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Общество с ограниченной ответственностью «Синапс»
107076, Москва, ул. Короленко, д.3А, офис 18Б
Тел.: (495) 777-41-17
E-mail: info@medarhive.ru

ГЕНЕРАЛЬНЫЙ ДИРЕКТОР
Чернова Ольга Александровна
o_chernova@medarhive.ru

АДРЕС РЕДАКЦИИ
107076, Москва, ул. Короленко, д.3А, офис 18Б
Тел.: (495) 777-41-17

Медицинский редактор
Ефремова Елена Владимировна, *к.м.н., доцент кафедры терапии и профессиональных болезней ФГБОУ ВО «Ульяновский государственный университет» (Ульяновск, Россия)*
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Верстка
Виталий Котов

Отдел распространения и рекламы
Бабяк Алина
reklama@medarhive.ru

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FOUNDER AND PUBLISHER
«SYNAPSE» LLC
107076, Moscow, Korolenko str., 3A, of. 18B
info@medarhive.ru

CHIEF EXECUTIVE OFFICER
Olga A. Chernova
o_chernova@medarhive.ru

JOURNAL EDITORIAL OFFICE
107076, Moscow, Korolenko str., 3A, of. 18B
Phone: +7(495)777-41-17

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Kotov Vitaly

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Babiak Alina
reklama@medarhive.ru

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С.Л. Бабак*, М.В. Горбунова, А.Г. Малявин, И.В. Шашенков

ФГБОУ ВО «Московский государственный медико-стоматологический университет им. А.И. Евдокимова», Минздрава России, Москва, Россия

КОНЦЕПЦИЯ СНИЖЕНИЯ ВРЕДА ОТ ТАБАКА: ПРОШЛОЕ, НАСТОЯЩЕЕ, БУДУЩЕЕ

S.L. Babak*, M.V. Gorbunova, A.G. Malyavin, I.V. Shashenkov

Moscow State University of Medicine and Dentistry named after A.I. Evdokimov

The Concept of Harm Reduction from Tobacco: Past, Present, Future

Резюме

Концепция «снижения вреда от табака» (СВОТ) является темой для дискуссии в контексте международной борьбы против употребления любых видов табака. Такая концепция предполагает предоставление потребляющим табак лицам, которые не могут или не желают прекратить табакокурение или потребление других видов табака (нюхательный, жевательный), менее вредную табачную продукцию с модифицированным риском (ТПМР) для дальнейшего употребления. Скептицизм в отношении СВОТ огромен и связан с негативным опытом табачных компаний по выпуску сигарет с низким содержанием табачных смол/никотина, которые должны были иметь существенно более низкие риски для здоровья чем обычные сигареты. Парадоксально, но именно такой опыт послужил трамплином к росту числа табачных изделий, которые потенциально обладают свойствами ТПМР. Более того, некоторые члены антитабачной коалиции, включая ВОЗ, рассматривают переход табакокурильщиков на ТПМР как стратегию с большим потенциалом. Однако, Европейская группа специалистов считает, что стратегия СВОТ не работает и приведёт к привыканию к табаку ещё одного поколения молодых лиц. В этой статье мы подвергли критическому анализу историю прошлого и настоящего табачных изделий, мифы и противоречия вокруг них. Мы постарались максимально объективно оценить современную концепцию СВОТ, обладающую высоким потенциалом к реальному сокращению числа смертей, связанных с табакокурением.

Ключевые слова: *снижение вреда от табака, СВОТ, табачная продукция с модифицированным риском, ТПМР, табакокурение*

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Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The concept of tobacco harm reduction (THR) is a speculative and controversial topic in the context of the international battle against the use of all types of tobacco. This concept involves providing tobacco users who are unable or unwilling to quit smoking or using other types of tobacco (snuff, chewing), with modified risk tobacco product (MRTP) for continued use. Skepticism about THR is huge and is associated with the negative experience of tobacco companies to produce cigarettes with a low content of tobacco tar/nicotine, which should have had significantly lower health risks than conventional cigarettes. Paradoxically, such an experience served as a springboard to an increase in the number of tobacco products that potentially have the properties of MRTP. Moreover, some members of the anti-smoking coalition, including WHO, consider the transition of tobacco smokers to MRTP as a strategy with great potential. However, the European Group of Experts believes that the MRTP strategy does not work and will lead to

*Контакты: Сергей Львович Бабак, e-mail: sergbabak@mail.ru
*Contacts: Sergei L. Babak, e-mail: sergbabak@mail.ru
ORCID ID: https://orcid.org/0000-0002-6571-1220

another generation of young people getting used to tobacco. In this article, we have critically analyzed the history of the past and present of tobacco products, myths and contradictions around them. We have tried to evaluate the modern concept of S THR as objectively as possible, which has a high potential for a real reduction in the number of deaths associated with smoking.

Key words: *tobacco harm reduction, THR, modified risk tobacco product, MRTP, tobacco smoking*

Conflict of interests

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ENDS — efficiency of Electronic Nicotine Delivery Systems, ERS — European Respiratory Society, FCTC — World Health Organization Framework Convention on Tobacco Control, FDA — Food and Drug Administration, MRTP — Modified Risk Tobacco Products, PMTA — premarket tobacco product application, THR — tobacco harm reduction, THS — tobacco heating system

Introduction

Today, there are about 1.3 billion tobacco smokers on our planet; six million of them die annually from smoking cigarettes and other combustible tobacco substances. Just in the USA, such a "tobacco landscape" causes 480,000 deaths a year, results in 16 million cases of tobacco-related diseases, and reduces the life expectancy of smokers by ten years [1, 2]. Moreover, the analysis of the current "tobacco scenario" revealed that the high costs (disease burden) due to tobacco-related deaths and diseases can be significantly reduced by implementing measures to stop widespread tobacco smoking [3]. There are effective tobacco control strategies, such as raising prices of cigarettes and tobacco products in general, anti-smoking awareness campaigns in media, smoking bans in public places and at work, and providing affordable evidence-based medical methods of quitting smoking. Such measures have contributed to a significant and consistent reduction in cigarette smoking. Nevertheless, the role and significance of such programs in "reducing the harm from tobacco and burned tobacco products" is still the subject of numerous discussions [4].

It is worth reminding that the "tobacco harm reduction" (THR) concept provides for "minimizing harm, overall mortality and morbidity among tobacco smokers without completely quitting tobacco and nicotine use" [5]. This means that THR recognizes tobacco smoking cessation/abstinence as a "required and achievable outcome", leaving a "window of opportunity" for alternative harm reduction for patients who would never be able to quit tobacco smoking. Moreover, THR has no advantages or precedence over complete cessation/abstinence from tobacco use. In fact, the THR concept is aimed at respecting certain human rights when patients with tobacco dependence are provided with modified risk tobacco products (MRTP) [5, 6]. THR is rather a measure of social justice that potentially eliminates medical and social inequalities between healthy and tobacco-dependent individuals. For example, tobacco dependence among people "below the poverty level" or with a low level of education is many times higher than among the general population [7]. This social group (poverty) smokes more often, has high tobacco dependence, and more often makes an attempt to quit smoking with an extremely low chance of success. This social group has a higher risk of developing lung cancer compared to individuals with high income and education. A similar scenario is observed among tobacco smokers with mental illnesses and type 2 diabetes mellitus (DM2) [8].

Considering the high prevalence of tobacco smoking and the practical difficulties in achieving complete tobacco cessation, access to MRTP for tobacco-dependent patients may be an alternative strategy to reduce the risks of health deterioration. However, the role of THR in tobacco control is poorly understood, controversial and disputable. In this analytical review, we tried to analyze the history of the past and present of tobacco products, present-day THR concepts, myths and contradictions around them, as well as the most promising approaches to implementing this concept for tobacco-dependent patients with a high potential for actual reduction of the number of smoking-related deaths.

1. Evolution of Risk Modified Tobacco Products

Much skepticism about the THR concept is fueled by negative experiences with low tar/nicotine cigarettes. In 1964, after the publication of an official medical report about the link between tobacco smoking and a number of fatal diseases, for the first time, serious concerns arose among different social groups (rich and poor) regarding health risks [9]. At the same time, cigarette manufacturers demonstrated a genuine interest in "safe cigarettes".

Moreover, an academic paper was published on the toxicity of cigarettes and the relationship between tar/nicotine levels and the number of cigarettes smoked with the development of malignant tumors/lung cancer [10]. These studies revealed that the health risk for a smoker will be significantly reduced if there is less tar and nicotine in cigarettes. Subsequently, the US Federal Chamber of Commerce approved testing of tar/nicotine levels in cigarettes using "smoking machines" with "standardized smoking parameters". Later, many tobacco companies started producing and extensively selling cigarettes with low tar and nicotine. It is hard to believe that health conscious tobacco smokers were advised to switch to "special cigarettes" rather than quit smoking! [11]. The tag lines of that time were: "SMOKE IT PROPERLY: JUST LIGHT CIGARETTES!"; smokers were portrayed as athletic, cheerful people in nice scenery with excellent health. Also, "SPECIAL CIGARETTES" were designated as "light", "ultralight", "soft", "zero" [12].

With the accumulation of scientific knowledge about tobacco-related health risks, the myth that cigarettes with low tar/nicotine content can reduce the risks of cancer and death among tobacco smokers compared to "conventional" cigarettes has been finally dispelled. It was found that the reduction of tar/nicotine, as measured by "smoking machines", was achieved only by the design of cigarettes, not by an actual reduction in tar/nicotine in the tobacco filler. For example, additional ventilation of the cigarette filter and adding special smoke vents are now the primary methods of reducing the "tobacco load" [13]. However, these "ventilated filters" have changed the behavior of smokers by developing a new "compensatory smoking technique". In fact, it made it possible to achieve high levels of "tobacco exposure" by increasing the puff time, blocking ventilation openings at the moment of inhalation and puffing, and also by increasing the number of cigarettes smoked per day [14]. As a result, the expected reduction in health risks to smokers did not correlate with that calculated by "smoking machines" [15]. It is possible that it was the "ventilated filters" of cigarettes that contributed to the increase in cases of peripheral lung cancer (adenocarcinoma) due to deep inhalation of toxic chemicals by the smoker and/or increased mutagenicity of tobacco smoke due to the specific features of the combustion of cigarettes with a ventilated filter [16].

A huge scandal erupted in 2006 when the US Department of Justice prosecuted a number of tobacco companies for racketeering and fraud. In her final opinion, Judge Gladys Kessler said that the tobacco companies were deliberately deceiving the public. The court found that, for decades, tobacco companies had been producing cigarettes with low tar/nicotine content, knowing that "light", "ultralight", "soft", and "zero" brought no health benefits to smokers compared to standard cigarettes. Nevertheless, they made smokers believe that these very cigarettes were a way of reducing the adverse health effects of smoking. Therefore, they could be an alternative to complete cessation/abstinence from tobacco smoking [17]. Later, the US Federal Chamber of Commerce (2008) completely removed tar/nicotine labeling on cigarette packs that could mislead smokers. Finally, in 2010, the Food and Drug Administration (FDA), in accordance with the Family Smoking Prevention and Tobacco Control Act (FSPTCA), banned the use of low-risk smoker labels on cigarette packs or in advertisements, including "light", "ultralight", "mild", "zero". Nevertheless, tobacco companies still use colors (e.g., silver, gold) to denote the particular delicacy of products, as well as the terms "thin" or "soft" that support the misconceptions about their low harm to the health of smokers [18].

In the context of THR, the publication by Prof. Michael Russell (UK) is of interest. It calls for reducing tar content in cigarettes but maintaining a moderate nicotine level. According to Michael Russell, "People smoke for nicotine and die from the tar. Moreover, as long as there is a sufficient amount of nicotine in the "cigarette puff", smokers will be able to easily tolerate the reduction to zero of any other harmful components" [19]. In a series of experiments, this approach relieved tobacco addicts from cigarettes and contributed to the cessation of tobacco smoking [20]. This "simple idea" was picked up in the 1990s by a number of tobacco companies targeting tobacco smokers with high health concerns through the provision of specialty products with potential harm reduction. These include: "premium taste" cigarettes with a "reduced level of carcinogens" and high level of nicotine; cigarettes with a "reduced level of nicotine" and zero nicotine cigarettes for "nicotine freedom"; and a variety of non-combustible tobacco systems. It is obvious that such tobacco products do not in any way reduce harm to the health of tobacco-dependent patients [16].

There is an interesting report published in Sweden (1994) on the reduction of harm to people who use snus. SNUS is a special type of unburned tobacco product in the form of a small bag with shredded and moist tobacco to be placed between the upper lip and gum for a long time (30–60 min). Nicotine from tobacco is absorbed/enters the body through the oral cavity. Harm reduction has been associated with low tobacco-specific nitrosamines (TSNA) and other toxic/harmful substances in snus [21]. The study demonstrated that among Swedish men who use snus, there is a sharp decrease in cigarette smoking and a decrease in the incidence of lung cancer and myocardial infarction. Also, the rate of return to cigarette smoking among snus users is significantly lower than among those who quit smoking [22]. Compared

to EU other countries, Sweden, which banned "tobacco burning", currently has the lowest incidence of tobacco-related diseases. However, the European Commission for Tobacco Control is seriously concerned that overall tobacco use remains high in Sweden and that SNUS cannot be considered a "safe tobacco product" [23]. The "Swedish experience" led cigarette manufacturers in the United States to start selling SNUS products (for example, Camel Snus®, Marlboro Snus®) as a substitute for cigarettes in places where smoking is prohibited or as a means of quitting smoking. For example, an advertisement for "Camel Snus®" included the following headings: "Freeze Fire", "Deceive the Old Flame", "New York City Smokers: Rise Above Prohibitions!" or "Friends Bar" [24].

2. Reducing Tobacco Harm: Risks, Benefits, Acceptability

In accordance with US law (FSPTCA, 2009), the main regulatory authority for standard cigarettes, smokeless tobacco, and alternative tobacco products is the FDA, which is the main regulator of THR in the world today. It should be noted that the emergence of new tobacco products with different levels of risk of harm to the health of tobacco smokers is more likely due to the desire of tobacco companies to remain on the market than their actual desire to improve the THR concept [3]. For example, the widespread adoption of "electronic cigarettes" created a break between those who perceived the technology as having the potential to replace traditional cigarettes and those who recognized it as even more harmful than cigarettes. Also, in 2013–2014, there was a public debate over an evidence-based plan for tobacco control that maximizes the benefits and minimizes harm to public health. Despite the consensus reached regarding the risks of various nicotine delivery systems to human health, the main question remained unanswered. The question was represented like this: "Should we save the millions of lives of tobacco dependent patients (who cannot stop using tobacco) or those who do not want to stop using tobacco by switching to modified risk tobacco products (MRTP), or fighting to prevent a new generation of nicotine addiction through an absolute ban on the use tobacco in any form?" (Fig. 1) [25].

Medical experts who favor absolute and total prohibition of using tobacco in any form express serious fears and concerns that MRTP and electronic cigarettes (e-cigarettes) can drive up the use of harmful substances by young people. According to the "gateway theory", this may discourage tobacco-dependent patients from trying to quit tobacco use. Their concerns were not unfounded. Studies carried out over the years revealed extremely contradictory data regarding the effectiveness of electronic nicotine delivery systems (ENDS) as a means of completely quitting smoking [6, 14]. However, the FDA has approved a global nicotine and tobacco regulatory plan to switch tobacco-dependent patients to MRTP as an additional strategy to improve public health [26].

However, the position of the FDA (2019), as the regulator of THR, on the one hand, provides for the abolition of restrictions regarding ENDS with cartridges without menthol/tobacco and discrimination against flavored cartridges. On the other hand, it requires focusing on preventing young people from accessing such products and their promotion among young people. The ban does not apply to ENDS that contain no fruit flavors, if there is no promotion of their use among young people. This allows adult tobacco-addicted patients who wish to quit smoking to use flavored e-cigarettes more efficiently. According to the US Secretary of Health and Human Services, Alex Azar, "Priority should be given to preventing young people from accessing ENDS with the right balance of using e-cigarettes by adults in order to quit smoking. All rules should be followed to ensure that ENDS do not lead to the development of "nicotine dependence" in our youth" [28].

At the same time, a group of experts from the European Respiratory Society (ERS) argue that the use of ENDS (electronic cigarettes) increases the number of patients with severe lung diseases by 1,600 cases/year, with 34 cases of being fatal. The Tobacco Control Committee of the ERS Consumer Protection Council published a paper that included seven of the main arguments of the ERS about the failure of the THR concept as a public tobacco control measure [29]. Let's consider them in more detail.

Figure 1. *Schematic representation of the main dilemma of the tobacco harm reduction concept (THR). The explanation is in the text. (Adapted from: Hatsukami DK et al. Prev Med. 2020 Nov; 140: 106099)*

Argument 1. THR strategy is based on the erroneous assertion that tobacco smokers are unable or unwilling to quit tobacco use. On the contrary, most of them do not want to be addicted to nicotine and want to stop smoking. Present-day tobacco smokers smoke fewer cigarettes, are more motivated to quit smoking, and are less tobacco-dependent than in the past. Moreover, there is safe and effective medical treatment for tobacco dependence [30].

Argument 2. THR strategy is based on poorly documented evidence that ENDS are highly effective in smoking cessation. It has been proven that 80% of people who quit smoking by switching to electronic cigarettes remain addicted to nicotine. Also, long-term use of ENDS (more than three months) reduces the patients' chance of abstaining from nicotine. Studies of smokeless tobacco as a cessation agent are controversial and revealed no convincing effects [31].

Argument 3. THR strategy is based on the erroneous assumption that tobacco smokers will completely stop smoking conventional cigarettes and switch to MRTP. It has been proven that 80% of patients who switch to electronic cigarettes continue to smoke conventional cigarettes. In addition, there are no reliable data on a significant reduction in their smoking of conventional cigarettes. Moreover, "double tobacco use" is becoming more common among tobacco-dependent patients who switch to smokeless tobacco, which causes double harm to the health of such patients [22].

Argument 4. THR strategy is based on poorly documented evidence of low harm and safety of ENDS. There is currently no proof of the safety of ENDS. On the contrary, a series of independent studies revealed their potential harm. For example, e-cigarette aerosols can cause acute endothelial vascular dysfunction and reactive oxidative stress. Short-term inhalations through ENDS systems causes airway obstruction and disrupt normal pulmonary homeostasis. Vape (cloud, vapor) of electronic cigarettes causes coughing and wheezing and can trigger suffocation and a bronchial asthma attack [32].

Argument 5. Even if ENDS at first glance seem less harmful than conventional cigarettes, they have an absolutely negative effect on public health. When assessing the pros and cons of the widespread use of ENDS, it is important to correctly consider their impact on all groups of the population, not only on a small group of tobacco smokers. Overall, considering this issue from the perspective of public health, ENDS potentially lead the new generation (youth), previously involved in tobacco smoking, to nicotine use, especially children and adolescents who like electronic cigarettes with candy or fruit flavors. Research has shown that there is a significant increase in the risk of early smoking and the chances of returning to traditional cigarettes among e-cigarette users. In this context, smokeless tobacco use significantly increases the possibility of switching to traditional cigarettes [33].

Argument 6. Tobacco smokers consider ENDS a viable medical alternative to tobacco quitting, which is wrong. This is why they abandon professional approaches and proven pharmacological treatments, which increases the number of failed cessation attempts and compromises the effectiveness of tobacco dependence therapy [34].

Argument 7. THR strategy is based on the erroneous claim that the "tobacco epidemic" cannot be controlled. On the contrary, the greatest success of modern-day public health is a significant reduction in the number of tobacco smokers due to tobacco bans. Countries with active control and bans on tobacco use have seen a significant and rapid decline in the prevalence of tobacco smokers and tobacco use in general [1, 35].

What is the conclusion made by the group of experts of the European Respiratory Society?

First, the THR concept is based on good intention (design) and poorly documented facts and assumptions. Human lungs are designed to breathe "clean air", not "reduced levels of toxins and carcinogens", and the human body should not be addicted to drugs, nicotine, tobacco. That is why more than 40 European countries have banned all ENDS [29].

Second, the ERS cannot recommend any modified product that is harmful to human health or lungs. This is why the ERS strongly supports the World Health Organization Framework Convention on Tobacco Control (FCTC), a treaty accepted by the World Health Organization (WHO) in response to the globalization of the tobacco epidemic, which regulates all types of tobacco products [29].

Third, at present, the ERS does not consider the THR concept as an alternative to the strategy of complete cessation of tobacco use, even for tobacco-dependent patients, as the main doctrine of improving public health [29].

3. Reducing Tobacco Harm: Current Perspective

Despite the differences in FDA and ERS approaches to tobacco harm reduction (THR), the THR concept has a right to life as a measure of social justice for nicotine and tobacco addicted patients (who cannot quit smoking) who experience the greatest medical and

social inequality. Switching them to modern high-tech products with a reduced nicotine and tar content, and tobacco combustion products opens a real "window of opportunity" in preserving their life span [36]. For example, switching tobacco smokers with more than ten years of experience to cigarettes with low and extremely low nicotine content halved the number of cigarettes smoked, reduced "tobacco dependence", exposure to toxic/carcinogenic substances, and doubled the number of attempts to quitting smoking [37]. However, a reduced nicotine level in cigarettes did not correlate with changes in mood, depression, and the frequency of alcohol and cannabinoid use in these patients. Moreover, the strategy of drastically reducing nicotine in cigarettes versus stepwise reduction (nicotine replacement therapy) inevitably leads to an increase in the number of people looking for it in other sources. These consequences and the low efficacy of low-nicotine products in encouraging tobacco-dependent patients to quit smoking deprives them of any prospects in the THR concept [38].

It should be noted that there are other innovative products that have passed the premarket tobacco product application (PMTA) and FDA-approved innovative products that can be used without burning tobacco ("unburned tobacco"): General Snus (Swedish Match) and IQOS (Phillip Morris International, PMI). Randomized clinical trials (RCTs) revealed that General Snus had lower levels of tobacco-specific nitrosamines (TSNAs) and other toxic substances compared to other brands of smokeless tobacco products. However, the very concept of SNUS/smokeless tobacco has not gained acceptance among smokers [3, 22, 25, 39].

Another product in the category of "unburned tobacco" is the tobacco heating system (THS) designed to evaporate nicotine from a special "tobacco stick" [40]. Its important difference from conventional cigarettes is that there is no combustion of tobacco and tobacco smoke, which means that the following gaseous components are not produced: carbon monoxide and carbon dioxide, hydrogen cyanide, ammonium, isoprene, acetaldehyde, acrolein, nitrobenzene, acetone, hydrogen sulfide, hydrocyanic acid and other hazardous substances. This reduces the aerosol cloud of all substances that are hazardous to the patient's health by 90–95%. For comparison: aerosol cloud during tobacco burning contains solid particles and tar, 50% glycerin and water, has more than 4,000 different chemical compounds, including more than 40 dangerous carcinogenic substances and at least 12 substances that cause cancer [41].

There are important RCTs that have been carried out to investigate the "toxicity" of THS aerosol to smokers. It has been proven that the aerosol produced by the THS system is ten times less dangerous than cigarette smoke in terms of triggering the mechanisms of atherosclerosis, premature cellular aging, endothelial dysfunction that play a major role in the development of cardiovascular diseases (Fig. 2) [42].

The practical interest of the applicability of THS systems in tobacco-dependent patients has been studied in large-scale RCTs conducted among patients from different countries, different ethnic groups and cultural traditions. For example, there was an interesting six-month multicenter RCT, further extended to 12 months, in healthy adult smokers with two parallel groups: 1) individuals who had switched to THS systems; 2) individuals who had completely stopped smoking. The potential of THS systems to influence eight key pathogenetic mechanisms of disease formation (inflammation, oxidative stress, lipid metabolism, blood clotting, endothelial function, pulmonary function, genotoxicity) was studied in comparison with patients who had completely stopped smoking. A total of 2,556 tobacco smokers were screened and 1,795 tobacco smokers were enrolled; 984 of them were randomized into three groups (traditional cigarettes n = 496; THS n = 488; quit smoking n = 811). A representative group and extension of the study to 12 months allowed to study clinically important long-term results of the THS system (Fig. 3) [43, 44]. The primary points of observation were the markers of disease development: 1) lipid metabolism — HDL-C (high density lipoproteins); 2) blood clotting — 11-DTX-B2 (11-dehydrothromboxane B2); 3) endothelial function — slCAM-1 (soluble intercellular adhesion molecule-1); 4) acute effects — COHb (carboxyhemoglobin); 5) inflammation — WBC (leukocytes); 6) oxidative stress — 8-epi-PGF2 (8-epi-prostaglandin F2 alpha); 7) pulmonary function — FEV1%pred (forced expiratory volume in 1 second from the due values); 8) genotoxicity — Total NNAL (total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol).

Secondary observation points were the components of tobacco aerosol: 1) carbon monoxide (CO) in exhaled air; 2) monohydroxy butenyl mercapturic acid (MHBMA); 3) 3-hydroxypropyl mercapturic acid (3-HPMA); 4) total N-nitrosonornicotine (Total NNN); 5) 2-cyanoethyl mercapturic acid (CEMA); 6) 3-hydroxybenzo(a)pyrene (3-OH-B[a]P); 7) 3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA); total 1-hydroxypyrene (Total 1-OHP). To describe the effects of nicotine, in addition to plasma levels of nicotine and cotinine, nicotine equivalents (NEQ) were determined as the molar sum of free nicotine, nicotine glucuronide, free cotinine, cotinine glucuronide and free trans-30-hydroxycotinine and trans-30-hydroxycotinine-glucuronide in urine (expressed as concentration adjusted for creatinine).

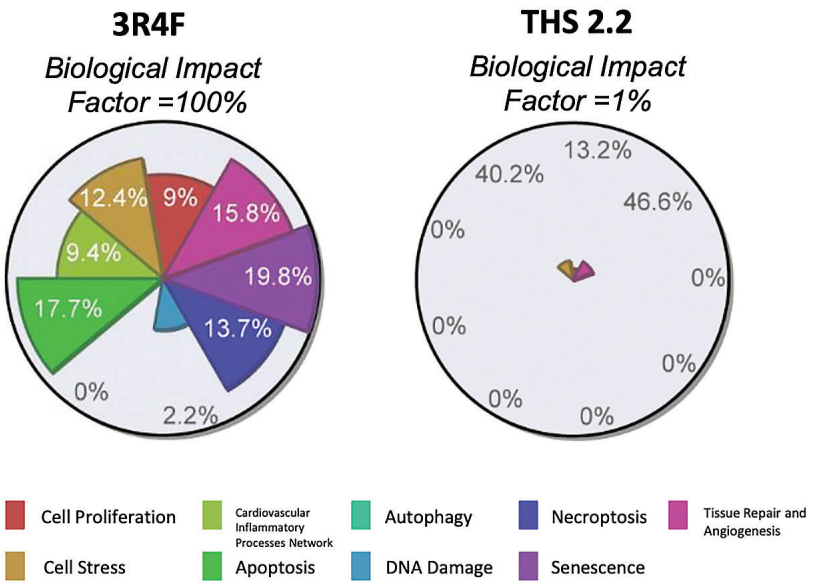

Figure 2. *Graphical representation of the study of the aerosol THS for toxicity in comparison with the smoke of a conventional cigarette (3R4F). The explanation is in the text. (Adapted from: Poussin C et al. Toxicology. 2016 Jan 2; 339: 73-86)*

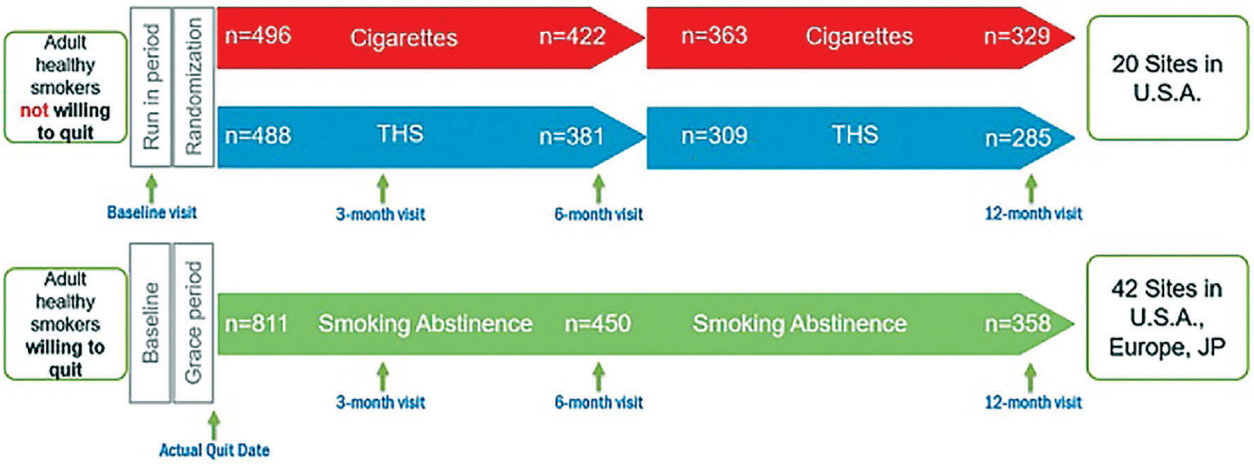

Figure 3. *Graphical representation of the design of a 12-month RCT. The explanation is in the text. (Adapted from: Ansari SM et al. JMIR Res Protoc. 2018 Aug 24;7(8):e11294).*

Results of this study demonstrated that all values of the endpoints of the main observation group (THS group) improved similarly to the values of the smoking cessation group. Moreover, five out of eight markers of inflammation development had statistically significant ($p < 0.05$) positive changes in comparison with the group of continuing smoking (traditional cigarette group) and were similar to those in the smoking cessation group (Table 1) [44].

All components of the "tobacco aerosol" were significantly reduced in the THS group compared to cigarette smokers, while there was no difference between the groups in nicotine exposure (NEQ) (Fig. 4) [44].

This study convincingly demonstrates the positive effects of the strategy of switching tobacco-dependent patients to THS systems. First, it demonstrated a statistically significant improvement in five of the eight major markers of inflammation development to the level observed only during smoking cessation. At the same time, these patients retained the level/dose of nicotine and subjective effects similar to those in the group of active tobacco smokers. This can be an important argument that THS systems can be a feasible alternative for tobacco-dependent patients. It is important that the positive biological effects in patients of the THS

group lead to a significantly lower health risk than continuing smoking. Using THS systems in tobacco-dependent patients in accordance with the THR concept is highly speculative. However, it is very promising with further improvement of "unburned tobacco" technology [45].

Another large-scale study by P.N. Lee et al. (2018) assessed the health effects of modified risk tobacco products (MRTP) on the health of the Japanese population by creating simulation models over a 20-year period starting from 1990. It was found that the overall decrease in the number of deaths from lung cancer, coronary heart disease, stroke, chronic obstructive pulmonary disease due to tobacco smoking among men/ women for 20 years amounted to 269,916 cases; with the complete cessation of tobacco smoking at the baseline. The decrease in the number of deaths ranged from 167,041 to 232,519 cases, if at baseline patients switched to MRTP systems (switching level is equivalent to 70–90% of complete cessation of smoking) [46].

In a meta-analysis, A. Ratajczak et al. (2020) included 15 RCTs from Cochrane, PubMed and Embase on acceptability, awareness, and patient switch to IQOS® MRTP. Results varied greatly due to smoking status: among young smokers, there was a high interest in the "heating tobacco" system. On the other hand, there was a similar interest in THS systems among nonsmokers, indicating the emergence of new tobacco users. Overall susceptibility/readiness to use IQOS was higher (25.1%) than among traditional cigarettes (19.3%) and lower than among e-cigarette users (29.1%). The authors concluded that THS systems could potentially be categorized as modified risk tobacco products considering their impact on chronic diseases traditionally associated with tobacco smoking. However, further large-scale studies are required to verify this potential [47].

Table 1. *Dynamics of markers of inflammation development*

Endpoint	Effect	96.875 % CI	P value
HDL-C (mg/dL)	3.09	[1.10; 5.09]	<0.001
WBC count (GI/L)	-0.420	[-0.717; -0.123]	0.001
sICAM-1 (%)	2.86 %	[-0.426; 6.04]	0.030
11-DTX-B2 (%)	4.74 %	[-7.50; 15.6]	0.193
8-epi-PGF2a (%)	6.80 %	[-0.216; 13.3]	0.018
COHb (%)	32.2 %	[24.5; 39.0]	<0.001
FEV1 %pred (post-bronchodil.)	1.28 %	[0.145; 2.42]	0.008
Total NNAL (%)	43.5 %	[33.7; 51.9]	<0.001

Note: Adapted from: Lüdicke F et al. Cancer Epidemiol Biomarkers Prev. 2019 Nov; 28(11): 1934-1943

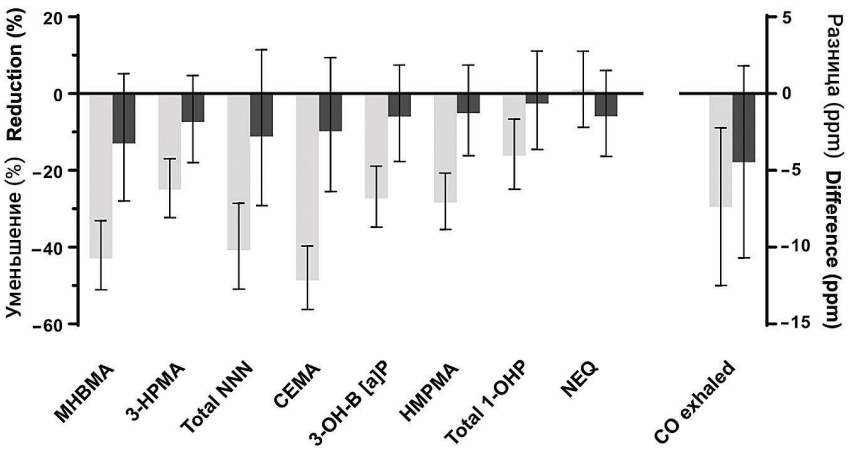

Figure 4. *Dynamics of reduction of toxic components of "tobacco aerosol" in the group of THS users (light gray) compared to the group of tobacco smokers (dark gray). The explanation is in the text. (Adapted from: Lüdicke F et al. Cancer Epidemiol Biomarkers Prev. 2019 Nov;28(11):1934-1943).*

4. Conclusion

Currently, there is considerable experience in the production and consumption of tobacco products with low tar/nicotine content, as well as knowledge and tools for the regulation of modified risk tobacco products (MRTP) for tobacco smokers with tobacco dependence or with no interest in quitting nicotine use [18]. There remains a fundamental disagreement over the benefits and risks of tobacco cessation/ abstinence and MRTP use for adult tobacco addicts. Obviously, the quickest way to reduce mortality and tobacco-related diseases is to "devalue" traditional cigarettes and other "burned tobacco" products by reducing their nicotine content to the minimum level of addiction [3]. Obviously, unburned tobacco products should also be tightly regulated in terms of toxicity, attractiveness, marketing and promotion in order to minimize their consumption by young people. On the other hand, adult tobacco-dependent patients should have a real opportunity to switch to MRTP [6, 17].

Today, the implementation of new pharmacological innovations in nicotine replacement therapy (NRT) provides real access to effective and well-known tools for the cessation of tobacco use [23]. It is NRT that has good potential to: 1) quickly eliminate "burned tobacco" from the market; 2) eliminate concerns about "unburned tobacco" products; 3) reduce the "double use" of tobacco products; 4) minimize the consumption of "burned tobacco" products among young people; 5) ensure the public that unburned tobacco products are MRTP products; 6) provide tobacco smokers and consumers of other forms of tobacco products with effective agents for nicotine addiction [25].

It is important that the "tobacco harm reduction" (THR) concept provides for "minimizing harm, overall mortality and morbidity among tobacco smokers without completely quitting tobacco and nicotine use" [5]. In fact, THR recognizes giving up/abstaining from tobacco as a required and achievable result, leaving a "window of opportunity" for tobacco-dependent (nicotine-dependent) patients to receive real help in maintaining their health while maintaining social justice measures, potentially eliminating medical and social inequalities between healthy and tobacco dependent individuals. Disputes and contradictions between the "Anglo-Saxon" and "European" views on the possibility of implementing THR can only be resolved through a global dialog [25]. In this context, unburned tobacco (THS) systems can be an acceptable alternative for tobacco-dependent patients. Of course, using THS systems in tobacco-dependent patients in accordance with the THR concept is highly speculative. However, it is promising with the further improvement of "unburned tobacco" technology [45–47].

Вклад авторов:

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Бабак С.Л. (ORCID: https://orcid.org/0000-0002-6571-1220): роль автора в обосновании и написании рукописи, вклад в разработку дизайна и метаанализа данных, ответственность за англоязычный перевод научного материала

Горбунова М.В. (ORCID: https://orcid.org/0000-0002-2039-0072): роль автора в разработке дизайна и метаанализа данных, в поиске литературных источников, оформлении работы в целом

Малявин А.Г. (ORCID: https://orcid.org/0000-0002-6128-5914): роль автора в обосновании и написании рукописи, в проверке критически важного интеллектуального содержания, в окончательном утверждении материала для публикации

Шашенков И.В. (ORCID: https://orcid.org/0000-0003-0233-7072): роль автора в поиске литературных источников, оформлении работы в целом

Author Contribution:

All authors made a significant contribution to the preparation of the work, read and approved the final version of the article before publication

Babak S.L. (ORCID: https://orcid.org/0000-0002-6571-1220): the role of the author in the justification and writing of the manuscript, contribution to the development of design and meta-analysis of data, responsibility for the English translation of scientific material

Gorbunova M.V. (ORCID: https://orcid.org/0000-0002-2039-0072): the role of the author in the development of design and meta-analysis of data, in the search for literary sources, and in the design of the work as a whole

Malyavin A.G. (ORCID: https://orcid.org/0000-0002-6128-5914): the role of the author in the justification and writing of the manuscript, in checking critical intellectual content, in the final approval of the material for publication

Shashenkov I.V. (ORCID: https://orcid.org/0000-0003-0233-7072): the role of the author in the search for literary sources, and in the design of the work as a whole

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Л.М. Фархутдинова

Башкирский государственный медицинский университет МЗ РФ, Уфа, Россия

ИЗ ИСТОРИИ ИЗУЧЕНИЯ ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ

L.M. Farkhutdinova

Bashkir State Medical University, Ufa, Russia

From the History of the Infection Study

Резюме

Статья отражает развитие представлений об инфекции, начиная с античного периода до сегодняшних дней. В V в. Гиппократом была предложена миазматическая теория, согласно которой заболевания обусловлены вредными испарениями. Данная парадигма оставалась господствующей в течение 2,5 тысячелетий. Хотя существование микроорганизмов известно с 1676 г., когда впервые их описал Антони ван Левенгук, долгое время обнаружение микробов в биосубстратах больного человека считалось явлением вторичным по отношению к заболеванию. Теоретической основой таких представлений была идея о самозарождении, доминировавшая со времен Аристотеля. Смена миазматической теории на инфекционную парадигму произошла благодаря фундаментальным открытиям Луи Пастера, доказавшего биологическую природу брожения и инфекционный генез болезней шелковичных червей. Перечисленные открытия поставили точку в дискуссии о самозарождении, стали научным обоснованием асептики и антисептики и нацелили на поиск возбудителей заразных заболеваний человека, что привело к всплеску открытий в микробиологии. Были выделены возбудители возвратного тифа (1868), проказы (1873), сибирской язвы (1876), туберкулеза (1882), холеры (1883), дифтерии (1884), чумы (1894) и др. В результате инфекционная теория окончательно завоевала мир. Важным достижением конца XIX в. стало выделение нового вида инфекционных агентов — вирусов, которые составляют самую многочисленную форму жизни. С признанием инфекционной теории еще в конце XIX в. начались активные поиски противомикробных средств. В 1943 г. было налажено массовое производство первого антибиотика — пенициллина, открытие которого называют одним из наиболее выдающихся достижений в истории человечества. Применение противомикробных препаратов наряду с массовой вакцинацией привело к значительному снижению доли инфекционных болезней в структуре смертности.

Ключевые слова: *инфекционная теория, инфекционные эпидемии, теория миазмов, инфекционные микроорганизмы*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The article reflects the development of ideas about infection, from the ancient period to the present day. In the V century Hippocrates proposed a miasmatic theory, according to which diseases are caused by harmful fumes. This paradigm remained dominant for 2.5 millennia. Although the existence of microorganisms has been known since 1676, when they were first described by Anthony van Leeuwenhoek, for a long time the detection of microbes in the biosubstrates of a sick person was considered as a secondary phenomenon in relation to the disease. The theoretical basis for such ideas was the concept of spontaneous generation, which has dominated since the time of Aristotle. The change from the miasmatic theory to the infectious paradigm was due to the fundamental discoveries of Louis Pasteur, who proved the biological nature of fermentation and the infectious genesis of silkworm diseases. The listed discoveries put an end to the discussion about spontaneous generation, became the scientific justification for asepsis and antiseptics and aimed at searching for pathogens of infectious human diseases, which led to a surge in discoveries in microbiology. The causative agents of fever (1868), leprosy (1873), anthrax (1876), tuberculosis (1882), cholera (1883), diphtheria (1884), plague (1894), etc. were discovered. As a result, the infectious theory finally conquered the world. An important achievement of the late 19th century was the allocation of a new type of infectious agents — viruses, which make up the most numerous form of life. With the recognition of the infectious theory at the end of the 19th century an active search for antimicrobial agents began. In 1943, the mass production of the first antibiotic, penicillin, was launched, the discovery of which is called one of the most outstanding achievements in the history of mankind. The use of antimicrobial drugs, along with mass vaccination, led to a significant decrease in the share of infectious diseases in the structure of mortality.

Key words: *infectious theory, infectious epidemics, theory of miasms, infectious microorganisms*

*Контакты: Лейла Муратовна Фархутдинова, e-mail: farkhutdinova@gmail.com
*Contacts: Leila M. Farkhutdinova, e-mail: farkhutdinova@gmail.com

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Human history in essence is the history of ideas.
H.G. Wells

The concept of infectious diseases dates back to antiquity. The ancient Greek philosopher Democritus (460–390 BC) believed that diseases were caused by tiny invisible organisms. His compatriot, the philosopher Thucydides (460–400 BC), shared this idea and called the pathogens "contagium[1] animatum" (from the Greek — live contagion), whence the concept of contagiousness, or infectiousness, comes from.

The father of medicine, Hippocrates (460–370 BC), also associated wound inflammation with pollution. Therefore, he used only boiled water during dressing and insisted that the doctor's hands and the surgical site be clean and the dressings prepared from new material. With that, Hippocrates laid the foundations for asepsis. However, European medicine only recognized its necessity 2,500 years later. He introduced the term epidemic. However, he believed that diseases were caused by harmful fumes — miasms (from the Greek — filth) emanating from rotting products in the soil and water. The irony is that, in contrast to the principles of asepsis, the miasmatic theory became widespread and remained dominant until the end of the 19th century.

The promotion of hygiene for health purposes by Hippocrates played an important role in the emergence of central water supply in the ancient world, the development of which peaked in the Ancient Rome. Aqueducts supplying water to public baths, toilets, fountains, private houses, gardens, farms, etc., were built throughout the Roman Empire. There was also a sewage system. Daily visits to the bathhouse were a custom in the Ancient Rome. One of the greatest achievements of the philosophical thought of Ancient Rome is the treatise of the philosopher Titus Lucretius Carus (appr. 99 BC. — appr. 55 AD) *On the Nature of Things,* in which he suggested that infectious diseases were caused by various "seeds" [1, 2].

In the Middle Ages, culture, science and hygiene were not as advanced as in antiquity. With the fall of the Roman Empire, aqueducts were destroyed, and personal hygiene, which was considered sinful in early Christianity, which placed more emphasis on the soul, declined as well. For example, Saint Benedict (480–547) recommended that young and healthy people wash as little as possible. This contributed to the spread of infectious diseases, among which the plague posed a particular threat. The plague epidemic that broke out in the middle of the 6th century lasted for more than two centuries and claimed about 25 million lives. In the middle of the 14th century, Europe was engulfed in an even larger epidemic of the plague, which killed between 30 and 50 million people. The main reason was the critical unsanitary conditions: not only rats, but parasite insects living on humans, were common; in the cities, garbage was thrown out from the windows directly into ditches dug along houses. And everything was then carried into the river, which served as a source of water for drinking and cooking.

In the 6th century, smallpox gripped Europe and, with the beginning of the Crusades[2], grew into an epidemic that lasted several centuries. By the 16th century, the disease was so widespread that a person without smallpox marks was a rarity; the mortality rate was about 30%. From the 11th century, leprosy became an infectious scourge in Europe. In 1084, the first leprosarium opened in England, and by the 13th century, their number in European countries had reached about 20 thousand. It should be noted that the isolation of patients proved effective, and in 200 years, in the 15th century, the number of patients began to decrease.

Flu epidemics began in the 12th century: the first influenza pandemic, which claimed many lives, was recorded as early as 1580. The spread of the disease was facilitated by the idea of its non-infectiousness, which is eloquently evidenced by the former name of this pathology — influenza (from Italian Influenza — influence), that is, cased by the influence of the stars [3].

Unlike Europe, in the Middle East, where Islam was widespread, in the Middle Ages, the achievements of antiquity were the foundation for the further development of science. All the major scientific manuscripts of ancient civilizations were translated into Arabic, and scientific and educational centers were established to study them. In 754, the world's first state pharmacy was established in Baghdad, which is associated with the achievements of Eastern scientists in chemistry and pharmaceuticals. In the middle of the 9th century (859), the world's first University, Al-Karaouin,

[1] lat. contagio — to touch

[2] Crusades — XI-XV centuries

was founded in the Moroccan city of Fez. In 873, the first state hospital in history opened in Egypt. Later, numerous state-funded hospitals with scientific libraries and educational institutions were established in the Arab Caliphate. In 1005, the Society of the Enlightened was set up in Cairo and became the prototype of future academies. Its members discussed the problems of epidemics, sanitary improvement, diagnosis and treatment of diseases.

The improvement of the paper manufacturing by the Arabs in the 8th century[3] made books more affordable. By the end of the first millennium, libraries numbering hundreds of thousands and even millions of volumes operated in Cordoba, Damascus, Baghdad, Cairo, Samarkand, Bukhara, while the Pope library in Avignon and the Sorbonne book collection numbered only about two thousand editions. Oriental medicine played a leading role until the 15th century, especially in the field of infectious diseases and hygiene. The world's primary sources of medical knowledge were the works of Ar-Razi (865–925) and Ibn-Sina (980–1037). Ar-Razi was the first to attempt to explain the cause of infectious diseases and the suppuration of wounds. While looking for a site to build a hospital in Baghdad, he hung chunks of meat around the city and chose the place where the rotting began later. He was the first to use cotton wool instead of lint[4] (rags split into threads), which significantly reduced the risk of wound infection. He was the first to carry out smallpox variolation — the inoculation of a mild form of human smallpox to protect against the serious illness.

In *The Canon of Medicine*, Ibn-Sina forbade to examine a wound with unwashed hands. He recommended closing the wound as quickly as possible with strips of clean material and using wine-soaked dressings. He emphasized that, among surgical instruments, "the best one is a clean hand."

Many cities in the Arab Caliphate had running water and sewerage systems. The Arabs were first to use paper packaging when selling foodstuffs, which was of great relevance for hygiene. Hygiene was also maintained due to religious beliefs. For example, one of the hadiths says: "Cleanliness is half of faith".

Arabic translators of literature from Arabic into Latin — the scientific language of medieval Western Europe — preserved, improved and returned to Europe the most important achievements of antiquity and the early Middle Ages [4, 5].

Italy was the cradle of the European Renaissance, where Europe's first university was established in 1088 and the Academy in 1459. The most prominent figure of the Renaissance is considered to be Leonardo da Vinci (1452–1519) — an artist, scientist and inventor, whose work is associated with progress in almost all fields of science of that period, including medicine. In 1485, after the plague epidemic in Milan, which claimed about 50 thousand lives, da Vinci developed a city project where he planned to eliminate unsanitary conditions and minimize the spread of diseases. Instead of narrow medieval streets, da Vinci's new city had wide roads, squares and avenues; water was supplied to houses via a hydraulic system; an improved sewerage and drainage system and garbage disposal were proposed. At that time, the Duke of Milan rejected the project, but several centuries later, da Vinci's ideas were used in many cities around the world.

An important contribution of the Italian medical school of this period was the work of Girolamo Fracastoro (1478–1553) *On contagion, on contagious diseases and treatment*. Fracastoro first coined the term *infection* and suggested that epidemics are caused by tiny particles that are transferred from the patient through direct and indirect contact. To prevent the spread of the disease, he proposed the isolation of the patient, as well as careful treatment and cleaning of the room. Fracastoro was the first to point out that the main source of the spread of phthisis is a sick person who secretes phlegm, which contaminates the air, linen, utensils, etc. However, he considered the disease-causing particles not as living organisms but as some kind of chemical substance.

An important step towards understanding the living nature of pathogenic particles was the discovery made in the next 17th century. In 1676, the Dutch naturalist Anthony van Leeuwenhoek (1632–1723), while examining a drop of water through a microscope, first described microorganisms and sent the results of his observations to the Royal Society of London. Until then, nothing was known about the existence of the microworld, and Leeuwenhoek's discovery aroused the distrust of scientists. An academic commission was sent to Leeuwenhoek, which confirmed the results of his research. However, the role of the discovered microorganisms remained unknown. Therefore, they were not given much importance, and the detection of microbes in the blood and other biological substrates of a sick person was considered a phenomenon secondary to the disease.

The theoretical basis for such ideas was the concept of spontaneous generation, which had dominated since the time of Aristotle (384–322 BC). In this regard, the debate over the spontaneous generation of microorganisms became a remarkable scientific event of the 18th century. English naturalist John Needham (1713–1781), an advocate of the theory of spontaneous generation, boiled lamb gravy, poured it into a bottle and plugged it with a cork. A few days later, he examined the gravy under a microscope and found a large number of microbes. The Italian naturalist Lazzaro Spallanzani (1729–1799), on the

[3] The Arabs began to use old fabrics to produce paper and implemented the mechanized grinding process — with millstones in paper mills (in China, where paper was invented in the 2nd century, it was made from fibers of oak, mulberry, flax, and the paper pulp was pounded in a mortar)

[4] The lint was made from old fabrics with the participation of many people and represented a source of infection.

contrary, considered the idea of spontaneous generation absurd and showed that the broth, which was boiled for an hour and remained in a sealed vessel, did not contain microbes. Therefore, the microbes either came from the air or had persisted due to insufficient heat treatment. Spallanzani's conclusion that microorganisms are able to withstand boiling for several minutes, was another important idea [6]. Despite their persuasiveness, Spallanzani's scientific achievements were not accepted by his contemporaries, with rare exceptions.

Such an exception, for example, was the renowned Russian doctor, one of the founders of Russian epidemiology, Daniil Samoilovich Samoilovich (1744–1805). He devoted his whole life to the fight against the plague and achieved great successes for that time. He was the first to use a microscope to search for the causative agent of the plague. He developed a system for disinfecting this disease, laid the foundation for vaccination. Samoilovich's works were highly appreciated abroad, where he was elected a member of 13 academies. It should be noted that the St. Petersburg Academy remained indifferent to the scientific achievements of their compatriot.

The medicine of the 19th century still remained in the "fog" of the miasmatic theory. The high mortality rate in industrial areas compared to rural areas was considered a confirmation of the role of the "miasms" of wastewater, slaughterhouse waste, etc. In the structure of mortality of that period, 70% was due to infectious diseases, of which cholera, smallpox, tuberculosis, diphtheria and measles were the most common.

In 1817, a wave of continuous[5] cholera pandemics began, which was second only to the plague in the number of victims. In the 19th century, it claimed more lives than any other disease. The most deadly pandemic was in the 1850s. In Russia alone, the number of victims exceeded one million. When in 1854, a cholera epidemic gripped the very center of London, the English physician John Snow (1813–1858) proved that the source of the contagious disease was drinking water, taken by water supplying companies from a section of the Thames polluted by the city sewage system. In the same year, the Italian anatomist Filippo Pacini (1812–1883), after examining the intestines of people who died of cholera, discovered the causative agent of the disease — the cholera vibrio. However, this discovery did not receive due recognition, and general acceptance of the infectious nature of the disease took decades.

By the early 19th century, more than 1.5 million people died of smallpox in Europe every year. An important step in solving this problem was made in the 1800s with widespread vaccination — inoculation of cowpox, characterized by a mild course, which was declared compulsory for the entire population in Bavaria and England. In other countries, including Russia[6], where no such law was passed, mortality from smallpox remained high.

Tuberculosis was considered the most common disease since the time of Hippocrates. And in the 19th century, it acquired a particularly high prevalence and claimed the lives of about one-quarter of the adult population of Europe, where it became the cause of death of one in ten people in cities. One of the reasons for such a difficult situation was the misconceptions about the non-infectiousness of the disease, although as early as 1540, Fracastoro, as mentioned earlier, pointed to the contagious nature of phthisis[7]. In 1720, the British physician Benjamin Martin discovered microbes in the sputum of patients and published a book where he proved the infectious nature of tuberculosis. But Martin's theory was not recognized due to the influence of Leeuwenhoek, who did not consider microbes pathogenic. In 1865, French naval physician Jean Antoine Vilmain (1827–1892) witnessed a tuberculosis epidemic on a ship as a result of one person contracting the disease. He caused the spread of the disease to guinea pigs by soaking the bedding with the sputum of the patients. However, the French Academy of Sciences once again rejected the conclusion that the disease was contagious.

Diphtheria and measles were frequent causes of infant mortality. Major diphtheria epidemics were reported in all countries, with a fatality rate of 50%. Epidemics of measles, the disease with the highest contagiousness (90%), recurred every 2–3 years, with mortality reaching 10% [7, 8].

Alongside infectious diseases, septic complications were another common cause of death in the 19th century. In 1847, Semmelweis analyzed mortality from sepsis among women in labor and proved that it was associated with insufficient treatment of hands before medical and diagnostic manipulations. Semmelweis introduced the rule of washing hands with bleach before examining women in labor, which brought mortality down ten-fold. However, Semmelweis's colleagues scoffed at him, and the director of the clinic regarded his data as slanderous. Despite all of Semmelweis' efforts to promote his results, they did not receive wide recognition. In July 1865, Semmelweis' colleagues fraudulently hospitalized him in a psychiatric clinic, where he soon died. Sepsis continued to claim up to 30% of the lives of women in labor in clinics in Europe.

In surgery, postoperative purulent complications were also the main problem, contributing up to 60% to mortality. In 1865, in support of the hypothesis of the infectious nature of wound infections, prominent Russian physician Nikolai Ivanovich Pirogov (1810–1881) wrote: "Purulent infection spreads not so much through the air, which becomes clearly harmful only when the wounded

[5] In total, seven pandemics stand out, six of which were in the 19th century.

[6] In the RSFSR, the Decree On Compulsory Vaccination was adopted on April 10, 1919.

[7] In 1839, the disease became known as tuberculosis.

are crowded in an enclosed space, but through the objects surrounding the wounded: linen, mattresses, dressings, walls, floors and even sanitary personnel." He was one of the first to successfully apply various aseptic and antiseptic methods. However, these innovations received strong opposition from the medical community, which could not be overcome at that time.

One of the founders of Russian gynecology, Professor Vladimir Fedorovich Snegirev (1847–1917), recalling the ovariotomy he had observed in 1870, wrote: "... the surgeons gathered around the operating table in uniforms and coats inserted their hands into the abdominal cavity in order to express their opinion afterwards. Everyone tried to help — took up a sponge and wiped off the blood in the wound." In the pre-antiseptic period, the suture material usually hung on the button of the uniform of a paramedic who helped during the operation, or on the window latch of the operating room, from where it was taken, moistened with saliva before being inserted into the eye of the needle, and handed over to the surgeon [1].

As for the methods of treatment, the most common remained laxatives and emetics, as well as bloodletting, since it was considered necessary to *cleanse* the body of *harmful miasms*. It was not uncommon for patients to die of repeated bloodletting. Medicine was in dire need of reform — scientific methods of treatment based on a firmly proven scientific theory [9–11].

The shift from the miasmatic theory to the infectious paradigm occurred in the late 19th century due to the fundamental discoveries of the outstanding French scientist — Louis Pasteur (1822–1895). In 1857, he proved the biological nature of fermentation, explaining this process by the vital activity of microorganisms — yeast fungi. In 1864, Pasteur showed that wine diseases are caused by bacteria, and each disease has a specific pathogen. A year later, in 1865, he established the infectious nature of silkworm diseases and developed hygienic rules for their prevention. The above-listed discoveries put an end to the discussion about spontaneous generation. It became the scientific justification of asepsis and antiseptics, and aimed at finding pathogens of infectious diseases in humans, which, according to Pasteur's theory, can be found in various biological substrates of a patient.

Having solved the problem of silkworm diseases, Pasteur turned to the problem of anthrax, which he considered infectious too. Anthrax has been known since the ancient times and, along with cholera and plague, is among particularly dangerous infections since it causes mass deaths of farm animals and infection in humans. In 1849–1850, several researchers described the anthrax pathogen, which became the first known pathogenic microorganism. Further, it was concluded that the outbreaks of the disease occurred on the same pastures. In 1876, the German scientist Robert Koch (1843–1910) isolated a pure culture of anthrax and explained the mechanisms of infection associated with the ability of bacteria to produce spores resistant to external factors. Pasteur proved that the spread of the pathogen in places of cattle burials is due to earthworms. He confirmed this conclusion by infecting guinea pigs with a preparation of the intestinal contents of earthworms collected from the burial sites of sick animals.

In May 1881, Pasteur used a vaccine made from weakened anthrax microorganisms in a public experiment. Its success had a tremendous public response and played a crucial role in the acceptance of the microbial theory. This date is considered the beginning of the era of vaccination.

An important milestone in infectology was the discovery of the causative agent of tuberculosis by Koch in 1882. He found tuberculous mycobacteria in a patient's sputum, isolated a pure culture and caused the development of the disease in experimental animals[8]. The scientist's lecture *The Etiology of Tuberculosis,* which took place on March 24, 1882, is considered a historical event. Koch was awarded the Nobel Prize (1905) in Physiology or Medicine "for his investigations and discoveries in relation to tuberculosis." On the initiative of the World Health Organization, World Tuberculosis Day is celebrated annually on March 24.

For several decades, whether bovine tuberculosis is infectious to humans remained debatable. Koch first stated that the causative agents of tuberculosis in animals and humans were identical. However, from 1891 he argued against the possibility of human infection with bovine tuberculosis. In this case, Koch's influence played a negative role — the introduction of milk pasteurization in Germany was hindered for many years, which caused high morbidity. Meanwhile, in France, state monitoring of animal tuberculosis was introduced as early as 1872.

Koch's name is also associated with the creation of tuberculin (an extract of tuberculous bacilli), which he proposed as a preventive and therapeutic drug in 1900. However, the use of tuberculin did not prove effective and was accompanied by cases of the disease, including deaths[9]. Tuberculin subsequently found application in the diagnosis of tuberculosis with cutaneous (Pirke test[10], 1907), and then intracutaneous injection (Mantoux test[11], 1910).

In 1884, during an expedition to India, where another cholera epidemic broke out, Koch isolated the causative agent of the disease from the corpses of sick people. It should be noted that Pacini is considered the discoverer of this infection, but his research results were not accepted

[8] Koch's postulates (Koch-Pasteur's postulates, Koch-Henle's postulates) are the necessary evidence of the pathogenicity of any microorganism: the microorganism must be isolated from a diseased organism and grown in pure culture, on which, if infected, the disease is observed.

[9] In 1921 French researchers Albert Calmette (1863-1933) and Camille Guerin (1872–1961) created the first human vaccine based on an attenuated live bovine tubercle bacillus — BCG (BCG — Bacille Calmette-Guerin)

[10] Clemens Peter von Pirke (1874–1929) — an Austrian pediatrician

[11] Charles Mantoux (1877–1947) — a French physician

in the middle of the 19th century. Koch's fame and the accumulated discoveries, which changed public opinion in favor of the microbial theory, facilitated the recognition of the infectious origins of cholera.

An active search for pathogens of various diseases, which began under the influence of Pasteur's ideas, led to a surge in discoveries in microbiology. Besides the listed pathogenic microorganisms, pathogens of relapsing fever (1868), leprosy (1873), diphtheria (1884), plague (1894), etc., were isolated.

It should be emphasized that the adoption of the infectious theory required overcoming the massive resistance of the scientific community, especially the medical community. One of the main complaints of doctors against Pasteur was his lack of medical education. For example, in 1880, one of the oldest members of the French Academy, orthopedic surgeon Jules Guerin, who categorically did not recognize the microbial origin of diseases, after Pasteur's presentation on chicken cholera at a meeting of the Academy of Sciences, tried to insult him, and then challenged him to a duel. The President of the Academy acted as a mediator and, with great difficulty, dissuaded both sides from the fight.

One of the first supporters of the microbial theory was Joseph Lister (1827–1912), who showed the effectiveness of carbolic acid as an antiseptic in surgical procedures in 1867. By the end of the 19th century, views on the need for asepsis and antiseptics had gained widespread acceptance, and surgery had become safer. Thanks to these advances and successes in microbiology, the infectious theory finally conquered the world [12].

In Russia, in 1895, the Bacteriological Institute opened at Moscow University[12]; it was set up by one of the founders of the study of bacteriology in Russia — Georgy Norbertovich Gabrichevsky (1860-1909). Under Gabrichevsky's leadership, it produced antidiphtheric, antitetanic, antistreptococcic sera and vaccines.

The discovery of pathogenic microorganisms and the study of the mechanisms of their transmission resulted in the understanding of the significance of public and personal hygiene for health and was a powerful stimulus for its development. For the first time, the achievements of hygiene were widely implemented in England — the introduction of plumbing, water purification, waste canal sewerage, etc., improved public health and reduced mortality from infections.

In Russia, the first hygienic laboratory opened in 1883. The Hygiene Institute of Imperial Moscow University was founded in 1890, and the first sanitary station in Moscow was founded in 1891. In 1898, the first stage of the Moscow sewerage system was commissioned.

An important achievement of the late 19th century was the isolation of a new type of infectious agent — viruses. The history of their discovery is associated with the study of the problem of rabies in Pasteur's laboratory. The rabies causative agent could not be detected by microscopy, and Pasteur suggested that this was due to its ultra-small size. In 1884, a student and colleague of Pasteur, Charles Édouard Chamberlain (1851–1908), invented a filtering device known as the Chamberlain-Pasteur filter, which retained bacteria in its pores. Using this filter in 1892, the Russian researcher Dmitry Iosifovich Ivanovsky (1864–1920) studied a tobacco disease, which caused significant losses to farmers. He showed that an extract of plants infected with tobacco mosaic retains its infectious properties after filtration. In 1898, the Dutch microbiologist Martin Beijerink (1851–1931) conducted similar experiments and concluded that the infectious properties of the diseased plant extract were due to the presence of a new form of an infectious agent called a virus[13]. The first report on viral pathology in animals — foot and mouth disease — appeared in the same year. Its causative agent was also filtered through a bacterial filter. However, it was believed that the virus was a kind of liquid substance, not a particle.

The early 20th century was marked by the birth of a new scientific branch — immunology, which studies the mechanisms of protection of a living organism from pathogenic factors, including infectious ones. The cellular theory of immunity was proposed in the late 1880s by a Russian scientist — Ilia Ilich Mechnikov (1845–1916). The history of this discovery is also associated with the name of Pasteur. In 1887, Mechnikov left Russia, and in 1888 Pasteur invited him to his newly created institute, where he was provided with a laboratory. The scientist worked there for the rest of his life. And those were the most fruitful years in his work[14]. In the 1890s, the German scientist Paul Ehrlich (1854–1915) proposed the humoral theory of immunity. The debate over which of these theories was correct raged for about two decades until it became clear that both the cellular and humoral links played a role in protecting the body. In 1908, Mechnikov and Ehrlich received the Nobel Prize for their work in the field of immunology.

In 1918–1920, the largest flu pandemic in the history of mankind broke out, killing between 25 and 100 million people — about 2% of the world's population. The pandemic was fueled by World War I and the associated overcrowding of people in military camps and refugee camps, malnutrition, and unsanitary conditions. At that time, influenza was considered a bacterial infection because in 1892, during the influenza pandemic of 1889–1890, Haemophilus influenzae was isolated in the blood of patients and was mistaken for the cause of the disease. The viral

[12] Moscow Research Institute of Epidemiology and Microbiology named after G.N. Gabrichevsky.

[13] In Latin, *virus* means poison

[14] In 1904, he was elected Vice-Director of the Pasteur Institute

nature of influenza was established in the 1930s, when the virus was isolated by crystallization and its corpuscular structure was proved.

In the same years, the nature of another viral disease — tick-borne encephalitis, which was initially considered one of the forms of influenza, was clarified. Russian scientist Lev Alexandrovich Zilber (1894–1966) played a decisive role in this discovery. In 1937, Zilber led an expedition to the Far East to study an unknown disease complicated by severe damage to the nervous system. He found that a tick was the carrier of the virus and isolated the virus. Later, under the leadership of Evgeny Nikanorovich Pavlovsky (1884–1965), a vaccine was developed. In 1941, these discoveries were awarded the Stalin Prize[15]. As for Zilber, he was among the millions of victims of Stalin's repressions. In 1937, immediately upon returning to Moscow, he was arrested and accused of trying to infect Moscow with encephalitis and narrowly escaped being shot[16].

The invention of the electron microscope, which found widespread application in scientific research, occurred in the 1960s and made it possible to obtain images of viruses. In the second half of the 20th century, more than 2000 types of viruses were discovered, including hepatitis B virus (1963), coronavirus (1965), human immunodeficiency virus (1983), etc. Today, viruses are the most numerous biological form[17]; their number is 10^{39}.

In 1982, new infectious agents — prions (from the English *protein*), were isolated; they consisted essentially of one protein and were much smaller than viruses. Prions are the causative agents of such rare neurodegenerative brain diseases as Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, kuru, fatal familial insomnia [13].

With the recognition of the infectious theory in the late 19th century, an active search for antimicrobial agents began. The first drug of this group was synthesized in 1907 by Paul Ehrlich; it is salvarsan, an arsenic-containing agent effective against the causative agent of syphilis.

Pasteur was the first to establish that some microorganisms could die under the effect of others, using the example of anthrax. In 1915, the English bacteriologist Frederick Twort (1877–1950) described a disease of staphylococci: its pathogen was filtered through a bacterial filter and could infect other colonies, that is, it met the criteria for a virus. In 1917, the French-Canadian microbiologist Felix D'Hérelle (1873–1949) discovered a filterable infectious agent that killed dysentery bacteria. He suggested the term *bacteriophage* — devouring bacteria, put forward the idea of using bacteriophages to treat bacterial pathology, and made the first successful attempts at phage therapy. In the 1920s and 1930s, treatment with bacteriophages was widely used, but their production turned out expensive and technologically difficult in comparison with sulfonamides and antibiotics that emerged soon. Phage therapy remains important as an additional and alternative antimicrobial method, in some cases more effective than antibiotics.

In 1934, the German bacteriologist Gerhardt Domagk (1895–1964) discovered the antimicrobial effect of prontosil, or red streptocide, a dye used in consumer goods manufacturing. A year later, scientists at the Pasteur Institute found that its antimicrobial activity was due to the sulfonamide molecule. As a result, the first sulfonamide drug, white streptocide, was manufactured, followed by many other antibacterial drugs in this group, which marked a revolution in the treatment of infections. In 1939, Domagk was awarded the Nobel Prize for his discovery.

In 1928, the British microbiologist Alexander Fleming (1881–1955) discovered that the growth of a Staphylococcus colony was interrupted in the presence of Penicillium molds and concluded that the mold produced a bactericidal substance, which he named penicillin. Ten years later, in 1938, Fleming's compatriots Howard Florey (1898–1968) and Ernst Chain (1906–1979) were able to isolate the pure form of penicillin. Mass production of this drug began in 1943 due to its high demand in World War II. For the discovery of the first antibiotic, which is considered one of the most outstanding achievements in human history, Fleming, Flory and Chain were awarded the Nobel Prize in 1945.

In the USSR, penicillin was first obtained in 1942 by Zinaida Vissarionovna Ermoleva (1998–1974), which saved hundreds of thousands of lives of Soviet soldiers. The personal courage of the inventor of penicillin is worth mentioning. She wrote to Stalin, pleading the innocence of Zilber[18], and made a lot of effort to free him, despite that in those years, such actions could have raised ominous suspicions.

One of the most brilliant achievements of 20th-century medicine was the solution to the problem of poliomyelitis, the prevalence of which in the 1950s had reached national disaster proportions in many countries. The anti-poliomyelitis vaccine was developed in 1955 by the American researcher Albert Bruce Seybin (1906–1993), and mass vaccination was first implemented in the USSR in 1957 under the leadership of Mikhail Petrovich Chumakov (1909–1993) and Anatolii Aleksandrovich Smorodintsev (1901–1986). As a result, the Soviet Union became the first country in the world where poliomyelitis was eradicated as a mass disease.

[15] Prize winners: E.N. Pavlovsky, A.A. Smorodintsev, E.N. Levkovich, P.A. Petrishcheva, M.P. Chumakov, V.D. Soloviev, A.K. Shubladze.

[16] During the Stalinist regime, the scientist was arrested three times — in 1930 on charges of infecting the population of Azerbaijan with plague, in 1937 for the same reason, and in 1940 after refusing to develop bacteriological weapons.

[17] The number of bacteria is 10^{30} — 10^{32}.

[18] L.A. Zilber was the first husband of Z.V. Ermoleva, and despite that they were divorced at the time of his arrest, Zinaida Vissarionovna made a lot of efforts to save him. Zilber was released in 1944.

The use of antimicrobial drugs, along with mass vaccination, drastically changed the structure of mortality in the second half of the 20th century, when the proportion of infectious diseases decreased to 30%. Today, developed countries, it is as low as about 7% [14–17].

The novel coronavirus pandemic broke out in 2019. The main strategy in the fight against Covid-19 was quarantine measures, personal protection, mass testing, as well as vaccination to achieve herd immunity. The active study of novel coronavirus and the collaboration of scientists from different countries in the fight against the global threat gives hope that this problem could be solved in the near future.

Today's medicine has a wide selection of antimicrobial drugs for the treatment of infectious pathology, and the arsenal continues to grow. The development of vaccines as the most effective means of preventing the mass spread of infection continues. As the history of medicine shows, even during deadly epidemics, there were people inexplicably unaffected by the disease, that is, their immunity was able to cope with the disease. The renowned philosopher Democritus lived for 104 years despite the fact that the average life expectancy at that time was 27 years. He considered contentment and peace of mind as the main guarantee of his physical and mental health. Today, it is known that the key factor for the effective functioning of the immune system is the state of the nervous system, the destabilization of which disrupts complex mechanisms of anti-infectious immune defense. Therefore, herd immunity depends not only on vaccination, but also on the moral environment in society, the benevolence and peacefulness of which contribute to the preservation of the health of the nation.

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К.А. Айтбаев[1], И.Т. Муркамилов*[2,3], Ж.А. Муркамилова[3], И.О. Кудайбергенова[2], Ф.А. Юсупов[4]

[1] — Научно-исследовательский институт молекулярной биологии и медицины, Бишкек, Кыргызстан
[2] — Кыргызская государственная медицинская академия имени И.К. Ахунбаева, Бишкек, Кыргызстан
[3] — ГОУ ВПО Кыргызско-Российский славянский университет, Бишкек, Кыргызстан
[4] — Ошский государственный университет, Ош, Кыргызстан

ЭПИГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ КАРДИОПРОТЕКЦИИ: В ФОКУСЕ — АКТИВАЦИЯ СИРТУИНОВ

K.A. Aitbaev[1], I.T. Murkamilov*[2,3], Zh.A. Murkamilova[3], I.O. Kudaibergenova[2], F.A. Yusupov[4]

[1] — Scientific and research Institute of molecular biology and medicine, Bishkek, Kyrgyzstan
[2] — I.K. Akhunbaev Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan
[3] — SEI HPE Kyrgyz Russian Slavic University, Bishkek, Kyrgyzstan
[4] — Osh State University, Osh, Kyrgyzstan

Epigenetic Mechanisms of Cardioprotection: Focus is on Activation of Sirtuins

Резюме

Окислительный стресс является общим признаком старения и сердечно-сосудистых заболеваний (ССЗ), включая атеросклероз, сердечную недостаточность, гипертонию, сахарный диабет и другие заболевания сосудистой системы. В этой связи, в последние годы исследователи проявляют повышенный интерес к сиртуинам (SIRT) — адаптерам стресса и эпигенетическим ферментам, участвующим в клеточных механизмах контроля возрастных патологий, рака и ССЗ. Среди сиртуинов, которых у млекопитающих семь (SIRT1-SIRT7), кардиопротекторными, противовоспалительными, атеропротекторными и антивозрастными свойствами в наибольшей степени обладают SIRT1 и SIRT6. В данном обзоре мы представляем всесторонний анализ последних событий в области клеточных и молекулярных сигнальных путей, контролируемых двумя посттрансляционными модификаторами — SIRT1 и SIRT6, которые доказали свою ценность в качестве инструментов для ослабления воспаления и окислительного стресса на уровне сердечно-сосудистой системы. Более глубокое понимание эпигенетических механизмов, через которые оказывают своё кардиопротекторное действие SIRT1 и SIRT6, будет иметь широкие последствия и ускорит разработку селективных и эффективных фармакологических препаратов для модуляции сиртуинов с целью профилактики и лечения ССЗ.

Ключевые слова: *SIRT1, SIRT6, окислительный стресс, эндотелиальная дисфункция, старение сосудов, сердечно-сосудистые заболевания*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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*Контакты: Илхом Торобекович Муркамилов, e-mail: murkamilov.i@mail.ru
*Contacts: Ilkhom T. Murkamilov, e-mail: murkamilov.i@mail.ru
ORCID ID: https://orcid.org/0000-0001-8513-9279

Abstract

Oxidative stress is a common sign of aging and cardiovascular disease (CVD), including atherosclerosis, heart failure, hypertension, diabetes mellitus and other diseases of the vascular system. In this regard, in recent years, researchers have shown increased interest in sirtuins (SIRTs) — stress adapters and epigenetic enzymes involved in cellular mechanisms for controlling age-related pathologies, cancer and CVD. Among sirtuins, of which there are seven in mammals (SIRT1-SIRT7), SIRT1 and SIRT6 possess the most cardioprotective, anti-inflammatory, atheroprotective and anti-aging properties. In this review, we present a comprehensive analysis of the latest developments in the field of cellular and molecular signaling pathways controlled by two post-translational modifiers — SIRT1 and SIRT6, which have proven their worth as tools to reduce inflammation and oxidative stress at the level of the cardiovascular system. A deeper understanding of the epigenetic mechanisms through which SIRT1 and SIRT6 exert their cardioprotective effect will have widespread implications and will accelerate the development of selective and effective pharmacological agents for modulating sirtuins for the prevention and treatment of CVD.

Key words: *SIRT1, SIRT6, oxidative stress, endothelial dysfunction, vascular aging, cardiovascular disease*

Conflict of interests

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BCA — ATP-binding cassette subfamily A, ABCG — ANP-binding cassette subfamily G, Akt — protein kinase B, AMPK — AMP-activated protein kinase, Ang II — angionensin II, ApoE — apolipoprotein E, AP-1 — activator protein 1, ATIR — angiotensin II type I receptor, Bcl-2 — B cell lymphoma 2, Bcl xL — B cell lymphoma-extra-large, CVD — cardiovascular diseases, CAT — catalase, CCR7 — C-C chemokine receptor 7, COL1A2 — collagen type 1, EC — endothelial cells, eNOS — endothelial nitric oxide synthase, ECP — endothelial cell precursors, EPCs — endothelial progenitor cells, ERR — estrogen-related receptors, ERK — extracellular signal-regulated kinase, FOXO — forkhead box O, I/R — ischemia-reperfusion, ICAM-1 — intercellular adhesion molecule-1, IGF — insulin-like growth factor, JNK — c-Jun N-terminal kinase, LKB1 — liver kinase B1, Lox-1 — lectin-like oxLDL receptor 1, LXR — liver X-receptor, MCP-1 — monocyte chemoattractant protein 1, MMP-9 — matrix metalloproteinase-9, MnSOD — manganese superoxide dismutase, NAD — nicotinamide adenine dinucleotide, NADPH — nicotinamide adenine dinucleotide phosphate, NAMPT — nicotinamide phosphoribosyltransferase, NBS-1 — Nijmegen breakage syndrome-1, NFkB — nuclear factor-kappa B, NKG2D — natural-killer group 2 member D, NO — nitric oxide, NRF1 — nuclear respiratory factor1, ox-LDL — oxidized low density lipoproteins, PARP1 — poly-(ADP-ribose) polymerase 1, PGC-1α — proliferator-activated receptor g coactivator-1α, PI3K — phosphoinositide 3-kinases, PIP3 — phosphatidylinositol-3,4,5-triphosphate, PCSK9 — proprotein convertase subtilisin/kexin type 9, PDK1 — 3-phosphoinositide-dependent kinase 1, PPAR-α — peroxisome proliferator-activated receptor coactivator-α, ROS — reactive oxygen species, SERCA2a — sarcoplasmic calcium ATPase, SIRT — sirtuin, SOD — superoxide dismutase, SREBP — sterol regulatory element-binding proteins, STAT3 — signal transducer and activator of transcription 3, TG — triglycerides, TIMP3 — tissue inhibitor of metalloproteinase, TNFSF4 — tumor necrosis factor superfamily member 4, VCAM-1 — vascular cell adhesion molecule-1

Introduction

Sirtuins (SIRT), nicotinamide adenine dinucleotide (NAD+)-dependent deacetylating enzymes, first found in yeast, are class III histone deacetylases. They all have a highly conserved NAD+ dependent catalytic core domain of 250–270 amino acid residues. Mammals have seven sirtuins (SIRT1–SIRT7). SIRT1 is localized in the nucleus and translocated to the cytosol under special conditions. It has been proven that SIRT6 is localized not only in the nucleus, but also in the cytosol. SIRT2 is primarily found in the cytosol, SIRT3, SIRT4 and SIRT5 in mitochondria, and SIRT7 is nuclear and nucleolar. Besides performing the well-known deacetylase function, sirtuins also function as mono-ADP-ribosyltransferase, lipoamidase (SIRT4), hydrolase (SIRT6), demalonylase, decrotonylase (SIRT3) and desuccinylase (SIRT5).

Sirtuins regulate important molecular pathways in eubacteria, archaea, and eukaryotes, and have a positive effect on life expectancy. They are involved in a variety of metabolic and homeostatic processes, including gluconeogenesis, fatty acid oxidation, oxidative phosphorylation, urea cycle, and endothelial homeostasis. Accumulated data have shown that sirtuins play an important role in cell adaptation to nutritional stress and are not only important sensors of energy status, but also counteract cellular metabolic stress by acting as stress adapters [1]. They play a central role in the development of age-related metabolic disorders, as well as stress resistance [2]. In addition to histone modifications, sirtuins directly modulate non-histone substrates, including DNA repair enzymes and other repair factors. The role of sirtuins in maintaining vascular homeostasis and in the development of cardiovascular diseases (CVD) is interesting. In endothelial cells (ECs), SIRT1 regulates cellular physiology in a unique way by controlling endothelial homeostasis and the functional state of blood vessels by modulating the activity of endothelial nitric oxide synthase (eNOS), p53, angiotensin II receptor (Ang II) of type 1 (AT1R, Ang II type 1 receptor) and transcription factor forkhead box O (FOXO) 1. SIRT2 is involved in vascular remodeling due to arterial hypertension [3], while SIRT3 controls systemic levels of oxidative stress and increases the survival rate of ECs in response to hypoxia [4]. SIRT4 and SIRT7 exacerbate

cardiac hypertrophy and negatively affect the proliferation and migration of ECs and vascular smooth muscle cells (VSMCs) [5]. The cardioprotective role of SIRT6 in the development of atherosclerotic plaque was recently established [6].

In this review, we discuss new views on cellular and molecular signals regulated by SIRT1 during the onset and development of CVD, as well as by SIRT6 during the formation of atherosclerotic plaques. In particular, we highlight their role in protection from pathological processes mediated by oxidative stress, including ischemia-reperfusion (I/R) heart damage, arterial wall remodeling, inflammation, vascular aging, and atherosclerosis.

Protective Role of SIRT1 and SIRT6 in Cases of Atherosclerosis

Aging processes are closely associated with atherosclerosis, which is the most common cause of death in elderly people, diabetes mellitus, dyslipidemia, metabolic syndrome, and hypertension. Atherosclerosis is triggered by SIRT1 deficiency in endothelial cells, smooth muscle cells, and monocytes/macrophages, which activates such processes as oxidative stress, inflammation, development of foam cells and impaired autophagy in the vascular wall. In turn, excessive autophagy triggered by high level of inflammation or oxidative stress contributes to decreased collagen synthesis, thinning of the fibrous cap and plaque destabilization, restenosis, and the development of acute coronary syndrome. In recent years, a link was also demonstrated between SIRT6 and the vulnerability of atherosclerotic plaque [6, 7].

Studies have shown that SIRT1 has an atheroprotective effect by increasing the nitric oxide (NO) level, degradation of serine-threonine kinase LKB1 (liver kinase B1), blocking NF-*k*B (nuclear factor-kappa B) — mediated inflammatory process, reducing the intensity of oxidative stress and control of autophagy [8]. In apolipoprotein E knockout (ApoE –/–) mice, endothelium-dependent vasorelaxation is usually reduced. However, if these mice are crossed with SIRT1-transgenic (SIRT1-Tg) mice, the endothelium-dependent vasorelaxation in their offspring, i.e. in SIRT1-Tg/ApoE (–/–) mice, is significantly improved and is accompanied by increased aortic eNOS [9]. Overexpression of endothelial SIRT1 in these mice, along with activation of eNOS expression, also prevents the expression of endothelial adhesion molecules and inhibits the development of aortic plaques in response to a high-fat diet [10].

Along with these data, SIRT1 involvement in preventing the progression of atherosclerotic lesions is evidenced by increased aortic eNOS activity and SIRT1 expression in hypercholesterolemic mice after oral administration of low doses of red wine as a source of resveratrol, a SIRT1 activator [11]. SIRT1 levels and activity were also significantly reduced in the lungs of ApoE –/– mice prone to atherosclerosis, which caused lung endothelium dysfunction due to increased acetylation and inactivation of eNOS [12]. Moreover, SIRT1 counteracted neointima development by suppressing the activity of the transcription factor AP-1 (activator protein 1) and decreasing the expression of cyclin D1 and MMP-9 (matrix metalloproteinase 9) [13].

At the level of smooth muscle cells, SIRT1 protects DNA from damage and inhibits atherosclerosis, in part, by activating NBS-1 (Nijmegen breakage syndrome-1) repair protein. It is notable that ApoE –/– mice expressing inactive truncated SIRT1 (Dex4) in smooth muscle cells demonstrate progressive atherosclerosis and signs of plaque vulnerability (relatively thin fibrous cap and media degeneration). In patients with type 2 DM, atherosclerotic plaques are usually characterized by increased MMP9 activity and decreased expression of TIMP3, tissue inhibitor of metalloproteinase 3. These changes in atherosclerotic plaques have been shown to be associated with significantly reduced SIRT1 levels [14]. In particular, overexpression of SIRT1 in smooth muscle cells increased the activity of gene promoter TIMP3, whereas inhibition of SIRT1 activity decreased TIMP3 expression. It is worth noting that SIRT1 in smooth muscle cells supports collagen synthesis and prevents the process of destabilization and destruction of plaque by promoting nuclear displacement and proteasomal degradation of the activity of the X-box transcription factor (RFX5, regulatory factor X5), thus weakening its binding to the promoter of the collagen I gene (COL1A2) [14]. In response to atheroprotective pulsatile shear stress, co-regulation of AMPK (adenosine monophosphate-activated protein kinase) and SIRT1 by CaMKKb (Ca2+ / calmodulin-dependent protein kinase b) promotes the development of an atheroprotective phenotype. In the proposed cell mechanism, AMPK and SIRT1 act in coordination in the cytoplasm in order to activate eNOS, thereby stimulating NO-mediated anti-inflammatory effects through the suppression of MCP-1 (monocyte chemoattractant protein-1), adhesive molecules VCAM-1 (vascular cell adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1) and E-selectin. Furthermore, AMPK and SIRT1 in the nucleus activate PGC1a (peroxisome proliferator-activated receptor gamma, coactivator 1 alpha), resulting in an increase in the level of antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) [15]. AMPK/NADPH (nicotinamide adenine dinucleotide phosphate)-oxidase / Akt (serine/threonine protein kinase B) / eNOS signaling pathway is also modulated

by quercetin, an antioxidant that activates SIRT1 and suppresses endothelial oxidative damage caused by oxidized low density lipoproteins (ox-LDL) [16]. Resveratrol, similarly to quercetin, reduces endothelial vascular inflammation and ox-LDL-induced damage by increasing the activity of AMPK/SIRT1 or cAMP-PRKA (serine/threonine protein kinase)-AMPK-SIRT1 signaling pathway [17]. In particular, ox-LDL inhibit autophagic flow due to a mechanism that includes ox-LDL-induced SIRT1-dependent lysosomal dysfunction [18].

The atheroprotective effect of SIRT1 is also mediated through the subtle modulation of the aging of endothelial cell precursors (ECP) and migration of adventitial fibroblasts [19]. In particular, in ECP, NAMPT (nicotinamide phosphoribosyltransferase), a rate-limiting enzyme in the NAD + biosynthetic pathway, diminishes ox-LDL-induced aging by increasing SIRT1 expression through the channel PI3K (phosphoinositide 3-kinases) / Akt / ERK (extracellular signal-regulated kinases) [19]. In peripheral blood mononuclear cells of individuals with metabolic syndrome, high glucose and palmitate-dependent damage to SIRT1 is associated with decreased NAMPT expression, subsequent depletion of cellular NAD+, and increased generation of reactive oxygen species (ROS).

The key event in atherogenesis is the infiltration of macrophages of monocytic origin into subendothelial space. The uptake of ox-LDL via lectin-like Lox-1 receptors determines the accumulation of cholesterol in macrophages and the subsequent development of foam cells. SIRT1 +/+ ApoE −/− mice demonstrated reduced rates of foam cell development and ox-LDL uptake that were accompanied by decreased Lox-1 receptor expression via NF-*k*B signaling pathway [20]. Accordingly, increased SIRT1 expression and decreased Lox-1 expression were also observed in ox-LDL-stimulated endothelial cells of the human umbilical vein that were exposed to ginkgolide B (biologically active terpene lactone found in Ginkgo biloba) — a platelet activating factor inhibitor with anti-inflammatory properties [21]. It is interesting that Lox-1 regulation of thrombus formation in vivo depended on the degree of ox-LDL activation. In particular, at low levels of ox-LDL, Lox-1 activated the SIRT1 protective pathway, whereas at higher levels of ox-LDL, it switched to the thrombogenic ERK1 / 2-dependent pathway [22].

SIRT1 controls the development of foam cells by deacetylation and activation of liver X-receptor (LXR), which, in turn, triggers the activity of member 1 of ATP-binding cassette subfamily A (ABCA1) and member 1 of ATP-binding cassette subfamily G (ABCG1), as well as C-C chemokine receptor 7 (CCR7), thereby contributing to the reverse transport of cholesterol and slowing down the development of foam cells [23].

SIRT6 inhibits triglyceride (TG) synthesis and fat metabolism, contributes to the β-oxidation of fatty acids, and maintains low LDL cholesterol levels through deacetylation of histone H3 at the lysine 9 (H3K9) position in the promoter of several genes involved in these metabolic processes [24]. Under nutritional stress, SIRT6 is positively modulated by SIRT1 through the development of SIRT1 / FOXO3a / nuclear respiratory factor 1 (NRF1) complex at the SIRT6 promoter, which, in turn, negatively regulates TG synthesis, lipogenesis, and glycolysis [24]. Accordingly, SIRT6-mediated histone deacetylation suppresses the transcription of proprotein convertase subtilisin / kexin type 9 (PCSK9) and transcriptional regulators SREBP (sterol regulatory element-binding proteins) 1 and 2. In particular, SIRT6 and FOXO3 can coordinate the regulation of cholesterol homeostasis through FOXO3-mediated recruitment of SIRT6 to the gene promoter *SREBP1/2* where it deacetylates histone H3 in lysine positions 9 (H3K9) and 56 (H3K56) and promotes the repressive state of chromatin [25]. Also, SIRT6 regulates cholesterol metabolism through suppression of lipogenic cholesterol transcription factors SREBP1 and SREBP2 and their target genes, inhibition of SREBP1/SREBP2 cleavage into their active forms, and activation of AMPK enzyme that phosphorylates and inhibits SREBP1 [26].

Recent *ex vivo* and *in vivo* studies demonstrated the direct involvement of SIRT6 in the development of atherosclerotic plaques in patients with diabetes and animal models of atherosclerosis [6]. In the carotid atherosclerotic plaques of patients with type 2 diabetes, SIRT6 expression was reduced compared to plaques in nondiabetic patients [6]. Also, decreased expression of SIRT6 protein in these atherosclerotic plaques was associated with decreased interstitial collagen content and increased levels of oxidative stress, pro-inflammatory cytokine NF-*k*B and MMP-9 [6]. All of these molecular events that characterize the phenotype of atherosclerotic carotid plaques in patients with asymptomatic type 2 diabetes are positively modulated by therapy with glucagon-like peptide-1 receptor agonists, a new class of antihyperglycemic agents with pleiotropic effects on arterial wall function.

Therefore, the short term *in vitro* effect of high glucose on EPCs (endothelial progenitor cells) and ECs induced suppression of SIRT6 and increased NF-*k*B [6]. *In vivo* studies of animal models of atherosclerosis confirmed the role of SIRT6 as a negative regulatory factor in the development of endothelial dysfunction and atherosclerosis. The expression of the SIRT6 gene and protein was suppressed in atherosclerotic plaques of ApoE −/− mice on a high cholesterol diet. In particular, SIRT6 knockdown ApoE −/− mice demonstrated impaired endothelium-dependent vasodilation,

increased size and increased vulnerability of plaques as evidenced by increased necrotic region of the nucleus, accumulation of macrophages, and decreased collagen amount.

In addition, SIRT6 heterozygous (SIRT6 +/–) mice demonstrated increased expression of natural killer (NKG2D) group 2 member D ligand on macrophages and ECs, which promoted activation of killer cells and increased levels of inflammatory cytokines. Finally, another key piece of evidence for the atheroprotective role of SIRT6 is the observation that SIRT6 +/– / ApoE –/– mice on a high-fat diet demonstrated significantly accelerated progression of atherosclerotic lesion along with increased expression of pro-inflammatory cytokine VCAM-1.

Analysis of potential targeting genes of SIRT6 revealed that SIRT6 binds to the promoter of the proatherogenic gene of tumor necrosis factor superfamily member 4 (TNFSF4) where it deacetylates histone H3 at the lysine 9 (H3K9) position, leading to SIRT6-dependent suppression of TNFSF4 transcription in ECs. However, we still have to figure out whether overexpression of SIRT6 and/or its modulation by specific activators can suppress vascular inflammation and slow down the development of atherosclerotic plaques. It was found just recently that SIRT6 protected against atherosclerosis by reducing the development of foam cells via the autophagy-dependent pathway [27]. Under ox-LDL conditions, SIRT6 reduces the development of foam cells of macrophages through the induction of autophagy and cholesterol efflux. In particular, overexpression of SIRT6 in foam cells increased ABCA1 and ABCG1 levels, activated cholesterol efflux, and reduced miR-33 levels. Moreover, transfection of miR-33 into cells with SIRT6 overexpression reduced the development of foam cells and resulted in reverse induction of the flow of autophagy.

SIRT1 and SIRT6 in Cardiac Diseases

SIRT1 and SIRT6 have different roles in maintaining cardiac function, especially in terms of protecting it from oxidative and ischemia-reperfusion (I/R) damage, as well as hypertrophic stimuli. SIRT1, which is the most important part in the pathogenesis of heart failure and regulation of cardiac electrical activity, was proposed as a tool for predicting the incidence of new myocardial infarctions.

In cardiac tissue, SIRT1 negatively regulates pro-apoptotic proteins Bax (BCL-2-associated X protein) and positively regulates the expression of anti-apoptotic protein of large B-cell lymphoma (Bcl-xL, B-cell lymphoma-xL) through FOXO activation. It is worth noting that SIRT1 has a protective effect via specific control of the acetylation and transcriptional activity of p53 in cardiomyocytes. In a chronic model of type 1 diabetes, decreased cardiac SIRT1 level is associated with decreased cardiac Ca-ATPhase levels of the sarcoplasmic reticulum (SERCA2a, cardiac sarcoplasmic calcium ATPase) [28]. More recently, Prola et al. reported that SIRT1 protects cardiomyocytes from endoplasmic reticulum (ER) stress through physical interaction and deacetylation of the eukaryotic protein translation initiation factor 2α (eIF2a) at lysine positions 141 (K141) and 143 (K143) [29]. In contrast, inhibition of SIRT1 induces nuclear fragmentation and cleavage of caspase-3, while SIRT1-deficient mice demonstrate abnormal heart development and prenatal mortality [30]. SIRT6 is valuable in cases of heart failure and control of cardiac fibrosis, a pathological condition that is critical in the development of heart failure [31]. SIRT6 negatively regulates the differentiation of cardiac fibroblasts into myofibroblasts; its depletion increases the proliferation of cardiac fibroblasts and the accumulation of extracellular matrix, and also stimulates genes associated with adhesion and fibrosis via the NF-*k*B signaling pathway [31].

Oxidative and Ischemia–Reperfusion (I/R) Damage

SIRT1 responds differently to various cardiac stresses. The expression of this protein increases during pressure overload, nutritional deficiencies, exercise and acute ischemic preconditioning and decreases with underlying I/R damage. SIRT1 protects cardiomyocytes from oxidative stress-mediated damage through the activation of CAT and MnSOD by deacetylation and activation of PGC-1a and FOXO [32].

SIRT1 expression in cardiac tissue decreases after I/R, while SIRT1 overexpression improves function recovery after I/R damage through increased MnSOD, thioredoxin-1 (Trx1), and Bcl-xL, as well as decreased activity of the proapoptotic protein Bax [32]. SIRT1 activation by resveratrol diminishes I/R damage to the heart by increasing ERK phosphorylation and decreasing p38 and JNK (c-Jun N-terminal kinase) expression. Also, exogenous administration of nicotinamide mononucleotide protects the heart from I/R damage by mimicking the cardioprotective effect of ischemic preconditioning and NAMPT overexpression, i.e. through a SIRT1-dependent mechanism. In contrast, autophagic flow in cardiac myocytes is impaired by a decrease in NAMPT, probably in conjunction with SIRT1 signaling pathway.

However, the effect of SIRT1 against oxidative stress in the heart depends on its concentration. In fact, at baseline, high cardiac expression of SIRT1 in mice, on the contrary,

induces oxidative stress through dysregulation of mitochondrial function. Hearts of male Wistar-Kyoto rats subjected to I/R were characterized by increased apoptosis of cardiomyocytes, cleavage of caspase 3, transient increase in SIRT1 level, increased expression of FOXO1 and binding to the SIRT1 promoter region, suppression of SIRT6 expression and AMPK-dependent reduction of NAD+ amount, reflecting a complex molecular network to protect the heart during I/R [33]. Moreover, in diabetic mice, resveratrol-enhanced autophagic flux prevented oxidative stress damage to the myocardium via the SIRT1/FOXO1/Rab7 pathway [34].

The protection provided by SIRT6 against cardiac I/R involves activation of FOXO3 in an AMPK-dependent manner, followed by the development of a complex with FOXO3 in the nucleus. Like SIRT1, the SIRT6-FOXO3 complex enhances the transcription of FOXO-dependent antioxidant genes (MnSOD and CAT) to counteract damage due to I/R [35]. Also, overexpression of SIRT6 protects cardiomyocytes from hypoxic stress by activating AMPK, increasing Bcl2 level, suppressing NF*k*B activity, and decreasing cell levels of ROS (reactive oxygen species) [36]. SIRT6 directly binds to PARP1 (poly-[ADP-ribose] polymerase 1) and increases its poly-ADP-ribosylase activity, thereby stimulating the restoration of double-strand break under oxidative stress [37]. Since excessive PARP1 activation can deplete NAD+ levels in cardiomyocytes, it is important to limit the excessive activation of SIRT6 in the heart to optimize its cardioprotective effects.

Finally, SIRT6 also protects against hypoxia/reoxygenation-induced damage by reducing hypoxia-induced apoptosis and mitochondrial defects through suppression and translocation of the p65 subunit of NF-β*k*B [38].

Cardiac Hypertrophy

Both SIRT1 and SIRT6 protect the heart from hypertrophy, although SIRT1 also demonstrates opposite effects depending on the interaction with other factors and stress severity [39]. Pressure overload in the heart causes cardiac hypertrophy and failure through an increase in PPAR-a (peroxisome proliferator-activated receptor coactivator-α) -SIRT1 complex and suppression of estrogen-related receptors (ERRs) of the transcriptional pathway [39]. Also, SIRT1-dependent activation of ACT exacerbates cardiac hypertrophy. In particular, SIRT1-mediated deacetylation as a plextrin homology (PH) domain of A*k*t and its upstream kinase PDK1 (3-phosphoinositide-dependent kinase 1) facilitates their interaction with phosphatidylinositol-3,4,5-trisphosphate (PIP3) in the plasma membrane where PDK1 phosphorylates and activates Akt, causing cardiac hypertrophy. SIRT1-deficient hearts demonstrated decreased Akt activation and less development of cardiac hypertrophy in response to exercise and Ang II stimulation.

In neonatal rat cardiomyocytes, inhibition of SIRT6-dependent NF-*k*B suppresses cardiomyocyte hypertrophy, and overexpression of wild-type SIRT6 diminishes Ang II-induced cardiac hypertrophy [40]. Interestingly, the overexpression of nicotinamide mononucleotide adenylyl transferase 2 (Nmnat2) prevented the development of Ang II-induced cardiac hypertrophy. Among all sirtuins, elevated mRNA levels in response to Ang II stimulation were observed for SIRT6 and SIRT1, with the predominant role of SIRT6 [40]. Therefore, a new PARP1 inhibitor, AG-690/11026014, a compound that can prevent Ang II-induced cardiomyocyte hypertrophy, reverses the depletion of cellular NAD+ and SIRT6 deacetylase activity. It is noteworthy that under normal conditions SIRT6 blocks the expression of genes associated with IGF (insulin-like growth factor) signaling, which is responsible for heart failure by deacetylation of H3 at Lys-9 (H3K9) and suppression of c-Jun activity. In contrast, the reduction of SIRT6 expression in the heart in cases of pathological stress leading to the development of cardiac hypertrophy, fibrosis, and heart failure was associated with increased H3K9 acetylation on the IGF signaling gene promoters and c-Jun-mediated transcriptional activation.

The attenuation of Akt signaling through SIRT6-dependent activation of FOXO3 also contributes to the pro-autophagic effect of SIRT6 in suppressing isoproterenol-induced cardiac hypertrophy. More recently, the protective role of SIRT6 with underlying cardiomyocyte hypertrophy was confirmed by the observation that the suppression of the signal transporter and transcription activator 3 (STAT3), critical for the development of cardiac hypertrophy and heart failure, was involved in signaling, which mediated the protective effect of SIRT6 [41].

SIRT1 and SIRT6 Modulators in Preclinical and Clinical Conditions

Today, intensive studies are focused on modulating SIRT1 and SIRT6 using pharmacological and natural food compounds, as well as miRs [42]. SIRT1 activation by resveratrol derivatives such as BTM-0512 demonstrated a beneficial effect on high glucose-induced dysfunction of ECs [43]. According to these results, eight-week male C57BL/6 mice treated with resveratrol demonstrated less significant development of insulin resistance and endoplasmic reticulum stress induced by a high-calorie diet through increased SIRT1 expression and reversal of adipokine expression in both subcutaneous and visceral adipose tissues. Another compound,

icariin, an important active ingredient in Herba Epimedii (horny goat weed), also acts as a SIRT6 activator and NF-inhibitor*k*B and demonstrated its potential efficacy in the treatment of CVD [44].

As was widely reported [42], the following clinical trials are currently underway or have been completed (http://clinicaltrials.gov): safety, efficacy, pharmacodynamics, and pharmacokinetics of natural and synthetic compounds that can modulate SIRT1 and SIRT6 in several diseases, including cardiovascular, inflammatory, metabolic syndrome, insulin resistance, type 2 diabetes and obesity. In this regard, clinical evaluations of the pharmacological activators of SIRT1 (SRT1720, SRT3025, SRT2104 and SRT501) have resulted in the prevention of metabolic diseases, decreased atherosclerotic plaque formation, improved lipid profile in cigarette smokers, and improved glucose tolerance in patients with type 2 diabetes [45]. Also, the results of a double-blind, placebo-controlled study in patients with carotid atherosclerosis revealed that treatment with metformin reduced the state of proinflammation in peripheral blood mononuclear cells through the induction of SIRT1, p65, as well as the blockade of NF-*k*B [46].

However, the problem of controlling SIRT1 and SIRT6 activity by specific compounds in order to achieve protection against CVD remains unresolved. And there is still a long way to go before sirtuin modulators can be used for therapeutic purposes. This is because clinical evaluations of SIRT6 are still limited, and clinical results on the effectiveness of SIRT1 modulators are contradictory. Nevertheless, studies on sirtuin modulation by pharmacological compounds remain significant today and are being carried out quite intensively. A sulfonylurea compound (G004) was recently synthesized. It had a positive impact on hyperglycemia and atherosclerosis due to its effect on the SIRT1/eNOS axis. A new PARP1 inhibitor (poly[ADP-ribose] polymerase 1) AG-690/11026014 demonstrated protective effects on Ang II-induced cardiac muscle remodeling by restoring SIRT1 activity in cardiac tissue [47].

Among natural nutrients that can modulate SIRT1 and SIRT6, ergothioneine has been shown to prevent high glucose-induced endothelial aging by modulating SIRT1/p66shc (one of the isoforms of SHC1 protein) and SIRT6/NF-*k*B [48]. Finally, the recently identified SIRT6 inhibitor, compound 1 (2,4-dioxo-N-(4- (pyridin-3-yloxy)phenyl)-1,2,3,4-tetrahydroquinazoline-6-sulfonamide), tested in a mouse model of type 2 diabetes reduced levels of insulin, triglycerides, and plasma cholesterol, and improved glycemic control by increasing the expression of GLUT (glucose transporter) 1 and GLUT4 in muscles and increased the activity of the glycolytic pathway [49].

Conclusions and Future Focus Areas

Studying the role of SIRT1 and SIRT6 signaling pathways in protection against CVD became relevant over the past couple of years. The beneficial effects of these compounds on inflammation, vascular aging, control of glucose homeostasis, atherosclerosis, and cardiac diseases are now intensively analyzed, and new targets are constantly being discovered within the complex structures [50]. In this regard, summarizing the achievements in the study of the role of SIRT1 and SIRT6 signals in protection against CVD, we can conclude that they are associated with the establishment of:

- dependence of SIRT1 and SIRT6 activity on the cellular redox state. This fact indicates that antioxidant compounds have a strong potential to protect against CVD, which compounds have an effect on the SIRT1/FOXO axis, SIRT1/NF-*k*B axis, SIRT1/p66Shc axis and SIRT6/NF*k*B axis;
- antiatherogenic role of SIRT6 *in vivo*, which makes this sirtuin a potentially new target in the prevention of atherosclerosis;
- effectiveness of SIRT1 synthetic activators with good tolerance and bioavailability in individuals who overcome the limit of low bioavailability of resveratrol;
- overlapping of regulatory mechanisms including transcription factors and miRs such as NF-*k*B and miR-34a, which indicates a regulatory interaction between these sirtuins.

Overall, regarding the mechanisms controlled by these sirtuins, recently obtained data linking SIRT6 with the development of atherosclerotic plaques and their vulnerability by NF-*k*B/NKG2D (natural-killer group 2 member D) indicate that the control of inflammatory pathways in CVD is very important, especially for SIRT1 and SIRT6. At the same time, equally important are cell mechanisms that influence intracellular glutathione levels under conditions of oxidative stress, which appears to be critical for controlling both SIRT1 and SIRT6.

Although these sirtuins control the mechanisms responsible for genome longevity and stability, and this fact makes them attractive in terms of their roles in the context of age-related diseases, the interactions between SIRT1 and SIRT6 signals clearly demonstrate the need to understand the set of their molecular targets in order to achieve highly specific and selective modulation at cardiovascular level. As demonstrated in this review, the discussion of both SIRT1 and SIRT6 signaling pathways in the protection against CVD, as well as the presence of common molecular targets, suggests that these sirtuins can act synergistically.

The complete discovery of the whole set of SIRT1 and SIRT6 signaling pathways, including their possible

associations with the cell mechanisms of vascular aging and CVD, remains a key challenge in this area, along with a deeper understanding of the redox regulation of these sirtuins. In this regard, the prospects for future research will be associated with the expected mapping of the epigenome in human diseases, which will allow the identification of epigenetic targets specific to a particular disease or disease stage. As for today, using dietary antioxidant compounds, as well as a healthy lifestyle with moderate exercise and calorie restriction, can be important for controlling the conditions of cellular oxidative stress that cause vascular aging and cardiovascular disease.

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Айтбаев К.А. (ORCID ID: https://orcid.org/0000-0003-4973-039X): редактирование текста **Муркамилов И.Т. (ORCID ID: https://orcid.org/0000-0001-8513- 9279):** анализ полученных данных, написание текста

Муркамилова Ж.А. (ORCID ID: https://orcid.org/0000-0002-7653-0433): сбор материала, анализ результатов

Кудайбергенова И.О. (ORCID ID: https://orcid.org/0000-0003-3007-8127): редактирование текста

Юсупов Ф.А. (ORCID ID: https://orcid.org/0000-0003-0632-6653): анализ полученных данных, написание текста

Contribution of Authors:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Aitbaev K.A. (ORCID ID: https://orcid.org/0000-0003-4973-039X): text editing

Murkamilov I.T. (ORCID ID: https://orcid.org/0000-0001-8513-9279): analysis of the received data, writing text

Murkamilova Zh.A. (ORCID ID: https://orcid.org/0000-0002-7653-0433): collection of material, analysis of the data

Kudaibergenova I.O. (ORCID ID: https://orcid.org/0000-0003-3007-8127): text editing

Yusupov F.A. (ORCID ID: https://orcid.org/0000-0003-0632-6653): analysis of the received data, writing text

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В.Н. Ларина*, И.А. Самкова, Е.В. Кудина

ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России,
кафедра поликлинической терапии лечебного факультета, Москва, Россия

ПАДЕНИЯ, КАК ПРОБЛЕМА СТАРЕЮЩЕГО НАСЕЛЕНИЯ ПЛАНЕТЫ, СОВРЕМЕННЫЙ ВЗГЛЯД НА ФАКТОРЫ РИСКА И МЕТОДИКИ ОЦЕНКИ. РОЛЬ СТРАХА ПАДЕНИЙ В УВЕЛИЧЕНИИ ИХ РИСКА

V.N. Larina*, I.A. Samkova, E.V. Kudina

Pirogov Russian National Research Medical University, Moscow, Russia,
department of outpatient medicine, Faculty of General Medicine

Falls As a Problem of an Aging Population, a Modern Look at Risk Factors and Assessment Methods. Role of Fear of Falls in Increasing their Risk

Резюме

В статье приводятся современные взгляды на проблему падений у пожилых людей. В связи с мировой тенденцией изменения демографической ситуации — постоянного увеличения доли лиц пожилого и старческого возраста в общей популяции, вопросы гериатрии, как одной из медицинских специальностей становятся наиболее актуальными. В ряду проблем, которые приходится решать гериатрам и всем специалистам, принимающим участие в лечении пожилых пациентов, одной из наиболее серьезных является проблема падений. В статье приводится обзор литературы, посвященный оценке частоты падений в зависимости от пола, возраста, наличия заболеваний и внешних факторов. Подробно разбираются основные факторы риска падений и меры их профилактики. Особое внимание уделяется страху падений, как значимому фактору их риска. Приводятся методы оценки данного фактора риска с применением унифицированных опросников — «Шкалы оценки страха падений» и «Шкалы эффективности падений». Целью данной статьи является привлечение внимания практикующих врачей к проблеме падений в целом и страху падений, как одному из значимых факторов риска, методам его выявления и профилактики.

Ключевые слова: *падения, старческая астения, пожилой возраст, страх падений*

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*Контакты: Вера Николаевна Ларина, e-mail: larinav@mail.ru
*Contacts: Vera N. Larina, e-mail: larinav@mail.ru
ORCID ID: https://orcid.org/0000-0001-7825-5597

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Abstract

The article presents modern views on the problem of falls in the elderly. There is a global trend of changing the demographic situation — the permanent increase in the proportion of elderly and senile people in the general population, the issues of geriatrics as one of the medical specialties are becoming the most relevant. Among the problems that geriatricians and all specialists involved in the treatment of elderly patients have to solve, one of the most serious is the problem of falls. The article provides a medical review of the assessment of the frequency of falls depending on gender, age, diseases and external factors. The main risk factors for falls and their prevention measures are discussed in detail. Special attention is given to the fear of falls as a significant risk factor. The methods of validation the risk factor with the use of unified questionnaires — "The scale of assessment of the fear of falls" and "the Falls efficacy scale" are presented. The purpose of this article is to attract the attention of practitioners to the problem of falls and the fear of falls as one of the significant risk factors, methods of its identification and prevention.

Key words: *falls, frailty, elderly age, fear of falls*

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BP — blood pressure, AH — arterial hypertension, VAS — visual analogue scale, WHO — World Health Organization, BMI — body mass index, SA — senile asthenia, DM — diabetes mellitus, CVS — cardiovascular system, FES — the Falls Efficacy Scale

The delivery of medical care and social support to elderly people is one of the most critical challenges for humanity.

The proportion of elderly and senile people among the world's population is steadily increasing. This is primarily due to the success of medicine, as well as the development of social and psychological services aimed at supporting the elderly. According to the World Health Organization (WHO), by 2050, the elderly population will constitute 22%, which corresponds to more than 2 billion people [1–3]. The fastest growing population group is expected to be 80+: they are expected to make up 25% of the world's elderly population by 2050 [4]. More than 30 million elderly and senile people currently live in Russia. Every year, their number increases by about one million [5]. According to the average forecast by the Federal State Statistics Service, the proportion of citizens above the working age will increase from 25.5% in 2018 to 27.4% in 2025 and will amount to 40.2 million people.

The importance of the problem of population aging for humanity as a whole, both from an economic and ethical viewpoint, facilitated the emergence and development of gerontology as a science and geriatrics as a field of medicine in the 20th century.

Unlike young and middle-aged people, for the elderly, the concept of "health" is not synonymous with the complete absence of diseases [6]. Health for an elderly person is, first of all, maintaining a satisfactory quality of life and independence from others. A combination of several factors plays an important role in maintaining the quality of life and good functional activity of the elderly. Above all, it is the adequate treatment of existing diseases and prevention of their progression and the development of complications. However, solutions to everyday and social problems and measures to preserve cognitive functions and ease depression play an equally important role. These problems can be solved only through the joint efforts of medical and social workers, together with the families of elderly people.

Assessing the possible consequences of disease, both for an individual patient and for society as a whole, WHO proposed the term "Global Burden of Disease". This concept includes years of life lost due to disability or premature death. DAlY (Disability And life-Year lost) is an important component of assessing the health of the population [6, 7]. The list of diseases and conditions that make up the main burden of disease differs among people of different ages. For people over 60 years of age, the main reasons for lost years of life due to disability are sensory disorders, pain in the spine, chronic obstructive pulmonary disease, depression and falls [6].

Falls are one of the most serious problems for elderly people. Today, the Russian Federation is actively implementing the federal project *Older Generation*. This project pays much attention to the implementation of a set of

measures to prevent falls and fractures as per the guidelines approved in 2019 [1].

Falling is an incident when a person suddenly finds himself/herself on the ground or another low surface, except for cases resulting from a blow, loss of consciousness, sudden paralysis or an epileptic seizure [8–10].

In young people, falls often occur due to external factors (ice, foreign objects under the feet, etc.) or in persons with severe diseases — neurological, cardiovascular, etc. In elderly people, falls are more often due to age-related functional disorders [11].

According to different authors, one-third of patients aged 65 years and older and half of patients older than 80 years have had a fall incident at least once in their life [3, 10, 12]. Fifteen percent of people aged 65+ had multiple falls [16]. Falls are the most common domestic accident in elderly people. Falls are especially frequent in people living in social institutions — about 40% of them fall at least twice a year . According to a study involving 92 patients, whose average age was 74.9 years ± 7.8 years, a history of falls was observed in 21.1% of men and 37.0% of women [11].

Falls in the elderly are closely associated with frailty syndrome. Senile asthenia (AS) is a key geriatric syndrome characterized by an age-associated decrease in the physiological reserve and functions of many body systems. This leads to increased vulnerability of the elderly person to the effects of endo- and exogenous factors, with a high risk of adverse health outcomes, loss of autonomy and death [13, 14].

Falls may result from such manifestations of senile asthenia as decreased muscle strength, visual impairment and impaired balance. On the other hand, repeated falls can trigger progression of SA. The senile asthenia syndrome can be considered a predictor of possible falls [13, 15]. This is because due to the consequences of injuries sustained during a fall, pain syndrome, as well as the fear of falling again, patients significantly reduce their physical activity [11]. Specifically, adequate physical activity is one of the key factors in the prevention of SA progression. In turn, the fear of falls and a decrease in functional activity, and, consequently, a complete or partial loss of independence from the people around them, leads to depression, which is another factor in the progression of SA. This creates a vicious circle — senile asthenia increases the risk of falls, repeated falls lead to increased manifestations of SA.

In a study of 3510 patients aged 60 and over (mean age 71 years ± 0.1 years) with three or more chronic diseases, falls in the anamnesis were registered in 645 (18.4%) patients. Senile asthenia was found in 54% of patients with falls, which is twice higher than in the group of patients without falls (26%). Also, such geriatric syndromes as weight loss (22 and 9%, respectively; $p < 0.001$); urinary incontinence (22% and 13%, respectively; $p < 0.001$); low mood (76 and 38%, respectively; $p < 0.001$); memory problems (74% and 42%, respectively; $p < 0.001$); difficulties in movement (31 and 27%, respectively; $p = 0.038$) were observed in the patients with falls much more often than in the main group, and the statistical significance of this difference is high [15].

The most serious consequence of falls is injury. Twenty to thirty percent of cases of falls result in injury [12, 16, 17]. In the elderly, injuries can be serious. At an older age, bone tissue restoration is slower, which results in longer immobilization, which is dangerous due to the development of complications associated with impaired blood circulation and the development or progression of depression. Also, in older people, pain syndrome is often more pronounced and prolonged, which also limits mobility and aggravates depression. The need to take more pain relievers and sleeping pills also adversely affects many body functions. One of the most serious injuries in elderly patients is the fracture of the proximal femur. In most cases, it is caused by a fall. Every year, there are 646,000 fatal falls in the world [18].

In cases where a fall does not end with an injury, it can also cause significant harm to health due to psychological consequences: feelings of fear and depression [16, 19]. Even after uncomplicated falls, the mobility of elderly patients is significantly reduced and mortality increases: in 50% of cases, after falls, patients lost the ability to move independently; in people over 85 years of age, 20% of deaths are associated with a previous fall [8].

The incidence of falls varies by gender and age. The likelihood of falls increases with age, which is due to the progression of senile asthenia and the development of sarcopenia. The age 65 to 74 is associated with a 31% risk of falling, which rises to 37% in the 80+ age group [18]. Women fall more often than men, but this difference is most evident in the older age group [2, 8]. More frequent falls in women could be related to their more intense everyday activity. Furthermore, gait significantly changes in elderly people. The foot is less lifted from the surface, which increases the risk of tripping over small objects and uneven floors or soil.

According to a study involving 628 patients aged 65+ (mean age 76.9 years ± 15.5 years), 56.5% of people had falls during the year. The highest incidence of falls (61.36%) was in the age group 85+ ($p < 0.001$). As risk factors for falls, decreased movement speed and balancing ability were statistically significantly more frequent in women than men ($p < 0.001$) [2].

There are differences in gait between elderly men and women. Women tend to waddle with legs close together, while men -usually have a flexor posture and gait with small steps with legs wide apart [20, 21]. These differences may also explain the greater risk of falls in women.

Women are at significantly higher risk of fractures from falls than men. This is associated not only with a higher incidence of falls, but also with more pronounced manifestations of osteoporosis.

The risk of falls depends on where the elderly person is: at home, in a nursing home or hospital. In hospitals, the risk of falls more than doubles [8]. This is because, in hospitals and social institutions, the high probability of falls is associated with an unusual environment — furniture, floor structure, etc. Besides, the patients who have to stay away from home have a higher level of depression. One should also take into account such an important fact that patients who need hospitalization or constant care in a boarding house are people with more severe somatic pathology or cognitive impairments.

Elderly lonely people are a special category of patients most vulnerable to falls. Often, they have to perform everyday activities that are excessive due to their somatic or cognitive state. Lonely people often cannot seek the necessary help on time after a fall or injury, which can lead to serious complications due to hypothermia, circulatory disorders, etc.

External and internal falls are distinguished depending on the place and conditions of occurrence. External falls include falls outside the home (on the street, in a store, clinic, etc.) and are more often associated with environmental factors (slippery road, uncomfortable steps). Such falls are typical for younger people who are independent of outside help. Internal falls occur in the house where the elderly person lives. Most often, they occur in persons over 80 years of age with senile asthenia syndrome [22]. The causes of internal falls can be divided into two categories: associated with the patient himself/herself and with his/her environment. The main reasons associated with the patient's health are muscle weakness, decreased vision, and dizziness. External factors are determined by poor arrangement of the apartment — slippery or rough floors, poor lighting, blocked walkways, wires on the floor, etc.

The analysis of the site of falls in 355 patients aged 65+ identified the difference in various age groups. In the 65–74 age group, falls occurred outdoors more often (in 66.25% of cases); at 75–84 years — falls indoors and outdoors occurred with a frequency of 34.88 and 48.84%, respectively. Over the age of 85, people were more likely to fall at home. [2].

Fall risk factors divided into unmodifiable (unmanaged), modifiable (managed) and partially modifiable.

Non-modifiable risk factors

- Age
- Female
- History of falls
- Multimorbidity
- Cognitive impairment
- Recent discharge from an inpatient hospital (no more than 1 month ago) due to a decrease in muscle strength and body asthenization during hospitalization [22].

Partially modifiable risk factors

- Depression
- Chronic pain syndrome
- Age-related musculoskeletal diseases
- Visual impairment
- Polypharmacy

Modifiable risk factors

- Low or high body mass index (BMI), eating disorders
- Lack of physical activity
- Smoking, alcohol abuse
- Movement and gait disorder of various origins
- Sarcopenia
- Fear of falls
- Low vitamin D levels
- Environmental factors

A common consequence of repeated falls is the fear of falling again, which leads to the development or intensification of depression. Even in the absence of trauma, loss of self-confidence, social isolation, and disorientation can develop.

Identification of risk factors and their severity is a key factor in the development of patient management tactics in order to prevent falls and their consequences.

In a study that surveyed 71 elderly patients with recurrent falls, only 21 (29.6%) patients were interviewed by a doctor about the causes and circumstances of the fall, and risk factors were corrected in only 14.1% of cases [8].

Methods of assessing the risks of falling, fear of falls

When assessing the risk of falls, data on the history and physical examination should be taken into account, and special tests and questionnaires should be used to determine the functional, cognitive and psychological characteristics of the patient's body.

The medical history should include concomitant diseases and the degree of their control, administered drugs, their amount, etc. In the structure of multimorbidity, which increases the risk of falls, the most significant are cardiovascular diseases (carotid sinus syndrome, atrial fibrillation, heart failure, orthostatic hypotension), chronic obstructive pulmonary diseases, and joint pathology [1, 8, 9].

In a study involving 155 people with a history of falls and arterial hypertension (AH), in 148 (95.5%) people, the most common risk factors for falls were previous falls (83.7%), visual (75%) and balance (63.5%) disorders, osteoarthritis (63.5%). Patients with BP below the target values had the lowest walking speed (0.48 m/s ± 0.28 m/s) compared with patients with controlled AH (0.83 m/s ± 0.34 m/s) and with BP above the target values (1.11 m/s ± 0.63 m/s), $p < 0.05$. In patients with BP below the target, the incidence of falls was 2.96, BP within the range of target values — 2.56, and high BP — 2.81 per year. Therefore, both inadequate BP control and excessive BP reduction are risk factors for falls. Slow walking, most pronounced in patients with low blood pressure, contributes to the high probability [23].

When more than four drugs were used at the same time, the risk of falling increased 1.3 times compared with patients receiving less than four drugs [10, 11]. The drugs that most significantly increase the risk of falls include nitrovasodilators, diuretics, antiarrhythmics, tricyclic antidepressants, antipsychotics, nonsteroidal anti-inflammatory drugs, and non-narcotic analgesics [22].

Also, a very important anamnestic factor is a previous fall. A fall in the previous 6–12 months is an independent factor that at least doubles the risk of falls [24].

During history-taking, the patient should be asked about the presence of possible external factors that may increase the risk of falls: poor arrangement of the apartment, wearing uncomfortable or slippery shoes, use of unsuitable walking aids, wrong spectacles, etc.

The level of the patient's physical activity should be determined while speaking with the patient. Lack of physical activity is a significant factor that increases the risk of falls due to the aggravation of muscle atrophy as a result of insufficient exercise. It has been shown that a decrease in daily physical activity due to illness for 14 days is associated with an increased risk of falls [8].

During a physical examination, the height and weight of the patient should be determined, and the BMI should be calculated. Determination of BMI helps identify a group of people with malnutrition or obesity. A low BMI, indicative of malnutrition, is associated with an increased risk of falls due to severe sarcopenia [22]. Patients with varying degrees of obesity also have an increased risk of falls, which is associated with low physical activity [2].

When examining a patient, besides measuring blood pressure, an orthostatic test should also be conducted. Detected orthostatic hypotension is also a risk factor for falls.

All patients aged 60 years and above who seek medical help should be screened for senile asthenia using the Age Is Not a Hindrance questionnaire and fall risk assessment using the Fall Risk Self-Assessment Questionnaire [25]. The "stand up and walk" test identifies gait and balance disorders and allows to estimate the strength of the patient's legs.

In the presence of pain syndrome of any origin, it is important to assess the degree of pain intensity using a visual analogue scale (VAS). The intensity of pain is considered high if it is ≥ 40 mm according to the VAS. In older age groups, chronic pain is associated with depression. The more pronounced the pain syndrome, especially when walking, the more pronounced the symptoms of depression are. Difficulty in sleeping associated with pain or depression can be a common contributing factor to falls. The geriatric depression scale and the health assessment scale are used to determine the emotional state [13].

In patients with intellectual and amnestic disorders, the validated Mini Mental State Examination (MMSE), the Montreal Cognitive Assessment Scale, should be used as reliable primary screening tools for cognitive impairment, including dementia.

In patients over 60 years of age with a risk of falls, a ten-year risk of osteoporotic fractures should be assessed using the FRAX scale (Fracture Risk Assessment Tool) and a decision should be made on the methods of prevention and treatment of osteoporosis [8].

Fear of falls is one of the important factors determining the quality of life in elderly patients and their functionality. Usually, doctors do not pay attention to this issue in their practical work. However, identifying the fear of falls and preventive work with the patient can improve the functional activity and reduce the risk of falls. Fear of falling is a psychological condition. Up to 70% of those who did not have it shortly before the fall, and up to 40% of those who did not fall, reported having a fear of falling. Up to 50% of people with a fear of falling limit or completely stop social and physical activity. There is a close relationship between fear and impaired postural responses [9]. About two-thirds of people experienced fear after falling, and about half subsequently tried to avoid vigorous activity due to the fear of falling [22].

To assess the fear of falls, a short scale for assessing the fear of falling is used (tab. 1). This scale assesses how much the patient is concerned about the possibility of falling while performing daily activities [1].

The falls efficacy scale (FES) evaluates the degree of fear that the patient experiences when performing everyday household activities. The patient must be assessed on a ten-point scale for the confidence of not falling when performing various activities. The scale lists the daily activities that a person needs to independently live in a social environment [26].

Table 1. *A short scale for assessing the fear of falling*

Action	Not at all concerned about the possibility of falling	A little concerned about the possibility of falling	Very concerned about the possibility of falling	Definitely concerned about the possibility of falling
Dressing or undressing	1	2	3	4
Taking a shower or bath	1	2	3	4
Getting up from the chair	1	2	3	4
Climbing the stairs	1	2	3	4
Going up or down the slope	1	2	3	4
Attending an event outside the home (for example, meeting with friends, relatives, religious services, theater, etc.).	1	2	3	4

Note: Interpretation of the results: 7-8 points — low fear of falling, 9-13 points-moderate fear of falling, 14-28 points-high fear of falling

Table 2. *The Falls Efficacy Scale*

Action	Meaning: 1 =absolutely sure 10 =not at all sure
Taking a shower or bath	
Reach for bedside tables or closets	
Moving around the house	
Prepare food, without having to carry heavy or hot objects	
Go to bed and get up from it	
Answering a doorbell or phone call	
Sit on a chair and get up from it	
Dressing or undressing	
Take care of yourself (for example, wash your face)	
Sit down on the toilet and get up from it	
Total score:	

Note: The presence of fear of falling is determined when the number of points ≥ 70

The patient must answer the question: How confident are you that you can do the following without falling? Confidence in performing the listed actions should be assessed on a scale from 1 to 10, where 1 means complete confidence, and 10 — complete lack of confidence (tab. 2).

Subsequently, the authors [27] suggested a modified scale, where they added six questions to the existing ten. These additional questions reflected more complex activities outside the home — the social life of older people: walking on slippery surfaces, visiting a friend/relative, visiting crowded places, walking on rough surfaces, walking up or down a hill, attending a social event. Concern for these activities was assessed using a four-point scale. This scale (FES I) measures anxiety when performing more challenging activities (including social activity) than the original Falls Efficacy Scale. The study, which aimed to modify the Falls Efficacy Scale, included 705 people aged 65 to 95 years (mean age 74.7 years). The FES-I scale was highly reliable (Cronbach's $\alpha = 0.96$). Compared to FES, the modified scale showed a greater capacity to differentiate fear of falling between groups, depending on gender, age, profession, past falls, and risk factors.

Fall prevention measures

Fall prevention measures can be divided into general and differentiated [28].

General Fall Prevention Measures

- Educational materials for patients on the prevention of falls — the main objective of education is to affect the modifiable risk factors using the educational program. Only the active participation of patients allows to effectively improve their quality of life, prevent the progression of diseases and contribute to the prolongation of active longevity;

- Physical activity at least 150 minutes per week. Physical exercises for balance training (health walking, running, playing sports, gymnastics); muscle strength (lifting weights, exercising on exercise machines, swimming, cycling); restorative exercises;
- vision correction;
- hearing correction;
- cognitive training;
- a diet with a sufficient protein content should be 68 g/day for men and 61 g/day for women at the age of 60+ [22];
- elimination of environmental safety hazards;
- choosing shoes, using hip protectors, ankle orthoses, walking sticks, walkers and other devices;
- revision of the list of prescribed drugs and their adjustment, especially when it comes to psychotropic drugs;
- adjustment of daily intake of vitamin D and prevention of its deficiency. It has been proven that the incidence of falls decreased by 34% when taking 800 IU of vitamin D every day [22].

The choice *differentiated individual measures to prevent falls* depends on the existing risk factors: cardiovascular diseases (CVD), diabetes mellitus (DM), malnutrition, anemia, dizziness, cognitive impairment, depression, chronic pain, urinary incontinence, sleep disturbances, foot problems. Non-drug and drug treatment of these diseases and conditions is carried out.

Fall prevention is one of the major challenges facing doctors and society as a whole. Falls in a particular person are usually caused by a combination of medical and social factors. Therefore, a multi-level system of prevention should be developed, including social, psychological and medical aspects, with the participation of doctors of different specialties, social workers, relatives and the patient himself/herself. Identification and maximum possible elimination of the causes of falls and psychological work with the patient will help reduce the feeling of fear, which itself is a serious risk factor.

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Ларина В.Н. (ORCID: 0000-0001-7825-5597): разработка концепции и дизайна, сбор, анализ и интерпретации данных, проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации, ответственный за все аспекты работы

Самкова И.А. (ORCID 0000-0001-5057-6890): сбор, анализ и интерпретации данных, подготовка рукописи, ответственный за все аспекты работы

Кудина Е.В. (ORCID 0000-0002-9547-078X): сбор, анализ и интерпретации данных, подготовка рукописи, ответственный за все аспекты работы

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Larina V.N. (ORCID ID: https://orcid.org/ 0000-0001-7825-5597): concept and design development, data collection, analysis and interpretation, critical intellectual content validation, final approval of the manuscript for publication, responsible for all aspects of the work

Samkova I.A. (ORCID: 0000-0001-5057-6890): collection, analysis and interpretation of data, preparation of a manuscript, responsible for all aspects of the work

Kudina E.V. (ORCID 0000-0002-9547-078X): collection, analysis and interpretation of data, preparation of a manuscript, responsible for all aspects of the work

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В.И. Шевцова*, А.А. Зуйкова

Кафедра поликлинической терапии ФГБОУ ВО Воронежского государственного медицинского университета им. Н.Н. Бурденко Минздрава России, Воронеж, Россия

АЛЬТЕРНАТИВНЫЕ ВАРИАНТЫ НУТРИТИВНОГО СТАТУСА ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ: ФЕНОТИП ХСН С САРКОПЕНИЧЕСКИМ ОЖИРЕНИЕМ

V.I. Shevtsova, A.A. Zujkova

Burdenko Voronezh State Medical University, Department of Polyclinic Therapy, Voronezh, Russia

Alternative Options for the Nutritional Status of Patients with Chronic Heart Failure: CHF Phenotype with Sarcopenic Obesity

Резюме

Более 7 % в общей популяции страдает хронической сердечной недостаточностью. Известно, что 65 % лиц, страдающих хронической сердечной недостаточностью, старше 60 лет, а средний возраст пациентов составляет 70 лет. Для пациентов с ХСН характерно изменение нутритивного статуса. Ожирение является одним из ведущих факторов риска заболеваний, ведущих к хронической сердечной недостаточности. Зачастую в исходе заболевания пациенты чаще приобретают недостаточность питания. С учетом саркопении, характерной для пациентов пожилого возраста, возможно формирование фенотипа ХСН с саркопеническим ожирением.

Для саркопенического ожирения характерна нормальная или повышенная жировая масса и миопения. Саркопеническое ожирение провоцирует гиподиагностику нарушений нутритивного статуса, а также, с учетом гормональной активности жировой массы, вносит вклад в прогрессирование хронической сердечной недостаточности. Все перечисленное ведет к потере функциональной активности пациентов, снижению качества их жизни и требует разработки индивидуального плана ведения.

Ключевые слова: *хроническая сердечная недостаточность, саркопения, саркопеническое ожирение*

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*Контакты: Вероника Ивановна Шевцова, e-mail: Shevvi17@yandex.ru
*Contacts: Veronica I. Shevtsova, e-mail: Shevvi17@yandex.ru
ORCID ID: https://orcid.org/0000-0002-1707-436X

Abstract

More than 7% in the general population suffers from chronic heart failure. It is known that 65% of people with chronic heart failure are over 60 years old, and the average age of patients is 70 years. Patients with CHF are characterized by a change in nutritive status. Often, patients suffer from malinutrition in the outcome of the disease. However, given the prevalence of obesity and this role in the pathogenesis of diseases leading to chronic heart failure, there are patients with increased body weight. Given the sarcopenia characteristic of elderly patients, it is possible to form a phenotype of CHF with sarcopenic obesity. Sarcopenic obesity is characterized by normal or increased fat mass and miopenia. Sarcopenic obesity provokes hypodiagnosis of disorders of nutritive status, and also, taking into account the hormonal activity of the fat mass, contributes to the progression of chronic heart failure. All this leads to a loss of functional activity of patients, a decrease in their quality of life and requires the development of an individual management plan for such a patient.

Key words: *chronic heart failure, sarcopenia, sarcopenic obesity*

Conflict of interests

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BMI — body mass index, HFpEF — heart failure with preserved ejection fraction, CVD — cardiovascular diseases, CHF — chronic heart failure

Healthy longevity is a current healthcare trend. This is due to the demographic situation — the growing proportion of the elderly population and improvements in the quality of medical care. The Action Strategy for the Benefit of Elderly People in the Russian Federation until 2025 determines the importance of the functional activity of elderly people. It is known that health indicators deteriorate with age, and comorbidity increases [1]. Due to the high prevalence of cardiovascular diseases, the number of patients with chronic heart failure (CHF) is growing year after year. CHF is an outcome of cardiovascular diseases and affects the quality of life and life expectancy.

Today, knowledge about non-drug and drug methods of treating CHF is being actively systematized. The two active areas of therapy are symptomatic treatment and treatment aimed at the prognosis of the disease. It is important to understand that most patients with CHF are old, which means that geriatric syndromes should be taken into account when planning management approaches [2, 3].

Nutritional status is of particular concern in the management of elderly patients. It has been proven that the pathogenetic changes characteristic of CHF cause hyperactivation of the neuroendocrine and humoral systems, the development of hypermetabolism, and impaired nutrient absorption. The result is protein-energy malnutrition [4].

Underweight is known to be a predictor of life expectancy. Cachexia is an extreme degree of malnutrition, accompanied by a decrease in fat and muscle mass, and is an independent predictor of decreased survival in patients with chronic heart failure [5, 6].

However, among patients with CHF, there are both underweight and overweight patients. Whereas protein-energy malnutrition is often an outcome of CHF, some researchers distinguish the obesity-dependent phenotype of heart failure, taking into account the prevalence of obesity worldwide and its definition as a risk factor for cardiovascular diseases (CVD) [6]. High body mass index (BMI) is a proven risk factor for new-onset heart failure (HF), regardless of systolic dysfunction. The presence of obesity in a patient complicates the diagnosis of HF, which is associated with similar clinical symptoms — dyspnea, low exercise tolerance, as well as the difficulties in instrumental diagnosis. This phenotype is more typical for individuals with CHF with preserved ejection fraction (HFpEF) [6, 7].

The specific features of the obesity phenotype in HFpEF are the correlation of obesity with arterial stiffness in women (but not in men), and the reversibility of left ventricular hypertrophy in response to weight loss, depending on the duration of morbid obesity [6]. Obesity is associated with a fourfold increase in the prevalence of obstructive sleep apnea syndrome, which, through various mechanisms (sympathetic activation and increased left ventricle afterload, hypoxic pulmonary vasoconstriction and decreased left ventricle preload, oxidative stress and stimulation of inflammation, hypoxia), is involved in the heart failure pathogenesis [6].

Subcutaneous and visceral adipose tissue produces neurohumoral factors that cause insulin resistance, arterial hypertension, dyslipidemia, oxidative stress, and systemic inflammation. Numerous metabolic disorders affect the structure of the heart and its function [8].

As a result of a metabolic shift, lipotoxic damage to the myocardium and other organs and tissues (liver, pancreatic β-cells, heart) may develop [9]. The correlation between obesity and structural and functional changes in the heart, including left ventricular hypertrophy,

contractile dysfunction, cardiomyocyte (CMC) apoptosis, has been demonstrated.

Several meta-analyzes show the presence of a J-shaped BMI-mortality association [10–12]. The minimum mortality rate is typical for persons with a BMI in the range of 20.0 up to 25 kg/m^2, and every extra five units of the indicator are associated with an increase in the relative risk (RR) overall and cardiovascular death by an average of one-third [13]. However, the literature describes the so-called *obesity paradox*: people with chronic diseases who have a higher BMI are characterized by better survival and a lower incidence of fatal events. For the first time, such a pattern was identified in persons with CHF. The I-PRESERVED study assessed the relationship between BMI and preserved ejection fraction, adverse outcomes in 4019 heart failure patients with preserved ejection fraction. The risk of all-cause mortality and hospitalization was significantly higher in patients with BMI ≥ 35 kg/m^2 and patients with BMI < 23.5 kg/m^2 compared with patients whose body mass index ranged from 23.5–26.4 kg/m^2, 26.5–30.9 kg/m^2, and 31–34.9 kg/m^2. Similar results were obtained in the CHARM study (7599 patients with heart failure) in a cohort of patients with heart failure with preserved ejection fraction [7, 13].

The functional activity of an elderly person, which means his/her physical independence, is determined by the state of his/her muscular system. Sarcopenia is one of the geriatric symptoms affecting the quality of life of patients. Sarcopenia is defined as a progressive skeletal muscle disease that increases the risk of adverse physical outcomes such as falls, fractures, impaired physical function, disability and mortality [14]. Sarcopenia is characterized by myopenia, dynapenia, and muscle dysfunction. Sarcopenia is often considered a condition associated with malnutrition or the risk of malnutrition [15].

Sarcopenia is associated with other abnormalities in body composition — low bone mass (osteosarcopenia), high fatty mass (sarcopenic obesity), or their combination (osteoarthritides obesity). The pathogenesis and clinical role of sarcopenia have been well studied, whereas sarcopenic obesity was relatively recently studied [15, 16].

The pathogenetic basis of sarcopenic obesity is systemic inflammation, oxidative stress, mitochondrial dysfunction, endocrine disorders and physical inactivity. Endocrine disorders include aberrant insulin-like growth factor/growth hormone levels, abnormal thyroid hormone levels, insulin resistance. These hormonal abnormalities alter skeletal muscle metabolism, leading to anabolic deficits with a consequent decline in functional capacity. Chronic inflammation in obesity can lead to myopenia and is partially regulated by adiponectin, leptin, and insulin [7]. Also, chronic inflammation is a factor contributing to the development of iron deficiency [17]. Hypoxia accompanying anemia may be one of the reasons for decreased exercise tolerance in patients with HFpEF. Reduced exercise tolerance is both a leading HFpEF symptom and a contributing factor to fat gain and muscle loss. Therefore, the likelihood of sarcopenic obesity increases in patients with HFpEF [17].

Aging is the most significant risk factor for cardiovascular disease, with CHF with preserved ejection fraction dominating among the elderly [18]. Therefore, elderly patients with CHF-pEF are at risk of sarcopenic obesity.

Due to the lack of uniform criteria for sarcopenic obesity, its prevalence in the older age group, according to different studies, varies from 4 to 84% in men and from 4 to 94% in women. Sarcopenic obesity is associated with deterioration in physical status to a greater extent than obesity alone or sarcopenia alone. Alongside limitations in everyday life, patients with sarcopenic obesity are characterized by a high level of disability and mortality [14, 19–23].

According to the literature, sarcopenic obesity is associated with a high risk of cardiovascular diseases, congestive heart failure, metabolic syndrome, arterial hypertension and dyslipidemia, and death from all causes [21, 23, 25, 26].

Sarcopenic obesity with low muscle mass may cause higher mortality in people with normal BMI, and, conversely, a higher lean mass is associated with lower mortality in patients with chronic CVD [27–30].

The high incidence of sarcopenic obesity in CHF was confirmed by the prospective multicenter study SICA-HF (Studies Investigating Co-morbidities Aggravating Heart Failure), which included more than 1,500 patients with chronic heart failure. The main objective of the study was to investigate diseases concomitant to heart failure, especially in relation to obesity, cachexia and type 2 diabetes mellitus. The progressive decline in muscle mass, strength and function accompanying aging, were associated with senile asthenia syndrome and HF progression [6, 31]. Importantly, this study demonstrates the lowest life quality score in sarcopenic obesity patients and a positive correlation between appendicular muscle mass, muscle strength, and life quality.

Reciprocal effects of sarcopenia and obesity are shown in Figure 1 [22].

The concept of obesity phenotypes proposed by Carbone S et al. (2015), which takes into account body composition (manifestation of adipose and lean tissue), physical activity and cardiorespiratory load level, suggests the impact of the combination of these factors on the state of the cardiovascular system, the development and progression of CVD, the risk of cardiovascular complications and death [32].

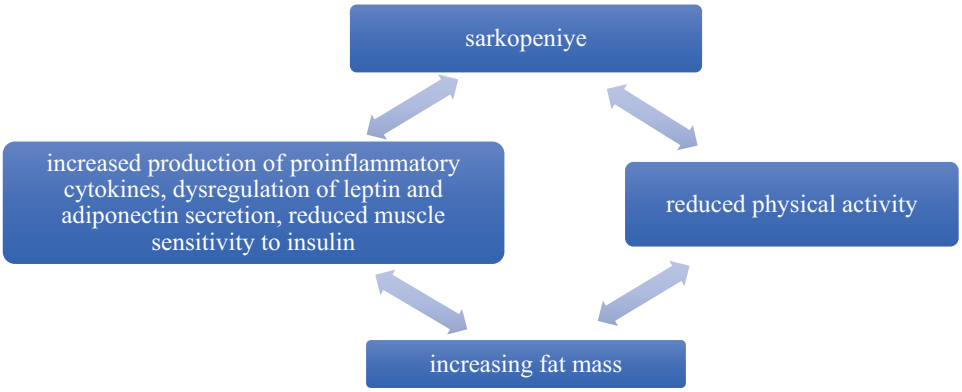

Figure 1. *The mutual impact of sarcopenia and obesity*

Therefore, there are different metabolic pathways for sarcopenia depending on changes in adipose mass with aging and chronic disease. This leads to two different paradigms of sarcopenia, i.e., cachexia and sarcopenic obesity. [32].

Sarcopenic obesity, which can be considered a complication of sarcopenia, limits mobility, resulting in dependence on physical assistance, disability and other adverse outcomes [20]. These facts must be taken into account in diagnosis and when planning the tactics of managing patients with CHF. In particular, it is possible to carry out dynamometry in an outpatient setting, as well as a short battery of tests of physical functioning [22]. These studies do not require material and time costs. However, they allow the assessment of the state of the muscular system. Comparison of anthropometry and assessment of muscular strength, mass and function will allow the doctor to develop an individual approach to the management of the patient.

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Зуйкова А.А. (ORCID http://orcid.org/0000-0003-2392-3134): проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации

Author Contribution:

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Shevtsova V.I. (ORCID http://orcid.org/0000-0002-1707-436X): author's role in substantiating and writing the manuscript, author agrees to be responsible for all aspects of the work

Zujkova A.A. (ORCID http://orcid.org/0000-0003-2392-3134): author's role in verifying critical intellectual content, in final approval for publication of manuscript, author agrees to be responsible for all aspects of work

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А.В. Мелехов[1,2], М.А. Сайфуллин[1,2], В.С. Петровичев[1], А.И. Агаева[2], К.Ю. Голубых*[2], И.Г. Никитин[1,2]

[1] — ФГАУ «Национальный медицинский исследовательский центр «Лечебно-реабилитационный центр» Министерства здравоохранения Российской Федерации Москва, Россия
[2] — ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Министерства здравоохранения Российской Федерации Москва, Россия

СОПОСТАВЛЕНИЕ ДАННЫХ КОМПЬЮТЕРНОЙ ТОМОГРАФИИ С ИСХОДАМИ, КЛИНИЧЕСКИМИ И ЛАБОРАТОРНЫМИ ХАРАКТЕРИСТИКАМИ ПАЦИЕНТОВ С COVID-19

A.V. Melekhov[1,2], M.A. Sayfullin[1,2], V.S. Petrovichev[1], A.I. Agaeva[2], K.Y. Golubykh*[2], I.G. Nikitin[1,2]

[1] — National Medical Research Center of Treatment and Rehabilitation, Moscow, Russia
[2] — Pirogov Russian National Research Medical University, Moscow, Russia

Association of Computer Tomography Features Of COVID-19 with Outcomes, Clinical and Laboratory Parameters

Резюме

Цель: сопоставить данные компьютерной томографии (КТ) с исходами, клиническими и лабораторными данными пациентов с коронавирусной инфекцией. **Материалы и методы:** ретроспективный анализ результатов 962 КТ исследований органов грудной клетки, клинических и лабораторных данных всех 354 пациентов, проходивших лечение от COVID-19 во ФГАУ «Лечебно-реабилитационный центр» Минздрава России с апреля по июнь 2020г. **Результаты:** Чувствительность и специфичность КТ при верификации диагноза с помощью полимеразной цепной реакции (ПЦР) составили: 98,0 % и 5,7 % соответственно; для ПЦР при верификации с помощью КТ: 54,6 % и 70,7 % соответственно. У пациентов с положительными и отрицательными результатами ПЦР тяжесть поражения легких и вероятность COVID-19 по системе CO-RADS статистически значимо не отличались (p=0.05). Кумулятивная выживаемость пациентов была лучше при меньшем объеме поражения легких (статистическая значимость достигалась на пике заболевания (p=0.05), но не в момент госпитализации (p=0.05)). У умерших (n=15) и выживших (n=339) пациентов градация поражения легких по данным КТ изменялась соответственно с 2 (1,5-3) до 4 (4-4), p=0,001 и с 2 (1-2) до 2 (1-2), p <0,001. Меньший объем поражения легочной ткани и лучшая кумулятивная выживаемость наблюдалась у женщин, пациентов младше медианы возраста (59 лет), с суммой баллов NEWS <3, без фибрилляции предсердий. Сахарный диабет и ожирение, не влияя на выживаемость, были ассоциированы с большей тяжестью поражения легких. Другие сопутствующие заболевания не были связаны с тяжестью поражения легочной ткани. Наличие хронической обструктивной болезни легких, ишемической болезни сердца и хронической сердечной недостаточности статистически значимо ухудшало прогноз. **Заключение:** КТ существенно улучшает точность диагностики COVID-19 в условиях недостаточной чувствительности молекулярно-биологических тестов и оценку прогноза пациентов.

Ключевые слова: *COVID-19, коронавирусная пневмония, компьютерная томография, полимеразная цепная реакция, чувствительность, специфичность, NEWS, прогноз, коморбидность*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

*Контакты: Константин Юрьевич Голубых, e-mail: kotor030@gmail.com
*Contacts: Konstantin Y. Golubykh, e-mail: kotor030@gmail.com
ORCID ID: https://orcid.org/0000-0002-4093-4639

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Abstract

Aim: to assess the results of chest computer tomography (CT) of patients with novel coronavirus infection in correspondence with their outcomes, clinical and laboratory data. **Methods:** retrospective analysis of 962 chest CT scans, outcomes, clinical and laboratory data of all 354 COVID-19 patients hospitalized from April to June 2020. **Results:** Sensitivity and specificity of CT with polimerase chain reaction (PCR) as a reference were: 98.0 % and 5.7 % respectively; for PCR with CT as a reference: 54.6 % and 70.7 % respectively. Patients with positive and negative PCR tests had no significant differences in mean CT score and CO-RADS score. Cumulative survival was better in patients with lower CT score (significant only for maximal, not baseline scores). CT score changed during hospitalization in survived patients clinically insignificant (from 2 (1-2) to 2 (1-2), p=0.001), and increased in dead (from 2 (1,5-3) to 4 (4-4), p <0.001). Lower CT score and better survival was in females, patient younger than 59 years, with NEWS score <3, without atrial fibrillation. Diabetes mellitus and obesity was associated with higher CT score, but not with survival. Chronic obstructive pulmonary disease, coronary heart disease and chronic heart failure was associated with lower survival, but not CT score. **Conclusion:** chest CT significantly increases diagnostic accuracy and assessment of the prognosis in COVID-19 patients.

Key words: *COVID-19, coronavirus pneumonia, computer tomography, polymerase chain reaction, sensitivity, specificity, NEWS, prognosis, comorbidities*

Conflict of interests

The authors declare no conflict of interests

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AF — atrial fibrillation, BMI — body mass index, CHF — chronic heart failure, COPD — chronic obstructive pulmonary disease, CO-RADS — COVID-19 Reporting and Data System, COVID-19 — novel coronavirus disease, CT — computed tomography, DM — diabetes mellitus, IHD — ischemic heart disease, NEWS — National Early Warning Score, PCR — polymerase chain reaction, P_{MW} — Mann-Whitney method, TO — thoracic organs, TRC — Treatment and Rehabilitation Center of the Ministry of Health of the Russian Federation

Introduction

As COVID-19 cases surge, given the insufficient sensitivity of routine X-ray examination, molecular biological tests, and in the absence of highly sensitive serological methods, the multispiral computed tomography (CT) of thoracic organs (TO) has become the most informative diagnostic method.

Due to the specific features of TO lesions in coronavirus disease, a CT scan is required if COVID-19 is suspected, both for the initial assessment of the lesion and further monitoring of changes [1]. As there is no correlation of auscultatory signs of pneumonia with the volume of the lung lesion and due to the frequent false-negative primary polymerase chain reaction (PCR) results, CT became a first-line method for diagnosing COVID-19 and assessing disease severity.

Definite patterns of TO lesions (bilateral changes, ground glass symptom, peripheral localization of lesions, localization in the lower lobes of lungs, involvement of more than three pulmonary fields) detected on CT made it possible to differentiate the manifestations of COVID-19 from other pneumonias and TO diseases [2].

For determining the probability of coronavirus disease based on typical patterns of changes detected by TO CT, the COVID-19 Reporting and Data System (CO-RADS) is used. It estimates the probability of coronavirus disease according to a 5-point scale, where 1 is a very low probability, and 5 is a very high probability of coronavirus pneumonia [3].

Russian studies of various aspects of CT in COVID-19 were mainly focused on X-ray patterns of coronavirus lung damage and their description [4–6]. The association of CT results with outcomes [7], clinical and laboratory [8], as well as autopsy [9] data has been studied in only a handful of studies.

It should be noted that there is a significant variability in the design of the studies performed, the heterogeneity of the enrolled patients in terms of the severity of clinical and radiological symptoms, the time of disease onset and the frequency of verification of coronavirus etiology (Tables 1, 2).

Table 1. *Distribution of CT score in patients with COVID-19 included in various Russian studies*

Study		CT0, 0 % n (%)	CT1, <25 % n (%)	CT2, 25-50 % n (%)	CT3, 50-75 % n (%)	CT4, 75-100 % n (%)	Positive PCR n (%)
Own data	During the admission	13 (4,0)	111 (32,1)	150 (43,4)	60 (17,3)	11 (3,2)	246 (69,5)
	At the peak of the disease	7 (2,0)	85 (24,4)	119 (34,2)	100 (28,7)	37 (10,6)	
Зельтер П.М. и соавт. [4]			142 (75,9)	37 (19,8)	7 (3,7)	1 (0,6)	
Устюжанин Д.В. и соавт. [5]			164 (25,7)	261 (41)	164 (25,7)	48 (7,6)	
Петриков С.С. и соавт. [6]		7 (11,7)	36 (60)	12 (20)	5 (8,3)		60 (100)
Морозов С.П. и соавт. [7]		5075 (39)	4004 (30,8)	2852 (21,9)	986 (7,6)	86 (0,7)	
Бойцов С.А. и соавт. [8]		29 (7,2)	66 (16,5)	127 (31,7)	139 (34,7)	40 (10,0)	258 (64,2)
Паршин В.В. и соавт. [9]			23 (12,17)	61 (32,27)	78 (41,26)	27 (14,3)	31 (49,2)
Кармазановский Г.Г. и соавт. [10]		34 (3,5)	180 (18,9)	341 (35,9)	261 (27,4)	136 (14,3)	
Корб Т.А. и соавт. [11]			48 (74)	13 (20)	5 (6)		65 (100)

Table 2. *The sensitivity and specificity of PCR, chest CT and X-ray for the diagnosis of COVID-19*

Study	n	Day of the disease at the moment of investigation	Sensitivity, %		Specificity, %		Diagnostic accuracy, %	
			CT verified by PCR	PCR verified by CT	CT verified by PCR	CT verified by PCR	CT verified by PCR	CT verified by PCR
Own data	354	8 (5-11)	98,0	54,6	5,7	70,7	70,7	98 %
Корб Т.А. и соавт. [11]	140		76,2		92			
Ai T et al [12]	1014		97	65,3	25	83,3	68	96,5
Long C et al [13]	36	3	97,2	83,3				
Bai HX et al [14]	424	4,9	67-97		7-100		53-97	
Fang Y et al [15]	51	3	98	71				
Mirahmadizadeh A et al [16]	54		78,6		42,3			
He JL et al [17]	82		77	79	96	100		
Duarte ML et al [18]	1204		95,3	81,4	43,8	100	63,3	92,3
Herpe G et al [19]	4824		90	87	91	99	90	97
Caruso D et al [20]	158		97		56		72	
Wong HYF et al [21] Рентгенография	64		69	91				

The purpose of our study was to compare TO CT results in patients with coronavirus disease with their clinical and laboratory test results.

Materials and Methods

We performed a retrospective analysis of medical records and computed tomograms of a continuous sample of all 354 patients hospitalized in the Treatment and Rehabilitation Center of the Russian Ministry of Health (TRC) from April to June 2020 with suspected or confirmed COVID-19.

The outcome was known for all patients, as well as the sum of NEWS scale points on admission, the results of SARS-CoV-2 RNA by PCR, and comorbidities; body mass index (BMI) was calculated retrospectively.

To assess the severity of patients at admission, the National Early Warning Score (NEWS) developed in 2012 in the UK was used; it was well validated not only in patients with acute infectious and non-infectious diseases but also in patients with COVID-19 [22].

To assess changes of pulmonary parenchyma in patients, we used temporary guidelines for the prevention, diagnosis and treatment of COVID-19 of the Ministry of Health of Russia, version 5 as of 04/08/2020, version 6 as of 04/28/2020, and version 7 as of 06/03/2020. The volume of lung tissue lesions was described by five grades: CT0 — no changes, CT1 — lesion < 25% of parenchyma, CT2 — 25–50%, CT3 — 50–75%, CT4 — > 75%. For the analysis, we used the data on lesion volume obtained at the time of hospitalization, at the latest CT scan before discharge, and the maximum volume of lesion recorded during the observation period ("disease peak"). To assess the specificity of the detected changes, the CO-RADS classification was used [3].

Sensitivity, specificity and diagnostic accuracy of methods were calculated using standard formulas (sensitivity = (number of true positive + false positive tests) / number of true positive tests; specificity = (number of true negative + false negative tests) / number of true negative tests; diagnostic accuracy = (number of true positive + true negative tests) / total number of tests).

Since the diagnosis of COVID-19 was established based on a combination of clinical, CT and molecular biology criteria, CT and PCR were mutually verified using each method in turn as the "gold standard".

Statistical processing of the data obtained was carried out using SPSS Statistics and Jamovi software. Data are presented as medians and interquartile ranges. Nonparametric statistical methods were used: for the analysis of qualitative features, the $\chi 2$ (p_{χ^2}) criterion was used; for comparing two independent values, the Mann-Whitney method (p_{MW}) was used; for dependent values, Wilcoxon's method (p_{Wilc}) was used. Cumulative survival rate was assessed by the Kaplan-Meier method with the assessment of the log-rank test and Gehan's test ($p_{log\text{-}rank}$, p_{Gehan}).

Results

Fifty-six percent of the 354 enrolled patients were female (n = 200). The patients were aged 59 (49–70) years, BMI — 28.7 (24.9–32.2) kg/m^2, the duration of COVID-19 at the time of admission was 8 (6–11) days, the sum of points on the NEWS scale at the time of admission was 2 (1–4) points, the duration of hospitalization was 16 (14–20) days. During inpatient treatment, 15 patients died (4.2%). The incidence of comorbidities was as follows: arterial hypertension 42.9% (n = 152), cancer — 13.0% (n = 46), diabetes mellitus (DM) — 12.4% (n = 44), ischemic heart disease (IHD) — 7.9% (n = 28), atrial fibrillation (AF) — 5.4% (n = 19), dementia — 4.5% (n = 16), history of stroke — 3.7% (n = 13), chronic obstructive pulmonary disease (COPD) — 2.0% (n = 7), chronic heart failure (CHF) — 2.0% (n = 7).

A total of 962 TO CT examinations conducted for 354 patients were analyzed; 867 (90.1%) of them were performed at the Treatment and Rehabilitation Center (TRC), and 95 (9.9%) at other hospitals prior to hospitalization at the TRC. Median and interquartile range of CT scan frequency per patient was 3 (2–3). Twenty-five (7%) patients underwent only one examination.

The first CT scan was performed for patients on day 8 (5–11) of disease, from 1 to 53 days.

On admission, 13 (3.6%) patients demonstrated no signs of pneumonia on CT; the appearance of inflammatory foci in lungs was registered during follow-up in two of them (0.5%).

Five (1.4%) patients had no CT signs of COVID-19; the diagnosis was made based on the detection of SARS-CoV-2 RNA by PCR; they were hospitalized for social and epidemiological reasons. One hundred (28.2%) patients had negative PCR results, and the diagnosis was made based on clinical and epidemiological data and CT signs. Another 2 (0.5%) patients were hospitalized with the consequences of past coronavirus disease. In 6 (1.7%) individuals, the diagnosis of COVID-19 was excluded (Fig. 1).

Therefore, sensitivity, specificity and diagnostic accuracy of CT in verifying the diagnosis using PCR were as follows: 98.0, 5.7 and 70.7%, respectively; for PCR with CT verification: 54.6, 70.7 and 98% respectively.

The frequency of different estimates of the COVID-19 probability according to the CO-RADS classification based on the data of the first CT scan in patients with at least one positive PCR result for SARS-CoV-2 RNA and in patients who had no positive test from the series demonstrated no statistically significant differences (5 (4–5) and 5 (4–5) respectively, $p_{MW} = 0.4$).

Medians and the distribution of lesion severity grades at the first CT scan and at the disease peak in patients with positive and negative PCR results demonstrated no statistically significant differences.

There were interesting changes of the distribution of the severity of pulmonary lesion assessed by CT in the observed patients as the disease progresses. Fig. 2 shows a tendency towards an increase in lesion volume from day 1 to day 10 of the disease. Starting from the third week of the disease, lesion volume slightly decreases. The number of studies conducted during the more distant period from disease onset was very small; this fact caused a wide range of volume and characteristics of lung tissue damage and did not allow to unambiguously evaluate the changes of the process. The duration of persistence of radiological changes and its association with the quality and longevity of patients who contracted COVID-19 is still to be determined during long-term observational studies. However, the correlation of changes on CT with disease duration was similar to other studies [1, 24, 25].

There were 13 (9–17) days between the first and the last examination. During this time, the grade of lesion severity statistically changed but with no clinically significant changes (2 (1–2) and 2 (1–2), $p_{Wilc} = 0.019$).

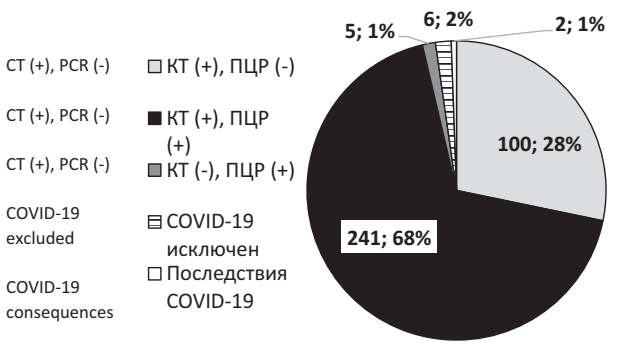

Figure 1. *The presence and absence of CT features of coronavirus pneumonia in patients with positive and negative PCR tests*

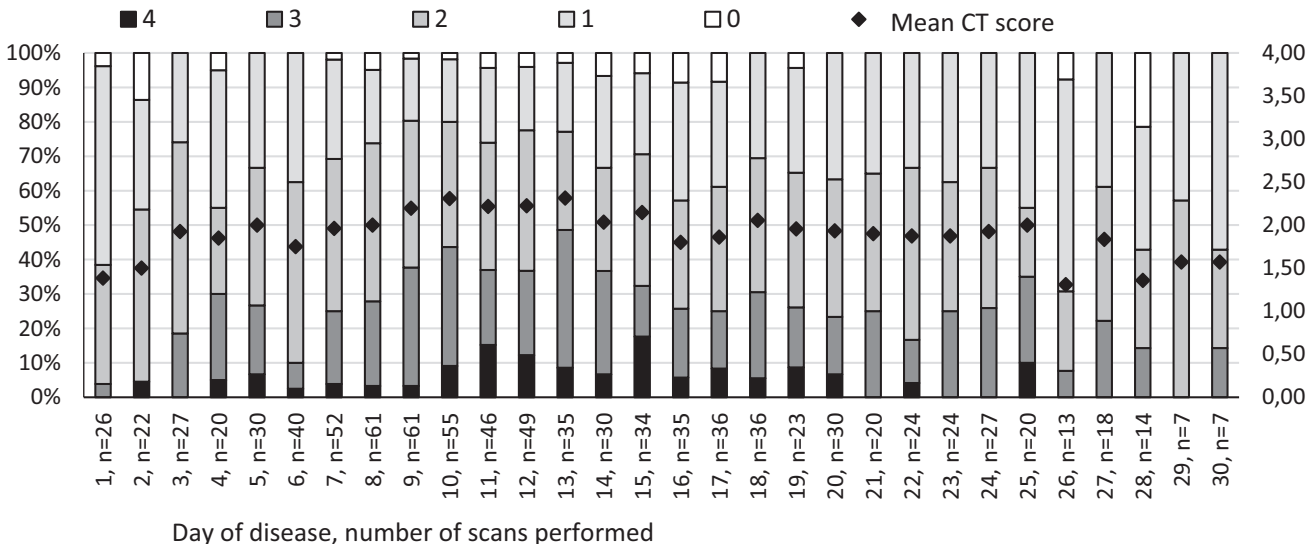

Figure 2. *The proportion of patients with different CT scores by the day of disease (CT 0-4, the axis of values is on the left). The markers indicate the mean CT score on a certain day of disease (the axis of values is on the right)*

Cumulative survival rate was better in patients with less lesion on CT and vice versa (Fig. 3). However, this relationship was statistically significant only for the maximum values of lesion volume recorded during hospitalization, but not for the results of the first CT studies ($p_{log\text{-}rank}$ and p_{Gehan} = 0.2); this fact somewhat reduces the value of CT for assessing the in-hospital prognosis.

In surviving (n = 339) and deceased (n = 15) patients, the differences in lesion grades at the first CT scan (2 (1–2) and 2 (1.5–3.0), respectively, p_{MW} = 0.25) and its distributions were not statistically significant (p_{X2}= 0.2). At the latest CT scan, lesion grades did not change significantly in the surviving patients, and were higher in deceased patients (2 (1–2) and 4 (4–4), respectively, p_{MW} < 0.001), as was the proportion of more extensive changes (Fig. 4). The maximum severity of lesion registered on CT was significantly higher in deceased patients (4 (3–4) and 2 (1–3), p_{MW} < 0.001).

The cumulative survival rate of patients with NEWS score ≥3 was statistically significantly worse than that of patients with lower scores (Fig. 5A).

In patients above the median age in comparison with younger patients at the time of admission, the gradation of the severity of pulmonary parenchyma lesions revealed no significant differences (2 (1–2) and 2 (1–2), p_{MW} = 0.056). However, at the peak of the disease, it was statistically significantly higher (2 (2–3) and 2 (1–3), p_{MW} = 0.003). The expected survival rate of younger patients was statistically significantly better than that of elderly patients (Fig. 5Б).

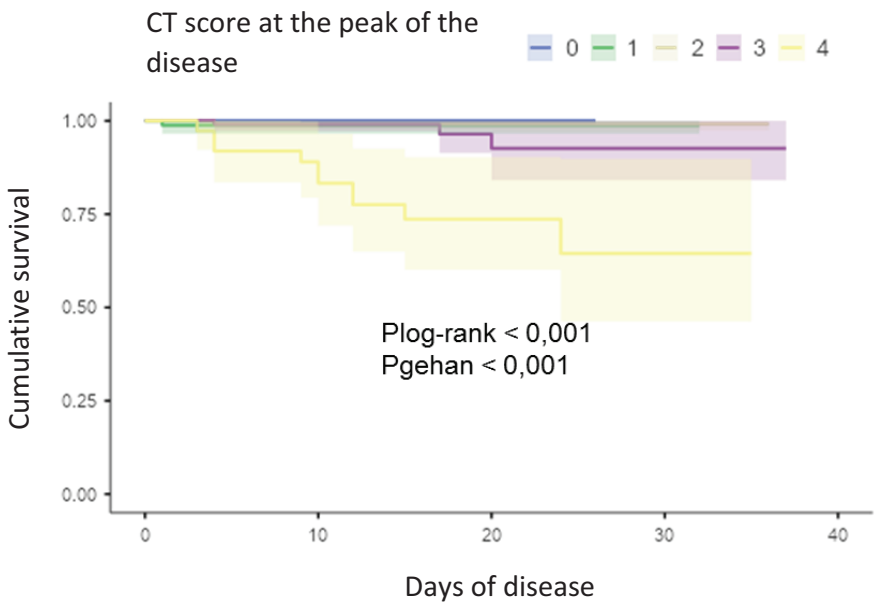

Figure 3. *Kaplan-Meier cumulative survival curves of patients with different CT scores at the peak of the disease. The colored areas represent the 95 % confidence interval*

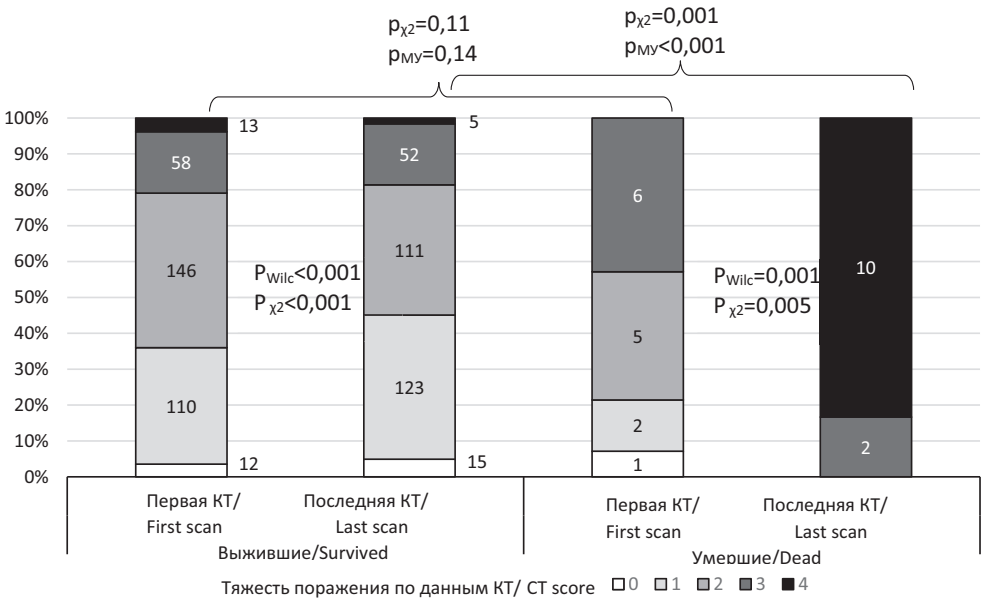

Figure 4. *CT scores in deceased and surviving patients at admission and in the end of follow up*

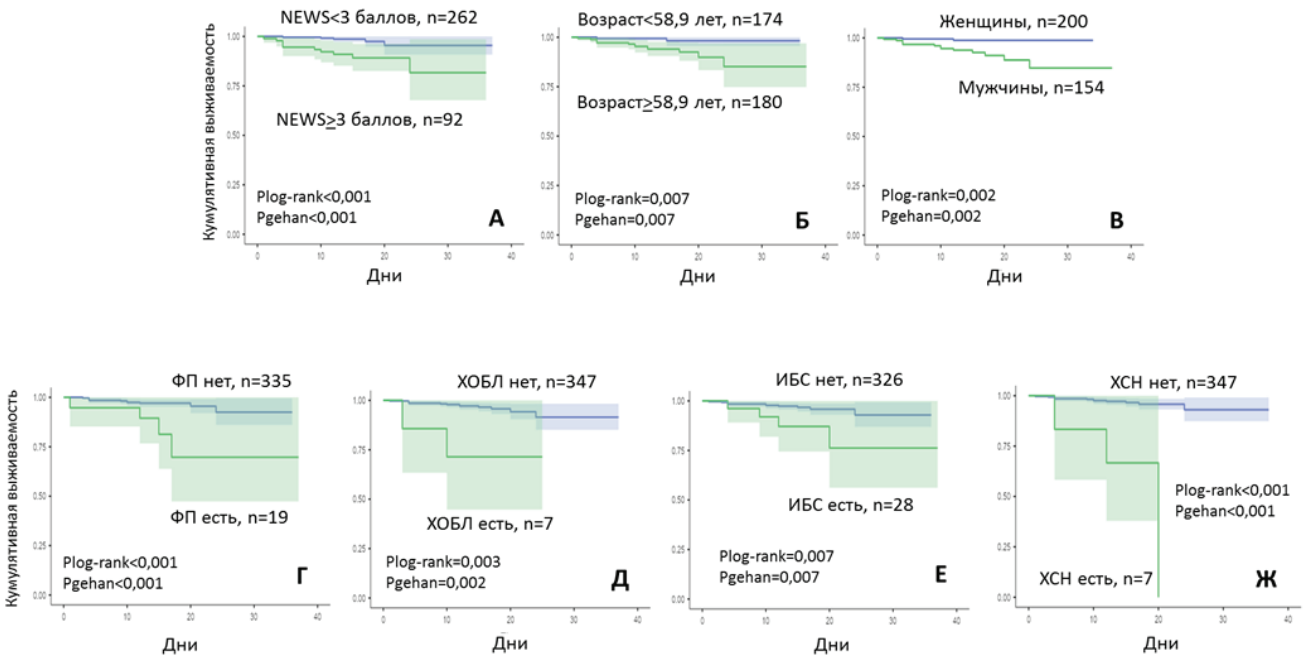

Figure 5. *Kaplan-Meier survival curves among observed patients after dividing them into subgroups based on: А — median of the total News score during the admission, Б — age median, В — sex, Г — presence or absence of Af, Д — Presence of Absence of COPD, Е — Presence or absence of CHD, Ж — presence or absence of CHF. Colored zones indicate 95 % confidence interval*

As shown in Fig. 6, more severe patients with NEWS score of 4–10 had a larger lung lesion volume more often than less severe patients with a score of 0-3, both at admission to the hospital (grade 2 (2–3) and 2 (1–2), respectively, $p_{MU} < 0.001$) and at the peak of disease (3 (2–3) and 2 (1–3), respectively, $p_{MW} < 0.001$). At the same time, 60% of clinically stable and asymptomatic patients at the time of hospitalization had lesion volume over 25%; some of them reached CT4 grade.

The cumulative survival rate of women was statistically significantly better than that of men (Fig. 5B); grades of lung tissue damage were as follows: 2 (1–2) and 2 (1–3), $R_{MW} = 0.3$ during the first examination and 2 (1–3) and 2 (2–3), $p_{MW} = 0.004$ at the peak of disease. The differences in the distribution of lung lesion severity in men and women are shown in Fig. 7.

Among patients with BMI more than the median value, the percentage of those with more severe lung

tissue lesions at the time of admission was statistically significantly higher than patients with a lower BMI (Fig. 8); lesion grades differed statistically, but not clinically significantly (2 (1–2) and 2 (1–2) respectively, p_{MW} = 0.021). Lesion severity at the peak of disease in these subgroups demonstrated no statistically significant differences (p_{X2} = 0.75), as well as the survival rate ($p_{log\text{-}rank}$ and p_{Gehan} = 0.9).

The presence of DM also did not statistically significantly affect survival ($p_{log\text{-}rank}$ and p_{Gehan} = 0.1). However, the percentage of patients with a large volume of lung tissue lesion was statistically significantly higher among patients with DM than without it (Fig. 9). Lesion severity grade at the time of admission was 2 (2–3) and 2 (1–2), p_{MW} = 0.003; at the peak of disease — 2 (2–3) and 2 (1–3), p_{MW} = 0.037, respectively.

The cumulative survival rate of patients with AF was worse than that of patients without AF (Fig. 5Г). In patients with AF, grades of lung lesion severity at the time of admission statistically insignificantly differed from that in patients with sinus rhythm (2 (1.5–3.0) and 2 (1–2), p_{MW} = 0.076), as well as its distribution. The grade of maximum lesion severity registered during hospitalization was higher in patients with AF (3 (2.0–3.5) and 2 (1–3), respectively, p_{MW} = 0.01). The distribution of lesion severity gradation at the peak of disease in patients with and without AF also demonstrated statistically significant differences (Fig. 10).

Both during hospitalization and at the peak of disease, there were no statistically significant differences in the grade of lesions and their distribution when the patients were divided according to the presence or absence of COPD (p_{MW} = 0.08 and 0.07, p_{X2} = 0.054

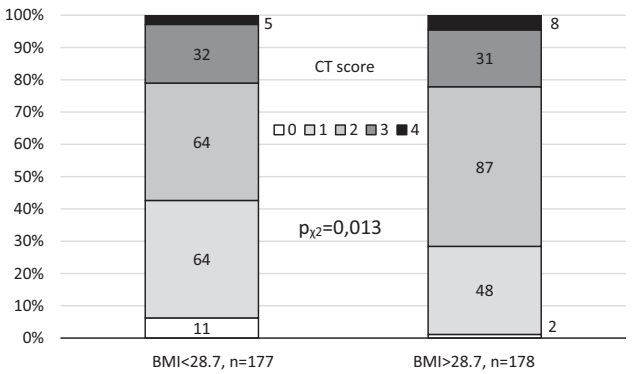

Figure 8. *CT scores at admission in patients with BMI greater or less than the median*

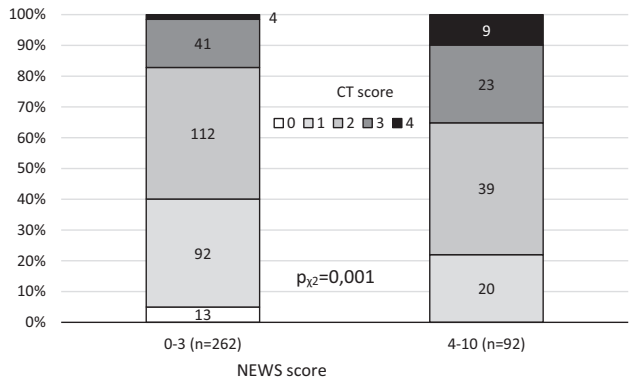

Figure 6. *CT scores at admission in patients with NEWS scores 0-3 and 4-10*

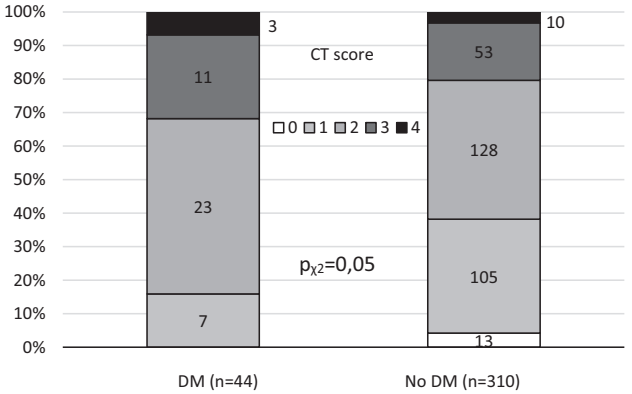

Figure 9. *CT scores at admission in patients with and without diabetes mellitus*

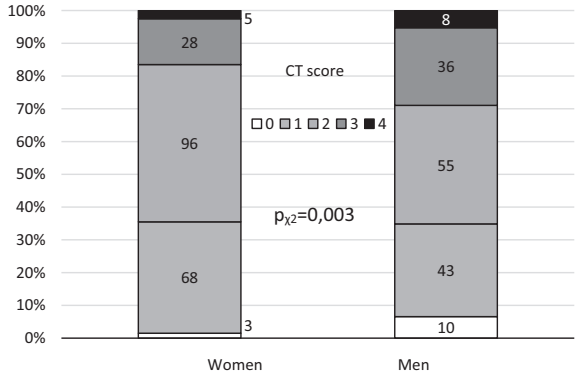

Figure 7. *Gender differences in the distribution of CT scores at admission*

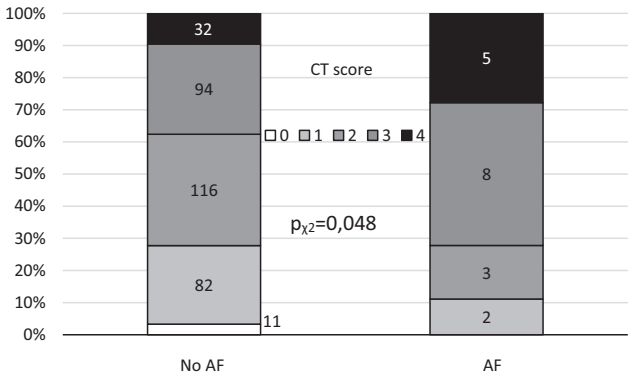

Figure 10. *CT scores at the peak of the disease in patients with and without atrial fibrillation*

and 0.1, respectively), arterial hypertension (p_{MW} = 0.4 and 0.3, p_{X2} = 0.2 and 0.5, respectively), ischemic heart disease (p_{MW} = 0.9 and 0.2, p_{X2} = 0.5 and 0.8, respectively), CHF (p_{MW} = 0.6 and 0.9, p_{X2} = 0.9 and 0.9, respectively), stroke (p_{MW} = 0.2 and 0.3, p_{X2} = 0.3 and 0.5, respectively), dementia (p_{MW} = 0.3 and 0.7, p_{X2} = 0.9 and 0.9, respectively), cancer (p_{MW} = 0.7 and 0.7, p_{X2} = 0.35 and 0.5, respectively), median duration of COVID-19 at the time of admission (p_{MW} = 0.2 and 0.2, p_{X2} = 0.1 and 0.5, respectively). At the same time, several listed comorbidities (COPD, IHD and CHF) significantly worsened the prognosis of patients (Fig. 5 Д, Е, Ж).

Discussion

The distribution of the patients we observed according to the severity of lung tissue damage detected by CT is presented in Table 1 in comparison with the data of other Russian studies of patients with COVID-19. Noticeable differences can be explained by the different principles of enrolling patients into studies (for example, depending on PCR results, the presence of symptoms, outpatient or inpatient care) or by different disease stages at the time of the study.

Since our study is a retrospective analysis of a continuous sample from actual clinical practice, we did not select patients based on the basis of stage, verification of disease etiology, severity of symptoms, or the volume of lung tissue lesions based on CT results.

Despite that the number of patients with PCR-verified coronavirus etiology in our sample was higher than in other observations [8, 9], the sensitivity of this test was low (Table 2). This, in particular, can be explained by the longer, compared to other works, disease duration at the time of the beginning of the diagnosis, as well as by possible errors during sampling for PCR. In our study, coronavirus disease was diagnosed based on clinical and radiological data with no verification by PCR in almost a third of the cases. This explains the observed low specificity of CT calculated using PCR as a "gold standard".

In a recent meta-analysis, the averaged values of sensitivity and specificity of CT in various studies were 91 and 31%, and PCR — 84 and 100%, respectively. This emphasizes the need for the combined use of these diagnostic methods [25].

The above reasons did not allow us to demonstrate in our sample a statistically significant relationship between PCR results and COVID-19 probability assessment according to the CO-RADS system. However, studies with different designs demonstrated the high diagnostic accuracy of this system [26, 27].

Our data confirm the results of studies that revealed the independent prognostic significance of CT symptoms typical for coronavirus pneumonia [28] and their severity [8, 29, 30].

In our study, the relationship between the volume of lung tissue lesion and in-hospital mortality was statistically significant only for CT studies performed at the peak of disease, but not for examinations at earlier stages. This complies well with the data of other studies that compared the probability of unfavorable outcomes with the volume of lung tissue lesion at different times from the onset of COVID-19 symptoms [31, 32].

At the same time, the integral clinical indicator of the patient's severity, the sum of points according to the NEWS scale, assessed at the time of admission was statistically significantly associated with the severity of lung lesion as measured by CT performed both at the time of admission and at the peak of disease. Similar correlations were demonstrated by other authors [33].

We observed an improvement in clinical and laboratory parameters in most patients, which allowed them to be discharged to continue treatment on an outpatient basis. The severity of changes detected by CT at the time of discharge may have remained significant but their quality notably changed: despite that the consolidation in most cases was "resorbed", areas of "ground glass" persisted, particularly in subpleural regions. Subpleural bands of high density were also evident, including among patients who underwent such changes in lung tissue as consolidation and "cobblestone appearance". These changes may represent the initial stages of pulmonary fibrosis; its development was noted in the cases of pneumonia caused by COVID-19 [23, 24]. Therefore, long-term changes on CT do not always reflect the severity of COVID-19 and have to be interpreted in the context of clinical findings.

Male gender is an independent unfavorable prognostic factor in COVID-19, and is also associated with a greater severity of lung tissue lesion according to CT results[34]; this fact is also confirmed by our data. However, one study showed that a less favorable prognosis in men is not accompanied by more severe lung lesion according to CT results [35].

Negative effects of age, overweight and comorbidity on prognosis are well known [8, 36]. In our sample, we were able to trace the relationship between in-hospital mortality and the presence of IHD, AF, CHF, and COPD. However, these diseases were not associated with the severity of lung tissue lesion according to CT results. Diabetes mellitus, overweight and obesity did not affect survival but were associated with a greater lung lesion volume. No such patterns were found in a smaller sample [37].

Conclusion

In actual clinical practice, the sensitivity and specificity of CT with diagnosis verification using PCR were as follows: 98.0 and 5.7%, respectively; for PCR with verification using CT: 54.6 and 70.7%, respectively. In patients with positive and negative PCR results, the severity of lung lesion and the probability of COVID-19 according to the CO-RADS system demonstrated no statistically significant differences.

Survival rate was better in patients with a smaller volume of lung lesion. However, the relationship between the grade of lung tissue lesion and prognosis was only revealed for CT studies performed at the peak of disease, not at the time of hospitalization.

Smaller volume of lung tissue lesion and better cumulative survival rate were observed in women, patients below the median age (58.9 years), with NEWS score < 3, with no atrial fibrillation. Diabetes mellitus, overweight and obesity did not affect survival but were associated with greater severity of lung lesion. No relationship between other comorbidities and the volume of lung tissue lesion was found.

Вклад авторов:

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Мелехов А.В. (ORCID: https://orcid.org/0000-0002-1637-2402): Сбор статистических данных, написание основного текста статьи и последующее ее редактирование, проведение статистических расчётов, обзор литературы

Сайфуллин М.А. (ORCID: https://orcid.org/0000-0003-1058-3193): Сбор статистических данных, написание основного текста статьи и последующее ее редактирование, обзор литературы

Петровичев В.С. (ORCID: https://orcid.org/0000-0002-8391-2771): Сбор статистических данных, написание основного текста статьи и последующее ее редактирование, обзор литературы

Агаева А.И. (ORCID: https://orcid.org/0000-0001-7559-135X): Сбор статистических данных, обзор литературы

Голубых К.Ю. (ORCID: https://orcid.org/0000-0002-4093-4639): Сбор статистических данных, написание основного текста статьи и последующее ее редактирование, обзор литературы

Никитин И.Г. (ORCID: https://orcid.org/0000-0003-1699-0881): Написание основного текста статьи и последующее ее редактирование, обзор литературы, руководитель исследовательского процесса

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Melekhov A.V. (ORCID: https://orcid.org/0000-0002-1637-2402): Collection of statistical data, writing the main text of the article and its subsequent editing, conducting statistical calculations, literature review

Sayfullin M.A. (ORCID: https://orcid.org/0000-0003-1058-3193): Collection of statistical data, writing the main text of the article and its subsequent editing, literature review

Petrovichev V.S. (ORCID: https://orcid.org/0000-0002-8391-2771): Collection of statistical data, writing the main text of the article and its subsequent editing, literature review

Agaeva A.I. (ORCID: https://orcid.org/0000-0001-7559-135X): Collection of statistical data, literature review

Golubykh K.Y. (ORCID: https://orcid.org/0000-0002-4093-4639): Collection of statistical data, writing the main text of the article and its subsequent editing, literature review

Nikitin I.G. (ORCID: https://orcid.org/0000-0003-1699-0881): Writing the main text of the article and its subsequent editing, literature review, head of the research process

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Е.В. Резник*[1,2,3,4], В.А. Лазарев[1,2], С.В. Борисовская[1,2], Г.Н. Голухов[3]

[1] — ФГАОУ ВО РНИМУ им. Н.И. Пирогова МЗ РФ, Москва, Россия
[2] — ГБУЗ ГКБ им. В.М. Буянова ДЗМ, Москва, Россия
[3] — ГКБ № 31 ДЗМ, Москва, Россия

ФИБРИЛЛЯЦИЯ ПРЕДСЕРДИЙ И СЕРДЕЧНАЯ НЕДОСТАТОЧНОСТЬ В ДЕБЮТЕ AL-АМИЛОИДОЗА

E.V. Reznik*[1,2,3], V.A. Lazarev[1,2], S.V. Borisovskay[1,2], G.N. Golukhov[3]

[1] — Russian National Research Medical University (RNRMU) n.a. N.I. Pirogov, Moscow, Russia
[2] — City Clinical Hospital n.a. V.M. Buyanov of Healthcare Department of Moscow, Moscow, Russia
[3] — City Clinical Hospital № 31 of Healthcare Department of Moscow, Moscow, Russia

Atrial Fibrillation and Heart Failure as the Onset of AL-Amyloidosis

Резюме

В практике кардиолога нередко встречаются пациенты с гипертрофией миокарда, фибрилляцией предсердий и сердечной недостаточностью. Выяснение причин этих состояний крайне важно для назначения этиологической терапии, улучшающей прогноз. В статье представлен клинический случай несвоевременно диагностированного амилоидоза у мужчины 53 лет. Несмотря на комплексную терапию, течение заболевания осложнилось развитием двусторонней пневмонии, сепсиса, синдрома диссеминированного внутрисосудистого свертывания, что привело к летальному исходу. На аутопсии подтвержден диагноз AL-системного амилоидоза (тип каппа) с массивным поражением сердца, почек, легких, печени, селезёнки, надпочечников, щитовидной железы, поджелудочной железы, желудочно-кишечного тракта, подкожной жировой клетчатки и артериальных сосудов костного мозга. Для прижизненной диагностики AL-амилоидоза и своевременного назначения патогенетической терапии необходимо проведение скрининга при выявлении гипертрофии левого желудочка, фибрилляции предсердий и сердечной недостаточности неясной этиологии.

Ключевые слова: *амилоидоз сердца, амилоидная кардиомиопатия, хроническая сердечная недостаточность с сохраненной фракцией выброса левого желудочка, фибрилляция предсердий, гипертрофия левого желудочка, хроническая болезнь почек, протеинурия, нефротический синдром, кардиоренальный синдром*

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Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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*Контакты: Елена Владимировна Резник, e-mail: elenaresnik@gmail.com
*Contacts: Elena V. Reznik, e-mail: elenaresnik@gmail.com
ORCID ID: https://orcid.org/0000-0001-7479-418X

Abstract

Left ventricular hypertrophy, atrial fibrillation and chronic heart failure are often in the practice of a cardiologist. The etiology of these conditions is very important because the correct early treatment. We are presenting a case of a late diagnosis of amyloidosis in a 53-year-old man. Despite the complex therapy, the course of the disease was complicated by the development of bilateral pneumonia, sepsis, disseminated intravascular coagulation and the patient died. Autopsy confirmed the diagnosis of systemic AL-amyloidosis (type Kappa) with massive damage to the heart, kidneys, lungs, liver, spleen, adrenal glands, thyroid gland, pancreas, gastrointestinal tract, subcutaneous fatty tissue and arterial vessels of the bone marrow. Thus, screening for amyloidosis is necessary in idiopathic LV thickening, atrial fibrillation, and heart failure for timely intravital diagnosis and therapy.

Key words: *cardiac amyloidosis, amyloid cardiomyopathy, chronic heart failure with preserved ejection fraction, atrial fibrillation, left ventricular hypertrophy, chronic kidney disease, proteinuria, nephrotic syndrome, cardiorenal syndrome*

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BP — arterial pressure, LV — left ventricle, GFR — glomerular filtration rate, AF — atrial fibrillation, ECG — electrocardiogram, EchoCG — echocardiography

Introduction

AL amyloidosis is the most aggressive form of systemic amyloidosis, which affects the heart in 60% of patients and kidneys in 74% of patients [1]. The median survival of patients with cardiac diseases, if untreated, is no more than one year, and after the onset of heart failure symptoms — nine months [2, 3]. The first signs of AL amyloidosis may be atrial fibrillation (AF) and heart failure, which are the reason for seeking the cardiologist's advice. It is important for practitioners to be vigilant and prescribe the necessary examinations for patients with myocardial hypertrophy, AF and heart failure of unknown etiology for the early diagnosis of amyloidosis and timely prescription of therapy to improve the prognosis of the disease. The presented clinical case demonstrates the debut of systemic amyloidosis with the development of AF and heart failure in a middle-aged patient.

Clinical case description

Male, 53 years old, without history of cardiovascular, thyroid and other diagnosed disease, or toxic exposure, presented with dyspnea on exertion. A month later, the electrocardiogram (ECG) recorded AF, tachysystole, low QRS complexes voltage in the precordial leads, signs of right ventricular hypertrophy with qR-type QRS complex, the absence of an adequate R-wave elevation in V3–V6 (Fig. 1).

The outpatient echocardiography (EchoCG) showed a 12 mm thickening of the walls of the left ventricle (LV) myocardium, 43 mm dilatation of the left atrium, with preserved LV ejection fraction — 59% based on the Simpson method. Attempts to restore sinus rhythm with amiodarone and electrical cardioversion had short-term results. However, AF recurrence occurred in 12 hours. Radiofrequency ablation was planned but postponed after finding thrombosis in the left atrial appendage by means of transesophageal echocardiography. The recommended drugs (vitamin K antagonist (warfarin 3.75–5 mg per day with INR monitoring), then rivaroxaban 20 mg/day; metoprolol succinate 25 mg/day, then bisoprolol 5 mg/day; perindopril 2.5 mg/day; torasemide 10 mg/day; spironolactone 25 mg/day) were taken regularly.

Five months after the onset of the disease, multislice computed tomography of the chest with contrast enhancement showed hyperuricemia 768 μmol/l, increased serum creatinine 155 μmol/l, a decrease in the calculated glomerular filtration rate (eGFR, CKD-EPI) 43.4 ml/min/1.73 m^2 (initial values of creatinine and eGFR are unknown, examined by a nephrologist, contrast-induced kidney damage is assumed, nephroprotective therapy is recommended).

Eight months after the onset of dyspnea for a week, there were syncopes with tongue biting, loss of bowel control, an episode of gross hematuria developed, which led to hospitalization to the V.M. Buianov State Clinical Hospital on October 24, 2018.

On admission, the condition was severe; the patient presented with the pallor of the skin, edema of the lower extremities, weakened breathing in the lower parts of both lungs, no wheezing, respiratory rate 23 per minute, blood saturation (SpO_2) 98%, irregular heart rate 90 beats per minute, blood pressure (BP) 116/68 mm Hg. Laboratory tests showed a decrease in hemoglobin to 104 g/l, hypoproteinemia — 55 g/l, hypoalbuminemia — 26 g/l, proteinuria — 10 g/l in a single portion of urine, increase in creatinine to 686 μmol/l, urea to 40.5 mmol/l, decrease in eGFR to 7.2 ml/min/1.73 m^2, aspartate aminotransferase — 58 IU/l (5–34), alanine aminotransferase — 45 IU/l (0–32), total creatine phosphokinase — 90 IU/l (21–215), MV fraction of creatine phosphokinase — 12 IU/l (0–25), total lactate dehydrogenase — 471 IU/l (225–450), gamma glutamyl transpeptidase — 1295 IU/l (9–39), alkaline phosphatase — 1598 IU/l (64–306), alpha-amylase — 392 IU/l (0–220), total bilirubin — 42.4 μmol/l (1.7–20.5), direct bilirubin — 35 μmol/l (0.86–5.00), troponin I — 0.120 μg/l (0.0–0.1, in real-time — an increase to 1.020 μg/l), antithrombin III — 67.8% of N (80.0–120.0), D-dimer — 324 ng/ml (64–550), N-terminal precursor of brain natriuretic peptide > 35 000 ng/l (Table 1).

Abdominal ultrasound showed a moderate increase in the size of both kidneys (left: 132 x 69 x 60 mm, volume 272 cm^3; right: 137 x 61 x 59 mm, volume 261 cm^3), hepatomegaly (left lobe oblique caudal size — 126 mm, thickness — 99 mm, right lobe oblique vertical dimension — 210 mm, thickness — 143 mm), splenomegaly (150 × 73 mm), a small amount of fluid in the abdominal cavity. Computed tomography of the brain showed no abnormality. EchoCG showed a thickening of the LV myocardium walls up to 22 mm with normal LV end-diastolic size (38 mm) and LV end-diastolic volume (60 ml), restrictive type of diastolic dysfunction with preserved LV ejection fraction (55%), left atrial size — 43 mm, left atrial volume — 98 ml end-diastolic right ventricular size — 42 mm, up to 7 mm pericardial separation (Table 2, Fig. 2).

Multislice computed tomography revealed bilateral hydrothorax, hydropericardium, signs of pulmonary congestion, ascites, enlargement of the liver, spleen and aortocaval lymph nodes up to 12 mm (Fig. 3).

Signs of hypertrophic cardiomyopathy in combination with nephrotic syndrome (proteinuria up to 10 g/l, daily proteinuria not assessed, hypoproteinemia 55 g/l, hypoalbuminemia 26 g/l, hypooncotic edema, hyperlipidemia) and decreased renal function allowed to suspect systemic amyloidosis in the patient. The hereditary (mutant) variant of transthyretin (ATTR) amyloidosis was excluded by direct sequencing of the entire coding sequence and regions of exon-intron junctions of the transthyretin gene, in which pathogenic and probably pathogenic variants of the nucleotide sequence were not detected in this gene. Immunochemical assay of 24-hour urine revealed an increase in the excretion of light chains of immunoglobulins — kappa up to 63.9 mg/l (norm < 7.31 mg/l), lambda up to 10 mg/l (norm < 4.03 mg/l). Bone marrow biopsy showed low plasma cell count (8%), which allowed to exclude multiple myeloma (Table 3).

Isolated amyloid deposits were found during aspiration biopsy of subcutaneous fat with Congo red staining and examination in polarized light (Fig. 4). Similar deposits were found in the walls of arterioles, the muscle lamina of the mucous membrane in the lamina propria of the colon mucosa, and the walls of the arterial vessels of the bone marrow trephine biopsy. When examined in polarized light, the birefringence with an apple-green and yellowish glow was demonstrated. Pachler's test with potassium permanganate excluded the AA-type amyloid.

After six sessions of veno-venous hemodiafiltration (VVHDF), a decrease in the level of serum creatinine to 169 μmol/l and urea to 6.2 mmol/l was observed. The course of the disease was complicated by bilateral pneumonia, sepsis (with an increase in procalcitonin up to 200 ng/ml, C-reactive protein up to 101 mg/l), disseminated intravascular coagulation syndrome (with a decrease in antithrombin III to 12.3% of N, an increase in D-dimer up to 21 400 ng/ml, a decrease in blood hemoglobin levels to 60 g/l, platelets up to 54 × 10^9/l). Transfusion of erythrocyte mass, fresh frozen plasma and antithrombin III was performed.

On the 26th day of hospitalization, with ultrasound Doppler in duplex mode of the veins of lower extremities, occlusive thrombosis of the sural veins of the left lower extremity was visualized.

Despite the antibiotic, infusion therapy, diuretic, antiarrhythmic, gastroprotective, and hepatoprotective therapy, the patient died on the 27th day of hospitalization.

Based on clinical, laboratory and other diagnostic test data, a clinical diagnosis was:

Principal diagnosis: Systemic AL amyloidosis with involvement of the heart (grade III amyloid cardiomyopathy), liver, spleen, gastrointestinal tract, kidney, subcutaneous fat.

Complications: Persistent AF of unknown duration. CHA2DS2-Vasc 2 points/ HAS-BLED 3 points. Chronic heart failure IIB stage, III FC. Nephrotic syndrome. Chronic kidney disease stage 5 (glomerular filtration rate according to the CKD-EPI formula 12 ml/min/1.73 m^2), A4. Nosocomial bilateral polysegmental pneumonia. Respiratory failure degree 2. Sepsis. Disseminated intravascular coagulation syndrome. Severe thrombocytopenia. Coagulopathy. Recurrent nosebleeds. Severe normochromic normocytic anemia. Occlusive thrombosis of the sural veins of the left lower extremity on November 20, 2018. Pulmonary embolism on November 21, 2019. Generalized convulsive seizure on October 24, 2018.

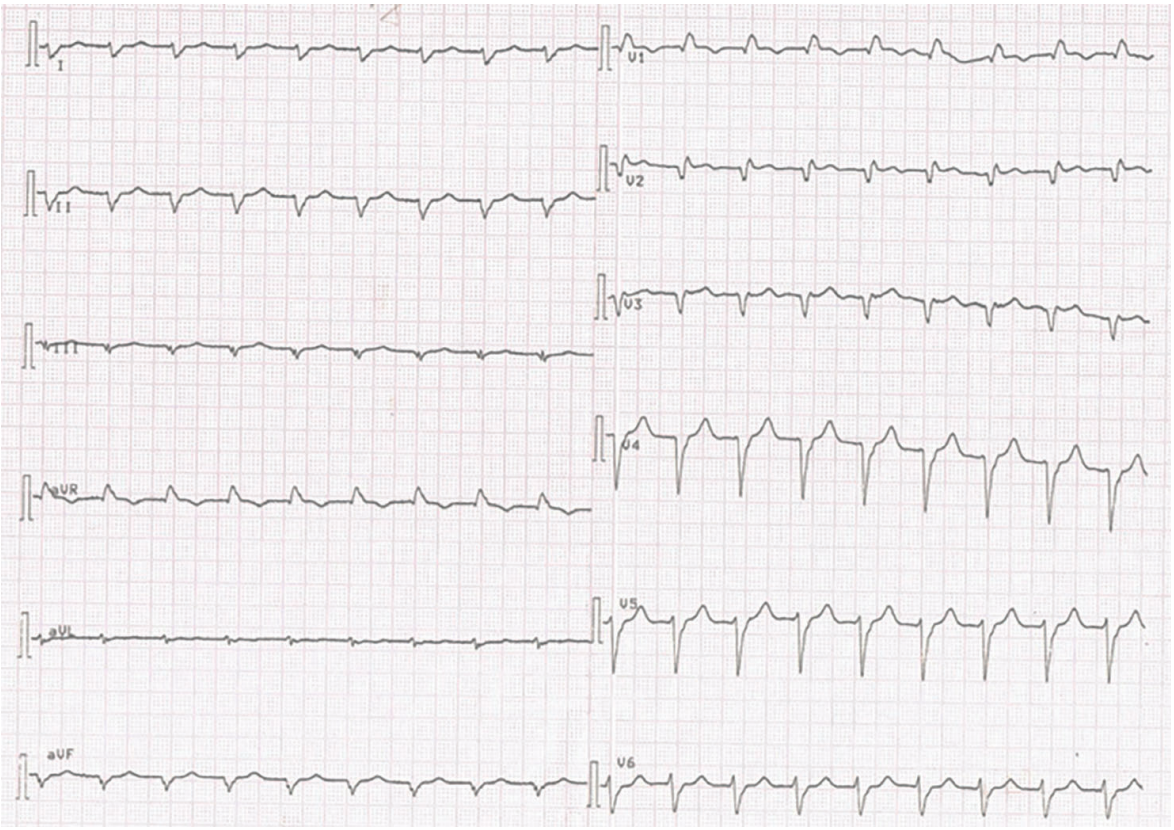

Figure 1. *Electrocardiogram. Atrial fibrillation with ventricular rate 115 per minute, decreasing of r voltage in I, II, III, avL, avF, V3-V6, right ventricular hypertrophy qR type*

Table 1. *Results of laboratory examinations in dynamics*

Parameter	At the onset of the disease	In 4 months	In 8 months	Normal value
Blood analisis				
Hemoglobin, g/l	165	111	104	130-170
Red blood cells, 10^{12}/l	5,29	3,8	3,46	4,28-5,78
Hematocrit, %	47,6	35,5	31	39,5-51,0
The volume of erythrocytes, fl	90	94	89,6	82-98
Red blood cell hemoglobin content, pg	31,2	29,4	30,1	27,9-33,2
Platelets, 10^9/l	292	160	291	150-340
White blood cells, 10^9/l	13,25	14,8	9,3	3,9-10,9
Blood chemistry				
Total protein, g/l	**67**	**61**	**55**	**65-85**
Albumin, g/l			26	35-55
Creatinine, μmol/l	155	231	**686**	71-115
Urea, mmol/l	11,4	16,5	40,5	2,5-8,3
Potassium, mmol/l	4,8	4,8	4,9	3,5-5,5
Sodium, mmol/l	142		138	135-150
Urine analysis				
Blood	Not	+	+	Not
Protein, g/l	Not	1	10	Not
Glucosae, μmol / l	Not	Not	Not	Not
Specific gravity, g/l	1001	1004	1016	1005-1030
Leukocytes, per 1 μl	0-1	17	500	0
pH	6	6	6	5-7

Table 2. *Dynamics of echocardiographic parameters*

Parameter	At the onset of the disease	In 6 months	In 8 months	Normal value
Interventricular septum thickness, mm	11	15	21	Up to 10
Left ventricular posterior wall thickness, mm	12	14	22	Up to 10
Left ventricular ejection fraction, %	59	52	55	>55
End-diastolic volume of the left ventricle, ml	98	-	60	

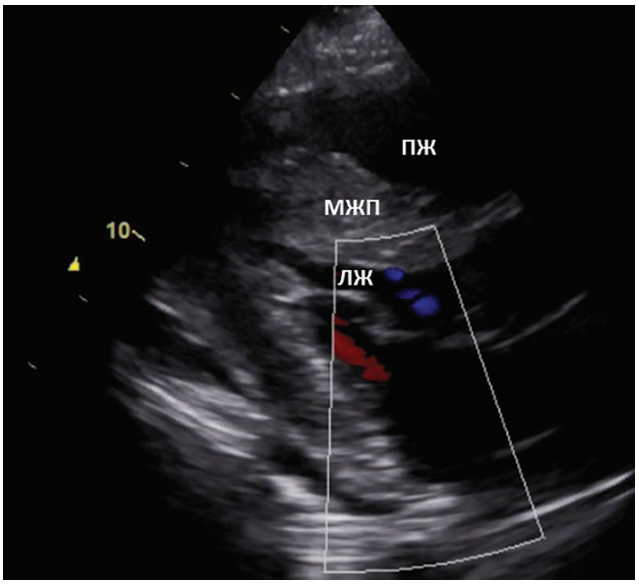

Figure 2 A. *Echocardiogram (Photo of Dr. I.I. Ganieva). Parasternal long axis position (dyastola): left ventricular hypertrophy*
ЛЖ — left ventricular, ПЖ — right ventricular, МЖП — interventricular septum

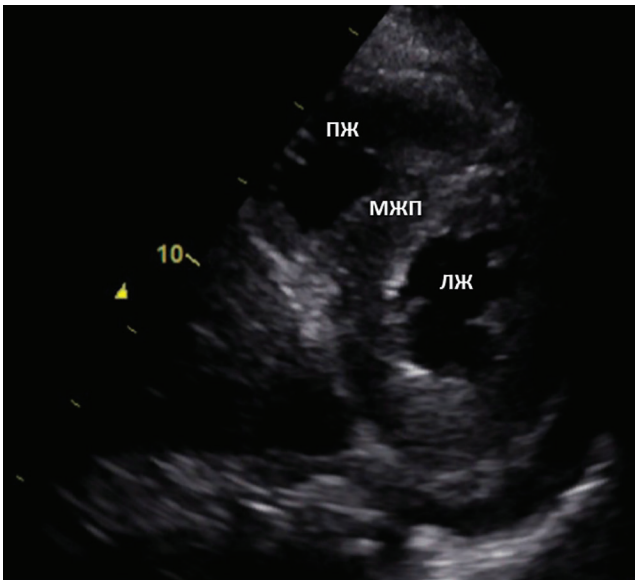

Figure 2 B. *Echocardiogram (Photo of Dr. I.I. Ganieva). Parasternal position along the short axis of the left ventricle: severe left ventricular hypertrophy*
ЛЖ — left ventricular, ПЖ — right ventricular, МЖП — interventricular septum

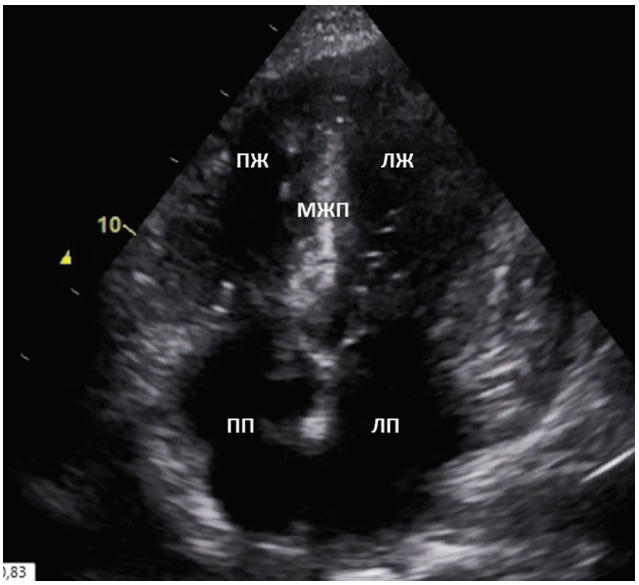

Figure 2 C. *Echocardiogram (Photo of Dr. I.I. Ganieva). Apical four-chamber position: severe left ventricular hypertrophy*
ЛЖ — left ventricular, ПЖ — right ventricular, МЖП — interventricular septum, ЛП — left atrium, ПП — right atrium

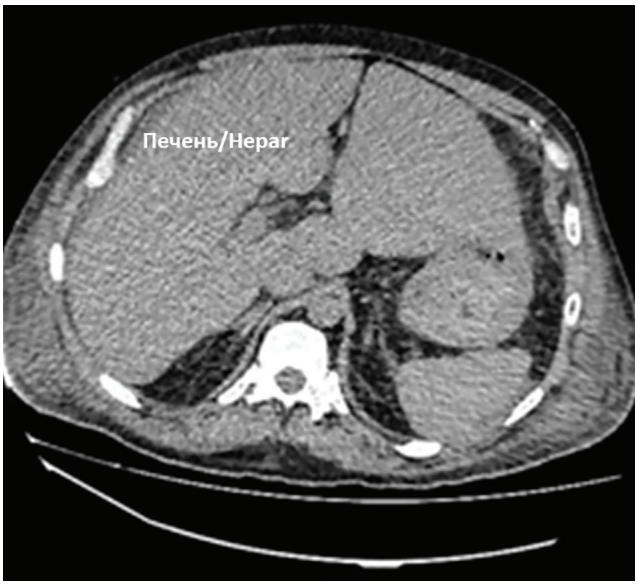

Figure 3. *Computed tomography of the abdominal organs: hepatomegaly*

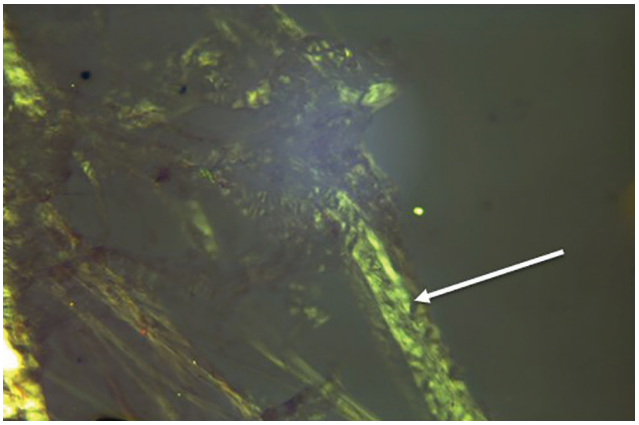

Figure 4. *Biopsy of subcutaneous adipose tissue (Photo of Dr. EA Stepanova). Single irregularly spaced congophilic deposits, birefringence with apple-green glow (arrow). On a visual grage scale CR 1+, sometimes CR 2+*

Concomitant disease: Mixed encephalopathy.

Invasive procedures: Sessions of VVGDF of November 06, 2018; November 07, 2018; November 10, 2018; November 14, 2018; November 15, 2018; November 16, 2018.

During autopsy, the diagnosis of systemic amyloidosis (AL, IgG, κappa) was confirmed, a massive lesion of the heart (weight 885 g, normal — 310 g), kidneys (weight of the left kidney 291 g, right kidney 313 g, normal — 320 g), lungs (weight of the left lung 571 g, right lung 817 g, normal left lung — 325–480, right lung — 360–570 g), liver (weight 4120 g, normal — 1600 g), spleen (weight 320 g, normal — 150 g), adrenal glands, thyroid, pancreas, gastrointestinal tract, subcutaneous adipose tissue and arterial vessels of the bone marrow. Immunohistochemistry showed AL amyloidosis, type Kappa (Fig. 5–6).

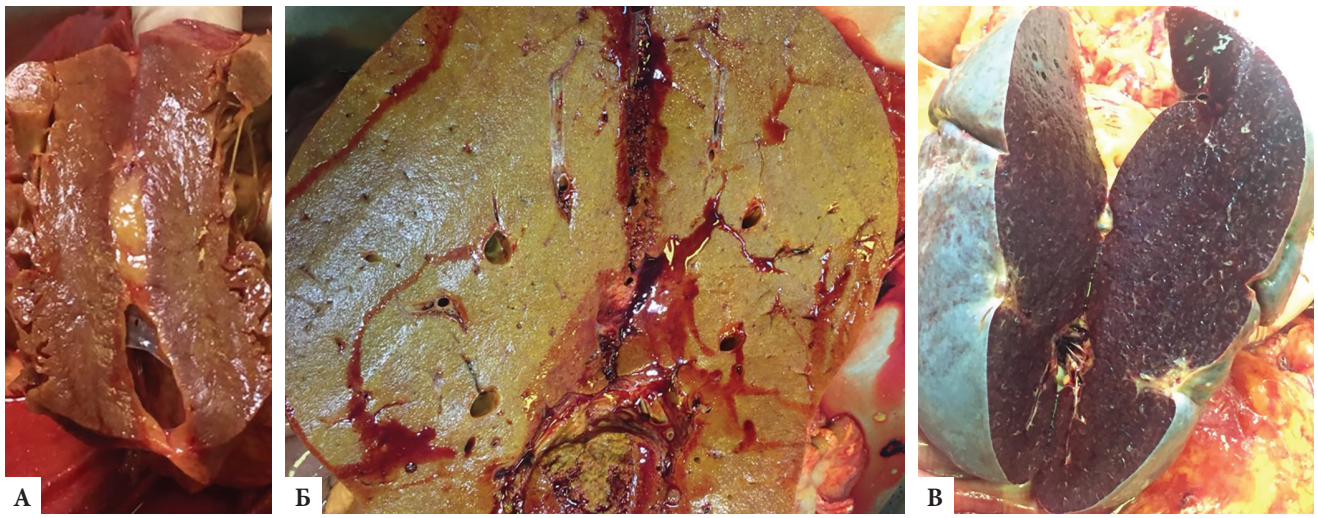

Figure 5. *Macroscopic picture at autopsy: revealed massive damage to the heart (А), liver (Б), spleen (В) (Photo courtesy of Dr. EA Stepanova)*

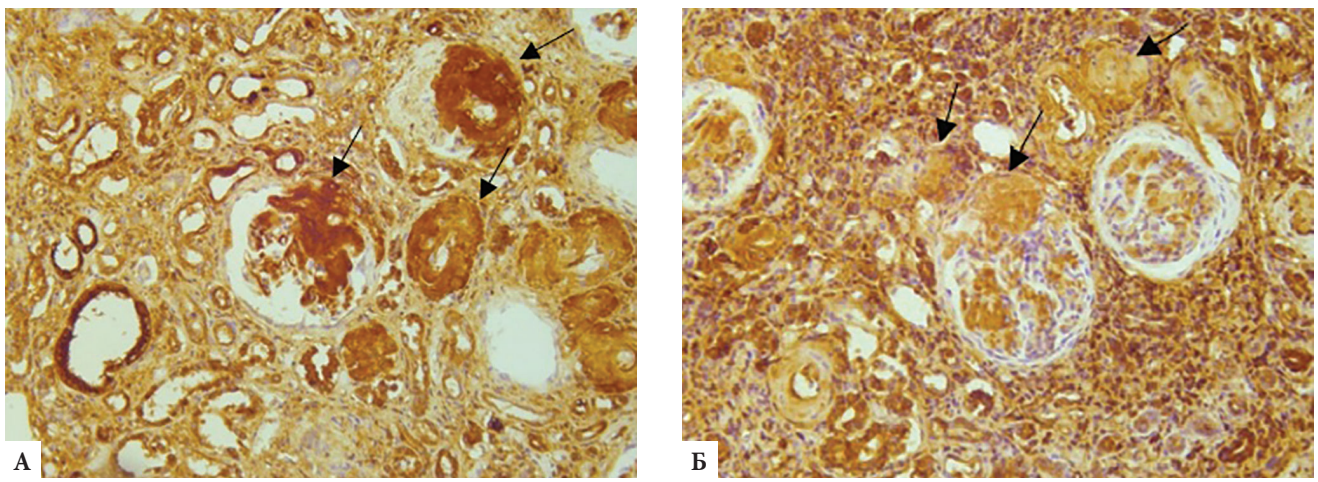

Figure 6. *Immunohistochemical study (Photos courtesy of Dr.E. A. Stepanova)*
А — Kidney, light chains K; Б — Kidney, light chains λ

Table 3. Myelogram

	Parameter	Normal value
Blasts, %	2	0,1-2,8
Neutrophilic promyelocytes, %	2	1-4,1
Neutrophilic myelocytes, %	10	7-12,2
Neutrophilic metmyelocytes, %	4	8-15
Neutrophilic stab, %	5	12,8-23,7
Neutrophil segmented, %	24	13,1-24,1
All neutrophilic elements, %	45	52,7-68,9
Eosinophils, %	1	0,5-5,8
Lymphocytes, %	9	4,3-13,7
Monocytes, %	4	0,7-3,7
Plasma cells, %	**8**	0,1-1,8
Erythroblasts polychromatophilic, %	10	8,9-16,9
Erythroblasts oxyphilic, %	13	0,8-5,6
Megaloblasts, %	6	0
All erythroid elements, %	31	14,5-26,5
Leukoerythroblastic index	1,8	2,1-4,5
Neutrophil Maturation Index	0,6	0,5-0,9
Maturation index of erythrokaryocytes	0,9	0,7-0,9
Megakaryocytes	+	+

The patient's death was caused by systemic amyloidosis with damage to the heart, kidneys, liver, adrenal glands, thyroid and pancreas, gastrointestinal tract, complicated by bilateral focal pneumonia and acute heart failure.

Discussion

Cardiac amyloidosis is observed in 33–60% of patients with AL amyloidosis [4, 5]. In AL amyloidosis, heart failure develops relatively early, in 22% of patients — as early as the onset of the disease [6, 7]. Cardiac damage in AL-amyloidosis is almost always associated with damage to other organs, most often the kidneys, as well as blood vessels, peripheral nervous system, the liver, gastrointestinal tract, and soft tissues [8]. Isolated cardiac involvement is observed in less than 5% of cases [4–6].

The presented patient with heart failure and AF had cardiorenal syndrome, monoclonal gammopathy, plasma cell dyscrasia [5, 9, 10]; the presence of amyloidosis was confirmed by an intravital morphological exam with Congo red staining and polarizing microscopy.

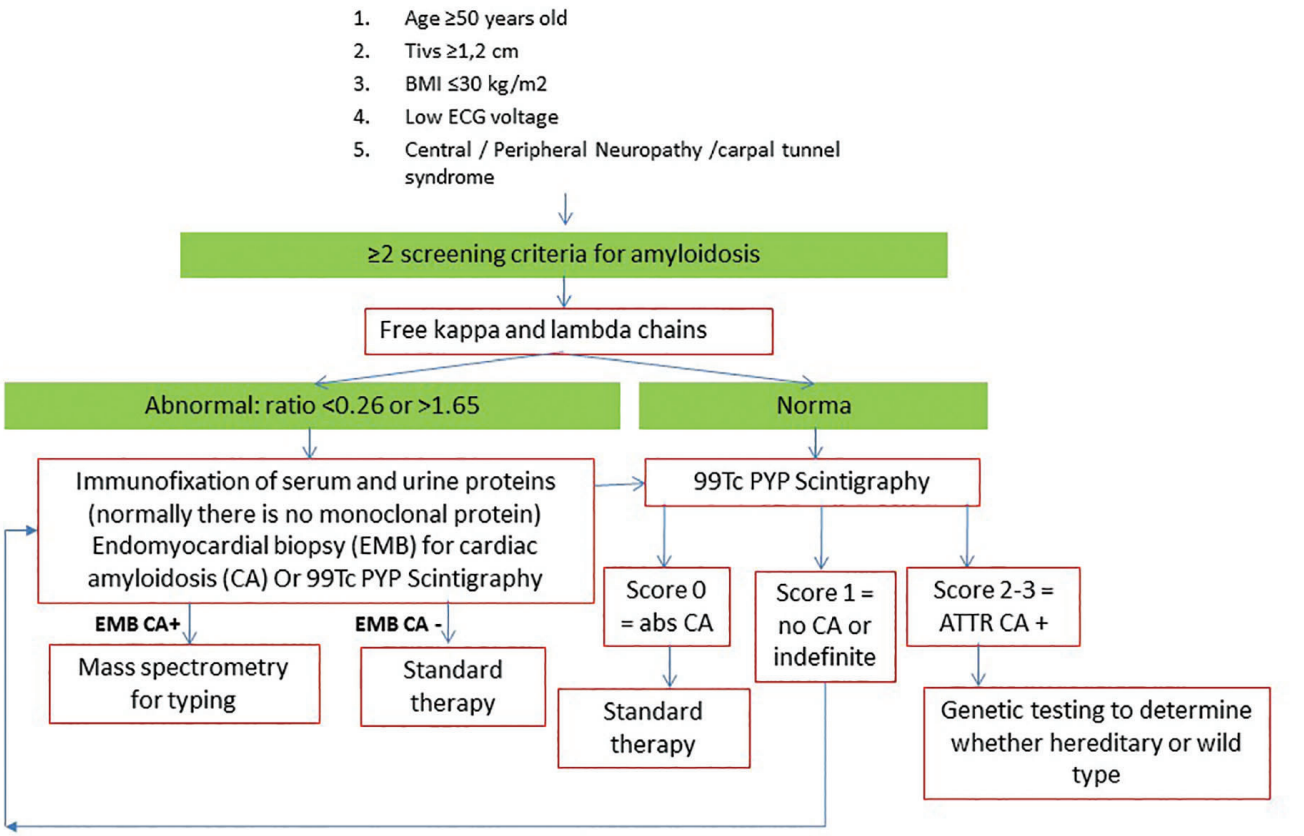

Figure 7. *Algorithm for the diagnosis of cardiac amyloidosis in CHFpEF [5, 13]*
ATTR CA — transtiretin cardiac amyloidosis, BMI — body mass index, CA — cardiac amyloidosis, CHFpEF — chronic heart failure with preserved ejection fraction; ECG — electrocardiogram; EMB AS — endomyocardial biopsy for cardiac amyloidosis; Tivs — interventricular septum thickness, 99mTc-PYP — 99mtechnetium pyrophosphate

Due to the severity of the condition and late intravital diagnosis of amyloidosis, pathogenetic antiamyloid therapy was not prescribed to this patient, which led to a rapid progression of the disease and death. [5, 6, 11, 12].

For the timely diagnosis of cardiac amyloidosis in chronic heart failure with preserved ejection fraction (HFpEF), it is advisable to use the procedure shown in Figure 7.

Therefore, the variety and non-specificity of the clinical signs of amyloidosis often lead to a fatally late diagnosis of the disease. Suspicion of cardiac amyloidosis should arise with the idiopathic thickening of the LV myocardium walls to 12 mm or more, the presence of a restrictive type of diastolic dysfunction, idiopathic AF, chronic heart failure of unknown etiology, refractoriness to therapy, low voltage of the ECG teeth, arterial hypotension, syncope of unknown origin, pulmonary hypertension, nephrotic syndrome, and stage 4–5 chronic kidney disease. Electrophoresis of blood and urine proteins, identification of light chains of immunoglobulins, detection of amyloid deposits during intravital histological examination of various organs and tissues enable early and accurate diagnosis of AL amyloidosis, which is extremely important for improving the prognosis in such patients.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Резник Е.В. (ORCID http://orcid.org/0000-0001-7479-418X): написание текста клинического случая, обзор литературы, идея, организация работы

Лазарев В.А. (ORCID https://orcid.org/0000-0001-8417-3555): подготовка материалов для описания клинического случая, обзор литературы

Борисовская С.В. (ORCID https://orcid.org/0000-0007-9365-1472): ведение больной, коррекция текста, предоставление и описание материалов обследований

Голухов Г.Н. (ORCID https://orcid.org/0000-0002-0161-005X): обзор литературы, коррекция текста, организация работы над публикацией

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Reznik E.V. (ORCID http://orcid.org/0000-0001-7479-418X): case description, literature review, idea, work organization

Lazarev V.A. (ORCID https://orcid.org/0000-0001-8417-3555): participation in case description, literature review

Borisovskaya S.V. (ORCID https://orcid.org/0000-0007-9365-1472): patient management, provision of examination materials, text correction

Golukhov G.N. (ORCID https://orcid.org/0000-0002-0161-005X): literature review, text correction, work organization

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Г.Ш. Сафуанова*[1], А.С. Константинова[1], А.А. Латыпова[2], А.У. Багаутдинова[2], Д.Р. Сафуанова [3]

[1] — Кафедра терапии и общей врачебной практики с курсом гериатрии ИДПО, Федеральное государственное бюджетное образовательное учреждение высшего образования «Башкирский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Уфа, Россия
[2] — Государственное бюджетное учреждение здравоохранения «Республиканская клиническая больница им. Г.Г. Куватова» Министерства здравоохранения Республики Башкортостан, Уфа, Россия
[3] — Федеральное государственное бюджетное образовательное учреждение высшего образования «Первый московский медицинский университет им И.М. Сеченова» Минздрава России, Москва, Россия

КЛИНИЧЕСКИЙ СЛУЧАЙ ДИАГНОСТИКИ АПЛАСТИЧЕСКОЙ АНЕМИИ ПОСЛЕ ПЕРЕНЕСЕННОЙ ИНФЕКЦИИ COVID-19

G.Sh. Safuanova*[1], A.S. Konstantinova[1], A.A. Latypova[2], A.U. Bagautdinova[2], D.R. Safuanova [3]

[1] — Department of Therapy and General Medical Practice with a Course of Geriatrics. Federal State Budgetary Educational Institution of Higher Education «Bashkir State Medical University» of the Ministry of Healthcare of the Russian Federation, Ufa, Russia
[2] — State Budgetary Healthcare Institution «Kuvatov Republican Clinical Hospital» of the Ufa Healthcare Department, Ufa, Russia.
[3] — Federal State Budgetary Educational Institution of Higher Education «I.M. Sechenov First Moscow Medical University», Ministry of Healthcare of the Russian Federation, Moscow, Russia

A Clinical Case of Aplastic Anemia After COVID-19 Infection

Резюме

Апластическая анемия — редкое заболевание системы крови, для которого характерно угнетение кроветворения во всех линиях гемопоэза, замещение кроветворной ткани на жировую и отсутствие других причин или заболеваний, которые могут подавлять гемопоэз. Частота заболеваемости составляет 2-3 случая на 1 млн населения в год в регионах Европы и Америки, показатели в 2-3 раза выше в Восточной Азии. Чаще заболевание начинается в возрастном промежутке от 10 до 25 лет и старше 60 лет. Этиология в 70-80 % случаях остается неизвестной. Частота приобретенных случаев заболевания преобладает над врожденными. Провоцирующими факторами могут быть химическое, физическое воздействие, лекарственные препараты, вирусные инфекции. В данной работе описан случай развития апластической анемии у пациентки после принесенной коронавирусной инфекции.

Ключевые слова: *апластическая анемия, панцитопения, аутоиммунные заболевания, COVID-19, коронавирусная инфекция*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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*Контакты: Гузяль Шагбановна Сафуанова, e-mail: safuanova@bk.ru
*Contacts: Guzyal Sh. Safuanova, e-mail: safuanova@bk.ru
ORCID ID: https://orcid.org/0000-0003-2627-0626

Для цитирования: Сафуанова Г.Ш., Константинова А.С., Латыпова А.А. и др. КЛИНИЧЕСКИЙ СЛУЧАЙ ДИАГНОСТИКИ АПЛАСТИЧЕСКОЙ АНЕМИИ ПОСЛЕ ПЕРЕНЕСЕННОЙ ИНФЕКЦИИ COVID-19. Архивъ внутренней медицины. 2021; 11(6):466-471. DOI: 10.20514/2226-6704-2021-11-6-466-471

Abstract

Aplastic anemia is a rare disease of the blood system characterized by suppression of hematopoiesis in all lines of hematopoiesis, replacement of hematopoietic tissue with fatty tissue and absence of other causes or diseases that can suppress hematopoiesis. The incidence is 2-3 cases per 1 million population per year in the regions of Europe and America, rates are 2-3 times higher in East Asia. The disease most often begins between the ages of 10 and 25 years and over 60 years. The etiology remains unknown in 70-80 % of cases. The frequency of acquired cases predominates over congenital cases. The triggering factors can be chemical, physical exposures, medications, and viral infections. This case report describes a case of a patient developing aplastic anemia, as a result of a coronavirus infection.

Key words: *aplastic anemia, pancytopenia, autoimmune disease, COVID-19, coronavirus infection*

Conflict of interest

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AA — aplastic anemia, MDS — myelodysplastic syndrome, CBC — complete blood count, ESR — erythrocyte sedimentation rate, CD — cluster of differentiation, COVID-19 — infection caused by the novel coronavirus SARS-CoV-2, FISH — fluorescent in situ hybridization, MCH — mean cell hemoglobin, MCHC — mean cell hemoglobin concentration, MCV — mean cell volume, NK — natural killer cells, RDW — red cell distribution width

Introduction

The etiology of aplastic anemia (AA) has not been fully studied yet. However, according to literature data, in most cases, viral infections can be the etiological factors (Epstein-Barr virus, hepatitis B and C, primary immunodeficiency, parvovirus); various drug products (cytostatics, antibacterial drugs, non-steroidal anti-inflammatory drugs, anticonvulsants); chemical compounds (benzene, pesticides, heavy metal salts, aromatic hydrocarbons); and ionizing radiation; the history of autoimmune diseases[1, 6, 7].

The pathogenesis is based on a significant activation of cytotoxic lymphocytes. Viral infection leads to the generation of viral proteins and excessive production of normal cellular proteins. They are captured by antigen-presenting cells; the latter form complexes with histocompatibility complex molecules and are naive T-lymphocytes, which destroy both infected and normal cells [3].

Clinical manifestations are due to bone marrow failure. They depend on the severity of pancytopenia, and are represented by anemic, hemorrhagic syndrome, infectious complications. In at least 80% of cases, the disease develops gradually, and the patients often see the doctor when they notice signs of hemorrhagic syndrome in the form of petechiae, ecchymoses, mucous membrane bleeding and hemorrhages in the conjunctiva, in combination with anemic syndrome and frequent infections. The disease may be asymptomatic and diagnosed by chance during a routine examination or a diagnostic search. In 15% of cases, the onset of aplastic anemia is acute, with severe hemorrhagic syndrome, fever, infectious and inflammatory complications [7].

To diagnose the disease, it is important to provide a thorough history-taking, identification of factors that could contribute have contributed to the disease and affected the patient for one to six months before the onset of the first symptoms: previous viral infections, taking medications, contact with chemical compounds, harmful industrial factors. The complete blood count (CBC) identifies pancytopenia with relatively normal lymphocyte counts. Normochromic anemia, low reticulocyte count. The myelogram shows the reduction of bone marrow cellularity and the absence of megakaryocytes according to bone marrow puncture. Low bone marrow cellularity in the trephine biopsy specimen. Hypocellular areas sometimes alternate with high cellularity areas [6, 7]. Lymphoid aggregation is sometimes detected in AA associated with an autoimmune process. In some cases, dyserythropoiesis, without dysplasia of other hematopoietic lineage [1].

Severe AA corresponds to:

1) bone marrow cellularity < 25%, or 25–50% with < 30% of residual hematopoietic cells.
2) the presence of two of three indicators: 1) neutrophils< 0.5×10^9/l; 2) platelets < 20×10^9/l;
3) reticulocytes < 20×10^9/l.

Super-severe AA meets the criteria for severe, with neutrophil count < 0.2×10^9/l. Non-severe AA is defined if criteria for severe and super-severe AA are not diagnosed [7].

Clinical case

Patient A.A., female 54 years old, nurse. Since 2005, the patient underwent regular endocrinologist's check-up with the diagnosis of "Autoimmune thyroiditis" and took levothyroxine sodium 75 mcg/day. The hormonal status was monitored, there were no complaints, the patient felt well. In June 2020, she complained of body temperature rise to 37.5°C, cough, headache for two days. The patient was treated on an outpatient basis: nasopharyngeal irrigation with furacilin solution for 5 days, ascorbic acid injections 100 mg per day IM 3 times daily, every other day. Considering the COVID-19 pandemic, the patient had a sputum PCR test, the result was positive. Chest computed tomography showed no pneumonia. CBC showed lymphocytosis — 48.35%, low white blood cell count of 2.0×10^9, neutrophils — 0.6×10^9, platelets — 138×10^9, which was regarded as a manifestation of a viral infection. There were no CBC changes since 2019 (Table 1). Further, the patient's condition deteriorated, weakness worsened, and hemorrhagic syndrome, manifested by bleeding gums and "bruising", developed. Progressive platelet count decrease from 138×10^9 to 50×10^9 was recorded in real-time for three months. In early October, the patient visited a hematologist and had a sternal puncture. Myelogram results: hypocellular bone marrow, megakaryocytes — 3%; myeloblasts — 1.0%; myelocytes — 10%; metamyelocytes — 5.5%; stab neutrophils — 4.0%; segmented neutrophils -18.5%; total neutrophils — 39%; eosinophils — 1%, basophils — 0.5%; lymphocytes — 28%; plasma cells — 4.5%; monocytes — 3.0%; basophilic normoblasts — 6.5%; polychromatophilic normoblasts — 11.5%; oxyphilic normoblasts — 6.0%; leuko-erythroblastic ratio — 3.2:1, low cellularity polymorphic punctate; blasts — 1.0%, monocytes — 3%. The myelogram results were regarded as secondary cytopenia associated with a viral infection.

The analysis of CBC changes from June to December 2020 showed a decrease in hemoglobin level from 132 to 68 g/l, red blood cell count — from 4.83×10^{12} to 1.83×10^{12}, platelets — from 243×10^9 to 13×10^9, white blood cell count — from 3.84×10^9 to 1.5×10^9, neutrophils — from 1.53×10^9 to 0.3×10^9; increased mean cell volume — from 79.1 to 103.2 fL, lymphocytosis — from 44.0% to 72.3%, ESR increased from 6 to 27 mm/h.

Table 1. *Dynamics of Patient A.A.'s general blood count from 2019 to 2021*

Complete blood count indicators	June 2019	June 2020	July 2020	September 2020	October 2020	November 2020	December 2020
Hematocrit	38,2 %	38,0 %	35,6 %	30,6 %	34,4 %	25,6 %	18,9 %
Hemoglobin	132 г/л	133 г/л	124 г/л	112 г/л	123 г/л	93 г/л	68 г/л
Erythrocytes	$4,83\times10^{12}$	$4,48\times10^{12}$	$4,22\times10^{12}$	$3,47\times10^{12}$	$3,74\times10^{12}$	$2,68\times10^{12}$	$1,83\times10^{12}$
MCV	79,1 фл	84,8 фл	84,4 фл	88,2 фл	92 фл	25,6 фл	103,2 фл
RDW	12,6 %	13,6 %	13,4 %	14,0 %	15,5 %	17,2 %	19,1 %
MCH	27,3 пг	29,7 пг	29,4 пг	32,3 пг	32,9 пг	34,6 пг	37,3 пг
MCHC	346 г/л	350 г/л	348 г/л	366 г/л	358 г/л	362 г/л	361 г/л
Platelets	234×10^9	138×10^9	148×10^9	57×10^9	50×109	19×10^9	13×10^9
Leukocytes	$3,84\times10^9$	$2,0\times10^9$	$2,56\times10^9$	$2,36\times10^9$	$2,2\times10^9$	$1,9\times10^9$	$1,5\times10^9$
Neutrophils	39,8 %	28,8 %	33 %	26 %	23,5 %	21,6 %	19,8 %
Lymphocytes	44,0 %	48,35 %	54 %	63 %	66,7 %	70,4 %	72,3 %
Monocytes	11,5 %	24 %	8 %	8 %	8.1 %	7,2 %	7,5 %
Eosinophils	4,4 %	0,8 %	1 %	2 %	1,2 %	0,5 %	0,3 %
Basophils	0,3 %	0,7 %	1 %	1 %	0,5 %	0,3 %	0,1 %
Neutrophils	$1,53\times10^9$	$0,6\times10^9$	$0,84\times10^9$	$0,61\times10^9$	$0,5\times10^9$	$0,4\times10^9$	$0,3\times10^9$
Lymphocytes	$1,69\times10^9$	1×10^9	$1,38\times10^9$	$0,49\times10^9$	$1,5\times10^9$	$1,3\times10^9$	$1,1\times10^9$
Monocytes	$0,44\times10^9$	$0,4\times10^9$	$0,20\times10^9$	$0,19\times10^9$	0.2×10^9	$0,1\times10^9$	$0,1\times10^9$
Eosinophils	$0,17\times10^9$	$0,01\times10^9$	$0,03\times10^9$	$0,05\times10^9$	$0,02\times10^9$	$0,01\times10^9$	$0,01\times10^9$
Basophils	$0,01\times10^9$	$0,01\times10^9$	$0,03\times10^9$	$0,02\times10^9$	$0,01\times10^9$	$0,01\times10^9$	$0,01\times10^9$
ESR	6 мм/ч	9 мм/ч	5 мм/ч	18 мм/ч	21 мм/ч	24 мм/ч	27 мм/ч

Note: MCV — mean corpuscular volume, RDW — red cell distribution width, MCH — mean corpuscular hemoglobin, MCHC — mean corpuscular hemoglobin concentration, ESR — erythrocyte sedimentation rate

Iron metabolism, tested in November 2020, demonstrated no major abnormalities of indicators: ferritin — 194.1μg/l; serum iron — 22.4 μmol/l.

Due to the deterioration of clinical and laboratory data in the beginning of December, the patient had a bone marrow trephine biopsy with the results showing a cellularity decrease and erythroid and myeloid lineage involvement. Medical report: bone marrow cellularity 30%, represented mainly by granulocytic lineage cells — promyelocytes, myelocytes, mature cells, single plasma cells, erythroblasts, adipose tissue 70%. Megakaryocytes — 2-0-1 in sight. CD20 — 10%, CD45 — 10%, myeloperoxidase — 35%; glycophorin A — 50%.

At the end of December, the patient was admitted to the hematology unit of the G.G. Kuvatov Republic Clinical Hospital. On admission, she complained of general weakness, rapid fatigability, dizziness, dyspnea on exertion, bruising, gum bleeding. The repeated sternal puncture demonstrated low bone marrow cellularity, the narrowing of the megakaryocytic lineage, an increased number of myelocytes, lymphocytes, and polychromatophilic normoblasts. Report: myelokaryocytes — 9.0 × 10^9/l; megakaryocytes -6 × 10^6 /l; undifferentiated blasts — 1.8%; neutrophilic myelocytes — 15.8%; neutrophilic metamyelocytes — 3.6%; stab neutrophils — 14.2% segmented neutrophils — 6.8%; eosinophils segmented — 1.0%; lymphocytes — 25.6%; monocytes — 3.6%; erythroblasts — 0.2%; basophilic normoblasts — 1.6%; polychromatophilic normoblasts — 20.2%; oxyphilic normoblasts — 4.2%; plasma cells — 1.4%; neutrophil maturation index — 0.92; leukoerythroblastic ratio — 2.7; erythrokaryocyte maturation index — 0.92 (Fig. 1)

Bone marrow immunophenotyping demonstrated no blast cells and immunophenotypic features of granulocytes. The predominance of cytotoxic cells (CD3+CD8+, NK) was noted in the lymphocytic link. T- and B- lymphocytes — without immunophenotypic features.

Immunophenotyping result: lymphocytes — 36.6%, CD3+ — 73.1%; CD4+ — 31%; CD8+ — 41%; CD57+ — 3%; CD77+ — 3%; CD56+ — 8%; CD19+ — 12.6%; CD11c — not found; CD103 — not found; CD10 — not found; CD34 — not found; CD117 — not found; CD1a — not found.

Abdominal ultrasound examination on 28.12.2020 demonstrated no abnormality.

Taking into account the previous coronavirus infection in June 2020, the three-lineage cytopenia present in the peripheral blood, and involvement of the erythroid and myeloid lineage based on the bone marrow biopsy, the following diagnosis was made: Myelodysplastic syndrome (MDS) with hypocellular bone marrow, unclassified, severe course. Complications: hemorrhagic syndrome (skin damage, bleeding gums). Aplastic anemia?

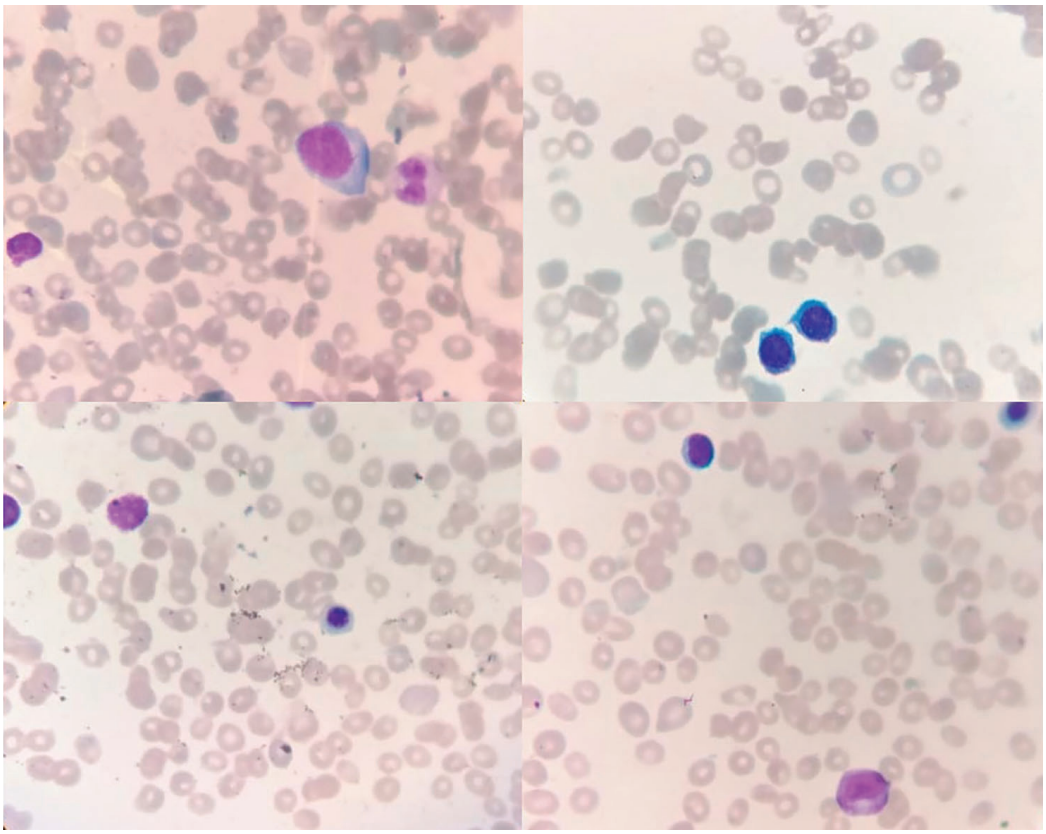

Figure 1. *Hypocellular bone marrow. Romanowsky-Giemsa staining*

To clarify the diagnosis, the bone marrow trephine biopsy block was sent to the National Medical Research Center for Hematology (Moscow) for review. The review enabled to exclude MDS and verify the diagnosis of aplastic anemia. Bone marrow biopsy specimen report: bone trabeculae with signs of resorption. Bone marrow cavities are wide, they contain hypocellular bone marrow (relative to the age norm). The granulocytic lineage is narrowed, rejuvenated. Erythroid lineage is moderately represented by clusters of normoblastic erythrokaryocytes. Megakaryocytes are single, small. Small lymphoid cells, mature plasma cells are interstitially scattered. Stroma with hemorrhages. A well-defined lymphoid accumulation of small cells, rather of reactive nature, is visualized intertrabecularly. To exclude the minimum signs of MDS, an immunohistochemical test was performed on paraffin block slices using antibodies to CD34 and CD42b. Upon reacting with antibodies to CD34, vessels and single positive cells are visualized. CD42b+ megakaryocytes are scarce, small and visually normal. Report: taking into account the immunohistochemical test, there is no convincing evidence of MDS in the examined material. The morphological pattern in the bone marrow characterizes the hypoplasia of hematopoietic tissue. Also, the material was sent for bone marrow cytogenetic FISH-test to the Republic Medical Genetic Center, which excluded the mutations characteristic of MDS**:** no translocation involving the MECOM/3q26 gene locus was identified; no deletion of 5p15.3 and 5q31.2 regions was identified; no deletion of regions 7q22.1–q22.2 and 7q31.2 was identified; no deletion of 20q12 and 20q13.12 was identified.

As a result, the final diagnosis was: Acquired severe aplastic anemia. Complications: hemorrhagic syndrome (skin damage, bleeding gums and nasal mucosa). Convalescent COVID-19 patient.

Erythrocyte mass and thrombocyte concentrate blood transfusion therapy was performed. The patient also received erythropoietin drugs subcutaneously every other day, etamsylate and folic acid. The patient was discharged with improvement at the end of December 2020 with the following blood counts: hemoglobin — 122 g/l, red blood cell count — 3.77 x 10^{12}, platelets — 18.0 × 10^9, leukocytes — 2.4 × 10^9, neutrophils — 0.6 × 10^9; mean cell volume — 92.3 fL, lymphocytes — 1.3 × 10^9, ESR — 22 mm/h

During the planned hospitalization to the hematology unit of the G.G. Kuvatov Republic Clinical Hospital at the end of January 2021, the patient complained of weakness and general malaise. The following decrease in blood counts was observed: hemoglobin — 76 g/l, red blood cell — 2.33 × 10^{12}, mean cell volume (MCV) — 94 fL, platelets — 12 × 10^9, white blood cell — 1.6 × 10^9, neutrophils — 0.4 × 10^9; lymphocytes — 1.1 × 10^9. The patient was administered erythropoietin subcutaneously every other day, received erythrocyte mass and thrombocyte concentrate transfusion therapy and ethamsylate and folic acid. She had a telemedicine consultation with the National Medical Research Center for Hematology in order to clarify the diagnosis and determine the treatment approach. The **report** was as follows: based on the examination performed, the patient is diagnosed with acquired aplastic anemia; recommendation: combined immunosuppressive therapy.

At the beginning of March 2021, the patient was admitted to the hematology unit of the G.G. Kuvatov Republic Clinical Hospital for combined immunosuppressive therapy. During admission, the blood counts were as follows: hemoglobin — 88 g/l, red blood cell count — 2.69 × 10^{12}/l, mean cell volume (MCV) — 93.8 fL, platelets — 16 × 10^9/l, white blood cell count — 2.3 × 10^9/l, neutrophils — 1.1 × 10^9/ l, lymphocytes — 1.2 × 10^9/l.

After a course of anti-thymocyte globulin and blood component transfusion, the patient was discharged with improvement. In CBC, the level of hemoglobin increased to 121 g/l, red blood cell count — to 3.77 × 10^{12}/l, white blood cell count — to 3.8 × 10^9/l, neutrophils — 1.4 × 10^9/l, platelets — 24 × 10^9/l, mean cell volume — 92.7 fL, lymphocytes — 1.0 × 10^9/l. Upon discharge, the patient was recommended to start taking Cyclosporin A, in accordance with National Guidelines. [9].

In mid-July 2021, a follow-up examination by a hematologist at the G.G. Kuvatov Republic Clinical Hospital showed an improvement of the general condition, and the absence of hemorrhagic syndrome. The changes included a slight decrease in hemoglobin to 115 g/l, leukocytes — to 2.5 × 10^9/l, neutrophils — to 0.6 × 10^9/l. Red blood cell count was 3.13 × 10^{12}/l, platelets — 46 × 10^9/l, lymphocytes — 1.6 × 10^9/l. According to the test results, the absence of hemorrhagic syndrome and blood transfusion dependence, the patient had partial clinical and hematological remission.

Discussion

AA is an orphan disease that occurs in most regions of Europe and America, with an incidence of 2–3 cases per 1 million population a year [7]. Because AA is a rare disease, it was not immediately suspected in this patient.

The hematological changes associated with COVID-19 were regarded as secondary cytopenia associated with a viral infection. In view of the pandemic, bone marrow trephine biopsy was not performed at that time, which made the timely diagnosis of AA difficult.

According to the literature data, some patients with COVID-19 may develop leukopenia and thrombocyto-

penia [8]. However, according to CBC in the presented clinical case, pancytopenia gradually progressed, lymphopenia was not observed, moderate manifestations of hemorrhagic syndrome appeared, which indicated the development of a hematological disease. Therefore, the diagnosis of AA was made after six months of observation, after a sternal puncture and trephine biopsy.

Taking into account the satisfactory condition and the absence of changes in the patient's blood tests before coronavirus disease, it can be assumed that COVID-19 was a trigger to the onset of AA in this case.

Conclusion

Therefore, AA must be differentiated from other conditions that lead to pancytopenia. The clinical case is given as an example that confirms the literature data on the impact of coronavirus on the development and course of autoimmune diseases. [2, 3, 4, 5]. We believe that in this case, the development of the autoimmune disease AA could have been triggered by the SARS-CoV-2 virus. The follow-up observation of patients in the post-COVID period will yield new information on the impact of COVID-19 on the hematopoietic system and the development and course of hematological diseases.

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Сафуанова Г.Ш. (ORCID ID: https://orcid.org/0000-0003-2627-0626): разработка концепции статьи, проверка критически важного интеллектуального содержания, редактирование текста, утверждение итогового варианта текста рукописи

Константинова А.С. (ORCID ID: https://orcid.org/0000-0003-2617-9347): сбор и обработка материала, написание текста, интерпретация и анализ данных, подбор литературы, редактирование статьи

Латыпова А.А. (ORCID ID: https://orcid.org/0000-0002-9508-3878): ведение пациентки в клинике, идея и описание клинического случая, интерпретация и анализ данных

Багаутдинова А.У. (ORCID ID: https://orcid.org/0000-0002-7021-7470): ведение пациентки в клинике, описание клинического случая, интерпретация и анализ данных, редактирование статьи

Сафуанова Д.Р. (ORCID ID: https://orcid.org/0000-0001-7944-8585): сбор и обработка материала, написание текста, интерпретация и анализ данных, перевод на английский язык

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Safuanova G.Sh. (ORCID ID: https://orcid.org/0000-0003-2627-0626): conceptualization of the article, verification of critical intellectual content, text editing, approval of the final version of the text of the manuscript

Konstantinova A.S. (ORCID ID: https://orcid.org/0000-0003-2617-9347): collecting and processing material, writing, interpreting and analyzing data, selecting literature, editing the article

Latypova A.A. (ORCID ID: https://orcid.org/0000-0002-9508-3878): Patient management in the clinic, idea and description of a clinical case, interpretation and analysis of data

Bagautdinova A.U. (ORCID ID: https://orcid.org/0000-0002-7021-7470): Patient management in the clinic, description of the clinical case, interpretation and analysis of the data, article editing

D.R. Safuanova. (ORCID ID: https://orcid.org/0000-0001-7944-8585): collecting and processing material, writing, interpreting and analyzing data, and translating into English

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Е.В. Шелеско, О.Э. Шарипов, Н.А. Черникова*, О.Н. Ершова, П.Л. Калинин, М.А. Кутин, Д.В. Фомичев

ФГАУ «Национальный медицинский исследовательский центр нейрохирургии им. акад. Н.Н. Бурденко» Минздрава России, Москва, Россия

ДИФФЕРЕНЦИАЛЬНЫЙ ДИАГНОЗ ПНЕВМОНИИ ПРИ НАЗАЛЬНОЙ ЛИКВОРЕЕ В УСЛОВИЯХ ПАНДЕМИИ COVID-19

E.V. Shelesko, O.E. Sharipov, N.A. Chernikova*, O.N. Ershova, P.L. Kalinin, M.A. Kutin, D.V. Fomichev

Federal State Autonomous Institution «N.N. Burdenko National Scientific and Practical Center for Neurosurgery» of the Ministry of Healthcare of the Russian Federation, Moscow, Russia

Differential Diagnosis of Pneumonia as a Complication of Nasal Liquorrhea in the Context of the COVID-19 Pandemic

Резюме

Назальная ликворея — истечение цереброспинальной жидкости из ликворных пространств полости черепа в полость носа или околоносовые пазухи вследствие наличия врожденного или приобретенного дефекта костей основания черепа и мозговых оболочек различной этиологии. Назальная ликворея приводит к потенциально смертельным осложнениям: менингит, менингоэнцефалит, пневмоцефалия, абсцесс мозга. Также при назальной ликвореи возможно возникновение менее опасных осложнений: аспирационного пневмонита и гастрита. В статье приводится случай аспирационного пневмонита у двух пациентов с назальной ликвореей, проходившими лечение в НМИЦН им. Н.Н. Бурденко во время пандемии COVID-19. Оба пациента отмечали профузный характер назальной ликвореи, жаловались на кашель в горизонтальном положении. В обоих случаях в ходе выполнения полимеразной цепной реакции РНК вируса (SARS-CoV-2) не обнаружена. Антитела (IgG, IgM) к коронавирусу не выявлены. На компьютерной томографии органов грудной клетки в обоих случаях выявлены участки затемнения по типу «матовое стекло». Так как данных за коронавирусную инфекцию не получено (отрицательные тесты на коронавирус, отсутствие антител), изменения в легких были интерпретированы как следствие постоянной аспирации ликвора. Пациентов госпитализировали в отдельную палату. Обоим пациентам проведена эндоскопическая эндоназальная пластика дефекта основания черепа. Послеоперационный период в обоих случаях протекал без особенностей. В обоих случаях пациенты выполнили через месяц компьютерную томографию органов грудной клетки. На снимках признаки поражения легочной ткани полностью регрессировали.

Ключевые слова: *назальная ликворея, дефект основания черепа, аспирационный пневмонит, основание черепа*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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*Контакты: Надежда Алексеевна Черникова, e-mail: Chernikhope@gmail.com
*Contacts: Nadezhda A. Chernikova, e-mail: Chernikhope@gmail.com
ORCID ID: https://orcid.org/0000-0002-4895-233X

Abstract

Nasal liquorrhea — the outflow of cerebrospinal fluid from the cerebrospinal fluid spaces of the cranial cavity into the nasal cavity or paranasal sinuses due to the presence of a congenital or acquired defect in the bones of the skull base and meninges of various etiologies. Nasal liquorrhea leads to potentially fatal complications: meningitis, meningoencephalitis, pneumocephalus, brain abscess. Also, with nasal liquorrhea, less dangerous complications may occur: aspiration bronchopneumonia and gastritis. The article presents a case of aspiration pneumonitis in two patients with nasal liquorrhea treated at the N.N. N.N. Burdenko during the COVID-19 pandemic. Both patients noted the profuse nature of the nasal liquorrhea, complained of coughing in a horizontal position. In both cases, no RNA virus (SARS-CoV-2) was detected during the polymerase chain reaction. Antibodies (IgG, IgM) to coronavirus were not detected. Computed tomography of the chest organs in both cases revealed areas of frosted glass darkening. Since no data was obtained for coronavirus infection (negative tests for coronavirus, lack of antibodies), changes in the lungs were interpreted as a consequence of constant aspiration of cerebrospinal fluid. The patients were admitted to a separate ward. Both patients underwent endoscopic endonasal plasty of the skull base defect. The postoperative period in both cases was uneventful. In both cases, the patients underwent computed tomography scan of the chest organs one month later. On the photographs, the signs of pneumontis completely regressed.

Key words: *nasal liquorrhea, skull base defect, aspiration pneumonitis, skull base*

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CT — computed tomography, TBI — traumatic brain injury

Introduction

Cerebrospinal fluid (CSF) rhinorrhea is the outflow of cerebrospinal fluid from the cerebrospinal fluid spaces of the cranial cavity into the nasal cavity or paranasal sinuses due to a congenital or acquired defect in the bones of the skull base and meninges of various etiologies [1].

CSF rhinorrhea leads to potentially fatal complications: meningitis, meningoencephalitis, pneumocephalus, brain abscess. CSF rhinorrhea can also cause less dangerous complications: aspiration pneumonitis and gastritis [2, 3]. With a pronounced outflow of cerebrospinal fluid in patients in a supine position, the cerebrospinal fluid often enters the lower respiratory tract through the nasal cavity and nasopharynx. In this case, aspiration pneumonitis occurs. Patients complain of cough that occurs mainly in the supine position [4].

Pneumonitis is a disease characterized by damage to the tissues that support the intralobular gas exchange and form pulmonary key structures — the alveoli. According to ICD-10, there are several types of pneumonitis:

J.67 — J.67.9 Hypersensitivity pneumonitis due to organic dust.

J68.0 Respiratory conditions due to inhalation of chemicals, gases, fumes and vapors.

J69 Pneumonitis due to solids and liquids.

The fundamental difference between pneumonitis and pneumonia is associated with etiology. In pneumonia, inflammation is caused by infectious agents such as bacteria, viruses, or fungi. The onset of pneumonitis is not associated with the above-listed infections, and inflammation is immunologically mediated [5]. Aspiration pneumonitis, triggered by the ingress of stomach contents into the lower respiratory tract (Mendelson syndrome) and also occurring after intubation, stands out [6]. In CSF rhinorrhea, cerebrospinal fluid enters the lungs in the supine position, which also causes symptoms of pneumonitis.

Differential diagnosis of pneumonitis is carried out with viral pneumonias, which are seasonal and occur mainly in winter. In December 2019, an epidemic of novel coronavirus disease caused by SARS-CoV-2 broke out in Wuhan (China) and rapidly spread across the world [7]. In February 2020 (02/12/2020), WHO officially named the infectious disease COVID-19 (Coronavirus disease 2019). The International Committee on Taxonomy of Viruses officially named the causative agent of the disease SARS-CoV-2 [8]. The main manifestation of the disease is pneumonia. There is also an asymptomatic or mild course with the involvement of the upper respiratory tract, which resolves within a week after infection [9]. According to the Internet resource https://www.worldometers.info/coronavirus as of January 31, 2021, the number of infected people exceeded 103 million; the death rate was approximately 2.2 million. In Russia, 3,850,439 cases of COVID-19 had been recorded; the death rate was 73,182 people [10].

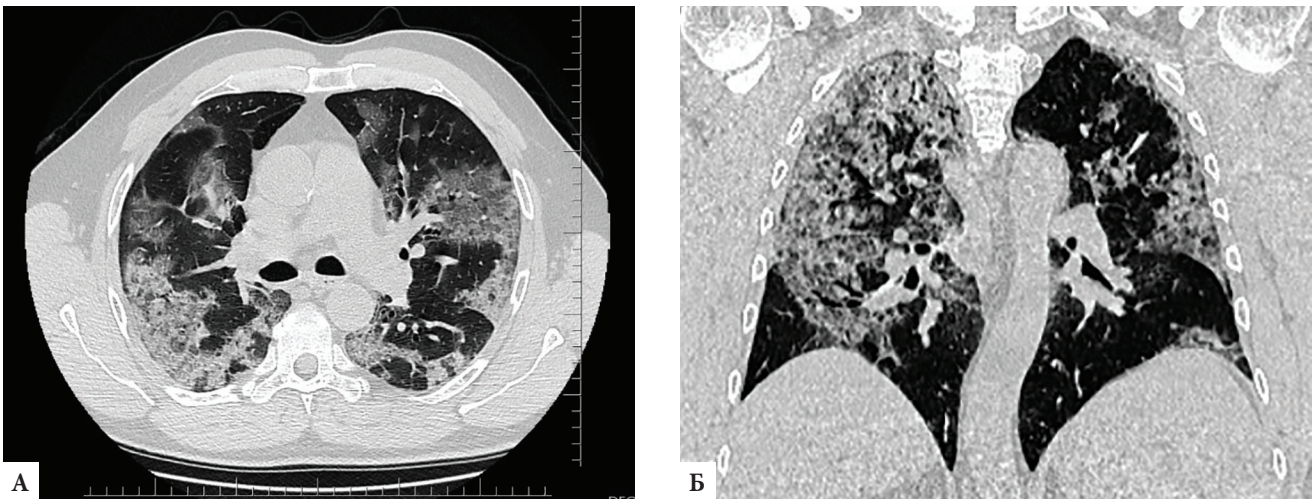


Figure 1 А, Б. *А — axial projection, Б — frontal projection. CT scan of the lungs of a patient with COVID-19 viral pneumonia*

Today, the gold standard for the diagnosis of COVID-19 is the polymerase chain reaction (PCR) for the detection of viral RNA with reverse transcription in real-time. Computed tomography (CT) data in patients with primary false-negative PCR results if COVID-19 is suspected, are an essential component of differential diagnosis [11, 12] (Fig. 1).

Case report № 1

Patient D. 67 years old; referred to N. N. Burdenko National Medical Research Center for Neurosurgery (N.N. Burdenko NMITsN) in May 2020 with complaints of a clear liquid discharge from the nose on the right when the head is tilted.

Past medical history: Hypertension stage II, grade 2, risk of cardiovascular complications, left ventricular myocardial hypertrophy. Chronic hyperplastic gastritis. Heart failure II FC, mitral regurgitation grade II-III, aortic regurgitation grade I-II, tricuspid regurgitation grade II, pulmonary hypertension grade II, diastolic dysfunction of the left ventricular myocardium degree I. The patient did not violate self-isolation restrictions, and had not been in contact with infectious patients. There were no COVID-19 cases in the family.

Medical history: According to the patient, about six months ago, he noted drip outflow of fluid from the nose when the head was tilted. After a month, the nasal discharge intensified. He was treated at the place of residence with a diagnosis of allergic rhinitis without effect. In June, he noted an episode of fever, 38-39 degrees, headaches. He was examined at the place of residence with suspected meningitis. Amoxicillin was empirically prescribed, with no beneficial effect. Magnetic resonance imaging identified a volumetric hypervascular formation of the chiasmatic-sellar region with infrasellar spread measuring 20 × 33 × 22 mm with sphenoid bone destruction. The meningitis diagnosis was not confirmed. The patient was referred to N.N. Burdenko NMITsN to determine the further therapeutic approach.

Neurological examination during the follow-up examination at the Neurosurgery Center identified no abnormalities. PCR identified no virus (SARS-CoV-2) RNA. Coronavirus antibodies (IgG, IgM) were also negative. Computed tomography of thoracic organs was performed. It identified infiltrative changes in the lower lobes of the lungs on both sides. Ground-glass opacity areas were seen on the right, in the lower segments. Calcifications were identified in the 6th segment of the right lung. The roots of the lungs were not dilated. No fluid in the pleural cavity was found. No diaphragm changes. The mediastinum was not displaced.

Complete blood count: white blood cell count is 4.35 10*9/l, neutrophils 72.4%, immature granulocytes 1.1%, lymphocytes 0.85 10*9/l. C-reactive protein was less than 5 mg/ml. The patient had a negative PCR test for coronavirus.

Given the chronic nature of CSF rhinorrhea, CT changes in the lungs may be due to the ingress of cerebrospinal fluid into the lungs. However, given the low lymphocytes in the blood, these changes are highly likely associated with SARS-CoV-2 viral pneumonia. It was decided to postpone the surgery by 10-14 days in order to assess CT changes over time and take repeated tests for coronavirus (swabs from the throat and nose, blood tests for IgM and IgG), followed by a decision regarding the patient's hospitalization at the Neurosurgery Center.

The patient was examined by an Infectious Disease physician at the place of residence. Laboratory tests for

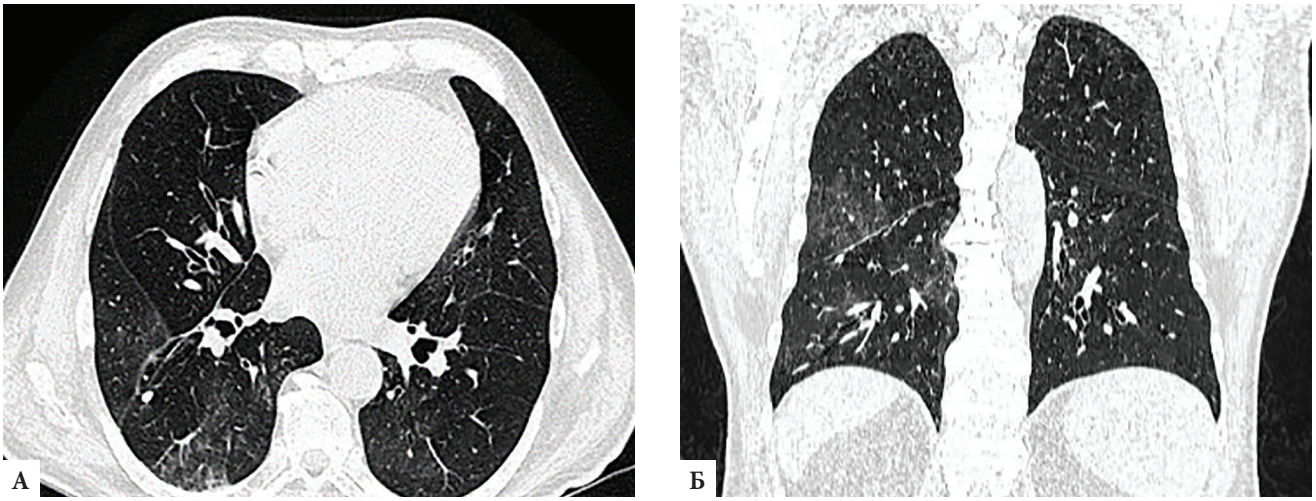


Figure 2 А, Б. *А — axial projection, Б — frontal projection. CT of the first patient's lungs before surgery. Multiple frosted glass areas are noted*

COVID-19, found no SARS-CoV-2 RNA and IgM and IgG antibodies to SARS-CoV-2.

A repeated CT scan of the lungs was performed 16 days later; it showed multiple focal infiltrative changes without changes compared with the previous examination (Fig. 2А, Б).

Repeated sampling and exam of biomaterial was carried out: SARS-CoV-2 viral RNA was not detected.

In view of such inconclusive data, a consultation was held with the chief physician, epidemiologist, therapist, anesthesiologist and neurosurgeons. Since no data were obtained for coronavirus (negative tests for coronavirus, no antibodies), the changes in the lungs were interpreted as a consequence of constant aspiration of cerebrospinal fluid. The patient was admitted to a separate ward. The diagnosis was made: Complex skull base defect in the sphenoid sinus area. Spontaneous CSF rhinorrhea on the right. Aspiration pneumonitis.

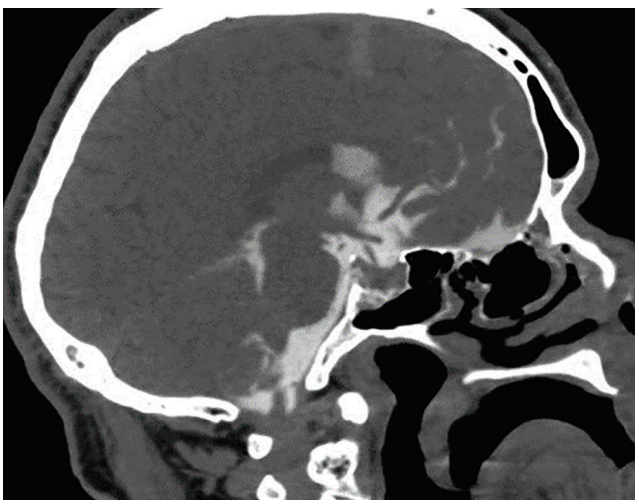


Figure 3. *CT cisternography. Frontal projection. Defect in the area of the Turkish saddle*

Before the surgery, CT cisternography was performed, which showed a defect in the base of the skull in the sella turcica area (Fig. 3).

Treatment progress:

The patient underwent surgery for "Endoscopic endonasal transphenoidal removal of an endosellar pituitary tumor, plastic closure of two CSF fistulas in the area of the sella turcica and posterior cells of the ethmoid bone on the right with auto- and allomaterials".

The postoperative period was satisfactory. Somatic and neurological status in the postsurgical period had no negative changes. In the early postsurgical period, there were no signs of CSF rhinorrhea. The patient was discharged from the hospital on the 9th day after the surgery.

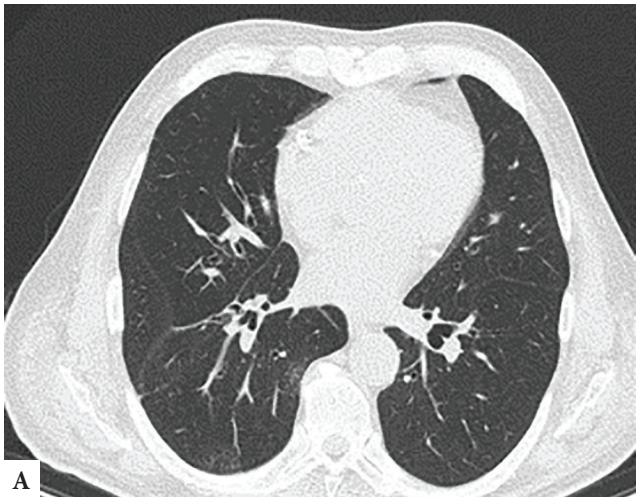
The histological report confirmed the diagnosis of pituitary adenoma.

One month after the surgery, the patient underwent follow-up CT of the chest: the signs of lung damage regressed completely (Fig. 4).

Case report № 2

Patient F., 40 years old, examined at N.N. Burdenko NMITsN for recurrent CSF rhinorrhea.

Medical history. The patient considers himself ill since August 2019, when a liquid discharge from the left side of the nose began for no apparent reason. He visited an otorhinolaryngologist at his place of residence, and was diagnosed with spontaneous CSF rhinorrhea. He underwent treatment in the center, where he underwent surgery for "Endoscopic endonasal plasty of the



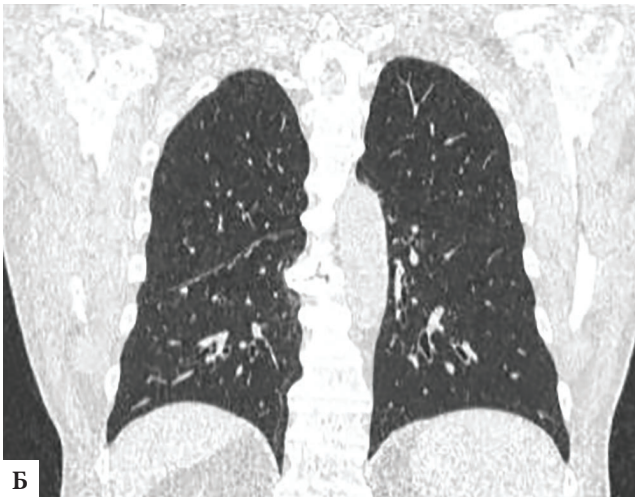


Figure 4 А, Б. *А — axial projection, Б — frontal projection. CT of the lungs one month after surgery*

skull base defect in the area of the lateral recess of the sphenoid sinus on the right". After the surgery he felt well, there was no leak. However, three months after the surgery, he noted a transparent discharge from the nose on the right when the head was tilted. He noted a cough at night and headaches. He visited N.N. Burdenko NMITsN with these signs for repeated surgical treatment. The otorhinolaryngologist's examination showed: Profuse CSF rhinorrhea. Defect in the area of the lateral recess of the sphenoid sinus on the right (Fig. 5).

Past medical history: Traumatic brain injury (TBI) 20 years ago, epilepsy. Degree I obesity.

During examination for hospitalization, the patient was twice tested for SARS-CoV-2 by PCR — no coronavirus RNA was detected. The computed tomography of the thoracic organs showed a pattern of infiltrative changes in the lower lobes of the lungs. No coronavirus antibodies were found. Clinical blood count and biochemical assay were normal. The patient showed no signs of intoxication. No enlargement of peripheral lymph nodes.

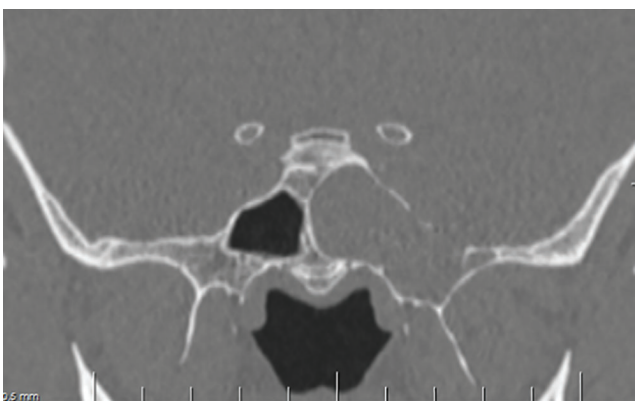


Figure 5. *CT of the brain, frontal projection. Defect of the skull base in the area of the lateral pocket of the sphenoid sinus on the left*

A consultation was held with the chief physician, epidemiologist, anesthesiologist, therapist, neurosurgeons, otorhinolaryngologists. Taking into account the profuse nature of liquorrhea, the inflammatory changes on CT were regarded as a consequence of aspiration pneumonitis due to the leak of cerebrospinal fluid into the lungs (Fig. 6).

Due to the lack of laboratory data for coronavirus (negative tests for coronavirus, lack of antibodies) and the absence of contraindications for anesthesia and surgical treatment, the patient was admitted to the hospital into a separate ward.

Treatment progress:

The patient underwent surgery for "Endoscopic endonasal plasty of the skull base defect in the area of the lateral pocket of the sphenoid sinus using autografts".

The postoperative period was satisfactory. Somatic and neurological status in the postsurgical period had no negative changes. In the early postsurgical period, there were no signs of CSF rhinorrhea. The patient was discharged for outpatient supervision on the 5th day after the surgery.

In the late postsurgical period (one month after the operation), signs of pneumonia according to the CT scan of thoracic organs had completely regressed. Antibodies to SARS-CoV-2 were not detected (Fig. 7).

Discussion

Aspiration is defined as the accidental ingress of oropharyngeal or gastric contents or fluid and particulate matter into the lower respiratory tract. The clinical response to aspiration depends on the nature of the aspirated material, microbiocenosis of the respiratory mucosa and colonization by pathogenic microflora [13, 14].

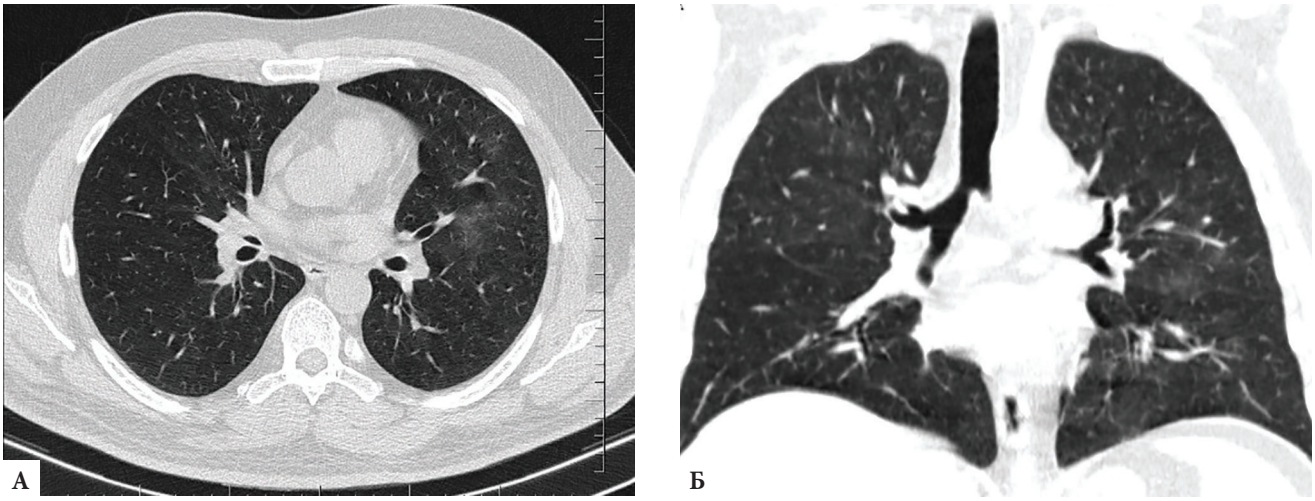


Figure 6 А, Б. *А — axial projection, Б — frontal projection of CT of the chest organs before surgery. There are multiple areas of frosted glass darkening in the left lung*

With profuse CSF rhinorrhea, cerebrospinal fluid may enter the bronchi, which can cause irritation in the respiratory tract. Although patients with skull base defects often complain of cough in the supine position, the literature has very few cases of pneumonitis as a complication of CSF rhinorrhea [15]. In 2016, Justin Seltzer et al. [16] published the first paper devoted to this condition. Until then, this complication was cited in the analysis of series of CSF rhinorrhea treatment cases. However, the diagnostic signs and methods of treatment of aspiration pneumonitis were not described. This is probably because this complication of CSF rhinorrhea was previously underestimated in clinical practice. However, it has acquired particular relevance in the context of the SARS-CoV-2 pandemic.

According to the etiology, CSF rhinorrhea can be spontaneous and traumatic [17]. Traumatic CSF rhinorrhea is associated with traumatic brain injury, and in 80% of cases, it ceases within the first two weeks. Also, traumatic liquorrhea includes liquorrhea arising from various surgical procedures [18]. In spontaneous CSF rhinorrhea, pathogenesis is associated with many factors, such as high body mass index (BMI), intracranial hypertension, empty sella syndrome, and arachnoid granulation [20]. Our patients were overweight. Also, the second patient showed signs of arachnoid granulations on CT. Obesity is accompanied with a decrease in the level of growth hormone, which leads to an increase in leptin secretion, which in turn induces osteopenia. Patients with metabolic syndrome also have a high level of cortisol, testosterone, and norepinephrine. These endocrine changes result in impaired calcium homeostasis, osteoblast function and, ultimately, bone demineralization and the development of osteoporosis, accompanied with skull base bones destruction [21].

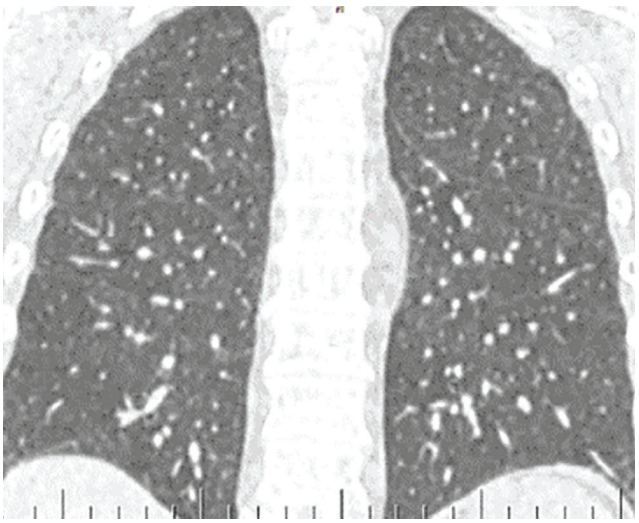


Figure 7. *CT of the lungs one month after surgery, frontal view*

Obesity directly affects the physiology of respiration by increasing the mass and reducing the compliance of the chest walls with the deposition of fat around the ribs, which significantly complicates inhalation. Fat deposition in the mediastinum also limits the lung mobility. With excessive fat deposition in the abdominal cavity, diaphragm dysfunction develops, which is expressed in the disproportion of the ratio between the length and tension of muscle fibers due to their overstretching, which limits the excursion of the diaphragm [22, 23]. All these factors decrease lung volume, especially the expiratory reserve volume (ERV) and functional reserve capacity, which play an important role in maintaining the patency of the distal airways. Therefore, the risk of aspiration pneumonitis in patients with spontaneous liquorrhea is significantly higher than in patients with traumatic liquorrhea [24].

Lung X-ray is used to diagnose pneumonitis. In this case, there is a characteristic localization in the posterior segments of the upper lobes and the upper segments of the lower lobes [25].

COVID-19-induced changes in the lungs are quite variable. However, most authors agree that the most frequent, and at the same time, the most characteristic changes are the "ground-glass" parenchyma compactions (single or multiple), as well as a combination of these changes with consolidation and/or with reticular changes (cobblestone changes) [26]. Most often, pneumonia data manifest on CT as bilateral changes with predominantly subpleural localization in the absence of pleural effusion. In this case, the dorsal arrangement of changes with the involvement of several lobes of the lungs, mainly the lower lobes, is the most typical. In our case, the patient had a ground-glass symptom. However, this symptom is not pathognomonic, but is an indicator of lung tissue density and is a sign of the interstitial nature of infiltration. "Ground glass" is represented by a certain area in which there is a moderately reduced respiratory tissue airiness. The causal factor for this phenomenon is the thickening of the interalveolar septa, as well as the partial filling of the alveoli with contents [27, 28].

According to the literature, no special treatment of pneumonitis with CSF rhinorrhea is required. The symptoms quickly regress after the successful closure of the CSF fistula [29]. Maya Or et al. in 2020 published a paper on aspiration pneumonitis in CSF rhinorrhea [30]. In their series of cases, respiratory symptoms were identified in 6 out of 20 patients with CSF rhinorrhea. The authors report that after the skull base defect plasty, the respiratory symptoms completely regressed without antibacterial treatment.

The Neurosurgery Center continued to provide high-tech medical care to patients at high risk of COVID-19. To reduce and prevent the intrahospital spread of infection among patients, an algorithm was developed. It takes into account data from the epidemiological history, close contact with COVID-19 patients, laboratory data (PCR for SARS-CoV-2 virus RNA) and prehospitalization lung CT data (Table 1).

Table 1. *Algorithm for making a decision on hospitalization of patients*

№	RNA	CT	Epidanamnesis	Clinic	Decision
1.	**NOT detected** RNA SARS-CoV-2 by PCR method with a prescription of material sampling 48 hours before hospitalization	There are no data for viral pneumonia on the CT scan of the chest organs 7 days before hospitalization	There is no contact with patients with COVID-19 for 14 days before hospitalization	There are no clinical signs of the disease	**Hospitalization possible**
2.	SARS-CoV-2 RNA was NOT detected by PCR method with a prescription of material 48 hours before hospitalization	There is evidence for viral pneumonia on the CT scan of the chest organs with a prescription of 7 days before hospitalization	History of transferred COVID-19, there is the presence of IgG antibodies in the blood	There are no clinical signs of the disease	Hospitalization postponed In the future, hospitalization is possible with two negative tests for SARS-CoV-2 by PCR with an interval of 1 day and positive dynamics on the CT scan of the chest organs after 10 days.
3.	SARS-CoV-2 RNA was NOT detected by PCR method with a prescription of material 48 hours before hospitalization	There is evidence for viral pneumonia on the CT scan of the chest organs with a prescription of 7 days before hospitalization	There are no indications of postponed COVID-19 in the anamnesis	There are no clinical signs of the disease	Hospitalization postponed and the patient is sent for observation to a medical organization at the place of residence with a recommendation to perform a test for antibodies of class M and G and repeat the CT scan of the chest organs in dynamics for 10 days.
4.	Detected RNA SARS-CoV-2 by PCR with a prescription of material sampling 48 hours before hospitalization	There are no data for viral pneumonia on the CT scan of the chest organs 7 days before hospitalization	There are no indications of postponed COVID-19 in the anamnesis	There are no clinical signs of the disease	Hospitalization postponed and the patient is sent for observation to a medical organization at the place of residence with a recommendation to undergo a full examination for COVID-19. Further hospitalization is possible no earlier than 4-5 weeks in the absence of a clinical picture and two negative tests for SARS-CoV-2 by PCR with an interval of 1 day and repeated CT scan of the chest organs.
5.	A test for SARS-COV-2 by PCR has been passed, the result will be ready the next day	There are no data for viral pneumonia on the CT scan of the chest organs 7 days before hospitalization	There are no indications of postponed COVID-19 in the anamnesis	The patient is in a serious or extremely serious condition due to the underlying disease.	The patient can be hospitalized in a separate ward of the department, strictly isolated with an accompanying person until the test result is obtained. Upon receiving a positive test for SARS-CoV-2, the patient is transferred to a specialized hospital for the treatment of COVID-19

In the case of CSF rhinorrhea, chest CT may detect aspiration pneumonitis. In this case, the PCR for coronavirus is advisably performed at least twice. If both tests are negative and there are no clinical symptoms of COVID-19 and no contraindications for general anesthesia and surgical intervention, the patient may be hospitalized in a separate ward for plastic closure of the skull base defect.

Conclusions

The changes in the lungs in patients with CSF rhinorrhea are the result of cerebrospinal fluid aspiration. In this case, the changes can be manifested by a short-term focal ground-glass opacity pattern due to the partial filling of the alveoli with fluid without any clinical signs.

In such cases, patients should undergo PCR for detection of SARS-CoV-2 virus RNA at least twice and computed tomography of the chest. If signs of ground-glass opacity are detected, it is recommended to postpone the surgery by 10–14 days in order to assess these changes in computed tomography in real-time and re-test for coronavirus to exclude the viral nature of lung damage.

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Шелеско Е.В. (ORCID http://orcid.org/0000-0002-8249-9153): концепция и дизайн, написание текста

Шарипов О.И. (ORCID http://orcid.org/0000-0003-3777-5662): концепция и дизайн, редактирование

Черникова Н.А. (ORCID http://orcid.org/0000-0002-4895-233X): написание текса, сбор и анализ информации

Ершова О.Н. (ORCID http://orcid.org/0000-0001-9658-807X): редактирование

Калинин П.Л. (ORCID http://orcid.org/0000-0001-9333-9473): редактирование

Кутин М.А. (ORCID http://orcid.org/0000-0002-6520-4296): концепция и дизайн, редактирование

Фомичев Д.В. (ORCID http://orcid.org/0000-0002-5323-1000): редактирование

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Shelesko E.V. (ORCID http://orcid.org/0000-0002-8249-9153): concept and design, text writing

Sharipov O.I. (ORCID http://orcid.org/0000-0003-3777-5662): concept and design, editing

Chernikova N.A. (ORCID http://orcid.org/0000-0002-4895-233X): text writing, collection and analysis of information

Ershova O.N. (ORCID http://orcid.org/0000-0001-9658-807X): editing

Kalinin P.L. (ORCID http://orcid.org/0000-0001-9333-9473): editing

Kutin M.A. (ORCID http://orcid.org/0000-0002-6520-4296): concept and design, editing

Fomichev D.V. (ORCID http://orcid.org/0000-0002-5323-1000): editing

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