза и оценивает заживление ран и новые или рецидивирующие заболевания, ограничивающие кровоток.

Ключевые слова: заболевания периферических артерий, эндоваскулярные вмешательства, сосудистые вмешательства, сосудистые заболевания конечностей, сосудистая хирургия, критическая ишемия, угрожающая конечности, баллоны с лекарственным покрытием, стент с лекарственным покрытием

INTRODUCTION

Critical limb threatening ischemia is a clinical syndrome of ischemic pain at rest and/or ischemic tissue loss such as non-healing ulcers or gangrene, related to peripheral artery disease of the lower limbs. It differs from acute limb threatening ischemia, which is a sudden loss of limb perfusion (defined as within 14 days) typically due to embolus or in-situ thrombus. In contrast, critical limb ischemia occurs over several weeks to months, but is at the extreme end of the spectrum of chronic limb ischemia (Rutherford classification 4–6, Fontaine III/IV, A.V. Pokrovsky IV — Table 1). Its importance is due to the much higher risks of limb loss and cardiovascular events than asymptomatic peripheral artery disease and intermittent claudication [1, 2]. The poor prognosis demands more rapid assessment, a greater role for wound care, and the earlier use of revascularization [3]. As a result, a multidiscipline approach involving specialists in endovascular revascularization, open surgical revascularization, podiatry, wound care, and other specialties is often required to maximize patient outcomes.

DEFINITIONS

Definitions of CLTI aim to identify patients who are risk of major limb amputation without specific treatment such as revascularization or wound care. Traditionally CLTI is defined as rest pain or tissue loss (ulcers, or gangrene) supported by ischemia defined by the hemodynamic criteria of low ankle or toe pressures, or low transcutaneous oxygen (TcO_2) values. Ankle pressure criteria range from less than 40–70 mmHg, toe pressures less than 30–50 mmHg, TcO_2 less than 20–40 mmHg. Higher cut points are often used for tissue

Table 1

Peripheral artery disease symptom classification: Fontaine stages, Rutherford categories and A.V. Pokrovsky classification

Таблица 1

Классификация симптомов заболеваний периферических артерий: Фонтена, Резерфорда и А.В. Покровского

Fontaine classification		Rutherford classification	
Stage	Symptoms	Category	Symptoms
I	Asymptomatic	**0**	Asymptomatic
II	Intermittent claudication	**1**	Mild claudication
		2	Moderate claudication
		3	Severe claudication
III	Ischemic rest pain	**4**	Ischemic rest pain
IV	Ulceration or gangrene	**5**	Ischemic ulceration (minor tissue loss)
		6	Ischemic gangrene (major tissue loss)

A.V. Pokrovsky classification	
Stage	Symptoms
I	Asymptomatic or pain in calf muscles (>1 km)
IIA	Intermittent claudication (>200 meters)
IIB	Intermittent claudication (>200 meters)
III	Intermittent claudication, rest pain
IV	Ulceration or gangrene

loss on the assumption that greater perfusion is required for wound healing, but expert consensus on these hemodynamic criteria differs between guidelines [2, 4–7]. The original definitions were designed to standardize entry criteria for clinical trials of CLTI in patients without diabetes to permit comparisons across studies [4, 6] or to assess the likelihood of wound healing [8]. However, their value as diagnostic tests of CLTI in clinical practice are more controversial [2, 5, 9]. Defining specific cut points of toe pressure or TcO_2 for the clinical diagnosis of CLTI is difficult because of the considerable overlap in values among CLTI patients who do or do not progress to major amputation or cardiovascular events (Fig. 1) [10, 11]. One trial suggests they don't impact the decision for revascularization [12]. Other definitions of CLTI incorporate wound infection and osteomyelitis in addition to ischemia [13].

For clinical purposes rest pain or non-healing wounds may suffice as a definition to justify the use of expensive technology (angiography and revascularization) which are fundamental to the clinical treatment of this condition.

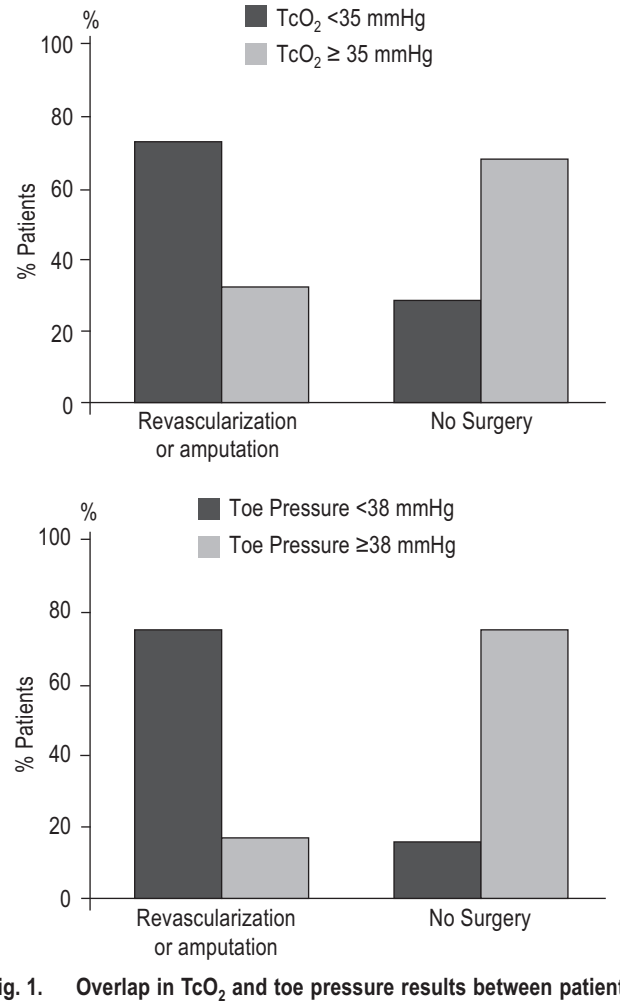

Fig. 1. Overlap in TcO_2 and toe pressure results between patients requiring revascularization or amputation for CLI and patients managed medically (from data in Ubbink et al. [11])

Рис. 1. Результаты перекрытия TcO_2 и давления на палец стопы у пациентов, нуждающихся в реваскуляризации или ампутации по поводу КИНК, и у пациентов, получающих медикаментозное лечение (по данным Уббинка и др. [11])

NATURAL HISTORY OF CLTI

Patient outcomes in critical limb ischemia are largely determined by morbidity and mortality due to cardiovascular events and functional impairment due to limb loss. Although, over the whole spectrum of PAD, cardiovascular events such as myocardial infarction and stroke occur in 30–50% of subjects over a 5 year period, patients with CLI face this risk over a one year period [1, 2, 14] — an outcome worse than many cancers or severe heart failure. Similarly, although the risk of major amputation (at or above the ankle) is less than 5% over 5–10 years in patients with claudication, it is at least 30–50% in the first year in patients with CLI who do not have revascularization [2].

ASSESSMENT AND INITIAL TREATMENT

The clinical presentation of CLI depends on the degree of ischemia, the presence of infection, and co-existing neuropathy [1]. Ischemic pain is usually worse when the patient is supine and often requires narcotics for analgesia. It may waken patients from sleep and prevent them from walking. Infection can increase pain even without severe ischemia. Neuropathy can contribute to tissue injury or mask pain from an ulcer.

Current guidelines recommend measuring the ankle pressure or ankle brachial index [1, 2, 5], although medial calcinosis may yield artificially high values in which case toe pressures may indicate arterial obstruction. TcO_2 or skin perfusion pressures may indicate the likelihood of wound healing.

The primary goal is to preserve limb function. Revascularization is a fundamental strategy to limb preservation, but in some patients, this does not improve limb function and mobility. For example, cognitive impairment, non-ambulatory status prior to CLI, and severe comorbidities portend a poor prognosis even with revascularization [15]. When revascularization is considered, arterial imaging identifies the targets and mode of revascularization.

Duplex ultrasound, and non-invasive angiography with computerized tomography (CTA) or magnetic resonance (MRA), can demonstrate arterial obstruction. Duplex ultrasound does not require contrast but requires specific training and may not image the tibial arteries very easily. In infra-inguinal disease, vein mapping is required to determine the feasibility of surgical bypass with autogenous vein.

CTA requires iodinated contrast and may cause contrast nephropathy in patients with impaired renal function. Heavily arterial calcification can create artefacts that limit CTA particularly in distal disease. Non-contrast time-of-flight MRA is prone to artifact with non-laminar flow typical of atherosclerotic plaque, and concerns of nephrogenic systemic fibrosis from gadolinium contrast limit its use in

advanced kidney disease [16]. CTA and MRA are sometimes inadequate to assess the smaller tibial arteries. Nevertheless, CTA and MRA can help localize disease targets and help plan the mode and approach to revascularization.

Due to limitations in imaging distal arteries non-invasively, invasive angiography is often used to clarify the potential for revascularization and should be considered prior to major amputation. Invasive angiography uses iodinated contrast and provides the highest spatial resolution. Diagnostic cases can use as little as 30 mL of contrast for both legs with conventional and digital subtraction angiography.

Initial treatments include control of pain, which may require narcotics, pressure relief of ulcers, sheepskin boots to increase superficial collateral supply, and tilting the bed downward to increase limb dependency and perfusion [2]. Pain relief may reverse sympathetic-mediated vasoconstriction. Although some of these measures only marginally improve perfusion, they may reduce the discomfort associated with CLI while planning definitive treatment.

ENDOVASCULAR REVASCULARIZATION

In many centers, endovascular revascularization is the favored approach to CLI, because of lower morbidity and mortality compared to open surgery (Fig. 2). The optimal treatment strategy (endovascular versus open surgery) will depend on anatomical factors, comorbidities, patient preference and operator experience and skill. Although claudication can be relieved by inflow revascularization (aorto-iliac and femoral), CLI is often associated with multilevel disease and usually requires outflow (tibial) revascularization as well as treating inflow disease. Much of the evidence for endovascular treatment of inflow disease is based on studies of patients with claudication or a mix of claudication and CLI [52].

INFLOW AND FEMORAL-POPLITEAL DISEASE

Aorto-iliac disease can be approached from the ipsilateral or contralateral common femoral arteries, or brachial and radial arteries. Rarely a retrograde approach from the popliteal artery can assist crossing superficial femoral artery occlusions which cannot be traversed antegrade [3] (Fig. 3). The retrograde popliteal approach requires access from above from the contralateral or antegrade common femoral artery, then turning the patient prone on the table and using ultrasound with a micro puncture needle to access the popliteal artery at or just above the knee joint. Small sheaths (4–5 French) provide access for a wire which can be snared from above once it traverses the occlusion. A wire that is exteriorized above and below and occlusion provides a rigid rail to assist pushing catheters and balloons through an occlusion (the “dental floss” technique).

A variety of systems are used to cross lesions including 0.035", 0.025", 0.018", and 0.014" diameter wires and balloons. Concerns of recoil of ostial lesions and dissections associated with occluded or calcified disease has led to the almost universal practice of primary stenting in iliac disease [17]. Balloon expandable stents offer greater radial force and a more precise deployment (especially useful in ostial locations), whereas nitinol self-expanding stents may useful in long tapered lesions. Covered stents are useful for life-threatening perforations of the iliac artery during endovascular treatment. Their value in preventing restenosis is uncertain [3], due to concerns of increased rates of stent thrombosis and the potential to jail and occlude branch vessels.

Common femoral disease often involves the profunda and SFA origins. Endovascular treatment alone can achieve durable results with acute dissection of the common femoral artery from arterial closure devices. Stents are avoided in this region due to the repeated flexion and extension of this artery and potential for stent fracture, as well as jailing the profunda artery — an important collateral

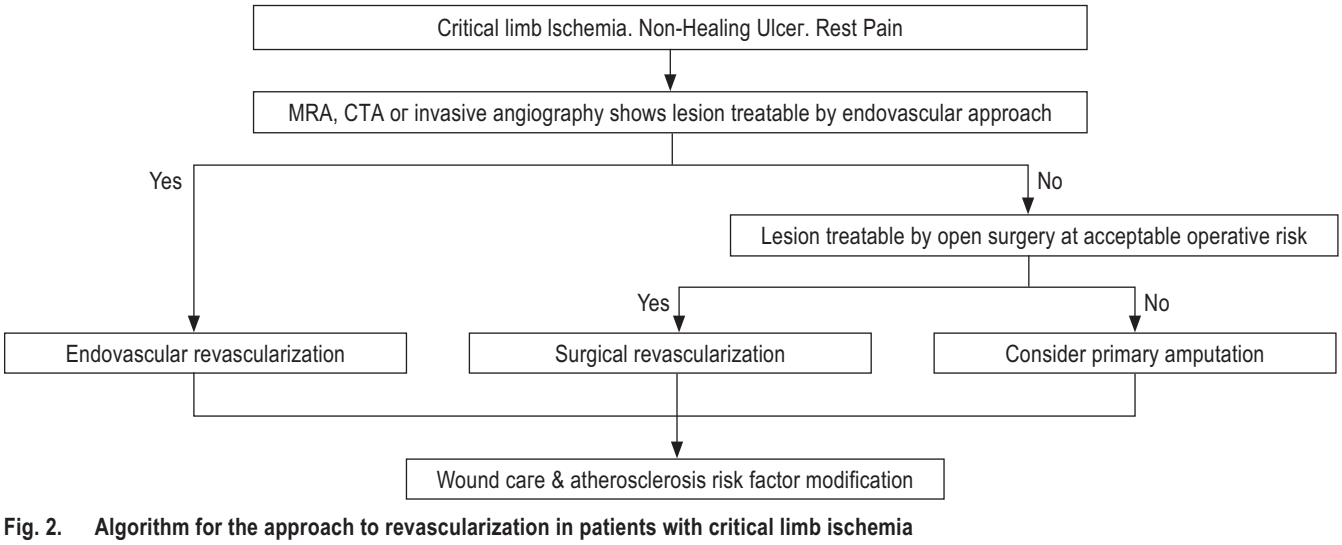

Fig. 2. Algorithm for the approach to revascularization in patients with critical limb ischemia

Рис. 2. Алгоритм подхода к реваскуляризации у больных с критической ишемией конечностей

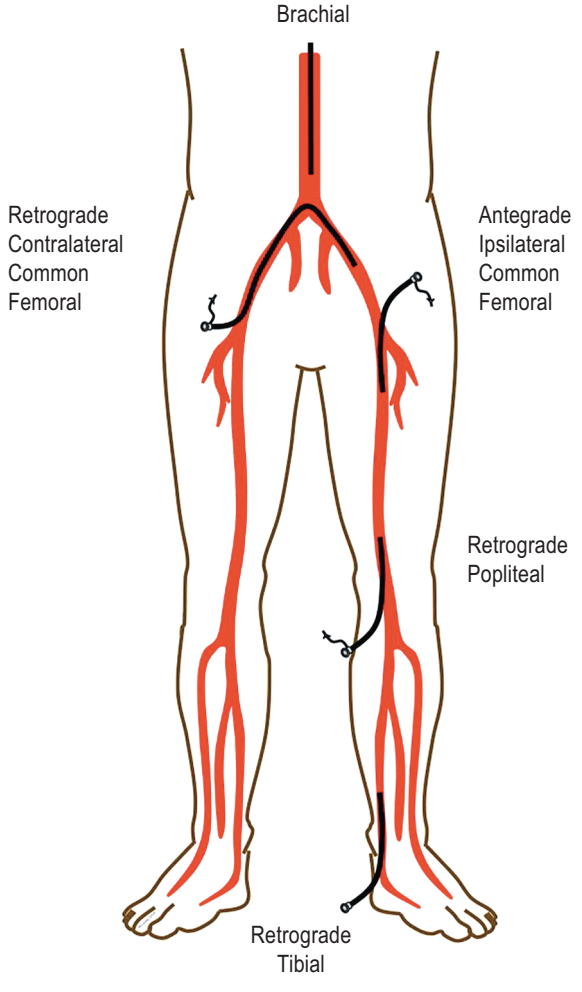

Fig. 3. Approach for arterial access for endovascular revascularization of the lower limbs

Рис. 3. Подход к артериальному доступу при эндоваскулярной реваскуляризации нижних конечностей

in the event of SFA occlusion [84–86, 91–93]. Preservation of both branches with balloon angioplasty alone can be difficult with complex calcified plaques, and often surgical endarterectomy with patch angioplasty offers a more durable result. Hybrid endovascular-surgical approaches using endovascular approaches for iliac or superficial femoral disease and endarterectomy for common femoral disease are increasingly used [18]. New developments in atherectomy and drug coated balloons have renewed interest in endovascular approaches for common femoral disease, although this paradigm needs formal testing in clinical trials.

The SFA is the longest artery in the leg and subject to flexion, compression and torsion. These forces are particularly important close to the knee and the common femoral artery. Balloon angioplasty offers similar results to stenting in short lesions (<100 mm) when there is good arterial expansion without flow limiting dissections [19]. Minor dissections often heal without long-term sequela. Nitinol self-expanding stents offer better long-term patency in longer lesions [20] and re-expand after external radial compression. Stent fracture is thought to increase instent restenosis, but is much rarer with the newer self-expanding stent platforms [20–23]. Recent drug-eluting stents designs offer a lower rate of restenosis compared to bare-metal self-expanding stents [24].

Drug-coated balloons offer lower rates of restenosis than balloon angioplasty alone in patients with SFA disease and claudication [25–27]. Drug-coated balloons also prevent restenosis when used prior to bare-metal stent deployment [28], and offer more durable treatment of instent restenosis of the femoral artery [29]. The evidence supporting drug-eluting stents and drug-coated balloons is much stronger than for covered-self expanding stents, which have uncertain effects on restenosis and stent thrombosis [30].

Chronic total occlusions of the SFA are common in symptomatic PAD [87–90]. A variety of techniques and devices for crossing total occlusions and re-entering the true lumen in the distal artery are available, but few have been tested in randomized trials. These include hydrophilic wires to dissect through the intima or the medial (“subintimal”) layers of the artery. Specialty catheters include those with dissection devices, vibrational energy, drilling heads, and laser capabilities to penetrate the fibrous cap and length of occluded plaque. Intravascular ultrasound can confirm an intraluminal location of a wire in an occlusion (Figure 4), and other devices to redirect a 0.014" wire from a dissection plane into the distal true lumen can facilitate crossing femoral artery occlusions. A number of atherectomy devices are also available to debulk lesions and may have utility in niche areas such as heavily calcified lesions resistant to balloon and stent dilation [3]. However, a meta-analysis suggested no clear benefit from using atherectomy devices alone compared to balloon angioplasty [31]. Recent interest in the use of atherectomy combined with drug-coated balloons requires further testing, particularly in areas where stents are avoided (over the knee and hip joints). Given the high risks of major amputation, stenting over the knee joint is sometimes required to maintain patency. A number of specialty stents with greater durability to repeated flexion are designed for the popliteal artery in particular [23].

TIBIAL DISEASE

There is rarely a justification for tibial interventions in claudication. However, wound healing and relief of CLTI is more dependent on establishing straight-line flow into the foot. Therefore below-knee popliteal and tibial artery interventions are more commonly pursued in CLTI.

Access is more limited for distal tibial disease as a contralateral common femoral approach or brachial approach are often too distant for most equipment based on 130–150 mm shaft lengths. An antegrade femoral approach also gives more “pushability” to drive through long occlusions. The retrograde tibial approach can be used for tibial and popliteal occlusions which cannot be crossed antegrade (Figure 3), but if unsuccessful may create a non-healing ulcer at the access site. The retrograde pedal

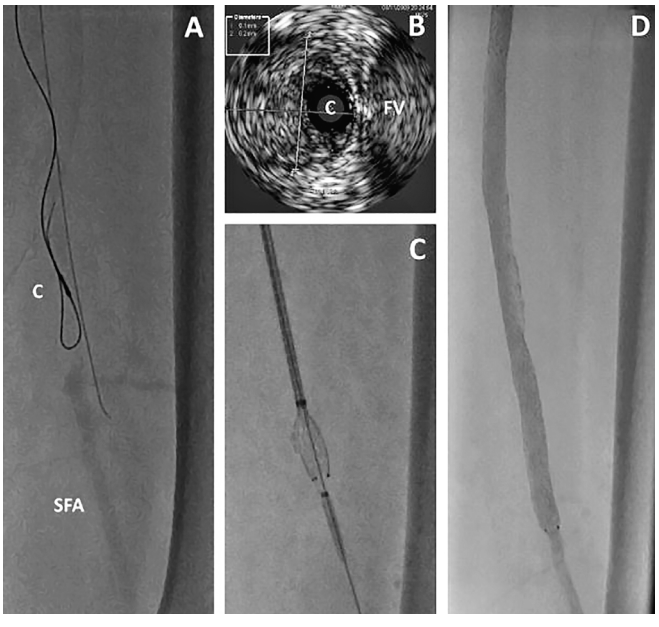

Fig. 4. **Intravascular ultrasound (IVUS) used to assess the intra-arterial location while traversing a long occlusion: A — the IVUS catheter (C) is seen over a looped wire in an occluded segment of the mid superficial femoral artery. An adjacent wire is extra-arterial. SFA indicates the distal superficial femoral artery beyond the occlusion; B — IVUS image showing the catheter (C) in the middle of the artery and adjacent to the femoral vein (FV). The diameter of the artery was 6.1×6.2 mm, which represents to media and intima and likely overestimates the reference lumen diameter; C — stent deployment after successfully traversing the occluded artery; D — final result on angiography**

Рис. 4. **Внутрисосудистое ультразвуковое исследование (ВСУЗИ) используется для оценки внутриартериального расположения при прохождении длительной окклюзии: А — катетер ВСУЗИ (С) виден через петлеобразную проволоку в окклюзированном сегменте средней поверхностной бедренной артерии. Прилегающий провод является внеартериальным. Поверхностная бедренная артерия (ПБА) указывает на дистальную поверхностную бедренную артерию за пределами окклюзии; В — изображение ВСУЗИ, показывающее катетер (С) в середине артерии, рядом с бедренной веной (БВ). Диаметр артерии составлял 6,1×6,2 мм, что соответствует среде и интиме и, вероятно, завышает эталонный диаметр просвета; С — раскрытие стента после успешного пересечения окклюзированной артерии; D — окончательный результат ангиографии**

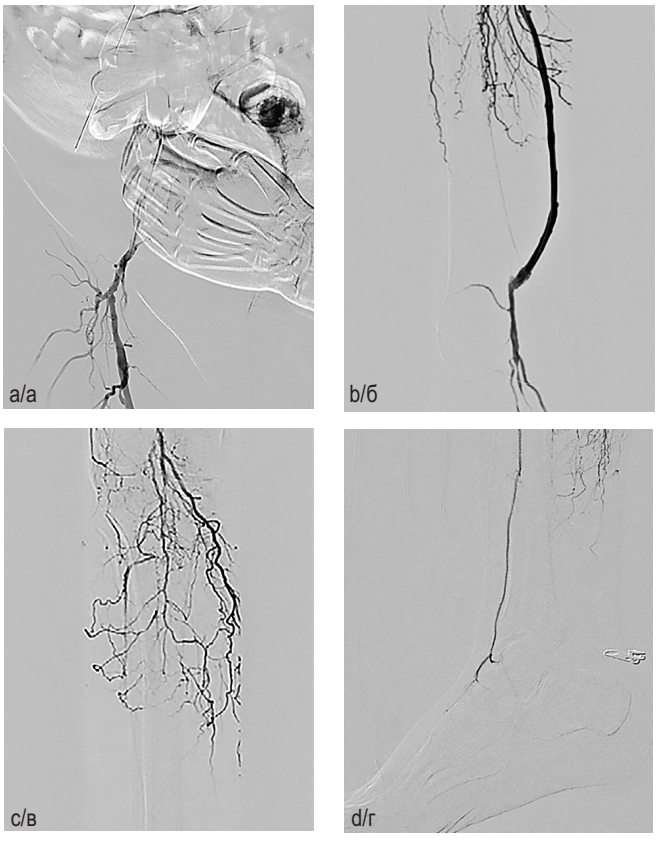

Fig. 5. **Antegrade femoral approach through CFA on the right side. Intraoperative angiography: a — CFA, DFA, proximal anastomosis DfPB; b — DfPB, distal anastomosis; c — blind segment of PopA; d — ATA, occlusion of the arteries of the leg**

Рис. 5. **Антеградный бедренный доступ через общую бедренную артерию (ОБА) справа. Интраоперационная ангиография: а — ОБА, глубокая бедренная артерия (ГБА), проксимальный анастомоз глубоко бедренно-подколенное шунтирование (ГбПШ); б — ГбПШ, дистальный анастомоз; в — слепой сегмент подколенной артерии (ПкА); г — передняя большеберцовая артерия (ПББА), окклюзия артерий голени**

or tibial artery approach uses ultrasound and a micropuncture needle for access and the dilator of the micropuncture kit or a small sheath for wire access. Access from above (e.g. antegrade femoral) allows a retrograde wire to be snared and exteriorized above and below the tibial or popliteal occlusion to provide a rigid rail to drive catheters and balloons through an occlusion (Fig. 5, 6, 7).

The value of angiosome directed revascularization versus restoring any straight-line flow into the foot is debated. The former assumes that revascularization of a tibial artery supplying the angiosome of the ulcer or gangrenous region (Fig. 8) is more likely to promote healing than non-angiosome revascularization which relies on increased collateral flow to an ischemic region. In observational studies, wound healing was greater and amputation lower with angiosome-directed compared to indirect (non-angiosome) tibial revascularization [32]. However, these observations may be confounded. Indirect revascularization, may be a marker for more complex tibial disease, which may be associated both with no option for angiosome directed revascularization and poorer limb salvage. In one study, changes in foot microcirculation assessed by skin perfusion pressure improved regardless of whether the angiosome related tibial artery or the non-angiosome related artery was revascularized [33]. Although it makes intuitive sense to use an angiosome directed treatment wherever possible, if this is not successful, any straight-line flow should be better than none.

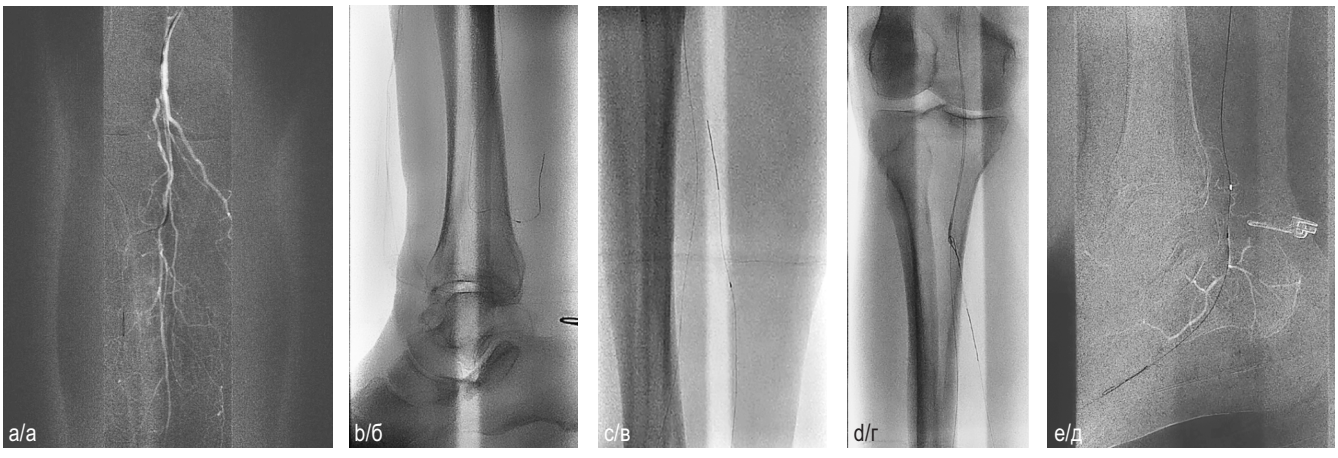

Fig. 6. **Stages of the operation: a — recanalization of the anterior tibial artery using a modified catheter; b — transcollateral recanalization of the posterior tibial artery through the communicating branch of the small tibial artery; c — retrograde recanalization of the posterior tibial artery; d — recanalization of the origin of the posterior tibial artery with counter conductors supported by a modified catheter; e — recanalization of the lateral plantar artery**

Рис. 6. **Этапы операции: а — реканализация передней большеберцовой артерии с использованием модифицированного катетера; б — трансколлатеральная реканализация задней большеберцовой артерии через коммуникантную ветвь малой берцовой артерии; в — ретроградная реканализация задней большеберцовой артерии; г — реканализация истока задней большеберцовой артерии встречными проводниками при поддержке модифицированного катетера; д — реканализация латеральной плантарной артерии**

Primary balloon angioplasty of tibial disease provides a good response in most situations. Long balloons are specifically designed to treat the often diffuse tibial disease with prolonged inflations. Stents are reserved for poor balloon results (re-occlusion, recoil to more than 50% stenosis, flow-limiting dissection). Tibial arteries are about 2.5–3.5 mm in diameter, and are usually treated with balloon expandable coronary stents with a spot-stenting philosophy. Proximal lesions are somewhat protected by the bulk of the calf muscle, but can theoretically be crushed by external compression. Stent crush is more likely with extensive stenting and stents in the distal calf. Poor outflow theoretically increases the risk of stent thrombosis and may reduce the enthusiasm for stenting. Randomized studies in tibial arteries show better patency and less need for reintervention with drug-eluting compared to bare-metal coronary stents [34–36], with one trial showing lower rates of amputation [35].

Compared to conventional balloon angioplasty, drug-coated balloons for tibial interventions provided promising results in early series and single center trials [37]. However, restenosis rates were higher than drug-eluting stents in one small trial [38], and the multicenter randomized IN.PACT DEEP study raised concerns because of a trend to more amputations in the drug-coated versus standard balloon angioplasty arms (8.8% versus 3.6%, p=0.08) [39]. Reasons for the lackluster results compared to femoral-popliteal disease include reduced drug delivery due to drug coating after balloon wrapping and poor drug-release characteristics. Further randomized trials will explore their value in tibial arteries.

Atherectomy in tibial arteries is of uncertain value beyond balloon angioplasty and stenting [31]. Long segment tibial atherectomy could cause embolization which decreases outflow and distal perfusion. One recent report showed greater acute success, but no difference in amputation, repeat revascularization or mortality with laser assisted versus conventional angioplasty [40].

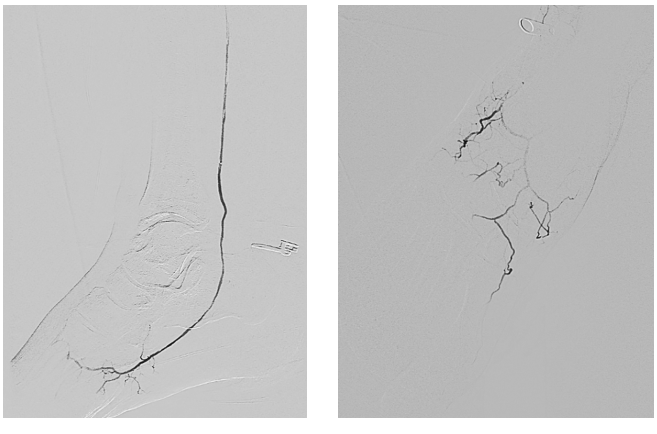

Fig. 7. **Control angiography — direct revascularization of the foot and trophic defects**

Рис. 7. **Контрольная ангиография — прямая реваскуляризация стопы и трофических дефектов**

Wire perforation of the tibial arteries is usually easily treatable by low-pressure balloon angioplasty, but larger perforations may require longer balloon inflations or covered stents to avoid a compartment syndrome which can cause ischemic muscle and nerve injury and threaten the viability of the lower limb.

OPEN SURGICAL REVASCULARIZATION

The goals of surgical revascularization are to provide straight-line flow into the foot, promote wound healing, and to

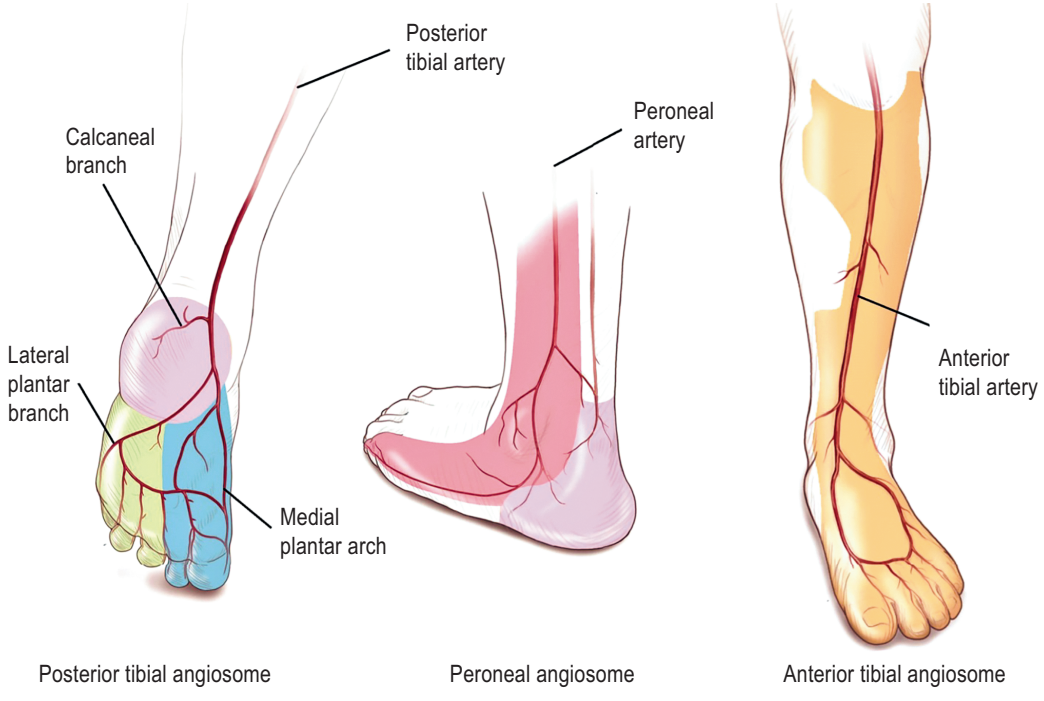

Fig. 8. Angiosomes of the below-the-knee lower extremity

Рис. 8. Ангиосомы нижней конечности ниже колена

limit the level of amputation. Open surgery has higher risks of peri-operative myocardial infarction, death and stroke than endovascular revascularization. However, in critical limb ischemia, the potential loss of limb and function may favor surgery when endovascular therapy is not possible or not successful and patients otherwise have a reasonable 2 year survival [18]. Risk scores can help risk-stratify CLTI patients having infrainguinal bypass surgery. For example, the PREVENT III risk score includes dialysis, tissue loss, age ≥75 years, and coronary artery disease [41]. A higher score associates with a lower risk of survival free from amputation. In addition to patient risk, assessment includes vein mapping of saphenous vein to determine available autogenous conduit. This is particularly important in patients who may have had vein harvested for coronary artery bypass in the past.

Multilevel disease is often treated with hybrid revascularization using endovascular techniques to treat inflow disease (e.g., iliac stenting), and surgical revascularization for femoral or infrainguinal disease (Figure 4) (e.g., common femoral endarterectomy, and femoral popliteal bypass) [18]. Rarely, occlusion of the distal aorta and iliac disease may require aorto-bifemoral bypass, contralateral femoral to femoral bypass [84–93], or axillary-femoral bypass [18] (Fig. 5, 6, 7).

Common femoral endarterectomy may extend into the proximal SFA or profunda artery. Closure is usually achieved with a bovine or synthetic patch to reduce restenosis, or sometimes with primary closure without a patch [18]. Complications include wound infection (particularly in obese patients), hematoma and lymph leak. This procedure offers a high long-term patency rate (>90%) and considered superior to endovascular treatment particularly for heavily calcified disease involving the SFA and profunda origins.

As with endovascular treatment, infrainguinal bypass relies on good inflow and outflow. The three types of saphenous vein bypass are reversed (translocated) vein, nonreversed vein, and in situ bypass where vein branches are ligated and the distal ends mobilized and anastomosed to the artery. The latter two configurations require excision of the valves with a valvulotome, which can sometimes injure the vein conduit. Observational studies suggest similar outcomes with all three configurations [18, 42]. Limb salvage and graft patency are best with good quality, long, single-segment, autogenous vein with a diameter of at least 3.5 mm [43–45]. In the PREVENT III trial, bypass grafts with these characteristics had a low 30day failure rate (less than 2%), and high secondary patency and limb salvage at one year (approximately 90%) [45].

In pooled analyses, autogenous saphenous vein provided better long-term patency than prosthetic grafts for above- and below-knee grafts [44, 46, 47]. Prosthetic grafts of heparin-bonded polytetrafluoroethylene may provide better outcomes than older prosthetic grafts [48] with comparable results to autologous vein in a one retrospective study [49]. Cryopreserved cadaveric vein has poorer long-term patency results [50].

AMPUTATION

Minor amputations such toe, ray (toe and metatarsal), or transmetatarsal amputations require an adequate blood supply into the foot to maximize healing and are usually part

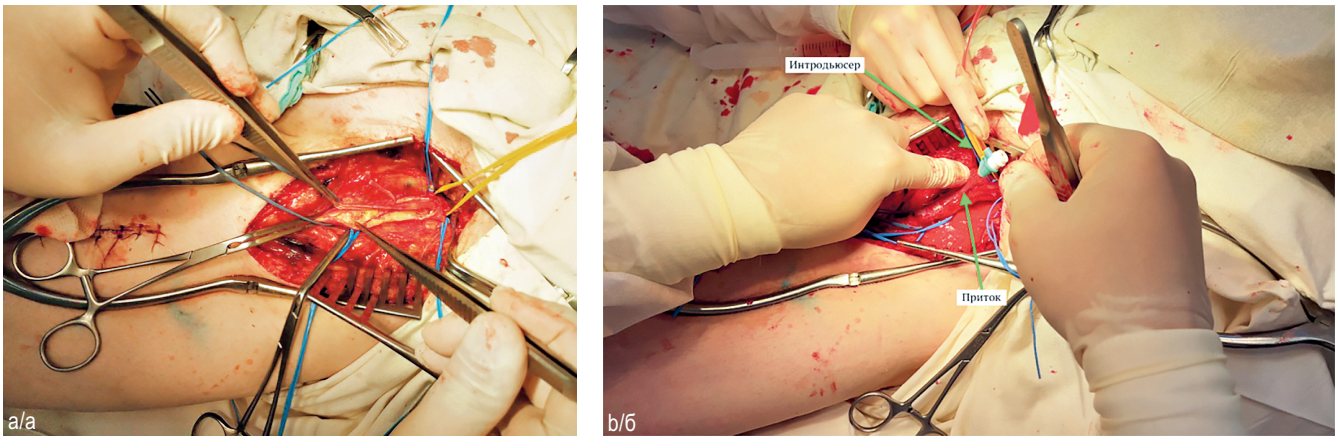

Fig. 9. **Endarterectomy from the CFA on the left side repair with an autovenous patch (a); insertion of the introducer/sheath into the inflow of the autovenous patch (b). An open endarterectomy was performed from the common femoral artery with autovenous patch repair. When the autovenous conduit is isolated, a large inflow is preserved, and an introducer is inserted**

Рис. 9. **Эндартерэктомия из ОБА слева с пластикой аутовенозной заплатой (а); заведение интродьюсера в приток аутовенозной заплаты (б). Выполнена открытая эндартерэктомия из общей бедренной артерии с пластикой аутовенозной заплатой. При выделении аутовенозного кондуита сохранен крупный приток, заведен интродьюсер**

of the treatment plan for gangrene or tissue loss after successful revascularization. Generally, minor amputation does not limit functional independence or require a prosthesis.

Major amputations (at or above the knee) limit functional independence and require a prosthesis to walk. Although preventing major amputation is a key goal, amputation may be indicated for failed revascularization, patients with extensive tissue loss or infection, patients unfit for surgical revascularization with no endovascular options, and potentially non-ambulating patients. Up to one third of below-knee amputations may require further surgery or an above-knee amputation due to poor healing [53]. A patent popliteal pulse reduces the failure rate of healing to less than 10%. More than 90% of above-knee amputations heal, but only about 20% of amputees regain full mobility with a prosthesis compared to 60% with a below-knee prosthesis [53, 54]. Factors related to poor prosthesis use and function after major amputation include increasing age, bilateral or above-knee amputations, dementia, and poor function prior to amputation [54].

WOUND CARE

Wound care principles include improving perfusion into the limb, treating infection, avoiding pressure on a wound, debridement, and adequate nutrition (Fig. 9, 10). Debridement of devitalized or infected tissue by scalpel, collagenases, or even maggots [55], promotes wound healing. Antibiotics may be required to treat infection to prevent osteomyelitis. Avoiding pressure on the wound (e.g., off-loading the foot) also assists wound healing [56]. The local temperature of the limb can be increased using sheepskin (Rooke) boots and may improve superficial collateral flow to help perfuse

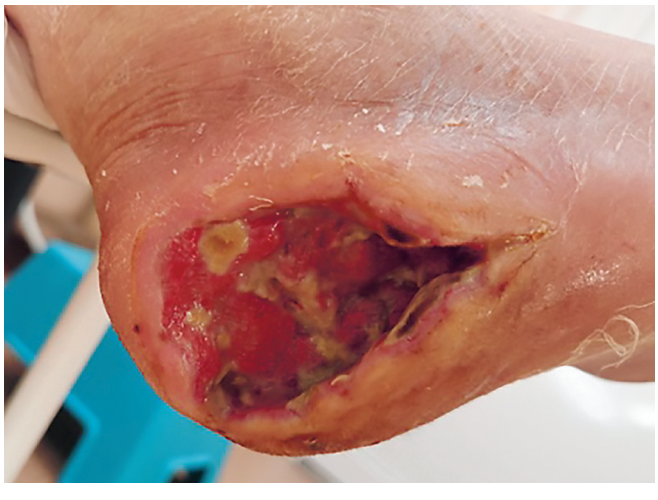

Fig. 10. ***St. localis*** **at the time of discharge. Actively granulating wound of the right heel area. On the third day after revascularization, a staged necrectomy of the trophic ulcer of the right calcaneal region was performed. Next two courses of NPWT therapy was done. The wound has cleaned up and is actively granulating. The patient was discharged for outpatient treatment on the 62nd day of hospitalization**

Рис. 10. ***St. localis*** **на момент выписки. Активно гранулирующая рана правой пяточной области. На третьи сутки после реваскуляризации выполнена этапная некрэктомия трофической язвы правой пяточной области. Далее два курса NPWT-терапии. Рана очистилась, активно гранулирует. Пациент выписан на амбулаторное лечение на 62-е сутки госпитализации.**

a limb [57]. Negative pressure dressings (e.g., vacuum-assisted) increase capillary flow and help drain wounds [58]. Hyperbaric oxygen therapy offers no advantages for am-

putation prevention, but may improve the more subjective endpoint of wound healing in diabetes [59].

In patients where there are no revascularization options, intermittent pneumatic compression may assist wound healing and prevent major amputation [54]. To date, cell-based therapies such as infusion of bone marrow derived mononuclear cells have not prevented major amputation in patients with no revascularization options [60].

MEDICAL THERAPY AND SURVEILLANCE AFTER REVASCULARIZATION

Failure of endovascular and surgical treatment of CLTI due to thrombosis, neointimal proliferation, or progression in atherosclerosis demands close surveillance of patients by providers with vascular expertise. Surveillance also includes intensively treating risk factors for atherosclerosis to reduce the high risk of cardiovascular events.

Recurrent ischemic pain in the leg, lack of progression in wound healing, or a decline in ABIs are indicators of restenosis or occlusion. Duplex ultrasound of bypass grafts is commonly practiced to identify graft stenoses for revision and preserve long-term patency. However, this practice was not associated with lower amputation or better patency in one randomized trial [61], and there are no randomized trials of its value after endovascular therapy. Our practice after endovascular therapy includes a history and exam, and to use duplex ultrasound in the femoral artery particularly after treating long segment disease or when symptoms or poor wound healing raise concerns of patency [62, 63].

Evidence for therapies to prevent thrombosis or restenosis after endovascular interventions is sparse and often extrapolated from studies of coronary artery interventions. Low-dose aspirin is usually given for life to prevent thrombosis of a treated segment, but also other cardiovascular events. The duration of clopidogrel to prevent occlusion of segments treated by endovascular techniques is uncertain. Most clinical trials of bare-metal stenting use dual-antiplatelet therapy for 1–3 months [19–21, 24], but data extrapolated from medical studies of patients with peripheral artery disease, could justify longer treatment [64]. Clinical studies from Japan suggest that cilostazol may reduce in-stent restenosis [65–67], but this is not yet incorporated in recent guidelines of revascularization for CLTI.

The value of anticoagulation for lower extremity bypass is conflicting with some trials showing benefit over aspirin for autogenous vein versus prosthetic conduit and vice-versa [18]. Given the increased risk of bleeding, most surgeons reserve anticoagulation for graft thrombosis, or hypercoagulable disorders. There is no benefit of adding clopidogrel to aspirin for graft patency [68].

Evidence for the value of intensive atherosclerosis risk factor reduction is derived largely from observational studies and subgroups of patients with PAD in clinical trials. For example, PAD patients who stop smoking have fewer cardiovascular events than those who continue smoking [69, 70, 84, 92, 93]. Antiplatelet therapy with aspirin [71, 72] or clopidogrel [73, 85], and angiotensin converting enzyme inhibitors [74] decrease cardiovascular events in patients with PAD. Intensive statin therapy consistently lowers cardiovascular events in PAD patients compared to no statin or low intensity statins [75–77]. In observational studies of patients receiving revascularization for PAD, statin therapy is associated with lower risks of cardiovascular events [63, 78–80], and limb loss [63,81,82, 84–93]. In population studies, intensive risk factor modification in patients with peripheral artery disease is improving, but still lags behind its use in patients with symptomatic coronary disease [83].

CONCLUSIONS

Patients with CLTI have a high risk of limb loss without revascularization and a high short term risk of cardiovascular events compared to less severe forms of chronic peripheral artery disease. Revascularization is indicated if it will prevent limb loss and preserve ambulation and function, while intensive medical therapy targets the risk factors for atherosclerosis progression and cardiovascular events. Endovascular revascularization offers a lower initial risk than open surgery, but recurrent disease from restenosis is common in patients with CLTI. New drug-eluting balloons and stents offer better longer-term outcomes after some endovascular revascularizations, but further long-term data on durability is required in order to assess their overall benefit given the increased costs of initial treatment. Close follow-up focusing on wound care and prevention, risk factor management, and surveillance for new and recurrent disease is required.

ADDITIONAL INFORMATION

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

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SARS CoV-2 PROTEINS AND HUMAN PROTEINS

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Abstract. SARS CoV-2 proteins are molecules with a mass of several tens to several thousand amino acid residues. There are structural and nonstructural proteins. The former include Spike glycoprotein (S), small membrane envelope protein (E), membrane protein (M), and nucleoprotein or nucleocapsid (N). The second group consists of 16 nonstructural proteins (Nsp1-16, including replicase polyproteins RPP 1a and 1ab) and 10 accessory factors or open reading frame proteins (ORF3a, 3b, 6, 7a, 7b, 8, 9b, 9c, 10 and 14). Proteins S, E and M, located outside and in the membrane of a virion, are involved in the contact of the virion with a cell and penetration into it. Other proteins are involved in the hijacking of intracellular mechanisms and their use in the virus's own interests. Most of these proteins contain numerous motifs that are homologous to human proteins including such important ones as Interleukin-7. Perhaps this homology is an important factor in deceiving the immune system at the initial stages of infection and provoking an autoimmune response later. The homology of SARS CoV-2 proteins on the one hand and taste and olfactory receptor proteins on the other hand may possibly explain the causes of the impaired perception of taste and olfactory stimuli characteristic of COVID infection.

Keywords: COVID-19, SARS CoV-2, protein homology, receptor-binding domain, interleukin-7, ACE2 receptor, congenital innunity, autoimmunity, sense of smell, sense of taste

БЕЛКИ SARS CoV-2 И БЕЛКИ ЧЕЛОВЕЧЕСКОГО ОРГАНИЗМА

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Резюме. Белки SARS CoV-2 представляют собой молекулы с массой от нескольких десятков до нескольких тысяч аминокислотных остатков. Существуют структурные и неструктурные белки. К первым относятся шиповый гликопротеин, или S-белок (S), малый мембранный оболочечный белок (E), мембранный белок (M) и нуклеопротеин или нуклеокапсид (N). Вторая группа состоит из 16 неструктурных белков (Nsp1-16, включая полипротеины репликазы RPP 1a и 1ab) и 10 вспомогательных факторов или белков открытой рамки считывания (ORF3a, 3b, 6, 7a, 7b, 8, 9b, 9c, 10 и 14). Белки S, E и M, расположенные снаружи и в мембране вириона, участвуют в контакте вириона с клеткой и проникновении в нее. Другие белки участвуют в захвате внутрикле-

точных механизмов и их использовании в собственных интересах вируса. Большинство этих белков содержат многочисленные мотивы, гомологичные человеческим белкам, в том числе таким важным, как интерлейкин-7. Возможно, эта гомология является важным фактором, позволяющим «обмануть» иммунную систему на начальных стадиях инфекции и спровоцировать аутоиммунный ответ впоследствии. Гомология белков SARS CoV-2, с одной стороны, и белков вкусовых и обонятельных рецепторов — с другой, возможно, объясняет причины нарушения восприятия вкусовых и обонятельных раздражителей, характерного для COVID-инфекции.

Ключевые слова: COVID-19, SARS CoV-2, гомология белка, рецептор-связывающий домен, интерлейкин-7, рецептор ACE2, врожденный иммунитет, аутоиммунитет, обоняние, вкус

INTRODUCTION

Why is the new SARS CoV-2 coronavirus so infectious? Why many cases of COVID-19 infection are so severe? Why many patients are reported with complete loss of smell and taste? Answers to these questions should be received as soon as possible. The COVID-19 pandemic, which has plagued humanity for almost two years now, does not allow us to follow the usual course of encyclopedia authors: wait, carefully sift through ideas and facts, and wait for new ones to come. In this case (which should not become a precedent), one has to pay attention not only to firmly established experimental data, but also to some *hypotheses*.

The study of the proteome of the original ("canonical" or Wuhan) variant of SARS CoV-2 proceeds in two directions. Using 3D models, the researchers can determine how the spike protein binds to the ACE2 receptor [1]. This knowledge will help in creating binding blockers.

The alignment method compares the primary structures of millions of proteins [2]. The method allows you to detect the homology of SARS CoV-2 proteins with proteins of humans and other organisms [3]. Probably, the information on homology makes it possible to understand the mechanisms of the virus bypassing the innate immunity system (evasion) at the early stages of the development of the infectious process and the process of provoking an autoimmune response at later stages.

The issue of mutations in SARS CoV-2, and especially of its S protein, is becoming increasingly important. With the help of mutations, the virus "learns" to avoid immune responses [4].

Table 1

SARS CoV-2 proteins: structural and nonstructural

Group	Proteins
Structural	Spike glycoprotein, S Envelope small membrane protein, E Membrane protein, M Nucleoprotein, N
Nonstructural	ORF3a, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF10, ORF14, RPP 1a, RPP 1ab

ORF, open reading frame. RPP, Replicase polyprotein.

SARS CoV-2 proteins vary significantly in length — from several tens to several thousands amino acid residues. They are traditionally divided into *structural* and *nonstructural* (Table 1).

STRUCTURAL PROTEINS

Spike glycoprotein

Spike (S) protein molecule consists of 1273 amino acid residues:

MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDK
VFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDN
PVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNA
TNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSS
ANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFK
IYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLALH
RSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTI
TDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESI
VRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSV
LYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVR
QIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGN
YNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCY
FPLQSYGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKK
STNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDI
ADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVL
YQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLI
GAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSI
IAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMTKTS
VDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQD
KNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPSKPSKRS
FIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICAQKFNG
LTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPF
AMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLS
STASALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLND
ILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRAS
ANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGV
VFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFVSNGT
HWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPL
QPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKE
IDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAG
LIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEP
VLKGVKLHYT

Table 2

SARS CoV-2 S protein domains

Subunit	Positions	Domain
S1	1-13	Signal peptide (N-terminus)
	14-305	N-terminus domain (NTD)
	306-318	Uncharacterized fragment
	319-541	Receptor-binding domain (RBD)
	542-787	Uncharacterized fragment
S2	788-806	Fusion peptide (FP)
	807-911	Uncharacterized fragment
	912-984	Heptapeptide repeat sequence 1 (HR1)
	985-1162	Uncharacterized fragment
	1163-1213	Heptapeptide repeat sequence 2 (HR2)
	1214-1237	Transmembrane tail (TM)
	1238-1273	Cytoplasm tail (CT)

See Table 2 for color code. Receptor-binding motif (RBM) S_{438} — Y_{508} underlined. Hereinafter, the primary structures of SARS CoV-2 proteins are given according to Uniprot database [5].

S protein molecule consists of subunits and domains (Table 2).

The Receptor-binding domain (RBD) continues to be of great interest to the researchers. RBD boundaries are estimated differently by different authors, namely: R_{319} — F_{541} (refs. see [3]) or T_{333} — T_{523} [1]. Within this region, the Receptor-binding motif ($RBM_{438-508}$) and amino acid residues N_{439}, L_{452}, T_{47K}, E_{484}, Q_{498}, and N_{501} are considered critical for binding affinity [6]:

SNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGS
TPCNGVEGFNCYFPLQSYGFQPTNGVGYQPY.

At the border between subunits S1 and S2, the S protein molecule forms a loop. The authors believe that the loop is a key component in determining virus stability and transmission [7].

There are more than two dozen hepta- and octamers homologous to human proteins in the S protein molecule. Localization of these n-mers is shown in the Table 3.

Of all the regions listed in Table 3 that are homologous to human proteins, only two, $KLNDLCF_{386-392}$ and $DEVRQIA_{405-411}$, are located in RBD and none are located in RBM.

Table 3 shows that heptamer $KLNDLCF_{386-392}$ is homologous to motif in the interleukin 7 ($IL\text{-}7_{149-155}$) molecule. In severe cases of COVID-19 patients have increased level of IL-7 [8, 9], which is highly associated with disease severity

Table 3

Localization of homologous hepta- / octamers in the S protein and human proteins

Subunit	SARS CoV-2 S protein domain	In S protein	In human proteins
S1	Signal peptide $(N\text{-terminus})_{1-13}$	none	–
	N-terminus domain NTD_{14-305}	$DKVFRSS_{40-46}$	Zinc finger protein $528_{275-281}$
		$FLPFFSN_{55-61}$	OTU domain-containing protein $6A_{185-191}$
		$VSGTNGT_{70-76}$	Lysosome-associated membrane glycoprotein $1_{171-177}$
		$SLLIVNN_{116-122}$	ATP-binding cassette sub-family A member $10_{825-831}$
		$FKNLREF_{186-192}$	Isovaleryl-CoA dehydrogenase, $mitochondrial_{77-83}$
		$TRFQTLL_{236-242}$	Disheveled-associated activator of morphogenesis $2_{251-257}$
		$KIYSKHT_{202-208}$	Uncharacterized protein $C1orf105_{7-13}$
		$SSSGWTA_{254-260}$	Uncharacterized protein KIAA1109 $(Fragment)_{610-616}$
	Uncharacterized $fragment_{306-318}$	none	–
	Receptor-binding domain $RBD_{319-541}$	$KLNDLCF_{386-392}$	Interleukin-$7_{149-155}$
		$DEVRQIA_{405-411}$	Histone-lysine N-methyltransferase $2C_{4530-4536}$
	Uncharacterized $fragment_{542-787}$	$VYSTGSN_{635-641}$	Neural cell adhesion molecule L1-like $protein_{341-347}$
		$IGAGICA_{666-672}$	Hepatitis A virus cellular receptor $2_{205-211}$
		$SPRRARS_{680-686}$	Hermansky-Pudlak syndrome 1 $protein_{258-264}$
		$RRARSVAS_{682-689}$	Amiloride-sensitive sodium channel subunit $alpha_{201-208}$
S2	Fusion peptide $FP_{788-806}$	none	–
	Uncharacterized $fragment_{807-911}$	$VTLADAG_{826-832}$	Non-receptor tyrosine-protein kinase $TNK1_{440-446}$
		$GLTVLPP_{857-863}$	FH1/FH2 domain-containing protein $3_{972-978}$

Ending of the Table 3

Subunit	SARS CoV-2 S protein domain	In S protein	In human proteins
		$LPPLLTD_{861-867}$	Maestro heat-like repeat-containing protein family member $9_{250-256}$
	Heptapeptide repeat sequence 1 $HR1_{912-984}$	$SSTASAL_{939-945}$	40S ribosomal protein $S13_{143-149}$
		$LVKQLSS_{962-968}$	E3 SUMO-protein ligase $PIAS1_{284-290}$
	Uncharacterized $fragment_{985-1162}$	$KVEAEVQ_{986-974}$	$Emilin\text{-}3_{625-631}$
		$TGRLQSL_{998-1004}$	Neuron navigator $3_{1610-1616}$
		$LIRAAEI_{1012-1018}$	Unconventional myosin-$XVIIIa_{1352-1358}$; SP-A receptor subunit SP-R210 $alphaS_{894-900}$
		$LDKYFKN_{1152-1158}$	Follistatin-related protein $1_{149-155}$
	Heptapeptide repeat sequence 2 $HR2_{1163-1213}$	$NASVVNI_{1173-1179}$	Thyroid adenoma-associated $protein_{1022-1028}$
		$EIDRLNE_{1182-1188}$	Protein $SETSIP_{64-70}$; Protein SET_{54-60}
	Transmembrane tail $TM_{1214-1237}$	none	–
	Cytoplasm tail $CT_{1238-1273}$	$DEDDSEPV_{1257-1264}$	Unconventional myosin-$XVI_{1404-1421}$

[3, adapted]. Hereinafter, the primary structures of human proteins are given according to Uniprot database — Homo sapiens [5].

Table 4

Localization of homologous hepta- / octamers in the transmembrane $domain_{8-38}$ E protein and human proteins [3, adapted]

In E protein	In human proteins
$VNSVLLF_{14-20}$	Heterogeneous nuclear ribonucleoprotein $L_{191-197}$
$VNSVLLFL_{14-21}$	Ran-binding protein $6_{409-416}$
$NSVLLFL_{15-21}$	Lysosomal amino acid transporter 1 $homolog_{133-139}$
$SVLLFLA_{16-22}$	Cytochrome P450 $2B6_{4-10}$; Cytochrome P450 $2B7_{4-10}$; GPI ethanolamine phosphate transferase 3_{5-11}
$LAFVVFL_{21-27}$	Solute carrier family 15 member $4_{235-241}$
$VFLLVTL_{25-31}$	Alpha-(1,3)-fucosyltransferase 10_{20-26}
$LAILTAL_{31-37}$	Transient receptor potential cation channel subfamily M member $6_{394-400}$; Transient receptor potential cation channel subfamily M member $3_{465-471}$
$TALRLCA_{35-41}$ [b]	Protein disulfide-isomerase $TMX3_{8-14}$

Heptamer $TALRLCA_{35-41}$ is located at the junction of the transmembrane $domain_{8-38}$ and internal domain 39-75.

[10]. IL-7 administered to critically ill COVID-19 patients has been associated with a return of lymphocytes to normal levels [11]. As a vaccine adjuvant, IL-7 could enhance the immune responses to vaccines against SARS CoV-2 [12]. IL-7 is beneficial cytokine to the pathophysiology of COVID-19 [13]. At the same time, IL-7 induces SARS CoV-2 receptor ACE2 expression in human vascular endothelial cells [14]. In patients with COVID-19, respiratory failure is associated with an increase in systemic blood pressure, probably due to modulation of the renin-angiotensin-aldosterone system by SARS-CoV-2 infection [15].

Heptamer $DEVRQIA_{405-411}$ is homologous to motif in the Histone-lysine N-methyltransferase 2C (HLNMT $2C_{4530-4536}$). Histone methylation plays an important role in such a critical process as the epigenetic regulation of genes [16].

Presumably, IL-7 is an outpost defense trigger. When cell destruction begins in COVID-19, IL-7 turns on the last reserve of life, activating immunological memory cells. SARS CoV-2 tricks the immune system into presenting a motif homologous to IL-7.

S protein is involved in the organization of virion assembly in the intermediate compartment ER-Golgi [17].The C-terminal truncation of the protein S molecule results in a variant that easily passes through the Golgi complex to the plasma membrane in a pre-activated conformation, causing increased syncytium formation [18].

Envelope small membrane protein

Envelope small membrane (E) protein is the shortest (75 amino acid residues) of all SARS CoV-2 structural proteins.

MYSFVSEETGTLIV**NSVLLFLAFVVFLLVTLAILTALRLCA**
YCCNIVNVSLVKPSFYVYSRVKNLNSSRVPDLLV

Transmembrane $domain_{8-38}$ is underlined. Hereinafter, n-mers homologous to human proteins are highlighted in red.

Only a small part of it, namely heptamer $M_1 – Y_6$, protrudes from the virion outwards.

E protein contains eight hepta- / octamer homologous to human proteins (Table 4).

Homologous n-mers merge into a single 2octamer, which is almost entirely located in the thickness of the envelope of the virion. A random selection of 28 letters in a word would require an astronomical number of iterations: $20^{28} = 2.7 \cdot 10^{36}$. (This number is slightly less than the mass of the Earth, measured in nanograms.)

The degree of homology within this 28-measure can be represented as follows:

VN**SVLLFLA**FVVFLLVT**L**AIL**TAL**RLCA,

where the size of the letters corresponds to the frequency of the viral hepta- / octamers in the human proteome.

Besides, the protein E transmembrane domain contains an octamer and a heptamer, homologous to the proteins of some gut bacteria *Lactobacillus sp.* and even cereals, including corn *Zea mays*, sorghum *Sorghum bicolor*, wheat *Triticum aestivum*, and barley *Hordeum vulgare* (Table 5).

Table 5

Localization of some of homologous n-mers in the E protein and human gut proteome [3]

In E protein	In bacterial and plant proteins
AFVVFLLV$_{22-29}$	Lpp126 large-conductance mechanosensitive channel: Lactobacillus casei$_{80-87}$; L. paracasei$_{80-87}$; L. florum$_{80-87}$
TLAILTA$_{30-36}$	Uncharacterized proteins: Zea mays$_{90-164}$; Sorghum bicolor$_{97-127}$; Triticum aestivum$_{116-190}$; Hordeum vulgare$_{87-161}$

E protein is integrated into the human cell membrane; later it is transported closer to the endoplasmic reticulum and the Golgi apparatus, where viral replication occurs [19]. E protein can affect the properties of S proteins and contribute to the assembly of viral particles [20].

Membrane protein

Membrane (M) protein consists of 222 amino acid residues, and its structure contains six heptamers homologous to human proteins (Table 6).

MADSNGTIT**VEELKKLLEQ**WNLVIGFLFLTWICLLQFAYAN RNRFLYIIKLIFLWLLWPVTLACFVLAAVYRINWITGGIAIAMACLV GLMWLSYFIASFRLFARTRSMWSFNPETNILLNVPLHGTILTRP **LLESELV**IGAVILRGHLRIAGHHLGRCDIKDLPKEITVATSRTLSY YKLGASQRV**AGDSGFA**AYSRYRIGNYKLNTDHSSSSDNIALLVQ

Four heptamers are located close to the N-terminus of the molecule, merging into a single decamer $V_{10} – Q_{19}$. Taking into account the number of homologous amino acid residues, this decamer can be represented as follows:

VEELKKLLEQ.

Table 6

Localization of homologous heptamers in the M protein and human proteins [3]

7bIn M protein	In human proteins
VEELKKL$_{10-16}$	Glutaredoxin-related protein 5, mitochondrial$_{135-141}$
EELKKLL$_{11-17}$	GDP-fucose protein O-fucosyltransferase 2$_{340-346}$
ELKKLLE$_{12-18}$	Cullin-1$_{335-341}$
LKKLLEQ$_{13-19}$	Filamin-A-interacting protein 1$_{211-217}$
LLESELV$_{133-139}$	Leucine-rich repeat-containing protein 71$_{439-445}$
AGDSGFA$_{188-194}$	Myosin-14$_{359-365}$

Outside of the decamer, there are two homologous heptamers. Protein M is a candidate for participation in mimicry processes.

Like E protein, M protein can affect the properties of S proteins and contribute to the assembly of viral particles [20].

S, E, and M proteins cause Golgi fragmentation; disruption of the Golgi apparatus appears to be a critical component of SARS CoV-2 replication [21].

Nucleoprotein

The nucleoprotein (N-protein) consists of 419 amino acid residues and contains eleven heptamers homologous to human proteins (Table 7).

MSDNGPQNQRNAPRITFGGPSDSTGSNQNGERSGARSKQR **RPQGLPN**NTASWFTALTQHGKEDLKFP**RGQGVPI**NT**NSSPDDQ** IGYYRRATRRIRGGD**GKMKDLS**PRWYFYYLGTGPEAGLPYGA NKDGIIWVATEGALNTPKDHIGTRNPANNAAI**VLQLPQG**TTLPK GFY**AEGSRGGSQA**SSRSSSRSRNSSRNSTPGSSRGTSPARM AGNGGDAALALLLLDRLNQLESKMSGKGQQQQGQTVTKKSAA EASKKPRQKRTATKAYNVTQAFGRRGPEQTQGNFGDQELIRQ GTDYKHWPQIAQFAPSASAFFGMSRIGMEVTPSGTWLTYTGAI KLDDKDPNFKDQVILLNKHIDAYKTFPPTEPKKDKKK**KADETQA** LPQRQKKQQTVT**LLPAADL**DDF**SKQLQQSMSSADS**TQA

Some of the heptamers fuse into several rather long fragments, including the decamer $A_{173} – A_{182}$, and 13-mer $S_{404} – S_{416}$. It increases the likelihood of the protein involvement in provoking an autoimmune response. Protein N is located completely inside the SARS CoV-2 virion and cannot participate in mimicry, but can be involved in provoking an autoimmune response.

In comparison with SARS-CoV, SARS-CoV-2 contains six times more acetyl-lysine residues. This suggests that acetylation of N proteins plays crucial roles in SARS-CoV-2 functions [22].

NONSTRUCTURAL PROTEINS

All nonstructural proteins of SARS CoV-2 (ORF3a, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF10, ORF14,

Table 7

Localization of homologous heptamers in the N protein and human proteins [3]

In N protein	In human proteins
$RPQGLPN_{41-47}$	GATOR complex protein $WDR59_{757-763}$
$RGQGVPI_{68-74}$	Putative uncharacterized protein encoded by $LINC00346_{154-160}$
$NSSPDDQ_{77-83}$	NEDD4-binding protein $2_{154-160}$
$GKMKDLS_{99-105}$	Chromodomain-helicase-DNA-binding protein 1-$like_{770-776}$
$VLQLPQG_{157-163}$	$Prestin_{92-98}$
$AEGSRGG_{173-179}$	snRNA-activating protein complex $subunit3_{2-8}$
$SRGGSQA_{176-182}$	Ras-associating and dilute domain-containing $protein_{886-892}$
$KADETQA_{375-381}$	$Myopalladin_{90-96}$
$LLPAADL_{394-400}$	Probable E3 ubiquitin-protein ligase $HERC1_{1098-1104}$
$SKQLQQS_{404-410}$	$Codanin\text{-}1_{259-265}$
$SMSSADS_{410-416}$	Protein $PRRC2B_{416-422}$

RPP 1a, and RPP 1ab) are located completely inside the SARS CoV-2 virion and, by definition, cannot be involved in the process of mimicry. What remains to consider the possibility of their implication in provoking an autoimmune process [3].

ORF3a protein

ORF3a protein molecule consists of 275 amino acid residues:

MDLFMRIFTIGTVTLKQGEIKDATPSDFVRATATIPIQASLPFG
WLI**VGVALLA**VFQSASKIITLKKRWQLALSKGVHFVCNLLLLF
VTVYSHL**LLVAAGL**EAPFLYLYALVYFLQSINFVRIIMRLWLCW
KCRSKNPLLYDANYFLCWHTNCYDYCIPYN**SVTSSIV**ITSGDG
TTSPISEHDYQIGGYTEKWESGVKDCVVLHSYFTSDYYQLYS
TQLSTDTGVEHVTFFIYNKIVDEPEEHVQIHTIDGSSGVVNPVME
PIYDEPTTTTSVPL

In the ORF3a protein molecule, there are five heptamers homologous to human proteins (Table 8).

Table 8

Localization of homologous heptamers in the ORF3a protein and human proteins [3]

In ORF3a protein	In human proteins
$VGVALLA_{48-54}$	Manganese-transporting ATPase $13A1_{876-882}$
$LLVAAGL_{95-101}$	Glycerophosphoinositol inositolphosphodiesterase $GDPD2_{129-135}$
$KCRSKNP_{132-138}$	Vacuolar protein sorting-associated protein $13A_{2066-2972}$
$SVTSSIV_{162-168}$	Protein $piccolo_{2779-2785}$
$TQLSTDT_{217-223}$	$Septin\text{-}14_{418-424}$

The heptamers scattered along the entire length of its molecule do not form long n-mers anywhere else. ORF3a does not appear to be involved in provoking an autoimmune response.

ORF6 protein

ORF6 protein molecule consists of 61 amino acid residues:

MFHLVDFQVTIAEILLIIMRTFKVSIWNLDYIINLIIKNLSKSLTENKY
SQLDEEQPMEID

In the molecule, there is no heptamers homologous to human proteins.

ORF7a protein

ORF7a protein molecule consists of 121 amino acid residues:

MKIILFLALITLATCELYHYQECVRGTTVLLKEPCSSGTYEGNSPF
HPLADNKFALTCFSTQFAFACPDGVKHVYQLRARSVSPKLFIRQ
EEVQELYSPIFLI**VAAIVFI**TLC**FTLKRKT**E

In the ORF7a protein molecule, there are only two heptamers homologous to human proteins located in close proximity to each other (Table 9).

Table 9

Localization of homologous heptamers in the ORF7a protein and human proteins [3]

In ORF7a protein	In human proteins
$VAAIVFI_{104-110}$	Transmembrane protein $255B_{86-92}$
$FTLKRKT_{114-120}$	Cytosolic 5'-nucleotidase $3A_{36-42}$

It is possible that ORF7a is involved in provoking an autoimmune response.

ORF7b protein

ORF7b protein molecule consists of 43 amino acid residues:

MIELSLIDFYLCFLAFLLFLVLIML**IIFWFSL**ELQDHNETCHA

In this polypeptide, there are only one heptamer homologous to the human protein (Table 10).

Table 10

Localization of the homologous heptamer in ORF7b and a human protein [3]

In ORF7b protein	In human protein
$IIFWFSL_{26-32}$	Olfactory receptor $7D4_{151-157}$

The ORF7b protein may be involved in provoking an autoimmune response and, in particular, contribute to olfactory dysfunction.

ORF8 protein

ORF8 protein molecule consists of 121 amino acid residues:

MKF**LVFLGIITTV**AAFHQECSLQSCTQHQPYVVDDPCPIHFYSK
WYIRVGARKSAPLIELCVDEAGSKSPIQYIDIGNYTVSCLPFTINC
QEP**KLGSLVV**RCSFYEDFLEYHDVRVVLDFI

Table 11

Localization of homologous heptamers in the ORF8 protein and human proteins [3]

In ORF8 protein	In human proteins
$LVFLGII_{4-10}$	Zinc finger protein 486_{49-55}
$LGIITTV_{7-13}$	D-2-hydroxyglutarate dehydrogenase, mitochondrial$_{262-268}$
$KLGSLVV_{94-100}$	Sodium leak channel non-selective protein$_{505-511}$

In this polypeptide, there are three heptamers homologous to human proteins (Table 11).

In this case, two heptamers merge into a decamer $L_4 – V_{13}$. Due to the fusion of two heptamers into a decamer $L_4 – V_{13}$, the ORF8 can be involved in provoking an autoimmune response.

ORF9b protein

ORF9b protein molecule consists of 97 amino acid residues:

MDPKISEMHPALR**LVDPQIQL**AVTR**MENAVGR**DQNNVGP
KVYPIILR**LGSPLSLN**MARKTLNSLEDKAFQLTPIAVQMTKLAT
TEELPDEFVVVTVK

Table 12

Localization some of homologous hepta- / octamers in ORF9b protein and human proteins [3]

In ORF9b protein	In human proteins
$LVDPQIQL_{14-21}$	Valine-tRNA ligase, mitochondrial$_{996-1002}$
$MENAVGR_{26-32}$	Neprilysin$_{419-425}$
$LGSPLSL_{48-54}$	Stress-responsive DNAJB4-interacting membrane protein 1_{37-43}
$GSPLSLN_{49-55}$	E3 ubiquitin-protein ligase $HERC2_{4533-4539}$
$TEELPDE_{84-90}$	KH homology domain-containing protein $4_{465-471}$
$ELPDEFVV_{86-93}$	Maestro heat-like repeat-containing protein family member $2B_{103-110}$

In the ORF9b protein molecule, there are six hepta- / octamers, homologous to human proteins (Table 12).

Some of these hepta- / octamers merge into octamer $L_{48} – N_{55}$ and decamer $T_{84} – V_{93}$.

Octamer $ELPDEFVV_{86-93}$ is homologous to the Maestro heat-like repeat-containing protein family member 2B, which may play a role in the sperm capacitation [23]. Male reproductive dysfunction has been proposed as a likely consequence of COVID-19 [24].

After the destruction of the SARS CoV-2 virion, ORF9b can take part in provoking an autoimmune response. This protein plays a special role in hijacking mitochondrial metabolic processes in COVID-19 infection [25].

ORF10 protein

ORF10 protein (traditional name, but more correctly: polypeptide) molecule consists of 38 amino acid residues:

MGYINVFAIPFTIYSLLLCRMNSRSYTAQVGIVNFNLT

In the molecule, there is no heptamers homologous to human proteins.

ORF14 protein

ORF14 protein (synonym: ORF9c) molecule consists of 73 amino acid residues:

MLQSCYNFLKEQHCQKASTQKGAEAAVKPLLVPHHVVATVQEI
QLQAAVGELLLLEWLAMAVMLLLLCCCLTD

In the molecule, there is no heptamers homologous to human proteins.

Replicase polyprotein RPP 1a

Replicase polyprotein 1a (RPP 1a) consists of 4405 amino acid residues.

MESLVPGFNEKTHVQLSLPVLQVRDVLVRGFGDSVEEVLSEARQHLKDGTCGL
VEVEKGVLPQLEQPYVFIKRSDARTAPHGHVMVELVAELEGIQYGRSGETLGVL
VPHVGEIPVAYRKVLLRKNGNKGAGGHSYGADLKSFDLGDELGTDPYEDFQEN
WNTKHSSGVTRELMRELNGGAYTRYVDNNFCGPDGYPLECIKDLLARAGKASCT
LSEQLDFIDTKRGVYCCREHEHEIAWYTERSEKSYELQTPFEIKLAKKFDTFN
GECPNFVFPLNSIIKTIQPRVEKKKLDGFMGRIRSVYPVASPNECNQMCLSTLM
KCDHCGETSWQTGDFVKATCEFCGTENLTKEGATTCGYLPQNAVVKIYCPACH
NSEVGPEHSLAEYHNESGLKTILRKGGRTIAFGGCVFSYVGCHNKCAYWVPRA
SANIGCNHTGVVGEGSEGLNDNLLEILQKEKVNINIVGDFKLNEEIAIILASFSAS
TSAFVETVKGLDYKAFKQIVESCGNFKVTKGKAKKGAWNIGEQKSILSPLYAFA
SEAARVVRSIFSRTLETAQNSVRVLQKAAITILDGISQYSLRLIDAMMFTSDLATN
NLVVMAYITGGVVQLTSQWLTNIFGTVYEKLKPVLDWLEEKFKEGVEFLRDGW
EIVKFISTCACEIVGGQIVTCAKEIKESVQTFFKLVNKFLALCADSIIIGGAKLKAL
NLGETFVTHSKGLYRKCVKSREETGLLMPLKAPKEIIFLEGETLPTEVLTEEVVLKT
GDLQPLEQPTSEAVEAPLVGTPVCINGLMLLEIKDTEKYCALAPNMMVTNNTFT
LKGGAPTKVTFGDDTVIEVQGYKSVNITFELDERIDKVLNEKCSAYTVELGTEVN
EFACVVADAVIKTLQPVSELLTPLGIDLDEWSMATYYLFDESGEFKLASHMYCS
FYPPDEDEEEGDCEEEEFEPSTQYEYGTEDDYQGKPLEFGATSAALQPEEEQE
EDWLDDDSQQTVGQQDGSEDNQTTTIQTIVEVQPQLEMELTPVVQTIEVNSFSG
YLKLTDNVYIKNADIVEEAKKVKPTVVVNAANVYLKHGGGVAGALNKATNNAM
QVESDDYIATNGPLKVGGSCVLSGHNLAKHCLHVVGPNVNKGEDIQLLKSAYE
NFNQHEVLLAPLLSAGIFGADPIHSLRVCVDTVRTNVYLAVFDKNLYDKLVSSFL
EMKSEKQVEQKIAEIPKEEVKPFITESKPSVEQRKQDDKKIKACVEEVTTTLEE
TKFLTENLLLYIDINGNLHPDSATLVSDIDITFLKKDAPYIVGDVVQEGVLTAVVIP
TKKAGGTTEMLAKALRKVPTDNYITTYPGQGLNGYTVEEAKTVLKKCKSAFYI
LPSIISNEKQEILGTVSWNLREMLAHAEETRKLMPVCVETKAIVSTIQRKYKGIK
IQEGVVDYGARFYFYTSKTTVASLINTLNDLNETLVTMPLGYVTHGLNLEEAAR
YMRSLKVPATVSVSSPDAVTAYNGYLTSSSKTPEEHFIETISLAGSYKDWSYSG
QSTQLGIEFLKRGDKSVYYTSNPTTFHLDGEVITFDNLKTLLSLREVRTIKVFTT
VDNINLHTQVVDMSMTYGQQFGPTYLDGADVTKIKPHNSHEGKTFYVLPNDD
TLRVEAFEYYHTTDPSFLGRYMSALNHTKKWKYPQVNGLTSIKWADNNCYL
ATALLTLQQIELKFNPPALQDAYYRARAGEAANFCALILAYCNKTVGELGDVRE
TMSYLFQHANLDSCKRVLNVVCKTCGQQQTTLKGVEAVMYMGTLSYEQFKKG
VQIPCTCGKQATKYLVQQESPFVMMSAPPAQYELKHGTFTCASEYTGNYQCG
HYKHITSKETLYCIDGALLTKSSEYKGPITDVFYKENSYTTTIKPVTYKLDGVVCT
EIDPKLDNYYKKDNSYFTEQPIDLVPNQPYPNASFDNFKFVCDNIKFADDLNQL
TGYKKPASRELKVTFFPDLNGDVVAIDYKHYTPSFKKGAKLLHKPIVWHVNNAT
NKATYKPNTWCIRCLWSTKPVETSNSFDVLKSEDAQGMDNLACEDLKPVSEE
VVENPTIQKDVLECNVKTTEVVGDIILKPANNSLKITEEVGHTDLMAAYVDNSSLT
IKKPNELSRVLGLKTLATHGLAAVNSVPWDTIANYAKPFLNKVVSTTTNIVTRCL
NRVCTNYMPYFFTLLLQLCTFTRSTNSRIKASMPTTIAKNTVKSVGKFCLEASFN
YLKSPNFSKLINIIIWFLLLSVCLGSLIYSTAALGVLMSNLGMPSYCTGYREGYLN
STNVTIATYCTGSIPCSVCLSGLDSLDTYPSLETIQITISSFKWDLTAFGLVAEWFL
AYILFTRFFYVLGLAAIMQLFFSYFAVHFISNSWLMWLIINLVQMAPISAMVRMYIF
FASFYYVWKSYVHVVDGCNSSTCMMCYKRNRATRVECTTIVNGVRRSFYVYA
NGGKGFCKLHNWNCVNCDTFCAGSTFISDEVARDLSLQFKRPINPTDQSSYIV
DSVTVKNGSIHLYFDKAGQKTYERHSLSHFVNLDNLRANNTKGSLPINVIVFDG
KSKCEESSAKSASVYYSQLMCQPILLLDQALVSDVGDSAEVAVKMFDAYVNTF
SSTFNVPMEKLKTLVATAEAELAKNVSLDNVLSTFISAARQGFVDSDVETKDV
VECLKLSHQSDIEVTGDSCNNYMLTYNKVENMTPRDLGACIDCSARHINAQVA
KSHNIALIWNVKDFMSLSEQLRKQIRSAAKKNNLPFKLTCATTRQVVNVVTTK
IALKGGKIVNNWLKQLIKVTLVFLFVAAIFYLITPVHVMSKHTDFSSEIIGYKA
IDGGVTRDIASTDTCFANKHADFDTWFSQRGGSYTNDKACPLIAAVITREV
GFVVPGLPGTILRTTNGDFLHFLPRVFSAVGNICYTPSKLIEYTDFATSACVL
AAECTIFKDASGKPVPYCYDTNVLEGSVAYESLRPDTRYVLMDGSIIQFPNT
YLEGSVRVVTTFDSEYCRHGTCERSEAGVCVSTSGRWVLNNDYYRSLPGV
FCGVDAVNLLTNMFTPLIQPIGALDISASIVAGGIVAIVVTCLAYYFMRFRRAF
GEYSHVVAFNTLLFLMSFTVLCLTPVYSFLPGVYSVIYLYLTFYLTNDVSFLA
HIQWMVMFTPLVPFWITIAYIICISTKHFYWFFSNYLKRRVVFNGVSFSTF
EEAALCTFLLNKEMYLKLRSDVLLPLTQYNRYLALYNKYKYFSGAMDTT
SYREAACCHLAKALNDFSNSGSDVLYQPPQTSITSAVLQSGFRKMAFP
SGKVEGCMVQVTCGTTTLNGLWLDDVVYCPRHVICTSEDMLNPNYEDLLI
RKSNHNFLVQAGNVQLRVIGHSMQNCVLKLKVDTANPKTPKYKFVRIQPG
QTFSVLACYNGSPSGVYQCAMRPNFTIKGSFLNGSCGSVGFNIDYDCVSF
CYMHHMELPTGVHAGTDLEGNFYGPFVDRQTAQAAGTDTTITVNVLAWLYAA
VINGDRWFLNRFTTTLNDFNLVAMKYNYEPLTQDHVDILGPLSAQTGIAVLDM
CASLKELLQNGMNGRTILGSALLEDEFTPFDVVRQCSGVTFQSAVKRTIKGT
HHWLLLTILTSLLVLVQSTQWSLFFFLYENAFLPFAMGIIAMSAFAMMFVKHKH
AFLCLFLLPSLATVAYFNMVYMPASWVMRIMTWLDMVDTSLSGFKLKDCVMY
ASAVVLLILMTARTVYDDGARRVWTLMNVLTLVYKVYYGNALDQAISMWALIISV
TSNYSGVVTTVMFLARGIVFMCVEYCPIFFITGNTLQCIMLVYCFLGYFCTCYFGL
FCLLNRYFRLTLGVYDYLVSTQEFRYMNSQGLLPPKNSIDAFKLNIKLLGVGGK
PCIKVATVQSKMSDVKCTSVVLLSVLQQLRVESSSKLWAQCVQLHNDILLAKDT
TEAFEKMVSLLSVLLSMQGAVDINKLCEEMLDNRATLQAIASEFSSLPSYAAFAT
AQEAYEQAVANGDSEVVLKKLKKSLNVAKSEFDRDAAMQRKLEKMADQAMTQ
MYKQARSEDKRAKVTSAMQTMLFTMLRKLDNDALNNIINNARDGCVPLNIIPLT
TAAKLMVVIPDYNTYKNTCDGTTFTYASALWEIQQVVDADSKIVQLSEISMDNSP
NLAWPLIVTALRANSAVKLQNNELSPVALRQMSCAAGTTQTACTDDNALAYYN
TTKGGRFVLALLSDLQDLKWARFPKSDGTGTIYTELEPPCRFVTDTPKGPKVK
YLYFIKGLNNLNRGMVLGSLAATVRLQAGNATEVPANSTVLSFCAFAVDAAKAY
KDYLASGGQPITNCVKMLCTHTGTGQAITVTPEANMDQESFGGASCCLYCRCH
IDHPNPKGFCDLKGKYVQIPTTCANDPVGFTLKNTVCTVCGMWKGYGCSCDQL
REPMLQSADAQSFLNGFAV

In the RPP 1a molecule, there are eleven octamers (Table 13) and more than a hundred heptamers homologous to human proteins.

Some of the octamers are found in more than one human protein, some fold into long n-mers, for example 16-mer EDIQLLKSAYENFNQH$_{1126\text{-}1141}$, 14-mer EVEKGVLPQLEQPY$_{55\text{-}68}$ and 13-mer SVEEVLSEARQHL$_{34\text{-}46}$. The question of the participation of this large molecule in provoking an autoimmune response requires further study.

Replicase polyprotein RPP 1ab

Replicase polyprotein 1ab (RPP 1ab) consists of 7096 amino acid residues. In the RPP 1ab molecule, there are 210 hepta- / octamer homologous to human proteins. Some of them fold into long (more than 15 amino acid residues) n-mers. The role of this huge molecule in provoking an autoimmune response also requires study.

EVASION AND PROVOCATION OF AUTOIMMUNE RESPONSE

Based on the fact that the external SARS CoV-2 proteins are the first to contact host's immune system, while

Table 13

Localization of homologous octamers in RPP 1a and human proteins [3, adapted]

In Replicase polyprotein 1a	In human proteins
$SVEEVLS_{34-40}$	$FLJ00176\ protein\ (Fragment)_{260-266}$
$SEARQHL_{40-46}$	Cytokine-inducible inhibitor of signaling type IV_{96-102}
$EVEKGVLP_{55-62}$	Bifunctional heparan sulfate N-deacetylase/N-sulfotransferase $1_{214-221}$
$ESGLKTIL_{390-397}$	Annexin $A7_{404-411}$
$REETGLLM_{724-731}$	Estrogen-related receptor $gamma_{30-37}$
$GGSCVLSG_{1100-1107}$	Sorting nexin-$27_{112-119}$
$DIQLLKSA_{1127-1134}$	Echinoderm microtubule-associated protein-like 1_{38-45}
$RRSFYVYA_{2431-2438}$	Transmembrane protein adipocyte-associated $1_{225-232}$
$AKKNNLPF_{2733-2740}$	Acyl-CoA:lysophosphatidylglycerol acyltransferase $1_{199-206}$
$YNYEPLTQ_{3500-3507}$	$DNA\ helicase_{199-206}$
$SLKELLQN_{3530-3537}$	Centromere protein $I_{496-503}$
$DTSLSGFK_{3671-3678}$	Solute carrier family 12 member $7_{995-1002}$
$PEANMDQE_{4312-4319}$	Arachidonate 5-lipoxygenase-activating $protein_{54-61}$

the internal proteins are only the second, it would be reasonable to divide the proteins of the virus into *external* and *internal* proteins. The difference from the generally accepted classification (structural / nonstructural) is minimal. The first group includes proteins S, E and M, the second — all the others, including the N protein. We will consider proteins of the first group as participants in the processes of mimicry and the second as provocateurs of an autoimmune response.

External proteins and mimicry

In the IT terminology, the word *evasion* means bypassing an information security device to deliver malware without being detected by the recipient. Virologists have long been familiar with viral immune evasion, having a variety of expressions to describe it, such as: *to avoid the immune response*, *to outwit the immune system*, *to outmaneuver your hosts*, *to subvert the host cellular response, viral mimicry*, *camouflage*, *subversion* and *piracy*. The growing virulence of SARS CoV-2 indicates that the virus's ability to deceive the innate immune system improves with some new mutations.

To mislead the immune system, the virus could have hijacked some regions of the genetic code from previous hosts. That makes its proteins similar to human proteins. Knowledge of the homology between the virus and human proteins might help understand the mechanisms of mimicry in the moment of infection and during the subsequent autoimmune response.

For evasion to occur, the virus must appear in front of the immune system and tell it: *don't shoot! I am one of you!* The traditional naming of a password is not suitable for such a message, since a password, by definition, must be known by a very limited number of people or devices. Virology needs a term for a universal password, known to an unlimited number of participants on both sides of the information exchange. There is a suitable term in IT — *shibboleth*. Reported to a computer security system without distortion, the shibboleth allows an intruder (person or device) to gain access to the desired resources.

The word shibboleth, borrowed from the Bible (*Judges* 12: 5-6), is used by linguists and literary men (see *Shitbroleeth* in episode 16 of *Ulysses* by James Joyce), from whom psychologists and psychiatrists adopted it. Dr Dmitry Kormilets in a private communication suggested using this term in virology as well. In our interpretation, shibboleth is an area of the surface of virion, according to which the immune system must mistakenly recognize the virus as a part of the host organism and turn off the mechanisms designed to inactivate and / or destroy the intruder.

Some viral proteins are homologues of human proteins. It appears they have been hijacked from the host and included in their own genomes [26].

Tables 3–6 show a lot of motifs common to the external SARS CoV-2 proteins and humans. Which of them are directly involved in mimicry, it is now impossible to say. One can only point to the motifs in the most functionally important regions of the external proteins of SARS CoV-2 and human proteins. In addition, those regions of the external proteins of SARS CoV-2, in which the frequency of occurrence of homologous regions is the highest, deserve special attention.

Perhaps this is how the SARS CoV-2 protects its most important site (RBD) from the immune system.

The narrow region of the E protein transmembrane domain contains a variety of motifs homologous to proteins from humans, food, and intestinal bacteria (Tables 4 and 5). In this regard, the participation of E protein in mimicry seems to be the most probable.

In the structure of M protein, there is also a high "concentration" of motifs homologous to human ones (Table 6). In the protein M, four heptamers homologues of human proteins are fused into a decamer V_{10}–Q_{19}. The hydrophilic composition indicates a possible contact with the extracellular environment and the host's immune system. This outer protein is the second most likely candidate for the role of mimicry organizer.

Provoking of Autoimmune Response

The most likely candidate is ORF9b protein. In its small molecule, regions which are homologous to human proteins

account for 34.0% (33 out of 97), the highest value of this indicator among all internal proteins. The biggest structural difference is found between SARS CoV-2 RF9b protein and similar bat and pangolin proteins compared to other SARS CoV-2 proteins, which indicates active mutagenesis [27].

The polyprotein molecules RPP 1a and RPP 1a b are huge, as is the number of homologous motifs in them. The possibility that the motifs take part in provoking an autoimmune response has not yet been proven. Enzymes and especially enzymes of the cell cycle are evolutionarily highly conserved. In the process of disintegration of microorganisms, permanent inhabitants of the human intestine, peptides homologous to human proteins must be released into the intestinal lumen. Perhaps it is they who interact with the host's immune system and tune it to non-resistance to virion proteins.

Dysfunction of olfactory and taste receptors

ACE2 protein has been found at high levels in the human olfactory epithelium. May this explain COVID-19-associated olfactory dysfunction [28]?

In the RPP 1a molecule, heptamers $SCGNFKV_{505-511}$ and $AIFYLIT_{2785-2791}$ are homologous to human Olfactory receptor proteins $52N2_{190-196}$ and $2W1_{32-38}$, respectively. ORF7b contains a heptamer homologous to the Olfactory receptor protein 7D4 and may be involved in provoking an autoimmune response, contributing to olfactory dysfunction. In the RPP 1a, a heptamer $LKTLLSL_{1556-1562}$ is homologous to the human Bitter taste receptor $T2R55_{181-187}$.

In S protein, the octamer $RRARSVAS_{682-689}$ is homologous to the Amiloride-sensitive sodium channel subunit $alpha_{201-208}$, which is involved in salt taste perception [29].

If homologous motifs in the SARS CoV-2 molecule can trigger an autoimmune response, then these facts may explain why COVID-19 disease so often affects the sense of smell and taste.

Mutations

Mutations are a mechanism for escaping immune responses [4]. Among the SARS CoV-2 proteins, protein S has been studied for mutations. Of the external proteins, it is the most susceptible to mutation [27].

The differences of human S-proteins from Asia, Africa, Europe, North America, South America and Oceania from the reference sequence of the SARS CoV-2 Wuhan-Hu-1 protein, China, are described. There were found 9654 mutations, which correspond to 400 different sites of mutations. RBD alone contained 44 mutations [30]. Of course, far from all of the effects of these mutations have now been studied. Fortunately, not all of them matter. In theory, the mutation can increase, decrease, or not affect the immune response to the S-protein [4].

The $D_{614}G$ mutation changes the conformation of the S protein [4]. SARS CoV and SARS CoV-2 recognize the ACE2 receptor through their S proteins. In the N-terminal domain, the sequences $MESEFR_{153-158}$ and $SYLTPG_{247-252}$ are specific for human SARS CoV-2. In RBD, the structural determinants for recognizing human ACE2 are the $VGGNY_{445-449}$ and $EIYQAGSTPCNGV_{471-483}$ sequences, as well as the disulfide bridge connecting C_{480} and C_{488} [31]. Note that none of the motives mentioned above coincide with regions homologous to human proteins.

S protein of SARS-CoV-2 variant Delta contains eight mutations, namely $T_{19}R$, $G_{142}D$, $\Delta_{156–157}$, $R_{158}G$, $L_{452}R$, $T_{478}K$, $P_{681}R$, and $D_{950}N$ [32]. S protein of variant Omicron, the most aggressive, contains many mutations, namely $V_{70}\Delta$, $T_{95}I$, $G_{142}D$, $V_{143}\Delta$, $Y_{144}\Delta$, $Y_{145}\Delta$, $G_{339}D$, $S_{371}L$, $S_{373}P$, $S_{375}F$, $K_{417}N$, $N_{440}K$, $G_{446}S$, $S_{477}N$, $T_{478}K$, $E_{484}A$, $Q_{493}R$, $G_{496}S$, $Q_{498}R$, $N_{501}Y$, $Y_{505}H$, $N_{655}Y$, $N_{679}K$, and $P_{681}H$, several of which overlap with those in the Alpha, Beta, Gamma, or Delta variants [33,34]. Due to the huge and continuous stream of data, the topic of mutations in SARS CoV-2 proteins can only be considered in periodicals for now.

CONCLUSION

Judging by the degree of homology between SARS CoV-2 proteins and humans, the main means of bypassing innate immunity (shibboleth) should be the E protein, while the main provocateur of the autoimmune response is the ORF9b protein. Accordingly, the attention of researchers and especially — developers of vaccines against SARS CoV-2 should be paid primarily to these two proteins. It also should be taken into consideration that vaccines affecting such homologous regions can damage proteins of the human body.

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5-HYDROXYTRIPTOPHAN IN RHEUMATOLOGICAL DISEASES: A SYSTEMATIC REVIEW

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Abstract. 5-hydroxytryptophan (5-HTP) has been used to treat neurologic and psychiatric diseases, including depression, insomnia, sleep apnea, cerebellar ataxia, and chronic cepheadaches. On the other hand, it has been prescribed in a few rheumatic disorders including fibromyalgia, ostheoarthritis, rheumatoid arthritis. Sleep disorders in syndromes accompanied by chronic pain have a significant negative impact on social aspects, provoke an earlier development of atherosclerotic lesions of the cardiovascular system, and can also lead to the development of depression and anxiety. There are 6 articles in this field, including 346 patients. Age varied from 40 to 51.1 years old, and female gender ranged from 22.2 to 84%. The 5-HTP dosage went from 60 mg to 4.000 mg a day. The study follow-up ranged from 4 weeks to 12 months. All of these articles demonstrated improvements in diverse fibromyalgia (FM) symptoms, including decreased pain intensity, improved sleep quality, improved mood and overall well-being, decreased anxiety, decreased fatigue, and decreased number of tender points. Presumably, the effect is associated with the metabolism of 5-HTP into serotonin, which is believed to decrease the sensitization of nerve endings associated with pain receptors. In addition, serotonin is a precursor of melatonin. Side effects were mild and varied from 8% to 30%. This review shows that 5-HTP is a promising and safe therapy for fibromyalgia. However, the data needs to be reproduced in future more extensive studies, including other rheumatic conditions.

Keywords: 5-hydroxytriptophan, 5-HTP, triptophan, rheumatic diseases, fibromyalgia

5-ГИДРОКСИТРИПТОФАН ПРИ РЕВМАТОЛОГИЧЕСКИХ ЗАБОЛЕВАНИЯХ: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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Резюме. 5-гидрокситриптофан (5-HTP) использовался для лечения нервных и психиатрических заболеваний, включая депрессию, бессонницу, апноэ сна, хроническую цефалгию, мозжечковую атаксию. В то же время была произведена оценка применения 5-HTP для лечения таких ревматологических заболеваний, как фибромиалгия (ФМ), ревматоидный артрит и остеоартрит. Нарушения сна при синдромах, сопровождающихся хронической болью, оказывают существенное негативное влияние на социальные аспекты, провоцируют более раннее развитие атеросклеротических поражений сердечно-сосудистой системы, а также могут приводить к развитию депрессии и тревожности. По данной тематике имеется 6 статей, в которых описаны результаты лечения 346 пациентов. Возраст варьировал от 40 до 51,1 года, доля женщин составила от 22,2 до 84%. Дозировка 5-HTP составляла от 60 мг до 4000 мг/день, длительность наблюдения варьировала от 4 до 12 недель. В статьях отражено улучшение различных симптомов фибромиалгии, включая снижение интенсивности боли, улучшение качества сна, настроения и общего самочувствия, снижение тревоги, усталости, уменьшение количества чувствительных точек. Предположительно, эффект связан с метаболизмом 5-HTP в серотонин, который снижает чувствительность нервных окончаний к болевым стимулам, и является прекурсором мелатонина. Побочные эффекты были легкими и варьировали от 8 до 30%. Этот обзор показывает, что 5-HTP является многообещающим и безопасным методом лечения фибромиалгии. Однако эти данные необходимо воспроизвести в будущих более обширных исследованиях, в которые будут включены другие ревматические состояния.

Ключевые слова: 5-гидрокситриптофан, 5-HTP, триптофан, ревматические заболевания, фибромиалгия

INTRODUCTION

Tryptophan is an essential amino acid and a precursor of the neurotransmitter serotonin. Tryptophan metabolites, such as serotonin and melatonin, are thought to participate in regulating mood, sleep, pain sensituvity, and tryptophan is used to treat insomnia, sleep apnea, and depression [8]. 5-HTP is an aromatic aminoacid naturally synthesized from the essential aminoacid L-tryptophan. In addition to depression, the therapeutic administration of 5-HTP is effective in treating various medical disorders, including fibromyalgia, ostheoarthritis, insomnia, cerebellar ataxia, and chronic cepheadaches [3].

Treatment of sleep disorders is one of the key aspects of therapy for rheumatic patients with chronic pain syndromes such as fibromyalgia (including that syndrome as a variant of long COVID and post-COVID health disorders), osteoarthritis, and rheumatoid arthritis. Insomnia has a significant negative impact on social aspects, the development of atherosclerotic cardiovascular diseases, and the onset of anxiety and depression. Given an aging population, constant use of electronic devices, and increased levels of stress, the problem of safe correction of sleep disorders becomes particularly challenging and relevant, where 5-HTP may find its place [1].

Tryptophan serves as the sole substrate for the synthesis of the biogenic amine serotonin, which is primarily produced in the distal parts of the gastrointestinal tract (90%) and to a lesser extent in the central nervous system (10%) [1]. Furthermore, tryptophan bioavailability could contribute to the activity of inflammatory system [19], that is often deeply disturbed in rheumatic patients. T-reg lymphocytes alter bioavailability of tryptophan by their enzyme indoloxidase (IDO), thus regulating T17/Treg balance and intensity of some autoimmune reactions as well [6, 7]. A significant portion of tryptophan is obtained from protein-rich food and metabolized in the gastrointestinal tract by gut microbiota, forming a range of biologically active molecules, including ligands for aryl hydrocarbon receptor. Tryptophan is also converted into kynurenines by immune system cells and epithelial cells of the intestine [1, 2]. 5-HTP may play a role in autoimmune diseases. In fact, in a mouse model for psoriasiform dermatitis, Hu et al. showed that 5-HTP reduced the cumulative scores and epidermal thickness and also reduced local and systemic inflammation biomarkers, including interleukin-6, the differentiation of IFN-γ- and IL-17A-expressing and related cytokine production (TNF-α, IL-6, IL-17A, and IFN-γ) in splenocytes [10]. Therefore, it is reasonable to speculate if 5-HTP may play a role in rheumatic diseases, including fibromyalgia and inflammatory conditions.

Theoretically, application of this amino acid and its derivatives in autoimmune disorders may result in some unequivocal sequels, because of its different influences on tryptophan bio-availability under various states of T-regs in concrete patients [6, 7]. For example, there were series of

studies documenting a connection between consuming of tryptophan dimers and provocation of eosinophilia-myalgia syndrome (EMS) in patients and experimental animals [4, 21]. Moreover, it was postulated that such dimers may incorporate into primary structure of proteins thus creating neoantigens and promoting autoimmunity [4].

Therefore, there is a need to review existing data on practical use of 5-HPT in rheumatology in order to evaluate its perspective. This study aimed to systematically review the articles that used 5-HTP to treat rheumatic diseases.

LITERATURE REVIEW

A systematic search of articles published in PubMed/MEDLINE, EMBASE, elibrary.ru and Scielo from 1966 to October 2023 using the following MeSH entry terms: “5-HTP” OR “5-hydroxytryptophan” OR “tryptophan” AND “rheumatic” OR “rheumatologic” OR “systemic lupus erythematosus” OR “lupus” OR “fibromyalgia” OR “rheumatoid arthritis” OR “spondyloarthritis” OR “Sjögren’s syndrome” OR “ myositis” OR “ systemic sclerosis” OR “vasculitis” OR “Takayasu disease” OR “Wegener’s disease” OR “granulomatosis with polyangiitis” OR “Kawasaki’s disease” OR “polyarteritis nodosa” OR “Livedoid vasculitis” OR Churg-Strauss” OR “eosinophilic granulomatosis with polyangiitis” OR “osteoarthritis” OR “gout”. The Russian equivalents were used for analysis of elibrary.ru database. The search had no language restriction. The reference lists of the selected articles were analyzed to identify other publications.

Two authors (JFC and AL) initially performed the literature search and independently selected the study abstracts. In the second stage, the same reviewers independently read the full-text articles selected by abstracts. The authors followed PRISMA guidelines [15]. Finally, a standardized form was designed to extract the information from relevant articles, including authors, year of publication, number of patients studied, demographic data, disease duration, study follow-up, 5-HTP posology, outcomes, and side effects. The same work with cyrillic sources was performed by Russian team members.

Table 1 summarizes the search results on 5-HTP treatment in fibromyalgia subjects [5, 9, 11, 14, 17, 18].

There are 6 articles in this field, including 346 patients. The countries that produced these articles were Italy (n=3), followed by Spain (n=2), Canada, and the United Kingdom (n=1). To date, we did not meet any academic or scientific publications in Russian, describing the studies related to the use of 5-HTP in rheumatology.

Most studies had a randomized controlled design trial as the study design (n=2), followed by double-blinded (n=1), prospective (n=1), open trial (n=1), and case report (n=1). Age varied from 40 to 51.1 years old, and female gender ranged from 22.2 to 84%. The 5-HTP dosage went from 60mg to 4,000 mg/day. The study follow-up ranged from 4 weeks to 12 months.

All these articles demonstrated improvements in the diverse FM parameters, since pain intensity, sleep quality, well-being, anxiety and mood symptoms, tender points count, and fatigue. Side effects were mild and varied from 8 to 30%.

This is the first study to systematically review the therapeutic effects of 5-HTP in all rheumatic diseases. Serotonin is the neurotransmitter that mediates slow-wave sleep and plays an essential role in pain perception. Moldofsky and Warsh have proposed that primary fibromyalgia syndrome may result from an insufficient concentration of circulating tryptophan, which then fails to provide adequate serotonin for maintaining slow-wave sleep [12].

Serotonin (5-hydroxytryptamine), which was discovered in the blood over 40 years ago [13], has subsequently been located in many parts of the body and has been shown to exert numerous effects on several body systems, including the brain and the gastro-intestinal tract, Reports of reduced blood serotonin concentrations in patients with FM and the symptomatic relief of these patients using tricyclic antidepressants, which probably act by blocking the reuptake of biogenic amines at nerve terminals, have implied the potential value of serotonin in the treatment of patients with FM [16].

In the absence of supplementation with 5-HTP, the amount of endogenous 5-HTP available for serotonin synthesis depends on the availability of the amino acid tryptophan and the activity of various enzymes, especially tryptophan hydroxylase, indoleamine 2,3-dioxygenase, and tryptophan 2,3-dioxygenase. In addition, the amount of 5-HTP reaching the central nervous system is affected by the extent to which 5-HTP is transformed to serotonin in the peripherical tissues [20].

Thus, in the context of treating rheumatological conditions such as fibromyalgia and osteoarthritis, 5-HTP may have several potential advantages.

1. Mood correction: rheumatological conditions can be accompanied by depression or mood disturbances. 5-HTP, a precursor to serotonin which plays a key role in mood regulation, may help increase serotonin levels in the brain and improve quality of life in patients with rheumatological conditions.

2. Sleep improvement: Pain from rheumatological conditions can significantly disrupt a patient’s sleep quality. Serotonin is a precursor to the melatonin, one of the main regulators of the sleep-wake cycle. 5-HTP may help increase melatonin levels and improve sleep quality in patients with rheumatological conditions.

3. Reduction of pain sensitivity: Serotonin is involved in the regulation of pain signals. It is believed that increasing

Table 1

Studies of 5-HTP in fibromyalgia

Author, reference	Study design	Co-untry	N	Age (years old)/gender	Disease duration	5-HTP dose (mg/day)	Follow-up	Outcome	Side effects
Gómez-Centeno et al., 2022 [9]	Pilot pros-pective	Spain	23	51.9±7.2 100% females	7.7±6.3 years	NA plus magne-sium and coenzyme Q10	12 weeks	5-HTP improved: • Sleep Quality • Functional capacity • Global well-being of patients.	NA
Martíznez-Rodríguez et al., 2020 [11]	Rando-mized, controlled trial	Spain	22	49±5 y; 100% females	NA	60mg plus magnesium 60 mg	16 weeks	5-HTP improved; • Trait anxiety (p=0.001), • Self-image perception (p=0.029) • Mood disturbance (p=0.001) Eating disorders	NA
Sharma & Barrett, 2001 [18]	Case report	UK Ca-nada	1	40 Female	NA	Gradually increased to 4g/day in 2 weeks	4 weeks	She has FM and severe depression, and after tryp-tophan, she improved her symptoms. She has been gainfully employed for more than 1 year and remains on the drug regimen of tryptop-han 2 g, lorazepam 1 mg, and oxazepam 25 mg daily	Well tolerated until 2g/day. When she used 4g, she felt irritability, agitation, racing thoughts, preoccupation with thoughts of suicide, and dysphoria
Sarzi-Puttini et al., 1992 [17]	Open study	Italy	50	46.6 (27–60) 86% Females	NA	100 mg TID	12 weeks	5-HTP improved: • Number of tender points • Anxiety • Pain intensity • Quality of sleep • Fatigue	30% has a side effect
Caruso et al., 1990 [5]	Double-blinded placebo-controlled trial	Italy	50	47.8(31-60) 14% females	NA	100 mg TID	4 weeks	• 90% of the physicians • and >85% of the patients assessed the • efficacy of SAMe as being "very good" or "good." • 18/97 became asymptomatic. • The complaint score dropped • from 20.3 to 4.5 • The score of the mental state rating (feelings) dropped from • 31.7 to 16.1	6 5-HTP vs. 3 placebo had mild side effects
Nicolodi & Sicuteri, 1996 [14]	Rando-mized, controlled trial	Italy	200	NA	NA	400 mg. 4 group: a) amitriptyline, b) pargyline or phenelzine, c) 5-HTP, d) association of pargyline (or phenelzine) and 5-HTP 200 mg	12 months	The combination of MAOIs with 5-HTP significantly improved fibromyalgia syndrome as determined by Visual Analogic Scale, whereas the other treatments yielded poorer benefits.	Stomachache (8%)

serotonin levels may decrease the sensitization of nerve endings associated with pain receptors. 5-HTP, as a precursor to serotonin, may contribute to increasing its levels and thus reducing pain sensitivity in patients with rheumatological conditions.

This systematic review showed that all studies that evaluated 5-HTP supplementation in fibromyalgia showed at least one benefit, with mild or absent adverse effects. This study's strengths are (1) the inclusion of studies with patients with international criteria for rheumatic diseases; and (2) the inclusion of all kinds of study designs for using 5-HTP in rheumatic diseases, except reviews, animal studies, and *in vitro* studies. In this way, the authors believe all published cases of 5-HTP in rheumatic patients were collected.

Some limitations were observed in this study. For instance, no comparison between classical treatments used in rheumatic diseases was available for the studied condition. In addition, the number of participants was low, and the follow-up was short for the diseases except for osteoarthritis. More important, just one rheumatic disorder was studied — fibromyalgia. It is reasonable to evaluate the effect of 5-HTP in other painful conditions associated with anxiety or depression. Therefore, future studies should include larger patient samples with more long-term observation, enabling a better understanding of the course of SAMe in rheumatic conditions.

CONCLUSION

A few articles in the literature evaluate the effects of 5-HTP in rheumatological diseases, and only fibromyalgia was assessed. In Russian scientiific literature this item still is out of scope. Nevertheless, almost all analyzed studies demonstrated that 5-HTP use is efficacious in treating signs and symptoms of this rheumatic disease (pain, FM scales, functioning) and with rare and minor side effects. So, 5-HTP emerges as an exciting option to be explored in the rheumatological field.

ADDITIONAL INFORMATION

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

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

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RATIONAL COMBINATION OF ONCOLYTIC VIRUSES AND RAPAMYCIN ANALOGUES IN CANCER THERAPY (LITERATURE REVIEW)

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Abstract. Malignant neoplasms are currently one of the main causes of death in most countries of the world, and therefore the issue of developing new drugs for the treatment of cancer is extremely acute. Among the possible promising ways to combat it, the use of drugs containing oncolytic viruses and drugs based on rapamycin attracts attention. Oncolytic viruses (viruses that mainly affect cancer cells) have a direct cytolytic effect, destroying a malignant tumor, and also stimulate the antitumor immunity of the body. Rapamycin is a potent inhibitor of the mTOR -mechanical (formerly mammalian) target of rapamycin signaling pathway. It has been proven that rapamycin and its analogues can be effectively used for the treatment and prevention of cancer, as well as affect the aging process. While each group of drugs individually has certain disadvantages, there is a possibility of leveling them when used together, which in a number of studies has shown a good therapeutic result. The synergistic effect of oncolytic viruses and rapamycin is primarily due to the ability of the latter to stimulate the replication of the virus in the affected cells, showing its own cytostatic effect in the unaffected ones. Replication stimulation can occur through Akt activation or through suppression of mTORC1-dependent interferon type I production. Also, the catalytic inhibitors mTORC1 and mTORC2 enhance the replication of the herpes simplex virus in cancer cells along the eIF4E/4EBP axis. The mechanisms of action of oncolytic viruses, rapamycin and their combinations on malignant cells are considered in this literature review.

Keywords: mTOR, rapamycin, rapalogs, oncolytic viruses, carcinogenesis, cancer, aging, antitumor immunity, T-VEC, myxoma virus

РАЦИОНАЛЬНОЕ СОЧЕТАНИЕ ОНКОЛИТИЧЕСКИХ ВИРУСОВ И АНАЛОГОВ РАПАМИЦИНА В ТЕРАПИИ РАКА (ЛИТЕРАТУРНЫЙ ОБЗОР)

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Резюме. Злокачественные новообразования являются в настоящее время одной из главных причин смертности в большинстве стран мира, в связи с чем крайне остро стоит вопрос разработки новых лекарственных

средств для лечения рака. Среди возможных перспективных направлений борьбы с ним обращает на себя внимание использование препаратов, содержащих онколитические вирусы, и препаратов на основе рапамицина. Онколитические вирусы, преимущественно поражающие раковые клетки, оказывают прямой цитолитический эффект, разрушая злокачественную опухоль, а также стимулируют противоопухолевый иммунитет организма. Рапамицин представляет собой мощный ингибитор сигнального пути mTOR — mechanistic (ранее mammalian) target of rapamycin. Доказано, что рапамицин и его аналоги могут эффективно применяться для лечения и профилактики рака, а также влиять на процессы старения. В то время как каждая группа препаратов в отдельности имеет определенные недостатки, существует возможность их нивелирования при совместном применении, которое в ряде исследований показало хороший терапевтический результат. Синергидное действие онколитических вирусов и рапамицина связано, прежде всего, со способностью последнего стимулировать репликацию вируса в пораженных им клетках, проявляя в непораженных свой собственный цитостатический эффект. Стимулирование репликации может происходить через активацию Akt или через подавление mTORC1-зависимой продукции интерферона I типа. Также каталитические ингибиторы mTORC1 и mTORC2 усиливают репликацию вируса простого герпеса в раковых клетках по оси eIF4E/4EBP. Механизмы действия онколитических вирусов, рапамицина и их комбинации на злокачественные клетки рассмотрены в данном литературном обзоре.

Ключевые слова: mTOR, рапамицин, рапалоги, онколитические вирусы, канцерогенез, рак, старение, противоопухолевый иммунитет, T-VEC, вирус миксомы

BACKGROUND

In recent years, scientific and technological progress, including in the medical area, has gone a long way forward. It has significantly improved the quality of life of people in most countries, as well as life expectancy. However, these achievements turned out to be dialectically connected with new difficulties. In particular, humanity has faced the aging of the population, and, accordingly, the so-called diseases of civilization. The most formidable pathology among them is undoubtedly malignant neoplasms, which are second only to cardiovascular diseases in terms of mortality. According to academician of the USSR Academy of Medical Sciences I.V. Davydovsky, “everyone will die of cancer, but not everyone will live to see it”, which implies, in fact, the inevitability of oncology development with a significant increase in life expectancy in the absence of other diseases. There is no doubt that the number of cancer patients will steadily increase in the coming years, and, therefore, the search for new ways of their treatment now is more relevant than ever.

Surgery, radiation and chemotherapy have proven themselves and have become the “gold standard” for the treatment of cancerous neoplasms. At the same time, even combined therapy is not always successful, especially in the late stages of oncology. In addition, there are a number of contraindications for it, often found in the elderly, and the consequences of such treatment are very severe and can lead to death. To the promising alternative directions of therapy of malignant neoplasms at the present time can be attributed virotherapy with the use of oncolytic viruses, as well as therapy using rapamycin and its analogs. Mechanisms of effect of oncolytic viruses, rapamycin and their combination on malignant cells and analysis of the possibility of their use both separately and in combination are analyzed in this literature review.

RAPAMYCIN

Rapamycin is a product of *Streptomyces hygroscopicus*, which were discovered in 1964 on Easter Island (Rapa Nui) by a Canadian expedition led by Suren Segal [1, 37].

Another common name for rapamycin is Sirolimus. It is a macrolipid in structure, which is currently produced using biosynthesis technology. In the course of trials, it became clear that rapamycin has unique immunosuppressive, antifungal, and antitumor properties that quickly found wide application in clinical practice, but further studies showed that the cause of these effects is much more fundamental than it seemed at the first glance [1, 37].

mTOR AND ITS FUNCTIONS

In 1994, a protein that is a direct target of rapamycin action was discovered — Mechanistic (formerly mammalian) target of rapamycin (abbreviated as mTOR). The mTOR protein is a serine/threonine protein kinase of the PI3K-kinase family, which forms the catalytic subunit of two different protein complexes: mTORC1 and mTORC2. These enzymes phosphorylate other proteins, thus forming an intracellular mTOR signaling network [1, 34].

It has been established that mTORC1 has a central role in controlling the balance between anabolism and catabolism in response to environmental conditions. Thus, it is activated when the cell receives sufficient energy, amino acids, oxygen, and growth factors (including steroid hormones). In contrast, stress and DNA damage inhibit mTORC1 activity [1, 37, 42]. In turn, mTORC1 itself stimulates mRNA translation, promotes lipid and nucleotide synthesis, shifts glucose metabolism from oxidative phosphorylation to glycolysis, and suppresses proteosome assembly, lysosome biogenesis, and autophagy. Thus, mTORC1 regulates the relationship between nutrition and cell growth [1, 37, 42].

mTORC2, in turn, is also activated by growth factors (including insulin) and stimulates cytoskeleton reorganization, cell migration, ion transport, regulates glucose metabolism and suppresses apoptosis. Thus, it is responsible for cell survival and tissue proliferation [1, 37, 42].

mTOR PATHWAY HYPERACTIVATION, AGING AND CANCEROGENESIS

Thus, it is obvious that mTOR regulates the processes of life activity of the cell and the whole organism at the deepest level. It is noteworthy that this signaling pathway is peculiar to almost all eukaryotes. In the course of experiments it was found that inhibition of the mTOR pathway by rapamycin leads to a marked increase in the life span of all model organisms and human cell cultures. A similar effect is also produced by limiting the amount of food without malnutrition, which led researchers to the idea that these phenomena are interrelated [4, 7, 37]. It is believed that in the wild, where animals face the constant need to search for food and periods of starvation, mTOR activity has a wave-like character. Modern humans and laboratory animals are deprived of this stress, resulting in stable mTOR hyperactivation in their organisms [6, 7, 42]. It was shown, for example, that short-term hyperactivation of mTORC1 leads to muscle hypertrophy due to cell growth, but further hyperfunction of this metabolic regulator leads to muscle atrophy and rapid death, presumably due to suppression of autophagy and, consequently, disruption of muscle tissue remodeling processes. This is one of the possible explanations for the influence of mTOR hyperfunction on the aging process [7, 42].

Another theory is “quasi-programmed aging”. It states that aging is a growth program that has not been turned off in time. Thus, mTOR, as it was said above, is responsible for cell growth, but having completed its program, it continues its action, which leads to the so-called cellular hyperfunction. Such enhanced work, as a rule, is destructive for cells, and at the organismal level it is manifested as aging [1, 11].

It has been shown that hyperactivated mTOR through a number of intermediates leads to such phenomena as excessive stimulation of protein biosynthesis in the cell, suppression of autophagy and proteosome assembly, which can lead to oxidative and proteotoxic stress, and, as a consequence, to cellular aging. This in turn leads to Alzheimer’s disease, muscle atrophy, ulcers and gastritis, anemia, joint disease and hair loss, senile hyperpigmentation of the skin. The role of mTOR hyperactivation in the pathogenesis of type 2 diabetes mellitus, obesity, atherosclerosis, etc. is great. [1, 3, 7, 38, 42].

It is obvious that if mTOR hyperfunction leads to such a large number of diseases associated with aging, it leads to aging itself. In addition, it has been found that mTOR activity in elderly people is indeed higher than in young people, which confirms the hypothesis [1, 7].

Among other things, mTOR hyperactivation can stimulate cancerogenesis, which should be discussed in more detail.

It has been found that mTORC1 activates the enzyme S6K (ribosomal protein kinase), which in turn phosphorylates and activates several substrates that promote mRNA translation, including eIF4B (a positive regulator of 5’cap complex binding). Also, S6K enhances the translation efficiency of spliced mRNA (EJK) through its interaction with SKAR (a component of exon-junction complexes) [27]. In addition, S6K suppresses the action of programmed cell death protein (PDCD4 — eIF4B inhibitor) [14]. On top of that, mTORC1 itself inhibits the action of the 4EBP complex (eukaryotic translation initiation factor eIF4E binding protein) [19]. All of the above induces protein synthesis in the cell. In addition, it was found that besides increasing the overall level of translation, mTORC1 particularly stimulates the translation of mRNAs rich in pyrimidine nitrogenous bases, which encode translational and ribosomal proteins, as well as metabolic genes [41].

Excessive accumulation of protein in the cell leads to deterioration of its stacking and also increases the risk of various pathological modifications (carbonylation, glycation and glycoxidation, cross-linking of proteins with fats, with DNA and among themselves). All this leads to the so-called proteotoxic stress and disruption of normal cell function [1, 7].

In addition, enhanced translation requires additional energy expenditure. In an effort to compensate for its deficiency, mitochondria quickly fail and release free radicals (reactive oxygen and nitrogen species) into the cell cytoplasm. Free radicals increase the toxicity of iron and copper ions, and oxidative stress occurs, leading to damage to DNA, proteins, and membranes [1, 7].

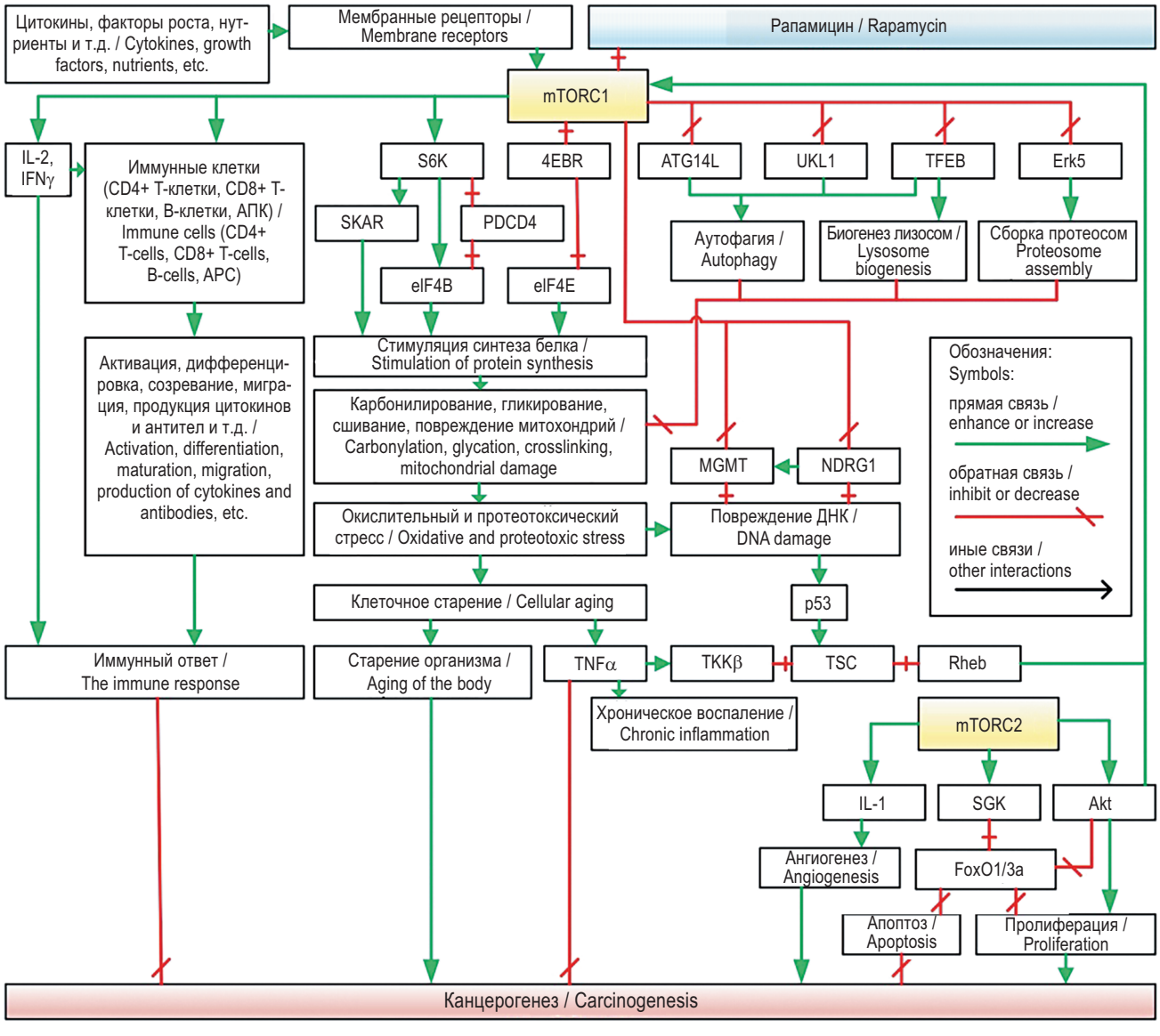

Fig. 1. **The connection of the mTOR signaling pathway with the process of carcinogenesis (compiled by Baranov I.A.). IL-2 — interleukin-2; IFNγ — interferon gamma; APK — antigen-presenting cells; S6K — ribosomal S6 Kinase; 4EBP — eukaryotic Translation Initiation Factor 4E Binding Protein; SKAR — a component of exon-junction complexes; PDCD4 — programmed cell death protein 4; eIF4B — eukaryotic translation initiation factor 4B; eIF4E — eukaryotic translation initiation factor 4E; ATG14L — autophagy related 14; ULK1 — unc-51 like autophagy activating kinase 1; TFEB — Transcription factor EB; ERK5 — extracellular signal-regulated kinase 5; MGMT — O6-alkylguanine DNA alkyltransferase; NDRG1 — N-myc downstream regulated 1; p53 — transformation-related protein 53; TNFα — tumor necrosis factor alpha; TSC — tuberous sclerosis complex; Rheb — Ras homolog enriched in brain; IL-1 — interleukin-1; SGK — serum/glucocorticoid regulated kinase; Akt — RAC-alpha serine/threonine-protein kinase; FoxO1/3a — forkhead box protein O1/3a**

Рис. 1. **Связь сигнального пути mTOR с процессом канцерогенеза (составлено Барановым И.А.). IL-2 — интерлейкин-2; IFNγ — интерферон гамма; АПК — антигенпредставляющие клетки; S6K — рибосомальная S6-киназа; 4EBP — белок, связывающий фактор инициации трансляции эукариот 4E; SKAR — компонент экзон-переходных комплексов; PDCD4 — белок программируемой клеточной гибели 4; eIF4B — фактор инициации трансляции эукариот 4B; eIF4E — фактор инициации трансляции эукариот 4E; ATG14L — связанный с аутофагией комплекс 14; ULK1 — unc-51-подобная киназа, активирующая аутофагию 1; TFEB — фактор транскрипции EB; ERK5 — киназа, регулируемая внеклеточным сигналом 5; MGMT — O6-алкилгуаниновая ДНК-алкилтрансфераза; NDRG1 — N-myc, регулируемый ниже по течению 1; p53 — связанный с трансформацией белок 53; TNFα — фактор некроза опухоли альфа; TSC — комплекс туберозного склероза; Rheb — гомолог Ras, обогащенный в мозге; IL-1 — интерлейкин-1; SGK — киназа, регулируемая сывороткой/глюкокортикоидами; Akt — RAC-альфа серин/треонин-протеинкиназа; FoxO1/3a — раздвоенный блок O1/3a**

Normally, damaged molecules and organoids should be destroyed by proteosomes and autophagy. However, mTORC1 blocks these processes. It suppresses the action of such important activators of autophagy as ULK1 (kinase) and ATG14L complex [24], inhibits the action of the transcription factor of lysosomal hydrolases and membrane proteins (TFEB) [29], and also reduces the activity of Erk5 complex, which leads to a decrease in the number of chaperone proteins providing protein folding and disrupts proteosome assembly [35]. This only aggravates proteotoxic and oxidative stresses, which in turn lead to damage of DNA molecules and, consequently, to malignant cell degeneration. Suppression of MGMT methyltransferase and NDRG1 regulatory protein also contributes to the accumulation of genomic mistakes [13].

In addition, hyperactivated mTORC2 complex contributes to carcinogenesis. It activates SGK (kinase), an inhibitor of FoxO1/3a substrate, which prevents cell apoptosis [16]. Along with this, mTORC2 activates Akt (a key effector of insulin signaling), which further inhibits FoxO1/3a substrate and also stimulates proliferation [36]. In addition, mTORC2 promotes the secretion of interleukin-1 (IL-1), which activates angiogenesis in growing tumor [25].

TNFα (tumor necrosis factor α) can cause rapid hemorrhagic necrosis of a number of tumors. However, it can also be released in large quantities by aging cells and activate mTORC1 through inhibition of TSC (tuberous sclerosis complex — the main inhibitor of mTORC1), forming a vicious circle. This leads to chronic inflammation in the elderly, which itself can cause some diseases [1, 5, 37].

Interestingly, mutations associated with TSC deficiency lead to the development of a polysystemic tumor disease, tuberous sclerosis [2]. It is also necessary to mention the role of the now widely known p53 protein, which activates TSC and thereby suppresses tumor growth [21].

In addition, mTOR is now believed to be a central regulator of immune responses. In particular, mTOR appears to function as a central node in the signaling cascade that directs the integration of various environmental factors into the immune microenvironment [33, 37].

Thus, antigen recognition by T-cell receptor, cytokines, growth factors, nutrients and costimulation lead to mTOR activation in CD4+ T-cells via membrane receptors, which, in turn, leads to their activation, differentiation, proliferation, and acquisition of periferic tolerance. Similar processes in CD8+ T cells also lead to their activation, differentiation, migration, and memory formation [33, 37].

Some other factors of extracellular signaling also mediated by mTOR cause activation, maturation, proliferation of antigen-presenting cells, their production of cytokines and costimulatory molecules [33, 37].

In B-lymphocytes, it leads to their activation, maturation, differentiation, antibody production and survival [33, 37].

In addition, mTORC1 stimulates T-cell synthesis of interleukin-2 (IL-2) and tumor necrosis factor-γ (TNFγ), which also plays an important role in the regulation of the immune response [28].

Table 1

mTOR inhibitors approved by the Food and Drug Administration (FDA) for the treatment of human cancer (USA) [32]

Таблица 1

Ингибиторы mTOR, одобренные Управлением по контролю за продуктами питания и лекарствами (FDA) для лечения рака человека (США) [32]

Препарат (торговое название) / Drug (trade name)	Показания / Indications	Дата утверждения / Approval date
Сиролимус (Рапамун) / Sirolimus (Rapamune)	Лимфангиолейомиоматоз / Lymphangioleiomyomatosis	Август 2000 г. / August 2000
Темсиролимус (Торизел) / Temsirolimus (Torisel)	Почечно-клеточный рак / Renal cell carcinoma	Май 2007 г. / May 2007
Эверолимус (Афинитор)/ / Everolimus (Afinitor)	• Почечно-клеточный рак / Renal cell carcinoma. • Прогрессирующий рак молочной железы HR+ / Advanced HR+ breast cancer. • Прогрессирующие нейроэндокринные опухоли поджелудочной железы, желудочно-кишечного тракта или легких / Progressive neuroendocrine tumors of pancreatic origin, of gastrointestinal or lung origin. • Ангиомиолипома почки / Angiomyolipoma of the kidney. • Субэпендимальная гигантоклеточная астроцитома, ассоциированная с комплексом туберозного склероза (TSC) / Subependymal giant cell astrocytoma associated with tuberous sclerosis complex (TSC)	Март 2009 г., август 2012 г., февраль 2016 г. / March 2009 August 2012, February 2016

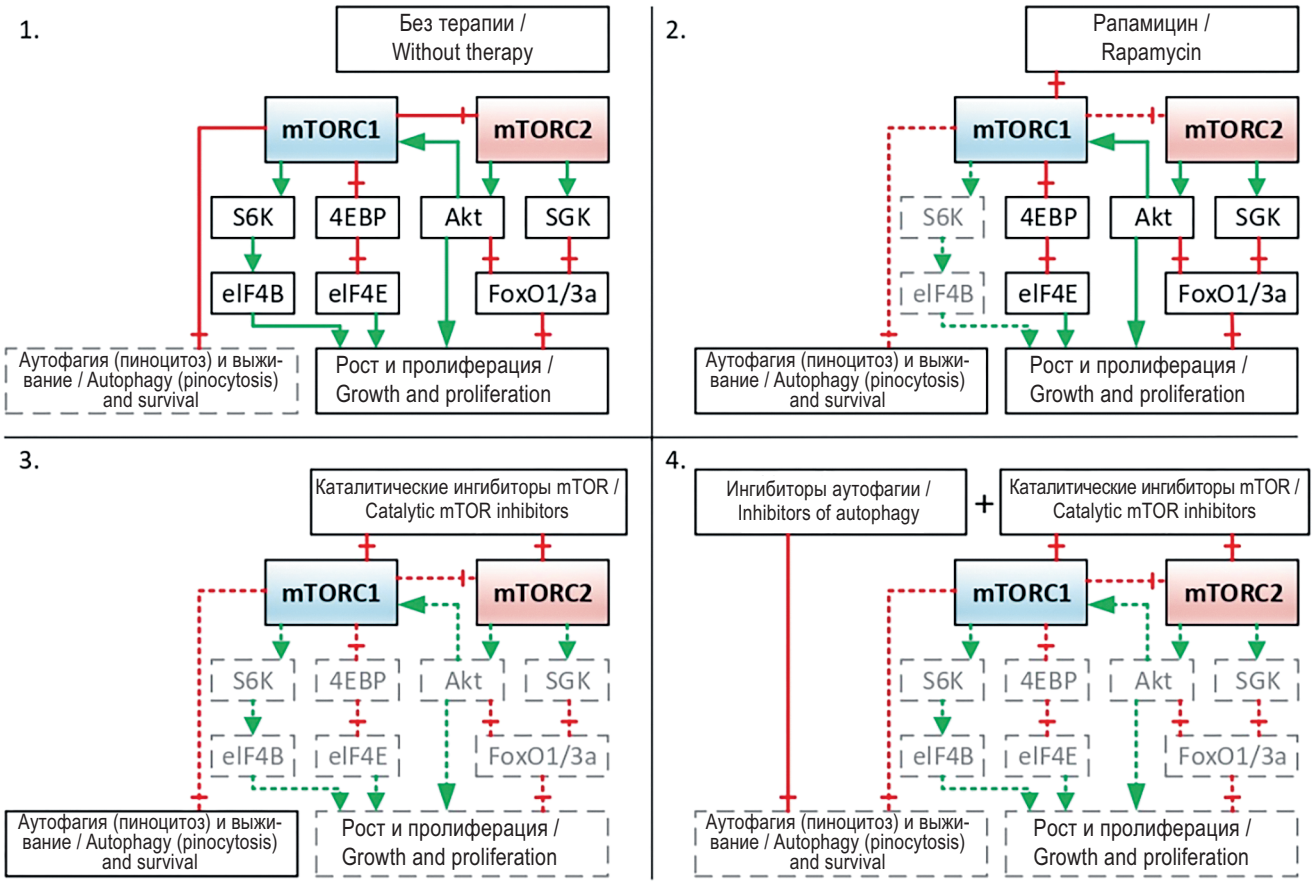

Fig. 2. Different effects of rapamycin, mTOR catalytic inhibitors and their combination with autophagy inhibitors on cancer cells. S6K — Ribosomal S6 Kinase; 4EBP — Eukaryotic Translation Initiation Factor 4E Binding Protein; eIF4B — eukaryotic translation initiation factor 4B; eIF4E — eukaryotic translation initiation factor 4E; Akt — RAC-alpha serine/threonine-protein kinase; SGK – serum/glucocorticoid regulated kinase; FoxO1/3a — forkhead box O1/3a

Рис. 2. Различное влияние на раковые клетки рапамицина, каталитических ингибиторов mTOR и их сочетания с ингибиторами аутофагии. S6K — рибосомальная S6-киназа; 4EBP — белок, связывающий фактор инициации трансляции эукариот 4E; eIF4B — фактор инициации трансляции эукариот 4B; eIF4E — фактор инициации трансляции эукариот 4E; Akt — RAC-альфа серин/треонин-протеинкиназа; SGK — киназа, регулируемая сывороткой/глюкокортикоидами; FoxO1/3a — раздвоенный блок O1/3a

This is what allowed rapamycin to be used as an immunosuppressor. All the above-mentioned interrelationships are clearly presented in the form of a summarizing scheme (Fig. 1).

mTOR INHIBITORS IN ANTI-TUMOR THERAPY

Thus, it is obvious that mTOR has a dual effect on the process of carcinogenesis, activating it on the one hand and inhibiting it on the other hand. This is what caused difficulties in the development of rapamycin-based antitumor therapy. First of all, it concerns the selection of adequate doses of the drug. As mentioned above, mTOR is one of the most important regulators of the immune response. Rapamycin, used as an immunosuppressant in organ transplantation, also suppresses antitumor immunity and may stimulate carcinogenesis [31, 33]. Interestingly, an imbalance of the human microbiota can also suppress antitumor immunity [8].

However, this does not prevent the use of rapamycin and its analogs in the therapy of malignant neoplasms due to careful selection of effective doses based on the ratio of harm to benefit for the patient in each specific case, which, in turn, becomes possible due to the dose-dependent effect of rapamycin. First, different doses of rapamycin are required to inhibit mTOR in different cell lines; second, different doses of rapamycin inhibit phosphorylation of different mTOR substrates; and third, there is different sensitivity of two complexes (mTORC1 and mTORC2) to rapamycin [31]. Interestingly, the enigmatic dosage properties of rapamycin may be explained largely by the competition between rapamycin and phosphatidic acid for mTOR. Rapamycin and phosphatidic acid have opposite effects on mTOR, with

rapamycin destabilizing and phosphatidic acid stabilizing both mTOR complexes [31].

Rapamycin-based drugs have undergone a significant evolution during the development of antitumor therapy [32]. Rapamycin and its analogs (rapalogs) are first-generation mTOR inhibitors that selectively inhibit mTORC1 activity by binding to FKBP-12 and forming a ternary complex with mTOR. Rapamycin is an allosteric inhibitor of mTOR, and it suppresses some functions of mTORC1, such as phosphorylation of protein kinase S6K1. The clinical use of rapamycin is limited due to its poor water solubility and insufficient stability; to overcome this drawback, pharmaceutical companies have developed rapamycin analogs with improved pharmacokinetic properties [32, 37].

Rapalogs differ in their chemical properties in terms of solubility and metabolism. For example, temsirolimus, a prodrug of rapamycin, and ridaforolimus are water soluble and can be administered intravenously, whereas rapamycin and everolimus have low solubility and are therefore only suitable for oral administration. Rapalogs have undergone clinical trials in various malignancies and have already been approved by the FDA for the treatment of certain types of cancer [32, 37].

However, in a number of cases, first-generation mTOR inhibitors showed insufficient efficacy and exhibited more cytostatic than cytotoxic effects [32, 37]. There are a number of explanations for that fact. Firstly, rapalogs block mTORC1 to a greater extent and hardly block mTORC2. Secondly, although rapamycin inhibits S6K, it does not completely inhibit 4EBP phosphorylation, making it ineffective in blocking cap-dependent translation in most cell types. In addition, suppression of mTORC1 activates autophagy but also activates both lysosome biogenesis and micropinocytosis, which may promote cancer cell survival in poorly vascularized, nutrient-poor tumor tissue (e.g., pancreatic tumor), as depicted in Figure 2 (2) [32, 37].

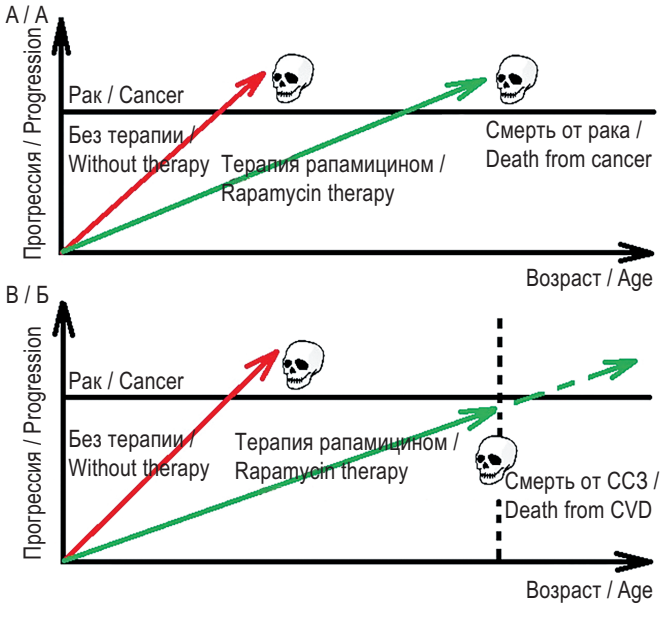

Fig. 3. Hypothetical scheme of preventive therapy with rapamycin. CVD — cardiovascular diseases

Рис. 3. Гипотетическая схема профилактической терапии рапамицином. ССЗ — сердечно-сосудистые заболевания)

The second generation of mTOR inhibitors is a series of ATP-competitive inhibitors (TORKIs), which are low-molecular-weight ATP analogs that compete with ATP to occupy the active site of mTOR kinase and block both mTORC1 and mTORC2. They are also called catalytic inhibitors. They have not yet been tested on a large scale and are not approved for cancer treatment. In addition, the problem of excessive activation of autophagy and pinocytosis (3) remains. In this situation, the combined use of mTOR catalytic inhibitors and autophagy inhibitors (4) seems promising (Fig. 2) [32, 37]. In addition, third-generation mTOR inhibitors, which are conjugated rapamycin and mTOR catalytic inhibitors, have been developed. The new compounds are called Rapalink. They exhibit greater efficacy and stability due to two points of application and are also under trial [32].

In addition, it should be noted that mTOR inhibitors are particularly effective in tumors characterized by mutations in the *mTOR gene (OMIM 601231*) accompanied by its increased expression. Detection of these mutations requires genetic research [17].

Another promising direction is cancer prevention with the help of rapalogs. As mentioned above, cancer is an age-related disease, and, figuratively speaking, by slowing down aging, rapamycin can delay the development of cancer as well. Thus, death may also occur from other causes, such as cardiovascular disease (Fig. 3). It is noted that in this case rapamycin is more effective at early stages of the disease development (at the precancer stage) [10]. Prophylactic treatment with rapamycin has been proposed for ex-smokers [18]. Many patients around the world are already taking off-label rapalogs, but rapamycin will never become an “old age pill”, because it is impossible to predict all the side effects of switching off such an important link in the regulation of metabolism as mTOR [1, 10, 11].

ONCOLYTIC VIRUSES

Another, no less promising area in the fight against cancer is oncolytic viruses, which predominantly affect malignant tumor cells but relatively neglect normal cells [23].

The idea of using viruses to fight cancer was first born at the beginning of the last century, but active research began only in the 1960s and continues to date [23].

The antitumor effect of viruses is believed to be realized through two main mechanisms [30]:

1) direct cytotoxic action of the virus;
2) stimulation of antitumor immunity of the organism.

Currently, a large number of different viruses are proposed and used as oncolytic [23], including:

- DNA viruses: adenovirus, cowpox virus, herpes virus, parvovirus H1;
- RNA viruses: reovirus, coxsackie virus, senecavirus (Seneca Valley virus), poliovirus, measles virus, Newcastle disease virus, vesicular stomatitis virus, etc.

Some of them are more or less promising for clinical application. In general, a number of requirements for oncolytic viruses can be put forward [22, 30]:

1) pronounced oncotropism of viruses;
2) a wide spectrum of target cells;
3) rapid spread of the virus in tumors;
4) efficient reaching of metastatic foci by the virus;
5) stability of the genome;
6) sufficient genome volume for trans-gene insertion;
7) high immunogenicity;
8) availability of antiviral drugs in case of unfavorable course, etc.

Why do a number of viruses exhibit increased tropism to tumor cells? There are also a number of explanations for this.

1) The antiviral defense system may be disrupted in tumor cells. For example, protein kinase R (PKR) is a critical factor that helps in eliminating intracellular viral infections. PKR may be absent in some cancer cells, which promotes increased viral replication in them [40].

2) Viruses can exploit the immune evasion ability of cancer cells. For example, key signaling pathways can be suppressed in cancer cells, which impairs recognition of viral particles by toll-like receptors (TLRs). Proapoptotic mechanisms are also suppressed in tumor cells [23].

3) In addition, tumor cells may express an excessive number of receptors on their surface through which viruses can enter. For example, herpes simplex virus 1 (HPV-1) utilizes herpes virus entry mediator (HVEM) and some nectins to enter cells. These surface receptors are overexpressed on some cancer cells, including melanoma cells [44].

Three generations of oncolytic viruses are distinguished [15]:

1) native (genetically unmodified) viruses;
2) modified viruses with increased “oncotropism”;

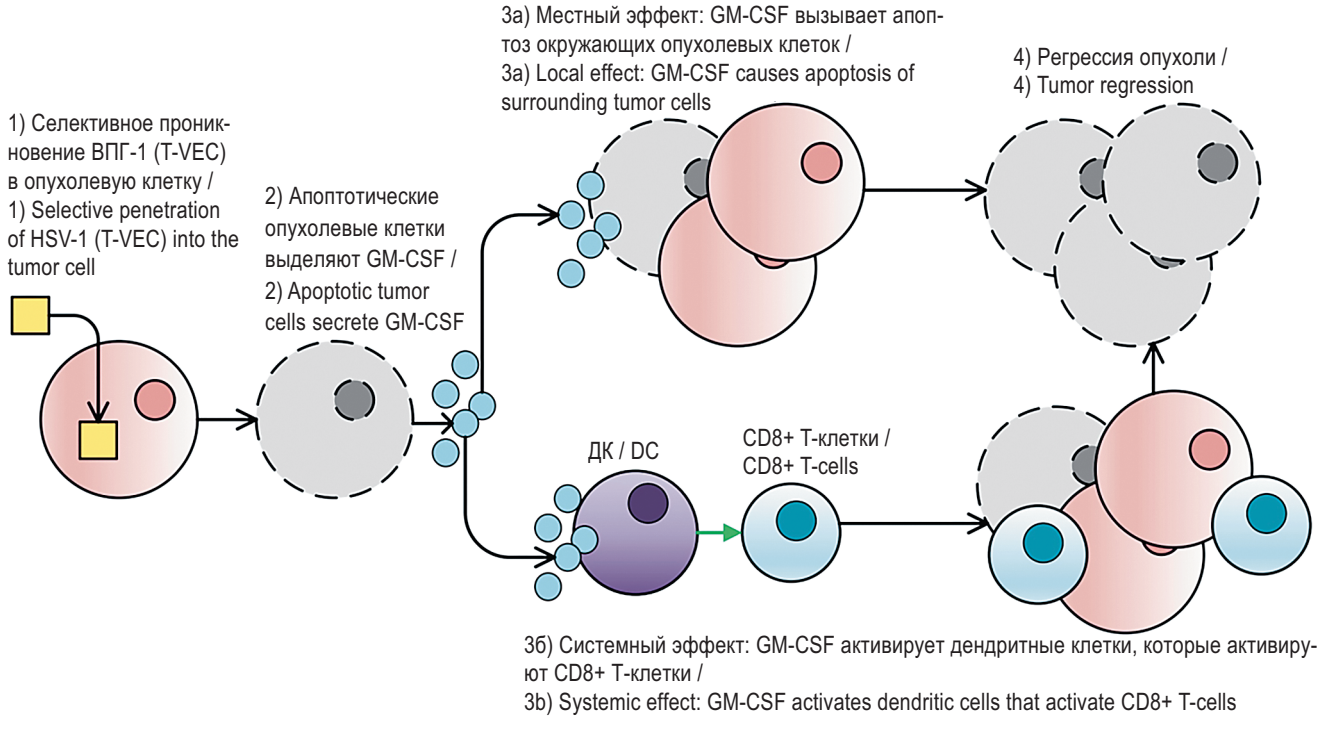

Fig. 4. Mechanism of action of T-VEC. HSV-1 — herpes simplex virus 1; T-VEC — talimogene laherparepvec; GM-CSF — granulocyte–macrophage colony stimulating factor; DC — dendritic cells

Рис. 4. Механизм действия препарата T-VEC. ВПГ-1 — вирус простого герпеса 1; T-VEC — талимоген лахерпарепвек; GM-CSF — гранулоцитарно-макрофагальный колониестимулирующий фактор; ДК — дендритные клетки

3) modified viruses which carry transgenes encoding cytokines or enzymes (a transgene is a DNA fragment transferred by genetic engineering manipulations into the genome of an organism in order to modify it).

It should be noted, that representatives of the first generation have not been practically used in clinical practice and are rather of research interest [15].

A representative of the third generation is, for example, a modified Herpes Simplex Virus — with the *GM-CSF* gene introduced into it, as well as reduced neurotoxicity (drug T-VEC) [30]. The *GM-CSF* gene encodes a protein of the same name — granulocyte-macrophage-colony stimulating factor.

That drug based on oncolytic viruses was first approved for melanoma treatment in the European Union, the USA and Australia. It is proposed to use it for other types of tumors as well. Let us briefly consider its mechanism of action (Fig. 4) [22].

The first step is the administration of the drug and selective penetration of the virus into the tumor cell (1) [22]. Then the affected cell starts to synthesize *GM-CSF* and release it during apoptosis (2) [22]. *GM-CSF* exhibits its action at two levels. At the local level, it induces apoptosis of surrounding tumor cells (3a) [22]. The systemic effect is the activation of CD8+ T cells by stimulating dendritic cells, which enhances antitumor immunity with long-term immunological memory (3b) [22]. All this leads to apoptosis and lysis of tumor cells and, ultimately, to regression of the tumor itself (4) [22].

However, the development of drugs based on individual oncolytic viruses has revealed a number of difficulties, including the toxic effect of viruses on the macroorganism, low bioavailability, difficulties in monitoring transgenes carried, the need for a special design of clinical trials, biosafety problems associated with virus persistence, etc. This explains the fact that over 60 years of research, only a few drugs have been approved for clinical use [22, 23].

Thus, it becomes obvious that both oncolytic virus-based and rapamycin-based drugs are extremely promising in the treatment of malignant neoplasms, but both have a number of drawbacks that limit their efficacy and clinical application. In this regard, proposals are made for their combined use, the rationality of which will be discussed further.

RATIONAL COMBINATION OF ONCOLYTIC VIRUSES AND RAPAMYCIN ANALOGS

In 2005, researchers found that everolimus increased the efficacy of oncolytic viruses in colorectal cancer therapy, but exactly how it increased treatment efficacy was not entirely clear [20]. In 2007, rapamycin was found to increase myxoma virus tropism to human cancer cells and thus enhance oncolytic virus therapy [26, 39].

The study showed that the wild strain of myxoma virus carries the *M-T5* gene encoding a protein of the same name that activates Akt (kinase), which in turn suppresses apoptosis and stimulates cell proliferation, promoting virus replication. A close analog of *M-T5*, the PIKE-A protein, which also activates Akt, was found in humans [26, 39, 42]. PIKE-A, and consequently Akt, is known to have

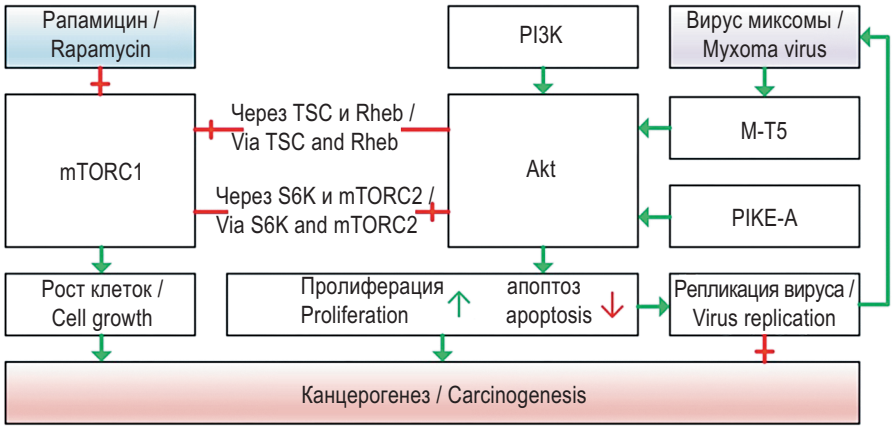

Fig. 5. **Scheme of combined use of rapamycin and oncolytic myxoma virus (compiled by Baranov I.A.). TSC — tuberous sclerosis complex; Rheb — Ras homolog enriched in brain; S6K — Ribosomal S6 kinase; Akt — RAC-alpha serine/threonine-protein kinase; PI3K — phosphoinositide 3-kinases; M-T5 — ankyrin repeat M-T5; PIKE-A — PI3-kinase enhancer activating AKT**

Рис. 5. **Схема сочетанного применения рапамицина и онколитического вируса миксомы (составлено Барановым И.А.). TSC — комплекс туберозного склероза; Rheb — гомолог Ras, обогащенный в мозге; S6K — рибосомальная S6-киназа; Akt — RAC-альфа серин/треонин-протеинкиназа; PI3K — фосфоинозитид-3-киназы; M-T5 — анкириновый повтор M-T5; PIKE-A — PI3-киназный энхансер, активирующий AKT**

increased activity in a number of malignant tumors. Myxoma virus strains devoid of the *M-T5* gene have been artificially produced. Such strains have increased oncotropism and practically do not affect healthy cells. At the same time, there are tumors with low Akt activity, against which these strains are ineffective [29, 39, 43].

It turned out that mTORC1 and Akt are in a complex antagonistic relationship mediated through a number of intermediates. Thus, rapamycin, inhibiting mTORC1, stimulates Akt activity according to the "principle of negative feedback" [12]. This explains the fact of increased efficacy of myxoma virus therapy in combination with rapamycin and is also consistent with the above-mentioned fact that rapamycin monotherapy has a cytostatic effect on tumors. Thus, rapamycin and myxoma virus is a very promising synergistic combination. Rapamycin stimulates replication of the virus in cells affected by it, while in unaffected cells it shows its usual effect by inhibiting cell growth [26, 39]. This relationship is presented in the form of a scheme (Fig. 5).

Later, this combination was also applied to smallpox virus, HSV, vesicular stomatitis virus, and ad-enovirus [46].

In addition, rapamycin can stimulate the replication of oncolytic viruses by disrupting mTORC1-dependent production of type I interferon (IFN), which has antiviral properties [9]. At the same time, we should not forget that type I IFN also has antitumor effects, which makes the selection of rational doses of drugs extremely important. It has also been shown that catalytic inhibitors of mTORC1 and mTORC2 (but not the rapamycin) enhance HSV replication in cancer cells along the eIF4E/4EBP axis [45].

It should be noted that combinations of oncolytic viruses with rapamycin have already been tested. It has proven itself in a number of studies both in vitro (on human tumor cell cultures) [26, 28] and *in vivo* (on laboratory mice) [26].

However, it is necessary to keep in mind the immunosuppressive function of rapamycin. Inadequate doses of rapamycin may not only level the antitumor immunity enhanced by oncolytic viruses, but also make the macroorganism vulnerable to the viruses themselves [1]. In addition, a number of pathways have been shown through which the antiviral effect of rapamycin can be realized. Among them are activation of natural killer cells, stimulation of interferon-α production, etc. [34]. This should be taken into account during the combination of rapamycin with oncolytic viruses and prevent them from antagonizing each other.

CONCLUSION

Both oncolytic viruses and rapamycin were discovered more than half a century ago, but their clinical use is currently limited. This is due to a number of their side effects, the difficulty of drug dosing, the need for special clinical trial designs, etc. At the same time, the possibility of overcoming the disadvantages and improving the effectiveness of treatment may lie in the combined use of drugs from these two groups. Such combined regimens have already been tested and have proven themselves in a number of studies. The mechanism of synergistic effect of combined therapy is primarily due to the ability of rapamycin to increase the tropism of a number of oncolytic viruses to tumor cells and stimulate their replication, disrupting mTORC1-dependent production of type I IFN. In addition, catalytic inhibitors of mTORC1 and mTORC2 enhance herpes simplex virus replication in cancer cells via the eIF4E/4EBP axis. Further research should be directed toward the selection of specific combinations and effective dosages of drugs based on rapamycin or other inhibitors of mTOR and oncolytic viruses, which may help mankind to take another step in the direction of the final victory over cancer.

ADDITIONAL INFORMATION

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

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

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SMALL FIBER NEUROPATHY IN THE PATHOGENESIS OF POST-COVID SYNDROME

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Abstract. ***Introduction.*** Small fiber neuropathy (SNF) is a condition that occurs due to hereditary, metabolic, autoimmune, infectious and other diseases. Data on the possible role of SNF in the pathogenesis of post-Covid syndrome (PCS) are rare. ***Aim:*** To review literature on small fiber neuropathy in the pathogenesis of post-Covid syndrome. Summarize the authors' many years of experience working with patients with post-viral immunological complications. ***Results.*** There are several stages in PCS pathogenesis including antigenic mimicry of viral particles with human proteins, activation of coagulation and neuroglia, and the long-term presence of residual viral particles in certain areas of the central nervous system. Increased production of nonspecific antibodies allows us to consider PCD as an immunological process. The lack of a gold standard for instrumental diagnostics, given the variety of clinical manifestations of PCS, makes diagnosis difficult. Neuropathic pain and autonomic dysfunction in PCS patients combined with normal electroneuromyography (ENMG) indicators can be explained by the presence of SNF in the structure of the pathogenesis of PCS. This hypothesis is confirmed by data from confocal microscopy and skin biopsy with determination of the density of intradermal nerve endings in patients suffering from PCS, as well as by the clinical observations of the authors of the article. ***Conclusion.*** Consideration of small fiber neuropathy as an important stage in the pathogenesis of post-Covid syndrome opens new horizons for the diagnosis of post-Covid syndrome.

Keywords: post-Covid syndrome, small fiber neuropathy, new coronavirus infection, COVID-19, SARS-CoV-2

НЕЙРОПАТИЯ МАЛЫХ ВОЛОКОН В ПАТОГЕНЕЗЕ ПОСТКОВИДНОГО СИНДРОМА

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Резюме. ***Введение.*** Нейропатия малых волокон (НМВ) — состояние, возникающее при наследственных, метаболических, аутоиммунных, инфекционных и других заболеваниях. Данные о возможной роли НМВ в патогенезе постковидного синдрома (ПКС) единичны. ***Цель*** — обзор литературы о нейропатии малых волокон в патогенезе постковидного синдрома и обобщение многолетнего опыта работы авторов с пациентами, имеющими поствирусные иммунологические осложнения. ***Результаты.*** Среди звеньев патогенеза ПКС выделяют антигенную мимикрию вирусных частиц с белками человека, активацию коагуляции и нейроглии, длительное присутствие резидуальных вирусных частиц в отдельных областях центральной нервной системы. Повышение выработки неспецифических антител позволяет рассматривать ПКС как иммунологический процесс. Отсутствие «золотого стандарта» инструментальной диагностики при разнообразии клинических проявлений ПКС затрудняет постановку диагноза. Нейропатическая боль и вегетативная дисфункция при ПКС на фоне нормальных показателей электронейромиографии (ЭНМГ) могут быть объяснены наличием НМВ в структуре патогенеза ПКС. Эта гипотеза подтверждается данными конфокальной микроскопии и биопсии кожи с определением плотности интрадермальных нервных окончаний у пациентов, страдающих ПКС, а также клиническими наблюдениями авторов статьи. ***Заключение.*** Рассмотрение нейропатии малых волокон в качестве важного звена патогенеза постковидного синдрома открывает новые горизонты для диагностики постковидного синдрома.

Ключевые слова: постковидный синдром, нейропатия малых волокон, новая коронавирусная инфекция, COVID-19, SARS-CoV-2

INTRODUCTION

On the 30th of January 2020, the World Health Organization (WHO) declared the risk of a new coronavirus infection (NCI), which subsequently killed at least 7 million people, with a cumulative incidence of more than 771 million [55]. On the 5th of May 2023, the official end of the pandemic was declared, but doctors are still struggling with the consequences of the disease: immunological, neurological, respiratory, cardiovascular and cognitive impairments that can significantly affect the quality of life and daily activity of patients [40].

According to WHO experts, 10-20% of NCI patients may develop a condition called post-COVID-19 syndrome (PCS, post-COVID-19 condition, post-COVID-19 syndrome, long-COVID) [56]. Practicing physicians experience considerable difficulties in the management of such patients. Due to the peculiarities of the course of new strains of NCI (asymptomatic course or course like acute respiratory viral infections (ARVI) in a mild form, without loss of sence of smell), it is difficult to establish the main criterion of PCS, i.e. the connection with the disease. Clinical manifestations of this syndrome are nonspecific and include manifestations characteristic of psychiatric, neurological, endocrine and some other diseases, so it often becomes a diagnosis of exclusion. The search for a “gold standard” of PCS diagnosis is still underway, as the links in the pathogenesis of this condition are not fully understood. One hypothesis that could explain the onset of most symptoms is small fiber neuropathy (SFN). This review summarizes our experience of many years of work with patients with postviral, including postviral immunologic complications, who were first studied at the Laboratory of Autoimmunity Mosaics of St. Petersburg State University and then at the Center of the Study of Autoimmune Diseases and Consequences of New Coronavirus Infection of N.I. Pirogovs Clinic of High Medical Technologies in St. Petersburg.

POSTOVOID SYNDROME: CLINICAL DESCRIPTION

According to the WHO Delphi Consensus, PCS develops in patients with confirmed or suspected NCI, most often within 3 months of the disease. The characteristic symptoms presented in the Consensus must persist for at least 2 months and cannot be explained by another diagnosis [16].

The prevalence of post-covid syndrome is independent of the severity and duration of NCI and is found in asymptomatic course, in young patients, and even in children. The difficulty in diagnosing PCS is obvious in the case of asymptomatic NCI — it is impossible to confirm the fact of the disease after virus elimination from the body and to associate with it the symptoms that appear within 2–3 months after the disease [54]. It is estimated that 10 to 60% of patients with mild to moderate NCI experience PCS-like symptoms for 12 weeks or more [10]. According to our experience, it is the asymptomatic or low-symptomatic course of NCI that leads to the development of PCS. This can be explained by the fact that patients genetically prone to severe course of viral and bacterial infections develop severe classical viral pneumonia in case of NCI.

If the outcome of this process is favorable, PCS or other immunological complications are not formed. There is another group of patients, where there is an immunologic predisposition to a pronounced immune response. Such patients tolerate NCI easily, but may develop PCS, which lasts for weeks, months and even years. Among the patients receiving immunological treatment for PCS at the postcovid center of the N.I. Pirogovs Clinic of High Medical Technologies. For more than two years of work, no patient who was in intensive care or needed active respiratory support in the acute period of NCI has been identified, which can indirectly confirm this notion.

The pathogenesis of PCS still requires comprehensive study. Let us briefly review those links of PCS pathogenesis that seem to us the most significant.

Some experts attribute the progression of PCS to the direct action of the virus, while others note the predominant role of immunologic complications. The first hypothesis may explain anosmia — the prolonged presence of residual viral particles in the olfactory epithelium may cause inflammation and loss of sense of smell, as *in vivo* experiments demonstrated [15]. The development of meningitis or encephalitis is also possible against the background of persistence of viral infection [26]. The second point of view suggests activation of the immune response, most likely by the mechanism of antigenic mimicry with human proteins [13], or direct damage to the structures of the organism against the background of long-term systemic action of inflammatory mediators [11]. In this case, such complications as small fiber neuropathy, acute and chronic demyelinating polyneuropathies are formed [36, 48]. There is evidence of neuroglia activation, which provokes persistent inflammation in nervous tissue even after virus elimination [49]. Coagulation activation, microthrombosis and vasculitis [5, 37], which may contribute to the development of cognitive and mental disorders, are no less important aspects of NCI. Indirectly, these processes are confirmed by a decrease in brain metabolic activity and dysregulation of GABAergic chains found in patients with complaints of anosmia, “brain fog”, and chronic fatigue [51].

The WHO document presents a list of clinical manifestations typical for PCS, but our experience allows us to distinguish three main groups of symptoms: flu-like symptoms, small fiber neuropathy, and CNS symptoms (Fig. 1).

The first group of clinical observations includes such immunologic manifestations as temperature fluctuations ranging from 34.0 to 37.5 °C, constant or wave-like influenza-like condition, arthralgias and myalgias, tendinitis, chills, and weakness. The second group of clinical manifestations may be due to the lesion of small nerve fibers developing against the background of systemic action of inflammatory mediators and includes sensory (pain) and vegetative manifestations. Patients may describe classic complaints typical for polyneuropathy — burning or crawling goosebumps in the hands and feet, mainly at night or after exercise. Autonomic manifestations are diverse and include orthostatic reactions, syncopal states, dyspnea, gastrointestinal dysfunction, mycosal dryness, and hyperhidrosis [44]. It cannot be excluded that anosmia and agenesis may also be a manifestation of neuropathy, but this issue requires further research. Finally, the third group consists of neuropsychiatric disorders — persistent fatigue, depression, and anxiety. There is a special type of cognitive dysfunction described as “brain fog” — decreased attention, concentration, speed of information processing, and impaired executive functions [1].

Fig. 1. Three main groups of clinical manifestations of post-Covid syndrome
Рис. 1. Три основные группы клинических проявлений постковидного синдрома

WHO declared a pandemic of NCI on the 30th of January 2020, i.e. the duration of the study of postcovirus syndrome is less than 4 years at the time of writing, so there is no reliable information on the duration of this condition. PCS-like complications have also been observed in patients with MERS and SARS-CoV-1 infections, which are also members of the highly pathogenic coronavirus family: myalgia, fatigue, and neuropsychiatric abnormalities persist in patients to date. The authors observed postherpetic patients with similar symptoms whose disease duration was 8 years or more. These observations suggest that PCS may last from a few months to several years [54].

SMALL FIBER NEUROPATHY AS A MANIFESTATION OF POSTCOVID SYNDROME

Small fiber neuropathy (SFN) is a selective lesion of myelinated A-delta fibers and unmyelinated C-fibers, which together account for up to 80–90% of all peripheral nerves and are responsible for the transmission of pain, temperature stimuli, and autonomic nervous system function.

According to a 2013 study in the Netherlands, the incidence of SFN is 52 per 100,000 and the incidence of new cases is 12 per 100,000 per year [35]. The prevalence is expected to increase with increasing awareness of this condition. SFN is somewhat more common in women [34]. Single clinical observations of SFN in children have been published [19, 29, 43]. The incidence of small fiber neuropathy in PCS is unknown due to the poorly studied nature of both conditions.

Metabolic disorders, especially diabetes mellitus [24], but also vitamin B12 deficiency and iron deficiency [7, 14] are frequent causes of SFN. Hereditary diseases can lead to this condition: Fabry disease [14, 23], Wilson disease [47], familial amyloidosis [3]. The relationship of SFN with HIV infection [17], hepatitis C [31], systemic tick borreliosis (Lyme disease) [32] has also been revealed. Toxic factors in the development of neuropathy include alcohol [25], neurotoxic drugs, and chemotherapy [9, 50]. SFN is often found in autoimmune diseases and immunologic conditions, which include fibromyalgia, systemic lupus erythematosus, sarcoidosis, and other systemic connective tissue diseases [20, 39]. In about 50% of cases, the cause remains unidentified, in which case idiopathic SFN is referred to [21].

With the growing interest in SFN, other causes for this condition are being identified, and novel coronavirus infection is one of them. There are observations that severe or moderate NCI can provoke neuropathy one month after the onset of the disease [33]. Other researchers claim that it may manifest during the course of the disease [2]. It cannot be ruled out that NCI vaccination may provoke the development of short-term autoimmune complications as well as SFN [22, 53].

The pathogenesis of SFN is still unclear, although some of its links are known. For example, antisulfatide antibodies, immunoglobulins M against trisulfated disaccharide heparan, and immunoglobulins G against fibroblast growth factor are found in patients [27]. A possible link between SFN and ion channel damage has been traced [45]. Antibodies against interferon-induced guanosine triphosphate (GTP)-binding protein MX1 may interact with a specific type of calcium channels that are found in the brain, astrocytes, pyramidal cells, neurons, and cerebral arteries [12]. Patients with intervertebral disc degeneration and chronic back pain have been found to have elevated levels of antibodies against interferon-induced GTP-binding protein MX1, which may cause pain through interaction with calcium channels, but this issue requires further study [41]. Antibodies against cytokeratin 8, a link in the pathogenesis of chronic demyelinating neuropathy, and drebrin-like protein, which plays an important role in synapse formation, endocytosis, and neuronal cytoskeleton function, have also been found in SFN patients [12]. It has been suggested that autoimmune damage may be mediated through tumor necrosis factor α (TNFα) and interleukins (ILs) -2, -6, and -8 [6, 52]. It is known that different genetic variants of peripheral potential-dependent ion channels play a role in the formation of neuropathic pain, and the peculiarities of their functioning may explain the occurrence of SFN [45]. Autopsy of postcovicular patients revealed neuritis with perivascular macrophage infiltrate, but there were no viral particles in the tissues. Thus, an inflammatory immune response persisted even after complete elimination of the virus. There is also evidence that up to a quarter of dorsal root neurons, which are the first neurons in the sensory pathways, express mRNA encoding receptors for SARS-CoV-2 and ACE2-protein. The development of a cross-reactive immune response activates the production of antibodies that can damage neural tissue [42]. In summary, it should be noted that despite the probable immunologic pathogenesis of SFN both in PCS and other nosologies, no unique and specific autoantibodies have been identified, which does not allow us to call SFN a classical autoimmune process. It would be more correct to call it an immunologic manifestation, and in the case of PCS — post-viral immunologic syndrome.

Within the clinical manifestations of PCS, clinical manifestations of SFN present as sensory disturbances and autonomic dysfunction. Patients describe tingling, burning or shooting pain, numbness, sensation of tactile stimuli as painful (allodynia), paresthesias, hyper- or hypoalgesia, temperature sensitivity disorder and other symptoms [38]. Lesions of the distal parts of the extremities in the type of “socks” and “gloves” are typical, but manifestations of gangliopathy in the

form of localized unstretched sensory disturbances in various parts of the body have also been described [6]. Autonomic nervous system damage in SFN can cause orthostatic hypotension, dry eyes and oral mucous membranes, disorders of the urogenital system (impotence, vaginal dryness, dysuria, incontinence), gastrointestinal tract (fecal incontinence, diarrhea or constipation, pseudoobstruction of the intestine), "hot flashes", accommodation disorders, palpitations [34]. New studies have shown that neurogenic rosacea may be one of the manifestations of SFN [28].

Diagnosis of SFN is difficult for several reasons. Firstly, clinical manifestations vary widely, as neuropathy affects both autonomic and sensitive fibers. Secondly, diagnostic criteria have been developed only for "sock" and "glove" type neuropathy of distal limbs, but not for localized lesions [46]. The third, reliable diagnosis is possible only with a combination of noninvasive methods and skin biopsy, which is a labor-intensive invasive procedure but is considered the "gold standard" [18].

Diagnostic measures possible in SFN [38, 46]:

1) quantification of small fibers:
   - skin biopsy;
   - confocal microscopy;
2) functional assessment of small fibers:
   - quantitative sensory testing;
   - microneurography;
   - evoked nociceptive potentials;
3) autonomic nervous system function testing:
   - thermoregulation study;
   - quantitative sensory testing;
   - quantitative study of axonal reflexes responsible for sweating;
   - study of cutaneous sympathetic reactions;
   - study of electrochemical potentials of the skin;
   - neuroindicator test (Neuropad©);
   - heart rate variability.

There are the following diagnostic criteria:

- *possible* SFN — there are symptoms and clinical manifestations of small fiber injury;
- *suspected* SFN — there is normal conduction of the calf nerve in combination with symptoms and clinical manifestations of small fiber damage;
- *confirmed* SFN — there is normal conduction of the calf nerve in combination with symptoms and clinical manifestations of small fiber damage, as well as decreased intraepithelial nerve fiber density and/or abnormal temperature thresholds on quantitative sensory testing (QST) [38].

The use of several diagnostic tests at once significantly increases the probability of a correct diagnosis. For example, it has been proposed to use a combination of 4 methods: quantitative sensory testing, skin biopsy, electrochemical skin potentials, and laser stimulation-induced potentials for the most reliable diagnosis [18].

We would like to emphasize two methods of SFN diagnosis in PCS for which there is international standardization.

The first one is skin biopsy with intraepidermal nerve fiber density examination, which is considered to be the "gold standard" for SFN diagnosis. Its positive aspects include a good level of evidence, the possibility of verifying the results by several histologists, the simplicity of calculations. The disadvantages include the need for an invasive procedure and a specialized histology laboratory. Also, the patient may not have nerve fiber lesions at the biopsy site, leading to a false-negative result. According to unpublished data from the authors, analysis of skin biopsies from patients with PCS showed that more than 60% of patients had decreased small nerve fiber density below age- and gender-specific norms.

The second, corneal confocal microscopy (CCM), is an opportunity for noninvasive assessment of SFN. It has been shown that NCI shows a decrease in the number of nerve fibers and an increase in the number of mature and immature dendritic cells compared to controls. It cannot be excluded that coronavirus has the ability to activate glial cells, provoking an immune system attack on neuronal tissues [8].

CCM data are consistent with individual clinical observations: autopsy of a patient who died of NCI revealed hyperactivation of neuroglia and neurophagia in some brain regions [4]. In a larger study of 184 patients, microglia activation was observed in 42.9% of cases, with microglial nodule formation in 33.3%, and astrogliosis was found in 27.7% of cases [30].

CONCLUSION

The relatively recent emergence of postcovid syndrome leaves many things unclear: prevalence, influence of the course of NCI on subsequent severity of symptoms, optimal diagnostic methods... The pathogenesis of postcovid syndrome also remains incompletely understood. Several possible variants of SARS-CoV-2 virus impact on the human nervous system are considered, including autoimmune damage, microglia activation, coagulation disorder, and prolonged presence of residual viral particles in certain regions of the CNS. All of the mentioned variants of virus exposure are capable of forming small fiber neuropathy, which, in our opinion, underlies such symptoms of postcoccygeal syndrome as dysautonomia and neuropathic pain. Understanding the pathogenesis of the pathological processes

underlying postcovical syndrome opens up the possibility of developing new methods of diagnosis and treatment that improve the quality of life of patients.

ADDITIONAL INFORMATION

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

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ANTHRAX: NEAR AND FAR

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Abstract. Anthrax refers to particularly dangerous infections with high mortality, which, with untimely diagnosis and the absence of etiotropic therapy, can reach 90%, and with the pulmonary form — 100%. According to WHO, from two to twenty thousand cases of anthrax in humans are registered annually in the world, including fatal cases, more often in developing countries. In August 2023, an anthrax outbreak was identified in Kazakhstan. In Russia, over the past 15 years, only about 10–30 cases of this disease in humans have been registered annually, while the last two ones were recorded in March 2023 in Chuvashia. At the same time, the risk of anthrax outbreaks in the country exists due to the large number of soil anthrax foci, both registered and not accounted for, spontaneous sanitation of which cannot be expected. The exposure of such foci can be facilitated by the currently increased risks of man-made and natural disasters, as well as stable trends in increasing the temperature regime. This is confirmed by the outbreak of anthrax in the Yamalo-Nenets Autonomous Okrug in July 2016, the provoking factor of which is considered to be an abnormally high temperature (more than 34 °C for several days). The increased relevance of this disease is also associated with a sharp increase in the threat of bioterrorism in modern conditions, the potential agent of which is the causative agent of anthrax. Due to the high resistance of the pathogen spores in the environment, the aerosol mechanism of disease transmission, the possibility of obtaining antibiotic-resistant strains and strains that cause disease in the immune body, the anthrax causative agent is one of the most likely infectious agents that can be used to create biological weapons.

Keywords: anthrax, epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment, prevention, anthrax vaccines, biological weapons

СИБИРСКАЯ ЯЗВА: ДАЛЕКАЯ И БЛИЗКАЯ

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Резюме. Сибирская язва (антракс) относится к особо опасным инфекциям с высокой летальностью, достигающей при несвоевременной диагностике и отсутствии этиотропной терапии 90%, а при легочной форме — 100%. По данным ВОЗ, ежегодно в мире регистрируется от двух до двадцати тысяч случаев сибирской язвы у людей, в том числе с летальным исходом, чаще в развивающихся странах. В августе 2023 г. была выявлена вспышка сибирской язвы в Казахстане. В России за последние 15 лет ежегодно регистрируются около 10–30 случаев этого заболевания у людей, при этом последние два были зафиксированы в марте 2023 г. в Чувашии. Несмотря на низкую заболеваемость в целом, риск возникновения вспышек сибирской язвы в стране остается высоким из-за большого числа почвенных сибиреязвенных очагов как зарегистрированных, так и неучтенных, самопроизвольной санации которых ожидать не приходится. Вскрытию таких очагов могут способствовать возросшие в настоящее время риски техногенных и природных катастроф, а также устойчивые тенденции в отношении повышения температурного режима. Это подтверждает вспышка сибирской язвы в Ямало-Ненецком автономном округе в июле 2016 г., провоцирующим фактором которой считается аномально высокая температура (более 34 °С в течение нескольких дней). Повышение актуальности данного заболевания связано также с резким возрастанием в современных условиях угрозы биотерроризма, потенциальным агентом которого является возбудитель сибирской язвы. Вследствие высокой устойчивости спор возбудителя во внешней среде, аэрозольного механизма передачи заболевания, возможности получения антибиотикорезистентных штаммов и штаммов, вызывающих заболевание в иммунном организме, возбудитель сибирской язвы является одним из наиболее вероятных инфекционных агентов, которые могут быть использованы для создания биологического оружия.

Ключевые слова: сибирская язва, эпидемиология, патогенез, клинические проявления, диагностика, лечение, профилактика, вакцины против сибирской язвы, биологическое оружие

ANTHRAX EPIDEMIOLOGY

Anthrax is ubiquitous almost all over the globe and registered everywhere except Alaska, Greenland and the Arctic Ocean islands. According to the World Health Organization (WHO), the global human incidence is estimated at two to twenty thousand cases per year [7, 9]. In recent decades, anthrax remains relevant for developed countries, including the Russian Federation [13], where it occurs in isolated cases [14], potentially possible within certain regions of the country. Thus, in Russia, on average, about 10–30 anthrax cases in humans are reported per year, with the last two recorded in March 2023 in Chuvashia. In 2023, animal anthrax cases were registered in five regions of the Russian Federation: the Chuvash Republic, Tambov, Ryazan, Voronezh oblasts and the Republic of Tyva. According to WHO, there are 250–300 outbreaks of anthrax among animals in the world each year and about one million animals die. Many animals, primarily herbivores — cattle, camels, deers (especially reindeers), horses, donkeys, etc. — are susceptible to anthrax. Animals are most often infected orally by two routes: alimentary, by eating infected food, including bone meal, grass or soil, or by water, by drinking water from water bodies contaminated with effluents from enterprises processing raw materials of animal origin or groundwater communicating with soil anthrax foci. A necessary condition for the oral mechanism is damage of the gastrointestinal tract (GIT) mucosa, which is observed when coarse food is consumed or in inflammatory diseases. Less frequently, a vector-borne mechanism of transmission is carried out. Carriers may be gadflies, fire flies, in whose mouth apparatus the pathogen remains viable for up to 5–7 days, mosquitoes, midges, as well as various species of ticks. Anthrax is characterized by seasonality, the greatest number of outbreaks is registered in the warm season, from May to September, when animals graze on pastures, but isolated outbreaks of anthrax are possible in winter when using infected fodder. Sick animals excrete the pathogen in saliva, urine, feces, and all organs and tissues of an anthrax-dead animal contain huge amounts of bacilli. Thus, 1 ml of blood of such animals contains 109 microbial cellsThe anthrax pathogen enters the environment, primarily the soil, from sick animals and humans, or from the burial of dead animal carcasses. There it forms spores and can persist for a very long time, remaining highly virulent, which determines the stationarity of anthrax. In the Russian Federation, practically every fifth settlement has a territorial connection with anthrax-affected stationary points, where there are burials of corpses of animals killed by anthrax [10].

According to the indicators of the anthrax epizootic process, the territory of Russia is divided into three zones:

1) zone of sporadic occurrence — the territory north of 56° latitude (Murmansk, Leningrad, Pskov, Novgorod

and other regions) and eastern regions of Transbaikal;
2) zone of periodic occurrence — territory between 56 and 52° latitude (Moscow, Smolensk, Nizhny Novgorod, Irkutsk and Kemerovo oblasts, Tatarstan and others);
3) zone of stable occurrence — from 53° latitude to southern borders (Kursk, Voronezh, Rostov, Volgograd and other regions).

In the general structure of anthrax morbidity, diseases among humans account for 1–2%. The mechanisms of human infection are diverse: contact, oral, aerogenic, and vector-borne transmission mechanisms can occur, with the contact mechanism being the main one, accounting for 90–99% of all cases of infection [4, 5]. As a rule, *B. anthracis* gets on human skin by direct contact during the care of sick animals, their slaughter, carcass cutting, as well as by contact with soil, water, raw materials of animal origin and finished products made of fur, leather, wool, bristles. Cases of infection have been described by walking barefoot on contaminated soil, by striking with a pick contaminated with infected soil, by using shaving brushes made of contaminated bristles, by injecting therapeutic drugs with needles contaminated with spores of the pathogen, and by wearing fur, leather and wool products infected with spores. Thus, during the Russo-Japanese War (1904–1905), an outbreak of anthrax (about a thousand patients) was described among the soldiers of the Russian army in the Far East, associated with the supply of sheepskin coats infected with *B. anthracis* spores. As already mentioned, a prerequisite for infection is the violation of the integrity of the skin, the presence of macro- or micro-damage on the skin. Oral mechanism (alimentary route) of transmission is possible through consumption of infected meat and meat products, milk without sufficient thermal treatment. Transmissible mechanism of transmission is realized by the bite of blood-sucking insects. The aerogenic mechanism of transmission, which is realized by air and dust, requires the presence of *B. anthracis* spores aerosol in the air, which is created at enterprises processing raw materials of animal origin, use of organic fertilizers, collection of waste materials, etc. The incidence of anthrax among humans is sporadic with isolated group outbreaks, with humans being an epidemiologic dead end. As a rule, human-to-human infection is not observed, a person is not a source of infection. This may be due to several reasons: the short duration and low intensity of excretion of the pathogen from the patient's body, changes in its properties, and the absence of transmission mechanisms characteristic of the disease between people. Three types of anthrax diseases can be distinguished in humans due to the peculiarities of their labor activity and everyday life: occupational-agricultural, which account for more than 60%, occupational-industrial which account about 20%, and non-occupational (casual) which account about 15% [6]. At the same time, the occupational-agricultural and non-occupational types of the disease are characterized by seasonality: they occur more often in the summer-autumn period and coincide with the corresponding epizootics in domestic animals. The occupational-industrial type does not depend on the time of year. The occupational-agricultural type of anthrax is characteristic of people working in public livestock farming, of the mechanisms of transmission is more often contact, oral (alimentary) route is possible, rarely vector-borne route is possible. Infection occurs, as a rule, by vegetative forms of *B. anthracis*. The latest anthrax outbreak in Yamal in July 2016 [6, 15] belongs to the occupational-agricultural type, as the source of infection was reindeer, and reindeer herders and their family members became ill.

The occupational-industrial type is characteristic of people working in industries that process raw materials of animal origin. This type of anthrax is characterized by contact and aerogenic transmission mechanisms, and infection occurs with spore forms of the pathogen. For the first time this type of anthrax was described in the middle of the XIX century in England at enterprises of the textile industry, it is also known under the names "wool sorters' disease", "rag makers' disease". The latter was common in Russia among collectors of landfill rags contaminated with excreta and animal dung. The unprofessional type is observed: in people who have had contact with a sick animal in the private sector or accidentally; during consumption of infected meat or products contaminated with soil containing spores; during use of fur and other products.

Sanitary and Epidemiological Rules 3.1.7.2629-10 "Anthrax Prevention" provide definitions of the following concepts important for epidemiologic surveillance and antisybriasis measures: epizootic center, epidemic center, stationary unfavorable point, soil hotspot and threatened area:

"Epizootic center is the location of the source or factors of transmission of the infectious agent within the boundaries in which the transmission of the agent to susceptible animals or humans is possible (pasture area, watering hole, livestock house, livestock processing plant and others).

An epidemic center is an area where a case or cases of human disease have been reported.

Stationary unfavorable point is a settlement, livestock farm, pasture, tract, on the territory of which an epizootic focus has been detected, regardless of the period of time of its occurrence.

Soil hotspot is a cattle burial ground, biothermal pit and other places where corpses of animals killed by anthrax are buried.

Threatened area is animal farms, populated areas, administrative districts where is a threat of anthrax cases in animals or people".

Currently, 8 thousand anthrax-infected cattle burial grounds are registered in Russia. In fact, the official statistics figures are greatly underestimated, as there are a large number of unrecorded cattle burial grounds in many areas. In the Russian Federation, there are more than 35,000 stationary anthrax-unfavorable points [4, 8] with soil anthrax foci, most of them located in Siberia and southern Russia. A settlement in which human or animal disease has once occurred is considered to be permanently anthrax-prone. Thus, the main sources of infection for humans are the organism of a sick animal and soil anthrax foci. Mass vaccination of animals is currently underway, so the role of soil anthrax foci in maintaining *B. anthracis* as a species in nature is crucial. In natural conditions they are sanitized extremely slowly, the factors contributing to sanitation are insolation, antagonism of microorganisms, bactericidal action of some plants. In this connection, the study and analysis of sibiriazvirus soil foci depending on soil-bioclimatic and geographical factors and the problem of their decontamination are very important.

Various chemical preparations are used for decontamination of soil outbreaks, the most effective ones being dry chlorine lime mixed with soil in the ratio of 1:10 and then moistened with water, and 5% formaldehyde in double treatment (Gruinard Island). There are prospects for application of biological methods of soil disinfection. Anthrax antagonist microbes can be used for this purpose. These include actinomycetes, *B. subtilis, B. mesentericus, B. mycoides.* Specific anthrax bacteriophages can be used, but *B. anthracis* strains resistant to them are found in nature. The All-Russian Research Institute of Veterinary Sanitation, Hygiene and Ecology has developed a method of decontamination of anthrax cattle burial grounds by burning, which is widely used in Canada [6, 8].

ANTHRAX PATHOGENESIS

The entry gate for anthrax is most often microdamage to the skin; less frequently, the pathogen can enter the body through damaged GI mucosa or through the epithelium of the upper respiratory tract (Fig. 1). An important factor in the development of infection is the form of the pathogen that entered the organism (spore or vegetative). For some time after penetration into the organism, spores behave as inert bodies (in particular, they are not capable of adhesion), at the same time they are taken up by macrophages and delivered by them to regional lymph nodes, where spores can be detected as early as 4–5 hours after infection. Then the process of spore germination into vegetative cells begins, which can occur both at the site of introduction and in regional lymph nodes. In macrophages vegetative cells divide, they form capsules, which promotes their rapid exit from phagocytes with subsequent multiplication in the lymphatic system, while the capsule prevents phagocytosis of vegetative forms. Multiplication of the pathogen in the area of the entrance gate and regional lymph nodes and its production of exotoxin are the cause of impaired vascular permeability, impaired microcirculation, local serous-hemorrhagic edema, inflammation, necrosis and loss of sensitivity in the gate of infection.

In the most common cutaneous form, a focus of hemorrhagic-necrotic inflammation with brown pigment (hemosiderin) is formed in the deep layers of the dermis and regional lymphadenitis develops. In the alimentary route of infection, the introduction of *B. anthracis* is possible throughout the GI tract, more often it occurs in the small intestine, and an important factor is the presence of micro-damage to the intestinal epithelium as a result of inflammatory diseases. In the aerogenic mechanism of infection, spores are taken up by alveolar macrophages, which carry them to tracheobronchial and mediastinal lymph nodes, where they germinate within 1–3 days (orpersist in alveoli or lymph nodes for up to 60 days), break their barrier function and penetrate into the bloodstream. As a result of exotoxin production, edema and necrotic changes, hemorrhagic mediastinitis and pleuritis develop, followed by generalization of the process and the emergence of secondary hemorrhagic sybilliform pneumonia with further fatal outcome. In all forms of infection, the generalization of the process may lead to the development of anthrax sepsis, which may be primary or secondary. The formation of septic foci in various organs and tissues with acute serous-hemorrhagic, hemorrhagic, less often fibrinous-hemorrhagic inflammation, replacement of lymphoid tissue in the spleen and lymph nodes by macrophages and incomplete phagocytosis of the pathogen is characteristic. Increasing toxinemia leads to the synthesis of a large number of proinflammatory cytokines, primarily tumor necrosis factor (TNF), interleukin-1 (IL-1) and others, and causes increased vascular permeability, the development of hemorrhagic manifestations, edema and hemostasis in organs and tissues. All this may eventually lead to the development of infectious toxic shock, Disseminated intravascular coagulation (DIC) and death of the patient.

Thus, the greatest role in the pathogenesis of anthrax belongs to the action of the *B. anthracis* toxin, and the septic course may occur either as a result of primary generalization or as a complication of the local form with the development of secondary generalization.

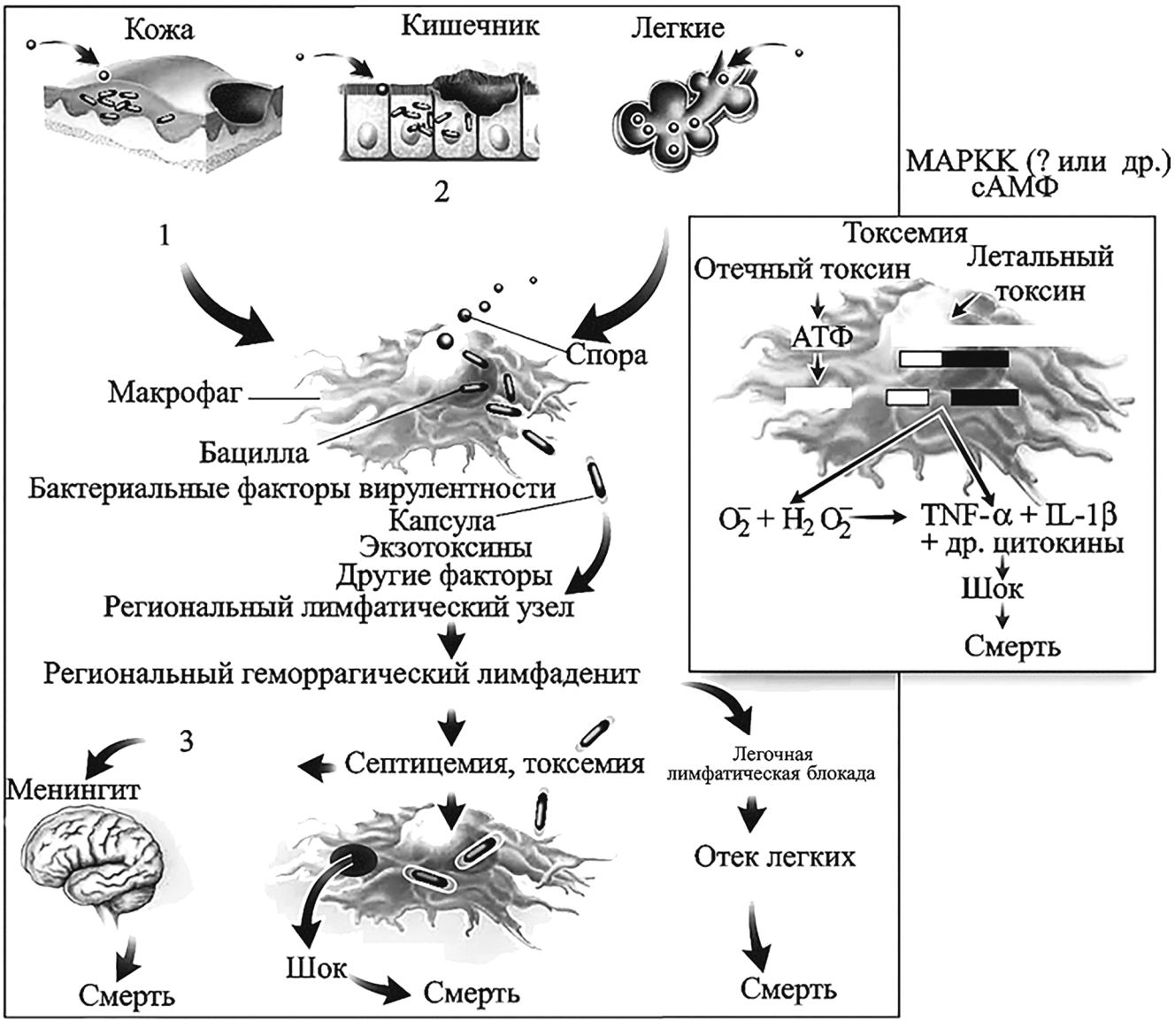

Рис. 1. Патогенез сибиреязвенной инфекции у млекопитающих (Супотницкий, http://supotnitskiy.ru/book/book4-2-2.htm): 1 — низкоуровневое прорастание и рост в участке инфицирования ведут к локальному отеку и некротическому поражению кожи; 2 — низкоуровневое прорастание и рост в участке инфицирования ведут к массивному выпоту, отеку слизистой и некротическому поражению кишечника; 3 — лимфогенное и гематогенное распространение *B. anthracis*. MAPKK (mitogen-activated protein kinase kinase) — митоген-активированный белок киназы киназы; TNF — фактор некроза опухолей; IL — интерлейкин (Dixon T.D. et al., 1999)

CLINICAL MANIFESTATIONS OF ANTHRAX

The incubation period for anthrax can last from a few hours to 14 days (more often 2–3 days). For vegetative forms the incubation period is usually short; for spore forms it is longer. In contact transmission and cutaneous form of the disease, the incubation period is 2–14 days, while in case of aerogenic and alimentary infection it may be reduced to a few hours. Cutaneous, inhalational (pulmonary), gastrointestinal and septic forms of anthrax are distinguished. The Iseptic form may be primary or secondary (Fig. 2). The International Classification of Diseases (ICD-10) includes cutaneous (A22.0), pulmonary (A22.1), gastrointestinal (A22.2), anthrax sepsis (A22.7), other forms of anthrax (A22.8), and anthrax unspecified (A22.9).

Cutaneous anthrax is the most common form, accounting for 95-99% of all anthrax cases. The skin of the upper limbs (about 50% of all cases) and head (20-30% of all cases) is mostly affected, while the trunk (3–6%) and legs (1-2%) are less frequently affected, with the exposed skin mostly affected. The cutaneous form is usually subdivided into

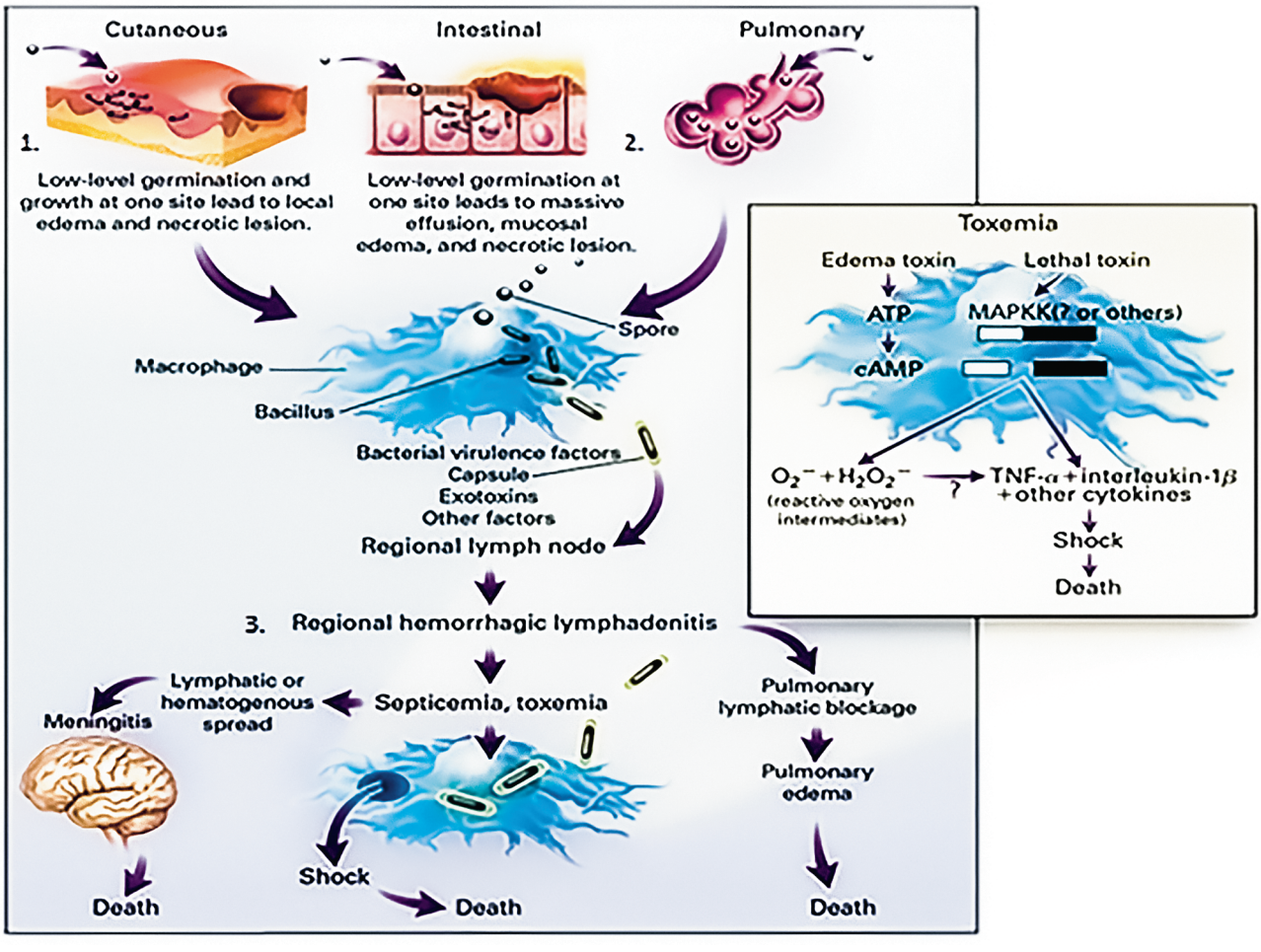

Fig. 1. **Pathogenesis of anthrax infection in mammals (Supotnitskiy, http://supotnitskiy.ru/book/book4-2-2.htm): 1 — low-level germination and growth at the site of infection lead to local swelling and necrotic skin lesions; 2 — low-level germination and growth in the site of infection lead to massive effusion, swelling of the mucous membrane and necrotic lesions of the intestine; 3 — lymphogenous and hematogenous spread of *B. anthracis*. MAPKK — mitogen-activated protein kinase kinase; TNF — tumor necrosis factor; IL — interleukin (Dixon T.D., et al., 1999)**

carbunculous (accounting for 99.1% of cutaneous manifestations), edematous (0.4%), bullous (0.4%), erysipeloid or rust-like (0.1%). Already by the end of the first day develops a pronounced intoxication syndrome that lasts 5–7 days: fever with a rise in temperature to 38–40 °C, chills, headache, weakness, sleep disorders, decreased appetite. At first, a reddish itchy spot similar to an insect bite is formed at the site of introduction of the pathogen (Fig. 3). After a few hours, the spot turns into a papule, then into a vesicle 2–3 mm in diameter, containing serous, then bloody fluid. The vesicle either by scratching or spontaneously opens, thus forming an ulcer with a dark brown or black bottom and raised edges, surrounded by a corolla of secondary pustules, due to which it increases. The skin around the ulcer is edematous and hyperemic.

A day later, the ulcer reaches the size of 8–15 mm. At the same time as the size of the ulcer increases,

Fig. 2. **Forms of the anthrax (compiled by the authors)**
Рис. 2. **Формы сибирской язвы (составлено авторами)**

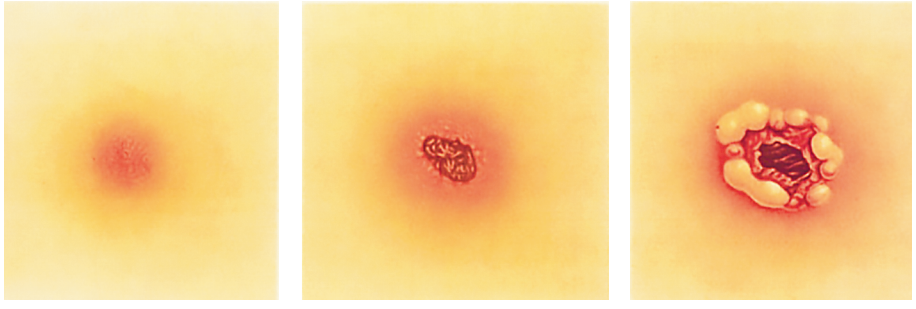

Fig. 3. Anthrax carbuncle formation. (URL: redkie-bolezni.com)

Рис. 3. Образование сибиреязвенного карбункула. (URL: redkie-bolezni.com)

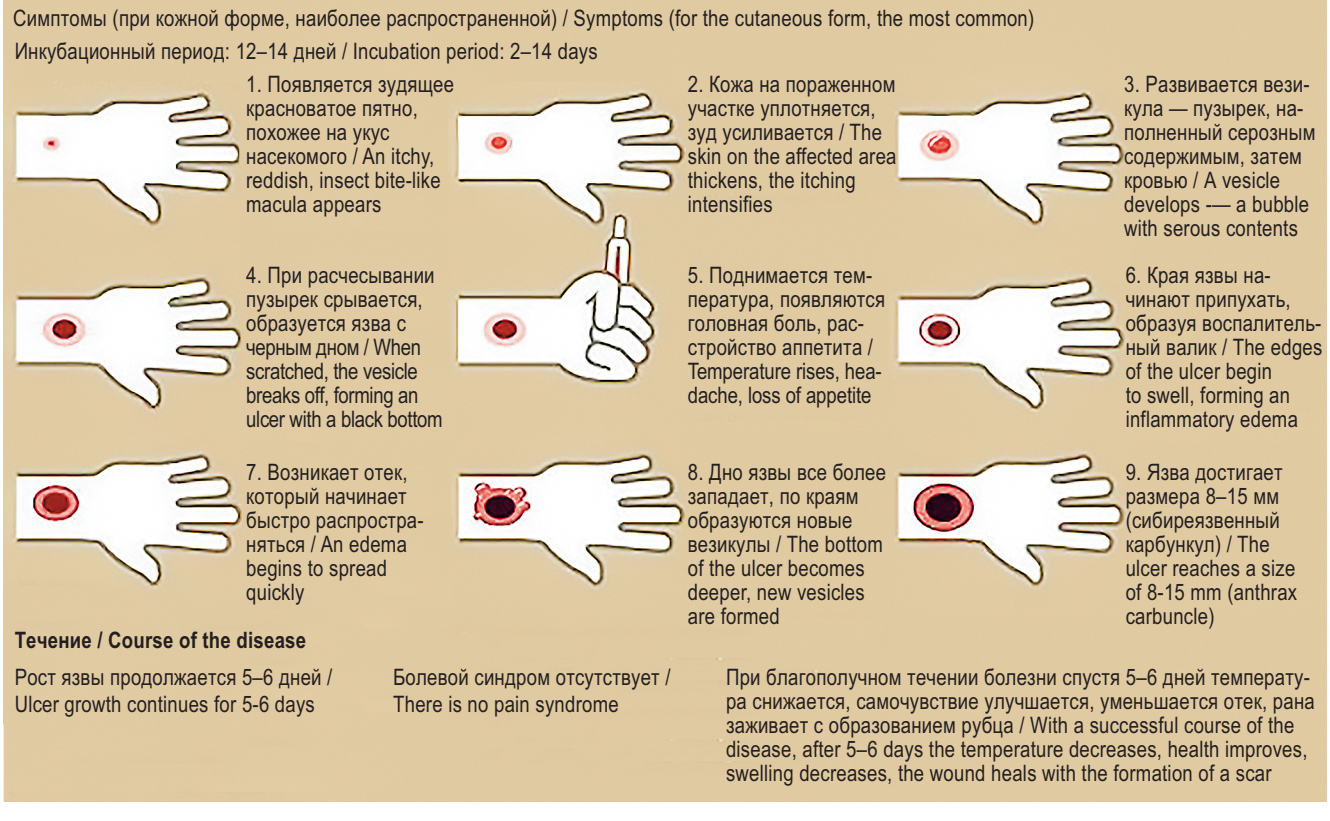

Fig. 4. Development of clinical manifestations in cutaneous anthrax

Рис. 4. Развитие симптомов при кожной форме сибирской язвы

regional lymph nodes become enlarged and thickened, but remain mobile and painless. After 2–3 weeks, due to necrosis, the central part of the ulcer turns into a painless dense scab, which quickly turns black and increases in size (Fig. 4). The scab rises above the skin surface, is surrounded by a pronounced zone of hyperemia and looks like a black coal on a red background ("coal on fire"), which is the basis for the name of the disease — anthrax (coal). There is a yellowish border between the black scab and the red area, making the ulcer tricolor (Fig. 5). By the fourth week, the scab is detached and a crater-shaped ulcer with a granulating floor and purulent discharge is formed; it subsequently undergoes secondary scarring.

Usually one carbuncle is formed, but there can be several, sometimes the number of them can reach 10–20 and more, the size of carbuncles can vary from a few millimeters to ten centimeters in diameter. The main distinguishing feature of the anthrax carbuncle is the absence of pain in the area of necrosis, practically painless is also the area of edema. The edematous form is characterized by the development of extensive edema without visible carbuncle. In the bullous form blisters with hemorrhagic content are formed immediately. In the erysipeloid form erythema with

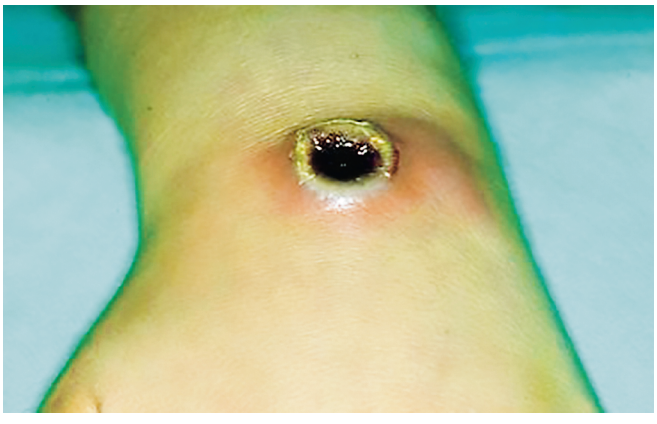

Fig. 5. Anthrax carbuncle. (URL: www.sibmedport.ru)

Рис. 5. Сибиреязвенный карбункул. (URL: www.sibmedport.ru)

whitish blisters develops, after opening of which shallow quickly drying ulcers are formed. Lethality in the cutaneous form, if untreated, may reach 20%, while treatment reduces to 2–3%. Intestinal anthrax is characterized by general intoxication, sharp cutting pain in the epigastric region, vomiting and diarrhea with an admixture of blood. The tongue is dry and covered with white plaque. Pulmonary anthrax is very severe. Against a background of high fever there is pain when breathing, cyanosis, dyspnea, wheezing, cough with frothy bloody sputum. The increase in peribronchial lymph nodes prevents the outflow of lymph and provokes pulmonary edema. Characteristic is a very rapid deterioration of the patient's condition and increasing changes in the lungs. Mortality, even with treatment, is up to 90% of cases. Septic or generalized form is rare. It is characterized by a decrease in body temperature, the development of infectious toxic shock, hypoxia, acidosis, multiorgan failure and disseminated intravascular coagulation. The death occurs on the 2–3rd day with the phenomena of acute collapse.

ANTHRAX AS A BIOLOGICAL WEAPON

Terrorism is currently one of the most acute and urgent problems, acquiring a global, international character in the modern world [6, 17]. It is very tempting for numerous terrorists to use biological weapons, which are no less dangerous than other types of weapons of mass destruction. The concept of bioterrorism has emerged, i.e. the threat of using means of mass destruction of biological (bacteriological) nature for terrorist purposes. Currently, there are at least 40 infectious agents that can be used as biological weapons. Among them, several pathogens, including anthrax, pose the greatest threat.

The latter fulfills most of the requirements for a potential biological weapon agent: it affects humans and animals, has a rapid effect, is highly virulent, extremely stable in the external environment, penetrates the organism by various routes, is easily cultivated in laboratories, and the selection of antibiotic-resistant strains is possible. The most probable way to use such a weapon is to atomize an aerosol containing spores, which would lead to a predominantly pulmonary form of the disease with high lethality. According to certain calculations, if an area of 20 km² is sprayed with sybillivorous spores for 2 hours over a city with a population of five million people, 500 thousand people will be exposed to the risk of infection, and the predicted number of people who fall ill may be 250 thousand, of whom 125 thousand are fatal [6].

The first serious use of *B. anthracis* as a biological weapon was carried out by nationalists against the aborigines of South Africa and Rhodesia (Zimbabwe) to suppress the liberation movement in 1978–1980. The major outbreak of anthrax in April 1979 in the Sverdlovsk region was connected, according to the main version, with the accidental release of pathogen spores from the laboratory of the military camp (Sverdlovsk-19) through damaged filters. According to another version it was made with enemy sabotage. In favor of the latter is the fact that foreign radio stations reported an anthrax epidemic on the 5th of April, while the first diagnosis was made on the 10th of April [16]. According to official data, 64 people died during the entire epidemic, while according to unofficial data there were more than a thousand deaths.

In 1993, the Japanese sect Aum Shinrikyo attempted bioterrorism by spreading *B. anthracis* in offices, which fortunately was unsuccessful. As of 2001, at least 17 countries already had bacteriological weapons at their disposal. New genetically modified strains of *B. anthracis* with increased virulence, polyantibiotic resistance, and the ability to cause disease in the immune system (such cultures are called vaccine-resistant) are constantly being developed. Work is under way to insert genes encoding the synthesis of anthrax toxin into the genome of other microorganisms, such as *B. cereus* and *B. thuringiensis*, for which there are no effective vaccines.

In Septeber 2001, an act of bio-terrorism was attempted in the USA by mailing mail containing anthrax spores, resulting in 22 people falling ill (11 of them felt ill with cutaneous anthrax and 11 felt ill with inhalational anthrax) and 5 deaths. This made obvious the potential danger of *B. anthracis* as an agent of bioterrorism and drew increased attention to the problem, resulting in the development of effective methods of treatment, prophylaxis and rapid diagnosis of anthrax. In 2001, only for the study of the genome of *B. anthracis* one of the scientific centers of the United States was allocated 200 thousand dollars. However, not

only acts of bioterrorism are dangerous, but also negligence when working with especially dangerous pathogens in specialized laboratories. After the events of 2001, under the pretext of combating bioterrorism, numerous biological research centers — laboratories for prevention of bioterrorism — were established in the USA and other countries. As of 2006, there were officially more than 400 such institutions in the U.S. alone, carrying out secret Pentagon programs. In June 2014, at the State Bioterrorism Prevention Laboratory in Atlanta, USA, B. antrhacis was handled in a routine laboratory not designed to handle highly dangerous pathogens, and the samples tested were not neutralized, exposing 75 people in the laboratory to the threat of infection. In May 2015, as a result of criminal negligence, live spores of *B. antrhacis* (68 parcels in total) were sent **by regular post** from a military laboratory at the Utah Proving Ground, USA, to 24 laboratories in 11 states and 5 countries (South Korea, Australia, Canada, United Kingdom, Japan).

Thus, such laboratories can become a source of new threats for spreading the pathogen worldwide.

PRINCIPLES OF LABORATORY DIAGNOSTICS

Effective anthrax therapy requires a diagnosis as soon as possible, but physicians rarely encounter this infection, making them less alert to it. In 10–40% of cutaneous infections, patients are diagnosed as “carbuncle”, “furuncle”, “insect bite” and other similar cases and sent for surgical treatment. A significant difficulty is the recognition of generalized anthrax. At the slightest suspicion of anthrax it is necessary to conduct laboratory diagnostics [1, 3, 12], which is carried out in strict accordance with the current instructions and rules (guidelines 4.2.2413-08, 4.2.2941-11). Microscopic, bacteriologic, biological methods, serodiagnosis, allergodiagnosis, and molecular biological methods [11], in particular molecular typing methods [2, 5], are used. These microbiological methods make it possible to confirm the etiology of the disease, while biochemical methods make it possible to assess its severity. For direct anthrax diagnostic methods (microscopic, bacteriological, biological and rapid diagnostic methods), the material to be examined is the content of vesicles, carbuncles, scabs, sputum, feces, blood, cerebrospinal fluid and sectional material. Materials from cadavers should be taken and examined as soon as possible after death, as extraneous microflora develops rapidly, making it difficult to isolate a pure culture. Clinical material is collected in medical and preventive institutions in protective clothing at the admission of the patient before the start of antibiotic therapy according to guidliness 4.2.2941-11. For this purpose a special kit is used — “universal stack for the collection of material from people and from environmental objects for the study of especially dangerous infectious diseases”. Laboratory personnel shall be provided with protective clothing and personal protective equipment for work with microorganisms of pathogenicity group II.

ANTHRAX TREATMENT AND PREVENTION

Complex therapy of anthrax patients includes two main directions: etiotropic antimicrobial and specific antitoxic therapy and nonspecific symptomatic and antishock therapy. The following antibacterial drugs are used for the treatment of anthrax in Russia: beta-lactams (benzylpenicillin, ampicillin), tetracyclines (tetracycline, doxycycline), fluoroquinolones (ciprofloxacin, pefloxacin, ofloxacin), and rifampicin. Until recently, penicillin was the main drug for the treatment of anthrax, but nowadays, due to the emergence of strains producing beta-lactamases, it should be used only if sensitivity to it has been confirmed. Reserve drugs include aminoglycosides (gentamicin, amikacin, sizomycin), since resistance to antibiotics of this group develops slowly. It is possible to use both individual drugs and their combinations, such as penicillin and tetracycline, ciprofloxacin and rifampicin. Antibiotics are most effective in cutaneous anthrax, while combinations are recommended in septic anthrax. In all cases, treatment should be started as early as possible from the onset of the first clinical symptoms. In the development of sepsis and toxinemia, the use of antimicrobials may be ineffective and even worsen the patient’s condition due to the death of microbes and the release of a large amount of exotoxin that has not yet had time to leave the cells. Neutralization of the toxin in moderate and severe anthrax requires administration of large doses of antisybriasis equine immunoglobulin, which contains active gamma- and beta-globulin fractions isolated from the blood serum of hyperimmunized horses. In addition to neutralizing the toxin, the drug inhibits spore germination and capsule formation (inhibition of glutamine polypeptide synthesis). Recently, the use of sibiriazoon immunoglobulin has been discontinued due to frequently developing allergic reactions. Anti-sybriasis human immunoglobulin, immunoglobulin based on Fab-fragments, preparations based on monoclonal antibodies to the protective antigen, lethal factor and polyglutamine capsule of *B. anthracis,* inhibitors of cell receptors of the protective antigen and others are being developed.

Nonspecific prophylaxis of anthrax in humans includes a set of veterinary and medical-sanitary measures (Sanitary and Epidemiologic Rules 3.1.7.2629-10). These include:

- vaccination of susceptible animals, which is effective, but does not ensure complete elimination of

the pathogen due to its prolonged persistence in the soil;
- identification, accounting and elimination of sybiraemic foci;
- sanitary and epidemiological control in anthrax-affected areas, as well as during the procurement, processing, transportation and storage of raw materials of animal origin;
- prophylactic, current and final disinfection, incineration rather than burial of corpses of infected animals and raw materials,
- sanitary and educational work with the population, etc.

Emergency prophylaxis is carried out when anthrax cases appear among animals or people, as well as when there is a threat of aerosol contamination in case of bioterrorism. It is carried out in the area of an active anthrax focus using antibiotics of different groups no later than five days after possible contamination — contact with infected animals or livestock products. Rifampicin, doxycycline, ampicillin, oxacillin, ciprofloxacin orally; gentamicin intramuscularly in maximum doses for five days are recommended for use. Equine anti-anthrax immunoglobulin can also be used: adults in a dose of 20–25 ml, adolescents from 14 to 17 years can get 12 ml, children can get 5 ml (methodological recommendations 0100/3556-04-34).

The optimal duration of emergency prophylaxis for suspected aerogenic anthrax infection has not been precisely determined. In 2001 in the USA, people at risk of such infection were given emergency prophylaxis with a course of an antimicrobial therapy (ciprofloxacin, doxycycline or amoxicillin) for 60 days, using 3.75 million tablets. The need for prolonged preventive antibiotic therapy is due to the effect of delayed spore germination in the lungs. Spores can persist in the alveoli for several weeks (up to 8 weeks or more), while antibiotics are active only against vegetative cells and germinating spores.

Vaccines are used for early anthrax prophylaxis (they create immunity lasting up to one year). Two vaccines are currently registered and used in Russia:

1) anthrax live dry vaccine for subcutaneous and scarification, containing live spores of the vaccine strain STI (after the name of the Sanitary and Technical Institute where the vaccine was developed);
2) combined liquid anthrax vaccine for subcutaneous administration, contains a mixture of live spores of vaccine strain STI-1 and purified concentrated protective anthrax antigen adsorbed on aluminum hydroxide.

An aerosolized vaccine has also been developed.

Risk contingents subject to prophylactic vaccination include:

- animal handlers and other persons professionally engaged in the pre-slaughter housing of livestock, as well as slaughtering, skinning and cutting of carcasses;
- persons engaged in the collection, storage, transportation and primary processing of raw materials of animal origin;
- laboratory personnel working with material suspected of being infected with anthrax;
- persons performing certain work in anthrax-enzootic areas (agricultural, agro- and hydromeliorative, construction and other work related to excavation and movement of soil; procurement, field, geological, survey, expeditionary);
- military personnel in the presence of epidemiological indications.

Foreign countries use chemical vaccines based on a protective antigen produced by a capsule-free nonproteolytic avirulent strain of *B. anthracis* adsorbed on aluminum hydroxide or alum. The best known vaccines from this group are the American AVA — Anthrax Vaccine Adsorbed (capsule-free strain V770-NP1-R) and the British AVP — Anthrax Vaccine Precipitated (avirulent strain Sterne 34F2) with a 30% increased amount of lethal factor.

Despite their efficacy, the existing vaccines have a number of drawbacks, which necessitates additional work on their improvement aimed at increasing immunogenicity and reducing reactogenicity. To increase the immunogenicity of recombinant vaccines, it is proposed to use *B. subtilis*, *B. brevis* and others synthesizing capsular polypeptides of *B. anthracis*. Vaccines based on recombinant DNA, polyvalent vaccines, including those against anthrax, etc., are being developed. Most researchers agree that a full-fledged chemical vaccine should contain antigens aimed at the production of anti-spore, anti-capsule and anti-toxic immunity in the body.

CONCLUSION

In modern conditions, anthrax maintains a global nosoareal and continues to be an urgent problem for many countries, including the Russian Federation. Vaccination of susceptible animals does not ensure elimination of the pathogen from environmental objects. The unpredictable long-term survival of *B. anthracis* spores in soil allows the pathogen to retain not only viability but also virulence. Hyperendemic foci remain on the territory of the country, the activation of which can occur as a result of natural disasters and climatic changes, as

well as anthropogenic impact and man-made disasters. We should not forget about the threat of importation of infected raw materials of animal origin into the territory of the country from neighboring countries, as well as the increasing threat of bioterrorism. The emergence of not only antibiotic-resistant but also vaccine-resistant strains of *B. anthracis* in nature is alarming. All this indicates the need to create a comprehensive anthrax control program aimed at improving the methods of its diagnosis, treatment and prevention, as well as the identification and sanitation of soil anthrax foci.

ADDITIONAL INFORMATION

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

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

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

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ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом и.о. ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 23.06.16

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРОМ

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

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

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

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

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

Все цитирования производятся следующим образом:

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

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

В виде исключения в тексте могут приводиться ФИО конкретных авторов в формате И. О. Фамилия, год и даже название источника, но при этом все равно обязательна ссылка (в квадратных скобках в конце предложения) на источник, включенный в список литературы.

(Например: «В 1892 году великий Эраст Гамильтонский описал в своем бессмертном труде «Об открытии третьего уха у человека» третье (непарное) ухо» [34].)

Литература (References)

Учитывая требования международных систем цитирования, список литературы приводится не только в обычном виде, но также и дополнительно в транслитерированном (см. Транслитерация).

В статье приводятся ссылки на все упоминаемые в тексте источники.

Фамилии и инициалы авторов в пристатейном списке приводятся в алфавитном порядке, сначала русского, затем латинского алфавита.

В описании указываются все авторы публикации.

Библиографические ссылки в тексте статьи даются в квадратных скобках.

Ссылки на неопубликованные работы не допускаются.

Список литературы комплектуется в следующем порядке:

Нормативные акты

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

Интернет-ресурс

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

2. Если есть только ссылка на сайт — вносится в список литературы в конце, с указанием даты обращения.

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

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

Книга

Автор(ы) название книги (знак точка) место издания (двоеточие) название издательства (знак точка с запятой) год издания. Если в качестве автора книги выступает редактор, то после фамилии следует ред.

Айламазян Э.К., Новиков Б.Н., Зайнулина М.С., Палинка Г.К., Рябцева И.Т., Тарасова М.А. Акушерство: учебник. 6-е изд. СПб.; 2007.

Преображенский Б.С., Темкин Я.С., Лихачев А.Г. Болезни уха, горла и носа. М.: Медицина; 1968.

Радзинский В.Е., ред. Перинеология: учебное пособие. М.: РУДН; 2008.

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

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

Глава из книги

Автор(ы) название главы (знак точка) В кн.: или In: далее описание книги [Автор(ы) название книги (знак точка) место издания (двоеточие) название издательства (знак точка с запятой) год издания] (двоеточие) стр. от и до.

Коробков Г.А. Темп речи. В кн.: Современные проблемы физиологии и патологии речи: сб. тр. Т. 23. М.; 1989: 107–11.

Статья из журнала:

Автор(ы) название статьи (знак точка) название журнала (знак точка) год издания (знак точка с запятой) том (если есть в круглых скобках номер журнала) затем знак (двоеточие) страницы от и до.

Кирющенков А.П., Совчи М.Г., Иванова П.С. Поликистозные яичники. Акушерство и гинекология. 1994; N 1: 11–4.

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

Simpson J. et al. Association between adverse perinatal outcomes and serially obtained second and third trimester MS AFP measurements. Am. J. Obstet. Gynecol. 1995; 173: 1742.

Deb S., Campbell B.K., Pincott-Allen C. et al. Quantifying effect of combined oral contraceptive pill on functional ovarian reserve as measured by serum anti-Müllerian hormone and small antral follicle count using three-dimensional ultrasound. Ultrasound. Obstet. Gynecol. 2012; 39 (5): 574–80.

Тезисы докладов, материалы научных конференций

Бабий А.И., Левашов М.М. Новый алгоритм нахождения кульминации экспериментального нистагма (миниметрия). III съезд оториноларинг. Беларуси: тез. докл. Минск; 1992: 68–70.

Салов И.А., Маринушкин Д.Н. Акушерская тактика при внутриутробной гибели плода. В кн.: Материалы IV Российского форума «Мать и дитя». М.; 2000; ч. 1: 516–9.

Авторефераты

Петров С.М. Время реакции и слуховая адаптация в норме и при периферических поражениях слуха. Автореф. дис. … канд. мед. наук. СПб.; 1993.

Прочее

World Health Organization. Prevalence and incidence of selected sexually transmitted infections, 2005 global estimates. Geneva: World Health Organization; 2011.

Транслитерация

Список литературы подается в двух вариантах: первый на языке оригинала (русскоязычные источники кириллицей, англоязычные латиницей), второй — (References) в романском алфавите (для Scopus и других международных баз данных, повторяя в нем все источники литературы, независимо от того, имеются ли среди них иностранные). Если в списке есть ссылки на иностранные публикации, они полностью повторяются в списке, готовящемся в романском алфавите.

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

Пример:

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

Технология подготовки ссылок с использованием системы автоматической транслитерации и переводчика:

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

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

Копируем транслитерированный текст в готовящийся список References. Переводим на английский язык название книги, статьи, постановления и т.д., переносим его в готовящийся список. **Внимание!** Необходим авторский корректный перевод названия. Автоматический перевод, предполагающий возможное искажение сути названия статьи, недопустим.

Объединяем описания в соответствии с принятыми правилами и редактируем список. В конце ссылки в круглых скобках указывается (in Russian). Ссылка готова.

Примеры транслитерации русскоязычных источников литературы для англоязычного блока статьи.

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

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

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

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

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

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

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

Тезисы докладов, материалы научных конференций

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

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

Авторефераты

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

Описание Интернет-ресурса

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

Пример списка литературы, включающего транслитерированный вариант:

ЛИТЕРАТУРА

1. Кофиади И.А. Генетическая устойчивость к заражению ВИЧ и развитию СПИД в популяциях России и сопредельных государств. Автореф. дис. ... канд. биол. наук. М.; 2008. Доступен

по: http://www.dnatechnology.ru/ files/images/d/0b136b567d25d4be1dfa26a8b39ec2b9.pdf (дата обращения 18.09.2014).
2. Flynn E., Eyre S., Packham J. Childhood Arthritis Prospective Study (CAPS), UKRAG Consortium, BSPAR Study Group, Barton A., Worthington J., Thomson W. Association of the CCR5 gene with juvenile idiopathic arthritis. Genes Immun. 2010; 11 (7): 584–89.
и т.д.

REFERENCES

1. Kofiadi I.A. Geneticheskaya stoychivost' k zarazheniyu VICh i razvitiyu SPID v populyatsiyakh Rossii i sopredel'nykh gosudarstv [Genetic resistance to HIV infection and development of AIDS in populations of Russia and neighboring countries]. PhD-thesis. M.; 2008. Available from: http://www.dna-technology.ru/files/images/d/0b136b567d25d4be1dfa26a8b39ec2b9.pdf (accessed 18.09.2014) (in Russian).
2. Flynn E., Eyre S., Packham J. Childhood Arthritis Prospective Study (CAPS), UKRAG Consortium, BSPAR Study Group, Barton A., Worthington J., Thomson W. Association of the CCR5 gene with juvenile idiopathic arthritis. Genes Immun. 2010; 11 (7): 584–89.
Etc.

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

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

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

АВТОРСКОЕ ПРАВО

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

1) Редакции передается право на оформление, издание, передачу Журнала с опубликованным материалом Автора для целей реферирования статей из него в Реферативном журнале ВИНИТИ, РНИЦ и базах данных, распространение Журнала/ авторских материалов в печатных и электронных изданиях, включая размещение на выбранных либо созданных Редакцией сайтах в сети Интернет в целях доступа к публикации в интерактивном режиме любого заинтересованного лица из любого места и в любое время, а также на распространение Журнала с опубликованным материалом Автора по подписке;
2) территория, на которой разрешается использовать авторский материал, — Российская Федерация и сеть Интернет;
3) срок действия Договора — 5 лет. По истечении указанного срока Редакция оставляет за собой, а Автор подтверждает бессрочное право Редакции на продолжение размещения авторского материала в сети Интернет;
4) Редакция вправе по своему усмотрению без каких-либо согласований с Автором заключать договоры и соглашения с третьими лицами, направленные на дополнительные меры по защите авторских и издательских прав;
5) Автор гарантирует, что использование Редакцией предоставленного им по настоящему Договору авторского материала не нарушит прав третьих лиц;
6) Автор оставляет за собой право использовать предоставленный по настоящему Договору авторский материал самостоятельно, передавать права на него по договору третьим лицам, если это не противоречит настоящему Договору;
7) Редакция предоставляет Автору возможность безвозмездного получения справки с электронными адресами его официальной публикации в сети Интернет;
8) при перепечатке статьи или ее части ссылка на первую публикацию в Журнале обязательна.

ПОРЯДОК ЗАКЛЮЧЕНИЯ ДОГОВОРА

Заключением Договора со стороны Редакции является опубликование рукописи данного Автора в журнале «Russian Biomedical Research» и размещение его текста в сети Интернет. Заключением Договора со стороны Автора, т.е. полным и безоговорочным принятием Автором условий Договора, является передача Автором рукописи и экспертного заключения.

РЕЦЕНЗИРОВАНИЕ

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

АВТОРСКИЕ ЭКЗЕМПЛЯРЫ ЖУРНАЛА

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

АДРЕС РЕДАКЦИИ

194100, Санкт-Петербург, Литовская ул., 2
e-mail: scrcenter@mail.ru
Сайты журнала: http://www.gpmu.org/science/pediatrics-magazine/Russian_Biomedical_Research, https://ojs3.gpmu.org/index.php/biomedical-research