Научно-практический журнал для работников здравоохранения

Включён в Перечень ведущих рецензируемых периодических изданий ВАК Минобрнауки РФ

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE

www.medarhive.ru

ИЮНЬ 2022 (№ 3(65))

УЧРЕДИТЕЛЬ И ИЗДАТЕЛЬ
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
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Верстка
Виталий Котов

Отдел распространения и рекламы
Бабяк Алина
reklama@medarhive.ru

Подписано в печать 29.04.2022 года
Тираж 3000 экземпляров.

Издание зарегистрировано в Федеральной службе по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор).

Свидетельство о регистрации
ПИ № ФС77-45961 от 26 июля 2011 г.

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Отпечатано в типографии «Onebook.ru»
ООО «Сам Полиграфист»
г. Москва, Волгоградский проспект, д. 42, корп. 5
www.onebook.ru

Журнал включен в Российский индекс научного цитирования (РИНЦ)

Статьи журнала представлены в Российской универсальной научной электронной библиотеке www.elibrary.ru

Подписной индекс в каталоге «Почта России» 87732

DOI: 10.20514/2226-6704-2022-3

Scientific and practical journal for health professionals

Included the List of the Russian reviewed scientific magazines in which the main scientific results of theses on competition of academic degrees of the doctor and candidate of science have to be published.

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE
www.medarhive.ru
JUNE 2022 (№ 3(65))

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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PAGE-PROOFS
Kotov Vitaly

ADVERTISING
Babiak Alina
reklama@medarhive.ru

Signed for printing on 29.04.2022
Circulation 3000 exemplars

It is registered by state committee of the Russian Federation on the press

The certificate on registration of mass media ПИ № ФС77-45961, 26 July 2011

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Printed «Onebook.ru»
«Sam Poligrafist»
Moscow, Volgograd Prospect, 42-5
www.onebook.ru

The journal is included in Russia Science Citation Index (RSCI)

Journal data are published on website of Russian General Scientific Electronic Library www.elibrary.ru

Subscription index in the catalogue «Russian Post» 87732

DOI: 10.20514/2226-6704-2022-3

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DOI: 10.20514/2226-6704-2022-12-3-165-174 УДК 616.132.2-007.271-089.81-06:616.127-005.4

А.И. Абдрахманова*[1,2], Н.А. Цибулькин[3], Н.Б. Амиров[1,4,5], И.М. Хабибуллин[2], Л.И. Горнаева[2], Л.А. Галимзянова[2], Д.С. Елагина[1]

[1]— ФГАОУ ВО «Казанский (Приволжский) федеральный университет» кафедра Фундаментальных основ клинической медицины, Казань, Россия
[2]— ГАУЗ «Межрегиональный клинико-диагностический центр», отделение кардиологии, Казань, Россия
[3]— ФГБОУ ДПО «Российская медицинская академия непрерывного профессионального образования» Минздрава России, кафедра кардиологии, рентгенэндоваскулярной и сердечно — сосудистой хирургии, Казань, Россия
[4]— ФГБОУ ВО «Казанский государственный медицинский университет» Минздрава России, кафедра поликлинической терапии и общей врачебной практики, Казань, Россия
[5]— МСЧ МВД России по РТ, Казань, Россия

БЕЗБОЛЕВАЯ ИШЕМИЯ МИОКАРДА У ПАЦИЕНТОВ ПОСЛЕ ПРОВЕДЕННОГО ЧРЕСКОЖНОГО КОРОНАРНОГО ВМЕШАТЕЛЬСТВА

A.I. Abdrahmanova*[1,2], N.A. Tsibulkin[3], N.B. Amirov[1,4,5], I.M. Khabibullin[2], L.I. Gornaeva[2], L.A. Galimzyanova[2], D.S. Elagina[1]

[1]— Kazan Federal University, Kazan, Russia
[2]— GAUZ "Interregional Clinical Diagnostic Center", Kazan, Russia
[3]— Kazan State Medical Academy, Kazan, Russia
[4]— Kazan state medical university, Kazan, Russia
[5]— MSU MVD, Kazan, Russia

Silent Myocardial Ischemia in Patients after Permanent Coronary Intervention

Резюме

По данным литературы были проанализированы частота и срок возникновения ишемии миокарда, в том числе безболевой ишемии, у пациентов после проведенного чрескожного коронарного вмешательства. Фактором риска возникновения рестеноза стента у пациентов после чрескожного коронарного вмешательства является безболевая ишемия миокарда. Наличие безболевой ишемии миокарда само по себе может указывать на степень тяжести органических изменений в коронарных артериях. Следствием этого является необходимость выявления рестеноза, которое может осуществляться с помощью нагрузочных проб с визуализацией. Данные пробы также помогают выявить ишемию миокарда и скрытую коронарную недостаточность. Безболевая ишемия миокарда обнаруживается у четверти пациентов после чрескожного коронарного вмешательства. Безболевой инфаркт миокарда составляет 22-78 % от всех инфарктов после чрескожного коронарного вмешательства. Для определения наличия ишемии миокарда, в том числе скрытой коронарной недостаточности, а также с целью своевременной диагностики рестеноза и снижения частоты осложнений, могут быть использованы диагностические нагрузочные пробы, в частности, однофотонная эмиссионная компьютерная томография. Ее использование может быть целесообразно для выявления пациентов с высоким риском развития рестеноза, определения показаний к проведению повторного чрескожного коронарного вмешательства, а также для оценки прогноза после реваскуляризации. При отсутствии клинической симптоматики коронарной

Контакты: Алсу Ильдусовна Абдрахманова, e-mail: alsuchaa@mail.ru
*Contacts: Alsu I. Abdrahmanova, e-mail: alsuchaa@mail.ru
ORCID ID: https://orcid.org/0000-0003-0769-3682

недостаточности после чрескожного коронарного вмешательства, пробы с физической нагрузкой рекомендуется проводить в первые два года после реваскуляризации. Пробы с физической нагрузкой необходимо проводить в более ранние сроки при следующих условиях: наличие высокого сердечно-сосудистого риска, неполная или субоптимальная реваскуляризация, стентирование коронарной артерии малого диаметра, бифуркационное или устьевое стентирование. Своевременная диагностика безболевой ишемии миокарда с помощью однофотонной эмиссионной компьютерной томографии у пациентов, перенесших чрескожное коронарное вмешательство, является важной задачей клинической практики.

Ключевые слова: *безболевая ишемия миокарда, чрезкожное коронарное вмешательство*

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

Статья получена 20.05.2021 г.

Принята к публикации 07.04.2022 г.

Для цитирования: Абдрахманова А.И., Цибулькин Н.А., Амиров Н.Б. и др. БЕЗБОЛЕВАЯ ИШЕМИЯ МИОКАРДА У ПАЦИЕНТОВ ПОСЛЕ ПРОВЕДЕННОГО ЧРЕСКОЖНОГО КОРОНАРНОГО ВМЕШАТЕЛЬСТВА. Архивъ внутренней медицины. 2022; 12(3): 165-174. DOI: 10.20514/2226-6704-2022-12-3-165-174. EDN: DNDKCS

Abstract

Frequency and timing of appearance of myocardial ischemia, including silent ischemia, were analyzed in published scientific sources. Silent myocardial ischemia is risk factor for stent restenosis after percutaneous coronary interventions. Patients with silent ischemia lack clinical symptoms while perfusion, metabolic and electrical activity of their myocardium may be compromised. These patients do not have warning clinical symptoms during physical exercise and do not stop inappropriate activity. Silent myocardial ischemia itself can indicate severity of atherosclerosis in coronary arteries. High probability of stent restenosis can be assessed by exercise tests prior to coronary angiography. These tests also allow to reveal clinically silent myocardial ischemia. Quarter of patients after coronary intervention develop silent myocardial ischemia. Silent myocardial infarction comprises 22-78 % of all infarctions after coronary interventions. Exercise tests based on single-photon emitting computed tomography can be used in diagnosing stent restenosis, silent ischemia and assessment of cardiovascular risk in patients after coronary interventions. Its results can be used as indications for repeated coronary interventions and for prognosis after revascularization. Exercise tests are recommended in two years after revascularization in absence of ischemic symptoms. Early tests are recommended in cases of high cardiovascular risk, suboptimal revascularization, stenting of arteries with small diameter or at bifurcation. Diagnosis of silent myocardial ischemia by single-photon emitting computed tomography in patients after coronary revascularization is significant for clinical practice.

Key words: *silent myocardial ischemia, percutaneous coronary intervention*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 20.05.2021

Accepted for publication on 07.04.2022

For citation: Abdrahmanova A.I., Tsibulkin N.A., Amirov N.B. et al. Silent Myocardial Ischemia in Patients after Permanent Coronary Intervention. The Russian Archives of Internal Medicine. 2022; 12(3): 165-174. DOI: 10.20514/2226-6704-2022-12-3-165-174. EDN: DNDKCS

24h ECG — 24h Holter ECG monitoring, CAG — coronary angiography, CHD — coronary heart disease, CKD — chronic kidney disease, DM — diabetes mellitus, ECG — electrocardiography, EchoCG — echocardiography, EF — ejection fraction, EL — exercise load, LV — left ventricle, MI — myocardial infarction, MRI — magnetic resonance imaging, PCI — percutaneous coronary intervention, PET — positron emission tomography, RF — radiopharmaceuticals, SCD — sudden cardiac death, SMI — silent myocardial ischemia, SPECT — single-photon emission computed tomography, stress echo — stress echocardiography

Introduction

Percutaneous coronary intervention (PCI) is widely used in the management of coronary heart disease (CHD). Its effectiveness is assessed by the elimination of episodes of myocardial ischemia, both painful and silent. Patients with silent myocardial ischemia (SMI) have no clinical manifestations, i.e. angina attacks or any equivalents, with underlying impaired perfusion, metabolism, function and electrical activity of the myocardium. In this regard, patients with SMI after PCI cannot control their level of physical activity because they have no pain as a limitation. Patients do not attempt to avoid factors that can lead to an angina attack or its equivalent. If patients have no clinical manifestations of disease progression, they may have no need to seek medical help. Therefore, the necessary treatment is not conducted on time. SMI leads to a worse prognosis in patients after PCI, with increased risk of myocardial infarction (MI) and sudden cardiac death (SCD) [1–4].

Myocardial ischemia after PCI and risk factors for restenosis

Restenosis is one of the complications after PCI. In patients without SMI, it is accompanied by the recurrence of angina pain or other clinical signs. Several factors that have an effect on the increase in the incidence of restenosis have been identified. They include: age, female sex, history of several diseases (diabetes mellitus (DM), chronic kidney disease (CKD), etc.), allergic reactions to metals, polymers and drugs, structural features of coronary vessels (stenting of small-diameter arteries), zones of atherosclerotic lesions (bifurcation or ostial stenting), etc. [5, 6].

A number of studies included the follow-up of patients who underwent PCI. Within two years, recurrences of myocardial ischemia were observed, which manifested as exertional angina, isolated SMI, or their combination. SMI was detected in 22.2 % of all patients with recurrent ischemia during exercise tolerance tests (EL). In rare cases, MI developed. In addition, recurrences of myocardial ischemia occurred more often during 3–8 months after PCI. If this process was due to stent restenosis, the recurrence developed earlier, within 3–6 months after PCI [7]. During 24h Holter monitoring (24h ECG), ischemic episodes were detected in 72 % of cases: 17 % of patients had only episodes of ischemia with classical signs of angina; 15 % had only silent episodes of ischemia (SMI type I). 40 % of patients had a combination of silent and painful ischemia (SMI type II) [8, 9].

After successful PCI, 14 % of patients showed signs of MI in the area of blood supply to the target vessel during exercise tolerance tests after six months of follow-up. Patients with SMI had a lower threshold of exercise load, which led to ischemia, compared to patients with angina without SMI episodes. The time of the onset of symptoms associated with stent restenosis after its placement ranged from 3 to 12 months; the average period of the development of stent restenosis after PCI was six months [10, 11]. Restenosis rates were found to range from 3 % to 20 % for drug-eluting stents and from 16 % to 44 % for non-drug-eluting stents. These data were obtained over a follow-up period of 3 to 20 months after stent placement [12].

The incidence of restenosis was 8–12 % in the period of 6 to 9 months after angioplasty, while three variants of ischemia recurrence were revealed: a pain attack, or SMI, or their combination [13]. Even after effective myocardial revascularization with a significant increase and stabilization of exercise tolerance, one year later, 54 % of the followed-up patients demonstrated an increase in the number of episodes, duration, and total index of painful ischemia and SMI compared with the results of examination one month after PCI with stenting [14].

Results of the 24h ECG in ten days and in three months after PCI were of prognostic value. Episodes of ischemia during these periods correlate with the increased incidence of CHD complications during one year of follow-up [15–17]. In a quarter of patients after PCI, restenosis may not be diagnosed in a timely manner due to the development of SMI [18].

According to 24h ECG results, in the group of patients with CHD who underwent stenting, SMI was detected in 6.6 % of cases after six months. According to the results of coronary angiography (CAG) in these patients, stent restenosis was found, which led to repeated stenting (stent-in-stent placement) [19].

The prevalence of silent MI after PCI is not fully understood. According to one study, silent MI (SMI) occurs in 3.7 % of patients [16]. A multicenter study was conducted, which included 15,991 patients who underwent PCI. Within two years after PCI, Q-wave MI was confirmed in 186 (1.16 %) patients; most cases (78 %) were classified as SMI due to the absence of clinical signs [20]. The actual incidence of SMI in this study was 0.9 %, which is four times lower than in the previous study. This difference is probably related to the follow-up period, which was limited to two years after PCI. Over time, the frequency of detection of MI, including silent MI, in patients increases [21, 22].

Patients with SMI found before PCI belong to a separate group. Clinical predictors of delayed adverse cardiovascular events in these patients remain unclear. The most common late events in this group of patients are acute coronary syndromes with and without ST elevation, revascularization, thrombosis of a previously placed stent, hospitalization for heart failure, and all-cause mortality. In their 2019 study that included follow-up for one and a half years, Doi S. et al. found late cardiovascular events in 10–15 % of cases; more than 60 % of them were due to repeated revascularization [23].

Factors of the development of late cardiovascular events in patients with SMI are CKD and DM, which increase the risk by more than eight times. CKD or DM can be an indicator of late adverse cardiovascular events in silent myocardial ischemia, even after a successful PCI [10, 23]. In patients who initially had SMI, even after a successful PCI and with complete or partial revascularization, there is a risk of SMI recurrence. It was found that after PCI, ischemia was found in one in every five patients with DM, and in half of the cases, it was silent [24].

Imaging methods used for the diagnosis of myocardial ischemia after PCI

When the myocardium is damaged due to its ischemia, the following pathological processes develop: perfusion heterogeneity, metabolic disorders, diastolic and systolic dysfunction of the left ventricle (LV), pathological changes according to electrocardiography (ECG) results. Then, the clinical presentation of angina or its equivalents develops.

In patients who underwent PCI, myocardial imaging should be performed with exercise tolerance tests. Non-invasive exercise tolerance tests help identify transient myocardial ischemia in a patient based on ECG changes, LV wall motion abnormalities on stress echo (stress echocardiography) or magnetic resonance imaging (MRI), or based on the occurrence/deterioration of myocardial perfusion, which can be detected during single-photon emission computed tomography (SPECT), positron emission tomography (PET), EchoCG with contrast enhancement, or MRI with contrast enhancement [25, 26].

Stress echo helps detect local contractility disorders associated with myocardial ischemia [27], while the location of the area of cardiac muscle contractility disorders most often corresponds to the areas of blood supply of the affected coronary artery. This method is helpful due to the detection of emerging impairments of regional contractility in short-term ischemia [28]. The following are key benefits of stress echo: imaging of each LV segment; assessment of changes during the test; multiple Echo-CG parameters of regional and global contractility; mobility of advanced ultrasonic devices; non-invasiveness; safety; good tolerance by patients; absence of ionizing radiation; the possibility of conducting repeated examination; relatively low cost. Sensitivity of stress echo with exercise load is 80–85 %, and its specificity is 80–88 % [27]. Shortcomings of stress echo include the poor quality of imaging heart structures in a number of patients; the human factor when processing the results; the quality of ultrasound imaging during the test; possible insufficient skills of the person conducting the test. To improve the quality of the visualization of the endocardium, special contrast agents are used ("microbubbles" coated with albumin, lipids or other polymers) [28]. The problem of the human factor in analyzing the results of stress echo can be solved with the help of tissue Doppler sonography [29, 30]; its results depend on the scanning angle, movement of neighboring myocardial regions, as well as movement of the entire heart. The possibility of analyzing myocardial deformation based on the speckle-tracking technique, which does not have the disadvantages of tissue Doppler sonography, for the quantitative assessment of myocardial kinetics during stress echo has been studied in recent years [31–33]. A description of stress echo is given in Figure 1.

Cardiac MRI is the method that allows determining the volume of heart cavities, the amplitude of movement of sections of the heart muscle, and ejection fraction. The resolution of this imaging method increases during exercise tolerance tests. The myocardial inotropic reserve is assessed via MRI and dobutamine test. The accuracy of examination increases with contrast enhancement. The sensitivity of stress perfusion MRI is 89 %, specificity — 80 %. New impairments of LV wall contractility (in three of 17 segments) or perfusion defect >10 % (more than two segments) may indicate a high risk of complications. The benefits of stress MRI include high spatial resolution and good reproducibility. Stress MRI is used in individuals with poor cardiac imaging on Echo-CG. MRI has contraindications, such as claustrophobia in a patient or foreign metal objects in the patient's body [34]. A description of MRI is given in Figure 2.

SPECT and PET help visualize the entire spectrum of myocardial viability: irreversible changes (postinfarction cardiosclerosis, fibrosis), transient ischemia, hibernation and myocardial stunning processes. CT absorption correction and the most advanced software improve image quality, allowing the visualization of increasingly small perfusion impairments [34].

The great significance of SPECT in the comprehensive analysis of the state of the heart muscle has been proven [35–37]. It helps find the first signs of impaired metabolism, perfusion, myocardial viability in the absence of angina attacks or their equivalents in a patient. Ischemia or damage to the myocardium leads to areas of reduced accumulation — perfusion defects. Synchronization with the patient's ECG allows using SPECT to observe the movement of myocardial walls depending on the phases of the heart cycle and assess the functional state of the LV myocardium, obtain additional information about the presence of reversible myocardial dysfunction

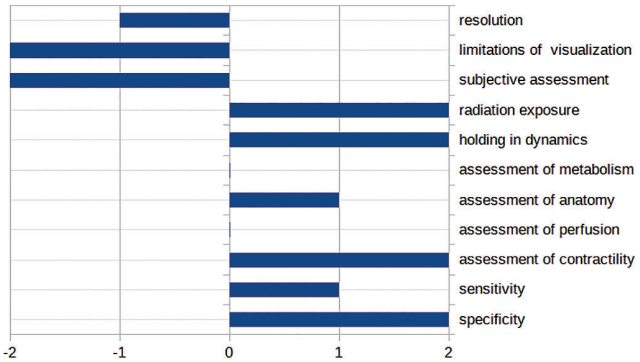


Figure 1. *Characterization of Stress-EchoCG*
Note: severe advantage: +2 points, moderate advantage: +1 point, moderate disadvantage: -1 point, significant disadvantage: -2 points, no sign: 0 points (this function is absent)

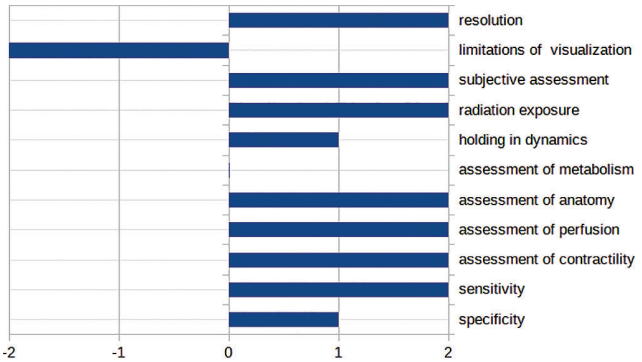


Figure 2. *Characterization of MRI*
Note: severe advantage: +2 points, moderate advantage: +1 point, moderate disadvantage: -1 point, significant disadvantage: -2 points, no sign: 0 points (this function is absent)

and its severity. In addition, global and local LV contractility is assessed, a quantitative analysis of LV systolic and diastolic functions is performed, and the diagnostic value of the examination increases. According to the literature, the sensitivity and specificity of SPECT are 87 % and 76 %, respectively. Synchronization with ECG increases the specificity of this method to 96 % [38–42]. SPECT results, primarily myocardial perfusion parameters, help define prognosis by suggesting the level and grade of coronary artery disease. However, data obtained during stress tests are more informative. The sensitivity and specificity of exercise tolerance tests are on average 85–90 % and 70–75 %, respectively [43]. Mortality in patients depends on the area of transient ischemia. It was found that with values of more than 20 % of the total LV area, it reaches 6.5 % per year. In addition, it was found that the development of ischemia in patients after MI around the scar area increases the risk of cardiac death compared with the identification of ischemic areas that are not associated with the scar. SPECT helps identify patients with the risk of restenosis, considering the presence, grade and area of ischemia that developed after an exercise tolerance test, its localization, transient LV dysfunction, and a decrease in LV ejection fraction. The advantage of SPECT, according to the "rest/stress" protocol, is the ease of use. At the same time, radiation exposure should be considered during repeated procedures [44–46]. A description of SPECT is given in Figure 3.

The advantage of PET is using radiopharmaceuticals (RF) to determine viable myocardium; one of such agents (13NH3, 82Rb-chloride, H215O) shows the state of cell perfusion, and another (18F-FDG) represents the level of glucose consumption by the myocardium, which, in the case of reversible ischemia, can be preserved or even increased. PET includes a range of metabolic radiopharmaceuticals, both for assessing fatty acid oxidation and for evaluating the functioning of the Krebs cycle and glycolysis. The technical advantage of PET over SPECT is its higher resolution and adjustment of the attenuation of photon radiation by soft tissues [27]. However, PET is not used often in clinical practice due to its high cost. The use of ultra-short-lived radioisotopes also limits the widespread use of PET [34]. A description of PET is given in Figure 4.

Table 1 presents the advantages and disadvantages of certain methods of non-invasive diagnosis of myocardial ischemia that can be used in patients after PCI (adapted [47]).

Management of patients after PCI

Based on the results of studies performed, recommendations were developed for the follow-up of patients after PCI. The ADORE study (Aggressive Diagnosis Of REstenosis) showed that there was no need to screen patients for SMI using ECG with exercise tolerance tests in six weeks and stress test with SPECT in six months after PCI compared with performing stress tests in patients with previously diagnosed painful myocardial ischemia. There was no significant difference between the groups of patients with painful myocardial ischemia and ischemia without clinical signs in predicting the likelihood of myocardial infarction, survival, functional state, quality of life, and frequency of invasive cardiac procedures after nine months of follow-up after PCI. The choice of the individual management approach for patients after PCI is of great importance; it depends on clinical and angiographic risk factors for the development of restenosis [6, 48, 49]. To confirm the preserved results of the resolution of coronary artery lesions in the absence ischemia signs in patients who underwent PCI, an exercise tolerance test should be performed after incomplete or suboptimal revascularization, as well as for patients who had silent myocardial ischemia before PCI [50].

Patients in a stable condition after PCI should undergo prophylactic medical examination once every six months [51]. If there are no clinical signs after PCI, it is recommended to conduct exercise tolerance tests no earlier than two years after revascularization [52].

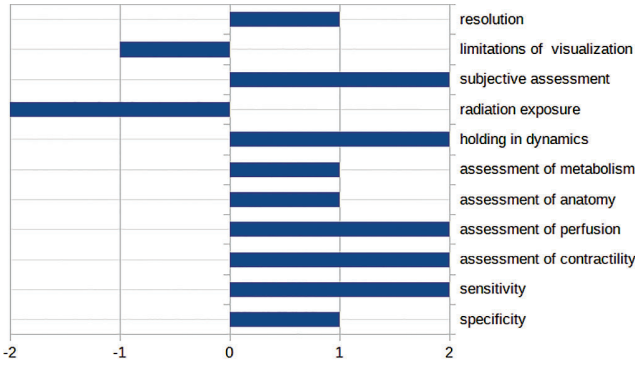


Figure 3. *Characterization of SPECT*
Note: severe advantage: +2 points, moderate advantage: +1 point, moderate disadvantage: -1 point, significant disadvantage: -2 points, no sign: 0 points (this function is absent)

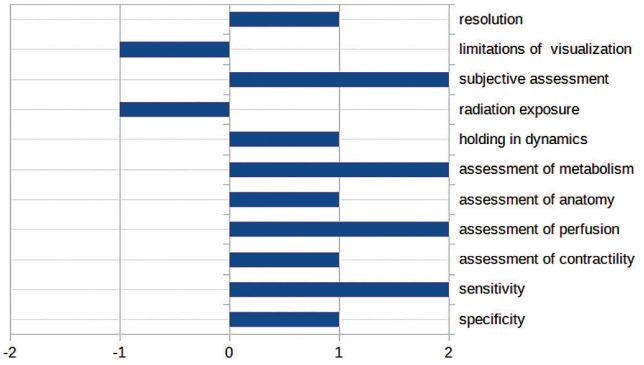


Figure 4. *Characterization of PET.*
Note: severe advantage: +2 points, moderate advantage: +1 point, moderate disadvantage: -1 point, significant disadvantage: -2 points, no sign: 0 points (this function is absent)

Table 1. Advantages and disadvantages of methods for non-invasive diagnosis of myocardial ischemia

Methods	Advantages	Disadvantages
Stress-EchoCG	• higher specificity than in radionuclide methods and MRI • multiple indicators of contractility • mobility of devices • non-invasive technic • good tolerance by patient • no ionizing radiation • safe for repeated use • high availability in clinics	• lower sensitivity than in radionuclide methods and MRI • poor visualization in some cases • technical difficulties during stress test • subjective assessment • depends on experience of operator
SPECT	• higher sensitivity compared to Echo-CG • combined study of perfusion and contractility	• radiation exposure • limited spatial resolution • low temporal resolution • lower specificity in Echo-CG • low availability • duration of procedure • uncertain data for basal inferior wall and apical septum • lower sensitivity for multiple coronary artery lesions • side reactions to RFP • limitations for patient's weight
MRI	• detection of scar tissue • possibly combined with perfusion assessment	• unsafe for pacemakers and cardioverters-defibrillators • lower risk for patients with renal insufficiency • arrhythmia/tachycardia impair image quality • claustrophobia and motionless issues • low availability • foreign metal objects
PET	• assessment of metabolism and perfusion • quantitative measurements • high resolution • correction of attenuation by soft tissues	• lower spatial resolution • exposure to radiation • limited availability

Note: MRI — magnetic resonance imaging, SPECT — single photon emission computed tomography, PET — positron emission tomography, RFP — radiopharmaceuticals, Stress-EchoCG — stress-echocardiography, EchoCG — echocardiography

A number of researchers recommend using radionuclide research methods after revascularization in patients with no signs of ischemia during the first two years after PCI [46].

Active clinical examination and follow-up of all patients after coronary artery stenting, especially women, is recommended, with exercise tolerance tests within nine months after intervention in the absence of pain syndrome or at any time in case of angina recurrence [25, 53, 54].

Summary

SMI is a risk factor for stent restenosis in patients after PCI. The presence of SMI itself may indicate the severity of organic changes in coronary arteries. Therefore, restenosis diagnosis is required, which can be carried out using stress tests with imaging, which helps determine myocardial ischemia and latent coronary insufficiency. Using SPECT to monitor the condition of patients after PCI with stenting is required to identify patients with a high risk of developing restenosis, determine indications for repeated PCI, and evaluate the prognosis after revascularization. Timely diagnosis and management of SMI in patients who underwent PCI are critical issues in clinical practice.

Conclusion

Timely diagnosis and management of SMI in patients who underwent PCI are critical issues in clinical practice.

Вклад авторов:

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

Абдрахманова А.И. (ORCID ID: https://orcid.org/0000-0003-0769-3682): разработка концепции и дизайна, обзор русскоязычных публикаций по теме статьи, анализ и интерпретация данных, ответственная за все аспекты работы

Цибулькин Н.А. (ORCID ID: https://orcid.org/0000-0002-1343-0478): разработка концепции и дизайна, обзор англоязычных публикаций по теме статьи, анализ и интерпретация данных

Амиров Н.Б. (ORCID ID: https://orcid.org/0000-0003-0009-9103): проверка критически важного интеллектуального содержания, окончательное утверждение для публикации рукописи

Хабибуллин И.М. (ORCID ID: https://orcid.org/0000-0003-0975-7002): анализ и интерпретация данных, написание первой версии статьи, одобрение окончательной версии статьи перед ее подачей для публикации

Горнаева Л.И. (ORCID ID: https://orcid.org/0000-0003-3991-2157): анализ и интерпретация данных, написание первой версии статьи, одобрение окончательной версии статьи перед ее подачей для публикации

Галимзянова Л.И. (ORCID ID: https://orcid.org/0000-0003-4359-4657): анализ и интерпретация данных, написание первой версии статьи, одобрение окончательной версии статьи перед ее подачей для публикации

Елагина Д.С. (ORCID ID: https://orcid.org/0000-0002-4925-7128): анализ и интерпретация данных, написание первой версии статьи, одобрение окончательной версии статьи перед ее подачей для публикации

Author Contribution:

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

Abdrakhmanova A.I. (ORCID ID: https://orcid.org/0000-0003-0769-3682): development of the concept and design, review of Russian-language publications on the topic of the article, analysis and interpretation of data, responsible for all aspects of the work

Tsibulkin N.A. (ORCID ID: https://orcid.org/0000-0002-1343-0478): development of the concept and design, review of English-language publications on the topic of the article, analysis and interpretation of data

Amirov N.B. (ORCID ID: https://orcid.org/0000-0003-0009-9103): verification of critical intellectual content, final approval for publication of the manuscript

Khabibullin I.M. (ORCID ID: https://orcid.org/0000-0003-0975-7002): contributed to the analysis and interpretation of the data, wrote the first version of the article, approved the final version of the article before submitting it for publication

Gornaeva L.I. (ORCID ID: https://orcid.org/0000-0003-3991-2157): contributed to the analysis and interpretation of the data, wrote the first version of the article, approved the final version of the article before submitting it for publication

Galimzyanova L.I. (ORCID ID: https://orcid.org/0000-0003-4359-4657): contributed to the analysis and interpretation of the data, wrote the first version of the article, approved the final version of the article before submitting it for publication.

Elagina D.S. (ORCID ID: https://orcid.org/0000-0002-4925-7128): contributed to the analysis and interpretation of the data, review of English-language publications on the topic of the article, approved the final version of the article before submitting it for publication.

Список литературы / References:

1. Cassese S., Byrne R.A., Schulz S. et al. Prognostic role of restenosis in 10 004 patients undergoing routine control angiography after coronary stenting. European Heart Journal. 2015; 36(2): 94-99. doi:10.1093/eurheartj/ehu383.
2. Коротаева Е.С., Королева Л.Ю., Ковалева Г.В. и др. Основные предикторы тромбоза стента у пациентов с острым коронарным синдромом после чрескожного коронарного вмешательства на фоне различной двойной антитромбоцитарной терапии. Кардиология. 2018;58(S1):12–21. Korotaeva E.S., Koroleva L.Yu., Kovaleva G.V. et al. Main predictors of stent thrombosis in patients with acute coronary syndrome after percutaneous coronary intervention on the background of various dual antiplatelet therapy. Cardiology. 2018; 58 (S1): 12-21. doi:10.1093/eurheartj/ehu383. [in Russian].
3. Marjan B, Magdalena O. In-Stent Restenosis in Drug-Eluting Stents: Issues and Therapeutic Approach. J Cardiol Curr Res. 2016; 6(3): 00206. doi: 10.15406/jccr.2016.06.00206
4. Абдрахманова А.И., Амиров Н.Б., Сайфуллина Г.Б. Безболевая ишемия миокарда (обзор литературы). Вестник современной клинической медицины. 2015; 6: 103—115. Abdrakhmanova A.I., Amirov N.B., Sayfullin G.B. Painless myocardial ischemia (literature review). Bulletin of modern clinical medicine. 2015; 6: 103-115. doi: 10.20969/VSKM.2015.6(8) [in Russian].
5. Воронина В.П., Киселева Н.В., Марцевич С.Ю. Пробы с дозированной физической нагрузкой в кардиологии: прошлое, настоящее и будущее. Часть I. Кардиоваскулярная терапия и профилактика, 2015; 14(2): 80-87. doi:10.15829/1728-8800-2015-2-80-87 Voronina V.P., Kiseleva N.V., Martsevich S.Yu. Dosed exercise testing in cardiology: past, present and future. Part I. Cardiovascular therapy and prevention, 2015; 14 (2): 80-87 doi:10.15829/1728-8800-2015-2-80-87 [in Russian].
6. Елканова М.М., Шитов В.Н., Ботвина Ю.В и др. Выявление безболевой ишемии миокарда при развитии рестеноза у больного после чрескожного коронарного вмешательства. Атеротромбоз. 2016; 1: 101-107. Elkanova MM, Shitov VN, Botvina Yu.V. et al. Revealing painless myocardial ischemia in the development of restenosis in a patient after percutaneous coronary intervention. Atherothrombosis. 2016; 1: 101-107 doi:10.21518/2307-1109-2016-1-101-107 [in Russian].
7. Lee M.S., Banka G. In-stent Restenosis. Interv Cardiol Clin. 2016; 5(2): 211-220. doi: 10.1016/j.iccl.2015.12.006
8. Conti C., Bavry A., Petersen J. Silent ischemia: clinical relev ance. J Am Coll Cardiol. 2012;59(5):435-441. doi: 10.1016/j.jacc.2011.07.050
9. Kokkinidis D., Waldo S., Armstrong E. Treatment of coronary artery in-stent restenosis. Expert Rev Cardiovasc Ther. 2017; 15(3): 191-202. doi: 10.1080/14779072.2017.1284588.
10. Лупанов В.П. Безболевая ишемия миокарда: диагностика, медикаментозное и хирургическое лечение, прогноз. Consilium Medicum. 2012; 10 (4): 36-44. Lupanov V.P. Painless myocardial ischemia: diagnosis, drug and surgical treatment, prognosis. Consilium Medicum. 2012; 10 (4): 36-44 [in Russian].
11. Alraies M.C., Darmoch F., Tummala R. et al. Diagnosis and management challenges of in-stent restenosis in coronary arteries. World J Cardiol 2017; 9(8): 640-651. doi: 10.4330/wjc.v9.i8.640
12. Alfonso F., Cuesta J.. The Therapeutic Dilemma of Recurrent In-Stent Restenosis. Circ Cardiovasc Interv. 2018; 11(8):e007109. doi: 10.1161/CIRCINTERVENTIONS.118.007109.
13. Alfonso F., Perez-Vizcayno M., Cuesta J., et al. 3-Year Clinical Follow-Up of the RIBS IV Clinical Trial: A Prospective Randomized Study of Drug-Eluting Balloons Versus Everolimus-

Eluting Stents in Patients With In-Stent Restenosis in Coronary Arteries Previously Treated With Drug-Eluting Stents. JACC Cardiovasc Interv. 2018; 11(10): 981-991. doi: 10.1016/j.jcin.2018.02.037

14. Nicolais C., Lakhter V., Virk H. et al. Therapeutic Options for In-Stent Restenosis. Curr Cardiol Rep. 2018;20(2):7. doi: 10.1007/s11886-018-0952-4
15. Farooq V., Gogas B.D., Serruys P.W. Restenosis: delineating the numerous causes of drug-eluting stent restenosis. Circ Cardiovasc Interv. 2011; 4: 195-205. doi: 10.1161/CIRCINTERVENTIONS.110.959882.
16. Березовская Г.А., Ганюков В.И., Карпенко М.А. Рестеноз и тромбоз стента: патогенетические механизмы развития и прогностические маркеры. Российский кардиологический журнал. 2012; 6: 91-95.
Berezovskaya G.A., Ganyukov V.I., Karpenko M.A. Restenosis and stent thrombosis: pathogenetic mechanisms of development and prognostic markers. Russian journal of cardiology. 2012; 6: 91-95 [in Russian]
17. Воробьева А.В., Бондаренко Б.Б., Барт В.А. и др. Оценка риска кардиальных событий у больных стабильной ишемической болезнью сердца после чрескожного коронарного вмешательства, сопровождающегося повреждением миокарда. Трансляционная медицина. 2019; 6(3): 15–24.
Vorobieva A.V., Bondarenko B.B., Bart V.A. Evaluation of the risk of cardiac events in patients with stable ischemic heart disease after percutaneous coronary intervention accompanied by myocardial injury. Translational medicine. 2019; 6 (3): 15-24 [in Russian].
18. Шиготарова Е.А., Кулюцин А.В., Олейников В.Э. Безболевая ишемия миокарда: современный взгляд на проблему. Международный медицинский журнал. 2016; 1(22): 11-16.
Shigotarova E.A., Kulyutsin A.V., Oleinikov V.E. Painless myocardial ischemia: a modern view of the problem. International Medical Journal. 2016; 1 (22): 11-16 [in Russian].
19. Тавкаева Д.Р., Маянская С.Д. Структура безболевой ишемии миокарда у больных с инфарктом миокарда после чрескожного коронарного вмешательства или консервативной терапии. Всероссийская конференция» Противоречия современной кардиологии: спорные и нерешенные вопросы». Самара: Медфорум, 2012: 181-182.
Tavkaeva D.R., Mayanskaya S.D. The structure of painless myocardial ischemia in patients with myocardial infarction after percutaneous coronary intervention or conservative therapy. Theses of the All-Russian Conference "Contradictions of Modern Cardiology: Controversial and Unresolved Issues". Samara: Medforum, 2012: 181-182 [in Russian].
20. Chang C.C., Spitzer E., Chichareon P., et al. Ascertainment of Silent Myocardial Infarction in Patients Undergoing Percutaneous Coronary Intervention (from the GLOBAL LEADERS Trial). Am J Cardiol. 2019; 12 (124): 1833-1840. doi: 10.1016/j.amjcard.2019.08.049.
21. Soliman E. Silent myocardial infarction and risk of heart failure: Current evidence and gaps in knowledge. Trends Cardiovasc Med. 2019;29(4):239-244. doi: 10.1016/j.tcm.2018.09.004.
22. Boateng S., Sanborn T. Acute myocardial infarction. Dis Mon. 2013; 59(3): 83-96. doi: 10.1016/j.disamonth.2012.12.004
23. Doi S., Suzuki M., Funamizu T., et al. Clinical Features of Potential After-Effects of Percutaneous Coronary Intervention in the Treatment of Silent Myocardial Ischemia. Heart Vessels. 2019; 12(34):1917-1924. doi: 10.1007/s00380-019-01444-8.
24. Perera D., Crake T., Lee V., et al. Angiography-guided Multivessel Percutaneous Coronary Intervention Versus Ischemia-guided Percutaneous Coronary Intervention Versus Medical Therapy in the Management of Significant Disease in Non-Infarct-related Arteries in ST-Elevation Myocardial Infarction Patients With Multivessel Coronary Disease. Crit Pathw Cardiol. 2018; 2 (17):77-82. doi: 10.1097/HPC.0000000000000144.
25. Knuuti J., Wijns W., Saraste A. и др. 2019 Рекомендации ESC по диагностике и лечению хронического коронарного синдрома. Российский кардиологический журнал. 2020; 25(2): 3757.
Knuuti J., Wijns W., Saraste A. et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Russian Journal of Cardiology. 2020;25(2):3757. doi.org/10.15829/1560-4071-2020-2-3757 [in Russian].
26. Knuuti J., Ballo H., Juarez-Orozco L.E., et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. Eur Heart J. 2018; 39: 3322- 3330. doi: 10.1093/eurheartj/ehy267.
27. Montalescot G., Sechtem U., Achenbach S., et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013; 34 (38): 2949–3003. doi: 10.1093/eurheartj/eht296.
28. Lang R.M., Badano L.P., Mor-Avi V., et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015; 16 (3): 233– 270. doi: 10.1093/ehjci/jev014.
29. Никифоров В.С., Тютин А.Р., Палагутин М.А. и др. Неинвазивная оценка гемодинамики с помощью тканевой допплерографии. Регионарное кровообращение и микроциркуляция. 2011; 10 (2): 13–18.
Nikiforov V.S., Tiutin A.R., Palagutin M.A., et al. Noninvasive evaluation of hemodynamic by tissue Doppler imaging. Regionarnoe krovoobrašenie i mikrocirkulâciâ. 2011; 10 (2): 13–18. doi.org/10.24884/1682-6655-2011-10-2-13-18 [in Russian]
30. Agarwal R, Gosain P, Kirkpatrick JN., et al. Tissue Doppler imaging for diagnosis of coronary artery disease: a systematic review and meta-analysis. Cardiovasc Ultrasound. 2012; 10: 47. doi: 10.1186/1476-7120-10-47.
31. Медведев П.И., Алехин М.Н., Сидоренко Б.А. Диагностические возможности спеклтрекинг эхокардиографии у больных ишемической болезнью сердца. Кардиология. 2016; 56 (2): 79–84.
Medvedev P.I., Alekhin M.N., Sidorenko B.A. Diagnostic Possibilities of Speckle-Tracking Echocardiography in Patients With Ischemic Heart Disease. Kardiologiia. 2016; 56 (2): 79–84. doi.org/10.18565/cardio.2016.2.79-84 [in Russian]

32. Wierzbowska-Drabik K., Hamala P., Roszczyk N., et al. Feasibility and correlation of standard 2D speckle tracking echocardiography and automated function imaging derived parameters of left ventricular function during dobutamine stress test. Int J Cardiovasc Imaging. 2014; 30: 729–37. doi: 10.1007/s10554-014-0386-z. Epub 2014 Feb 13.
33. Никифоров В.С., Марсальская О.А., Новиков В.И. Эхокардиографическая оценка деформации миокарда в клинической практике. Спб.: Культинформпресс, 2015; 28 с. Nikiforov V.S., Marsal'skaia O.A., Novikov V.I. Echocardiographic assessment of myocardial deformity in clinical practice. St.Petersburg: Cult Inform Press, 2015; 28 p. [in Russian]
34. Никифоров В.С. Методы сердечно-сосудистой визуализации в диагностике ишемической болезни сердца. Consilium Medicum. 2017; 19 (1): 18–24. Nikiforov V.S. Methods of cardiovascular imaging for the detection of ischemic heart disease . Consilium Medicum. 2017; 19 (1): 18–24. [in Russian]
35. Патеюк И.В., Митьковская Н.П., Терехов В.И. и др. Однофотонная эмиссионная компьютерная томография и скрининг коронарного кальция в диагностике ишемии миокарда и стратификации риска у пациентов с бессимптомной депрессией сегмента ST. Лечебное дело. 2015; 5: 33–37. Pateyuk I.V., Mitkovskaya N.P., Terekhov V.I. et al. Single-photon emission computed tomography and coronary calcium screening in the diagnosis of myocardial ischemia and risk stratification in asymptomatic ST-segment depression patients. General medicine. 2015; 5: 33-37 [in Russian].
36. Абдрахманова А.И., Сайфуллина Г.Б., Амиров Н.Б. Место перфузионной сцинтиграфии миокарда в диагностике синдрома такоцубо. Российский кардиологический журнал. 2018; 12: 125–130. Abdrakhmanova A.I., Sayfullina G.B., Amirov N.B. The place of myocardial perfusion scintigraphy in the diagnosis of takotsubo syndrome. Russian journal of cardiology. 2018; 12: 125-130. doi.org/10.15829/1560-4071-2018-12-125-130 [in Russian].
37. Аншелес А.А., Шульгин Д.Н., Соломяный В.В. и др. Сопоставление результатов нагрузочных проб, данных однофотонной эмиссионной компьютерной томографии и коронарографии у больных ишемической болезнью сердца. Кардиологический вестник. 2012; 2: 10–16. Ansheles A.A., Shulgin D.N., Solomyany V.V. et al. Comparison of the results of stress tests, data from single-photon emission computed tomography and coronary angiography in patients with coronary heart disease. Cardiological Bulletin. 2012; 2: 10-16. [in Russian].
38. Рыжкова Д.В., Салахова А.Р. Технические основы и клиническое применение позитронной эмиссионной томографии для оценки перфузии миокарда как самостоятельной процедуры и в составе гибридных систем. Трансляционная медицина. 2015; 5:113-122. Ryzhkova D.V., Salakhova A.R. Technical fundamentals and clinical application of positron emission tomography for the assessment of myocardial perfusion as an independent procedure and as part of hybrid systems. Translational medicine. 2015; 5: 113-122. doi.org/10.18705/2311-4495-2015-0-5-113-122 [in Russian].
39. Bourque J.M., Patel C.A., Ali M.M., et al. Prevalence and predictors of ischemia and outcomes in outpatients with diabetes mellitus referred for single-photon emission computed tomography myocardial perfusion imaging. Circ Cardiovasc Imaging. 2013; 6(3): 466-77.
40. Spitzer E., Ren B., Zijlstra F., et al. The Role of Automated 3D Echocardiography for Left Ventricular Ejection Fraction Assessment. Card Fail Rev. 2017; 3(2): 97-101. doi: 10.1161/CIRCIMAGING.112.000259.
41. Труфанов Г.Е., Декан В.С., Романов Г.Г. и др. Перфузионная сцинтиграфия миокарда. СПб.: Элби, 2012; 80 с. Trufanov G.E., Dean V.S., Romanov G.G. and other Perfusion scintigraphy of the myocardium. SPb .: Elby, 2012; 80 p. [in Russian].
42. Abdrahmanova A.I., Oslopova J.V., Esin O.R. et al. Main metod of diagnosis of silent myocardial ischemia. International Journal of Pharmacy and Technology IJPT. 2016; 4(8): 24400–24406.
43. Митьковская Н.П., Патеюк И.В., Статкевич Т.В. и др. Безболевая ишемия миокарда у пациентов с метаболическим синдромом: стратификация кардиоваскулярного риска. Новости медико-биологических наук. 2015; 3: 39-42. Mitkovskaya N.P., Pateyuk I.V., Statkevich T.V. et al. Painless myocardial ischemia in patients with metabolic syndrome: stratification of cardiovascular risk. Biomedical Science News. 2015; 3: 39-42 [in Russian].
44. Яковлев В.М., Мартынов А.И., Ягода А.В. Клинико-визуальная диагностика безболевой ишемии миокарда. Ставрополь: Ставрополье. 2012; 214 с. Yakovlev VM, Martynov AI, Yagoda AV Clinical and visual diagnostics of painless myocardial ischemia. Stavropol: Stavropol. 2012; 214 p. [in Russian].
45. Абдрахманова А.И., Амиров Н.Б., Цибулькин Н.А. Применение перфузионной томосцинтиграфии миокарда при безболевой ишемии миокарда (обзор литературы). Архивъ внутренней медицины. 2020; 10(5): 340-347. Abdrakhmanova A.I., Amirov N.B., Tsibulkin N.A. The use of myocardial perfusion tomoscintigraphy in painless myocardial ischemia (literature review). The Russian Archives of Internal Medicine. 2020; 10 (5): 340-347. doi.org/10.20514/2226-6704-2020-10-5-340-347 [in Russian].
46. Кузнецов В.А., Ярославская Е.И., Горбатенко Е.А. Предикторы гемодинамически значимых коронарных стенозов у пациентов с нарушениями миокардиальной перфузии по данным однофотонной эмиссионной компьютерной томографии миокарда. Клиническая медицина. 2012; 7: 25-30. Kuznetsov V.A., Yaroslavskaya E.I., Gorbatenko E.A. Predictors of hemodynamically significant coronary stenoses in patients with myocardial perfusion disorders according to single-photon emission computed tomography of the myocardium. Clinical medicine. 2012; 7: 25-30. [in Russian].
47. Никифоров В.С. Методы сердечно-сосудистой визуализации в диагностике жизнеспособного миокарда при ишемической болезни сердца. СПб.: Издательство «КультИнформПресс», 2012; 33 с. Nikiforov V.S. Methods of cardiovascular imaging in the diagnosis of viable myocardium in ischemic heart disease. St. Petersburg: Publishing house «Kultinformpress», 2012; 33 p. [in Russian].

48. Harb S.C., Marwick T.H. Prognostic value of stress imaging after revascularization: a systematic review of stress echocardiography and stress nuclear imaging. Am Heart J. 2014; 1(167): 77-85. doi: 10.1016/j.ahj.2013.07.035.
49. Abdrahmanova A.I, Tsibulkin N.A., Silent myocardial ischemia in patients after emergency coronary intervention (Literature reviev). Revista Latinoamericana de Hipertension. 2020; 4(15): 297-300.
50. Acampa W., Petretta M.P., Daniele S., et al. Myocardial perfusion imaging after coronary revascularization: a clinical appraisal. European Journal of Nuclear Medicine and Molecular Imaging. 2013; 8 (40): 1275–1282. doi: 10.1007/s00259-013-2417-8
51. Recommendations for the treatment of stable coronary heart disease 2013 (ESC). Russian Journal of Cardiology. 2014; 7 (111): 7-79. https://doi.org/10.15829/1560-4071-2014-7-7-79
52. Shilov A.A., Kochergin N.A., Ganyukov V.I., et al. Comparability of scintigraphy data with coronary angiography after surgical myocardial revascularization. Regional blood circulation and microcirculation. 2019; 3(18): 23–28. doi: 10.24884/1682-6655-2019-18-3-23-28
53. Мальгина М.П., Недошивин А.О., Бондаренко Б.Б. Рецидив ишемии после реваскуляризации миокарда методом чрескожного коронарного вмешательства. Кардиоваскулярная терапия и профилактика. 2011; 10(7): 18-22. Malgina M.P., Nedoshivin A.O., Bondarenko B.B. Recurrence of ischemia after myocardial revascularization by percutaneous coronary intervention. Cardiovascular therapy and prevention. 2011; 10 (7): 18-22 [in Russian].
54. Singh A., Singal A., Mian A., et al. Recurrent Drug-Eluting Stent In-Stent Restenosis: A State-of-the-Art Review of Pathophysiology, Diagnosis, and Management. Cardiovasc Revasc Med. 2020;21(9):1157-1163. doi: 10.1016/j.carrev.2020.01.005

DOI: 10.20514/2226-6704-2022-12-3-175-186 УДК 616.72-002.77-089.163

В.В. Лялина*[1], С.В. Борисовская[1,2], Э.А. Скрипниченко[1,2], О.А. Эттингер[1,2], Т.М. Паджева[3], С.Л. Мигачёв[4], И.А. Борщенко[4], И.Г. Никитин[1,5]

[1] — Кафедра госпитальной терапии № 2 ЛФ ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, Москва, Россия
[2] — ГБУЗ «ГКБ имени В.М. Буянова ДЗМ», Москва, Россия
[3] — ГБУЗ «ГКБ № 40 ДЗМ», Москва, Россия
[4] — Клиника «Ортоспайн», Москва, Россия
[5] — ФГАУ «НМИЦ «ЛРЦ» Минздрава России, Москва, Россия

ПЕРИОПЕРАЦИОННОЕ ВЕДЕНИЕ ПАЦИЕНТОВ С РЕВМАТОЛОГИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ: КАРДИОВАСКУЛЯРНЫЕ РИСКИ, ПРОФИЛАКТИКА ИНФЕКЦИОННЫХ И ТРОМБОЭМБОЛИЧЕСКИХ ОСЛОЖНЕНИЙ, ОТДЕЛЬНЫЕ СОСТОЯНИЯ

V.V. Lyalina *[1], S.V. Borisovskaya[1,2], E.A. Skripnichenko[1], O.A. Ettinger[1,2], T.M. Padzheva[3], S.L. Migachev[4], I.A. Borshchenko[4], I.G. Nikitin[1,5]

[1] — Pirogov Russian National Research Medical University (Pirogov Medical University), Moscow, Russia
[2] — Buyanov City Clinical Hospital, Moscow, Russia
[3] — Moscow City Clinical Hospital № 40 Moscow, Russia
[4] — Orthospine Clinic, Moscow, Russia
[5] — Medical and Rehabilitation Center, Moscow, Russia

Perioperative Management of Patients with Rheumatic Disease: Cardiovascular Risks, Prevention of Infectious and Thromboembolic Complications, Other Conditions

Резюме

В данной статье обсуждаются риски и профилактика инфекционных, тромбоэмболических осложнений, кардиоваскулярные риски, а также различные структурные изменения опорно-двигательного аппарата и неопорных суставных структур, которые затрудняют периоперационное ведение ревматологических пациентов.

Ключевые слова: *ревматоидный артрит, периоперационное ведение, эндопротезирование, антифосфолипидный синдром, атланто-аксиальная нестабильность, височно-нижнечелюстные суставы, перстнечерпаловидные суставы*

*Контакты: Вера Валерьевна Лялина, e-mail: vera_lyalina@mail.ru
*Contacts: Vera V. Lyalina, e-mail: vera_lyalina@mail.ru
ORCID ID: https://orcid.org/0000-0002-4262-4060

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

Статья получена 23.08.2021 г.

Принята к публикации 18.11.2021 г.

Для цитирования: Лялина В.В., Борисовская С.В., Скрипниченко Э.А. и др. ПЕРИОПЕРАЦИОННОЕ ВЕДЕНИЕ ПАЦИЕНТОВ С РЕВМАТОЛОГИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ: КАРДИОВАСКУЛЯРНЫЕ РИСКИ, ПРОФИЛАКТИКА ИНФЕКЦИОННЫХ И ТРОМБОЭМБОЛИЧЕСКИХ ОСЛОЖНЕНИЙ, ОТДЕЛЬНЫЕ СОСТОЯНИЯ. Архивъ внутренней медицины. 2022; 12(3): 175-186. DOI: 10.20514/2226-6704-2022-12-3-175-186. EDN: ENIHUJ

Abstract

In the first part we reviewed the issues of perioperative administration of steroids, disease-modifying antirheumatic drugs, biologics and nonsteroidal anti-inflammatory drugs. In this part we will discuss cardiovascular risks, prevention of infectious and thromboembolic complications and the impact of some structural alteration on the process of surgery and perioperative management.

Key words: *rheumatoid arthritis, perioperative management, arthroplasty, antiphospholipid syndrome, atlantoaxial subluxation, temporomandibular joints, cricoarytenoid arthritis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 23.08.2021

Accepted for publication on 18.11.2021

For citation: Lyalina V.V., Borisovskaya S.V., Skripnichenko E.A. et al. Perioperative Management of Patients with Rheumatic Disease: Cardiovascular Risks, Prevention of Infectious and Thromboembolic Complications, Other Conditions. The Russian Archives of Internal Medicine. 2022; 12(3): 175-186. DOI: 10.20514/2226-6704-2022-12-3-175-186. EDN: ENIHUJ

AAI — atlantoaxial instability, AAJ — atlantoaxial joint, ABP — antibiotic prophylaxis, ADI — atlantodental interval, AOJ — atlantooccipital joint, APLAT — antiphospholipid antibodies, APS — antiphospholipid syndrome, CT — computed tomography, CS — cervical spine, CVR — cardiovascular risk, DVT — deep vein thrombosis, IE — infective endocarditis, JIA — juvenile idiopathic arthritis, LMWH — low molecular weight heparins, MRI — magnetic resonance imaging, RA — rheumatoid arthritis, RDs — rheumatological diseases, SAI — subaxial instability, SLE — systemic lupus erythematosus, TMJ — temporomandibular joint, UFH — unfractionated heparin, VTE — venous thromboembolism

Risk of developing infectious complications

Patients with rheumatological diseases (RDs) have an increased risk of infectious complications, primarily due to the long-term use of immunosuppressants. In this regard, preventive measures should be carefully taken. The decision on the use of antibiotics should be taken with consideration to the type of surgical intervention and risk-benefit evaluation.

1. Detection of latent infections and antibiotic prophylaxis (ABP)

When preparing patients with RDs for surgical intervention, one should look for caries, asymptomatic bacteriuria, cystitis, pharyngitis, skin infections (special attention should be paid to the skin of the feet) [1]. All these conditions can become a source of postoperative infectious complications.

In patients with RD, physicians use the same perioperative protocols for ABP in regard to surgical infections as in the general population [2].

In particular, endoprosthesis replacement in patients with normal kidney function requires the use of cefazolin 1 g i.v. in case of a patient with body weight less than 80 kg, and 2 g i.v. in case of a patient with body weight more than 80 kg; the agent is administered within 60 minutes after incision, and then every eight hours for one day. In patients with an allergic reaction to penicillin, it is recommended to use vancomycin i.v. at a dose of 1 g (10–15 mg/kg) two hours before surgery with a single repeated administration during the postoperative period after 12 hours, or clindamycin at a dose of 600–900 mg i.v. with repeated administration twice during the postoperative period with an interval of six hours. Clindamycin is less effective against coagulase-negative staphylococci and MRSA (methicillin-resistant Staphylococcus aureus) than vancomycin. Continued prophylactic administration of antibiotics for more than 24 hours after surgery is not advisable [3].

2. Prevention of infective endocarditis (IE) in patients with valvular heart diseases due to RDs during dental procedures and minimally invasive interventions (based on the European Society of Cardiology (ESC) Guidelines for the management of infective endocarditis, 2015) [4].

The idea of IE ABP was developed based on survey studies and animal models [5]. It was assumed that ABP

would interfere with bacterial adhesion to the endocardium during transient bacteremia after invasive procedures. This led to the mass prophylactic prescription of antibiotics to patients with the structural features of heart valves before various interventions, including dental procedures.

In recent years, the development of pathophysiological concepts, as well as the study of the risks and benefits of IE ABP, narrowed down the indications for this type of prophylaxis in patients with valvular heart diseases. Current ideas about the advisability of IE ABP are based on the following provisions:

- Low-level and recurring bacteremia often develops during normal daily activities such as tooth brushing, flossing, or chewing gum, especially in patients with incomplete oral sanation. Therefore, the risk of IE is probably associated with cumulative exposure to mild bacteremia throughout the day rather than with single severe bacteremia after dental procedures.
- Most case-control studies showed no link between invasive dental procedures and IE development.
- The estimated risk of IE after dental interventions is very low. Therefore, ABP can prevent a very small number of IE cases (approximately 1 in 150,000 interventions with antibiotics, or 1 in 46,000 without antibiotics) [4].
- Using antibiotics is associated with a certain risk of allergy and anaphylaxis.
- Heavy use of antibiotics contributes to the emergence of resistant microorganisms.
- Efficacy of ABP against bacteremia and IE development was confirmed only in animal models; there are contradictory data in humans.

Recommendations support the advisability of ABP in patients with a high risk of developing IE that can be divided into three categories. In particular, *ABP is recommended for patients with prosthetic valves; patients with previous IE, and patients with untreated cyanotic congenital heart diseases (CHD) and CHD after palliative bypass surgery, conduits or other prostheses.*

ABP is not recommended for patients with an intermediate risk of IE that includes any other form of native valvular heart disease.

Therefore, *patients with non-operated valvular heart disease are at intermediate risk, and patients with operated/prosthetic valves are at high risk.* The population of rheumatological patients is primarily understood as patients with valvular heart diseases that have developed as a result of acute rheumatic fever. Also, it should be borne in mind that heart damage with the development of valvular disease can also occur as a part of other RDs, particularly seronegative spondyloarthritis, systemic lupus erythematosus (SLE), and antiphospholipid syndrome (APS).

ESC Guidelines emphasize that both intermediate and high-risk patients should be advised on the importance of oral and skin hygiene. Particular attention should be paid to the general compliance with basic hygiene standards, since IE often develops in individuals with no known heart disease.

3. IE ABP in dental procedures

Procedures in the gums and periapical region of the teeth associated with possible injury to the oral mucosa (including procedures with roots and removal of tartar) carry a certain risk of infection. Dental implants are also associated with the potential risk of infection from the buccal region entering the bloodstream. However, there is very scarce information on this subject, and there is no sufficient evidence of contraindications to implants in high-risk patients.

ABP is advisable in patients with a high risk of IE who undergo these high-risk dental procedures and is not recommended in other situations [4]. Streptococci of the oral cavity are the main object of ABP in such cases. Table 1 presents basic ABP regimens recommended before dental procedures. Fluoroquinolones and glycopeptides are not recommended due to their unclear efficacy and potential development of resistance. Cephalosporins should not be used in patents with a history of anaphylaxis, angioedema, or urticaria to penicillin or ampicillin due to cross-sensitivity.

ABP in non-dental procedures and interventions

There is no strong evidence that bacteremia after interventions in respiratory, gastrointestinal and genitourinary tracts, including vaginal delivery and caesarean section, as well as dermatological and musculoskeletal procedures, causes IE. Systemic ABP of IE is not recommended for non-dental interventions. Antibiotics are required only when invasive procedures are performed with an underlying infectious process [4].

Table 1. *Recommended prophylaxis for high-risk dental procedures in high-risk patients [4]*

Situation	Antibiotic	Single-dose 30-60 minutes before procedure	
		Adults	Children
No allergy to penicillin or ampicillin	Amoxicillin or ampicillin*	2 g orally or IV	50 mg/kg orally or IV
Allergy to penicillin or ampicillin	Clindamycin	600 mg orally or IV	20 mg/kg orally or IV

Note: *Alternatively, cephalexin 2 g IV for adults or 50 mg/kg IV for children, cefazolin or ceftriaxone 1 g IV for adults or 50 mg/kg IV for children. IV — intravenous

Assessment of cardiovascular risk and prevention of thrombotic complications

Patients with RDs (especially those with rheumatoid arthritis, SLE, and systemic vasculitis) have an increased cardiovascular risk (CVR) compared to the general population. Therefore, regular risk assessment is required (at least once every 5 years) [6]. Assessment of CVR in patients with RDs is based on special scales and periodic examinations aimed at identifying risk factors.

First of all, the patient's CVR should be evaluated according to the SCORE algorithm or Framingham Risk Score. There are special features of using SCORE in patients with RA: in certain cases it is recommended to multiply the SCORE value by 1.5, that is, with a disease duration of more than 10 years, with positive rheumatoid factor (RF) or cyclic citrulline peptide antibodies (CCPA), with extra-articular manifestations of RA [6].

Furthermore, in order to get more specific information on the risk, a Doppler scan of carotid arteries is recommended [6].

CVD risk factors in patients with high and very high CVR should be promptly corrected [6].

Assessing exercise tolerance in patients with rheumatologic diseases can be difficult, as these patients often have limited mobility due to musculoskeletal diseases, or reduced overall physical activity due to the damage to the heart, lungs, and other disease-related changes. In this regard, standard functional tests with exercise are challenging or impossible for such patients. Currently, there are no strong recommendations on alternative methods for assessing exercise tolerance in patients with RDs.

In addition, specific CVR factors in rheumatological patients, such as signs of antiphospholipid syndrome (APS), should be considered. See features of the management of patients with APS in "Prevention of thrombotic complications".

Perioperative administration of acetylsalicylic acid

It is recommended to stop the administration of acetylsalicylic acid 7–10 days before surgery, that is, for the platelets' lifespan [7]. This excludes patients with a high risk of myocardial infarction, transient ischemic attacks and stroke; risks in such cases should be assessed individually [7].

According to the American College of Chest Physicians (ACCP) recommendations [8], patients with moderate to high CVR receiving acetylsalicylic acid as secondary prophylaxis should continue taking it in the perioperative period. Also, it should be considered that rheumatic disease itself is a factor for CVR. Patients with signs of APS, positive antiphospholipid antibodies (especially with triple positivity) deserve special attention. These patients are at high risk of a first thrombotic event. Therefore, considering the relatively low risk of life-threatening bleeding in connection with the administration of acetylsalicylic acid, and if there are no other serious contraindications, patients with RDs can continue taking acetylsalicylic acid in the perioperative period. The therapeutic approach to the perioperative management of a patient with APS (using the example of endoprosthesis replacement) is demonstrated in Diagram 1 [2].

In some cases, hydroxychloroquine and statins can be recommended as additional angioprotective measures [2].

Prevention of venous thrombosis

1. Basic principles of the management of patients with RDs in the perioperative period in order to prevent venous thrombosis [1]:

- reducing time without anticoagulants;
- not using vitamin K;
- minimizing all factors of Virchow's triad (stasis, hypercoagulable state and endothelial damage): using external pneumatic compression during the operative and postoperative period, if possible, inflating the tonometer cuff less often, avoiding the use of tourniquets, motivating the patient towards early activation, limiting the use of intravenous infusion systems and removing them as early as possible.

1. Standard approaches [1]:

Warfarin sodium (WS) for 10 days after surgery with dose titration in order to achieve target prothrombin time 16–18 seconds, or INR 2–3. WS continued up to 42 days after hip joint surgery may be associated with a lower risk of deep vein thrombosis. WS for more than 10 days in the postoperative period after knee arthroplasty has no additional effect.

Unfractionated heparin (UFH) 5,000 IU subcutaneously before surgery, then 5,000 IU every 8 hours after surgery. Subsequently, the dose is titrated daily depending on the activated partial thromboplastin time (aPTT) that should increase 1.5–2.5 times higher than the control one. The frequency of administration, the need for frequent testing for aPTT and the cost limit the advisability of using UFH.

Low molecular weight heparins (LMWHs) may also be effective for prevention. The most effective regimen includes starting administration before surgery and continuing for at least 10 days after surgery. It was demonstrated that in cases of hip arthroplasty, continued use of LMWHs up to 42 days during the postoperative period reduces the incidence of deep vein thrombosis with no significant increase in the frequency of bleeding episodes.

Fondaparinux sodium (synthetic heparin) — administration before surgery with a continuation of up to 10-42 days the during postoperative period.

Acetylsalicylic acid (325 mg/s) moderately reduces the incidence of deep vein thrombosis. However, it is associated with an increased risk of bleedings and is not recommended for routine perioperative prophylaxis of deep vein thrombosis.

Pneumatic compression devices applied to the lower extremities should be used from the morning before surgery until the moment of discharge. **Compression stockings** provide minimal protection against deep vein thrombosis and are not recommended as monotherapy.

2. Specific features of DVT prevention in patients with RA in the perioperative period after knee or hip arthroplasty [7]:

Before surgery, all patients should undergo ultrasound of the veins of lower extremities with re-examination before the "verticalization" of a patient after surgery and before his/her discharge from the hospital.

Ten to fourteen days before surgery, patients receiving **WS** should be switched to LMWHs under the control of coagulogram and several parameters:

- before starting LMWHs — CBC (including platelets), blood biochemistry to exclude renal failure (creatinine);
- after 5–7 days of LMWHs administration — repeated control of platelets (to exclude heparin-induced thrombocytopenia).

In the postoperative period, early activation of patients is recommended, as well as exercises for lower extremities with the mandatory engagement of the muscles of lower legs; elastic bandages or special garment (socks, stockings) for at least 60–90 days from the day of surgery, and administration of dabigatran etesquilate or rivaroxaban.

Dabigatran etexilate is a selective direct thrombin inhibitor:

- the first dose (110 mg) should be administered 1–4 hours after surgery;
- from day 2 — 220 mg (2 capsules 110 mg once a day); for patients aged 75+ — 150 mg (2 capsules 75 mg); duration of administration — at least 35 days;
- this agent does not require individual dose titration or laboratory control (approved by the European Medical Agency (EMEA) for thromboprophylaxis after knee or hip arthroplasty).

Rivaroxaban is a selective direct inhibitor of blood coagulation factor Xa: the first dose (10 mg) should be administered 6–10 hours after surgery, then 10 mg once a day for at least 35 days.

For patients undergoing major orthopedic surgery, the American College of Chest Physicians recommends extending outpatient thromboprophylaxis up to 35 days from the date of surgery, and using an intermittent pneumatic compression device during hospital stay [2].

3. Special features of the perioperative management of patients with APS [2]

There are procedures for primary and secondary prevention of thromboembolic complications in patients with APS.

For ***primary prevention*** in patients with RDs, perioperative risk stratification should be based on the antiphospholipid antibody (APL-Ab) profile and other cardiovascular risk factors, considering that the RD itself increases the risk of venous thromboembolism.

The strongest predictors of clinical manifestations in APS are lupus anticoagulant, which increases the risk of thrombosis by about four times [2], as well as "triple positivity", which is a significant increase of all three APL-Abs (lupus anticoagulant, anticardiolipin, anti-b2-glycoprotein antibodies), while Ig G isotype is clinically more significant compared to Ig M one (Diagram 1) [8].

Other risk factors for cardiovascular diseases should also be included in the risk assessment, such as arterial hypertension, obesity (body mass index > 30 kg/m^2), diabetes mellitus, smoking, active or treated cancer, oral contraceptives, underlying systemic autoimmune diseases, and genetic hypercoagulant conditions that may require an increased dose of anticoagulants during the perioperative period [9].

Patients with RDs and clinically significant APS have a very high risk of thrombosis. Therefore, physicians should try to perform the least invasive type of surgery. On the other hand, the following is required to reduce the risk of bleeding [2]:

- discontinuing oral anticoagulation agents 3–5 days before surgery;
- treatment with heparin or LMWHs should be discontinued 4 or 24 hours before surgery, respectively,
- re-starting anticoagulants 24–48 hours after the intervention if hemostasis is adequate (Scheme 1).

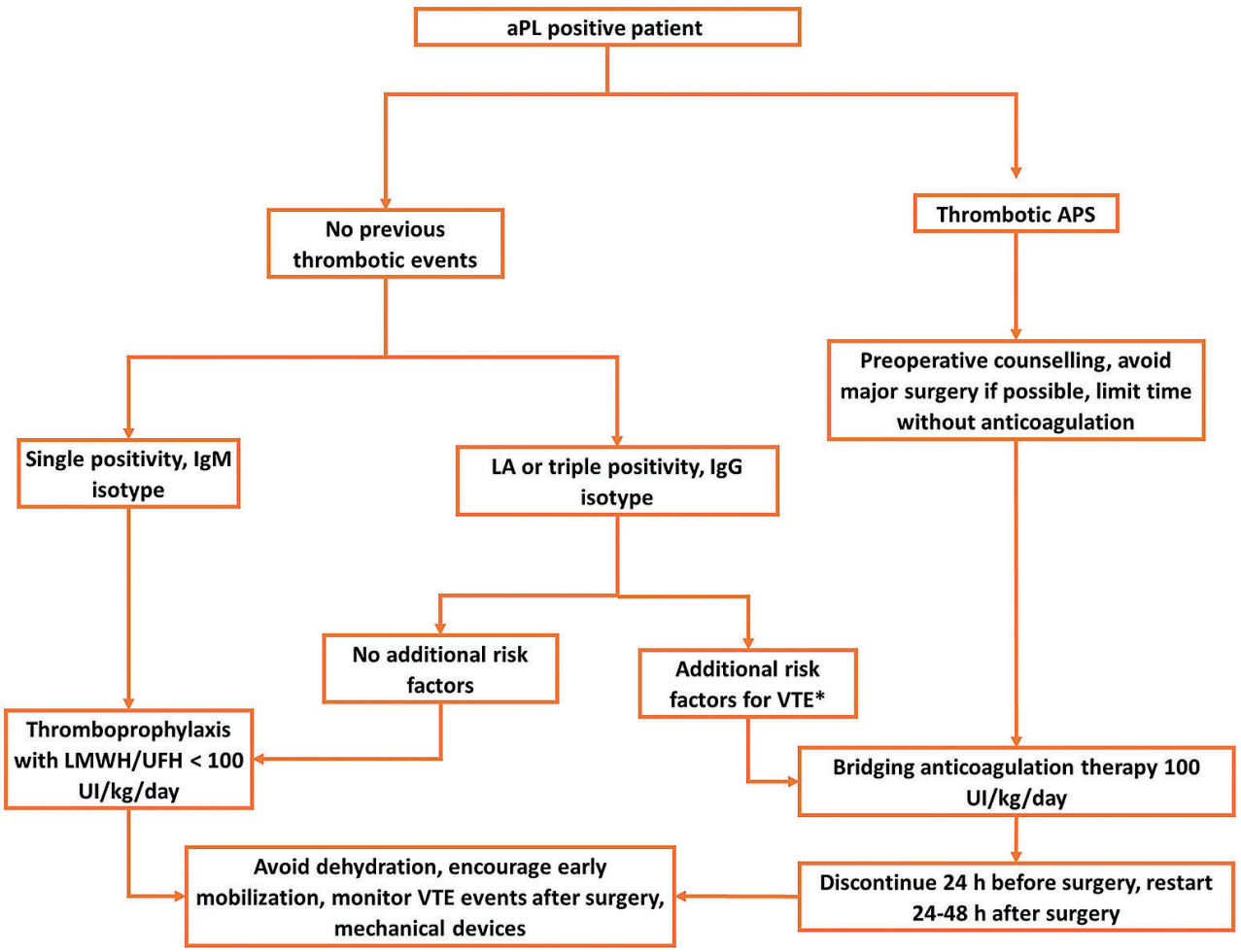
For ***secondary prevention*** of venous thromboembolism, considering the risk of recurrence after the first episode of thrombosis, patients with APS receive oral anticoagulants for a long time. Therefore, they also need bridge therapy with subcutaneous LMWHs or intravenous UFH [2].

According to the literature, hydroxychloroquine reduces the risk of venous thromboembolism in SLE [10] and slows down the progression of atherosclerosis [11].

Structural changes in the spine and joints that affect the perioperative management of patients with RDs

1. Pathology of the upper cervical spine in patients with rheumatoid arthritis (RA)

Rheumatoid arthritis can affect all parts of the spine. However, the cervical region is most commonly affected (in 59–88 % of patients), which is associated with the risk of severe complications [12].



Scheme 1. *Perioperative approach to a patient with inflammatory rheumatic disease and venous thromboembolic risk [2]*

Note: aPL — antiphospholipid antibodies, LA — lupus anticoagulant, APS — anti-phospholipid syndrome, VTE — venous thromboembolism, LMWH — low molecular weight heparin, UFH — unfractionated heparin

*Additional risk factors for VTE: arterial hypertension, obesity, diabetes mellitus, smoking, neoplasia, oral contraceptives, underlying inflammatory joint disease, genetic hypercoagulable state

There are 32 synovial joints in the cervical spine (CS) [13], and all of them can be exposed to inflammation and further destruction. Atlantoaxial (AAJ), atlantooccipital (AOJ), and facet joints of the upper cervical vertebrae are most commonly affected. In most cases, arthritis of these joints is asymptomatic. However, in cases of especially aggressive inflammation and proliferation of rheumatoid pannus, there is significant degeneration and destruction of all joint structures [14]. As a result, static and/or dynamic instability of CS develops, which can lead to the compression of the spinal cord and brainstem. There are three types of CS deformities in cases of RA: atlantoaxial instability, basilar impression (atlantooccipital instability), and subaxial cervical instability [13]. AAJ and AOJ instability develop due to the degeneration of the ligamentous apparatus, while the destruction of facet joints plays the central role in the pathomorphosis of subaxial instability [13].-

Atlantoaxial instability (AAI). Atlantoaxial instability (subluxation) is the most common pathology of the cervical region in the cases of RA (65 % of CS deformities in RA), which raises the threat of developing cervical myelopathy [13]. Depending on the direction of dislocation of C1 relative to C2, AAI can be divided into anterior (most common), posterior, vertical, lateral and rotational[14]. AAI develops when the integrity of the ligamentous apparatus is impaired due to synovial proliferation: primarily when the transverse (prevents anterior displacement of atlas) and alar (stabilization during axial rotation of the head) ligaments are weakened (Figure 1).

Most patients with AAI are asymptomatic. [15]. However, *deep flexion/extension in the cervical region (for example, during intubation) can result in a significant displacement of the odontoid process with the development of spinal cord compression*. In this regard, patients with RA, during their preparation for surgery, should undergo X-ray of the cervical spine with functional tests (anteroposterior, lateral, with the mouth open, flexion, extension) [14].

X-ray to detect instability is mandatory for the following groups of patients [12]:

- RA duration of at least 10 years;
- aggressive course of RA with a disease duration of less than 10 years;
- patients with symptoms of AAI (pain and/or paresthesia in the neck and nape, signs of cervical myelopathy).

There is also an opinion that X-ray should be performed in all patients with RA, especially in those who are scheduled for general anesthesia, since about half of patients with radiological instability are asymptomatic [12].

X-ray or computed tomography (CT) can help detect AAI by diagnosing the displacement of the odontoid process. To this end, *anterior and posterior atlantodental intervals (ADI) are measured* [13].

Anterior ADI is the distance from the lower edge of the C1 anterior arch to the anterior surface of the C2 odontoid process (see Figure 2). *The normal interval should not be more than 3 mm on lateral radiographs in the position of flexion and extension.* A distance of more than 3 mm indicates the failure of the transverse ligament. A displacement of more than 7–8 mm indicates complete destruction of ligaments and high risk of spinal cord compression. A displacement of 9 mm is accompanied by the development of severe neurological symptoms.

Posterior ADI is the distance from the posterior surface of the odontoid process to the anterior edge of the C1 arch plate (see Figure 2). At a distance of less than 13 mm, there is a risk of spinal cord compression.

All patients with radiographic evidence of instability are recommended to undergo more detailed imaging by CT or magnetic resonance imaging (MRI) of CS [14].

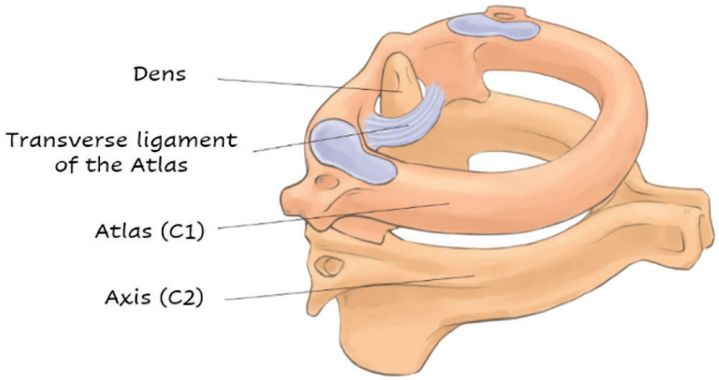


Figure 1. *Atlantoaxial joint. Illustrator Rudykh A.K.*

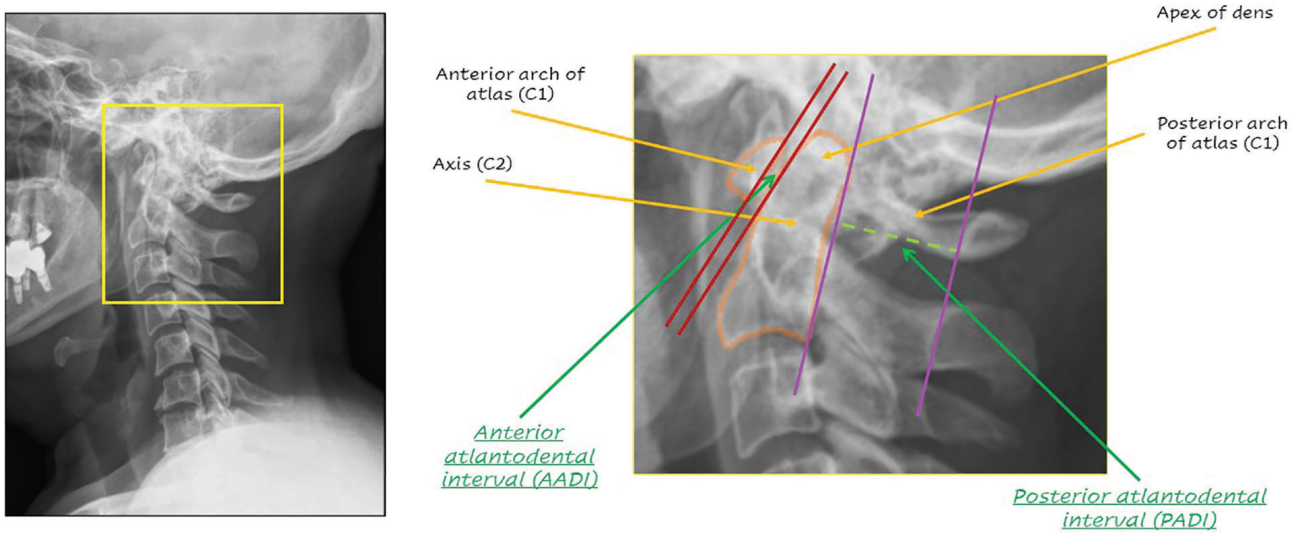


Figure 2. *Measurement of the anterior and posterior atlantodental interval*

Figure **caption 2** [16]**:**
Measuring the anterior atlantodental interval: A line is drawn along the anterior arch of the atlas connecting the most posterior points of its superior and inferior borders. Then a second, parallel line is drawn along the anterior aspect of the dens. The distance between the two lines is the anterior atlantodental interval (AADI), which can be measured in the neutral position and also in flexion and extension. Values > 3 mm are considered suspicious. Widening of the AADI to > 5 mm strongly suggests rupture or inflammatory damage to the transverse atlantal ligament.
Measuring the posterior atlantodental interval: A line is drawn along the posterior arch of the atlas connecting the most anterior points of its superior and inferior borders. The distance between that line and a parallel line along the posterior aspect of the dens is the posterior atlantodental interval (PADI). In patients with atlantoaxial instability due to rheumatoid arthritis, values < 10 mm are critical in terms of spinal canal encroachment and possible spinal cord compression.

Benefits and capabilities of CT CS [14]**:**

- good visualization of bone contours (assessment of the position of the C1, C2 odontoid process relative to the foramen magnum and the relation between upper cervical vertebrae, measurement of intervals);
- detection of spinal cord compression by assessing subarachnoid space, weakening of the transverse ligament, as well as changes in bones and soft tissue;
- contrast-enhanced CT visualizes vascular abnormalities and inflammatory soft tissue proliferation in cases when MRI cannot be performed. However, MRI is usually better for soft tissue imaging.

Benefits and capabilities of MRI CS in a patient with RA [14]**:**

- assessment of nervous structures (MRI is the method of choice for the symptoms of myelopathy or radiculopathy);
- assessment of pannus prevalence;
- assessment of the degree of damage to the ligaments (rupture or sprain);
- high sensitivity for detecting inflammation in joints before the development of instability;
- visualization of vertebral bone marrow edema;

It should be noted that in many cases, MRI underestimates the degree of atlantoaxial subluxation compared to common functional X-ray [17]. In this regard, MRI should be augmented with X-ray, if it has not already been performed.

Other types of cervical spine instability in RA

The second most common cervical lesion in RA (20 %) is *basilar impression (cranial lowering, or superior odontoid migration)*. It develops as a result of the impaired integrity of AOJ and AAJ, which leads to the displacement of the odontoid process into the foramen magnum. Compression of the brainstem may result from such displacement. Detecting superior migration of the odontoid process on X-ray images is extremely difficult, as bone erosion and/or superimposition of various structures of the skull and spine make the identification of anatomical landmarks difficult. Therefore, X-ray is recommended as a screening examination with data assessment according to Clark's, Ranawat's and Redlund-Jonell's criteria [13].

The third most common cervical damage in RA (15 %) is *subaxial (C3–C7) instability (SAI)*. This deformation is due to synovitis and the destruction of facet joints, ligaments and intervertebral discs. The horizontal displacement of vertebrae relative to each other can lead to the compression of the spinal cord and/or cervical nerve roots. Such instability develops on several levels at once and can be fixed or mobile. According to X-ray results, a vertebral displacement of more than 20 % or 3.5 mm is considered significant. The diameter of the subaxial spinal canal should be measured from the posterior surface of the vertebral body to the ventral plate. A canal diameter of less than 13 mm on its sagittal view suggests an increased risk of developing a neurological deficit. MRI is helpful in diagnosing SAI, as the actual canal diameter may be smaller than suggested by bone measurements due to pannus [13].

Clinical signs that point to CS damage in RA patients

Structural abnormalities in CS may be accompanied by the symptoms of myelopathy, radiculopathy, vertebrobasilar insufficiency, cranial nerve involvement, and episodes of medulla oblongata dysfunction, as well as auscultatory and positional phenomena [14].

The earliest and the most common symptom of CS instability is neck pain radiating to the nape due to synovitis.

Typical signs of cervical **myelopathy** are paresthesia and numbness in the limbs, muscle weakness, spasticity or atrophy, gait disturbance, loss of agility in movement, increased deep tendon reflexes, Babinski and Hoffman symptoms, clonus, impaired bowel and bladder functions. Ranawat's classification can be used to assess the severity of myelopathy [18].

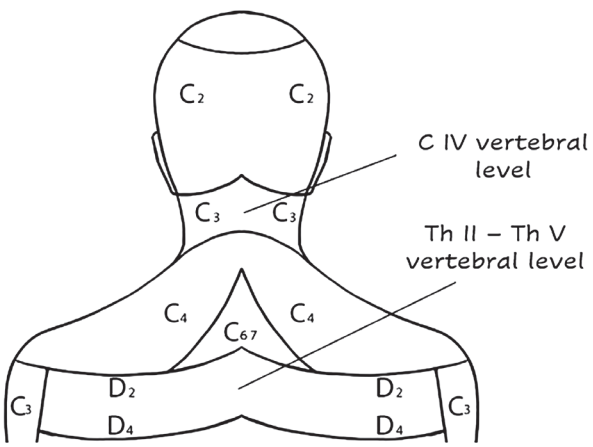


Figure 3. *Innervation of the cervical segments*

Symptoms of **radiculopathy** depend on the affected root (Figure 3) and are represented by decreased deep tendon reflexes, weakness, sensory loss, as well as positive Spurling test. Radiculopathy is especially common in patients with *subaxial subluxations* [14].

The development of **vertebrobasilar insufficiency** can be indicated by dizziness, sometimes accompanied by syncopal episodes, drop attacks, when the patient suddenly feels weak in the legs and falls without loss of consciousness, diplopia and loss of vision, etc. [14].

In some cases, the compression of V and VIII pairs of **cranial nerves** develops. An impaired V pair (trigeminal nerve) primarily leads to decreased sensitivity in the area of its innervation. Compression of the VIII pair (vestibulocochlear nerve) can be evidenced by oscillopsia (feeling of constant movement of surrounding stationary objects). C2 *superior odontoid migration* may lead to medulla oblongata compression and transient episodes of **medulla oblongata dysfunction** (for example, irregular breathing and bradycardia, etc.). Sudden death due to medulla oblongata compression was described in 10 % of cases of superior C2 migration. However, the actual frequency is unknown due to the difficulty in determining the cause of death [19].

Atlantoaxial subluxation can lead to symptoms of myelopathy, sensor loss and paresthesia in the area of C2 innervation (greater occipital neuralgia), decreased sensitivity in the area of the trigeminal nerve, nystagmus. When tilting the head forward, one can hear a dull click and/or feel the head "falling".

Therefore, when examining a patient with suspected structural changes in CS, attention should be paid to the following signs [20]**:**

- feeling of the head "falling" during flexion in the cervical region;
- changed level of consciousness;
- drop attacks;
- bowel and bladder dysfunction (loss of sphincter control);
- respiratory dysfunction;
- dysphagia, dizziness, convulsions, hemiplegia, dysarthria, nystagmus;
- peripheral paresthesia with no signs of peripheral nerve compression;
- Lhermitte phenomenon ("electrical" sensation in the neck with irradiation through the spine or into the upper limbs that occurs during cervical flexion);
- instability that cannot be explained by rheumatic joint disease;
- hand clumsiness, falling of objects from the hands that cannot be explained by rheumatic joint disease.

Identification of these signs raises the need to consult a spinal surgeon to define further treatment approach.

Patients with severe instability are recommended to undergo a stabilizing surgery in the upper cervical region, and only after that — elective surgical treatment with tracheal intubation [12].

In general, in cases of CS involvement, fiberoptic intubation or, in some cases, tracheostomy is recommended [12].

2. Pathology of temporomandibular joints (TMJ)

More than 50 % patients with RA have symptoms of TMJ damage; radiological changes in these joints are found in 78 % of patients [21]–[23] TMJ involvement can lead to narrowed mouth opening, which makes it difficult to intubate the trachea [12]. In this regard, when planning a surgery, it is recommended to palpate TMJ for soreness and/or crepitus when opening the mouth and assess the oral aperture. Measurement of mouth opening can be carried out, particularly using a three-finger index [24].

3. Arthritis of cricoarytenoid joints

Cricoarytenoid joints are formed by the articular surfaces at the base of the arytenoid cartilage and the upper edge of the cricoid cartilage plate (Figure 4). Movements in this area occur around a vertical axis.

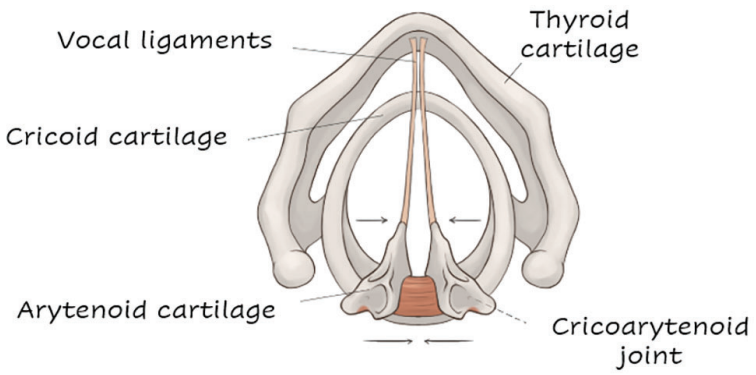


Figure 4. *Cricoarytenoid joint.*
Illustrator Rudykh A.K. According to Gross anatomy, D.A. Morton et al. with modifications [26]

The work of these joints ensures the narrowing and expansion of the glottis. Cricoarytenoid joint involvement in RA patients is found in 45–88 % of pathological examinations and in 30 % of patients in clinical trials [21, 23, 25]. Clinically, synovitis of these joints is manifested by pain in the throat, the anterior neck, sudden shortness of breath on exertion, hoarseness, dysphagia, odynophagia, and in rare cases, suffocation [23], [25]. Attempts of endotracheal intubation by standard methods in such patients, especially after several attempts to insert the tube, lead to trauma of the vocal cords [12]. After extubation, stridor and airway obstruction may develop, which requires emergency tracheostomy [12]. In cases of damage to cricoarytenoid joints, fiberoptic intubation is recommended [12].

If cricoarytenoid joint damage is suspected, preoperative indirect laryngoscopy is advised [12]. Prophylactic minitracheostomy should also be considered in several cases [16]. It should be borne in mind that patients with RA may have combined damage to the cervical spine, TMJ, and cricoarytenoid joints.

4. Kyphotic spine deformity

Kyphotic deformity of the spine is a condition when there is an increase in the natural curvature of the spine in the sagittal plane, leading to a typical deformity [27]. The three most common causes are postural kyphosis, Scheuermann's kyphosis secondary to Scheuermann-Mau disease, and congenital kyphosis [28]. In addition, such a deformity may be due to an injury or fracture, as well as a degenerative process [27]. In rheumatologic cases, the kyphotic deformity is more common compared to the others due to the development of Bechterew's disease with a typical "beggar's posture", as well as in osteoporosis ("widow's hump") (Figure 5).

Spondyloarthritis in Bechterew's disease starts with the lumbar spine, gradually involving the thoracic and cervical areas [29]. In the case of ankylosis, mobility of the spine is completely lost. Two types of deformation may develop: excessive thoracic kyphosis ("beggar's posture") or loss of physiological spine curves ("proud posture") [30]. In both cases, intubation by standard methods will be difficult due to the lost mobility of the neck and the risk of injury when trying to force flexion/extension. Fiberoptic intubation is recommended in these patients. Moreover, extensive calcification of ligaments and heterotopic ossification may result in difficulties when performing regional anesthesia [31].

In case of excessive thoracic kyphosis, a patient is unable to place his/her head with the nape on a horizontal surface; it should be considered when laying the patient. It is important to keep in mind that many patients with ankylosing spondylitis have limited chest expansion and associated ventilation problems [31].

Conclusion

Rheumatological diseases lead to motor restrictions, impaired structure and decreased function of many organs and systems, as well as the need for constant administration of various medications. All this raises the risk of various intraoperative and postoperative complications. Specific features of patients with rheumatological diseases should be considered in perioperative management.

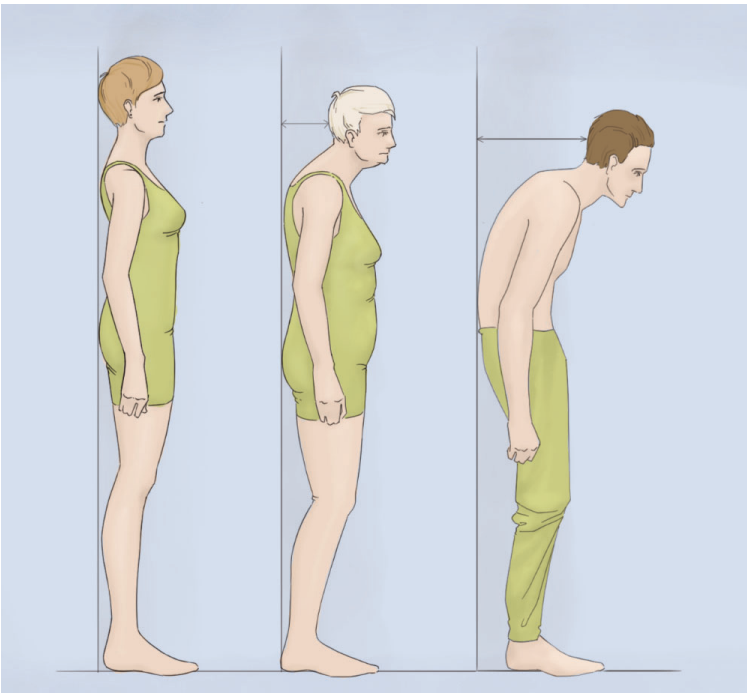


Figure 5. *Kyphotic deformity of the spine in patients with osteoporosis and ankylosing spondylitis. Illustrator Rudykh A.K.*

Вклад авторов:

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

Лялина В.В. (ORCID ID: https://orcid.org/0000-0002-4262-4060): концепция и дизайн статьи, редактирование текста, обзор публикаций по теме, взаимодействие авторов

Борисовская С.В. (ORCID ID: https://orcid.org/0000-0002-9365-1472): научная консультация, редактирование текста

Скрипниченко Э.А. (ORCID ID: https://orcid.org/0000-0001-6321-8419): концепция статьи, обзор публикаций по теме, взаимодействие авторов

Эттингер О.А. (ORCID ID: https://orcid.org/0000-0002-1237-3731): научная консультация, редактирование текста

Паджева Т.М. (ORCID ID: https://orcid.org/0000-0003-0877-9672): научная консультация, редактирование текста

Мигачёв С.Л.: научная консультация, редактирование текста

Борщенко И.А. (ORCID ID: https://orcid.org/0000-0002-8128-5364): научная консультация, редактирование текста

Никитин И.Г. (ORCID ID: https://orcid.org/0000-0003-1699-0881): редактирование текста, утверждение финального варианта статьи

Author Contribution:

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

Lyalina V.V. (ORCID ID: https://orcid.org/0000-0002-4262-4060): concept and design of the article, review of literature, authors interaction, text editing;

Borisovskaya S.V. (ORCID ID: https://orcid.org/0000-0002-9365-1472): scientific advising, text editing

Skripnichenko E.A. (ORCID ID: https://orcid.org/0000-0001-6321-8419): concept of the article, review of literature, authors interaction

Ettinger O.A. (ORCID ID: https://orcid.org/0000-0002-1237-3731): scientific advising, text editing

Padzheva T.M. (ORCID ID: https://orcid.org/0000-0003-0877-9672): scientific advising, text editing

Migachev S.L.: scientific advising, text editing

Borshchenko I.A. (ORCID ID: https://orcid.org/0000-0002-8128-5364): scientific advising, text editing

Nikitin I.G. (ORCID ID: https://orcid.org/0000-0003-1699-0881): text editing, approval of the final version of the article

Список литературы/ References:

1. Тайлер К. Н., Дин К. Д. Периоперативное ведение пациентов с ревматическими заболеваниями. Секреты ревматологии. Дж.Уэст С. ГЭОТАР-Медиа. 2018; 111-118
Tailer K. N., Din K. D. Perioperative management of patients with rheumatic diseases. Rheumatology Secrets. Sterling West GEOTAR-Media. 2018; 111-118 [In Russian]
2. Gualtierotti R., Parisi M., Ingegnoli F. Perioperative Management of Patients with Inflammatory Rheumatic Diseases Undergoing Major Orthopaedic Surgery: A Practical Overview. Advances in Therapy. 2018; 35(4): 439-456. doi: https://doi.org/10.1007/s12325-018-0686-0
3. Teixeira L. Prophylactic antibiotic use in patients with rheumatic diseases. Perioperative Management of Patients with Rheumatic Disease. Springer Science+Business Media. 2013; 87-90. DOI 10.1007/978-1-4614-2203-7_7
4. Habib G., Lancellotti P., Antunes M.J., и др. Рекомендации ESC по ведению больных с инфекционным эндокардитом 2015. Российский кардиологический журнал. 2016; 5(133): 65-116. DOI:10.15829/1560-4071-2016-5-65-116
Habib G., Lancellotti P., Antunes M.J., et al. 2015 ESC guidelines for the management of infective endocarditis. Russian Journal of Cardiology. 2016; 5(133): 65-116. DOI:10.15829/1560-4071-2016-5-65-116 [In Russian]
5. Zoumpoulakis M., Anagnostou F., Dalampiras S., Zouloumis L., Pliakos C. Infective Endocarditis Prophylaxis in Patients Undergoing Oral Surgery. Balkan Journal of Dental Medicine. 2016; 1(20): 5–14. DOI:10.1515/bjdm-2016-0001
6. Agca R., Heslinga S.C., Rollefstad S., et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Annals of the Rheumatic Diseases. 2017; 1(76): 17–28. DOI:10.1136/annrheumdis-2016-209775
7. Амирджанова В. Н., Макаров М. А., Бялик Е. И. и др. Периоперационное ведение больных ревматоидным артритом. Научно-практическая ревматология. 2014; 52: 366-375. doi: http://dx.doi.org/10.14412/1995-4484-2014-366-375
Amirdzhanova V. N., Makarov M. A., Byalik E. I. et al. Perioperative management of patients with rheumatoid arthritis. Scientific and practical rheumatology. 2014; 52: 366-375. [In Russian] doi: http://dx.doi.org/10.14412/1995-4484-2014-366-375
8. Ruffatti A., Ross T. Del, Ciprian M., et al. Risk factors for a first thrombotic event in antiphospholipid antibody carriers. A multicentre, retrospective follow-up study. Annals of the Rheumatic Diseases. 2009; 3(68): 397–399. DOI:10.1136/ard.2008.096669
9. Raso S., Sciascia S., Kuzenko A., et al. Bridging therapy in antiphospholipid syndrome and antiphospholipid antibodies carriers: Case series and review of the literature. Autoimmunity Reviews. 2015; 1(14): 36–42. DOI:10.1016/j.autrev.2014.09.002
10. Ruiz-Irastorza G., Egurbide M.-V., Pijoan J.-I., et al. Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. Lupus. 2006; 9(15): 577–583. DOI:10.1177/0961203306071872
11. Fasano S., Pierro L., Pantano I., et al. Longterm Hydroxychloroquine Therapy and Low-dose Aspirin May Have an Additive Effectiveness in the Primary Prevention of Cardiovascular Events in Patients with Systemic Lupus Erythematosus. The Journal of Rheumatology. 2017; 7(44): 1032–1038. DOI:10.3899/jrheum.161351
12. Schroeder L.L., Wasko M.C.M. Perioperative management of patients with rheumatoid arthritis. Perioperative Management of Patients with Rheumatic Disease. Springer Science+Business Media. 2013; 209-220. DOI 10.1007/978-1-4614-2203-7_7
13. Moskovich R. Rheumatoid arthritis. Spine Secrets. Elsevier. 2012; 668-678. ISBN: 978-0-323-63662-9
14. Currier B.L., Coblyn J. Cervical subluxation in rheumatoid arthritis. 2021. [Electronic resource]. URL: https://www.uptodate.com/contents/cervical-subluxation-in-rheumatoid-arthritis#:~:text=The discovertebral joints in the,%2C neurologic deficits%2C and deformity (date of the application: 17.09.2021).
15. Manaster B.J. Rheumatoid Arthritis of Axial Skeleton. Diagnostic imaging: musculoskeletal: non-traumatic disease, second edition. Elsevier. 2016; 10–16. ISBN: 978-0-323-39252-5
16. Waldt S., Woertler K. Eds. Craniocervical Junction and Cervical Spine. Measurements and Classifications in Musculoskeletal Radiology. Thieme Medical Publishers. 2014; 149-156. ISBN 978-3-13-169281-8
17. Laiho K. Can we rely on magnetic resonance imaging when evaluating unstable atlantoaxial subluxation? Annals of the Rheumatic Diseases. 2003; 3(62): 254–256. DOI:10.1136/ard.62.3.254
18. Ranawat C.S., O'Leary P., Pellicci P., et al. Cervical spine fusion in rheumatoid arthritis. Journal of Bone and Joint Surgery — Series A. 1979; 7(61). DOI:10.2106/00004623-197961070-00006

19. Mikulowski P., Wollheim F.A., Rotmil P., et al. Sudden Death in Rheumatoid Arthritis with Atlanto-axial Dislocation. Acta Medica Scandinavica. 2009; 1–6(198): 445–451. DOI:10.1111/j.0954-6820.1975.tb19573.x
20. Mayer J.W. Brain stem compression in rheumatoid arthritis. JAMA: The Journal of the American Medical Association. 1976; 18(236). DOI:10.1001/jama.236.18.2094
21. Harris E.D., Firestein G.S. Clinical Features of Rheumatoid Arthritis. Kelley's Textbook of Rheumatology. Elsevier. 2021; 1236-1257. ISBN: 978-0-323-63920-0
22. Reddy D., Trost L.W., Lee T., et al. Rheumatoid arthritis: Current pharmacologic treatment and anesthetic considerations. Middle East Journal of Anesthesiology. 2007; 2(19): 33-311. PMID: 17684873
23. Matti M. V., Sharrock N.E. Anesthesia on the rheumatoid patient. Rheumatic Disease Clinics of North America. 1998; 1(24): 19-34. DOI:10.1016/S0889-857X(05)70375-6
24. Wood G.D., Branco J.A. A comparison of three methods of measuring maximal opening of the mouth. Journal of Oral Surgery. 1979; 3(37): 7-175
25. Lyssy L., Escalante A. Perioperative management of rheumatoid arthritis: Areas of concern for primary care physicians. Postgraduate Medicine. 1996; 2(99): 199-201. PMID: 8632966
26. Morton D., Foreman K., Albertine K. Chapter 28. Larynx. Gross Anatomy. McGraw-Hill Education. 2019; 289-298. ISBN: 978-1-25-986264-9
27. Parvizi J. Kyphosis. High Yield Orthopaedics. 1st ed. Elsevier. 2010; 266–267. ISBN 9780323314985
28. Lam J., Mukhdomi T. Kyphosis. 2021. [Electronic resource]. URL: https://www.ncbi.nlm.nih.gov/books/NBK558945/ (date of the application: 16.09.2021).
29. Brent L.H. Ankylosing Spondylitis and Undifferentiated Spondyloarthropathy Clinical Presentation. 2021. [Electronic resource]. URL: https://emedicine.medscape.com/article/332945-clinical#b1 (date of the application: 17.09.2021)
30. Ассоциация ревматологов России. Глава 2. Анкилозирующий спондилит. Ревматология. Российские клинические рекомендации под ред. Насонова Е.Л. ГЭОТАР-Медиа. 2020; 69 Russian Association of Rheumatologists. Chapter 2. Ankylosing spondylitis. Rheumatology. Russian Clinical guidelines, ed. Nasonov E.L., GEOTAR-Media. 2020; 69 [In Russian]
31. Axford J. S. Preoperative evaluation and perioperative management of patients with rheumatic diseases. 2021. [Electronic resource]. URL: https://www.uptodate.com/contents/preoperative-evaluation-and-perioperative-management-of-patients-with-rheumatic-diseases#H11 (date of the application: 16.09.2021).

DOI: 10.20514/2226-6704-2022-12-3-187-194 УДК 618.177-06:616.89-008-085

В.Э. Медведев

Кафедра психиатрии, психотерапии и психосоматической патологии факультета непрерывного медицинского образования медицинского института Российского университета дружбы народов, Москва, Россия

ПСИХОСОМАТИЧЕСКИЕ ОСЛОЖНЕНИЯ СНИЖЕНИЯ ИЛИ НАРУШЕНИЯ ГЕНЕРАТИВНОЙ ФУНКЦИИ У ПАЦИЕНТОК ОБЩЕСОМАТИЧЕСКОЙ СЕТИ (ОБЗОР ЛИТЕРАТУРЫ)

V.E. Medvedev

Department of Psychiatry, Psychotherapy and Psychosomatic Pathology, Faculty of Con-tinuing Medical Education, Medical Institute, Peoples' Friendship University of Russia (RUDN University), Ministry of Education and Science of Russia, Moscow, Russia

Psychosomatic Complications of Decreased or Impaired Generative Function in General Medical Patients (Review)

Резюме

Помимо целого ряда соматических недугов у 49-100 % пациенток с бесплодием верифицируются психические расстройства: 35-56 % — депрессии разной степени тяжести, 25-76 % — тревожные и психосексуальные расстройства, 40 % — тревожно-депрессивные расстройства, 50 % — расстройства адаптации, к 9,5 % — суицидальные мысли и попытки. У 75 % женщин, обращающихся за медицинской помощью в период менопаузы, также выявляются расстройства тревожного, депрессивного, дисморфического и психотического спектров.

Психофармакотерапия у пациенток проводится с использованием современных антидепрессантов, анксиолитиков, антипсихотиков с акцентом на хорошую переносимость, совместимость с гормональной терапией, удобство дозирования.

Психотерапия, психологическое сопровождение и психокоррекционная работа позволяют уменьшить выраженность тревожно-депрессивной симптоматики и существенно повысить успешность лечебных процедур

Ключевые слова: *психические расстройства, бесплодие, менопауза, климакс, депрессия, тревога, дисморфическое расстройство, психоз, инволюция, лечение, терапия*

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

Статья получена 23.11.2021 г.

Принята к публикации 09.02.2022 г.

*Контакты: Владимир Эрнстович Медведев, e-mail: melkorcord@mail.ru

*Contacts: Vladimir E. Medvedev, e-mail: melkorcord@mail.ru

ORCID ID: https://orcid.org/0000-0001-8653-596X

Для цитирования: Медведев В.Э. ПСИХОСОМАТИЧЕСКИЕ ОСЛОЖНЕНИЯ СНИЖЕНИЯ ИЛИ НАРУШЕНИЯ ГЕНЕРАТИВНОЙ ФУНКЦИИ У ПАЦИЕНТОК ОБЩЕСОМАТИЧЕСКОЙ СЕТИ (ОБЗОР ЛИТЕРАТУРЫ). Архивъ внутренней медицины. 2022; 12(3): 187-194. DOI: 10.20514/2226-6704-2022-12-3-187-194. EDN: KJMNH

Abstract

In 35-56 % of patients depression of varying severity was diagnosed, in 25-76 % — anxiety and psychosexual disorders, in 40 % — anxiety and depressive disorders, in in 50 % — adjustment disorders, to 9.5 % — suicidal thoughts and attempts. Anxiety, depressive, dysmorphic and psychotic spectrum disorders are identified in 75 % of women seeking medical care during the menopause.

Psychopharmacotherapy in female patients includes modern antidepressants, anxiolytics, and antipsychotics, with an emphasis on good tolerability, compatibility with hormone therapy, and easy dosing.

Psychotherapy, psychological support and psychocorrectional work can reduce the severity of anxiety and depressive symptoms and significantly increase the success of treatment procedures

Key words: *mental disorders, infertility, menopause, depression, anxiety, dysmorphic disorder, psychosis, involution, treatment, therapy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 23.11.2021

Accepted for publication on 09.02.2022

For citation: Medvedev V.E. Psychosomatic Complications of Decreased or Impaired Generative Function in General Medical Patients (Review). The Russian Archives of Internal Medicine. 2022; 12(3): DOI: 187-194. DOI: 10.20514/2226-6704-2022-12-3-187-194. EDN: KJMNH

According to present-day literature, sharp and cyclic fluctuations of estrogens, changes in the level of estrogen receptors in brain structures (including amygdala, hippocampus, hypothalamus), as well as the suppression of the activity of GABAergic neurons by progesterone, decreased secretion of GnRH and melatonin, decreased stimulating effect of thyreoliberin on the secretion of TSH, corticoliberin on ACTH, and vasopressin on cortisol [1–2] lead not only to infertility or the early onset of the perimenopausal period, but also to a significant deterioration in the somatic and mental health of female patients seeking medical help in general healthcare facilities.

The objective of this review was to analyze the results of core studies on the psychosomatic complications of a decrease or impairment of the generative function in female patients of general healthcare facilities.

Search by keywords “mental disorders”, “infertility”, “menopause”, “climacteric”, “depression”, “anxiety”, “dysmorphic disorder”, “psychosis”, “involution”, “treatment”, “therapy” was conducted in the databases of articles published by domestic and foreign authors over last 25 years (PubMed, eLibrary, Scopus, and ResearchGate). The material obtained was of three types: reviews, books, and original research articles. For this analysis, domestic and foreign literature sources were selected, which revealed the nature of the studied population and were available to the authors of this publication.

The negative impact of impaired fertility (in cases of infertility) is accompanied by a deterioration in family and work adaptation, decreased regularity (50.4 %) and satisfaction (62.2 %) with sexual life, long duration and clinical severity of premenopausal symptoms [3]; female patients seek medical advice for these signs, primarily from general physicians.

It should be noted that heterogeneous causes of infertility[1] include such somatogenic factors as chronic immunological and endocrine disorders, urogenital infections, anomalies and pathologies of the uterus and fallopian tubes, substance abuse, and psychosexual disorders [6, 7].

In turn, the complications of infertility, along with an increased incidence of diseases of internal organs (endocrine, cardiovascular, reproductive systems), include psychogenic mental disorders [3, 6, 8, 9], all falling under the concept of “biopsychosocial crisis” [10].

In general medical practice, typical signs of a “biopsychosocial crisis” for women in connection with infertility are behavioral disorders, such as proneness to conflict, accusing physicians of incompetence, dedicating life to the fixed (up to obsession) idea of getting pregnant with a radical change in lifestyle, refusal to eat certain products, exhausting physical exercises, diets, developing a special sleep schedule, etc. [11], as well as the dissimulation of bodily health problems in order to appear “healthier than they really are” [12].

Emotionally, patients are characterized by mood swings, anxiety, infantilism, dependence, loss of control over ongoing events, unstable or low self-esteem, negative attitude towards themselves, a sense of shame that impedes their empathy with others, absence of a holistic cognitive concept of the disease, and the dominance of mystical ideas about the unfulfillment of the maternal role [13–14].

[1] Infertility is the inability of a sexually active couple to achieve pregnancy after one year of unprotected sex [4]. In clinical studies and medical practice, infertility is a disease of the reproductive system that is manifested in the absence of a clinical pregnancy after 12 or more months of regular unprotected sex [5].

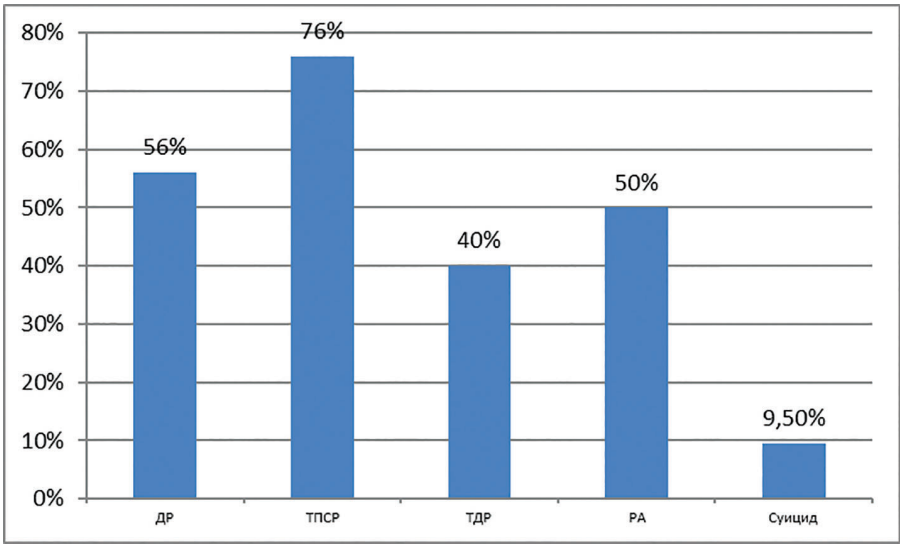


Figure 1. *Frequency of mental disorders in infertility*
Note: ДР — Depression, ПТСР — Posttraumatic Stress Disorder, ТДР — Anxiety & Depression Disorders, Suicide

The development of clinically defined forms of mental disorders with an underlying "biopsychosocial crisis" is confirmed in 49–100 % of female patients [1, 8, 15, 16]: 35–56 % develop depression of varying severity (VD) [17, 18], 25–76 % — anxiety and psychosexual disorders (APSD) [16, 18], 40 % — anxiety-depressive disorders (ADD), 50 % — adjustment disorders (AD) [18]. 9.5 % of patients have suicidal thoughts and attempts [6, 19] (Figure 1).

It should be emphasized that in case of depression due to infertility, patients often have complaints of hypersomnia, hyperphagia, and somatization (hysteralgia) disorders that become the reason for seeing a general physician and require differential diagnosis with laboratory tests and instrumental examinations.

In order to facilitate and accelerate the correct diagnosis, physicians can perform an additional examination of patients, including psychometric scales that allow establishing increased levels of asthenic and apathetic, anxiety and phobic symptoms, dysphoria, lethargy, and mood lability.

The period of decline and end of fertility (premenopausal period, menopause, climacteric) is characterized by other endocrinological changes. Physiologically, the whole menopausal period is characterized by a decrease in reproductive function with a gradual increase in the threshold of sensitivity of the hypothalamic-pituitary complex to homeostatic regulation of estrogens by feedback type, as well as a decreased level of receptors for peptide and steroid hormones in the hypothalamus, increased concentration of pituitary FSH, and impaired melatonin production [21, 22].

The duration of premenopause varies from 2 to 15 years. Menopause starts with the last spontaneous period. Menopausal age is determined retrospectively, after 12 months of the absence of periods. Early menopause happens when a woman's periods stop before the age of 45; late menopause — after the age of 55. The perimenopausal period includes premenopause and two years after the last spontaneous menstruation. Postmenopausal period lasts from menopause to almost complete end of ovarian function [20].

From a therapeutic point of view, it is significant that 35–80 % of women have climacteric syndrome (N95.1 according to ICD-10, pathological "climacteric comorbidity" [23]), with the combination of menopausal signs (vasomotor: hot flashes, night sweats; urogenital and metabolic, somatized, cognitive and, finally, anxiety and depressive signs (Table 1) [1, 21, 24, 25].

A specific feature of the clinical presentation of such women during their appointment is the verbalization of statements indicating the presence of one or more pathopsychological symptom complexes: "midlife crisis", "pension bankruptcy", "loneliness phenomenon" [26],

Table 1. *Symptoms of pathological «menopausal comorbidity»*

Symptom group	Symptom
Urogenital	Vaginal dryness, dyspareunia, decreased sexual activity
Metabolic	Slower metabolism and lower energy level
Somatized	Pain symptoms of various localizations, distress, breathing difficulties
Cognitive	Impaired attention and memory
Anxiety-depressive	Depression, irritability, sleep disturbances

"downhill of life", "empty nest syndrome" [27], "loss of female attractiveness" syndrome (body image, physical self-concept, self -image [28]), "generation gap" and "sandwich syndrome" (the need to solve a dilemma between the supporting different generations of the family: children with their problems (enrollment into university, marriage) and somatically aging parents [29]), etc.

Also, the main complaints in 75 % of women seeking medical care during menopause are low mood and sleep disturbances [50, 56–62]. Depression is diagnosed in 15.8–20 % of women [24].

Predictors of depression in the perimenopausal period include the manifestation of somatic diseases, low physical activity, early onset of menopause, changes in family roles, social functioning, financial status, stressful situations, mental disorders that developed in the postpartum period [2].

The identification by a general physician of any specialization of depressive states in female patients in involution has a critical prognostic and social significance.

Firstly, involutional depressions are characterized by a high level of irritability, anxiety, fears ("imminent old age", loneliness, financial insecurity, loss of external attractiveness), multiple asthenic and somatovegetative signs (conversion, somatization, vegetative: hot flashes or chills, increased sweating, intolerance to stuffiness, sense of not getting enough air, sense of "burning" in the body, palpitations, algia, dyspepsia, "squeezing" sensation in the heart, trembling, pseudosyncope, dizziness, "spasms" in throat) and hypochondriacal phobias (hysterophobia, obsessive fears of a serious disease) with active seeking of medical advice from general physicians, "extortion of care", ostentation, dramatic "grieving", suicidal threat. All these symptoms greatly complicate the diagnosis of actual somatic disorders and delay the choice of adequate pharmacotherapy and referral of the patient to a psychiatrist or psychotherapist.

Secondly, the late involvement of a mental health specialist in the joint management of patients in menopause can often lead to a sharp aggravation of the mental (Table 2) and somatic condition of the patients.

Involutional melancholy is observed in 82 % of women and 10–46 % of patients of a general practitioner [24]. Its causes can be somatogenic (genetic predisposition, hypertension, coronary heart disease, cardiac arrhythmias), endocrine (hypoestrogenia, hormonal disorders in the reproductive system due to uterine fibroids, endometriosis, hystero- or oophorectomy) and psychogenic (chronic or subjectively severe conflicts, death in the family, loss or change of job, place of residence, financial difficulties, etc.) [30–31].

Typical features of ***involutional psychosis*** [32] are an illusory perception of the world around, agitation, Charpentier symptom of impaired adaptation (when the anxiety of patients increases when changing location or being transferred to another ward or hospital), Cotard's syndrome (patients cry, wring their hands, are sure that their "body has died, decomposed", or that their "children, relatives have died"; sometimes with the ideas of the death of the world), Kleist's symptom (a woman whines for a long time, asks for help; if the physician tries to talk to her, she immediately stops talking, refuses to talk, as soon as the physician leaves, she starts whining again), autoaggressive and suicidal tendencies (Table 2) [33–36].

Patients with ***hypochondriacal delusion*** try to normalize/restore functions of internal organs (respiratory, digestive, cardiovascular systems) that are lost from their point of view. The absurdity of the substance of such a delusion (a deviated septum "affects the supply of oxygen to different lungs", the shape of cheekbones has an effect on the development of obstipation, etc.) is combined with a high degree of systematization, detailed elaboration based on data obtained from specialized literature sources. Patients interpret the lack of results expected from treatment as a sign of "undertreatment" and the need to continue that or another type of treatment until full recovery (Table 2) [37–40].

Involutional paranoid disorder starts gradually with the development of persistent delusional ideas. Patients are convinced that their neighbors or relatives enter their apartment at night or in their absence, using specially made keys, steal things, poison food, release toxic gas, pour poisonous powder (small delusions), meet at night, arrange gatherings of suspicious people with "loud voices that can be heard behind the wall". The behavior of patients is characterized by suspicion, distrust, tendency to various quarrels and squabbles. They file complaints with various authorities (police, community courts, prosecutor's office), demand punishment for people who have caused material damage, and they lock everything that can be locked — boxes, cupboards and even pots. The condition is accompanied by verbal and olfactory hallucinations. Change of residence does not help eliminate such painful experiences (Table 2) [33–36].

Involutional catatonia is characterized by staged development of symptoms in the form of depression, hypochondriacal phobias, unmotivated anxiety coupled with delusional ideas of persecution, self-accusation, development of Cotard's syndrome, and a stuporous state with complete immobility and mutism. Psychosis ends with the development of presenile dementia.

With a malignant form of involutional catatonia, i.e., ***presenile psychosis***, anxiety and depressive state, incoherent speech, confusion with massive psychomotor agitation are replaced by inhibition with clouded consciousness of the oneiroid type and illusory delusions, Cotard's syndrome. Patients think they are attending their own funeral or the funeral of relatives or acquaintances, that they see various events and regard them as "the death of the Earth, the catastrophe of the Universe". Patients refuse to eat, cachexia is registered. Death in such cases can occur from an associated/exacerbated somatic disease (Table 2) [33–36].

Patients with ***dysmorphic delusions*** (dysmorphomania regarding "beauty", "ugliness", "nose", "weight", "appearance", etc.) have dominating erroneous uncorrectable and behavior-determining ideas about "ugliness", "abnormal structure" or "deformities" of certain

parts of their body. Overestimation and enthusiastic admiration of the appearance of others are combined with categorical, multiple and inconsistent complaints against one's own appearance, active and annoying visits to several specialists at once in order to correct a "physical defect", requirements of ever new methods of examination and therapy with inability to comply with medical recommendations and to wait for the effect, as well as litigious reactions on dissatisfaction with the results of surgeries, demands for material compensation (paranoia of struggle, 24.1 %) [41, 42]. The behavior of patients is also characterized by the use of protective camouflage of imaginary defects with the help of special hairstyles or make-up, wearing of extravagant clothes or eye-catching jewelry, darkened glasses, hats, clothes of a special cut that cover the "ugly" parts of the body.

A typical sign is auto-aggression with a desire to remove (sometimes with a razor, knife, hot objects) "pigmented spots" and other "ugly" skin areas or correct a "defect" (shaving and pulling out hair, cutting nose, filing teeth) on their own, with subsequent visit to a cosmetologist or plastic surgeon to correct the results of such interventions (Table 2) [37–42].

Patients with involutional ***erotomanic delusions*** constantly visit specialists in aesthetic medicine in order to correct their appearance to achieve sexual attractiveness for a partner. The requests do not fit the patient's age and/or somatic condition: physical abilities are overestimated, the difference in age and social status is not considered. Patients are convinced that after cosmetic or surgical treatment, they will "certainly" acquire an appearance that is "irresistible" for the object of their ecstatic affection, achieve mutual feelings, and enter into marriage or intimate relationships. Having failed to achieve what they were looking for, patients return to aesthetic medicine specialists with complaints of poorly performed treatment and ask for repeated and additional interventions. In 6.9 % of female patients, the physician becomes involved in the system of erotic delusions and persecuted by the patient (Table 2) [37–42].

Therefore, mental disorders that develop with underlying impairment, decline and loss of fertility are heterogeneous. Their effect on the somatic state of patients, as well as clinical and dynamic diversity requires timely diagnosis, as early as the stage of contacting general physicians and joint management with psychiatrists.

Dealing with the management of psychosomatic complications and reducing the generative cycle in women in general healthcare facilities require emphasizing the obligatory joint management of patients with psychotic conditions with a psychiatrist and optional consultation for anxiety and depressive disorders, due to the likelihood of the manifestation/exacerbation of these disorders that are both independent of the somatic status of the patient, and caused by changes in her somatic and endocrinological state.

Table 2. *Main clinical symptoms of involutional psychoses*

Involutional psychosis [32-36]	Illusory perception Agitation Charpentier's symptom Cotard syndrome Kleist symptom Autoagressive and suicidal tendencies
Involutional paranoid [33-36]	Suspiciousness, mistrustfulness Delusion of detriment Verbal and olfactory hallucinations Querulousness Suffocation
Hypochondriacal delusion [37-40]	Absurd systematized delusion Uncorrected desire to normalize/restore «lost» internal organ functions
Involutional catatonia	Depression Unmotivated anxiety Delusion of persecution, self-blame Cotard syndrome Stupor Mutism Presenile dementia
Presenile psychosis [33-36]	Involutionary catatonia Oneiroid Manichean delirium Eating disorders
Dysmorphic delusion [37-42]	Uncorrected and behavior-defining ideas of «ugliness», «structural abnormalities», or «deformities» of certain body parts Protective camouflage Autoaggression The demands of ever-new examination and therapy methods Sutile reactions
Erotomania [37-42].	Inconsistent with somatic and social status demand for correction of appearance to achieve erotic attractiveness for a partner

Psychopharmacotherapy in female patients with infertility is carried out using advanced antidepressants, anxiolytics, antipsychotics with an emphasis on good tolerance, compatibility with hormonal therapy, and easy dosing. When choosing agents, in addition to following the standard recommendations, one should consider risk factors (heredity, comorbid disorders, sex, age, etc.) for the development of adverse events (AEs), the range of somatotropic and endocrine side effects typical for each drug, the balance of efficacy and safety, the possibility of drug-drug interactions with therapeutic medications.

Psychotherapy, psychological support, and psychocorrection work can also reduce the severity of anxiety and depressive symptoms and increase the success of treatment procedures (for example, in cases of IVF, from 29.8 % to 42.1 %) [43].

In our opinion, the effectiveness of hormone replacement therapy (HRT, including those with "general tonic" drugs, vitamins, dietary supplements, physiotherapy) is not obvious in cases of mental disorders in the pre- and menopausal periods. Some studies indicate that estrogen replacement therapy is moderately effective in preventing and managing menopausal depression [44]. Others suggest that women receiving HRT in the perimenopausal period have a higher level of depression than those who do not receive such agents [45]; that using hormonal agents is ineffective, and can even trigger an exacerbation of psychopathological symptoms and worsening of patient's condition [46].

The use of estrogen and melatonin to augment psychopharmacotherapy has been discussed in recent years [40].

SSRIs (fluvoxamine, citalopram), SNRIs (duloxetine) and agomelatine are among the preferred antidepressants [47].

Long-term use of any antidepressants can result in decreased bone mineral density, increased body weight, and metabolic syndrome [21].

According to post-marketing studies, non-benzodiazepine agents, such as fabomatizole [48], 4,6,8-tetramethyl-2,4,6,8-tetraazabicyclo-(3,3,0)-octanedione-3,7 (mebicarum, adaptol) [49] and nootroph D-,L-hopantenic acid, are recommended as drugs with an anxiolytic effect for use in the perimenopausal period [50].

Psychotherapy is aimed at building a constructive psychological defense (in particular, self-control and responsibility) and adaptive behavioral coping strategies (reattribution with a decreased threatening meaning of somatized symptoms, creating the conviction that there is no life-threatening physical disease, proper assessment of the actual situation, and desisting from manipulations) [30].

Список литературы/ References:

1. Васильева А.В. Проблемы женского психического здоровья — междисциплинарный ракурс. РМЖ. Медицинское обозрение. 2018; 2(10): 51-56.
   Vasil'eva AV. Problems of women's mental health — an interdisciplinary perspective. breast cancer. Medical review. 2018; 2(10): 51-56 [In Russian].
2. Мазо Г.Э., Незнанов Н.Г. Депрессивное расстройство. Москва: ГЭОТАР-Медиа, 2019; 112 с.
   Maso GE, Neznanov NG. Depressive disorder. Moscow: GEOTAR-Media, 2019; 112 p. [In Russian].
3. Тювина Н.А., Воронина Е.О., Балабанова В.В., Гончарова Е.М. Взаимосвязь и взаимовлияние менструально-генеративной функции и депрессивных расстройств у женщин. Неврология, нейропсихиатрия, психосоматика. 2018; 10(2): 45–51 DOI: 10.14412/2074-2711-2018-2-45-51
   Tjuvina NA, Voronina EO, Balabanova VV, Goncharova EM. Interrelation and mutual influence of menstrual-generative function and depressive disorders in women. Neurology, neuropsychiatry, psychosomatics. 2018; 10(2): 45–51. [In Russian]. DOI: 10.14412/2074-2711-2018-2-45-51
4. National Collaborating Centre for Mental Health (UK). Antenatal and Postnatal Mental Health: The NICE Guideline on Clinical Management and Service Guidance. Leicester (UK): British Psychological Society; 2007. [Electronic resource]. URL: https://pubmed.ncbi.nlm.nih.gov/21678630/ (date of the application: 09.03.2022).
5. Zegers-Hochschild F., Adamson G.D., de Mouzon J., et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology. Fertility and Sterility. 2009; 92(5): 15-282. doi:10.1016/j.fertnstert.2009.09.009
6. Тювина Н.А., Николаевская А.О. Бесплодие и психические расстройства у женщин. Сообщение 1. Неврология, нейропсихиатрия, психосоматика. 2019; 11(4): 117-124. https://doi.org/10.14412/2074-2711-2019-4-117-124
   Tjuvina NA, Nikolaevskaja AO. Infertility and mental disorders in women. Message 1. Neurology, neuropsychiatry, psychosomatics. 2019;11(4):117-124. [In Russian]. https://doi.org/10.14412/2074-2711-2019-4-117-124
7. Леваков С.А., Павлова С.А., Бугрова Т.И., и др. Современный взгляд на бесплодный брак. Клиническая практика. 2010; 1(3): 92-97. DOI: https://doi.org/10.17816/clinpract1392-97
   Levakov SA, Pavlova SA, Bugrova TI, et al. A modern view of infertile marriage. Clinical practice. 2010;1(3):92-97. [In Russian]. DOI: https://doi.org/10.17816/clinpract1392-97
8. Гарданова Ж.Р., Брессо Т.И., Есаулов В.И. и др. Особенности формирования материнской доминанты у молодых девушек. Наука, техника и образование. 2017; 11(41): 70-74.
   Gardanova ZhR, Bresso TI, Esaulov VI.et al. Features of the formation of the maternal dominant in young girls. Science, technology and education. 2017; 41(11): 70-74. [In Russian].
9. Тювина Н.А., Коробкова И.Г. Сравнительная характеристика клинических особенностей депрессии при биполярном аффективном расстройстве I и II типа. Неврология, нейропсихиатрия, психосоматика. 2016; 8(1): 22-28. https://doi.org/10.14412/2074-2711-2016-1-22-28
   Tjuvina NA, Korobkova IG. Comparative characteristics of clinical features of depression in bipolar affective disorder type I and II. Neurology, neuropsychiatry, psychosomatics. 2016;8(1):22-28. [In Russian]. https://doi.org/10.14412/2074-2711-2016-1-22-28
10. Van den Broeck U., Emery M., Wischmann T., et al. Counselling in infertility: individual, couple and group interventions. Patient Educ Couns. 2010 Dec; 81(3): 422-428. doi: 10.1016/j.pec.2010.10.009.
11. Karimzadeh M., Rostami M., Teymouri R., et al. The association between parental mental health and behavioral disorders in preschool children. Electron Physician. 2017 Jun 25; 9(6): 4497-4502. doi: 10.19082/4497.

12. Rooney K.L., Domar A.D. The relationship between stress and infertility. Dialogues Clin Neurosci. 2018 Mar; 20(1): 41-47. doi: 10.31887/DCNS.2018.20.1/klrooney.
13. Дементьева Н.О., Бочаров В.В. Психологические аспекты исследования женского бесплодия «неясной этиологии», Вестник СПбГУ. Сер. 12, 2010, вып. 1.
Dementieva N.O., Bocharov V.V. Psychological aspects of the study of female infertility of "unclear etiology", Bulletin of St. Petersburg State University . Ser. 12, 2010, vy`p. 1. [In Russian].
14. Agarwal A., Gupta S., Sharma R.K. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol. 2005 Jul 14; 3: 28. doi: 10.1186/1477-7827-3-28.
15. Насырова Р.Ф. Современное состояние проблемы изучения психического здоровья женщин с патологией репродуктивной системы. Сибирский вестник психиатрии и наркологии. 2010; 1 (58): 52-55.
Nasyrova RF. The current state of the problem of studying the mental health of women with pathology of the reproductive system. Siberian Bulletin of Psychiatry and Narcology. 2010;1 (58): 52-55. [In Russian].
16. Volgsten H., Skoog Svanberg A., Ekselius L., Lundkvist O., Sundström Poromaa I. Risk factors for psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. Fertil Steril. 2010 Mar 1; 93(4): 1088-1096. doi: 10.1016/j.fertnstert.2008.11.008.
17. Holley S.R., Pasch L.A., Bleil M.E., et al. Prevalence and predictors of major depressive disorder for fertility treatment patients and their partners. Fertil Steril. 2015 May; 103(5): 1332-1339. doi: 10.1016/j.fertnstert.2015.02.018.
18. Peterson B.D., Sejbaek C.S., Pirritano M., et al. Are severe depressive symptoms associated with infertility-related distress in individuals and their partners? Hum Reprod. 2014 Jan; 29(1): 76-82. doi: 10.1093/humrep/det412
19. Shani C., Yelena S., Reut B.K., et al. Suicidal risk among infertile women undergoing in-vitro fertilization: Incidence and risk factors. Psychiatry Res. 2016 Jun 30; 240: 53-59. doi: 10.1016/j.psychres.2016.04.003.
20. Harlow S.D., Gass M., Hall J.E., et al. STRAW + 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012 Apr; 97(4): 1159-1168. doi: 10.1210/jc.2011-3362.
21. Мазо Г.Э., Ганзенко М.А. Депрессии у женщин в период менопаузального перехода. Психиатрия и психофармакотерапия. 2016; 18 (6): 30–36.
Mazo GJe, Ganzenko MA. Depression in women during the menopausal transition. J Psychiatry and psychopharmacotherapy. 2016; 18(6): 30–36. [In Russian].
22. Hale G.E., Robertson D.M., Burger H.G. The perimenopausal woman: endocrinology and management. J Steroid Biochem Mol Biol. 2014 Jul; 142: 121-131. doi: 10.1016/j.jsbmb.2013.08.015.
23. Bezerra A.G., Andersen M.L., Tufik S., et al. Approach towards mild depression: shortest way to treat climacteric syndrome? Maturitas. 2013 Jan; 74(1): 105. doi: 10.1016/j.maturitas.2012.10.009.
24. Мазо Г.Э., Горобец Л.Н. Предменструальный синдром: взгляд психиатра. Психические расстройства в общей медицине. 2017; 3–4: 31–36.
Mazo GJe, Gorobec LN. Premenstrual syndrome: a psychiatrist's view. J Mental disorders in general medicine. 2017; 3–4: 31–36. [In Russian].
25. Сметник В.П., Ткаченко Н.М., Глезер Г.А. и др. Климактерический синдром. М., 1988; 286 с.
Smetnik VP, Tumilovich LG, Glezer GA et al. Climacteric syndrome. M.,, 2006. 1988; 286 p. [In Russian].
26. Полищук Ю.И., Баранская И.В., Голубцова Л.И., с соавт. Основные факторы, определяющие развитие состояний одиночества с депрессивными расстройствами в позднем возрасте. Социальная и клиническая психиатрия. 2000; S1: 164-165.
Polishhuk YuI, Baranskaya IV, Golubczova LI, et al. The main factors determining the development of loneliness with depressive disorders in late life. J Social and clinical psychiatry. 2000;S1: 164-165. [In Russian].
27. Schmidt P.J., Murphy J.H., Haq N., Rubinow D.R., Danaceau M.A. Stressful life events, personal losses, and perimenopause-related depression. Arch Womens Ment Health. 2004 Feb; 7(1): 19-26. doi: 10.1007/s00737-003-0036-2.
28. Bloch A. Self-awareness during the menopause. Maturitas. 2002 Jan 30; 41(1): 61-68. doi: 10.1016/s0378-5122(01)00252-3.
29. Helson R., Soto C.J. Up and down in middle age: monotonic and nonmonotonic changes in roles, status, and personality. J Pers Soc Psychol. 2005 Aug; 89(2): 194-204. doi: 10.1037/0022-3514.89.2.194.
30. Медведев В.Э. Психопатологические аспекты инволюционной истерии. Consillium medica [женское здоровье]. 2012; 6: 26-9.
Medvedev VE. Psychopathological aspects of involutional hysteria. Consillium medica [Women's health]. 2012; 6: 26-9. [In Russian].
31. Волель Б.А., Яньшина Т.П. Инволюционная истерия в рамках динамики расстройств личности. Журнал неврологии и психиатрии им. С.С.Корсакова. 2005; 105(8): 18-23
Volel BA, Yanshina TP. Involutional hysteria within the dynamics of personality disorders. Journal of Neurology and Psychiatry named after S.S.Korsakov. 2005; 8 (105): 18-23 [In Russian].
32. Kraepelin E. Zur Entartungsfrage. Zentralblatt für Nervenheilkunde und Psychiatrie, Jg. 31, Neue Folge Bd. 19, 1908, S. 745-751.
Kraepelin E. On the degeneracy question. Zentralblatt für Nervenheilkunde und Psychiatrie, Jg. 31, New Episode Vol. 19, 1908, S. 745-751.
33. Волель Б.А., Яньшина Т.П. Инволюционная истерия в рамках динамики расстройств личности. Журн. невр. и психиатр. им. С.С. Корсакова. 2004; 11: 47–54.
Volel' BA, Jan'shina TP. Involutional hysteria within the dynamics of personality disorders. Journal of Neurology and Psychiatry named S.S. Korsakov.2004;11:47–54. [In Russian].
34. Гиляровский В.А. Психиатрия. М: Медгиз 1954.
Gilyarovskij VA. Psychiatry. M: Medgiz. 1954. [In Russian].
35. Гейер Т.А. К постановке вопроса об «инволюционной истерии». Тр. психиатр. клин. I Моск. ун-та. 1927; 2: 45–51.
Gejer TA. To raise the question of "involutional hysteria". Tr. psychiatrist. wedge. I Moscow. un-ty. 1927; 2: 45–51. [In Russian].
36. Bumke O. Lehrubuch des Geisteskrankheiter 1924; 438–456.
37. Медведев В.Э., Фролова В.И., Авдошенко К.Е., с соавт. Патохарактерологические и патопсихологические расстройства у пациентов пластического хирурга и косметолога. Экспериментальная и клиническая дерматокосметология. 2012; 3:60-64.
Medvedev VE, Frolova VI, Avdoshenko KE, et al. Pathoharacterological and pathopsychological disorders in patients of plastic surgeon and cosmetologist. Experimental and clinical dermatocosmetology. 2012; 3:60-64. [In Russian].
38. Медведев В.Э., Фролова В.И., Гушанская Е.В., с соавт. Депрессии с расстройствами пищевого поведения: клиника и терапия. Неврология, нейропсихиатрия, психосоматика. 2020; 12(4): 49–56. DOI: 10.14412/2074-2711-2020-449-56
Medvedev VE, Frolova VI, Gushanskaya EV, et al. Depression with eating disorders: clinic and therapy. J Neurology, neuropsychiatry,

psychosomatics. 2020;12(4):49–56. [In Russian]. DOI: 10.14412/2074-2711-2020-4-49-56

39. Медведев В.Э., Фролова В.И., Мартынов С.Е., с соавт. Психические расстройства с необоснованным недовольством собственной внешностью у пациентов пластического хирурга и косметолога. Психиатрия и психофармакотерапия. 2016; 6: 49-54.
Medvedev VE, Frolova VI, Marty`nov SE et al. Mental disorders with unreasonable dissatisfaction with their own appearance in patients of a plastic surgeon and cosmetologist. J Psychiatry and psychopharmacotherapy. 2016; 6: 49-54 [In Russian].
40. Фофанова Ю.С., Медведев В.Э., Фролова В.И. Психосоматические аспекты атипичных прозопалгий. Психическое здоровье. 2015; 9: 43-49.
Fofanova JuS., Medvedev VE, Frolova VI. Psychosomatic aspects of atypical prosopalgia. J Mental health.2015; 9: 43-49. [In Russian].
41. Медведев В.Э. Дисморфическое расстройство: клиническая и нозологическая гетерогенность. Неврология, нейропсихиатрия и психосоматика. 2016; 1: 49-55.
Medvedev VE. Dysmorphic disorders: clinical and nosological heterogeneity. Neurology, neuropsychiatry, psychosomatics. 2016; (8)1: 49–55. [In Russian].
42. Медведев В.Э., Фролова В.И., Мартынов С.Е., с соавт. Дисморфическое расстройство в структуре психических расстройств пациентов пластического хирурга и косметолога. Психическое здоровье. 2017; 2: 48-55.
Medvedev VE, Frolova VI, Martynov SE, et al. Dysmorphic disorder in the structure of mental disorders of plastic surgeon and cosmetologist patients. J Mental health.2017;2:48-55. [In Russian].
43. Van Batenburg-Eddes T., Brion M.J., Henrichs J., et al. Parental depressive and anxiety symptoms during pregnancy and attention problems in children: a cross-cohort consistency study. J Child Psychol Psychiatry. 2013 May; 54(5): 591-600. doi: 10.1111/jcpp.12023.
44. Дубницкая Э.Б. Непсихотические депрессии, связанные с репродуктивным старением женщин (лекция). Психические расстройства в общей медицине. 2010; 4: 18-21.
Dubnickaja JeB. Non-psychotic depressions associated with reproductive aging of women (lecture). J Mental disorders in general medicine. 2010; 4: 18-21. [In Russian].
45. Palinkas L.A., Barrett-Connor E. Estrogen use and depressive symptoms in postmenopausal women. Obstet Gynecol. 1992 Jul; 80(1): 30-36.
46. Юренева С.В., Ильина Л.М., Якушевская О.В. Менопаузальная гормональная терапия в постменопаузе: качество жизни сегодня и в долгосрочной перспективе. Гинекология. 2016; 18(1): 24-29.
Yureneva SV, Il`ina LM, Yakushevskaya OV. Menopausal hormone therapy in postmenopause: quality of life today and in the long term. Gynecology. 2016; (18): 24-29. [In Russian].
47. Медведев В.Э. Терапия непсихотических депрессий в рамках инволюционной истерии (опыт применения Вальдоксана). Психиатрия и психофармакотерапия. 2011; 4: 14-18.
Medvedev V. Treatment of non-psychotic depressions in the framework of involutional hysteria (experience of Valdoxan use). Psychiatry and Psychopharmacotherapy. 2011; 42: 14–18. [In Russian].
48. Соловьева И.К. Афобазол в терапевтической практике. РМЖ. 2006; 29: 2075.
Solov`eva IK. Afobazole in therapeutic practice. RMJ. 2006; 29: 2075. [In Russian].
49. Мкртчян В.Р. Терапевтические возможности адаптола в лечении вегетативных нарушений у женщин. Киев, 2012.
Mkrtchyan VR. Therapeutic possibilities of adaptol in the treatment of vegetative disorders in women. Kiev, 2012. [In Russian].
50. Шишкова В.Н., Зотова Л.И. Применение D-, L-гопантеновой кислоты в терапии когнитивных и тревожных расстройств у женщин с хронической ишемией головного мозга и климактерическим синдромом. РМЖ. 2015; 24: 1470–1475.
Shishkova VN., Zotova LI. The use of D-, L-hopanthenic acid in the treatment of cognitive and anxiety disorders in women with chronic cerebral ischemia and menopausal syndrome. RMJ. 2015; 24: 1470–1475. [In Russian].

DOI: 10.20514/2226-6704-2022-12-3-195-202 УДК 616.329-008-036-07-085

А.Е. Шкляев, В.М. Дударев*

Федеральное государственное бюджетное образовательное учреждение высшего образования «Ижевская государственная медицинская академия» Министерства здравоохранения Российской Федерации, кафедра факультетской терапии с курсами эндокринологии и гематологии, Ижевск, Россия

ГАСТРОЭЗОФАГЕАЛЬНАЯ РЕФЛЮКСНАЯ БОЛЕЗНЬ: ДИАГНОСТИКА, МЕДИКАМЕНТОЗНОЕ ЛЕЧЕНИЕ, БАЛЬНЕОТЕРАПИЯ

A.E. Shklyaev, V.M. Dudarev*

Izhevsk State Medical Academy, department of faculty therapy with endocrinology and hematology courses, Izhevsk, Russia

Gastroesophageal Reflux Disease: Diagnosis, Medication, Balneotherapy

Резюме

В статье приведены современные взгляды на проблему гастроэзофагеальной рефлюксной болезни (ГЭРБ). Представлены данные о распространенности и факторах риска развития заболевания. Сделан акцент на особой роли слабокислых и слабощелочных рефлюксов в патогенезе ГЭРБ, которые, в сочетании с дисфункцией нижнего пищеводного сфинктера и нарушениями моторно-эвакуаторной функции желудка, являются важными факторами, определяющими недостаточную эффективность стандартной антисекреторной терапии. Подчеркивается исключительная важность метода 24-часовой pH-импедансометрии для дифференциальной диагностики неэрозивной формы ГЭРБ с функциональной изжогой и гиперчувствительностью пищевода к рефлюксу (т.н. гиперсенситивный пищевод). Приведены данные результатов отечественных и зарубежных исследований, посвященных оценке эффективности применения физиотерапевтических методов и питьевой бальнеотерапии у больных ГЭРБ.

Ключевые слова: *гастроэзофагеальная рефлюксная болезнь, нижний пищеводный сфинктер, мониторинг pH пищевода, бальнеотерапия*

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

Статья получена 27.12.2021 г.

Принята к публикации 16.03.2022 г.

Для цитирования: Шкляев А.Е., Дударев В.М. ГАСТРОЭЗОФАГЕАЛЬНАЯ РЕФЛЮКСНАЯ БОЛЕЗНЬ: ДИАГНОСТИКА, МЕДИКАМЕНТОЗНОЕ ЛЕЧЕНИЕ, БАЛЬНЕОТЕРАПИЯ. Архивъ внутренней медицины. 2022; 12(3): 195-202. DOI: 10.20514/2226-6704-2022-12-3-195-202

Abstract

The article presents modern views on the problem of gastroesophageal reflux disease (GERD). Data on the prevalence and risk factors for the development of the disease are presented. Emphasis is placed on the special role of slightly acidic and slightly alkaline reflux in the pathogenesis of GERD, which, in combination with dysfunction of the lower esophageal sphincter and impaired motor-evacuation function of the stomach, are important factors, determining the the lack of effectiveness of standard antisecretory therapy. The exceptional importance of the 24-hour pH impedanceometry method is emphasized for the differential diagnosis of the non-erosive form of GERD with functional heartburn and

*Контакты: Валерий Михайлович Дударев, e-mail: flatly@yandex.ru
*Contacts: Valery M. Dudarev, e-mail: flatly@yandex.ru
ORCID ID: https://orcid.org/0000-0002-5840-461X

hypersensitivity of the esophagus to reflux (the so-called hypersensitive esophagus). The data of the results of domestic and foreign studies devoted to the evaluation of the effectiveness of the use of physiotherapeutic methods and drinking balneotherapy in patients with GERD are given.

Key words: *gastroesophageal reflux disease, lower esophageal sphincter, esophageal pH monitoring, balneotherapy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 27.12.2021

Accepted for publication on 16.03.2022

For citation: Shklyaev A.E., Dudarev V.M. Gastroesophageal Reflux Disease: Diagnosis, Medication, Balneotherapy. The Russian Archives of Internal Medicine. 2022; 12(3): 195-202. DOI: 10.20514/2226-6704-2022-12-3-195-202. EDN: MNAWEH

FH — functional heartburn, GERD — gastroesophageal reflux disease, HE — hypersensitive esophagus, LES — lower esophageal sphincter, NO — nitric oxide, PPIs — proton pump inhibitors

For years, gastroesophageal reflux disease (GERD) has been one of the most complex challenges in gastroenterology and therapy. In the guidelines for the diagnosis and management of GERD developed by the Russian Gastroenterological Association, this nosology is defined as a chronic relapsing disease caused by impaired motor-evacuation function of organs of the gastroesophageal zone. It is characterized by regularly repeated reflux of gastric and, in some cases, duodenal contents into the esophagus, leading to the development of clinical symptoms that worsen the quality of life of patients. It also results in damage to the mucous membrane of the distal esophagus, with the development of dystrophic changes of the non-keratinizing stratified squamous epithelium, catarrhal or erosive and ulcerative esophagitis (reflux esophagitis), and in some patients, cylindrical metaplasia [1].

Epidemiology of GERD

Epidemiological studies show that GERD prevalence in the population varies from 8.8 to 33.1 %, and incidence rates have a steady upward trend in all regions of the world. The highest rates of GERD prevalence are in Europe and North America, and the lowest rates are in Asia [1, 2]. In our country, according to various sources, the incidence of GERD ranges from 11.3 to 23.6 %. Esophagitis in the overall population is registered in 5–6 % of cases; in 65–90 % of such patients, the process has moderate severity, and 10–35 % of them have signs of severe esophagitis. The prevalence of Barrett's esophagus (replacement of the squamous epithelium in the mucosa of the distal esophagus with the glandular metaplastic cylindrical epithelium, which increases the risk of developing esophageal adenocarcinoma) among individuals with esophagitis is close to 8 %, with fluctuations ranging from 5 to 30 % [1, 3].

The past decade has seen significantly more cases of GERD in the young population and more erosive and ulcerative forms of reflux esophagitis [4]. GERD is characterized by an extremely negative impact on the quality of life of patients; in this regard, this disease even "surpasses" such nosologies as peptic ulcer, angina and chronic heart failure [5].

Some pathophysiological mechanisms of GERD development

The following predisposing factors are important for the development of GERD: psycho-emotional disorders, smoking, excessive alcohol consumption, repeated pregnancies, hiatal hernia [4]. Overweight and obesity, conditions that are extremely common in the population, are essential in the pathogenesis of this disease [6]. It is known that obesity is accompanied by a significant increase in blood leptin level, which stimulates the production of gastrointestinal peptides, primarily ghrelin, as well as neuropeptides (vasoactive intestinal peptide), which, in turn, causes the formation of nitric oxide (NO) in the myocytes of the esophagus and stomach. It is known that NO reduces the tone of the lower esophageal sphincter (LES), which is the primary mediator that determines the degree of its relaxation; in addition, NO reduces peristaltic movement of the esophagus, which ultimately leads to a decreased antireflux barrier [7]. On the other hand, adipose tissue is "responsible" for the hyperproduction of pro-inflammatory cytokines (interleukins-1β and -6, tumor necrosis factor α) that play an important role in the pathogenesis of GERD; the latter cause inflammation of the esophageal mucosa and impair its barrier properties, making the mucosa particularly susceptible to disease-induced damage [8, 9].

According to experts, GERD is a complex disease with heterogeneous symptoms and multifactorial pathogenesis. Therefore, simplified diagnostic algorithms and classifications are unacceptable for its management [10, 11]. Although GERD is a so-called acid-related disease, its pathogenesis is complex and multicomponent in nature, which apparently causes the problem of insufficient control of symptoms, even with

the most advanced pharmacotherapy available. In addition to the effects associated with aggressive refluxate containing hydrochloric acid and pepsin in the lower third of the esophagus, the failure of the antireflux barrier is of great importance in the pathogenesis of GERD; it occurs due to the impaired intramural innervation of LES, as well as its spontaneous functional relaxation [12, 13].

In most cases, current antisecretory drugs allow controlling intragastric acidity at pH 5–6. However, they have no effect on the function of the lower esophageal sphincter and cannot prevent the reflux of contents neutralized to slightly acidic values into the esophagus; this fact probably explains the persistence of GERD symptoms when taking proton pump inhibitors (PPIs). Studies show that reflux of acidic nature occurs only in 50 % of patients with GERD, while acid reflux with a bile component is detected in 39.7 % of cases, and reflux is registered in 10.3 % of patients. These non-acidic (slightly acidic and slightly alkaline) refluxes are apparently why antisecretory therapy is not sufficiently effective [14]. It should be noted that multichannel daily impedance pH-metry plays a key role in the diagnosis of the so-called non-acidic refluxes [15].

An important role in the pathogenesis of GERD is played by the so-called impaired esophageal clearance, which is manifested by the failure of the secondary esophageal peristalsis, which determines the reverse "evacuation" of the refluxate into the stomach [16]; researchers emphasize the importance of reduced production of bicarbonates in the esophagus [4, 12]. Increased intragastric pressure due to impaired motor-evacuation function, as well as duodenostasis, are of particular importance in the development of this disease [17]. In cases of chronic duodenostasis and duodenogastric reflux, alkaline reflux enters the stomach, which increases the risk of developing erosive and ulcerative reflux esophagitis and Barrett's esophagus [18].

According to Ya. S. Zimmerman et al. (2016), one of the key pathogenetic factors in the development of GERD is decreased resistance of the esophageal mucosa to aggression factors due to an imbalance of pre-epithelial, epithelial, post-epithelial and functional protective components [4]. The pre-epithelial protective barrier is brought into action by the mucous membrane and bicarbonate ions that neutralize the protons of acid reflux in the esophagus; it maintains pH in the esophagus in the range of 7.3–7.4. In case of GERD, the formation of pre-epithelial protective factors is significantly reduced. Structural and functional features of esophageal epitheliocytes, as well as the process of their continuous regeneration, are the basis of the epithelial level of protection, which prevents damage to the mucous membrane. The state of microcirculation of the esophageal mucous membrane determines the so-called post-epithelial level of protection and is the basis of cellular resistance, which counters the proton aggression of gastric juice.

More on the differential diagnosis of GERD

A very important and challenging clinical aspect of GERD is the differential diagnosis of the non-erosive form of this disease with the so-called functional heartburn (FH) and hypersensitivity of the esophagus to reflux — hypersensitive esophagus (HE). It has recently been suggested that visceral hypersensitivity due to the state of vanilloid receptors 1 is significant in the occurrence of reflux symptoms [19]. In clinical practice, the "gold standard" for the differential diagnosis of these conditions in patients with heartburn and normal endoscopic results is the 24-hour pH impedance test [20]. In accordance with the Rome IV criteria for functional esophageal disorders, patients with complaints of heartburn and no pathological changes in the esophageal mucosa according to endoscopic results can be divided into two groups (Fig. 1): patients with no previously verified GERD, and patients with already confirmed diagnosis of GERD (for example, based on the results of pH-metry). Before the prescription of PPIs or after the so-called "washout" period (discontinuing PPIs in seven days), individuals of group 1 should take a 24h intraesophageal pH-impedance test; based on the results of this test, patients of group 1 are divided into three subgroups: individuals with increased exposure of the esophageal mucosa to hydrochloric acid (non-erosive GERD); individuals with normal acid exposure and association between the onset of symptoms and episodes of physiological reflux (that is, esophageal reflux hypersensitivity), and finally, individuals with normal acid exposure in the esophagus and no association between the onset of symptoms and reflux episodes (FH). For patients with an established diagnosis of GERD (group 2), an intraesophageal pH-impedance test should be performed while these patients take PPIs. The diagnosis of "refractory GERD" is established if increased exposure of the esophageal mucosa to hydrochloric acid is established despite ongoing antisecretory treatment. Patients with normal acid exposure during treatment with PPIs and episodes of physiological reflux (usually non-acidic) are considered patients with GERD and esophageal reflux hypersensitivity simultaneously; patients with symptoms during therapy that are not compliant to reflux episodes are most likely to have a combination of GERD and FH [21].

GERD management: problems and approaches

One of the biggest challenges in the case of GERD is ineffective acid suppression therapy. Despite the high efficacy of PPIs, there is a lot of evidence of their clinical "failure" in a number of patients. It is known that at least a third of patients with GERD continue to experience symptoms caused by reflux while taking PPIs [22].

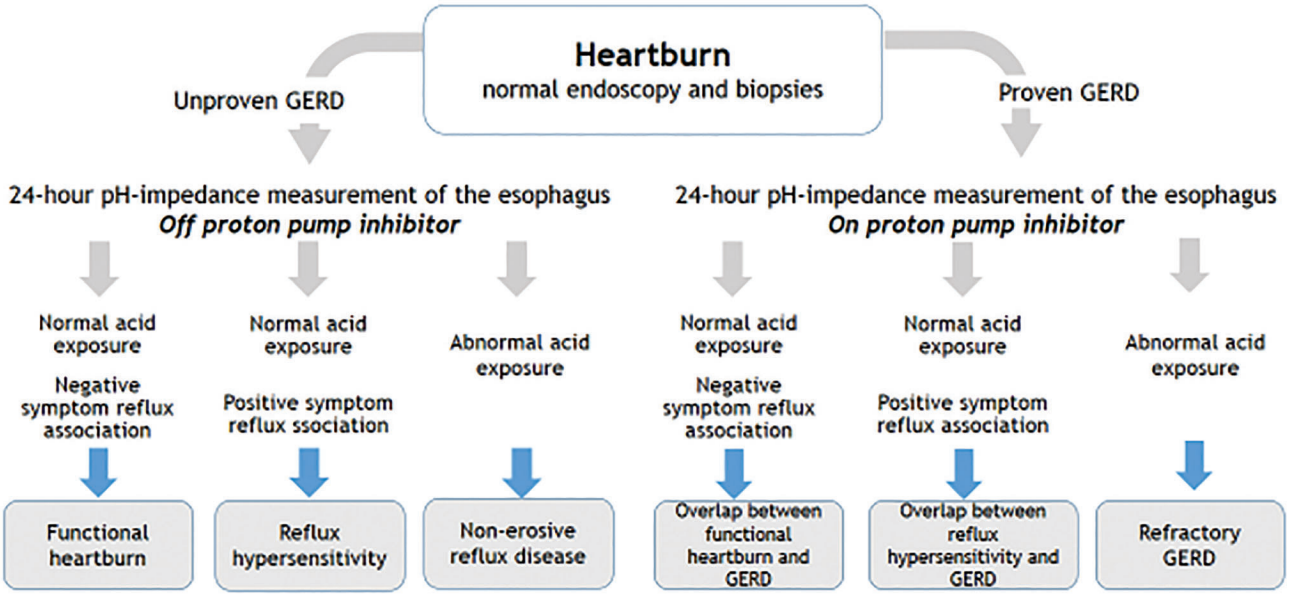


Figure 1. *Differential diagnosis of heartburn against the background of a normal endoscopic and histological picture of the esophageal mucosa [21]*

Refractory GERD usually occurs in the absence of complete healing of the esophageal mucosa and/or satisfactory relief of bothersome symptoms after a full course of PPIs at a standard (once a day) dose (treatment course for erosive esophagitis lasts eight weeks, and for non-erosive GERD — four weeks) [1]. There are several reasons for the ineffectiveness of acid suppression therapy for GERD. The first reason is the genetically determined inability of PPIs to maintain pH in the esophagus above 4 for at least 16 hours a day due to the rapid metabolism and elimination of the drug (the problem of genetic polymorphism of the cytochrome P450 isoenzyme CYP2C19) [23]. Secondly, slight acidic reflux, as well as the predominance of generally alkaline duodenal contents in the refluxate can be the reason for the ineffectiveness of PPIs. As mentioned already, reflux is mainly acidic in only half of patients with GERD [24]. The ineffectiveness of PPIs is often due to non-compliance with the physician's recommendations or the wrong choice of the daily dose and treatment duration [25]. In addition, one of the mechanisms for the development of resistance to therapy in patients with GERD may be an imbalance between cellular and humoral components of immunity, determined both by the macrophage phenotype and by other immune and non-immune cells that secrete cytokines. In particular, it was found that a high level of tissue interleukin-1β is a predictor of the torpid course of GERD, especially in the long-term presence of acid reflux. A high tissue level of interleukin-8, which is a potent chemoattractant and activator of WBC and other non-immune cells, predetermines the recurrence of GERD within three years despite ongoing therapy [26].

Approaches to the management of refractory GERD include: doubling the dose of PPIs, using modified-release PPIs, adding histamine H2-blockers (to control nocturnal secretion), prokinetic agents and ursodeoxycholic acid preparations [1, 4]. In this regard, we ought to mention the results of recent studies that suggest an increased risk of contracting COVID-19 for individuals taking PPIs at high doses [27].

Approaches to the management of FH and HE deserve special attention. Individuals with HE, who have physiological acid reflux, tend to respond well to treatment with PPIs. Patients with slightly acid and alkaline refluxes are usually refractory to antisecretory agents. Considering the role of visceral hypersensitivity, disorders of perception and signal processing in the central nervous system in the development of these conditions, tricyclic antidepressants in low doses (imipramine 50 mg per day, and amitriptyline 10–20 mg per day), as well as selective serotonin reuptake inhibitors (sertraline 50–200 mg per day, paroxetine 50–75 mg per day, citalopram 20 mg per day) are effective for the treatment of patients with FH and HE [20].

The high prevalence of GERD in the population and the ineffectiveness of acid suppression therapy raise the need for alternative methods of managing this disease, with physiotherapy and balneotherapy as important treatment options. Physiotherapeutic methods used for the management of GERD include sinusoidal modulated current (SMT) therapy, pulsed low-frequency electrotherapy using the electrosleep technique and transcranial electrical stimulation, ultrahigh frequency electromagnetic fields, structural resonance electromagnet therapy, low-frequency alternating magnetic

field, low-intensity laser radiation; the therapeutic use of these methods is based on complex reflex reactions of the body that lead to the normalization of changes in the nervous and endocrine systems, with an improvement in adaptive, protective and compensatory functions [28]. In particular, A. M. Korepanov and M. D. Mikhailova (2011) suggested using SMT-phoresis of chloride-iodine-bromine brine in patients with GERD. Positive changes in several clinical and functional parameters were registered, specifically, the disappearance or abatement of dyspeptic signs and pain syndrome, favorable changes in the esophageal mucosa, and decreased level of anxiety [29].

Earlier studies showed the effectiveness of balneotherapy in patients with GERD. Back in 2006, M. T. Efendieva et al. presented the results of the therapeutic use of hydrocarbonate-sulfate magnesium-sodium mineral water in patients with non-erosive GERD with cardiac manifestations. It was observed that a course of balneotherapy with potable mineral water contributes to the improvement of LES function (reflux index decreased by three times), resolution of hyperemia and edema of the esophageal mucosa (in 62 % of patients); the authors attribute the positive effects to the normalization of autonomic regulation processes [30]. L. G. Vologzhanina and E. V. Vladimirsky conducted an analysis of the treatment of 30 patients with GERD, who were divided into two groups. Group 1 patients received drug treatment (omeprazole 20 mg twice a day, motilium 10 mg three times a day) and Klyuchi sulfate-magnesium-calcium mineral water (200 ml three times a day). Group 2 patients received the same medications but no mineral water; the effectiveness of treatment was assessed based on the results of EGD fibroscopy, morphological analysis of gastric and esophageal biopsy specimens, 24h pH-metry of the esophagus and stomach. The results obtained by the authors revealed that the addition of Klyuchi mineral water to the standard treatment of GERD reduces the time required to stabilize the clinical, endoscopic, and morphological signs of the disease [31]. A study performed in Bashkortostan demonstrated that a course of potable Kazanchinskaya low-mineralized bicarbonate-sulphate calcium-magnesium mineral water in patients with non-erosive GERD improves the functional state of LES, with a significant decrease in reflux index (apparently due to the normalization of the production of the vasoactive interstitial polypeptide); it also has a pronounced anti-inflammatory effect that persists for six months [32]. A. N. Kazyulin et al. (2016) presented the results of a study of the effectiveness of mineral natural bicarbonate sodium water of the Borjomi deposit in patients with GERD and with no esophagitis. The group of patients who received combined treatment (PPIs and mineral water) experienced a faster resolution of such GERD signs as heartburn, belching, bitter taste in the mouth, and sleep disturbances than the group that received monotherapy with PPIs. The authors suggest that the positive clinical effect in patients who received combination therapy was due to its more pronounced acid suppression effect, as well as the normalizing effect of micronutrients in mineral water on the functional state of the upper digestive tract [33]. An open-label, single-center, experimental clinical trial conducted in Germany evaluated the efficacy and safety of high bicarbonate mineral water in patients with GERD [34]. The high efficacy of balneotherapy in reducing the frequency and severity of heartburn episodes was demonstrated; this improved the quality of life of patients. The study conducted by Dragomiretska N. et al. (2020) included 90 patients with GERD. After a preliminary assessment, all patients were randomly divided into three groups of 30 individuals. The control group (group 1) received PPIs; group 2, in addition to PPIs, received highly mineralized boron-bicarbonate-sodium water. In addition to basic therapy, group 3 patients were prescribed a course of treatment with highly mineralized sulfate-hydrocarbonate sodium-magnesium water. Basic therapy for one month in the control group resulted in no significant resolution of dyspeptic and asthenic syndromes. Using highly mineralized boron-bicarbonate water led to a significant decrease in abdominal pain and dyspeptic signs and improved acid secretion function of the stomach. However, there were no significant changes in the parameters of cytolytic, mesenchymal-inflammatory and cholestatic syndromes. Using highly mineralized sulfate-bicarbonate sodium-magnesium water contributed to the elimination of dyspepsia and pain syndrome, as well as to the normalization of the functional state of the liver [35].

Investigation of the mechanisms of the effect of mineral water on the functional state of the gastrointestinal tract in patients with GERD deserves special attention. Among the probable ones are the direct buffering effect of mineral water anions on gastric fluid protons [36], decreased activity of lipid peroxidation [37], anti-inflammatory effect of balneotherapy with potable mineral water [38], neurohumoral regulation of the motility of the lower esophageal sphincter due to the normalization of the production of the vasoactive interstitial polypeptide [32], positive effect of balneotherapy on carbohydrate metabolism in patients [39]. Many aspects of the rationale for the therapeutic use of potable mineral water in patients with GERD require thorough analysis.

Therefore, the issue of controlling signs and improving the prognosis for patients with GERD remains relevant despite the availability of advanced diagnostic methods and pharmacotherapy. This disease has a complex and multicomponent pathogenesis; many of its components require thorough analysis and clarification, and approaches to its treatment should be improved and individualized. Balneotherapy with potable mineral water can be one of the methods to increase the effectiveness of treatment of patients with GERD.

Вклад авторов:

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

Шкляев А.Е. (ORCID ID: https://orcid.org/0000-0003-4479-508X): разработка концепции и дизайна, сбор, анализ и интерпретации данных, проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации, ответственный за все аспекты работы

Дударев В.М. (ORCID ID: https://orcid.org/0000-0002-5840-461X): 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.

Shklyaev A.E. (ORCID ID: https://orcid.org/0000-0003-4479-508X): 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

Dudarev V.M. (ORCID ID: https://orcid.org/0000-0002-5840-461X): collection, analysis and interpretation of data, preparation of a manuscript, responsible for all aspects of the work.

Список литературы / References:

1. Ивашкин В.Т., Маев И.В., Трухманов А.С., и др. Рекомендации Российской гастроэнтерологической ассоциации по диагностике и лечению гастроэзофагеальной рефлюксной болезни. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2020; 30(4): 70–97. https://doi.org/10.22416/1382-4376-2020-30-4-70-97.
Ivashkin V.T., Maev I.V., Trukhmanov A.S., et al. Recommendations of the Russian Gastroenterological Association in Diagnosis and Treatment of Gastroesophageal Reflux Disease. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2020; 30(4): 70–97. https://doi.org/10.22416/1382-4376-2020-30-4-70-97 [In Russian].
2. El-Serag H.B., Sweet S., Winchester C.C., Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2014; 63: 871-880.
3. Лазебник Л.Б., Машарова А.А., Бордин Д.С., и др. Результаты многоцентрового исследования «Эпидемиология гастроэзофагеальной рефлюксной болезни в России» (МЭГРЕ). Терапевтический архив. 2011; 83 (1): 45-50.
Lazebnik L.B., Masharova A.A., Bordin D.S., et al. Results of a multicenter trial «Epidemiology of gastroesophageal reflux disease in Russia» (MEGRE). Terapevticheskii arkhiv. 2011; 83 (1): 45-50 [In Russian].
4. Циммерман Я.С., Вологжанина Л.Г. Гастроэзофагеальная рефлюксная болезнь: современное состояние проблемы и перспективы. Клин. мед. 2016; 94 (7): 485—496. DOI 10.18821/0023-2149-2016-94-7-485-496.
Tsimmerman Ya.S.,Vologzhanina L.G. Gastroesophageal reflux disease: current views and prospects. Klin. med: 2016; 94 (7): 485—496. DOI 10.18821/0023-2149-2016-94-7-485-496 [In Russian].
5. Mittal R., Vaezi M. Esophageal Motility Disorders and Gastroesophageal Reflux Disease. N Engl J Med. 2020 Nov 12;383(20):1961-1972. doi: 10.1056/NEJMra2000328.
6. Mehta R.S., Nguyen L.H., Ma W., et al. Association of diet and lifestyle with the risk of gastroesophageal reflux disease symptoms in US women. JAMA Intern Med. 2021 Apr 1;181(4):552-554. doi: 10.1001/jamainternmed.2020.7238.
7. Звенигородская Л.А., Нилова Т.В., Бондаренко Е.Ю. Регуляция оксида азота и терапия при гастроэзофагеальной рефлюксной болезни у больных с абдоминальным ожирением. Русский медицинский журнал. 2011; 19 (17): 1097—1099.
Zvenigorodskaya L.A., Nilova T.V., Bondarenko E.Yu. Regulation of nitric oxide and therapy for gastroesophageal reflux disease in patients with abdominal obesity. Russian medical journal. 2011; 19 (17): 1097—1099 [In Russian].
8. Лямина С.В., Маев И.В., Калиш С.В., и др. Особенности функциональной активности макрофагального звена иммунитета при ГЭРБ в зависимости от типа рефлюктата: in vitro модель. Терапевтический архив. 2018; 90 (2): 19-23. https:// doi.org/10.26442/terarkh201890219-23.
Lyamina S.V., Maev I.V., Kalish S.V., et al. Features of the functional activity of macrophage link of immunity with gastroesophageal refluxdisease depending on the type of reluctate: in vitro model. Terapevticheskii arkhiv. 2018; 90 (2): 19-23. https:// doi.org/10.26442/terarkh201890219-23 [In Russian].
9. Paris S., Ekeanyanwu R., Jianghttps Y., et al. Obesity and its effects on the esophageal mucosal barrier. Am J Physiol Gastrointest Liver Physiol . 2021 Sep 1; 321(3): G335-G343. https://doi.org/10.1152/ajpgi.00199.2021
10. Gyawali C.P., Kahrilas P.J., Savarino E., et al. Modern diagnosis of GERD: the Lyon Consensus. Gut Published Online First: 03 February 2018. doi:10.1136/gutjnl-2017–314722.
11. Zheng Z., Shang Y., Wang N. et al. Current Advancement on the Dynamic Mechanism of Gastroesophageal Reflux Disease. Int J Biol Sci 2021; 17(15): 4154-4164. doi:10.7150/ijbs.65066.
12. Tack J., Pandolfino J. Pathophysiology of Gastroesophageal Reflux Disease. Gastroenterology. 2018 Jan; 154(2): 277-288. doi: 10.1053/j.gastro.2017.09.047.
13. Altomare A., Guarino M.P., Cocca S., Emerenziani S., Cicala M. Gastroesophageal reflux disease: Update on inflammation and symptom perception. World J Gastroenterol. 2013;19: 6523-6528.
14. Лищук Н.Б., Симаненков В.И., Тихонов С.В. Дифференцированная терапия «некислых» форм гастроэзофагеальной рефлюксной болезни. Терапевтический архив. 2017; 89 (4): 57-63. doi: 10.17116/terarkh101789457-63.
Lishchuk N.B., Simanenkov V.I., Tikhonov S.V. Differention therapy for non-acidic gastroesophageal reflux disease. Terapevticheskii arkhiv. 2017; 89 (4): 57-63. doi: 10.17116/terarkh101789457-63 [In Russian].
15. Сторонова О.А., Трухманов А.С. 24-часовая pH-импедансометрия. Дифференциальный диагноз функциональных заболеваний пищевода. Пособие для врачей. Под ред. Ивашкина В.Т. М. МЕДПРАКТИКА-М. 2018; 32 с.
Storonova O.A., Trukhmanov A.S. 24-hour impedance pH measurement. Differential diagnosis of functional diseases of the esophagus. The guide for doctors. ed. Ivashkin V.T. M. MEDPRACTICA-M. 2018; 32 p. [In Russian].
16. Евсютина Ю.В., Трухманов А.С. Роль двигательных нарушений пищевода и желудка в патогенезе гастроэзофагеальной рефлюксной болезни. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2015; 25 (5): 10–15.

Yevsyutina Yu.V., Trukhmanov A.S. The role of esophageal and stomach motility disorders in pathogenesis of gastroesophageal reflux disease. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2015; 25 (5): 10–15 [In Russian].

17. Джулай Г.С., Секарева Е.В. Секреторная и моторно-эвакуаторная активность желудка и двенадцатиперстной кишки у пациентов с ГЭРБ, ассоциированной с разными типами рефлюкса. Терапевтический архив. 2016; 88 (2): 16-20. doi: 10.17116/terarkh201688216-20.
Dzhulay G.S., Sekareva E.V. Gastric and duodenal secretory and motor-evacuatory activity in patients with gastroesophageal reflux disease associated with different types of reflux. Terapevticheskii arkhiv. 2016; 88 (2): 16-20. doi: 10.17116/terarkh201688216-20 [In Russian].
18. Souza R.F. Reflux esophagitis and its role in the pathogenesis of Barrett's metaplasia. J Gastroenterol. 2017; 52: 767-76. doi: 10.1007/ s00535-017-1342-1.
19. Ustaoglu A., Sawada A., Lee Ch., et al. Heartburn sensation in nonerosive reflux disease: pattern of superficial sensory nerves expressing TRPV1 and epithelial cells expressing ASIC3 receptors. American Journal of Physiology-Gastrointestinal and Liver Physiology. 2021 May 1; 320(5): G804-G815. doi: 10.1152/ajpgi.00013.2021.
20. Баркалова Е.В., Кучерявый Ю.А., Овсепян М.А., и др. Изжога у больных без эзофагита: дифференциальная диагностика. Экспериментальная и клиническая гастроэнтерология. 2018; 158(10): 74–79. DOI: 10.31146/1682-8658-ecg-158-10-74-79.
Barkalova E. V., Kucheryavyy Y. A., Ovsepian M. A., et al. Heartburn in patients without esophagitis. diff erential diagnosis. Experimental and Clinical Gastroenterology. 2018; 158 (10): 74–79. DOI: 10.31146/1682-8658-ecg-158-10-74-79 [In Russian].
21. Шептулин А.А., Кайбышева В.О. Функциональная изжога и гиперчувствительность пищевода к рефлюксу (По материалам Римских критериев функциональных заболеваний пищевода IV пересмотра). Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2017; 27(2): 13-18.
Sheptulin A.A., Kaybysheva V.O. Functional heart-burn and reflux hypersensitivity syndrome (according to the Rome-IV functional esophageal disease diagnostic criteria). Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2017; 27(2): 13-18 [In Russian].
22. Ивашкин В.Т., Маев И.В., Трухманов А.С., Румянцева Д.Е. Современные достижения в диагностике и лечении рефрактерной формы гастроэзофагеальной рефлюксной болезни. Терапевтический архив. 2018; 90(8): 4–12. https://doi.org/10.26442/terarkh20189084-12.
Ivashkin V.T., Maev I.V., Trukhmanov A.S., Rumyantseva D.E. Modern achievements in the diagnosis and treatment of the refractory gastroesophageal reflux disease. Terapevticheskii arkhiv. 2018; 90(8): 4–12. https://doi.org/10.26442/terarkh20189084-12 [In Russian].
23. Ichikawa H., Sugimoto M., Sugimoto K., et al. Rapid metabolizer genotype of CYP2C19 is a risk factor of being refractory to proton pump inhibitor therapy for reflux esophagitis. Journal of Gastroenterology and Hepatology. 2016; 31:716–26. DOI: 10.1111/jgh.13233.
24. Кайбышева В.О., Сторонова О.А., Трухманов А.С., Ивашкин В.Т. Внутрипищеводная pH-импедансометрия в диагностике ГЭРБ. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2013; (2): 4–12.
Kaibysheva V.O., Storonova O.A., Trukhmanov A.S., Ivashkin V.T. Intraesophageal impedance pH measurement in the diagnosis of GERD. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2013; (2): 4–12 [In Russian].
25. Евсютина Ю.В., Трухманов А.С. Алгоритм ведения пациентов с рефрактерной формой ГЭРБ. Русский медицинский журнал. 2015; 28:1682–1683.
Yevsyutina Yu.V., Trukhmanov A.S. Algorithm for the management of patients with refractory GERD. Russian medical journal. 2015; 28:1682–1683 [In Russian].
26. Евсютина Ю.В., Трухманов А.С. Новый взгляд на проблему гастроэзофагеальной рефлюксной болезни, рефрактерной к лечению ингибиторами протонной помпы. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2014; 5: 4–9.
Yevsyutina Yu.V., Trukhmanov A.S. A new look at the problem of gastroesophageal reflux disease, refractory to treatment with proton pump inhibitors. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2014; 5: 4–9 [In Russian].
27. Almario Ch.V., Chey W.D., Brennan M. R., Spiegel B.M.R. Increased risk of COVID-19 among users of proton pump inhibitors. The American Journal of Gastroenterology: October 2020 — Volume 115 — Issue 10 — p 1707-1715 doi: 10.14309/ajg.0000000000000798.
28. Разумов А.Н., Эфендиева М.Т., Бадтиева В.А. Гастроэзофагеальная рефлюксная болезнь с кардиальными проявлениями: перспективы немедикаментозных методов лечения. Вопросы курортологии, физиотерапии и лечебной физической культуры. 2020; 97(1): 75-81. https://doi.org/10.17116/kurort20209701175.
Razumov A.N., Efendieva M. T., Badtieva V. A. Gastroesophageal reflux disease with cardial manifistations: perspectives of non-pharmacological treatment methods. Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury. 2020; 97(1): 75-81. https://doi.org/10.17116/kurort20209701175 [In Russian].
29. Корепанов А.М., Михайлова М.Д. Применение курортных факторов в лечении гастроэзофагеальной рефлюксной болезни. Вопросы курортологии, физиотерапии и лечебной физической культуры. 2011; 2: 27-30.
Korepanov A.M., Mikhailova M.D. The use of spa factors in the treatment of gastroesophageal reflux disease. Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury. 2011; 2: 27-30 [In Russian].
30. Эфендиева М.Т., Бадтиева В.А., Русенко Н.И. Магнийсодержащие минеральные воды в лечении больных с кардиальными проявлениями ГЭРБ. Вопросы курортологии, физиотерапии и лечебной физической культуры. 2006; 6: 31-34.
Efendieva M.T., Badtieva V.A., Rusenko N.I. Magnesium-containing mineral waters in the treatment of patients with cardiac manifestations of GERD. Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury. 2006; 6: 31-34 [In Russian].
31. Вологжанина Л.Г., Владимирский Е.В. Эффективность применения питьевой сульфатной магниево-кальциевой минеральной воды в комплексном лечении больных язвенной болезнью двенадцатиперстной кишки, сочетающейся с

гастроэзофагеальной рефлюксной болезнью. Вопросы курортологии, физиотерапии и лечебной физической культуры. 2005; 6: 17-19.
Vologzhanina L. G., Vladimirsky E. V. The effectiveness of the use of drinking sulphate magnesium-calcium mineral water in the complex treatment of patients with duodenal ulcer disease, combined with gastroesophageal reflux disease. Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury. 2005; 6: 17-19 [In Russian].

32. Усманов Ф.Ф., Гильмутдинов А.Р., Кунафин А.Ф., и др. Применение питьевой минеральной воды в терапии больных с гастроэзофагеальной рефлюксной болезнью. Медицинский вестник Башкортостана. 2013; 8(6): 135-137.
Usmanov F.F., Gilmutdinov A.R., Kunafin A.F., et al. Potable mineral water in the treatment of patients with gastroesophageal reflux disease. Bashkortostan medical journal. 2013; 8(6): 135-137 [In Russian].
33. Казюлин А.Н., Дичева Д.Т., Парцваниа-Виноградова Е.В. Изучение терапевтической эффективности применения минеральной природной воды Боржомского месторождения у пациентов с ГЭРБ. Фарматека. 2016; 15: 44–53.
Kazyulin A.N., Dicheva D.T., Partsvaniya-Vinogradova E.V. Evaluation of the therapeutic effectiveness of the use of natural borjomi mineral water in patients with gastroesophageal disease. Farmateka. 2016; 15: 44–53 [In Russian].
34. Beer A.M., Uebelhack R., Pohl U. Efficacy and tolerability of hydrogen carbonate-rich water for heartburn. World J Gastrointest Pathophysiol 2016; 7(1): 171-180. DOI: 10.4291/wjgp.v7.i1.171.
35. Dragomiretska N., Babov K., Gushcha S., et al. Application of mineral waters in the complex treatment of patients with gastroesophageal reflux disease. Minerva Gastroenterol Dietol . 2020 Sep; 66(3): 225-237. doi: 10.23736/S1121-421X.20.02601-X.
36. Jamie A Koufman J.A., Johnston N. Potential benefits of pH 8.8 alkaline drinking water as an adjunct in the treatment of reflux disease. Ann Otol Rhinol Laryngol. 2012 Jul; 121(7): 431-4. doi: 10.1177/000348941212100702.
37. Costantino M., Giampaolo C., Filippelli A. Effects of drinking spa therapy on oxidative stress. Clin Ter. 2012; 163(1): e13-7.
38. Silva A.,Oliveira A.,Vaz C., Correia S., Ferreira R. Anti-inflammatory potential of Portuguese thermal waters Sci Rep . 2020 Dec 18; 10(1): 22313. doi: 10.1038/s41598-020-79394-9.
39. Naumann J, Biehler D, Lüty T, Sadaghiani C. Prevention and Therapy of Type 2 Diabetes-What Is the Potential of Daily Water Intake and Its Mineral Nutrients? Nutrients. 2017 Aug 22; 9(8): 914. doi: 10.3390/nu9080914.

DOI: 10.20514/2226-6704-2022-12-3-203-211 УДК 616.72-002.772-02-07:616.314.17-02-07

Г.В. Порядин[1], А.Н. Захватов*[2], А.Ю.Паршина[2]

[1]— Федеральное государственное автономное образовательное учреждение высшего образования «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова», Москва, Россия
[2]— Федеральное государственное бюджетное образовательное учреждение высшего образования «Национальный исследовательский Мордовский государственный университет им. Н.П. Огарёва», Медицинский институт, Саранск, Россия

ПАТОГЕНЕТИЧЕСКАЯ ВЗАИМОСВЯЗЬ ИММУНОЛОГИЧЕСКИХ НАРУШЕНИЙ ПРИ ХРОНИЧЕСКОМ ГЕНЕРАЛИЗОВАННОМ ПАРОДОНТИТЕ И РЕВМАТОИДНОМ АРТРИТЕ

G.V. Poryadin[1], A.N. Zakhvatov*[2], A.Yu. Parshina[2]

[1] — Pirogov Russian National Research Medical University, Moscow, Russia
[2] — National Research Ogarev Mordovia State University, Medical institute, Saransk, Russia

Pathogenetic Relationship of Immunological Disorders in Chronic Generalized Periodontitis and Rheumatoid Arthritis

Резюме

Патогенетическое единство механизмов прогрессирования хронического пародонтита и ревматоидного артрита подтверждается общими звеньями иммуновоспалительных реакций.

Повреждение тканей пародонта опосредовано цитотоксическими эффектами вырабатываемых бактериями Porphyromonas gingivalis ферментов и их метаболитов. Нейтрофилы способствуют развитию пародонтита и участвуют в его прогрессировании, рекрутируя Т-хелперы 17 (Th17) и способствуя накоплению плазматических клеток в поражённых тканях. Активация иммунокомпетентных клеток способствует генерации активных форм кислорода, инициирующих свободнорадикальное окисление липидов, что в сочетании с невозможностью их нейтрализации вследствие сниженного антиоксидантного потенциала приводит к развитию оксидативного стресса.

Связь между ревматоидным артритом и хроническим пародонтитом была в центре внимания многочисленных исследований, что обусловлено их общими патогенетическими механизмами. Хроническое воспаление, связанное как с ревматоидным артритом, так и с хроническим пародонтитом, сходно по преобладающему адаптивному иммунному фенотипу, дисбалансу между про — и противовоспалительными цитокинами. Значимым является вовлечение микроорганизма Porphyromonas gingivalis в генерацию антител к цитруллинированным пептидам у пациентов с ревматоидным артритом. Общность эпитопа (SE)-кодирующего аллель HLA-DRB1, связывающего цитруллинированные пептиды, может служить основанием для утверждения генетической предрасположенности и взаимопотенцирования данных заболеваний. Таким образом, имеющаяся взаимосвязь хронического пародонтита и ревматоидного артрита обосновывает необходимость проведения исследований, направленных на разработку новых методов в диагностике, лечении и профилактике рассматриваемых заболеваний с целью разобщения общих патогенетических механизмов воспалительных реакций и процессов остеорезорбции, приводящих к стойким функциональным и органическим расстройствам.

Ключевые слова: *пародонтит, ревматоидный артрит, цитокины, воспалительный ответ, остеорезорбция*

*Контакты: Алексей Николаевич Захватов, e-mail: zachvatan78@mail.ru
*Contacts: Alexey N. Zakhvatov, e-mail: zachvatan78@mail.ru
ORCID ID: https://orcid.org/0000-0003-1433-0337

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

Статья получена 12.11.2021 г.

Принята к публикации 04.02.2022 г.

Для цитирования: Порядин Г.В., Захватов А.Н., Паршина А.Ю. ПАТОГЕНЕТИЧЕСКАЯ ВЗАИМОСВЯЗЬ ИММУНОЛОГИЧЕСКИХ НАРУШЕНИЙ ПРИ ХРОНИЧЕСКОМ ГЕНЕРАЛИЗОВАННОМ ПАРОДОНТИТЕ И РЕВМАТОИДНОМ АРТРИТЕ. Архивъ внутренней медицины. 2022; 12(3): DOI: 203-211. DOI: 10.20514/2226-6704-2022-12-3-203-211. EDN: TBTUHN

Abstract

The pathogenetic mechanisms of progression of chronic periodontitis accompanied with rheumatoid arthritis is confirmed by the common parts of immune-inflammatory reactions.

Damage to periodontal tissues is indirectly made by cytotoxic effects of enzymes and their metabolites produced by Porphyromonas gingivalis bacteria. Neutrophils contribute to the progression of periodontitis and participate in its amplification by recruiting T-helper cells 17 and contributing to the accumulation of plasma cells in the affected tissues. Activation of immunocompetent cells promotes the generation of reactive oxygen species that initiate free radical oxidation of lipids, which, combined with the inability to neutralize them due to reduced antioxidant potential, leads to the development of oxidative stress.

The connection between rheumatoid arthritis and chronic periodontitis has been the focus of numerous studies, due to their common pathogenetic mechanisms. Chronic inflammation associated with both rheumatoid arthritis and chronic periodontitis is similar in its prevailing adaptive immune phenotype, an imbalance between pro- and anti-inflammatory cytokines. The involvement of the Porphyromonas gingivalis microorganism in the generation of antibodies to citrullinated peptides in patients with rheumatoid arthritis is significant. The similarity of the epitope (SE) encoding the HLA-DRB1 allele, binding citrullinated peptides, can act as a basis for the approval of the genetic predisposition and mutual potential of these diseases. Thus, the proven connection between chronic periodontitis and rheumatoid polyarthropathies determines the significance of the analysis of the data obtained and substantiates the need for strategic research aimed at developing new methods in the diagnosis, treatment and prevention of the diseases for the purpose of breaking and separation of the common pathogenetic mechanisms of inflammatory reactions and osteoresorption processes leading to persistent functional and organic disorders.

Key words: *periodontitis, rheumatoid arthritis, cytokines, inflammatory response, osteoresorption*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 12.11.2021

Accepted for publication on 04.02.2022

For citation: Poryadin G.V., Zakhvatov A.N., Parshina A.Yu. Pathogenetic Relationship of Immunological Disorders in Chronic Generalized Periodontitis and Rheumatoid Arthritis. The Russian Archives of Internal Medicine. 2022; 12(3): DOI: 203-211. DOI: 10.20514/2226-6704-2022-12-3-203-211. EDN: TBTUHN

ACPA — antibodies to citrullinated peptides, IL — interleukin, IL-1β — interleukin-1β, MMP — matrix metalloproteinases, PPAD — peptidyl arginine deaminase, RA — rheumatoid arthritis, RANKL — membrane-bound receptor activator of nuclear factor kappa-β, ROS — reactive oxygen species, TNF — tumor necrosis factor

Introduction

Periodontal inflammatory diseases are one of the most challenging socially-significant pathologies in the world [1]. Their prevalence in the world is about 98 % and they are one of the main causes of tooth loss [2]. According to the World Health Organization (WHO), the incidence of periodontal diseases peaks at 35–45 years; in recent years, such diseases have increasingly been found in younger individuals [3]. The prevalence of periodontal diseases in Russia has age-related features. In particular, their incidence in patients at the age of 32 is 48.2 %, in patients aged 45 — up to 86 %, and in patients aged 65 — 100 % [4].

Currently, odontogenic infection is thought to play an important role in the development of somatic pathology [5]. Periodontal pathogens, increased synthesis of pro-inflammatory cytokines contribute to the development of a systemic response and/or a number of systemic autoimmune diseases; rheumatic diseases with joint damage are of the greatest significance among such conditions. In this group, rheumatoid arthritis has the strongest pathogenetic relationship with inflammatory periodontal diseases [6].

The NHANES (National Health and Nutrition Examination Survey) showed that the prevalence of chronic periodontitis, as measured by the number of missing

teeth, was four times higher in patients with rheumatoid arthritis (RA) [7]. This conclusion is supported by epidemiological and case-control studies, which have demonstrated that patients with active RA have a significantly higher prevalence of chronic periodontitis (defined by various parameters, including bleeding, gingivitis, and increased probing pocket depth) compared to patients without RA [8]. In addition, the prevalence of RA in patients with chronic periodontitis is higher than among those without such pathology [6].

Confirmation of the pathogenetic relationship between chronic periodontitis and rheumatoid arthritis requires pointing out the much higher prevalence of rheumatoid arthritis in patients with chronic periodontitis (3.95 % compared to 1 % in the overall population) [9]. Interestingly, with high activity of rheumatoid arthritis, the increase in the RBC sedimentation rate and the increase in the level of C-reactive protein correlate with a more severe degree of periodontal bone resorption [8].

There are similar genetic factors in patients with chronic periodontitis and rheumatoid arthritis that contribute to the development of these pathologies. More than 50 % of the risk of developing RA is associated with genetic factors, and the most significant genetic association in RA is the SE-coding gene HLA-DRB1, which contributes more than 80 % susceptibility to periodontal tissue damage [7].

Immunological aspects of the development of chronic periodontitis

According to some sources, there are about 700 microorganisms in the oral cavity [10]. Microbiological aspects of the pathogenesis of chronic periodontitis are the colonization of gingival pockets, mainly by gram-negative anaerobic bacteria *Porphyromonas gingivalis* together with *Agregatibacter actinomycetemcomitans*, etc. Under the conditions of impaired microbiota composition in combination with the effects of certain immune cells, the above component is brought into action as a pathological component [7]. *P. Gingivalis* are primarily localized on the supragingival surface of teeth and in the subgingival fissure, causing the destruction of periodontal supporting tissues by the produced enzymes — proteinases, hemolysins, peptidyl-arginine deaminases (PPAD) — and reacting with cellular components [11]. These enzymes and metabolites (alkaline and acid phosphatases, volatile sulfur compounds — hydrogen sulfide, methyl mercaptan and dimethyl sulfide) have cytotoxicity as a result of the inhibition of phospholipase A_2 and protein synthesis. The severity of the inflammatory reaction is determined by local and general, specific and nonspecific resistance [12]. Microorganisms form a dental plaque 24–48 hours after brushing is stopped. The supragingival part of dental plaque is predominantly represented by gram-positive microorganisms, and the subgingival part — by gram-negative microorganisms. [13]. The antigenic load and effect of toxins increase the permeability of the epithelium of the gingival sulcus and hypersecretion of sulcular fluid, which potentiates a further increase in capillary permeability, together with the effects of bacteria and leukotoxins. Phagocytes enter the connective tissue and gingival fluid [14].

Periodontal damage starts as an acute inflammation characterized by an increase in the number of neutrophils that migrate into the gingival fissure through the periodontal epithelium and have the capacity for biosynthesis of chemokines and cytokines with pro-inflammatory, anti-inflammatory and immunoregulatory properties. Neutrophils can induce the recruitment of interleukin-17-producing CD4-positive T helper cells 17 at the site of infection or inflammation by releasing chemokines. In addition, they may promote the proliferation and differentiation of B cells into plasma cells, which are responsible for antibody production. Activated neutrophils express the activator of the membrane-bound receptor for nuclear factor kappa-β (RANKL), a key osteoclastogenic cytokine, thereby promoting bone resorption by osteoclasts [15]. These latter ideas suggest that neutrophils may contribute to the development of periodontitis, not only by initiating damage but also by participating in its progression [15].

Macrophages are an important source of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor (TNF), matrix metalloproteinases (MMP), and prostaglandin E2 [16], which play an important role in the development of inflammation. Also, an increase in their level in gingival tissue and gingival fissure fluid is observed in patients with chronic periodontitis [17].

According to current concepts, the chronization of the inflammatory process primarily contributes to the hyperproduction of non-specific body defense factors by cells: pro-inflammatory cytokines (IL-1β, IL-6, IL-8, IL-18, TNF) in response to the action of pathogenic microorganisms [18].

Due to the chemotactic action of pro-inflammatory mediators, periodontal tissues are infiltrated by neutrophils and macrophages. Their subsequent secretory degranulation leads to the release of matrix metalloproteinases (MMP), which are important in the development and maintenance of chronic inflammation [19]. MMP are Zn^{2+} and Ca^{2+}-dependent endopeptidases, which are catabolism enzymes for most extracellular matrix proteins. Collagenase-1 (MMP-1) is responsible for the cleavage of type I collagen. It is produced mainly by fibroblasts, as well as such cells as macrophages, monocytes, osteoblasts, endothelial cells, and chondroblasts. Several studies showed increased levels of MMP-8 and MMP-9 in periodontal tissues [20].

MMP-8 (collagenase-2) plays a critical role in the final stages of the development of chronic periodontitis and remodeling of periodontal tissues. It is secreted mainly by neutrophils and their precursors, as well as fibroblasts, monocytes, macrophages, plasma cells, and differentiated granulocytes [19]. It should be noted that an increased level of MMP-8 (up to 65 ng/mL) in gingival fluid was found in patients with severe chronic periodontitis, as well as patients with untreated forms of aggressive types [21]. Some authors established that Il-1β and tumor necrosis factor (TNF) contribute to excessive production of MMP-9 (collagenase-4), which stimulates increased permeability, damage to the structure of tooth tissues, and tooth decay [22].

The generation of pro-inflammatory cytokines by lymphocytes and the direct effect of the enzymes produced by bacterial cells on collagen structures [18] play an essential role in the destructive processes of the periodontium.

Free radical oxidation processes [23] play a significant role in the etiopathogenesis of chronic periodontitis. Due to an excessive inflammatory response to bacterial plaque, tissue destruction occurs, which leads to increased generation of reactive oxygen species (ROS) by WBC [24]. The cytotoxic effect of ROS is brought into action in the peroxidation of lipid structures of both cell membranes and the extracellular matrix. ROS peroxidation disrupts the physicochemical properties of proteins, which leads to the manifestation of oxidative degradation and protein aggregation. Impaired functions of proteins as the components of transport and enzyme systems of cells result in the impaired constancy of the internal environment [25]. In addition, ROS can cause depolymerization of the extracellular matrix (particularly glycosaminoglycans) and enzymes (particularly MMR) [26].

Lack of control over lipid peroxidation (LPO) reactions not only causes impaired metabolic processes, but also contributes to the development of structural changes in tissues and suppression of body defense mechanisms [25]. According to several reports, LPO activation results in the destruction of the intermediate epithelium and periodontal tissues, leading to pathological tooth mobility. Also, due to the activation of free radical oxidation processes, regeneration processes are impaired, periodontal pockets and bone resorption develop [26].

With periodontitis, there is a decreased activity of key enzymes of the body's antioxidant defense: catalase, superoxide dismutase, glutathione peroxidase, cytochrome oxidase. An increase in sulfhydryl groups is observed, which indicates the cleavage of proteins. In addition, the triggering of free radical oxidation processes is indicated by an increased level of active products of thiobarbituric acid in gingival fluid; these are the main products of the free radical peroxidation of polyunsaturated fatty acids [27].

Pathogenetic relationship between chronic periodontitis and rheumatoid arthritis

The unity of general pathological processes in the progression of periodontitis and rheumatoid arthritis, i.e., concomitant action of cellular and humoral immunity through cytokine regulation (IL-1β, IL-6, IL-8, IL-18, TNF), as well as the role of LPO in the destruction of collagen structures, extracellular matrix of subgingival spaces, as well as the predominant activation of osteoclasts, confirm the possibility of interdependence and mutual potentiation of these pathological conditions [28].

Exposure to certain environmental factors, such as smoking, genetic background (HLA-DRB1-SE), gut microbiome, P. gingivalis infection, and more recently, A. actinomycetemcomitans (microbial dysbiosis), leads to local changes in proteins due to citrullination [28, 29].

P. Gingivalis causes the activation of proteases and peptidyl-arginine deaminase (PPAD), which generates citrullinated proteins via post-transcriptional removal of the guanidine group of terminal arginine from proteins (keratin, felargin, collagen, fibrin) and triggers the synthesis of antibodies to citrullinated proteins (ACPA), which are represented by antibodies to cyclic citrullinated peptide (ACCP), modified citrullinated vimentin (AMCV), and some other antibodies [30, 31].

The consequence of impaired tolerance to citrullinated proteins is the triggering of the activation of immunocompetent cells (dendritic cells, macrophages, T and B lymphocytes), which triggers the subsequent production of pro-inflammatory cytokines and, as a result, the activation of type 1 T helper cells (Th1) and Th17 cells. Their stimulation results in the production of interferon-γ (IFN-γ), IL-2, IL-17, IL-21, TNF, leading to the activation of B lymphocytes, which are subsequently transformed into plasma cells responsible for the production of autoantibodies of the IgG isotype [32]. Therefore, the received signal against citrullinated epitopes in joints leads to increased expression of rheumatoid factor (RF) and antibodies to citrullinated peptides, which contributes to the development of immune complexes. The resulting immune complexes are phagocytized by neutrophils and macrophages of the synovial membrane, which leads to damage to neutrophils, the release of lysosomal enzymes, histamine, serotonin, kinins, prostaglandins, leukotrienes and the development of exudative and proliferative changes in the synovium and cartilage. Damage to the joint tissues by immune complexes leads to further autoantibody production and contributes to the chronicity of the inflammatory process [7].

Hyperproduction of pro-inflammatory cytokines (TNF, IL-1, IL-6, IL-17) leads to the increased production of RANKL. Moreover, TNF can bind to the type 1 TNF receptor on the surface of osteoclasts, thereby stimulating osteoclastogenesis [33].

Notably, *A. actinomycetemcomitans* leads to the hypercitrullination of neutrophils and the activation of citrulline enzymes, which are also involved in the impaired immune tolerance to host molecules. These immune complexes intensify the inflammatory process, which can aggravate the course of rheumatoid arthritis. Also, autoantibodies may contribute to the inflammatory process by direct activation of osteoclasts by interacting with citrullinated vimentin, which is expressed on the membrane of osteoclast precursors, leading to bone and cartilage damage (Fig. 1) [7].

The activation of mast cells that secrete heparin and serotonin should be noted. It leads to exudative and proliferative inflammation of the synovial membrane of joints (synovitis), which is characterized by the production of lymphocytic infiltrates, accumulation of macrophages, development of neoangiogenesis, proliferation of synovial membrane cells and fibroblasts, with the formation of an aggressive tissue — pannus. [33, 34]. Synovitis causes changes to the cellular structure of synovia due to the increased number of macrophage-like (MLS) and fibroblast-like synoviocytes (FLS). MLS produce chemokines and growth factors, which leads to the activation of local FLS expressing IL-6, prostanoids, MMP, as well as chronic synovitis [35].

Therefore, citrullination of proteins may represent a biological mechanism that strengthens mutual influence between rheumatoid arthritis and chronic periodontitis.

Wagner et al. (2015) proposed a "two-hit" model of the impact of chronic periodontitis on rheumatoid arthritis: the first "hit" is initiated by an increase in the prevalence of PAD-producing *P. gingivalis* in the periodontal microenvironment, which increases local citrullination of peptides and the generation of antibodies to citrullinated proteins. The second "hit" is represented by the cross-reactivity of periodontal-generated ACPA to antigens that are in the microenvironment of a joint, which further exacerbates chronic autoimmune inflammation caused by rheumatoid arthritis [36].

In addition, there are similar genetic factors in patients with chronic periodontitis and rheumatoid arthritis that contribute to the development of these pathologies. It is possible that several common genetic disorders are associated with increased susceptibility to these diseases. One of the potential genetic mechanisms linking rheumatoid arthritis and chronic periodontitis is a common epitope (SE)-coding HLA-DRB1 allele [37]. HLA-DRB1 alleles that encode the major histocompatibility complex class II beta chain can bind citrulliniropeptides, which can increase the immunogenicity of autoantigenic citrullinated arthritis peptides [38, 39].

Therefore, a growing number of experimental and clinical studies has undoubtedly demonstrated that there is a strong link between rheumatoid arthritis and chronic periodontitis (Figure 2) [7].

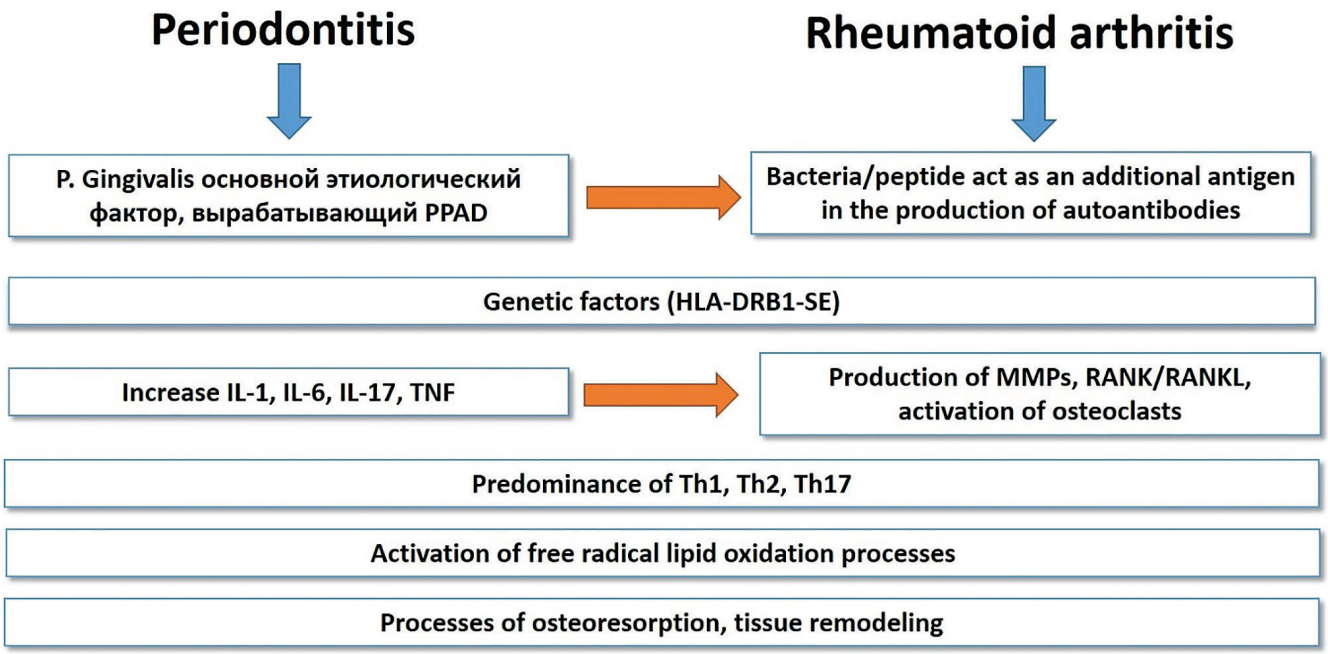


Figure 1. *The main factors of the formation of chronic generalized periodontitis and rheumatoid arthritis [7]*

Notes. PPAD –peptidyl-arginine deiminase; Th1 — T-helper cell type 1; Th2 — T-helper cell type 2; Th17 — T-helper cell type 17; IL-1 — interleukin-1; IL-6 — interleukin-6; TNF — tumor necrosis factor; IL-17 — interleukin-17; RANK-L — receptor activator of nuclear factor kappa-β; MMP — matrix metalloproteinase

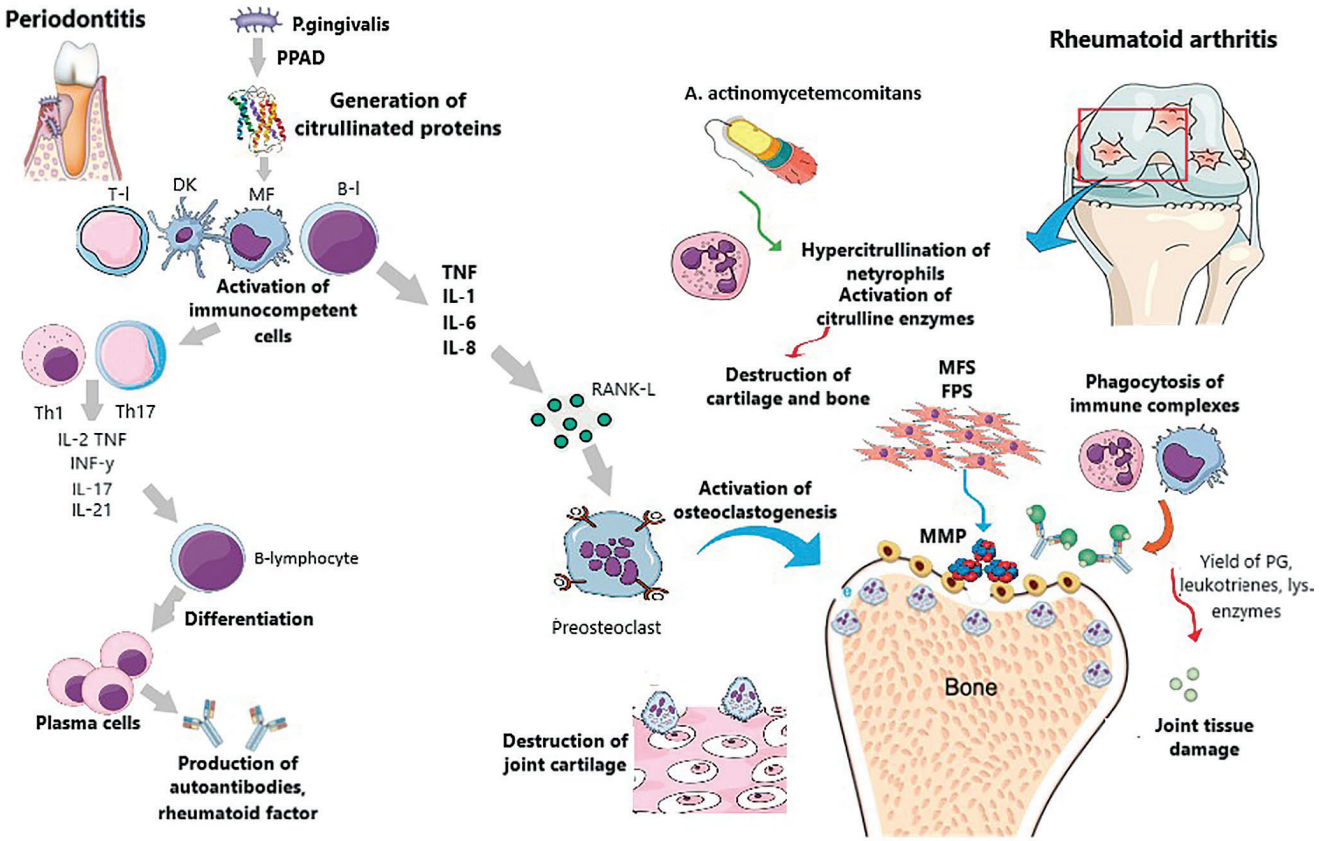


Figure 2. *Pathogenetic connection of chronic generalized periodontitis and rheumatoid polyarthritis [7]*

Notes. PPAD — peptidyl-arginine deiminase; T-l — T-lymphocyte; DK — Dendritic cell; MF — macrophage; B-l — B-lymphocyte; Th1 — T-helper cell type 1;Th17 — T-helper cell type 17; IL-1 — interleukin-1; IL-2 — interleukin-2;IL-6 — interleukin-6;IL-8 — interleukin-8; TNF — tumor necrosis factor; IL-17 — interleukin-17;IL-21 — interleukin-21; RANK-L — receptor activator of nuclear factor kappa-β; MFS — macrophage-like synoviocytes; FLS — fibroblast-like synoviocytes; MMP — matrix metalloproteinase; PG — prostaglandins

Conclusion

The presented summarized studies make a strong case for a pathogenetic relationship between the mechanisms of progression of chronic periodontitis and rheumatoid arthritis.

The correlation between both diseases is confirmed by the high incidence of the combination of both pathologies in the population, the presence of a common epitope (SE) encoding HLA-DRB1 allele, the production of cross-reacting antibodies that cause the combined effect of autoimmune and inflammatory processes, leading to systemic effects of cytokines at the body level, which explains the increased risk of this pathology in chronic periodontitis.

The link between rheumatoid arthritis and chronic periodontitis is due to the infection of periodontal tissues with *P. Gingivalis,* leading to the activation of proteases, PPAD and the production of citrullinated proteins, impaired tolerance to which leads to the activation of immunocompetent cells. Such triggering of autoaggressive reactions is critical in the development of rheumatoid arthritis in chronic periodontitis. Several proinflammatory cytokines (TNF, IL-1, IL-6, IL-17) increase the production of RANKL and stimulate osteoclastogenesis inducing bone resorption.

Further study of the mutual influence of these pathologies will allow developing new methods for diagnosing and managing these nosologies and preventing their progression at the early stages of their development. Good oral hygiene and timely detection of the initial stages of periodontitis can prevent the possible development of rheumatoid arthritis in individuals with a genetic predisposition to this pathology. Available evidence of the presence of systemic inflammation makes a strong case for introducing genetically engineered biological preparations into the treatment algorithms for these diseases. The identification of close relationships will facilitate the development and manufacturing of agents that will have an effect on both RA and chronic periodontitis. The summarized study results indicate the need for close interaction between dentists and rheumatologists, as well as for screening immunological examination of individuals with chronic periodontitis, especially those of early working age, in order to prevent the development or slow down the progression of rheumatoid arthritis.

Вклад авторов:

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

Порядин Г.В. (ORCID ID: https://orcid.org/0000-0003-2010-3296): разработка концепции и дизайна, сбор, анализ и интерпретация данных, редактирование текста рукописи, утверждение окончательного варианта рукописи

Захватов А.Н. (ORCID ID: https://orcid.org/0000-0003-1433-0337): разработка концепции и дизайна, сбор, анализ и интерпретация данных, написание и редактирование текста рукописи, утверждение окончательного варианта рукописи.

Паршина А.Ю. (ORCID ID: https://orcid.org/0000-0003-0415-1132): сбор, анализ и интерпретация данных, написание и редактирование текста рукописи, утверждение окончательного варианта рукописи.

Author Contribution:

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

Poryadin G.V. (ORCID ID: https://orcid.org/0000-0003-2010-3296): conception and design; collection, analysis and interpretation of the data, edit of the submitted article, approval of the final version of the submitted article.

Zakhvatov A.N. (ORCID ID: https://orcid.org/0000-0003-1433-0337): conception and design; collection, analysis and interpretation of the data, edit of the submitted article, approval of the final version of the submitted article.

Parshina A.Yu. (ORCID ID: https://orcid.org/0000-0003-0415-1132): collection, analysis and interpretation of data, writing and editing of the text of the submitted article, approval of the final version of the submitted article.

Список литературы/ References:

1. Tibúrcio-Machado CS, Michelon C, Zanatta FB, et al. The global prevalence of apical periodontitis: a systematic review and meta-analysis. Int Endod J. 2021; 54(5):712-735. doi: 10.1111/iej.13467.
2. Jakovljevic A, Nikolic N, Jacimovic J, et al. Prevalence of Apical Periodontitis and Conventional Nonsurgical Root Canal Treatment in General Adult Population: An Updated Systematic Review and Meta-analysis of Cross-sectional Studies Published between 2012 and 2020. J Endod. 2020; 46(10):1371-1386. doi: 10.1016/j.joen.2020.07.007.
3. Блашкова С. Л., Мартьянова М. В. Роль средств гигиены в предупреждении кариеса и заболеваний пародонта у лиц молодого возраста. Российская стоматология. 2016; 9(4):51-53. doi:10.17116/rosstomat20169451-53 Blashkova S L, Martyanova M V. The role of preventive hygiene in the prevention of caries and periodontal disease in young age. Russian Stomatology. 2016;9(4):51-53. doi:10.17116/rosstomat20169451-53
4. G. A. Roth, M. Cunningham, A. Afshin et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018; 392(10159):1736-1788. doi:10.1016/S0140-6736(18)32833-2.
5. Зорина О.А., Аймадинова Н.К., Борискина О.А., и др. Основные изменения нормальной микрофлоры пародонта при хроническом генерализованном пародонтите, выявленные с помощью метагеномного секвенирования. Российская стоматология. 2017; 10(2):41-48. doi: 10.17116/rosstomat201710241-48. Zorina OA, Aymadinova NK, Boriskina OA, et al. Major changes in the normal periodontal microbiome associated with chronic generalized periodontitis as detected by metagenomic sequencing. Russian Stomatology. 2017; 10(2):41-48. doi: 10.17116/rosstomat201710241-48. [In Russian]
6. Madianos, P.N., Bobetsis, Y.A., Offenbacher S. Adverse pregnancy outcomes (APOs) and periodontal disease: pathogenic mechanisms. Journal of Clinical Periodontology. 2013; 40(14): 170-180. doi: 10.1111/jcpe.12082.
7. de Molon RS, Rossa C Jr, Thurlings RM, et al. Linkage of periodontitis and rheumatoid arthritis: current evidence and potential biological interactions. International journal of molecular sciences. 2019; 20(18):4541-4586. doi:10.3390/ijms20184541.
8. P. Bender, W.B. Bürgin, A. Sculean et al. Serum antibody levels against Porphyromonas gingivalis in patients with and without rheumatoid arthritis — a systematic review and meta-analysis. Clin Oral Investig. 2017; 21(1):33-42. doi: 10.1007/s00784-016-1938-5.
9. Esberg A, Johansson L, Johansson I, Dahlqvist SR. Oral Microbiota Identifies Patients in Early Onset Rheumatoid Arthritis. Microorganisms. 2021; 9:1657. doi: 10.3390/microorganisms9081657.
10. Lundmark A, Hu YOO, Huss M, et al. Identification of Salivary Microbiota and Its Association With Host Inflammatory Mediators in Periodontitis. Front Cell Infect Microbiol. 2019; 21(9):216. doi: 10.3389/fcimb.2019.00216.
11. Nadim R, Tang J, Dilmohamed A et al. Influence of periodontal disease on risk of dementia: a systematic literature review and a meta-analysis. Eur J Epidemiol. 2020;35(9):821–833. doi: 10.1007/s10654-020-00648-x.
12. Bobetsis YA, Graziani F, Gürsoy M, et al. Periodontal disease and adverse pregnancy outcomes. Periodontol 2000. 2020; 83(1):154–174. doi: 10.1111/prd.12294.
13. Bilyi A.K., Antypenko L.M., Ivchuk V.V., at al. I2-heteroaryl-[1,2,4]triazolo[1,5-c]quinazoline-5(6 H)-thiones and their S-substituted derivatives: Synthesis, spectroscopic data, and biological activity. ChemPlusChem. 2015; 80(6): 980-989. doi: 10.1002/cplu.201500051.
14. Curtis MA, Diaz PI, Van Dyke TE. The role of the microbiota in periodontal disease. Periodontol 2000. 2020; 83(1):14–25. doi: 10.1111/prd.12296.
15. Hajishengallis G, Korostoff JM. Revisiting the Page & Schroeder model: The good, the bad and the unknowns in the periodontal host response 40 years later. Periodontology 2000. 2017; 75(1): 116-151. doi: 10.1111/prd.12181.

16. Cekici A, Kantarci A, Hasturk H, et al. Inflammatory and immune pathways in the pathogenesis of periodontal disease. Periodontology 2000. 2014; 64(1):57-80. doi: 10.1111/prd.12002.
17. Kang W, Hu Z, Ge S. Healthy and Inflamed Gingival Fibroblasts Differ in Their Inflammatory Response to Porphyromonas gingivalis Lipopolysaccharide. Inflammation. 2016; 39(5):1842-1852. doi: 10.1007/s10753-016-0421-4.
18. Huang, N., Dong, H., Luo, Y., et al. Th17 Cells in Periodontitis and Its Regulation by A20. Frontiers in immunology. 2021; 12:125-137. doi: 10.3389/fimmu.2021.742925.
19. Zhang Y., Li X. Lipopolysaccharide–regulated production of bone sialoprotein and interleukin–8 in human periodontal ligament fibroblasts: the role of toll–like receptors 2 and 4 and the MAPK pathway. Journal of periodontal research. 2015; 50(2):141-151. doi: 10.1111/jre.12193.
20. Григоркевич О.С., Мокров Г.В., Косова Л.Ю. Матриксные металлопротеиназы и их ингибиторы. Фармакокинетика и Фармакодинамика. 2019; 2: 3-16. doi: 10.24411/2587-7836-2019-10040.
Grigorkevich O.S., Mokrov G.V., Kosova L.Yu. Matrix metalloproteinases and their inhibitors. Pharmacokinetics and Pharmacodynamic. 2019; 2: 3-16. doi: 10.24411/2587-7836-2019-10040 [InRussian].
21. Базарный В.В., Полушина Л.Г., Максимова А.Ю. и др. Клинико-диагностические характеристики саливарных матриксных металлопротеиназ как потенциальных биомаркеров при хроническом пародонтите. Лабораторная служба. 2020; 9(4): 54-58. doi: 10.17116/labs2020904154.
Bazarny V.V., Polushina L.G., Maksimova A.Yu., et al. Clinical and diagnostic characteristics of salivary matrix metalloproteinases as potential biomarkers in chronic periodontitis. Laboratory service. 2020; 9(4): 54-58. doi: 10.17116/labs2020904154[In Russian].
22. Leone A., Uzzo M. L., Rappa F., et al. Immunohistochemical expression of apoptotic factors, cytokeratins, and metalloproteinase-9 in periapical and epithelialized gingival lesions. FoliaHistochemCytobiol. 2012; 50(4): 497-503. doi: 10.5603/FHC.2012.0070.
23. Савельева Н. Н. Состояние системы перекисного окисления липидов и антиоксидантной защиты у пациентов хроническим генерализованным пародонтитом I-II степени тяжести, сочетающегося с паразитозами. JournalofEducation, HealthandSport. 2015; 5(12): 465–476. doi: 10.5281/zenodo.35707.
Savel'eva N.N. The state of the lipid peroxidation system and antioxidant protection in patients with chronic generalized periodontitis I-II severity, combined with parasitosis. Journal of Education, Health and Sport. 2015; 5(12): 465-476. doi: 10.5281/zenodo.35707 [In Russian].
24. Callaway D. A. Jiang J. X. Reactive oxygen species and oxidative stress in osteoclastogenesis, skeletal aging and bone diseases. Journal of Bone and Mineral Metabolism. 2015; 33(4): 359–370. doi: 10.1007/s00774-015-0656-4.
25. Almubarak A, Tanagala KKK, Papapanou PN, et al. Disruption of Monocyte and Macrophage Homeostasis in Periodontitis. Front Immunol. 2020; 11: 330. doi:10.3389/fimmu.2020.00330.
26. Fang C, Wu L, Zhao MJ, et al. Periodontitis Exacerbates Benign Prostatic Hyperplasia through Regulation of Oxidative Stress and Inflammation. OxidMedCellLongev. 2021; 2021: 2094665. doi:10.1155/2021/2094665.
27. Кондюрова Е.В., Прытков В.А., Власов А.П., и др. Метаболические нарушения при хроническом генерализованном пародонтите. Российский стоматологический журнал. 2016; 20(5): 251-256. doi: 10.18821/1728-28022016;20(5):251-256.
Kondjurova E.V., Prytkov V.A., Vlasov A.P., et al. Metabolic disorders in chronic generalized periodontitis. Russian Journal of Dentistry. 2016; 20(5): 251-256. doi: 10.18821/1728-28022016;20(5):251-256 [In Russian].
28. Perricone C, Ceccarelli F, Saccucci M, et al. Porphyromonas gingivalis and rheumatoid arthritis. Curr Opin Rheumatol. 2019; 31(5):517-524. doi:10.1097/BOR.0000000000000638.
29. Engstrom, M., Eriksson, K., Lee, L., et al. Increased citrullination and expression of peptidylarginine deiminases independently of P. gingivalis and A. actinomycetemcomitans in gingival tissue of patients with periodontitis. Journal of Translational Medicine. 2018; 16(1): 214-240. doi:10.1186/s12967-018-1588-2.
30. Poulsen TBG, Damgaard D, Jørgensen MM, et al. Identification of potential autoantigens in anti-CCP-positive and anti-CCP-negative rheumatoid arthritis using citrulline-specific protein arrays. Sci Rep. 2021;11(1):17300. doi:10.1038/s41598-021-96675-z.
31. Konig, M.F., Abusleme, L., Reinholdt, J, et al. Aggregatibacter actinomycetemcomitans-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis. Science translational medicine. 2016; 8(369): 176-369. doi: 10.1126/scitranslmed.aaj1921.
32. Bettner LF, Peterson RA, Bergstedt DT, et al. Combinations of anticyclic citrullinated protein antibody, rheumatoid factor, and serum calprotectin positivity are associated with the diagnosis of rheumatoid arthritis within 3 years. ACR Open Rheumatol. 2021; 3(10): 684-689. doi:10.1002/acr2.11309
33. Захватов А.Н., Козлов С.А., Аткина Н.А. и др. Динамика уровня цитокинов при экспериментальном посттравматическом артрите. Медицинская иммунология. 2016; 18(1): 91-96. doi: 10.15789/1563-0625-2016-1-91-96.
Zahvatov A.N., Kozlov S.A., Atkina N.A., et al. Time course of cytokine levels in experimental posttraumatic arthritis. Medical Immunology (Russia). 2016; 18(1): 91-96. doi: 10.15789/1563-0625-2016-1-91-96 [In Russian].
34. B McInnes, Georg Schett.Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet. 2017; 389(10086): 2328-2337. doi: 10.1016/S0140-6736(17)31472-1.

35. Михайлова А.С., Лесняк О.М. Регуляторы роста паннуса при ревматоидном артрите, являющиеся потенциальными мишенями биологической терапии. Современная ревматология. 2018; 12(1): 55-59. doi: 10.14412/1996-7012-2018-1-55-59.
Mikhaylova A.S., Lesnyak O.M. Pannus growth regulators as potential targets for biological therapy in rheumatoid arthritis. Modern Rheumatology Journal. 2018; 12(1): 55-59. doi: 10.14412/1996-7012-2018-1-55-59 [In Russian].
36. Wagner CA, Sokolove J, Lahey LJ, et al. Identification of anticitrullinated protein antibody reactivities in a subset of anti-CCP-negative rheumatoid arthritis: association with cigarette smoking and HLA-DRB1 'shared epitope' alleles. Ann Rheum Dis. 2015; 74(3):579–586. doi: 10.1136/annrheumdis-2013-203915.
37. Varshney S, Sharma M, Kapoor S et al. Association between rheumatoid arthritis and periodontitis in an adult population — A cross sectional study. J Clin Exp Dent. 2021; 13(10):980-986. doi:10.4317/jced.57562.
38. Choi YY, Lee KH. Periodontitis as a Risk Factor for Rheumatoid Arthritis: a Matched-Cohort Study. Int Dent J. 2021; 71(6): 516-521. doi:10.1016/j.identj.2021.01.006.
39. Machado, Pedro M. Measurements, composite scores and the art of 'cutting-off'. Annals of the rheumatic diseases. 2016; 75(5): 787-790. doi: 10.1136/annrheumdis-2015-208274.

DOI: 10.20514/2226-6704-2022-12-3-212-220 УДК 616.24-002.153: 616-002-008.953-092

С.С. Бондарь[1], И.В. Терехов*[2], В.С. Никифоров[3], В.К. Парфенюк[4], Н.В. Бондарь [5]

[1] — Калужская областная клиническая больница, Калуга, Россия
[2] — Медицинский институт ФГБОУ ВО «Калужский государственный университет им. К.Э. Циолковского», Калуга, Россия
[3] — ФГБОУ ВО «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Минздрава России, Санкт-Петербург, Россия
[4] — ФГБОУ ВО «Саратовский государственный медицинский университет», Саратов, Россия
[5] — ФГБОУ ВО «Орловский государственный университет им. И.С. Тургенева», Орел, Россия

РОЛЬ СУПРЕССОРА ЦИТОКИНОВОЙ СИГНАЛИЗАЦИИ SOCS2 В РЕГУЛЯЦИИ ПРОВОСПАЛИТЕЛЬНОЙ АКТИВНОСТИ КЛЕТОК ЦЕЛЬНОЙ КРОВИ ПОСЛЕ ПЕРЕНЕСЕННОЙ ИНФЕКЦИИ НИЖНИХ ОТДЕЛОВ РЕСПИРАТОРНОГО ТРАКТА

S.S. Bondar[1], I.V. Terekhov*[2], V.S. Nikiforov[3], V.K. Parfenyuk[4], N.V. Bondar[5]

[1] — Kaluga Regional Clinical Hospital, Kaluga, Russia
[2] — Kaluga State University, Kaluga, Russia
[3] — North-Western State Medical University n. a. I. I. Mechnikov, Saint-Petersburg, Russia
[4] — Saratov State Medical University, Saratov, Russia
[5] — Orel State University, Orel, Russia

The Role of SOCS2 Cytokine Signaling Suppressor in the Regulation of Pro-Inflammatory Activity of Whole Blood Cells after Lower Respiratory Tract Infection

Резюме

Цель исследования — изучение взаимосвязи содержания в мононуклеарных лейкоцитах цельной крови при пневмонии и у практически здоровых лиц супрессора цитокиновой сигнализации 2 (SOCS2) с продукцией цитокинов (ФНОα, TGFb, ИФНα, ИФНβ, ИФНγ, ИЛ-1β, ИЛ-2, ИЛ-4, ИЛ-5, ИЛ-10, ИЛ-12, ИЛ-17А, РАИЛ-1, RANTES) и отдельными факторами NF-kB и JAK/STAT-сигнальных путей (NF-kB2, p65, p50, STAT1, STAT3, STAT5B, STAT6). **Материалы и методы исследования.** Материалом исследования служили мононуклеарные клетки, выделяемые из образцов венозной крови, а также плазма крови практически здоровых лиц и больных пневмонией. В ядерно-цитоплазма-

*Контакты: Игорь Владимирович Терехов, e-mail: trft@mail.ru
*Contacts: Igor V. Terekhov, e-mail: trft@mail.ru
ORCID ID: https://orcid.org/0000-0002-6548-083X

тических лизатах мононуклеарных клеток крови методом иммуноферментного анализа оценивали концентрацию компонентов ядерного фактора транскрипции NF-κB: p65, p50, NF-κB2, факторов STAT1, STAT3, STAT5B, STAT6, протеина SOCS2. Также определяли концентрацию ФНОα, ИЛ-1β, TGFb, ИФНα, ИФНβ, ИФНγ, ИЛ-1β, ИЛ-2, ИЛ-4, ИЛ-5, ИЛ-10, ИЛ-17А, РАИЛ-1, RANTES. **Результаты** проведенного исследования свидетельствует о том, что стадия реконвалесценции пневмонии сопровождается дисрегуляцией продукции основных провоспалительных цитокинов, проявляющейся снижением уровня ФНОα, TGFb, RANTES, ИЛ-4, ИЛ-17А, ИФНβ, ИФНγ и повышением продукции ИЛ-2 и ИФНα. На этом фоне отмечено снижение фосфорилирования факторов STAT3 и STAT4, а также снижение содержания в МНК протеинов p50 и p65. Указанные изменения ассоциировались с повышенным содержанием в МНК фактора SOCS2. Проведенный анализ показал, что повышение содержания в МНК SOCS2 от минимального уровня, определяющегося концентрацией, соответствующей 1 квартилю выборки (1,3 нг/мл) до максимального, определяющегося 4-м квартилем выборки (1,7 нг/мл) ассоциировано со снижением продукции ИЛ-1β, ИЛ-4, ИЛ-4, ИЛ-5, ИЛ-10, ИЛ-17А, TGFb, RANTES и ИФНβ на фоне повышения уровня ИНФα, ИНФγ и ИЛ-2. Изменения продукции цитокинов сопровождались повышением содержания STAT5B, STAT4 и NF-kB2 и снижением фосфорилирования STAT3. уменьшением содержания в клетке компонентов ядерного фактора транскрипции NF-κB, в частности, p50, p65. **Заключение.** Особенности взаимосвязей SOCS2 с исследуемыми факторами позволяет говорить о том, что его высокий уровень способствует ограничению продукции провоспалительных цитокинов, в особенности, продуцирующихся Т-хелперами 2 типа и Th17, стимулирует усиление чувствительности ИКК к ИЛ-2 и стимуляции Т-хелперов 1 типа. Указанные эффекты реализуются за счет повышения фосфорилирования факторов STAT5 и STAT4, снижения активности STAT3, изменения соотношения в клетке компонентов p50, p65 и NF-κB2 ядерного фактора транскрипции NF-κB.

Ключевые слова: *SOCS2, NF-κB, STAT3, STAT5, ИФНα, ИЛ-2, пневмония*

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

Статья получена 17.10.2021 г.
Принята к публикации 16.03.2022 г.

Для цитирования: Бондарь С.С., Терехов И.В., Никифоров В.С. и др. РОЛЬ СУПРЕССОРА ЦИТОКИНОВОЙ СИГНАЛИЗАЦИИ SOCS2 В РЕГУЛЯЦИИ ПРОВОСПАЛИТЕЛЬНОЙ АКТИВНОСТИ КЛЕТОК ЦЕЛЬНОЙ КРОВИ ПОСЛЕ ПЕРЕНЕСЕННОЙ ИНФЕКЦИИ НИЖНИХ ОТДЕЛОВ РЕСПИРАТОРНОГО ТРАКТА. Архивъ внутренней медицины. 2022; 12(3): DOI: 212-220. DOI: 10.20514/2226-6704-2022-12-3-212-220. EDN: UJRNMF

Abstract

The aim of the investigation was to study the relationship between the content of whole blood in mononuclear leukocytes in pneumonia and in apparently healthy individuals of cytokine signaling suppressor 2 (SOCS2) with the production of cytokines (TNFα, TGFb, IFNα, IFNβ, IFNγ, IL-1β, IL-2, IL-4, IL-5, IL-10, IL-12, IL-17A, RAIL-1, RANTES) and individual factors of the NF-kB and JAK / STAT signaling pathways (NF-kB2, p65, p50, STAT1, STAT3, STAT5B, STAT6). **Materials and research methods.** The research material was mononuclear cells isolated from venous blood samples, as well as blood plasma of practically healthy individuals and patients with pneumonia. In nuclear-cytoplasmic lysates of mononuclear blood cells, the concentration of the components of the nuclear transcription factor NF-κB, p65, p50, NF-κB2, factors STAT1, STAT3, STAT5B, STAT6, and protein SOCS2, was assessed by enzyme immunoassay. We also determined the concentration of TNFα, IL-1β, TGFb, IFNα, IFNβ, IFNγ, IL-1β, IL-2, IL-4, IL-5, IL-10, IL-17A, RAIL-1, RANTES. **The results** of this study indicate that the stage of pneumonia convalescence is accompanied by dysregulation of the production of the main proinflammatory cytokines, manifested by a decrease in the level of TNFα, TGFb, RANTES, IL-4, IL-17A, IFNβ, IFNγ and an increase in the production of IL-2 and IFNα. Against this background, a decrease in the phosphorylation of the STAT3 and STAT4 factors was noted, as well as a decrease in the content of p50 and p65 proteins in MNCs. These changes were associated with an increased content of the SOCS2 factor in MNCs. The analysis showed that an increase in the content of SOCS2 in MNCs from the minimum level determined by the concentration corresponding to the 1st quartile of the sample (1.3 ng / ml) to the maximum, determined by the 4th quartile of the sample (1.7 ng / ml) is associated with a decrease in production IL-1β, IL-4, IL-4, IL-5, IL-10, IL-17A, TGFb, RANTES and IFNβ against the background of an increase in the level of INFα, INFγ and IL-2. Changes in cytokine production were accompanied by an increase in STAT5B, STAT4, and NF-kB2 levels and a decrease in STAT3 phosphorylation. a decrease in the content in the cell of the components of the nuclear transcription factor NF-κB, in particular, p50, p65. **Conclusion.** The peculiarities of the relationship of SOCS2 with the studied factors suggests that its high level helps to limit the production of proinflammatory cytokines, in particular those produced by type 2 T-helpers and Th17, stimulates an increase in ICC sensitivity to IL-2 and stimulation of type 1 T-helpers. These effects are realized due to an increase in the phosphorylation of the STAT5 and STAT4 factors, a decrease in the STAT3 activity, and a change in the ratio of the components p50, p65 and NF-κB2 of the nuclear transcription factor NF-κB in the cell.

Key words: *NF-kB, STAT3, STAT5, SOCS2, IFNa, IL-2, pneumonia*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 17.10.2021
Accepted for publication on 16.03.2022

For citation: Bondar S.S., Terekhov I.V., Nikiforov V.S. et al. The Role of SOCS2 Cytokine Signaling Suppressor in the Regulation of Pro-Inflammatory Activity of Whole Blood Cells after Lower Respiratory Tract Infection. The Russian Archives of Internal Medicine. 2022; 12(3): DOI: 212-220. DOI: 10.20514/2226-6704-2022-12-3-212-220. EDN: UJRNMF

BMI — body mass index; CAP — community-acquired pneumonia; CCL5 — chemokine (c-c motif) ligand 5; CRP — C-reactive protein; ICC — immunocompetent cells; GM-CSF — granulocyte-macrophage colony-stimulating factor; IFN — interferon; IL — interleukin; JAK — Janus kinase; LDH — lactate dehydrogenase; Me — sample median value; MNC — mononuclear cells; NF-κB — transcription factor nuclear factor-kappa B; p50, p52, p65 — subunits of nuclear factor-kappa B; PIAS — protein inhibitor of activated STAT; SOCS — suppressor of cytokine signaling proteins; STAT — signal transducer and activator of transcription; TGF — transforming growth factor; 25 %, 75 % — 25th and 75th percentiles of the sample; TNF — tumor necrosis factor

The reactivity of immunocompetent cells (ICC) with respect to cytokines is largely determined by the state of the JAK/STAT/SOCS signaling pathway [1]. By participating in the regulation of inflammatory response, this signaling pathway plays a critical role in the development and maintenance of the activity of adaptive immune response in cases of various infectious, autoimmune or allergic pathologies, ensuring the perception of signals by a cell and their transmission by cytokines to the executive apparatus [2–4]. The development of an infectious process that initiates an acute phase response is accompanied by the production of cytokines, such as tumor necrosis factor-alpha and interleukin-1, which ensure the activation of non-specific defense mechanisms, as well as innate and acquired immunity. The activation of NF-κB transcription factor, a dimer that may include subunits p65, p52, p50, etc., plays a key role in the production of these cytokines [1].

Exposure to these cytokines increases the production of cytokines that stimulate an adaptive immune response, particularly IL-2, IL-4, IL-5, interferon-gamma (IFNγ), IL-10, IL-17A, TGFβ1; the balance of their production determines the ratio between humoral and cell-mediated immune responses. In response to chemokines, particularly CCL5, activated cells of adaptive immune response are attracted to the inflammatory focus. Janus kinase 1 (JAK1) provides intracellular signal transmission from interferon receptors, cytokines of the IL-10 family, IL-6, JAK2 — IL-3, -5 receptors, erythropoietin, granulocyte-macrophage colony-stimulating factor (GM-CSF), etc., JAK3 — IL-2, IL-4, IL-7, etc. Therefore, phosphorylation in response to cytokine stimulation of Janus kinases, followed by phosphorylation and dimerization of transducers and activators of transcription (STAT), leads to the activation of this signaling pathway and differentiation of ICC, particularly T- and B-lymphocytes and NK cells, which largely determines the nature of the developing pathological process and its outcome [2, 4]. In addition, the activation of STAT1 factors in cells under the influence of interferons alpha and beta (IFNα, β) contributes to an increase in their antiviral protection due to the expression of specific proteins [3]. In turn, the activation of STAT3, -4, -6 determines the differentiation of different subpopulations of T helper cells (T helper cells of types 1 and 2, T helper cells 17, etc.), phosphorylation of STAT5 is required for the normal course of hematopoietic processes [2, 4].

It should also be noted that the activation of the signaling pathway under consideration plays an important role in repair processes, promoting the proliferation and differentiation of mesenchymal fibroblast progenitor cells, which is most important in the reparative phase of pathological processes [3].

Negative regulation of the immune response mediated by the JAK/STAT/SOCS signaling pathway is provided by a family of cytokine signaling suppressors, represented by SOCS1-7 and PIAS proteins capable of dephosphorylating Janus kinases and STAT factors, as well as other intracellular proteins, particularly components of NF-κB transcription factor [2, 4]. It should be noted that the production of SOCS proteins is stimulated by STAT factors [5–8]. Therefore, suppressors of cytokine signaling reduce the sensitivity of the corresponding cells to cytokines by regulating the activity of Janus kinases and STAT factors.

One of the regulators of the JAK/STAT signaling pathway is SOCS2 protein, which plays an essential role in the regulation of infectious inflammatory and autoimmune processes. Its role in the differentiation of T helper cells of types 1 and 2, T helper cells 17, and T regulatory cells was demonstrated. A low level of SOCS2 contributes to the differentiation of type 2 T helper cells and the development of an allergic response [9–12]. The important role of SOCS2 in the processes of sanogenesis during autoimmune inflammation in its recovery phase was also established [13]. Controlling the activity of SOCS proteins can be considered a promising therapeutic approach to the management of pathological conditions associated with increased activation of the JAK/STAT signaling pathway, as well as in patients with certain types of immunodeficiencies [14, 15].

Considering the important role of SOCS2 in the processes of sanogenesis and regulation of JAK/STAT activity, as well as of NF-κB signaling pathways, the aim of this study was to analyse the relationship between cytokine signaling suppressor SOCS2 in the MNC of patients with past community-acquired pneumonia and the blood levels of cytokines that regulate adaptive immune response, as well as JAK/STAT and NF-κB signaling pathway components in cells.

Material and methods

In accordance with the objective of this work, 45 male patients with non-severe bacterial community-acquired pneumonia were examined on days 13–15 of the disease before their discharge from the hospital; they were the test group. The diagnosis was confirmed in accordance with national guidelines for the diagnosis of pneumonia [16]. The control group included 15 apparently healthy young individuals who were blood donors.

Clinical features and laboratory test results of the examined individuals are presented in Table 1.

S. pneumoniae was found during the microbiological test of sputum samples in 34 (76 %) patients of the test group; S. aureus was found in three cases (6.7 %); E. coli — in one case (2.2 %). The causative agent of the disease in other patients was not identified. All patients of the test group received antibiotic therapy. Empiric antibiotic therapy in cases of non-severe pneumonia included protected aminopenicillins (amoxicillin / clavulanic acid, or amoxicillin/sulbactam; in case of intolerance, respiratory fluoroquinolones — levofloxacin). In severe cases, combined antibiotic therapy was prescribed, which included third-generation cephalosporins (ceftriaxone or cefotaxime) and respiratory fluoroquinolones (levofloxacin or moxifloxacin) at medium therapeutic doses. Antibacterial therapy was adjusted according to the results of bacteriological tests. According to indications, patients also received symptomatic, respiratory and infusion therapy [16].

The material for the study of cytokines and immunoregulatory factors was venous blood taken in the morning from the cubital vein of examined individuals. For the detection of intracellular markers, 1 mL of whole blood was put into a vial with 4 mL of DMEM medium, heparin (2.5 U/mL), gentamicin (100 μg/mL) and L-glutamine (0.6 mg/mL), followed by isolation of MNC using ficoll-verographin density-gradient separation (ρ = 1.077) and preparation of cell lysates [5, 8]. Nuclear cytoplasmic lysates of MNC were assessed for the concentration of the components of NF-κB transcription factor — p65, p50, p52, signal transducers and activators of transcription (STAT) — STAT1, STAT3, STAT5B, STAT6, as well as suppressor of cytokine signaling proteins

Table 1. *Clinical and laboratory characteristics of the examined persons*

Characteristic	Main group (n = 45)	Control group (n = 15)
Age (years), mean (minimum, maximum)	25 (18 — 42)	26 (18 — 44)
Gender, n (%)		
Male	24 (53,3)	9 (60,0)
Female	21 (46,7)	6 (40,0)
Concomitant pathology, n (%)		
Obesity (BMI >35 kg/m^2)	8 (17,8)	3 (20,0)
Chronical bronchitis	7 (15,6)	2 (13,3)
Arterial hypertension	4 (8,8)	1 (6,7)
Diabetes	5 (11,1)	2 (13,3)
Clinical symptoms, n (%)		
Fever	38 (84,4)	-
Cough	30 (66,7)	-
Chest pain	5 (11,1)	-
Dyspnea	22 (48,8)	-
Laboratory indicators, n (%)		
Leukocytosis >12.0×10^9 /l	40 (88,9)	-
CRP >10 mg/l	45 (100,0)	-
Urea >7 mmol/l	14 (31,1)	-
LDH >300 mg/l	16 (35,6)	-
Saturation less than 90 %	11 (24,4)	-
Severity of condition on admission, n (%)		
Non-Severe Condition	32 (71,1)	-
Grave condition	13 (28,9)	-
X-ray symptoms, n (%)		
Alveolar type of infiltration	38 (84,4)	-
Focal type of infiltration	7 (15,6)	-
Unilateral lesion within 1-2 segments of the lung	36 (80,0)	-
Polysegmental lesion	5 (11,1)	-
Bilateral localization	8 (17,8)	-
Exudative pleurisy	6 (13,3)	-
The presence of residual (small) forms of infiltration at discharge (low-intensity focal, peribronchial infiltration, increased vascular pattern)	5 (11,1)	-

Note: BMI — body mass index, CRP — C-reactive protein, LDH — lactate dehydrogenase

(SOCS) SOCS2 by enzyme immunoassay (ELISA). The concentration of tumor necrosis factor-alpha (TNFα), interleukins (IL) — IL-1β, IL-4, IL-5, IL-10, IL-17A, interferons (IFN) — IFNα, IFNβ, IFNγ, and CCL5 chemokine was defined in cell supernatants. ELISA was performed using Cusabio Biotech (PRC) reagent kits. Statistical analysis was performed using Statistica 7.0 software. The study results are presented as follows: median (Me); 25th and 75th percentiles (25 %, 75 %). The statistical significance (p) for intergroup differences was assessed using the Mann-Whitney U-test.

Results

The analysis revealed that the recovery phase of CAP was characterized by a statistically significant decrease in the production of TNFα, CCL5, IL-4, IL-17A, IFNβ, and increased production of IFNα. In this context, in MNC, there was decreased phosphorylation of STAT3 factors with increased levels of STAT5B and STAT1, as well as decreased levels of proteins p50, p65, JAK1 protein kinase in cells and increased levels of JAK3 and SOCS2. It should be noted that there was no statistically significant difference in the production of IL-1β, IL-5 and IL-10, as well as the level of JAK2, STAT4, STAT6 and p52 factors in MNC in convalescents and apparently healthy individuals.

The results of the study are presented in Table 2.

Therefore, the production of cytokines that regulate adaptive immune response is inhibited in CAP convalescents, which is associated with decreased intracellular levels of certain components of NF-κB and the JAK/STAT signaling pathway. In this context, there is a statistically significant increase in the production of IL-2 and phosphorylation of STAT5B factor, as well as the level of Janus kinase 3 in MNC. The data obtained indicate a decrease in the activity of type 2 T helper cells and T helper cells 17 (Th17), as well as in the sensitivity of MNC to IL-2, IL-4, IL-7, IL-15, and IL-21 in convalescents. It should be noted that the changes found are associated with an increased SOCS2 / STAT3 ratio.

In accordance with the objective of this study, depending on the level of SOCS2 in the MNC of CAP

Table 2. *The level of the studied factors in the groups*

Исследуемый фактор/ Researched factor	Группа контроля/ Control group	Основная группа/ Main group	Δ, %	p
	Me (25; 75 %)	*Me* (25; 75 %)		
TNFa, pg/ml	15,3 (14,7; 16,3)	14,0 (13,6; 14,9)	-8,5	0,047
CCL5, pg/ml	7,36 (6,3; 8,7)	6,5 (5,8; 7,1)	-11,7	0,0001
IL-1b, pg/ml	16,1 (12,7; 18,1)	14,7 (12,5; 17,4)	-8,7	0,58
IL-4, pg/ml	3,15 (2,7; 3,4)	2,50 (2,0; 2,6)	-20,6	0,0001
IL-5, pg/ml	2,47 (2,0; 3,1)	2,42 (2,2; 2,8)	-2,0	0,71
IL-10, pg/ml	13,4 (12,9; 15,7)	14,1 (12,8; 16,0)	5,2	0,56
IL-17A, pg/ml	2,59 (2,3; 2,8)	2,24 (1,9; 2,4)	-13,5	0,0023
IFNa, pg/ml	11,4 (10,1; 13,1)	17,2 (15,5; 19,6)	50,9	0,0001
IFNb, pg/ml	2,46 (2,0; 2,8)	1,84 (1,7; 1,9)	-25,2	0,005
IFNg, pg/ml	3,1 (2,9; 3,9)	3,06 (2,8; 3,3)	-1,3	0,31
STAT5B, ui/ng	0,73 (0,6; 0,8)	1,45 (0,9; 1,7)	98,6	0,0001
STAT6, ui/ng	2,35 (2,2; 2,5)	2,21 (2,0; 2,9)	-6,0	0,26
STAT1, ui/ng	1,1 (0,8; 1,6)	1,37 (1,1; 1,5)	24,5	0,06
STAT3, ui/ng	1,42 (1,0; 2,1)	1,13 (1,0; 1,5)	-20,4	0,051
STAT4, ui/ng	0,8 (0,7; 1,4)	0,86 (0,7; 1,1)	7,5	0,96
p50, ng/ml	0,73 (0,7; 0,8)	0,68 (0,4; 0,7)	-6,8	0,002
p65, ng/ml	0,58 (0,5; 0,7)	0,56 (0,3; 0,6)	-3,4	0,03
p52, ng/ml	0,75 (0,68; 0,82)	0,71 (0,67; 0,87)	-5,3	0,88
JAK1, ng/ml	52,0 (51,3; 52,5)	51,2 (50,7; 52,7)	-1,5	0,05
JAK2, ng/ml	5,28 (4,9; 5,4)	5,3 (5,1; 5,4)	0,4	0,18
JAK3, ng/ml	24,8 (22,5; 25,0)	26,27 (24,2; 27,0)	5,9	0,007
SOCS2, ng/ml	1,38 (1,31; 1,4)	1,59 (1,5; 1,7)	15,2	0,0001
SOCS2 / STAT3, ui.	1,07 (0,66; 1,41)	1,33 (1,09; 1,77)	24,3	0,0001

Note: Δ is the difference in the concentration of the studied factors in the first and third subgroups against the background of low and high levels of SOCS2, respectively (%); Me, 25 %, 75 % — median, percentile values of the sample, IL-1β — interleukin 1 beta, IL-4 — interleukin-4, IL-5 — interleukin-5, IL-10 — interleukin-10, IL-17A — interleukin 17A, IFNα — interferon alpha, IFNβ — interferon beta, IFNγ — gamma interferon, STAT1 — signal transducer and transcription activator 1, STAT3 — signal transducer and transcription activator 3, STAT4 — signal transducer and transcription activator 4, STAT5B — signal transducer and transcription activator 5B, STAT6 — signal transducer and transcription activator 6, p50 — p50 subunit of nuclear transcription factor NF-kB, p52 — p52 subunit of nuclear transcription factor NF-kB, p65 — p65 subunit of nuclear transcription factor NF-kB, JAK1 — Janus kinase 1, JAK2 — Janus kinase 2, JAK3 — Janus kinase 3, SOCS2 — cytokine signaling suppressor 2

convalescents (Table 1), the test group was divided into three subgroups. Subgroup 1 included MNC samples with SOCS2 levels less than 1.48 pg/mL (corresponding to the 1st quartile of the sample); subgroup 2 included samples with levels from 1.48 pg/mL to 1.66 pg/mL, which corresponds to the 2nd quartile of the sample; subgroup 3 included samples with SOCS2 levels of more than 1.66 pg/mL, which corresponds to the 3rd quartile. Therefore, subgroup 1 includes samples with a minimum level of SOCS2, subgroup 2 corresponds to the average values, and subgroup 3 represents samples with the maximum level of the studied factor in the sample population.

The concentration of the studied factors depending on the SOCS2 level in MNC is presented in Table 3.

The analysis showed that the increased level of the suppressor of cytokine signaling proteins SOCS2 in MNC contributed to a decrease in the production of IL-1β, IL-4, IL-5, IL-10, IL-17A, CCL5, and IFNβ. At the same time, the increased level of SOCS2 was associated with a statistically significant increase in the production of IFNα and IL-2. It should be noted that the production of IL-4, IL-5, IL-17A, and CCL5 decreased most significantly in connection with the increased level of SOCS2.

These changes were accompanied by the increased phosphorylation of factors STAT5B and STAT4, increased level of the component of NF-κB transcription factor — p52 and Janus kinase 3 in MNC, a decrease in STAT3 phosphorylation and the levels of factors p50 and p65, as well as Janus kinase 1. It should be noted that the suppression of the production of key cytokines that determine the activity of adaptive response in CAP convalescents compared with practically healthy individuals is a potentially unfavorable factor in terms of the development of recurrent pneumonia and other infectious and inflammatory pathologies [16, 17].

Results of this study suggest that SOCS2 is one of the regulators of the activity of intracellular signaling pathways, which affects not only the production of cytokines (primarily IL-5, IL-12, IL-17A, CCL5), but also ICC reactivity to them, which is determined by changes in the phosphorylation of STAT5B, STAT3, and STAT4 factors, as well as the level of NF-κB nuclear factor components in cells, particularly p50, p65, and NF-κB2 [15].

Table 3. *The level of the studied factors depending on the content of the SOCS2 protein in the MNC*

Factor	Subgroup № 1 n = 16	Subgroup № 2 n = 15	Subgroup № 3 n = 14	Δ, %	p
	Me (25 % 75 %)	*Me* (25 % 75 %)	*Me* (25 % 75 %)		
IL-1b, pg/ml	16,1 (15,8; 16,3)	15,9 (11,9; 18,3)	13,6 (12,4; 17,0)	-15,5	0,028
IL-4, pg/ml	2,72 (2,3; 3,2)	2,62 (2,4; 3,1)	2,24 (1,9; 2,5)	-17,6	0,0028
IL-5, pg/ml	2,9 (2,3; 3,5)	2,38 (2,1; 2,8)	2,37 (2,0; 2,5)	-18,3	0,0028
IL-10, pg/ml	15,2 (12,8; 17,5)	14,1 (12,9; 14,9)	13,5 (12,8; 15,4)	-11,2	0,29
IL-17A, pg/ml	2,57 (2,3; 2,8)	2,36 (2,2; 2,6)	1,87 (1,6; 2,3)	-27,2	0,0005
IFNg, pg/ml	2,89 (2,7; 3,1)	3,02 (2,8; 3,3)	3,19 (2,8; 3,4)	10,4	0,053
TNFa, pg/ml	14,7 (14,2; 15,2)	15,0 (14,3; 17,2)	13,7 (13,6; 14,4)	-6,8	0,005
CCL5, pg/ml	8,65 (8,1; 9,2)	6,84 (5,9; 7,1)	5,97 (5,7; 6,5)	-31,0	0,0001
IFNa, pg/ml	11,0 (9,6; 12,4)	15,5 (13,8; 17,1)	17,4 (15,6; 19,6)	58,2	0,0002
IFNb, pg/ml	2,04 (1,5; 2,5)	1,93 (1,8; 2,3)	1,72 (1,7; 1,8)	-15,7	0,87
STAT5B, ui/ng	0,81 (0,8; 0,8)	0,86 (0,7; 1,5)	1,45 (1,0; 1,7)	79,0	0,0028
STAT6, ui/ng	2,34 (2,1; 2,5)	2,24 (2,0; 2,4)	2,47 (2,0; 2,9)	5,6	0,26
STAT1, ui/ng	1,31 (0,8; 1,8)	1,44 (0,9; 1,5)	1,33 (1,1; 1,4)	1,5	0,88
STAT3, ui/ng	1,68 (1,0; 2,4)	1,37 (1,1; 1,9)	1,01 (0,9; 1,3)	-39,9	0,08
STAT4, ui/ng	0,72 (0,7; 0,8)	0,89 (0,7; 1,6)	1,00 (0,8; 1,1)	38,9	0,0005
p50, ng/ml	0,74 (0,6; 0,8)	0,68 (0,6; 0,7)	0,68 (0,4; 0,7)	-8,1	0,06
p65, ng/ml	0,62 (0,5; 0,7)	0,49 (0,3; 0,6)	0,56 (0,5; 0,6)	-9,7	0,051
p52, ng/ml	0,68 (0,6; 0,7)	0,74 (0,7; 0,9)	0,78 (0,6; 0,9)	14,7	0,038
JAK1, ng/ml	51,3 (51,3; 51,4)	52,0 (51,2; 52,5)	50,9 (50,4; 52,5)	-0,8	0,004
JAK2, ng/ml	5,05 (4,6; 5,5)	5,20 (5,1; 5,3)	5,36 (5,2; 5,4)	6,1	0,53
JAK3, ng/ml	25,0 (24,8; 25,2)	24,7 (23,7; 26,3)	26,3 (23,4; 27,0)	5,2	0,02
SOCS2, ng/ml	1,3 (1,26; 1,33)	1,47 (1,4; 1,5)	1,66 (1,6; 1,7)	27,7	0,001
SOCS2 / STAT3, ui.	0,97 (0,53; 1,42)	1,18 (0,78; 1,38)	1,68 (1,20; 1,91)	73,2	0,0001

Note: Δ is the difference in the concentration of the studied factors in the first and third subgroups against the background of low and high levels of SOCS2, respectively (%); Me, 25 %, 75 % — median, percentile values of the sample, IL-1β — interleukin 1 beta, IL-4 — interleukin-4, IL-5 — interleukin-5, IL-10 — interleukin-10, IL-17A — interleukin 17A, IFNα — interferon alpha, IFNβ — interferon beta, IFNγ — gamma interferon, STAT1 — signal transducer and transcription activator 1, STAT3 — signal transducer and transcription activator 3, STAT4 — signal transducer and transcription activator 4, STAT5B — signal transducer and transcription activator 5B, STAT6 — signal transducer and transcription activator 6, p50 — p50 subunit of nuclear transcription factor NF-kB, p52 — p52 subunit of nuclear transcription factor NF-kB, p65 — p65 subunit of nuclear transcription factor NF-kB, JAK1 — Janus kinase 1, JAK2 — Janus kinase 2, JAK3 — Janus kinase 3, SOCS2 — cytokine signaling suppressor 2

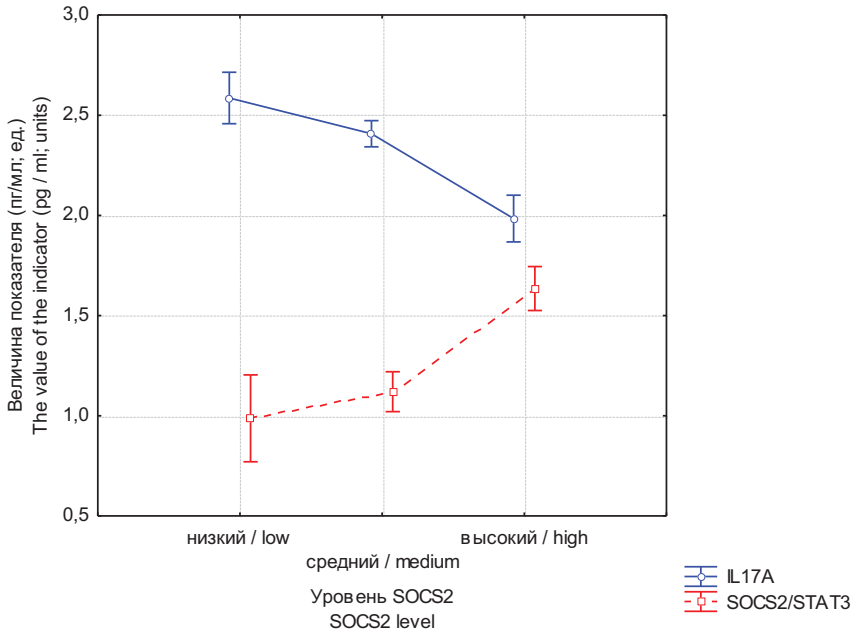


Figure 1. *Dynamics of SOCS2 / STAT3 ratio and IL-17A production depending on the content of SOCS2 protein in MNCs*

Figure 1 demonstrates changes in the SOCS2 / STAT3 ratio and IL-17A production depending on the level of SOCS2 protein in cells.

Graphical analysis of changes in the SOCS2 / STAT3 ratio and IL-17A production suggests a functional relationship between them, as indicated by the mirror reflection of the graphs. The SOCS2 / STAT3 ratio under normal conditions and in apparently healthy individuals is close to 1.0 and is significantly higher in patients after CAP. An increase in this ratio of more than 1.0, accompanied by a proportional decrease in the production of IL-17A, one of the key cytokines that protect the lower respiratory tract from bacterial infection, below the level of healthy individuals, indicates the development of an immunosuppressive response in such patients. Therefore, the results of this study suggest that the SOCS2/STAT3 ratio in the range of physiological values typical for healthy individuals, i.e., 0.66–1.41, determines the optimal reactivity of ICC. An increase in this ratio is associated with the suppression of the activity of T helper cells 17.

Therefore, this suggests that the observed features of the cytokine profile in patients after pneumonia can be largely determined by changes in the level of cytokine signaling suppressors in MNC; in particular, they can be associated with an increased level of SOCS2.

Discussion

The results obtained suggest that the recovery stage of CAP progresses with underlying suppression of the activity of the monocyte and macrophage pool of immunocompetent cells, as well as T helper cells, which can be considered as signs of dysregulation in connection with excessive suppression of immune response. Clearly, one of the mechanisms of the observed phenomenon is the decreased activity of NF-κB transcription factor and certain STAT proteins. Also, the identified changes that limit the effectiveness of both innate and acquired mechanisms of infectious immunity are one of the predisposing factors for reinfection and superinfection [6, 9, 17].

Under these conditions, the ability of the suppressor of cytokine signaling proteins SOCS2 to modulate the activity of the JAK/STAT signaling pathway and NF-κB transcription factor, thereby regulating the pro-inflammatory reactivity of ICC and their sensitivity to cytokines, was demonstrated. Moreover, the anti-inflammatory effect of SOCS2, which is clearly determined by its effect on the level of certain components of NF-κB transcription factor, is combined with an immunoregulatory effect, which is expressed in the change in the phosphorylation of certain STAT factors, which, in turn, determines changes in the sensitivity of ICC to cytokines and the formation of stimuli to the differentiation and proliferation of the corresponding ICC populations, including T helper cells [9–12, 16, 17]. A relatively high level of SOCS2 is associated with decreased STAT3 phosphorylation, which is accompanied by a decrease in the production of IL-17A, which indicates the decreased activity of T helper cells 17. In turn, increased STAT4 phosphorylation determines an increase in IFNγ production and activation of type 1 T helper cells. The level of the components of NF-κB transcription factor in cells can decrease due to the stimulation of ubiquitinylation processes and their subsequent proteasomal degradation under the action of SOCS2 [18, 19]. It is apparent that the immunosuppressive effects that develop in patients after CAP and determine the decreased reactivity of their adaptive immune response can be determined by the emerging balance of SOCS2/STAT3 activity in MNC.

The effect of SOCS2 on physiological processes in MNC can be demonstrated using the diagram shown in Fig. 2.

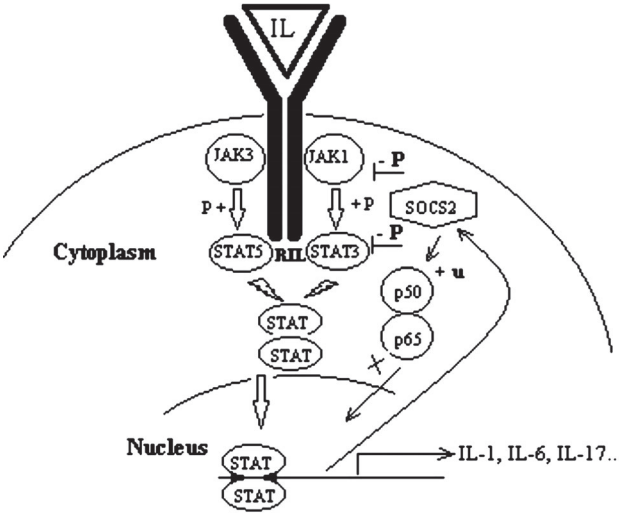


Figure 2. *Possible mechanism of immunoregulatory influence of SOCS2*

Note: IL — interleukins, RIL — receptor for type I and III interleukins, Cytoplasm — cell cytoplasm, Nucleus — cell nucleus, +P — phosphorylation, -P — dephosphorylation, + u — ubiquitinylation, x — blocking of translocation to the nucleus

The data obtained in this study, including those indicating the important role of the JAK/STAT signaling pathway and the SOCS2/STAT3 balance in the regulation of sanogenesis in CAP convalescents, enable to consider these factors as potential therapeutic targets; the impact on them can increase the activity of sanogenesis processes, as well as the restoration of impaired immunological reactivity at the stage of rehabilitation of patients after pneumonia [14, 20–22]. It is clear that the restoration of the initial reactivity of ICC in CAP convalescents determines the normal restoration of tissue repair and regeneration processes, and is also a factor preventing the development of recurrent infectious diseases, including recurrent pneumonia, as well as superinfections [17].

Conclusion

1. The recovery stage of community-acquired pneumonia progresses with underlying dysregulation of the production of pro- and anti-inflammatory cytokines, as well as impaired functional state of the JAK/STAT signaling pathway. An increased level of cytokine signaling suppressor SOCS2 in MNC in patients with pneumonia is associated with decreased production of IL-1β, IL-4, IL-5, IL-10, IL-17A, CCL5, and IFNβ in connection with increased levels of IFNα, IFNγ and IL-2. Changes in the production of these cytokines were accompanied by increased levels of STAT5B, STAT4 and p52 and decreased levels of JAK1 and STAT3.

2. Analysis of the specific features of the relationship between SOCS2 and the studied factors revealed that its high level helped limit the production of pro-inflammatory cytokines and increase the sensitivity of ICC to IL-2, as well as enhance the proliferation and differentiation of type 1 T helper cells. These effects are brought into action by increasing the phosphorylation of STAT5 and STAT4 factors and changes in the ratio of the components of NF-κB transcription factor: p50, p65, and p52. However, the overexpression of this factor is associated with the inhibition of IL-17A production, which may contribute to the weakening of the anti-infectious protection of the lower respiratory tract.

3. The suppressor of cytokine signaling proteins SOCS2 can be considered a potential therapeutic target in terms of the management of immunopathological disorders associated with the development of immunosuppression or excessive activation of the immune system.

Вклад авторов:

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

Никифоров В.С. (ORCID: https://orcid.org/0000-0001-7862-0937): разработка дизайна, основной сбор, анализ, интерпретация данных

Бондарь С.С. (ORCID: https://orcid.org/ ORCID: 0000-0003-2749-8366): сбор и анализ данных, участие в разработке дизайна исследования

Терехов И.В. (ORCID: https://orcid.org/0000-0002-6548-083X): анализ и интерпретация данных, участие в разработке дизайна, окончательное утверждение рукописи к публикации, создание критически важного интеллектуального содержания, готовность принять ответственность за все аспекты работы

Парфенюк В.К. (ORCID: https://orcid.org/0000-0003-1329-4178): разработка дизайна, математический анализ и интерпретация данных

Бондарь Н.В. (ORCID: https://orcid.org/0000-0001-7806-5320): математический анализ и интерпретация данных

Author Contributions:

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

Nikiforov V.S. (ORCID: https://orcid.org/0000-0001-7862-0937): design development, basic collection, analysis, data interpretation

Bondar S.S. (ORCID: https://orcid.org/ORCID: 0000-0003-2749-8366): data collection and analysis, participation in study design

Terekhov I.V. (ORCID: https://orcid.org/0000-0002-6548-083X): data analysis and interpretation, participation in design development, final approval of the manuscript for publication, creation of critical intellectual content, willingness to accept responsibility for all aspects of the work

Parfenyuk V.K. (ORCID: https://orcid.org/0000-0003-1329-4178): design development, mathematical analysis and data interpretation

Bondar N.V. (ORCID: https://orcid.org/0000-0001-7806-5320): mathematical analysis and data interpretation

Список литературы / References:

1. Кетлинский С.А., Симбирцев А.С. Цитокины. СПб: ООО «Издательство Фолиант». 2008; 552 с.
Ketlinskij S.A., Simbirtsev A.S. Citokiny. SPb: OOO «Izdatel'stvo Foliant». 2008; 552 p. [in Russian].
2. Шапошников А.В., Комарьков И.Ф., Лебедева Л.А. и др. Строение сигнального пути JAK/STAT и его взаимосвязь с аппаратом транскрипции. Молекулярная биология. 2013; 47(3): 388-397.
Shaposhnikov A.V., Komar'kov I.F., Lebedeva L.A. et al. Molecular components of JAK/STAT signaling pathway and its interaction with transcription machinery. Molecular Biology. 2013; 47(3): 343-351. [in Russian]. doi: 10.7868/S0026898413030130

3. Liu S., Liao Y., Chen B., Chen Y. Critical role of Syk-dependent STAT1 activation in innate antiviral immunity. Cell Rep. 2021; 34(3): 108627. doi: 10.1016/j.celrep.2020.108627
4. Зюзьков Г.Н., Удут Е.В., Мирошниченко Л.А. Роль JAK/STAT3-сигналинга в стимуляции функций мезенхимных клеток-предшественников фактором роста фибробластов. Бюллетень экспериментальной биологии. 2018; 165(1): 25-28.
Zyuz'kov G.N., Udut E.V., Miroshnichenko L.A. et al. Role of JAK/STAT3 signaling in functional stimulation of mesenchymal progenitor cells by fibroblast growth factor. Bulletin of Experimental Biology and Medicine. 2018; 165(1):18-21. [in Russian].
5. Терехов И.В., Никифоров В.С., Бондарь С.С. и др. Изменение содержания компонентов IL/TOLL-сигнального пути и NF-kB в мононуклеарных клеток цельной крови под влиянием низкоинтенсивного электромагнитного излучения частотой 1 ГГц. Гены и клетки. 2017; 12(2): 90-96.
Terekhov I.V., Nikiforov V.S., Bondar' S.S. et al. The effect of low-intensity electromagnetic irradiation with a frequency of 1 GHZ on the content of the components of the IL/TOLL signaling pathway and NF-kb in mononuclear cells of whole blood. Geny i kletki. 2017; 12(2): 90-96. [in Russian]. doi: 10.23868/201707020
6. Visekruna A., Volkov A., Steinhoff U. A key role for NF-κB transcription factor c-Rel in T-lymphocyte-differentiation and effector functions. Clin Dev Immunol. 2012; 2012: 239368. doi: 10.1155/2012/239368.
7. Сорокина Л.Н., Минеев В.Н., Лим В.В. Роль негативных регуляторов транскрипции генов SOCS1, SOCS3 и SOCS5 в системе негативной регуляции клеточной сигнализации при бронхиальной астме. Терапевтический архив. 2017; 89(3): 43-47.
Sorokina L.N., Mineev V.N., Lim V.V. Role of negative regulators of SOCS1, SOCS3, and SOCS5 gene transcription in the negative cell signaling regulation system in asthma. Terapevticheskii Arkhiv. 2017; 89(3): 43-47. [In Russian]. doi: 10.17116/terarkh201789343-47
8. Бондарь С.С., Терехов И.В., Никифоров В.С. и др. Роль супрессора цитокиновой сигнализации SOCS7 в регуляции фосфорилирования ингибитора ядерного фактора транскрипции NF-KB в мононуклеарных лейкоцитах и продукции цитокинов у реконвалесцентов внебольничной пневмонии. Медицинский совет. 2018; 15: 138-140.
Bondar S.S., Terekhov I.V., Nikiforov V.S. et al. The role of suppressor of cytokine signaling SOCS7 in the regulation of the phosphorylation of inhibitor of nuclear transcription factor NF-KB in mononuclear leukocytes and production of cytokines in community-acquired bacterial pneumonia. Meditsinskiy sovet=Medical Council. 2018; (15): 138-140. [in Russian]. doi: 10.21518/2079-701X-2018-15-138-140
9. Терехов И.В., Никифоров В.С., Бондарь С.С. и др. Состояние RIG-I- и NF-KB-сигнальных путей в мононуклеарных клетках цельной крови практически здоровых лиц и реконвалесцентов пневмонии, подвергнутых митогенной стимуляции. Гены и клетки. 2019; 3(14): 131-136.
Terekhov I.V., Nikiforov V.S., Bondar' S.S. et al. Condition of RIG-I and NF-KB-signal pathways in mononuclear cells of whole blood of practically healthy people and reconvalescents of pneumonia affected by mitogenic stimulation. Geny i kletki. 2019; 3(14): 131-136. [in Russian]. doi: 10.23868/201906023
10. Keating N., Nicholson S.E. SOCS-mediated immunomodulation of natural killer cells. Cytokine. 2018. pii: S1043-4666(18)30119-4. doi: 10.1016/j.cyto.2018.03.033
11. Knosp C.A., Carroll H.P., Elliott J. et al. SOCS2 regulates T helper type 2 differentiation and the generation of type 2 allergic responses. J Exp Med. 2011; 208(7): 1523-31. doi: 10.1084/jem.20101167
12. Knosp C.A., Schiering C., Spence S. et al. Regulation of Foxp3+ inducible regulatory T cell stability by SOCS2. J Immunol. 2013;190(7):3235-45. doi: 10.4049/jimmunol.1201396
13. Letellier E., Haan S. SOCS2: physiological and pathological functions. Front Biosci (Elite Ed). 2016; 8: 189-204. doi: 10.2741/E760
14. Cramer A., de Lima Oliveira B.C., Leite P.G. et al. Role of SOCS2 in the Regulation of Immune Response and Development of the Experimental Autoimmune Encephalomyelitis. Mediators Inflamm. 2019; 2019: 1872593. doi: 10.1155/2019/1872593
15. Durham G.A., Williams J.J.L., Nasim M.T. et al. Targeting SOCS Proteins to Control JAK-STAT Signalling in Disease. Trends Pharmacol Sci. 2019; 40(5): 298-308. doi: 10.1016/j.tips.2019.03.001
16. Пульмонология. Национальное руководство. Краткое издание/под ред. А.Г. Чучалина. М.: ГЭОТАР-Медиа, 2014; 800 с.
Pulmonology. National leadership. Short edition/ed. A.G. Chuchalin. M.: GEOTAR-Media, 2014; 800 p. [in Russian].
17. Лебедева М.Н., Грищенко А.В. Особенности течения повторных внебольничных пневмоний у военнослужащих по призыву. Военно-медицинский журнал. 2009; 330(7): 24-8.
Lebedeva M.N., Grishchenko A.V. Features of the course of repeated community-acquired pneumonia in conscripted servicemen. Voenno-medicinskij zhurnal. 2009; 330(7): 24-8. [in Russian]. doi: 10.17816/RMMJ72650
18. McBerry C., Gonzalez R.M., Shryock N. et al. SOCS2-induced proteasome-dependent TRAF6 degradation: a common anti-inflammatory pathway for control of innate immune responses. PLoS One. 2012; 7(6): e38384. doi: 10.1371/journal.pone.0038384
19. Paul I., Batth T.S., Iglesias-Gato D. et al. The ubiquitin ligase Cullin5 SOCS2 regulates NDR1/STK38 stability and NF-κB transactivation. Sci Rep. 2017; 7: 42800. doi: 10.1038/srep42800
20. Monti-Rocha R., Cramer A., Gaio Leite P. et al. SOCS2 Is Critical for the Balancing of Immune Response and Oxidate Stress Protecting Against Acetaminophen-Induced Acute Liver Injury. Front Immunol. 2019; 9: 3134. doi: 10.3389/fimmu.2018.03134
21. Chen Y., Menger M.M., Braun B.J., Schweizer S. Modulation of Macrophage Activity by Pulsed Electromagnetic Fields in the Context of Fracture Healing. Bioengineering (Basel). 2021; 8(11): 167. doi: 10.3390/bioengineering8110167
22. Бондарь С.С., Терехов И.В., Никифоров В.С. и др. Взаимосвязи компонентов JAK/STAT- и MAPK/SAPK-сигнальных путей, а также NF-kB и содержания в мононуклеарных клетках цельной крови тиоредоксинредуктазы в постклиническую стадию внебольничной пневмонии. Consilium Medicum. 2018; 20 (11): 61-65.
Bondar S.S., Terekhov I.V., Nikiforov V.S. et al. The relationship of JAK/STAT and MAPK/SAPK signaling pathways, NF-kB and content in the mononuclear cells of whole blood thioredoxins in the post-clinical stage of community-acquired pneumonia. Consilium Medicum. 2018; 20 (11): 61-65. [in Russian]. doi: 10.26442/20751753.2018.11.180091

DOI: 10.20514/2226-6704-2022-12-3-221-227 УДК 616.711-002.1-07:616.12-008-084

К.Д. Дорогойкина*[1], К.Н. Сафарова[1], Э.А. Федотов[2], А.П. Ребров[1]

[1]— ФГБОУ ВО «Саратовский государственный медицинский университет им. В.И. Разумовского» Минздрава России, Кафедра госпитальной терапии лечебного факультета, Саратов, Россия
[2] — Областная станция переливания крови, Саратов, Россия

ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ УРОВНЯ РАСТВОРИМОГО СТИМУЛИРУЮЩЕГО ФАКТОРА РОСТА У ПАЦИЕНТОВ СО СПОНДИЛОАРТРИТАМИ КАК РАННЕГО МАРКЕРА СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИИ

K.D. Dorogoykina*[1], K.N. Safarova[1], E.A. Fedotov[2], A.P. Rebrov[1]

[1]— Saratov State Medical University named after V.I. Razumovsky, Ministry of Health of Russian Federation, Department of the Internal Medicine, Saratov, Russia
[2]— Saratov Regional Blood Center, Saratov, Russia

Diagnostic Significance of the Level of Soluble Stimulating Growth Factor in Patients with Spondyloarthritis as an Early Marker of Cardiovascular Pathology

Резюме

Цель — определить клинико-лабораторные взаимосвязи уровня растворимого стимулирующего фактора роста, экспрессирующегося геном 2 (sST2), с показателями, характеризующими развитие сердечно-сосудистой патологии у пациентов со спондилоартритами (СпА). **Материалы и методы.** Обследовано 46 пациентов со СпА, из них 40 (87 %) с анкилозирующим спондилитом, 6 (13 %) — с псориатическим артритом. Средний возраст пациентов — 39,2±10,2 лет. Среди обследованных 36 (78,3 %) мужчин, 10 (21,7 %) женщин. Из 32 обследованных пациентов у 27 (84,4 %) выявлен HLA-B27. Для оценки активности СпА использовали индексы BASDAI и ASDAS, учитывали значения скорости оседания эритроцитов и С-реактивного белка; определяли уровни фактора некроза опухоли-альфа, N-терминального фрагмента мозгового натрийуретического пептида (NT-proBNP), интерлейкина-6, sST2 в сыворотке крови. Оценивали традиционные факторы сердечно-сосудистого риска, скорость распространения пульсовой волны в аорте (СПВА), результаты стандартной электрокардиографии, трансторакальной эхокар-

*Контакты: Ксения Дмитриевна Дорогойкина, e-mail: dorogoykinakd@mail.ru
*Contacts: Ksenia D. Dorogoykina, e-mail: dorogoykinakd@mail.ru
ORCID ID: https://orcid.org/0000-0003-1765-2737

диографии, дуплексного исследования сонных артерий. **Результаты.** Средний уровень sST2 составил 33,34±11,2 нг/мл, уровень sST2 выше порогового значения зафиксирован у 19 (41,3 %) пациентов. Значимых взаимосвязей между уровнем sST2 и показателями активности СпА, параметрами эхокардиографии, нарушениями ритма и/или проводимости на электрокардиограммах не обнаружено. У пациентов с уровнем sST2 выше среднего отмечена более высокая СПВА (p=0,036); уровень NT-proBNP чаще был повышен у пациентов с высоким уровнем sST2 (p=0,085). У пациентов, получающих генно-инженерные биологические препараты в связи с высокой активностью СпА, отмечены более высокие уровни sST2 (p=0,039). **Заключение.** У 41,3 % пациентов со СпА установлен уровень sST2 выше порогового значения. Повышение уровня sST2 ассоциируется с увеличением СПВА и повышением уровня NT-proBNP, что может свидетельствовать о начавшихся процессах ремоделирования миокарда, фиброзе миокарда и начальных этапах развития сердечной недостаточности. Полученные новые данные свидетельствуют о целесообразности планирования и выполнения более крупных проспективных исследований пациентов со СпА для раннего выявления доклинических признаков поражения сердечно-сосудистой системы, процессов ремоделирования миокарда, оценки эффективности проводимой терапии.

Ключевые слова: *спондилоартриты, анкилозирующий спондилит, уровни sST2, NT-proBNP*

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

Статья получена 07.09.2021 г.
Принята к публикации 30.11.2021 г.

Для цитирования: Дорогойкина К.Д., Сафарова К.Н., Федотов Э.А. и др. ДИАГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ УРОВНЯ РАСТВОРИМОГО СТИМУЛИРУЮЩЕГО ФАКТОРА РОСТА У ПАЦИЕНТОВ СО СПОНДИЛОАРТРИТАМИ КАК РАННЕГО МАРКЕРА СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИИ. Архивъ внутренней медицины. 2022; 12(3): 221-227. DOI: 10.20514/2226-6704-2022-12-3-221-227. EDN: WDNYEB

Abstract

Aim to determine the clinical and laboratory relationships of the level of soluble stimulating growth factor expressed by genome 2 (sST2) with indicators characterizing the development of cardiovascular pathology in patients with spondyloarthritis (SPA). **Materials and methods.** A total of 46 patients aged 39.2 ± 10.2 years with SpA (including 40 (87 %) with ankylosing spondylitis, 6 (13 %) with psoriatic arthritis) were examined. There were 36 (78.3 %) males, 10 (21.7 %) females among the enrolled patients. 27 (84.4 %) of 32 examined patients had HLA-B27. To assess the disease activity the BASDAI and ASDAS scores were used, the erythrocyte sedimentation rate and C-reactive protein values were measured; the levels of tumor necrosis factor-alpha (TNF-alpha), N-terminal fragment of brain natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), sST2 in blood serum were evaluated. Traditional cardiovascular risk factors, aortic pulse wave velocity (PWVAo), the results of standard electrocardiography, transthoracic echocardiography, carotid duplex ultrasonography were assessed. **Results.** The mean sST2 level was 33.34±11.2 ng/ml, an sST2 concentration above the threshold value was found in 19 (41.3 %) patients. No significant relationships between serum sST2 level and disease activity indicators, echocardiographic parameters, rhythm and/or conduction disturbances on electrocardiograms were found. A higher PWVAo was noted in patients with sST2 level above the average (p=0.036); the level of NT-proBNP was more often increased in patients with high levels of sST2 (p=0.085). Higher sST2 concentrations were found in patients treated with biological disease-modifying antirheumatic drugs due to the high disease activity (p=0.039). **Conclusion.** An increase in sST2 levels was found in 41.3 % of patients with SpA. An increase in serum sST2 concentration is associated with an elevated PWVAo and an increase in the level of NT-proBNP, which may indicate incipient cardiac remodeling, cardiac fibrosis, and the initial stages of the development of heart failure. The new data obtained indicate the advisability of planning and performing larger prospective studies of patients with SpA for the early detection of preclinical signs of damage to the cardiovascular system, cardiac remodeling, and assessment of the effectiveness of therapy.

Key words: *spondyloarthritis, ankylosing spondylitis, sST2, NT-proBNP*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 07.09.2021
Accepted for publication on 30.11.2021

For citation: Dorogoykina K.D., Safarova K.N., Fedotov E.A. et al. Diagnostic Significance of the Level of Soluble Stimulating Growth Factor in Patients with Spondyloarthritis as an Early Marker of Cardiovascular Pathology. The Russian Archives of Internal Medicine. 2022; 12(3): 221-227. DOI: 10.20514/2226-6704-2022-12-3-221-227. EDN: WDNYEB

aPWV — aortic pulse wave velocity, AS — ankylosing spondylitis, ASDAS — Ankylosing Spondylitis Disease Activity Score, BASDAI — Bath Ankylosing Spondylitis Disease Activity Index, CRP — C-reactive protein, CVD — cardiovascular disease, CVR — cardiovascular risk, DMARDs — basic disease-modifying antirheumatic drugs, ECG — electrocardiography, EchoCG — echocardiography, ESR — erythrocyte sedimentation rate, GEBDs — genetically engineered biological drugs, HLA-B27 — human leukocyte antigen-B27, IL-6 — interleukin-6, IMT — intima-media thickness, NSAIDs — non-steroidal anti-inflammatory drugs, NT-proBNP — N-terminal fragment of brain natriuretic peptide, PsA — psoriatic arthritis , SpA — spondyloarthritis, sST2 — soluble stimulating growth factor expressed by genome 2, ST2 — stimulating growth factor expressed by genome 2, TNF-α — tumor necrosis factor-alpha

Introduction

The medical and social significance of spondyloarthritis (SpA) is determined not only by deterioration of quality of life but also by its short duration, primarily due to damage to the cardiovascular system [1]. It has been shown that the incidence of cardiovascular diseases (CVD) in patients with SpA is higher than in the overall population [1]. This may be due to a higher prevalence of standard CVD risk factors associated with active systemic inflammation and endothelial dysfunction [2–4], hypercoagulability due to chronic systemic inflammation [3], and participation of several pro-inflammatory cytokines (tumor necrosis factor-alpha (TNFα) and interleukins (IL) -1, -6) in atherogenesis [2, 5, 6]. The development of CVD can also be influenced by ongoing treatment: TNFα inhibitors and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs), which reduce the risk of CVD due to their anti-inflammatory activity [7, 8]. In ankylosing spondylitis (AS), the most common disease of the SpA group, the aortic valve and aortic bulb are often affected, rhythm and conduction disorders develop, as well as myocardial infarction, diastolic dysfunction and decreased reserve of coronary blood flow [9].

In this regard, the pathology of the cardiovascular system should be identified as soon as possible. The well-studied N-terminal fragment of the brain natriuretic peptide (NT-proBNP) is a marker of "hemodynamic" myocardial stress, while the stimulating growth factor expressed by gene 2 (ST2) can be considered a marker of "mechanical" myocardial stress [10]. ST2 protein belongs to the IL-1 family and has four isoforms; soluble ST2 (sST2) is of particular interest [11]. It competitively binds to IL-33, which is released from damaged or necrotic cells and prevents the development of the cardioprotective effect [11]. Vascular endothelial cells were found to be the main source of sST2 [11, 12]. There are also studies that confirm the involvement of sST2 in the pathogenesis of many inflammatory diseases. Patients with AS have higher levels of sST2 than patients of the control group, and an association with the parameters of disease activity was found [13, 14]. In psoriatic arthritis (PsA), patients with atherosclerotic plaques in carotid arteries have higher levels of sST2 [15]. Soluble sST2 can be considered one of the "bridges" between inflammation and fibrosis in AS [14]. In this regard, the role of sST2 in the early diagnosis of the pathology of the cardiovascular system in patients with SpA is of particular interest.

The objective is to determine clinical and laboratory relationships between the level of soluble stimulating growth factor expressed by gene 2 (sST2) and the parameters characterizing the development of cardiovascular pathology in patients with spondyloarthritis (SpA).

Materials and methods

Forty-six patients with SpA were examined, including 40 (87 %) patients with AS who met the international New York criteria (1984), six (13 %) patients with PsA who met the CASPAR criteria (2006). The mean age of the patients was 39.2 ± 10.2 years. There were 36 (78.3 %) male and 10 (21.7 %) female patients. Twenty-seven (84.4 %) of the 32 examined patients had human leukocyte antigen-B27 (HLA-B27).

BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score) scales were used to assess the disease activity. Sacroiliitis (SI) stage was assessed according to Kellgren (1966). Peripheral joint arthritis and coxitis, dactylitis, enthesitis, current or past uveitis, family history of SpA, and age of disease onset were considered. Serum levels of TNFα, NT-proBNP, IL-6, and sST2 were analyzed.

The investigated parameters in patients were determined by enzyme immunoassay using commercial reagent kits. To determine NT-proBNP, we used the NTproBNP-IFA-BEST reagent kit (ZAO Vektor-Best, Novosibirsk, Russia), for IL-6 — Interleukin-6-IFA-BEST kit (ZAO Vektor-Best, Novosibirsk, Russia), for TNF-alpha — Alpha-FNO-IFA-BEST kit (ZAO Vektor-Best, Novosibirsk, Russia), for sST2 — Presage® ST2 Assay kit (ZAO BioKhimMak, Moscow, Russia). The level of NT-proBNP ≤ 125 pg/mL was considered normal, the threshold value for sST2 was ≤ 35 ng/mL [10].

The following conventional cardiovascular risk factors (CVRs) were considered: age, smoking, overweight/obesity, hypercholesterolemia, family history; arterial hypertension; cardiovascular risk (CVR) was defined using QRISK3. Results of standard electrocardiography (ECG) and transthoracic echocardiography (EchoCG) were evaluated. Aortic pulse wave velocity (aPWV) was determined via the oscillographic method using the TensioClinic arteriograph (Tensiomed, Hungary).

The thickness of the intima-media complex (IMT) was determined with duplex ultrasound of carotid arteries using the Acuson 128 XP/100 ultrasound system equipped with a 7 MHz phased array linear transducer. IMT was measured in carotid arteries at three points: in the area of bifurcation of the common carotid artery, in the common carotid and internal carotid arteries (10 mm proximal and distal to the bifurcation); the structure of the wall and the diameter of the vessel lumen were assessed. Mean IMT was calculated (the sum of IMT values at three points in both carotid arteries/6), and the presence of atherosclerotic plaques was detected.

The nature of the quantitative trait distribution was evaluated using the Shapiro-Wilk test; distribution at $p > 0.05$ was considered normal. Quantitative traits with normal distribution were described with the indication of the arithmetic mean (M) and standard deviation (SD). Quantitative traits with non-normal distribution were described with the median value (Me) and upper and lower quartiles [Q1; Q3]. Comparison of two independent groups of quantitative traits with normal distribution was carried out using Student's t-test. Comparison of two independent groups of quantitative traits with non-normal distribution was carried out using the

Mann-Whitney test. Pearson's χ^2 test or Fisher's exact test were used to assess differences in the frequency of the trait in two independent groups. Relationships between two qualitative traits with normal distribution were analyzed by calculating the Pearson correlation coefficient. Relationships between two qualitative traits with non-normal distribution were analyzed by calculating the non-parametric Spearman coefficient. Differences and relationships were considered statistically significant at $p < 0.05$; $p < 0.1$ was considered as a trend towards a significant difference or relationship between parameters.

Results

Most of the examined patients were middle-aged male individuals, the average duration of the disease was 15.9 ± 7.5 years, 35 (76.1 %) patients demonstrated high and very high activity of the disease. The description of SpA in the examined patients is presented in Table 1.

Among the conventional factors of cardiovascular risk in the examined patients were the high prevalence of overweight, smoking, hypercholesterolemia and arterial hypertension (Table 2). All patients had no signs of coronary heart disease or heart failure. Results of ECG demonstrate rhythm disorders in 10 (21.7 %) patients, and conduction disorders in 7 (15.2 %) patients. Three (6.5 %) patients had left ventricular hypertrophy.

Relationships between the level of NT-proBNP and laboratory parameters of disease activity were revealed: ESR (R = 0.432, p = 0.003), CRP (R = 0.343, p = 0.024), TNFα (R = 0.451, p = 0.011), and ASDAS score (R = 0.330, p = 0.025); relationships were found between the levels of IL-6 and CRP (R = 0.536, p = 0.003), the level of TNF-α (R = 0.458, p = 0.01).

The mean value of sST-2 level was 33.34 ± 11.2 ng/mL; sST-2 level above the threshold value of 35 ng/mL was found in 19 (41.3 %) patients. No significant relationships between the sST2 level and SpA activity parameters,

Table 1. *Characteristics of spondyloarthritis in the examined patients*

Characteristics	All patients (n=46) M±SD / Me [Q1;Q3] / n (%)	sST-2 > 35 ng/ml (n=19) M±SD / Me [Q1;Q3] / n (%)	sST-2 ≤ 35 ng/ml (n=27) M±SD / Me [Q1;Q3] / n (%)	p
Age, years	39,2±10,2	41,7±11,2	37,4±9,2	0,159
Men	36 (78,3 %)	16 (84,2 %)	20 (74,1 %)	0,328
Women	10 (21,7 %)	3 (15,8 %)	7 (25,9 %)	
Age of debut, years	21 [17;28]	21 [20;31]	21,5±9,1	0,240
Debut at the age of 18 and younger				
Yes	14 (30,4 %)	4 (21,1 %)	10 (37,0 %)	0,246
No	32 (69,6 %)	15 (78,9 %)	17 (63,0 %)	
Arthritis				
Yes	35 (76,1 %)	15 (78,9 %)	20 (74,1 %)	0,492
No	11 (23,9 %)	4 (21,1 %)	7 (25,9 %)	
Dactylitis				
Yes	10 (21,7 %)	4 (21,1 %)	6 (22,2 %)	0,610
No	36 (78,3 %)	15 (78,9 %)	21 (77,8 %)	
Enthesitis				
Yes	16 (34,8 %)	6 (31,6 %)	10 (37,0 %)	0,702
No	30 (65,2 %)	13 (68,4 %)	17 (63,0 %)	
Uveitis				
Yes	15 (32,6 %)	7 (36,8 %)	8 (29,6 %)	0,607
No	31 (67,4 %)	12 (63,2 %)	19 (70,4 %)	
Family history of the spondyloarthritis				0,267
Yes	8 (17,4 %)	2 (10,5 %)	6 (22,2 %)	
No	38 (82,6 %)	17 (89,5 %)	21 (77,8 %)	
Sacroiliitis				
1 stage	2 (4,3 %)	0 (0,0 %)	2 (7,4 %)	
2 stage	10 (21,7 %)	7 (36,8 %)	3 (11,1 %)	-
3 stage	15 (32,6 %)	6 (31,6 %)	9 (33,3 %)	
4 stage	19 (41,3 %)	6 (31,6 %)	13 (48,2 %)	
ASDAS	3,5 [3,0;4,0]	3,7 [2,4;4,0]	3,5±1,0	0,973
BASDAI	5,5±2,2	5,4±2,5	5,5±2,0	0,769
ESR, mm/h	15,5 [8,0;26,0]	19,7±13,7	16,4±9,6	0,383
CRP, mg/ml	11,2 [23,0]	18,0±13,9	11,0 [3,95;20,75]	0,301
TNF-α, pg/ml (n=31, n=15, n=16)	3,2 [2,4;6,3]	3,3 [2,4;7,0]	3,15 [2,5;4,9]	0,740
IL-6, pg/ml (n=31, n=15, n=16)	4,4 [2,0;11,7]	2,9 [1,7;12,6]	6,35 [2,3;10,48]	0,599

Notes: sST2 — soluble stimulating growth factor expressed by gene 2, ASDAS — Ankylosing Spondylitis Disease Activity Score, BASDAI — Bath Ankylosing Spondylitis Disease Activity Index, ESR — the erythrocyte sedimentation rate, CRP — C-reactive protein, TNF-α — tumor necrosis factor-alpha, IL-6 — interleukin-6

cardiovascular risk factors (except for age), EchoCG parameters, rhythm and/or conduction disorders on ECG were found. Patients with an above-average sST2 level had higher aPWV (p=0.036).

Groups of patients with sST2 levels above 35 ng/mL (n = 19) and below 35 ng/mL (n = 27) were identified. The average age of patients with sST2 levels above 35 ng/mL was 41.7 ± 11.2 years; this group included 16 (84.2 %) men and 3 (15.8 %) women; 17 (89.5 %) patients with AS and 2 (10.5 %) with PsA. Eleven (84.6 %) of the 13 examined patients were found to be carriers of HLA-B27. The average age of patients with sST2 levels below the threshold value was 37.4 ± 9.2 years. This group included 20 (74.1 %) men and 7 (25.9 %) women; 23 (85.2 %) patients with AS and 4 (14.8 %) with PsA. Sixteen (84.2 %) of the 19 examined patients were found to be carriers of HLA-B27. The description of SpA in the examined patients of the two groups is presented in Table 1, assessment of the cardiovascular risk and state of the cardiovascular system — in Table 2. When comparing the studied parameters, no significant differences were found. However, in patients with sST-2 levels above the threshold

Table 2. *Traditional factors of cardiovascular risk, echocardiography parameters, the average thickness of the intima-media complex and aortic pulse wave velocity in the examined patients with spondyloarthritis*

Характеристики / Characteristics	Все пациенты / All patients (n=46) M±SD / Me [Q1;Q3] / n (%)	sST-2 > 35 нг/мл / sST-2 > 35 ng/ml (n=19) M±SD / Me [Q1;Q3] / n (%)	sST-2 ≤ 35 нг/мл / sST-2 ≤ 35 ng/ml (n=27) M±SD / Me [Q1;Q3] / n (%)	p
Family history of early development of coronary heart disease				0,233
Yes	10 (21,7 %)	3 (15,8 %)	7 (25,9 %)	
No	36 (78,3 %)	36 (84,2 %)	36 (74,1 %)	
Overweight/obesity				
Yes	18 (39,1 %)	6 (31,6 %)	12 (44,4 %)	0,379
No	28 (60,9 %)	13 (68,4 %)	15 (55,6 %)	
Smoking				
Yes	15 (32,6 %)	3 (15,8 %)	12 (44,4 %)	0,101
No	27 (58,7 %)	14 (73,7 %)	13 (48,2 %)	
In the anamnesis	4 (8,7 %)	2 (10,5 %)	2 (7,4 %)	
Arterial hypertension				
Yes	18 (39,1 %)	7 (36,8 %)	11 (40,7 %)	0,912
No	28 (60,9 %)	12 (63,2 %)	16 (59,3 %)	
Total cholesterol, mmol/l	4,9±1,0	4,6±1,1	4,6±0,9	0,954
Hypercholesterolemia				
Yes	17 (37 %)	7 (36,8 %)	10 (37,0 %)	0,912
No	29 (63 %)	12 (63,2 %)	17 (63,0 %)	
QRISK3	2,1 [0,75;8,5]	2,1 [0,7;11,6]	2,4 [0,68;6,68]	0,605
NT-proBNP, pg/ml	2,75 [0,0;52,7]	25,7 [0,0;86,2]	0,0 [0,0;43,2]	0,242
NT-proBNP level above the normal level	5 (10,9 %)	4 (21,1 %)	1 (3,7 %)	
Normal level of NT-proBNP	41 (89,1 %)	15 (78,9 %)	26 (96,3 %)	0,085*
sST-2, ng/ml	33,34±11,2	43,6 [38,5;46,4]	25,6±5,5	0,0001**
Average thickness of the intima-media complex, mm	0,717 [0,633;0,833] (n=39)	0,667 [0,621;0,796] (n=16)	0,764±0,149 (n=23)	0,263
Atherosclerotic plaque	n=39	n=16	n=23	
Yes	8 (20,5 %)	4 (25,0 %)	4 (17,4 %)	0,425
No	31 (79,5 %)	12 (75,0 %)	19 (82,6 %)	
Aortic pulse wave velocity, m/s	7,14 [6,73;8,74] (n=37)	7,61 [7,01;9,83] (n=14)	7,0 [6,68;8,62] (n=23)	0,077*
Diastolic function	n=33	n=10	n=23	
Yes, broken by the relaxation type	16 (48,5 %)	5 (50,0 %)	11 (47,8 %)	0,603
No	17 (51,5 %)	5 (50,0 %)	12 (52,2 %)	
Ejection fraction, %	63,5±3,8 (n=33)	64,0±3,6 (n=10)	64,0 [61,425;65,75] (n=23)	0,867
Left ventricular hypertrophy (n=33)	n=33	n=10	n=23	
Yes	7 (21,2 %)	3 (30,0 %)	4 (16,7 %)	0,330
No	26 (78,8 %)	7 (70,0 %)	20 (83,3 %)	
Condition of the aortic valve flaps	n=33	n=10	n=23	
Normal	10 (30,3 %)	2 (20,0 %)	8 (34,8 %)	0,339
Compacted	23 (69,7 %)	8 (80,0 %)	15 (65,2 %)	
Condition of the aortic walls	n=33	n=10	n=23	
Normal	7 (21,2 %)	2 (20,0 %)	5 (21,7 %)	0,648
Compacted	26 (78,8 %)	8 (80,0 %)	18 (78,3 %)	

Notes: NT-proBNP — N-terminal fragment of brain natriuretic peptide. * — p<0,1, ** — p<0,05

value, there was a tendency towards a more frequent high level of NT-proBNP and higher aortic pulse wave velocity (p = 0.085 and p = 0.077, respectively). The level of sST2 above the threshold value probably indicates early preclinical changes in the myocardium and vascular wall, i.e., remodeling processes.

All patients with sST2 levels above the threshold were taking NSAIDs, 14 (73.7 %) of them additionally received synthetic DMARDs, 9 (47.4 %) — genetically engineered biological drugs (GEBDs), while 7 (36.8 %) patients required a combination of DMARDs and GEBDs to control disease activity, 11 (57.9 %) patients required additional oral glucocorticoids (GCs). Among patients with sST2 levels below the threshold, 26 (96.3 %) were taking NSAIDs, 15 (55.6 %) were taking DMARDs, and 7 (25.9 %) were taking GEBDs. The combination of DMARDs and GEBDs was prescribed to 3 (11.1 %) patients, oral GCs — to 12 (44.4 %) patients. Patients with high disease activity and unable to achieve remission at the previous stages of treatment and, therefore, receiving GEBDs, demonstrated higher levels of sST2 (p = 0.039), which may also indicate the processes of myocardial remodeling and fibrosis that have already started.

Discussion

One of the tasks facing modern medicine is the detection of developing pathology as early as possible. Therefore, there is a constant search for laboratory markers that would be as informative as possible. The choice of the optimal method for diagnosing damage to the cardiovascular system and myocardium in comorbid patients is a huge challenge.

The role of several markers for diagnosing myocardial stress is discussed. NT-proBNP is a more labile parameter and, according to our results, it depends on the activity of systemic inflammation at a given point in time. Changes in the cardiovascular system in patients with AS develop quite early, even before clinical manifestations; therefore, it is advisable to search for the markers of this early damage to the heart and vascular wall [14]. There is insufficient data in literature sources on the role of sST2 in the pathogenesis of cardiovascular pathology in SpA. In our study, sST2 levels above the threshold value were found in 41.3 % of patients with no history of CVD, which may indicate changes in the cardiovascular system. However, sST2 level is not associated with laboratory parameters of the activity of systemic inflammation at a given point in time, which differs from the available literature data, as in the case of studying patients with AS [13]. Information about sST2 levels in rheumatoid arthritis is also contradictory: despite the absence of a clear relationship between sST2 levels and parameters of disease activity, according to some studies, there are lower levels of sST2 in patients with a good response to basic treatment [16]. A number of large studies (CORONA, PHFS) demonstrated the prognostic value of sST2 level [10]. Therefore, a more complete assessment of the value of sST2 level in patients with SpA requires further follow-up, with the allocation of patients with an elevated level of this marker to a high-risk group.

Conclusion

The sST2 level was above the threshold value in 41.3 % of patients with SpA. An increase in the sST2 level is associated with increased aortic pulse wave velocity and increased NT-proBNP level, which may indicate the onset of myocardial remodeling, myocardial fibrosis, and the initial stages of heart failure. The new results obtained suggest there is a need to plan and conduct larger prospective studies on patients with SpA for the early detection of preclinical signs of damage to the cardiovascular system, myocardial remodeling processes, and evaluation of the effectiveness of ongoing therapy.

Limitations

The study was conducted on a small sample of patients, with follow-up starting at different stages of the disease, with different duration and different treatment. Extrapolating the results of this study to all patients with SpA should be done with caution.

Вклад авторов:

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

Дорогойкина К.Д. (ORCID: https://orcid.org/0000-0003-1765-2737): концепция и дизайн исследования, получение, анализ и интерпретация данных, написание текста статьи, утверждение итогового варианта текста рукописи

Сафарова К.Н. (ORCID: https://orcid.org/0000-0002-8989-8405): концепция и дизайн исследования, получение, анализ и интерпретация данных

Федотов Э.А. (ORCID: https://orcid.org/0000-0003-3563-5535): получение, анализ и интерпретация данных

Ребров А.П. (ORCID: https://orcid.org/0000-0002-3463-7734): концепция и дизайн исследования, получение, анализ и интерпретация данных, написание текста статьи, утверждение итогового варианта текста рукописи

Author Contribution:

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

Dorogoykina K.D. (ORCID: https://orcid.org/0000-0003-1765-2737): research concept and design, obtaining, analyzing and interpreting data, writing article, approving the final version of the publication

Safarova K.N. (ORCID: https://orcid.org/0000-0002-8989-8405): research concept and design, obtaining, analyzing and interpreting data

Fedotov E.A. (ORCID: https://orcid.org/0000-0003-3563-5535): obtaining, analyzing and interpreting data

Rebrov A.P. (ORCID: https://orcid.org/0000-0002-3463-7734): research concept and design, obtaining, analyzing and interpreting data, writing article, approving the final version of the publication

Список литературы / References:

1. Braun J., Krüger K., Manger B., et al. Cardiovascular Comorbidity in I nflammatory Rheumatological Conditions. Dtsch Arztebl Int. 2017; 114(12): 197-203. doi: 10.3238/arztebl.2017.0197.

2. Tournadre A., Mathieu S., Soubrier M. Managing cardiovascular risk in patients with inflammatory arthritis: practical considerations. Ther Adv Musculoskelet Dis. 2016; 8(5): 180-191. doi: 10.1177/1759720X16664306.
3. Ungprasert P., Srivali N., Kittanamongkolchai W. Risk of coronary artery disease in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Transl Med. 2015; 3(4): 51. doi: 10.3978/j.issn.2305-5839.2015.02.05.
4. Ter Maaten J.M., Damman K., Verhaar M.C., et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail. 2016; 8(6): 588-598. doi: 10.1002/ejhf.497.
5. Mozos I., Malainer C., Horbańczuk J., et al. Inflammatory Markers for Arterial Stiffness in Cardiovascular Diseases. Front Immunol. 2017; 8: 1058. doi: 10.3389/fimmu.2017.01058.
6. Heslinga S.C., Van Sijl A.M., De Boer K., et al. Tumor necrosis factor blocking therapy and congestive heart failure in patients with inflammatory rheumatic disorders: a systematic review. Curr Med Chem. 2015; 22(16): 1892-902. doi: 10.2174/0929867322666150209160701.
7. Tsai W.C., Ou T.T., Yen J.H., et al. Long-term frequent use of non-steroidal anti-inflammatory drugs might protect patients with ankylosing spondylitis from cardiovascular diseases: a nationwide case-control study. PLoS One. 2015; 10(5): e0126347. doi: 10.1371/journal.pone.0126347.
8. Lee J.L., Sinnathurai P., Buchbinder R., et al. Biologics and cardiovascular events in inflammatory arthritis: a prospective national cohort study. Arthritis Res Ther. 2018; 20(1): 171. doi: 10.1186/s13075-018-1669-x.
9. Amin A., Chitsazan M., Navid H. Left ventricular systolic dysfunction in two patients with ankylosing spondylitis: What is the role of corticosteroids? Eur J Rheumatol. 2016; 3(4): 179-181. doi: 10.5152/eurjrheum.2016.15069.
10. Камардинов Д. Х., Сонгуров Р. Н., Иошина В. И. и др. Растворимый ST2 — как биомаркер, инструмент стратификации риска и терапевтическая мишень у пациентов с хронической сердечной недостаточностью. Кардиология. 2020; 60(2): 111–121. https://doi.org/10.18087/cardio.2020.2.n816 Kamardinov D.K., Songurov R.N., Ioshina V.I., et al. Soluble ST2 — as a biomarker, a tool for risk stratification and therapeutic target in patients with chronic heart failure. Kardiologiia. 2020; 60(2): 111–121. https://doi.org/10.18087/cardio.2020.2.n816 [In Russian]
11. Dudek M., Kałużna-Oleksy M., Migaj J., et al. Clinical value of soluble ST2 in cardiology. Adv Clin Exp Med. 2020; 29(10): 1205–1210. doi:10.17219/acem/126049.
12. Bartunek J, Delrue L, Van Durme F, et al. Nonmyocardial production of ST2 protein in human hypertrophy and failure is related to diastolic load. J Am Coll Cardiol. 2008; 52(25): 2166–2174. doi:10.1016/j. jacc.2008.09.027.
13. Li X.L., Lin T.T., Qi C.Y., et al. Elevated serum level of IL-33 and sST2 in patients with ankylosing spondylitis: associated with disease activity and vascular endothelial growth factor. J Investig Med. 2013; 61(5): 848-51. doi: 10.2310/JIM.0b013e31828deed2.
14. Ozkaramanli Gur D., Ozaltun D.N., Guzel S., et al. Novel Imaging Modalities in Detection of Cardiovascular Involvement in Ankylosing Spondylitis. Scandinavian Cardiovascular Journal. 2018; 52(6): 320-327. doi: 10.1080/14017431.2018.1551564
15. Shen J., Shang Q., Wong C.K., et al. Carotid plaque and bone density and microarchitecture in psoriatic arthritis: the correlation with soluble ST2. Sci Rep. 2016; 6: 32116. doi: 10.1038/srep32116.
16. Shi L.J., Liu C., Li J.H., et al. Elevated Levels of Soluble ST2 were Associated with Rheumatoid Arthritis Disease Activity and Ameliorated Inflammation in Synovial Fibroblasts. Chin Med J. 2018; 131: 316-322. doi: 10.4103/0366-6999.223847.

DOI: 10.20514/2226-6704-2022-12-3-228-233 УДК 616.8-089-06:616.124.2-008.46

Е.В. Резник*[1,2,3], А.А. Пазова[3], А.М. Дунаева[3], М.Э. Туршева[3], Е.В. Селезнева[1,2]

[1] — ФГАОУ ВО «РНИМУ им. Н.И. Пирогова» Минздрава России, кафедра пропедевтики внутренних болезней и лучевой диагностики лечебного факультета, Москва, Россия
[2] — ГБУЗ «ГКБ № 31» ДЗМ, Москва, Россия
[3] — ГБУЗ «ГКБ имени В.М. Буянова», ДЗМ, Москва, Россия

ВТОРИЧНЫЙ СИНДРОМ ТАКОЦУБО У МОЛОДОЙ ПАЦИЕНТКИ ПОСЛЕ НЕЙРОХИРУРГИЧЕСКОГО ВМЕШАТЕЛЬСТВА

E.V. Reznik*[1,2,3], A.A. Pazova[3], A.M. Dunaeva[3], M.E. Tursheva[3], E.V. Selezneva[1,2]

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

Takotsubo Syndrome in a Young Patient After a Neurosurgical Operation

Резюме

Синдром такоцубо (кардиомиопатия такоцубо, стрессиндуцированная кардиомиопатия, транзиторная кардиальная дисфункция) — клинический синдром, характеризующийся остро возникающей, обратимой систолической дисфункцией левого (реже правого) желудочка сердца, развивающийся в условиях отсутствия стенозирующего атеросклеротического поражения или тромбоза коронарных артерий. В статье приводится клинический случай развития синдрома такоцубо, развившегося после нейрохирургической операции. **Цель наблюдения:** продемонстрировать случай развития синдрома такоцубо у молодой пациентки в раннем послеоперационном периоде. **Основные положения:** пациентка 21 года находилась на стационарном лечении в отделении нейрохирургии в связи с сохраняющимся в течение года после оперативного вмешательства болевым синдромом в области левого локтевого сустава с иррадиацией в 4, 5 пальцы левой руки, нарушением функции левого локтевого сустава. Проведена декомпрессия левого локтевого нерва на уровне кубитального канала с его транспозицией. В послеоперационном периоде течение заболевания осложнилось развитием стресс-индуцированной кардиомиопатии, подтвержденной результатами лабораторного обследования, электрокардиографии, эхокардиографии, а также отсутствием атеросклеротических изменений коронарных артерий по данным коронароангиографии. **Заключение.** Ранний послеоперационный период может осложниться развитием синдрома такоцубо, в т.ч. после нейрохирургических вмешательств у пациентов молодого возраста.

Ключевые слова: *синдром апикального баллонирования, синдром такоцубо, стресс-индуцированная кардиомиопатия, сердечная недостаточность, периоперационный период, постоперационные осложнения*

Благодарности

Авторы благодарят заведующего отделения рентгенохирургии ГБУЗ ГКБ им. В.М. Буянова ДЗМ, д.м.н. Миронкова Алексея Борисовича, ассистента кафедры госпитальной терапии № 2 Лазарева Владимира Андреевича, ассистента кафедры пропедевтики внутренних болезней ФГАОУ ВО РНИМУ им. Н.И. Пирогова МЗ РФ Луценко Альфию Раисовну за помощь в подготовке работы к публикации

Конфликт интересов

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

*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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 07.10.2021 г.

Принята к публикации 04.02.2022 г.

Для цитирования: Резник Е.В., Пазова А.А., Дунаева А.М. и др. ВТОРИЧНЫЙ СИНДРОМ ТАКОЦУБО У МОЛОДОЙ ПАЦИЕНТКИ ПОСЛЕ НЕЙРОХИРУРГИЧЕСКОГО ВМЕШАТЕЛЬСТВА. Архивъ внутренней медицины. 2022; 12(3): 228-233. DOI: 10.20514/2226-6704-2022-12-3-228-233

Abstract

Cardiomyopathy syndrome (stress-cardiomyopathy) is an acute reversible systolic dysfunction of left (or rare right) ventricle without stenotic atherosclerosis and/or thrombosis of coronary artery. We are presenting a case of stress-cardiomyopathy after the neurosurgery. **Aim:** The aim of this observation is to demonstrate a case of takotsubo syndrome in a young patient in the early postoperative period. **Key points:** A 21-years-old woman was hospitalized in the neurosurgery department. Hospitalization was performed due to persistent pain in the left elbow joint with irradiation to left 4 & 5 hand fingers as well as dysfunction of the left elbow joint, as a result of previous surgical intervention for a fracture one year before. Due to the lack of a positive effect from conservative therapy, it was decided to conduct a second surgical treatment. Decompression of the left ulnar nerve was performed at the level of the cubital canal with its transposition. This was complicated by the development of takotsubo syndrome in the postoperative period, confirmed by echocardiography, ECG, as well as the absence of atherosclerotic changes in the coronary artery according to coronary angiography. **Conclusion:** The early postoperative period may complicate of development of takotsubo syndrome, in the neurosurgical operations and in the young age too.

Key words: *apical ballooning syndrome, takotsubo cardiomyopathy, stress-induced cardiomyopathy, heart failure, postoperative period, postoperative comlications*

Acknowledgements

The authors would like to thank the head of the X-ray surgery department of the City Clinical Hospital named after V.M. Buyanova, MD Aleksey B. Mironkov, Assistant of the Department of Hospital Therapy № 2 Vladimir A. Lazarev, Assistant of the Department of Propaedeutics of Internal Diseases N.I. Pirogov of the Ministry of Health of the Russian Federation Alfiya R. Lutsenko for help in preparing the work for publication

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 07.10.2021

Accepted for publication on 04.02.2022

For citation: Reznik E.V., Pazova A.A., Dunaeva A.M. et al. Takotsubo Syndrome in a Young Patient After a Neurosurgical Operation. The Russian Archives of Internal Medicine. 2022; 12(3): 228-233. DOI: 10.20514/2226-6704-2022-12-3-228-233

BP — blood pressure, CAG — coronary angiography, ECG — electrocardiography, EchoCG — echocardiography, EF — ejection fraction, IVS — interventricular septum, LV — left ventricle, mPAP — mean pulmonary arterial pressure, RV — right ventricle

Takotsubo cardiomyopathy (stress-induced cardiomyopathy, apical ballooning syndrome, ampulla cardiomyopathy, broken heart syndrome) is a clinical syndrome characterized by acute, reversible systolic dysfunction of the left (rarely right) ventricle (LV, RV) of the heart, which develops in the absence of stenosing atherosclerotic lesions of coronary arteries and resolves spontaneously within a few days or weeks [1, 2]. Experts of the European Society of Cardiology (ESC) recently recommended using the definition "takotsubo syndrome", avoiding the term "cardiomyopathy" [1, 3, 4]. Takotsubo syndrome was first described by Sato et al. in 1990 [5]. Translated from Japanese, Tako-Tsubo is a pot-shaped octopus trap. The left ventricle of the heart acquires a similar shape in this pathology; its basal segments contract during relative hypokinesis or dyskinesis of the apical segments [1]. This disease is caused by physical or psychological overexertion (primary takotsubo syndrome). If the disease develops with underlying severe non-cardiac pathology or surgical treatment, it is considered as a secondary takotsubo syndrome. Usually, patients with takotsubo syndrome are admitted to the hospital with a referral diagnosis of acute coronary syndrome. The incidence of takotsubo syndrome is approximately 0.00006 % of the population, approximately 1–2 % of patients with ST-elevation myocardial infarction [6]. Takotsubo syndrome occurs more often in women (80–90 %) than in men; the average age of patients is 61–76 years [1]. Cases of this condition in young patients are rare.

Clinical case

A female patient, 21, was routinely admitted to the neurosurgical department with complaints of recurring pain in the area of the left elbow joint radiating to the 4th and 5th fingers of the left hand and joint dysfunction. Twelve months before this hospitalization, surgical treatment was performed for a fracture of radius, a month later the abovementioned complaints appeared.

Due to no effect of conservative therapy, a decision was made to perform surgery — decompression of the left ulnar nerve at the level of the cubital canal with its transposition. Three years prior to this hospitalization, the patient was diagnosed with chronic gastritis, multinodular goiter, and hypothyroidism. She constantly took levothyroxine sodium 25 μg/day. The patient had no cardiovascular risk factors or bad habits.

On admission to the neurosurgical department, the patient's condition was satisfactory. Regular body type, body mass index (BMI) 27 kg/m^2. No signs of edematous syndrome were found. On auscultation: vesicular breathing in the lungs, with no side breath sounds. Clear heart tones, regular rhythm with a heart rate (HR) 80 bpm. Blood pressure (BP) 110/70 mm Hg. After a successful surgical intervention under general anesthesia, the patient was transferred to the intensive care unit for follow-up. After 10 hours of the postoperative period, the patient complained of shortness of breath, pressing pain in the chest for more than 20 minutes, palpitations, and decrease in blood pressure down to 80/40 mm Hg.

An electrocardiogram (ECG) revealed ST segment elevation in leads I, aVL, as well as ST depression in leads III, aVF, V1–V5 (Fig. 1).

Echocardiography (EchoCG) revealed normal LV wall thickness, areas of impaired local contractility of the LV myocardium in the form of dyskinesia of the anterior wall, interventricular septum (IVS), lateral and inferior walls at the apical and middle levels; decreased LV ejection fraction (EF) to 29 % according to Simpson, as well

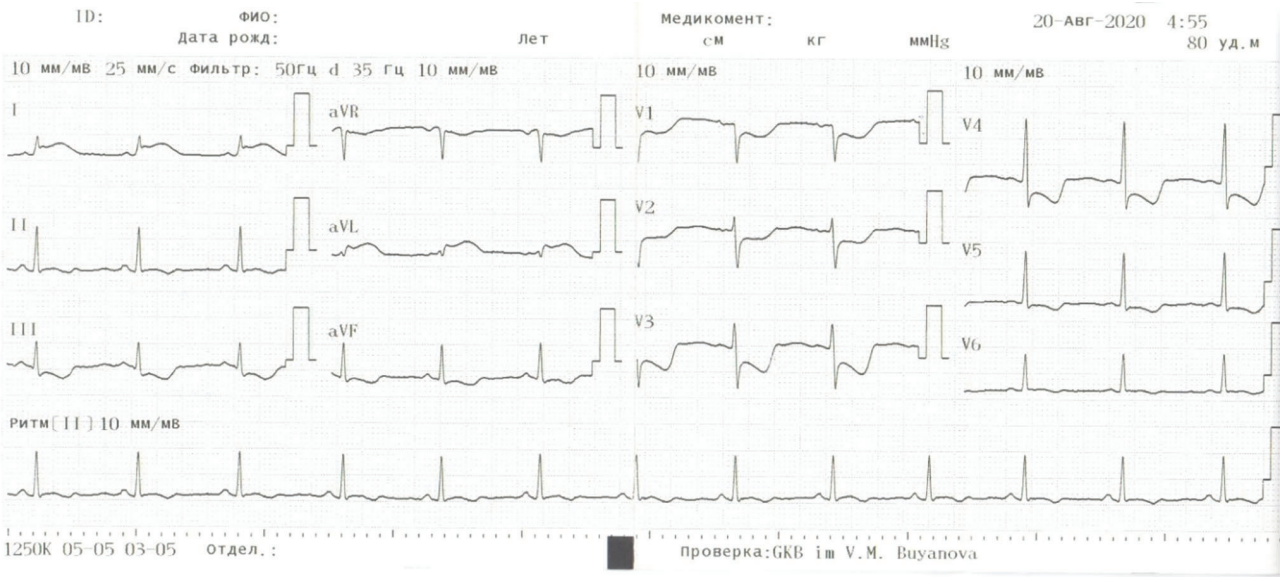


Figure 1. *ECG of the patient 10 hours after surgery: ST segment depression and negative T wave in leads III, avF, V1-5, ST elevation in leads I, avL*

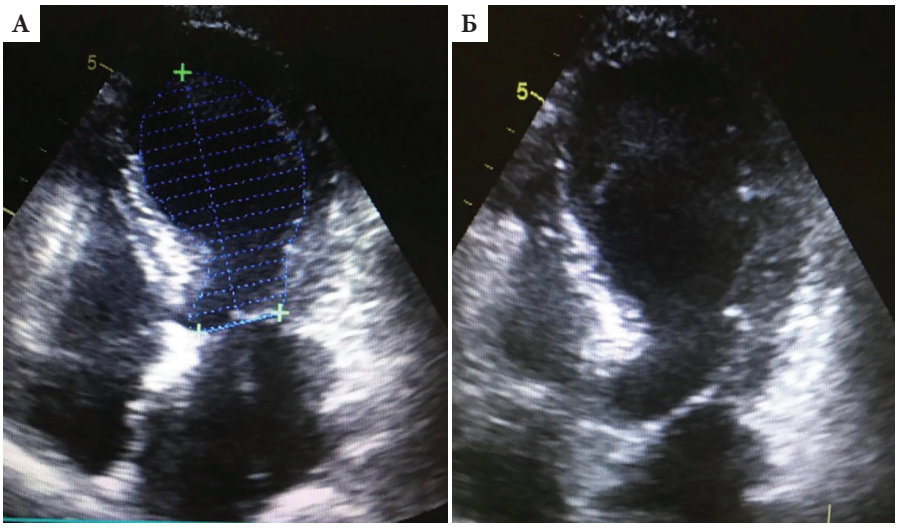


Figure 2. *Echocardiography of a patient in the postoperative period, after the onset of pain in the chest, apex ballooning, B-mode, systole: А — apical 4-chamber position, Б — apical 5-chamber position*

as signs of moderate pulmonary hypertension: mean pulmonary artery pressure (mPAP) 46 mm Hg. (Figure 2).

Laboratory tests revealed increased troponin level up to 0.71 μg/L (normal 0–0.1 μg/L), increased level of N-terminal precursor of brain natriuretic peptide — 3,280 ng/L (normal 12–133 ng/L), increased levels of cholesterol up to 5.4 mmol/L, low-density lipoprotein cholesterol up to 3.28 mmol/L, fibrinogen up to 5.01 g/L, D-dimer up to 1,231 μg/L, ESR up to 46 mm/h, with no clinically significant changes in other parameters.

Coronary angiography (CAG) revealed no atherosclerotic changes, no thrombosis of coronary arteries, as well as no plaque rupture or intimal dissection (Fig. 3).

Considering the signs of moderate pulmonary hypertension (mPAP 46 mm Hg) found during EchoCG and increased D-dimer, the patient underwent ultrasound dopplerography of the veins of lower extremities and angiopulmonography, which revealed no signs of venous thrombosis or pulmonary embolism.

The patient was prescribed a beta-blocker (bisoprolol at a dose of 2.5 mg a day) and acetylsalicylic acid at a dose of 75 mg a day. Forty-eight hours later, considering the satisfactory condition of the patient, complete resolution of clinical signs and normalization of blood troponin level, the patient was transferred to the neurosurgical department.

On day 6 of the postoperative period, normalization of the N-terminal precursor of brain natriuretic peptide was found, regression of the identified pathological changes was registered on ECG (Fig. 4), and EchoCG revealed restoration of LV EF and local myocardial contractility.

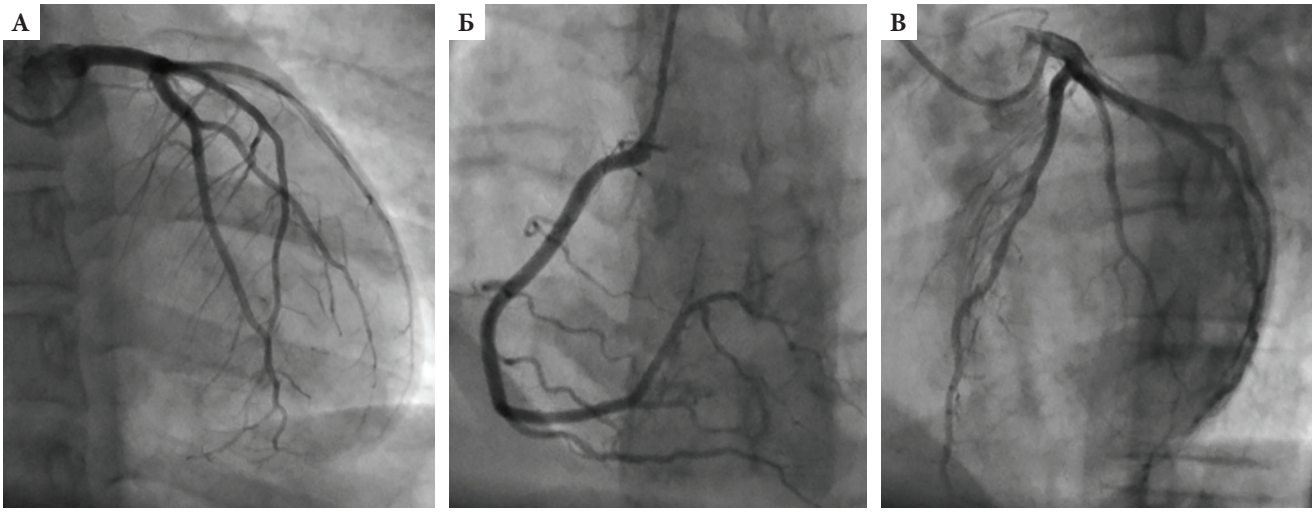


Figure 3. *Intact coronary arteries during emergency coronaroangiogramm. A. Left coronary artery: AP view, 0⁰. Б. Left coronary artery: left oblique view, 45⁰. Right coronary artery: left oblique view, 30⁰*

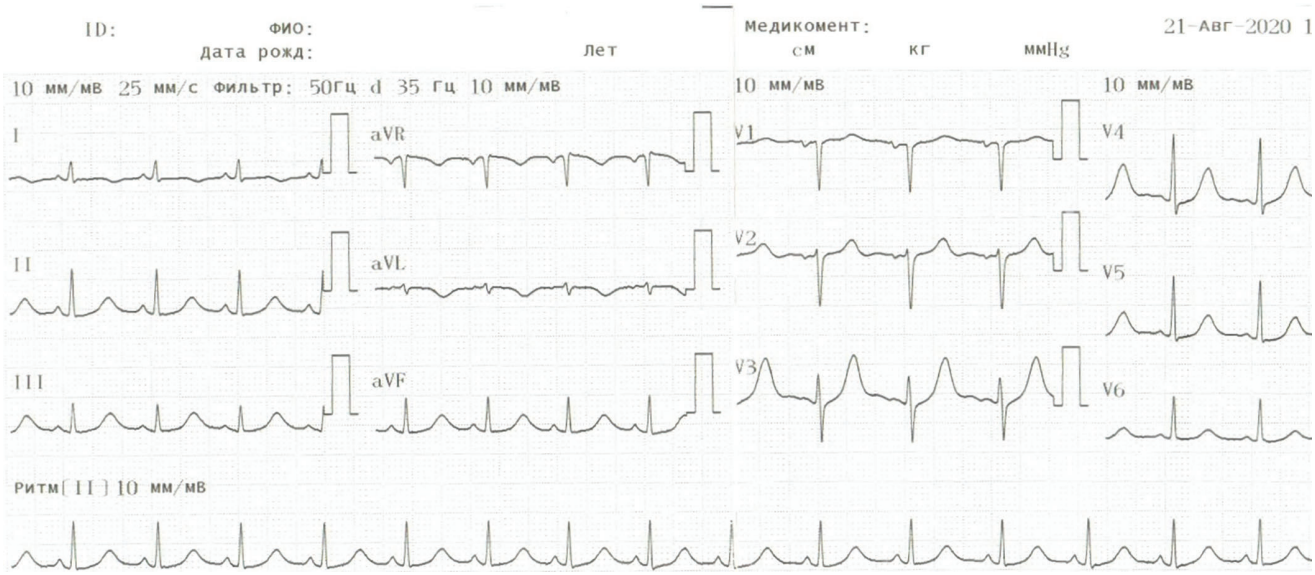


Figure 4. *ECG of the patient on the 6th day of the postoperative period. Regression of pathological changes: return of the ST segment to the isoline in leads III, avF, V1-5, I, avL, positive T wave in these leads*

Massively parallel sequencing of dried blood spots revealed no mutations in genes ACTC1, DES, FLNC, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, TTR[1].

Based on clinical, laboratory and instrumental results, acute myocardial infarction and myocarditis were excluded. Considering the reversibility of local contractility disorders, normalization of LVEF, N-terminal precursor of brain natriuretic peptide (NT-proBNP), troponin, regression of ECG changes, the patient was diagnosed with stress-induced cardiomyopathy (takotsubo).

The patient was discharged on day 8 in satisfactory condition under outpatient follow-up by a cardiologist.

During two years of follow-up, the patient did not experience any recurrence of symptoms.

Discussion

Immediately after neurosurgical intervention, the young patient developed a presentation of anginal pain, acute left ventricular heart failure, hypotension, ECG and laboratory signs of acute myocardial injury, impaired local contractility of the left ventricular myocardium extending beyond the blood supply zone of a certain coronary artery, systolic myocardial dysfunction in intact coronary arteries.

The described patient has all diagnostic criteria for takotsubo syndrome according to the recommendations of the Heart Failure Association of the European Society of Cardiology (ESC) 2016 [6]:

1. Transient local disorders of LV myocardial contractility that are often, but not always, preceded by a stressful trigger (emotional or physical).
2. Local impairments of contractility that go beyond the blood supply zone of one coronary artery and are manifested by circular dysfunction of the involved areas of the heart muscle.
3. Absence of atherosclerotic lesions of the coronary artery leading to myocardial infarction, including acute plaque rupture, thrombosis, coronary artery dissection, and other pathological conditions (for example, hypertrophic cardiomyopathy, viral myocarditis) that could cause transient LV dysfunction.
4. New reversible ECG changes (*ST* elevation, *ST* depression, inversed *T* wave and/or prolonged *QTc*) during the acute phase.
5. Significant increase in natriuretic peptide level (BNP or NT-proBNP) during the acute phase.
6. Relatively small increase in cardiac troponin levels compared with the area of myocardial dysfunction.
7. Recovery of myocardial function according to the results of imaging methods during follow-up [1].

In the described clinical case, the neurosurgical decompression of the left ulnar nerve at the level of the cubital canal with its transposition became a trigger for takotsubo cardiomyopathy in the patient. This suggests secondary takotsubo syndrome in this patient with another underlying (neurological) disease. With primary (caused by emotional or physical stress) takotsubo syndrome, cardiac symptoms are the reason for seeking medical help. Some cases of takotsubo syndrome are detected among patients hospitalized for other medical, surgical, gynecological and even psychiatric diseases [1]. There are cases of takotsubo syndrome in the literature in connection with such neurological pathology as stroke, subarachnoid hemorrhage, acute neuromuscular crisis, encephalitis, epileptic seizures, encephalopathy [2].

Russian researchers described three clinical cases of cardiomyopathy after induction with general anesthesia, which accounted for 0.04 % of all anesthesias performed in a year [7]. These cases, as well as the one we described, indicate the need for strict control of hemodynamic parameters in patients in the early postoperative period, performing ECG and, if necessary, EchoCG, informing anesthetists about the possibility of takotsubo syndrome,

[1] **1. Genetic testing — cardiomyopathy panel:** ACTC1 actin alpha cardiac muscle 1; DES desmin; FLNC filamin C; GLA alpha galactosidase A; LAMP2 lysosomal-associated membrane protein 2; MYBPC3 myosin binding protein C3; MYH7 myosin heavy chain 7; MYL2 myosin regulatory light chain 2; MYL3 myosin regulatory light chain 3; PLN phospholamban; PRKAG2 protein kinase AMP-activated non-catalytic subunit gamma 2; PTPN11 protein tyrosine phosphatase non-receptor type 11; TNNC1 troponin C1, slow skeletal and cardiac type; TNNI3 troponin I3, cardiac type; TNNT2 troponin T2, cardiac type; TPM1 tropomyosin 1; TTR transthyretin

2. Criteria for risk stratification of cardiac complications (including acute left ventricular failure, malignant arrhythmias, and myocardial rupture) in takotsubo syndrome [1].

Major risk factors for a poor outcome:

- age 75+;
- systolic BP < 110 mm Hg;
- pulmonary edema;
- VT, VF, syncope that cannot explained by other reasons;
- LVEF < 35%;
- pressure gradient in LV outflow tract 40 mm Hg or higher. (It would seem that its appearance, which indicates the high contractility of the intact myocardium, indicates reserves of LV systolic function as well. However, the obstruction of the outflow tract, which also develops due to the anterior systolic movement of the anterior mitral leaflet with mitral regurgitation of different severity, can result in intraventricular blood regurgitation into a stretched akinetic/dyskinetic apex and aggravation of left ventricular failure.)
- moderate or severe mitral regurgitation;
- LV apex thrombosis;
- IVS rupture;
- rupture of LV free wall.

Minor risk factors:

- age 70–75 years;
- lengthening QTc up to 500 ms or more;
- pathological Q wave;
- ST elevation for three days or more;
- LVEF 35–45%;
- presence of a physical stressor;
- BNP level 600 pg/ml or higher;
- NT-proBNP level 2,000 pg/ml or higher;
- concomitant obstructive coronary pathology;
- involvement of both ventricles.

A marker of high risk is the presence of at least **one major or two minor criteria**.

as well as the diagnostic and therapeutic approach for the management of this condition.

The risk of developing cardiac complications in takotsubo syndrome (including cardiogenic shock, malignant arrhythmias, and even myocardial rupture), which are observed in about half of patients, [3, 4] was high in this patient (Appendix 2): there were two major (systolic BP < 110 mm Hg, LVEF < 35 %) and one minor (0 NT-proBNP level of 2,000 pg/mL or higher) risk factors for a poor outcome.

The clinical presentation of takotsubo cardiomyopathy is transient, and in the described clinical case, it resolved within six days. Drug therapy at the initial stage of treatment usually includes standard therapy for systolic heart failure. Due to hypotension in this patient, no angiotensin-converting enzyme inhibitors (as well as angiotensin II receptor blockers, angiotensin /neprilysin receptor inhibitors) and no diuretics were prescribed; low doses of a beta-blocker and antiplatelet agents were recommended for four weeks.

The annual recurrence rate of takotsubo syndrome during the first few years is 2.9 % [1]. Our patient experienced no recurrence during two years of follow-up.

Conclusion

We presented a case of takotsubo cardiomyopathy in the early postoperative period after neurosurgical intervention. Such cases are extremely rare, especially in young patients. Prognosis in cases of timely diagnosis and adequate treatment is usually favorable.

Вклад авторов:

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

Резник Е.В. (ORCID ID: https://orcid.org/0000-0001-7479-418X): разработка дизайна публикации; написание текста рукописи; обзор публикаций по теме статьи; взаимодействие с редакцией в процессе подготовки публикации и печати

Пазова А.А. (ORCID ID: https://orcid.org/0000-0002-1194-8281): написание проекта рукописи; обзор публикаций по теме статьи

Дунаева А.М. (ORCID ID: https://orcid.org/0000-0002-2125-5278): ведение пациентки, предоставление иллюстративного матириала коррекция рукописи

Туршева М.Э. (ORCID ID: https://orcid.org/0000-0002-1484-6141): ведение пациентки, предоставление иллюстративного матириала коррекция рукописи

Селезнева Е.В. (ORCID ID: https://orcid.org/0000-0001-8926-6435): написание проекта рукописи; обзор публикаций по теме статьи

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 ID: https://orcid.org/0000-0001-7479-418X): article design development; writing the text of the manuscript; review of publications on the topic of the article; interaction with the editors in the process of preparing a publication for printing

Pazova A.A. (ORCID ID: https://orcid.org/0000-0002-1194-8281): writing a draft manuscript; review of publications on the topic of the article

Dunaeva A.M. (ORCID ID: https://orcid.org/0000-0002-2125-5278): case management, provision of illustrative material; correction of the manuscript

Tursheva M.E. (ORCID ID: https://orcid.org/0000-0002-1484-6141): case management, provision of illustrative material; correction of the manuscript

Selezneva E.V. (ORCID ID: https://orcid.org/0000-0001-8926-6435): writing a draft manuscript; review of publications on the topic of the article

Список литературы/ References:

1. Резник Е.В., Селиванов А.И., Утюжанин Д.В. и др. Кардиомиопатии. Москва: РНИМУ им. Н.И. Пирогова; 2020; 248 с, УДК 616.127(075.8), ББК 54.101я73, К219, ISBN 978-5-88458-505-8.
Reznik E.V., Selivanov A.I., Ustyuzhanin D.V. Cardiomyopathy. Moscow: RNIMU n.a. N.I. Pirogov; 2020; 248p. [In Russian], ISBN 978-5-88458-505-8.
2. Baker C., Muse J., Taussky P. Takotsubo Syndrome in Neurologic Disease. World neurosurgery. 2021; 149: 26-31. doi: 10.1016/j.wneu.2021.01.139.
3. Ghadri J.R., Wittstein I.S., Prasad A. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. Eur Heart J. 2018; 39(22): 2032-46. doi: 10.1093/eurheartj/ehy076.
4. Ghadri J.R., Wittstein I.S., Prasad A. International Expert Consensus Document on Takotsubo Syndrome (Part II): Diagnostic Workup, Outcome, and Management. Eur Heart J. 2018; 39(22): 2047-62. doi: 10.1093/eurheartj/ehy077.
5. Sato H.; Tateishi H.; Uchida T. Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K.; Haze K.; Hon M., editors. Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure. Tokyo, Japan: Kagakuhyouronsha; 1990. p. 56-64.
6. Lyon A.R., Bossone E., Schneider B. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2016; 18(1): 8-27. doi: 10.1002/ejhf.424.
7. Климов А.А., Булдаков М.Ю., Грицкевич М.В. и др. Три клинических случая синдрома такоцубо после индукции общей анестезии. Альманах клинической медицины. 2019; 47(3): 236-43. doi: https://doi.org/10.18786/2072-0505-2019-47-032.
Klimov A.A., Buldakov M.Yu., Gritskevich M.V. Takotsubo syndrome after induction of general anesthesia: three clinical cases. *Almanac of Clinical Medicine*. 2019;47(3):236-243. [In Russian]. https://doi.org/10.18786/2072-0505-2019-47-032

DOI: 10.20514/2226-6704-2022-12-3-234-239 УДК 616.36-004.4-06:616.98:578.834.1-036

Е.Ю. Кудашкина*[1], Л.Ю. Ильченко[1], И.Г. Федоров[1,2]

[1] — Кафедра госпитальной терапии имени академика Г.И. Сторожакова ЛФ Федерального государственного автономного образовательного учреждения высшего образования «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова» Минздрава России, Москва, Россия
[2] — Государственное бюджетное учреждение здравоохранения «Городская клиническая больница имени В.М. Буянова» Департамента здравоохранения города Москвы, Москва, Россия

ТЕЧЕНИЕ АЛКОГОЛЬНОГО ЦИРРОЗА ПЕЧЕНИ У ПАЦИЕНТА С COVID-19

E.Yu. Kudashkina*[1], L.Yu. Ilchenko[1,2], I.G. Fedorov[1,2]

[1] — Department of Hospital Therapy named after Academician G.I. Storozhakov Medical Faculty, Moscow, Russia
[2] — State Clinical hospital named after V. M. Buyanov, Moscow, Russia

The Course of Alcoholic Cirrhosis of The Liver in a Patient with COVID-19

Резюме

В статье приведены особенности течения цирроза печени (ЦП) у пациента с новой коронавирусной инфекцией. У пациента отсутствовали характерные респираторные симптомы COVID-19 (новой коронавирусной инфекции), а поводом для амбулаторного обследования на наличие РНК SARS-CoV-2 (severe acute respiratory syndrome coronavirus — коронавирус тяжелого острого респираторного синдрома) послужил контакт с заболевшими COVID-19 родственниками. Ранее пациент Е. находился на стационарном обследовании и лечении по поводу нарастания живота в объеме на фоне длительной алкоголизации, был установлен диагноз ЦП алкогольной этиологии класса В по Чайлд-Пью. Проведена консервативная терапия, пациент был выписан с регрессом асцита. В течение недели после идентификации SARS-CoV-2 у пациента Е. были выявлены признаки декомпенсации ЦП в виде нарастания живота в объёме, что потребовало стационарного лечения, в период которого выявлен тромбоз воротной вены (ТВВ) и прогрессирование ~~стадии~~ хронического заболевания печени (ХЗП) в постковидном периоде. Представлены литературные данные о 30-дневной летальности у пациентов с ЦП на фоне COVID-19, а также собственные наблюдения на примере 580 пациентов, проходивших лечение в ГБУЗ «Городской клинической больнице имени В.М. Буянова» (ГКБ им. В.М. Буянова) за период 01.04.2020-01.10.2021гг. Рассмотрены осложнения новой коронавирусной инфекции у пациентов с ХЗП, методы их коррекции. Наше наблюдение демонстрирует социальную значимость проблемы заболеваемости COVID-19 у пациентов с ЦП, необходимость скрининга на COVID-19 при наличии эпизодов декомпенсации, а также активной профилактики инфекции у данных пациентов.

Ключевые слова: *COVID-19, хронические заболевания печени, постковидный синдром*

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

Статья получена 02.02.2022 г.
Принята к публикации 09.03.2022 г.

Для цитирования: Кудашкина Е.Ю., Ильченко Л.Ю., Федоров И.Г. ТЕЧЕНИЕ АЛКОГОЛЬНОГО ЦИРРОЗА ПЕЧЕНИ У ПАЦИЕНТА С COVID-19. Архивъ внутренней медицины. 2022; 12(3): 234-239. DOI: 10.20514/2226-6704-2022-12-3-234-239. EDN: YUXAUO

*Контакты: Екатерина Юрьевна Кудашкина, e-mail: fire0808@mail.ru
*Contacts: Contacts: Ekaterina Yu. Kudashkina, e-mail: fire0808@mail.ru
ORCID ID: https://orcid.org/0000-0002-8819-8511

Abstract

This article presents the features of the course of liver cirrhosis (LC) in a patient with a new coronavirus infection. The patient had no specific respiratory symptoms of COVID-19 (CoronaVirus Disease 2019), and the reason for outpatient examination for SARS-CoV-2 (severe acute respiratory syndrome coronavirus) RNA was the presence of these symptoms in relatives. Previously, patient E. had been undergoing in-patient examination and treatment for abdomen volume build-up against the background of prolonged alcoholization, and was diagnosed with alcoholic class B LC according to Child-Pugh classification. Conservative therapy was administered, and the patient was discharged with regression of ascites. Within a week after SARS-CoV-2 identification, patient E. showed signs of LC decompensation in the form of increasing abdominal volume, which required repeated inpatient treatment, during which portal vein thrombosis (PVT) and progression of chronic liver disease (CLD) in the post-coid period were revealed. Literature data on 30-day mortality in patients with LC against COVID-19 background are presented, as well as my own observations on the example of 580 case histories. Complications of new coronavirus infection in patients with CLD, methods of their correction are considered here. This observation demonstrates the social significance of the problem of COVID-19 incidence in patients with LC, the necessity for screening for COVID-19 in case of the presence of decompensation episodes, as well as active prevention of infection in these patients.

Key word: *COVID-19, chronic liver disease, postcovid syndrome*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 02.02.2022

Accepted for publication on 09.03.2022

For citation: Kudashkina E.Yu., Ilchenko L.Yu., Fedorov I.G. The Course of Alcoholic Cirrhosis of The Liver in a Patient with COVID-19. The Russian Archives of Internal Medicine. 2022; 12(3): 234-239. DOI: 10.20514/2226-6704-2022-12-3-234-239. EDN: YUXAUO

ALD — alcoholic liver disease; ALT — alanine aminotransferase; AP — alkaline phosphatase; ACLF — acute-on-chronic liver failure; AST — aspartate aminotransferase; CAI — chronic alcohol intoxication; chest CT — computed tomography of thoracic organs; CLD — chronic liver diseases; COVID-19 — CoronaVirus Disease, 2019 coronavirus infection; DUS — Doppler ultrasound; EV — esophageal varices; GGTP — gamma-glutamyl transpeptidase; IL — interleukin; LC — liver cirrhosis; MELD — Model for End-Stage Liver Disease; N — normal; PH — portal hypertension; PV — portal vein; PVT — portal vein thrombosis; SARS-CoV-2 — severe acute respiratory syndrome coronavirus; TNF-A — tumor necrosis factor alpha; US — ultrasound examination; WHO — World Health Organization

Relevance

The COVID-19 pandemic caused by SARS-CoV-2 has spread rapidly around the world since March 2020. To this day, novel coronavirus disease has resulted in the death of more than 5 million people [1].

COVID-19 refers to diseases primarily involving the respiratory system. However, this virus can infect various organs and systems of the body, including the gastrointestinal tract and the liver. The following are the basic mechanisms of liver damage in the case of COVID-19: direct cytotoxic effect of the virus on cholangiocytes and hepatocytes; immune-mediated as a result of a systemic inflammatory response; drug-induced damage (hepatotoxic effect of antibacterial and antiviral drugs, non-steroidal anti-inflammatory drugs, glucocorticosteroids, etc.); ischemia as a result of microangiopathy, microthrombosis with underlying endothelial dysfunction [2–5].

According to the international collaboration of scientists "The Global, Regional and National Burden of Cirrhosis 2017", Russia ranks fourth in the world in terms of increased mortality from cirrhosis, where alcoholic liver damage plays a critical role [6]. Alcohol relates to direct hepatotoxic agents; its long-term consumption leads to the development of alcoholic liver disease (ALD), which manifests itself in three main forms: steatosis, hepatitis and cirrhosis. Russia is one of the countries with high alcohol consumption: 11.7 liters per capita per year [7]. Reports of increased alcohol consumption during the COVID-19 pandemic are of particular concern [8].

Patients with CLD are at high risk of infection and severe course of COVID-19. J. Ge et al., 2021 [9], compared 30-day mortality in patients with coronavirus disease with no cirrhosis and those with cirrhosis. Patients with CLD at the LC stage had a 2.38-fold risk of adverse outcome than patients with CLD and with no cirrhosis.

Patients with CLD, including those of alcoholic etiology, do not always have symptoms typical for COVID-19. According to T. Marjot et al., 2021 [10], at the time of diagnosis, 22 % of patients with decompensated CLD had no respiratory symptoms typical for the clinical presentation of novel coronavirus infection. This complicates the diagnosis of COVID-19 in this category of patients.

For illustrative purposes, we describe a case of LC with alcoholic etiology during and after COVID-19.

Patient E., 46, auto mechanic; in November 2020, he was urgently hospitalized in the Gastroenterology Department due to the enlargement of the abdomen, yellowing of the skin and sclera, and moderate general weakness.

The patient has a history of consistent consumption of strong alcoholic beverages (vodka, cognac) in hepatotoxic doses for 10 years. The last alcoholization was two months before admission. The patient did not consult a narcologist. Since adolescence, the patient has smoked a pack of cigarettes per day (smoking index — 30 pack/years).

The patient considers himself ill since the autumn of 2017 when he first observed yellowness of the skin and sclera. Inpatient treatment was conducted; the patient was diagnosed with liver cirrhosis of alcoholic etiology.

In October 2020, after alcoholization (250 ml of vodka, 500 ml of champagne), the patient observed enlargement of the abdomen, yellowness of the sclera, and general weakness. The patient was hospitalized in the Gastroenterology Department. To confirm chronic alcohol intoxication (CAI), the AUDIT (Alcohol Use Disorders Identification Test) questionnaire was used [11]. During the examination, CBC was within normal. Blood biochemistry revealed an increased level of transaminases (aspartate aminotransferase (AST), alanine aminotransferase (ALT)) up to 4 x normal value (N), bilirubin up to 3.5 x N, gamma-glutamyl transpeptidase (GGTP) up to 10 x N, alkaline phosphatase (AP) 1.5 x N; decreased albumin level down to 27 g/L (N 35–55 IU/L). Esophagogastroduodenoscopy revealed esophageal varices (EV) up to 3 mm. According to the ultrasound examination (US), there was free fluid in the abdominal cavity, increased diameter of the portal vein (PV) up to 27 mm, the splenic vein — 20 mm, splenomegaly. Computed tomography of thoracic organs (chest CT): no results for focal and infiltrative changes in the lungs were obtained. Conservative treatment was conducted (diuretic, hepatotropic, infusion, antibacterial), adequate diuresis was achieved, regression of edema-ascites syndrome. The patient was discharged with a diagnosis of liver cirrhosis of alcoholic etiology, Child-Pugh class B (9 points), MELD (Model for End-Stage Liver Disease) — 14 points; Complication: portal hypertension (PH): esophageal varices grade 1-2, dilatation of portal and splenic veins, splenomegaly, ascites grade 2. Liver cell failure: encephalopathy of mixed etiology (toxic and hepatic), type C, persistent, hyperbilirubinemia, hypoalbuminemia. As outpatient treatment, the patient took esomeprazole 40 mg/day, spironolactone 300 mg/day, furosemide 60 mg/day, propranolone 40 mg/day, ademetionine 800 mg/day, acetylcysteine 600 mg/day, kept a low-salt diet, stopped drinking alcoholic beverages.

Two weeks after discharge from the hospital, patient E. received a positive nasopharyngeal and oropharyngeal swab for RNA of SARS-CoV-2. There were no typical for COVID-19 respiratory symptoms, no increased body temperature. It is also known that the patient's wife and child, in addition to a positive test for SARS-CoV-2 RNA, had respiratory symptoms and increased body temperature up to 38.6 °C. The patient received no treatment for novel coronavirus infection. Chest CT performed in an outpatient setting demonstrated no signs of viral pneumonia. Gradual enlargement of the abdomen was observed a week after the positive diagnostic result for COVID-19, which was the reason for hospitalization.

On admission to the Gastroenterology Department, the patient's condition was assessed as moderately severe. Clear consciousness, the patient was cooperative, with appropriate behavior, countdown test was performed, number connection test — 86 s. Body temperature was 36.7 °C. Skin was icteric, of moderate moisture, peripheral edema of lower extremities to the level of the middle third of lower legs, symmetrical. There were "small liver signs" — telangiectasia on the skin in the area of the shoulders and chest, palmar erythema. Lymph nodes were not enlarged. Musculoskeletal system with no visible pathology. Body mass index was 28.7 kg/m^2. Vesicular breathing in the lungs, respiratory rate 18 per minute. Regular heart rhythm with heart rate 82 bpm, clear heart tones, blood pressure 107 and 75 mm Hg on both arms. Tongue was moist, covered with a whitish-yellow fur. Abdomen was enlarged due to ascites, not tense, painless on palpation. Liver and spleen palpation cannot be performed due to ascites. Peristalsis was heard. Stool was regular, formed, brown, with no pathological admixtures. No costovertebral angle tenderness on both sides. Urination was free, painless.

Complete blood count for the first time revealed mild normochromic macrocytic anemia (hemoglobin — 122 g/L, RBC — 3.46×10^{12}/L, hematocrit — 34 %, MCV (Mean Corpuscular Volume) — 103 fl).

Blood biochemistry: AST — 77 IU/L (N 5–34 IU/L), ALT — 48 IU/L (N 0–32 IU/L), GGTP — 266 IU/L (N 9–39 IU/L), total bilirubin — 146.4 μmol/L (N 1.7–20.5 μmol/L), conjugated bilirubin — 106.8 (N 0.86–5 μmol/L), urea — 6.0 mmol/L (N 2.5–8.33 mmol/L), creatinine — 82 μmol/L (N 53–88 μmol/L), alpha-amylase — 53 IU/L (N 0–220 IU/L), glucose — 6.1 mmol/L (N 3.8–6.1 mmol/L), AP — 307 IU/L (N 64–306 IU/L), C-reactive protein — 69.3 mg/L (N 0.1–7 mg/L).

Coagulogram revealed increased international normalized ratio up to 1.4 (N 0.85–1.15), prothrombin time — 16.4 s (N 10.6–13.4 mg/L). Increased level of D-dimer up to 4,443 μg/L (N 64–550 μg/L) was also observed.

Ultrasound examination of the hepatobiliary system revealed diffuse changes in the liver, pancreas, dilatation of PV (16 mm), with no signs of blood flow (portal vein thrombosis, PVT), dilatation of the splenic vein (12 mm), blood flow is visualized, splenomegaly, free fluid in the abdominal cavity.

The patient was seen by a vascular surgeon, PVT was confirmed.

During hospital stay, conservative treatment was carried out: infusion therapy 500 ml (sodium chloride 0.9 % + papaverine hydrochloride 40 mg) IVFD; ademetionine 400 mg once a day as IV bolus; the following medications were also prescribed: rivaroxaban 30 mg/day (15 mg twice daily), spironolactone 300 mg/day, furosemide 60 mg/day, omeprazole 40 mg/day, propranolol 20 mg/day, lactulose 30 ml/day, ursodeoxycholic acid preparations 1,250 mg/day, folic acid 6 mg/day, B vitamins.

Patient E. was discharged on day 8 of hospital stay with positive changes in the form of decreased intensity of jaundice, decreased edema-ascites syndrome and general weakness. The patient was advised to keep a protective diet, limit physical activity, continue taking spironolactone 300 mg/day, furosemide 60 mg/day, propranolol 10 mg four times a day, ademetionine 800 mg/day, rivaroxaban 30 mg/day, ursodeoxycholic acid preparations

1,250 mg/day, lactulose 30 ml/ day, monitor Doppler ultrasound (DUS) of the vessels of the abdominal cavity in one month.

Ultrasound follow-up control in one month revealed that blood flow in the portal vein was restored. In one year, the patient demonstrated no signs of cirrhosis decompensation; moderate general weakness persisted for 5–6 months.

Discussion

The presented case illustrates the course of cirrhosis of alcoholic etiology with underlying COVID-19, which was complicated by the development of portal vein thrombosis and the progression of the CLD stage to Child-Pugh class C during the post-COVID period.

Patients with CLD, especially at the cirrhosis stage, may be more susceptible to SARS-CoV-2 infection due to a systemic immunodeficiency state. In addition to the effect of LC on the hepatic immune system, cellular and humoral immune response of the whole body also changes. These changes can be described by the inhibition of CD4 +/CD8 + cells and increased production of pro-inflammatory cytokines, mainly TNF-A (tumor necrosis factor alpha), IL (interleukin) 6, 10. It was demonstrated that the severity of cirrhosis correlates with the degree of depression of cellular immunity and humoral activation [12]. Increased intensity of cytokine synthesis exacerbates inflammatory response. The study conducted by M. Premkumar et al., 2009 [13], revealed that 82 % of patients with cirrhosis and H1N1/09 influenza died from pneumonia and acute respiratory distress syndrome (ARDS) despite timely antiviral treatment. There is evidence of the immunomodulatory effect of high alcohol doses, which may predispose to the addition of concomitant bacterial infections in patients infected with SARS-CoV-2, as well as to the development of ARDS [14].

A multinational cohort study with an open online reporting form included information on 220,727 cases of the disease from 214 centers (29 countries); it resulted in the development of an international registry of patients with CLD and laboratory-confirmed SARS-CoV-2 infection. According to the results obtained by T. Marjot et al., 2021 [10], patients with LC are at increased risk of adverse outcomes when infected with SARS-CoV-2. The mortality rate in the group of patients with LC and COVID-19 is different. However, it is especially high among patients with Child-Pugh class C cirrhosis (mortality in cases of class A cirrhosis — 19 %, B — 35 %, C — 51 %). Death in most cases of LC was associated with lung damage (71 %). Therefore, the liver disease stage is closely associated with mortality from novel coronavirus infection.

According to a retrospective analysis of patients with ALD hospitalized in the V.M. Buyanov City Clinical Hospital from April 01, 2020 to October 01, 2021 (n = 580), SARS-CoV-2 RNA was detected on days 1–7 of hospitalization in 5.7 % (33/580) of patients, and markers of past COVID-19 (SARS-CoV-2 IgG) were detected in 25.2 % of patients (146/580). Patients vaccinated against COVID-19 were not included in this study. Thirty-day mortality in the group of patients with ALD and COVID-19 (RNA+) was 69.7 % (23/33), in the post-COVID period — 37.7 % (55/146), and in the absence of SARS-CoV-2 markers (no past COVID-19) — 25.4 % (102/401).

The results presented demonstrate a high incidence of adverse outcomes in patients with CLD with underlying novel coronavirus infection and higher mortality in the post-COVID period.

It should be noted that according to our study, 76 % (111/146) of patients with ALD and SARS-CoV-2 IgG were unaware of the disease and had no symptoms typical for COVID-19. However, the reason for hospitalization was CLD decompensation during the previous 2–4 weeks. Therefore, this suggests an atypical presentation of the course of novel coronavirus infection in most patients with CLD, especially at the stage of cirrhosis. The clinical pattern of COVID-19 in these patients was characterized by the absence of respiratory symptoms and significant temperature rise and by the presence of signs of decompensation of the underlying disease. In the analyzed case, patient E. also had no typical COVID-19 symptoms. The reason for the patient being tested for SARS-CoV-2 RNA in an outpatient setting was respiratory symptoms in his relatives. After a short period (one week), the patient showed signs of LC decompensation.

The most common variants of CLD decompensation upon admission to the hospital include the following: increased edema-ascites syndrome, hepatic encephalopathy, bleeding from EV, development of ACLF (acute-on-chronic liver failure), addition of infectious complications. Since COVID-19 was reported, the number of PVT cases has increased significantly.

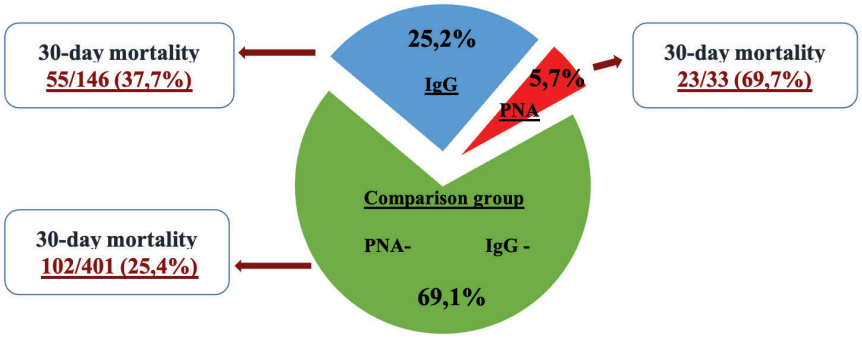


Figure 1. *Retrospective analysis data*

Note: Blue sector — patients with IgG SARS-CoV-2, who have undergone COVID-19; Red sector — patients with SARS-CoV-2 RNA detected; Green sector — patients without SARS-CoV-2 markers (RNA, IgM, IgG)

Thromboses of various locations are one of the frequent complications of novel coronavirus infection, both during disease and in the post-COVID period. According to various reviews, the incidence of thrombotic complications ranges from 7 to 40 % [15]. The most common locations of thrombosis are deep veins of the lower legs, with the development of pulmonary embolism in several cases.

According to the American Association the Study of Liver Diseases [16], the frequency of PVT among patients with LC with no COVID-19 is 0.6–26 % depending on its Child-Pugh severity class. The pathogenesis of PVT in LC is primarily due to the development of PH syndrome, decreased blood flow velocity through PV, as well as changes in hemostasis, which raise the risk of both hemorrhagic and thrombotic complications [17]. On the one hand, in LC, there is hypocoagulation associated with decreased synthesis of coagulation factors (II, VII, IX, X) and thrombocytopenia; on the other hand, the deficiency of protein S, C, antithrombin III, decreased thrombomodulin activity, increased factor VIII and von Willebrand factor are accompanied by increased thrombin generation. Thrombinemia increases the risk of venous thrombosis, including PVT. The incidence of PVT and the percentage of recanalization during the post-COVID period in patients with CLD remain unknown.

Management of PVT is based on ancoagulant therapy. In clinical practice, coagulopathy in patients with LC is often a deterrent to prescribing anticoagulant agents. According to meta-analyses and systematic reviews of cohort studies [18], treatment with heparin or direct-acting oral anticoagulants (rivaroxaban, apixaban, dabigatran) does not increase the risk of bleeding, and the frequency of PVT recanalization increases significantly.

According to S. Rajan et al., 2021 [19], after recovering from COVID-19, up to 25 % of patients report a variety of complaints, ranging from slight weakness to memory problems and shortness of breath. This condition is considered as a post-COVID syndrome and is included by World Health Organization (WHO) experts in ICD-10 as a post COVID-19 condition (U09.9). Post-COVID syndrome has a significant impact on the quality of life of patients and their ability to work. Increased levels of AST, ALT, and bilirubin persist in a number of patients with no CLD [20]. There are no results of monitoring clinical signs and outcomes in patients with CLD in the delayed period after novel coronavirus infection in the available medical literature. In the analyzed case, the sign of post-COVID syndrome was moderate general weakness, which persisted for 5–6 months after the patient's recovery from COVID-19.

Conclusion

This clinical case demonstrates a relatively favorable outcome of LC with underlying COVID-19. Within a month, PVT recanalization occurred, and clinical signs of LC decompensation regressed. However, there were signs of post-COVID syndrome over time. According to the literature and our own retrospective analysis of the case histories of patients in the Gastroenterology Department, mortality in patients with CLD and detected SARS-CoV-2 RNA/IgG is higher than in patients with CLD and with no past COVID-19. Therefore, this group of patients requires active preventive measures (personal protective equipment, thorough hand washing, limiting attendance of mass events), as well as mandatory vaccination against novel coronavirus infection.

A significant number of patients with CLD and COVID-19 have an atypical course of infection, which hinders detection, timely treatment of this group of patients, as well as the prevention of complications, including thrombotic complications. Diagnosis of COVID-19 in patients with CLD should be based on the determination of SARS-CoV-2 markers, especially if there were episodes of decompensation.

The long-term prognosis and specific features of the CLD course in the post-COVID period require further observation and analysis. The frequency and manifestations of the post-COVID syndrome in this category of patients also remain unclear.

Вклад авторов:

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

Кудашкина Е.Ю. (Orcid ID: https://orcid.org/0000-0002-8819-8511): написание статьи

Ильченко Л.Ю. (Orcid ID: https://orcid.org/0000-0001-6029-1864): редактирование текста

Федоров И.Г. (Orcid ID: https://orcid.org/0000-0003-1003-539X): ведение пациента

Author Contribution:

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

Kudashkina E. Yu. (Orcid ID: https://orcid.org/0000-0002-8819-8511): writing the article

Ilchenko L.Yu. (Orcid ID: https://orcid.org/0000-0001-6029-1864): editing the paper

Fedorov I.G. (Orcid ID: https://orcid.org/0000-0003-1003-539X): patient care

Список литературы/ References:

1. Johns Hopkins University. COVID-19 Data Visualization Center. New Cases of COVID-19 In World Countries. 2021. [Electronic resource]. URL:https://coronavirus.jhu.edu/data/new-cases (date of the application: 29.12.2021).
2. Amin M. COVID-19 and the liver: overview. J Gastroenterol Hepatol. 2021; 3(33): 309-311. doi: 10.1097/MEG.0000000000001808.
3. Dawood R., Salum G., El-Meguid M. The Impact of COVID-19 on Liver Injury: COVID-19 and Liver Injury. J Med Sci. 2021; S0002-9629(21)00400-6. doi:10.1016/j.amjms.2021.11.001
4. Ильченко Л.Ю., Никитин И.Г., Федоров И.Г. COVID-19 и поражение печени. Архивъ внутренней медицины. 2020; 3(10): 188-197. doi.org/10.20514/2226-6704-2020-10-3-188-197.
Ilchenko L.Yu., Nikitin I.G., Fedorov I.G. COVID-19 and Liver Damage. The Russian Archives of Internal Medicine. 2020; 3(10): 188-197. doi.org/10.20514/2226-6704-2020-10-3-188-197. [In Russian].

5. Никитин И.Г., Ильченко Л.Ю., Федоров И.Г. и др. Поражение печени при COVID-19: два клинических наблюдения. Альманах клинической медицины. 2020; 6(48): 412-421. doi.org/10.18786/2072-0505-2020-48-053.
Nikitin I.G., Ilchenko L.Yu., Fedorov I.G. et al. Liver injury in COVID-19: two clinical cases. Almanac of Clinical Medicine. 2020; 6(48): 412-421. doi.org/10.18786/2072-0505-2020-48-053. [In Russian].
6. GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2020; 3(5): 245-266. doi: 10.1016/S2468-1253(19)30349-8.
7. World Health Organization. 2018 Global status report on alcohol and health. 2018. [Electronic resource]. URL: https://apps.who.int/iris/handle/10665/274603. (date of the application: 29.12.2021).
8. Ramalho R. Alcohol consumption and alcohol-related problems during the COVID-19 pandemic: a narrative review. Australas Psychiatry. 2020; 28(5): 524-526. doi: 10.1177/1039856220943024.
9. Ge J., Pletcher M., Lai J. N3C Consortium Outcomes of SARS-CoV-2 infection in patients with chronic liver disease and cirrhosis: a National COVID cohort collaborative study. Gastroenterology. 2021; 5(161): 1487-1501. doi:10.1053/j.gastro.2021.07.010.
10. Marjot T., Moon A., Cook J. et al. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. J Hepatol. 2021; 3(74): 567-577. doi:10.1016/j.jhep.2020.09.024.
11. Babor, T., Fuente, J., Saunders J., Grant M. The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Health Care. WHO/MNH/DAT 89.4, World Health Organization, Geneva, 1989.
12. Albillos A., Lario M., Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol. 2014; 6(61): 1385-1396. doi:10.1016/j.jhep.2014.08.010.
13. Premkumar M., Devurgowda D., Dudha S. et al. A/H1N1/09 Influenza is Associated With High Mortality in Liver Cirrhosis. J Clin Exp Hepatol. 2019; 9(2): 162-170. doi: 10.1016/j.jceh.2018.04.006.
14. Szabo G., Saha B. Alcohol's Effect on Host Defense. Alcohol Res. 2015; 2(37): 159-170.
15. Kunutsor S., Laukkanen J. Incidence of venous and arterial thromboembolic complications in COVID-19: a systematic review and meta-analysis. Thromb Res. 2020; 196: 27–30. https://doi.org/10.1016/j.thromres.2020.08.022.
16. Northup P., Garcia-Pagan J., Garcia-Tsao G. et al. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021; 1(73): 366-413. doi:10.1002/hep.31646.
17. Turon F., Driever E., Baiges A. et al. Predicting portal thrombosis in cirrhosis: A prospective study of clinical, ultrasonographic and hemostatic factors, J Hepatology. 2021; 6(75): 1367-1376. doi:10.1016/ j.jhep.2021.07.020.
18. O'Shea R., Davitkov P., Ko C. et al. AGA Clinical Practice Guideline on the Management of Coagulation Disorders in Patients With Cirrhosis. Gastroenterology. 2021; 5(161): 1615-1627. doi:10.1053/j.gastro.2021.08.015
19. Rajan S., Khunti K., Alwan N. et al. In the wake of the pandemic: Preparing for Long COVID. Copenhagen (Denmark): European Observatory on Health Systems and Policies. 2021. [Электронный ресурс]. URL: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2021/in-the-wake-of-the-pandemic-preparing-for-long-covid-2021 (дата обращения 27.12.2021.).
20. Zeng Q., Yu Z., Ji F. et al. Dynamic changes in liver function parameters in patients with coronavirus disease 2019: a multicentre, retrospective study. BMC Infect Dis. 2021; 1(21): 818. doi:10.1186/s12879-021-06572-z.

Clin Infect Dis 2022 Apr 28;74(8):1442-1449.
doi: 10.1093/cid/ciab632.

Прогнозирование развития эндокардита у больных бактериемией, вызванной золотистым стафилококком
Prediction Rules for Ruling Out Endocarditis in Patients With Staphylococcus aureus Bacteremia

Thomas W van der Vaart, Jan M Prins, Robin Soetekouw, Gitte van Twillert, Jan Veenstra, Bjorn L Herpers, Wouter Rozemeijer, Rogier R Jansen, Marc J M Bonten, Jan T M van der Meer

Введение: бактериемия, вызванная золотистым стафилококком (SAB), в 10-20 % случаев осложняется инфекционным эндокардитом. Клинические прогностические шкалы могут использоваться у пациентов с SAB с самым высоким риском эндокардита, улучшая процесс диагностики эндокардита. Аторы сравнили точность прогнозирования инфекционного эндокардита Staphylococcus aureus: время до положительного бак. посева, внутривенное введение наркотиков, сосудистые явления, ранее существовавшее заболевание сердца (POSITIVE), прогнозирование риска эндокардита с использованием клинического инструмента (PREDICT) и баллы VIRSTA для классификации вероятности эндокардита у больных SAB.

Методы. В период с августа 2017 г. по сентябрь 2019 г. мы последовательно включали взрослых пациентов с SAB в проспективное когортное исследование в 7 больницах в Нидерландах. Используя модифицированные критерии Дьюка для подтверждения диагноза эндокардита в качестве эталонного стандарта, были определены чувствительность, специфичность, отрицательное прогностическое значение (NPV) и положительное прогностическое значение для баллов POSITIVE, PREDICT и VIRSTA. NPV не менее 98 % считалось безопасным для исключения эндокардита.

Результаты. Из 477 пациентов с SAB, включенных в исследование, у 33 % был внебольничный SAB, у 8 % был протез клапана и у 11 % — имплантируемое электронное устройство. Эхокардиография была выполнена у 87 % пациентов, а 42 % — чреспищеводная эхокардиография (ЧПЭ). У 87 (18,2 %) был установлен диагноз эндокардита. Чувствительность составила 77,6 % (65,8 %-86,9 %), 85,1 % (75,8 %-91,8 %) и 98,9 % (95,7 %-100 %) для POSITIVE (n=362), PREDICT и VIRSTA баллов шкал соответственно. NPV составила 92,5 % (87,9 %-95,8 %), 94,5 % (90,7 %-97,0 %) и 99,3 % (94,9 %-100 %) соответственно. По шкалам POSITIVE, PREDICT и VIRSTA 44,5 %, 50,7 % и 70,9 % пациентов с SAB соответственно были отнесены к группе высокого риска эндокардита.

Выводы: Только показатель VIRSTA имел NPV не менее 98 %, но за счет большого числа пациентов, отнесенных к группе высокого риска и, следовательно, нуждающихся в проведении чреспищеводной эхокардиографии.

J Ren Nutr 2022 Mar;32(2):161-169.
doi: 10.1053/j.jrn.2021.03.006. Epub 2021 Apr 28.

Когортное исследование EQUAL: нутритивный статус при ХБП стадии 4-5 по данным опросов пациентов
Patient-Reported Measures and Lifestyle Are Associated With Deterioration in Nutritional Status in CKD Stage 4-5: The EQUAL Cohort Study

Karin Windahl, EQUAL study investigators; Gerd Faxén Irving, Tora Almquist, Maarit Korkeila Lidén, Peter Stenvinkel, Nicholas C Chesnaye, Christiane Drechsler, Maciej Szymczak, Magdalena Krajewska, Edouard L Fu, Claudia Torino, Gaetana Porto, Paul Roderick, Fergus J Caskey, Christoph Wanner, Friedo W Dekker, Kitty J Jager, Marie Evans

Цель. Целью этого исследования было изучение изменений нутритивного статуса до начала диализа и выявление модифицируемых факторов риска ухудшения нутритивного статуса у пожилых людей с прогрессирующим заболеванием почек.

Дизайн и методы: Европейское исследование качества лечения прогрессирующей хронической болезни почек (EQUAL) представляет собой проспективное обсервационное когортное исследование с участием шести европейских стран. В исследование были включены 1103 взрослых старше 65 лет со скоростью клубочковой фильтрации <20 мл/мин/1,73 м2, не находящихся на диализе, посещающих нефролога. Нутритивный статус оценивали с помощью 7-балльной субъективной общей оценки (7-p SGA), опрос пациентов проводился с помощью RAND-36 и Индекса симптомов диализа. Логистическую регрессию использовали для оценки связи между потенциальными факторами риска и снижением SGA.

Результаты. Большинство пациентов исходно имели нормальный нутритивный статус, 28 % страдали умеренным недоеданием (SGA ≤5). В целом среднее значение SGA уменьшилось на -0,18 балла/год (95 % доверительный интервал -0,21; -0,14). Более чем у трети участников исследования (34,9 %) ухудшилось нутритивное состояние (снижение SGA на 1 балл), а у 10,9 % наблюдалось серьезное снижение SGA (≥2 баллов). Доля пациентов с низким SGA (≤5) увеличивалась каждые 6 мес. У тех, у кого отмечено снижение SGA, также снизились расчетная скорость клубочковой фильтрации и оценка психического здоровья. Каждые 10 баллов снижения физической активности увеличивали вероятность снижения SGA на 23 %. Более низкая физическая активность на исходном уровне, желудочно-кишечные симптомы и курение были факторами риска нарушения нутритивного статуса. Наблюдалась взаимосвязь между диабетом и физической активностью при снижении SGA.

Выводы. Нутритивный статус ухудшился более чем у трети участников исследования в течение первого года наблюдения. Более низкая физическая активность, о которой сообщают пациенты, более выраженные желудочно-кишечные симптомы и курение были связаны со снижением нутритивного статуса.