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

ФЕВРАЛЬ 2021 (№ 1(57))

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

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Верстка
Виталий Котов

Отдел распространения и рекламы
Бабяк Алина
reklama@medarhive.ru

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: 10.20514/2226-6704-2021-1

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
FEBRUARY 2021 (№ 1(57))

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
Badiak Alina
reklama@medarhive.ru

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: 10.20514/2226-6704-2021-1

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DOI: 10.20514/2226-6704-2021-11-1-5-10

А.П. Ребров, М.А. Тяпкина*, Н.А. Кошелева

ФГБОУ ВО «Саратовский государственный медицинский университет им. В.И. Разумовского» Минздрава России, кафедра госпитальной терапии лечебного факультета, Саратов, Россия

ПАЦИЕНТЫ С СЕРДЕЧНО-СОСУДИСТЫМИ ЗАБОЛЕВАНИЯМИ И ПРИЕМ НПВП: РЕАЛЬНАЯ КЛИНИЧЕСКАЯ ПРАКТИКА

A.P. Rebrov, M.A. Tyapkina*, N.A. Kosheleva

Saratov State Medical University named after V.I. Razumovsky, Ministry of Health of Russian Federation, Department of the Internal Medicine, Saratov, Russian Federation

Patients with cardiovascular diseases and NSAIDs use: real clinical practice

Резюме

Цель — изучить частоту и особенности применения нестероидных противовоспалительных препаратов (НПВП) у пациентов с сердечно-сосудистыми заболеваниями, госпитализированных в отделения экстренной кардиологии. **Материалы и методы.** Обследовано 190 пациентов, госпитализированных в отделения экстренной кардиологии ГУЗ «Областная клиническая больница» г. Саратова с января по март 2020г. Исследование являлось непрерывным, анкетирование проводилось всем пациентам, госпитализированным в указанный период. В исследовании приняли участие 103 (54%) мужчины и 87 женщин, средний возраст пациентов составил 62,05 ± 11,11 года. Причиной госпитализации у большинства пациентов явилась острая коронарная патология — 116 (61%), у 34 (18%) пациентов — декомпенсация сердечной недостаточности, у 21 (11%) — различные нарушения ритма; у 15 (8%) — гипертонический криз на фоне неконтролируемой артериальной гипертензии, у 4 (2%) пациентов — тромбоэмболия легочной артерии. **Результаты.** В течение месяца перед госпитализацией НПВП по различным причинам принимали 92 (48%) пациента: 42 (46%) мужчины и 50 (54%) женщин. Средний возраст пациентов, принимавших НПВП, выше, чем у пациентов, не принимавших НПВП (63,98±11,62 года и 60,20±10,27 лет, соответственно, p=0,018). Среди пациентов, вынужденных принимать НПВП в течение последнего месяца, боль в суставах, как основную причину или одну из причин приема НПВП указали 43 (47%) пациента, головную боль — 40 (43%) пациентов, боль в спине — 30 (33%) больных. У 15 (16%) пациентов причиной приема НПВП явилась зубная боль, у 14 (15%) — боль в грудной клетке, у 11 (12%) больных — мышечно-скелетные боли. Несколько причин для приема НПВП отметили 40 (43%) пациентов (в основном, сочетание суставных болей и болей в спине). **Заключение.** Почти половина пациентов, госпитализированных в отделения экстренной кардиологии, в течение предшествующего месяца принимали НПВП. Большая часть пациентов вынуждена принимать НПВП часто, регулярно и продолжительно. Более трети обследованных пациентов использовали различные способы введения препаратов, в том числе неоправданно частое и длительное парентеральное применение или одновременное использование различных способов введения различных лекарственных препаратов.

Ключевые слова: *сердечно-сосудистые заболевания, нестероидные противовоспалительные препараты*

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 28.10.2020 г.

Принята к публикации 24.12.2020 г.

Для цитирования: Ребров А.П., Тяпкина М.А., Кошелева Н.А. ПАЦИЕНТЫ С СЕРДЕЧНО-СОСУДИСТЫМИ ЗАБОЛЕВАНИЯМИ И ПРИЕМ НПВП: РЕАЛЬНАЯ КЛИНИЧЕСКАЯ ПРАКТИКА. Архивъ внутренней медицины. 2021; 1(1): 5-10. DOI: 10.20514/2226-6704-2021-11-1-5-10

*Контакты: Мария Александровна Тяпкина, e-mail: mariya-tyapkina@yandex.ru

*Contacts: Maria A. Tyapkina, e-mail: mariya-tyapkina@yandex.ru

ORCID ID: https://orcid.org/0000-0002-1860-3171

Abstract

Objective — to study the frequency and characteristics of the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with cardiovascular diseases hospitalized in the emergency departments of cardiology. **Materials and methods**. Examined 190 patients hospitalized in the emergency cardiology departments of the State Healthcare Institution Regional Clinical Hospital of Saratov from January to March 2020. The study was continuous, a questionnaire was conducted for all patients hospitalized during the specified period. The study involved 103 (54%) men and 87 women, the average age of the patients was 62.05 ± 11.11 years. The reason for hospitalization in most patients was acute coronary pathology — 116 (61%) patients, 34 (18%) patients — decompensated heart failure, 21 (11%) patients — various rhythm disturbances; in 15 (8%) patients — hypertensive crisis against the background of uncontrolled arterial hypertension, in 4 (2%) patients — pulmonary embolism. **Results.** During the last month, 92 (48%) patients took NSAIDs for various reasons: 42 men (46%) and 50 women (54%). The average age of patients taking NSAIDs is higher than that of patients who did not take NSAIDs (63.98 ± 11.62 years and 60.20 ± 10.27 years, respectively, p = 0.018). Among patients forced to take NSAIDs over the past month, joint pain — 43 (47%) patients, headache — 40 (43%) patients, back pain — 30 (33%) were indicated as the main cause or one of the reasons sick. In 15 (16%) patients, the reason for taking NSAIDs was toothache, in 14 (15%) patients — chest pain, musculoskeletal pain — in 11 patients (12%). Several reasons for taking NSAIDs were indicated by 40 (43%) patients, the majority — a combination of joint pain and back pain. **Conclusion**. Almost half of patients admitted to emergency cardiology departments had taken NSAIDs in the previous month. Most patients have to take NSAIDs often, regularly, for a long time. More than a third of the examined patients used various methods of drug administration, including unreasonably frequent and prolonged parenteral use or the simultaneous use of various methods of administration of various drugs.

Key words: *cardiovascular diseases, nonsteroidal anti-inflammatory drugs*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 28.10.2020

Accepted for publication on 24.12.2020

For citation: Rebrov A.P., Tyapkina M.A., Kosheleva N.A. Patients with cardiovascular diseases and NSAIDs use: real clinical practice. The Russian Archives of Internal Medicine. 2021; 1(1): 5-10. DOI: 10.20514/2226-6704-2021-11-1-5-10

FC — functional class, GIT — gastrointestinal tract, GFR — glomerular filtration rate, IHD — ischemic heart disease, NSAIDs — non-steroidal anti-inflammatory drugs

Introduction

Today, there are many publications on the rational use of non-steroidal anti-inflammatory drugs (NSAIDs) and possible risks of adverse events in patients with cardiovascular diseases while taking NSAIDs [1–4]. The possible increase of the risk of acute coronary syndrome, myocardial infarction [1, 2], stroke [3], destabilization of blood pressure in patients with arterial hypertension [4], and the worsening of edematous syndrome in patients with heart failure have been described [4]. This information formed the basis of the developed and published recommendations, algorithms for rational choice, and use of NSAIDs in patients with various comorbidities [5]. These recommendations and procedures are intended for physicians who must choose the optimal strategy for using NSAIDs considering all risks. However, in real-life clinical practice, patients often start taking NSAIDs on their own and without considering all recommendations and algorithms. This applies not only to patients with cardiovascular diseases but also to those with other comorbidities, including chronic kidney disease. In this case, patients can take several drugs simultaneously and use different administration routes for a period ranging from several months to several years. This situation is aggravated by the fact that physicians are often unaware of patients taking NSAIDs on their own, or, unfortunately, do not always keep this possibility in mind. The problem of patients with cardiovascular comorbidity taking NSAIDs remains unresolved in real-life clinical practice.

The **objective** of this study was to assess the frequency and peculiarities of the usage of NSAIDs in patients with cardiovascular diseases admitted to the Emergency Cardiology Department.

Materials and methods

This study enrolled 190 patients (87 women and 103 men, mean age 62.05 ± 11.11 years) admitted to the Emergency Cardiology Department of the Saratov Regional Clinical Hospital from January to March 2020. This study was scheduled to continue until December 2020 in order to obtain a large sample of patients with subsequent analysis of the peculiarities of the usage of NSAIDs in real-life clinical practice for various cardiovascular diseases. Unfortunately, due to the COVID-19 pandemic, the recruitment of patients was suspended. However, it was decided to publish some preliminary data. This was a full-design study. The questionnaire

survey was conducted for all patients hospitalized during this period, except for patients with dementia (23 points or less on the Montreal Cognitive Assessment Scale [6]). All patients signed informed consent to participate in the study. The questionnaire included questions on the use of NSAIDs, reasons for their use, and peculiarities of their use during the month before hospitalization. The use of acetylsalicylic acid in low doses as antiplatelet therapy was not considered NSAID use.

Statistical processing of the obtained data was carried out using Statistica 8.0 software (StatSoft Inc. USA). Normally distributed quantitative characteristics are presented as M ± SD, where M is arithmetic mean, SD is standard deviation. The median (Me) and interquartile range [25th; 75th percentile] were used to describe parameters with distribution other than normal. Comparison of two groups was carried out using Student's t-test or Mann-Whitney test (if distribution was other than normal). A 2 × 2 table (Fisher's exact two-sided test, χ^2-test with Yates correction) was used to compare relative frequencies in two groups. Differences were considered significant at $p < 0.05$.

The structure of cardiac pathology in patients enrolled in this study is presented in Table 1. Acute coronary syndrome and decompensation of heart failure were the reasons for hospitalization in most patients. Ischemic heart disease (IHD) in 116 (71%) patients was represented by its acute forms, unstable angina and myocardial infarction. These were the onset of ischemic heart disease in 51 patients (44%); 65 patients (56%) had a history of IHD in different forms. The diagnosis of acute coronary syndrome was established based on European recommendations for the management of patients with this disease [7, 8]. At the time of present hospitalization, 48 (29%) patients were diagnosed with chronic forms of IHD without symptoms of acute coronary syndrome. Exertional angina as the only form of IHD was found in 12 patients (7%); a history of myocardial infarction was revealed in 36 patients (21%), including 25 patients currently suffering from exertional angina. Among 162 patients with signs of chronic heart failure (CHF), 56 patients (35%) were diagnosed with acute decompensation of heart failure [9]. In 34 patients, acute decompensation of CHF was the main reason for hospitalization. Patients without acute decompensation at the time of hospitalization mostly had CHF functional classes II and III (47% and 33%, respectively). Most patients with acute decompensation of CHF (70%) were diagnosed with CHF functional class III in the period before decompensation.

Such routine cardiovascular risk factors as smoking and overweight were analyzed in patients enrolled in this study. Smoking at the time of hospitalization was registered in 52 patients (27%). A history of smoking was reported by 43 patients (23%); 28 of them (15% of the total number enrolled in the study) quit smoking less than a year ago. Therefore, 80 patients (42%) currently smoke or stopped smoking less than a year ago; 69 of them (86%) were male. Therefore, 69 (67%) male patients admitted to the Emergency Cardiology Department had such a cardiovascular risk factor as smoking. Smoking was also registered in 11 female patients (13%), which is significantly less than in male patients ($p = 0.0001$). The smoking index was also higher in men than in women: 20 [10; 25] and 13 [7; 15], respectively, $p = 0.014$. Overweight (body mass index more than 25 kg/m^2) was observed in 101 (53%) patients — 60 men and 41 women. The distribution of the analyzed risk factors according to gender is presented in Fig. 1.

Table 1. *The cardiovascular diseases in patients*

Index	Value
The reason for hospitalization, abs (%):	
• acute coronary pathology	116 (61%)
• decompensated heart failure	34 (18%)
• rhythm disturbances	21 (11%)
• hypertensive crisis against the background of uncontrolled arterial hypertension	15 (8%)
• pulmonary embolism	4 (2%)
Clinical forms of cardiac pathology, abs (%):	
• arterial hypertension	168 (88%)
• coronary heart disease	164 (86%)
• chronic heart failure	162 (85%)
• atrial fibrillation	60 (32%)
Functional class of chronic heart failure in patients without acute decompensation, abs (%):	
• I	11 (10%)
• II	50 (47%)
• III	34 (33%)
• IV	11 (10%)
Functional class of chronic heart failure preceding acute decompensation, abs (%):	
• I	0 (0%)
• II	9 (16%)
• III	39 (70%)
• IV	8 (14%)

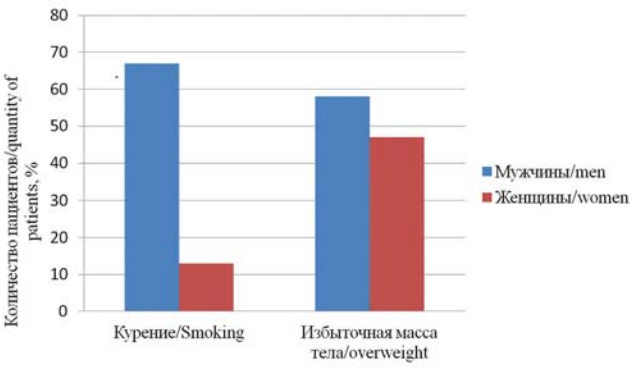

Figure 1. *Distribution cardiovascular risk factors in patients according to gender*

Comorbidity was analyzed in this study only based on the questionnaire filled by the patients on their own. Patient awareness of nosological forms requiring administration of NSAIDs was of particular interest. The following are the comorbidities indicated in the questionnaire by the patients on their own: disease of the gastrointestinal tract — 46 (24%) patients, diabetes mellitus — 36 (19%) patients, osteoarthritis — 24 (13%) patients, cancer — 7 (4%), gout — 6 (3%) patients.

This study did not analyze other medications used, including cardiotropic agents, since its purpose was to investigate the peculiarities and frequency of NSAID usage.

Results

One month before hospitalization, 92 (48%) patients took NSAIDs for different reasons: 42 (46%) men and 50 (54%) women. The mean age of these patients was higher than that of patients who did not require NSAIDs (63.98 ± 11.62 years and 60.20 ± 10.27 years, respectively, p = 0.018). Among the surveyed patients, 30 (16%) occasionally took NSAIDs but did not need to take them during the last month. Therefore, occasional use of NSAIDs over a longer period was observed in 122 (64%) patients: 57 men (47%) and 65 women (53%).

The main reasons, frequency, and duration of NSAID use one month before hospitalization are presented in Table 2. «Joint pain» as the main or one of the reasons for taking NSAIDs was indicated by 43 (47%) patients, headache — by 40 (43%) patients, back pain — by 30 (33%) patients. Almost half of the patients taking NSAIDs in the last month had been taking them for more than three years. During the month before hospitalization, 57 patients (62%) took NSAIDs at least once a week. That is one-third of the total number of patients enrolled in this study.

The following non-selective NSAIDs agents were the most commonly used: diclofenac — 37 (40%) patients, ibuprofen — 35 (38%) patients, ketorolac — 23 (25%) patients. Patients took the following selective NSAIDs less frequently: nimesulide — 22 (24%) patients, meloxicam — 13 (14%) patients; and coxibs were used only by 7 (8%) patients. An important aspect of self-treatment by patients is the fact that 26 (28%) patients simultaneously took two or more NSAIDs during the previous month. Most patients (59; 64%) took NSAIDs per os; intramuscular injections were used by 15 (16%) patients; the combination of simultaneous oral and intramuscular administration was used by 11 (12%) patients; other combinations, including intravenous and rectal administration — by 7 (8%) patients.

Table 2. *The reasons for taking NSAIDs, distribution of patients depending on the duration and frequency of taking NSAIDs during the last month*

Index	Value
The reasons for taking NSAIDs, abs. (%):	
• joint pain	43 (47%)
• headache	40 (43%)
• back pain	30 (33%)
• toothache	15 (16%)
• chest pain	14 (15%)
• musculoskeletal pain	11 (12%)
The duration of taking NSAIDs, abs. (%):	
• less than 3 months	14 (15%)
• from 3 months to 1 year	6 (7%)
• from 1 year to 3 years	27 (29%)
• more than 3 years	45 (49%)
Frequency of taking NSAIDs in the last month before hospitalization, abs. (%):	
• daily	13 (14%)
• 3 times a week	13 (14%)
• 2 times a week	13 (14%)
• once a week	18 (20%)
• less than once a week, but more often than once every 3 months	19 (21%)
• once within 3 — 6 months	16 (17%)

Only 55 (60%) patients used NSAIDs as prescribed by their physicians. Physicians inquired about cardiovascular diseases in 34 cases (62%). 37 patients (40%) used NSAIDs on their own, without recommendation by a physician.

Most patients (57; 62%) could not tell the potential adverse effects of NSAIDs. The possibility of kidney damage when taking NSAIDs was mentioned by 22 (24%) patients, liver damage — by 23 (25%) patients, cardiovascular disorders — by 6 (7%) patients, and gastric and intestinal lesions — by 10 (11%) patients. The possibility of damage to all these organs was mentioned by 11 (12%) patients. 45 (49%) patients took gastroprotectors. 6 (6.5%) patients reported worsening of edematous syndrome and increased blood pressure in connection with NSAIDs.

Laboratory tests revealed that hemoglobin level was significantly lower in patients who took NSAIDs one month before hospitalization than in patients who did not take NSAIDs (134 [122; 148] g/l and 144 [131; 151] g/l, respectively, p = 0.004). Anemia (decrease in hemoglobin level below 120 g/l in women and below 130 g/l in men) was found in 20 (22%) patients who took NSAIDs one month before hospitalization. No statistical differences were found in the incidence of anemia in patients taking NSAIDs (20; 22%) and in patients not taking these agents (14; 14%) (p = 0.177). This may be due to an insufficient number of patients in the compared groups. Therefore, analysis of the incidence of anemia due to NSAIDs requires further investigation when the study resumes.

Discussion

Almost half (48%) of patients admitted to the Emergency Cardiology Department took NSAIDs one month before hospitalization. Most of the patients belonged to the elderly population and had cardiovascular comorbidity. The reasons why patients with significant cardiovascular disease had to use NSAIDs do not differ from those in the general population of the corresponding age. Most patients cited joint pain, back pain and headaches as the reason for taking NSAIDs. Many patients (43%) listed several reasons for using NSAIDs. Our data match the results of the European study of NSAIDs in real-life clinical practice, suggesting that joint pain syndrome is one of the main reasons forcing patients to take NSAIDs for a long time and in high doses [1, 2].

We currently have results of a meta-analysis indicating that the risk of myocardial infarction associated with NSAIDs increases within one to seven days and when taking various drugs, including naproxen, which was considered relatively safe [2]. Of note is a small proportion of patients taking highly selective COX-2 inhibitors (coxibs) — agents with the lowest risk of gastrointestinal (GI) adverse events. However, a large proportion of patients had a high risk of gastrointestinal damage while taking NSAIDs. This is due to the use of antiplatelet agents and/or anticoagulants, the patients' age, possible ischemic lesions of the gastrointestinal mucosa with underlying severe cardiac disease. The rare prescription of coxibs in this category of patients is probably associated with the fear of cardiovascular emergencies. However, recent studies showed that these complications are class-specific; they can develop with any NSAIDs, and the probability of their occurrence is determined by individual features and the dose of a particular agent [1–4].

Taking NSAIDs per os is currently considered the most rational route of administration. It is on par with other methods in terms of effectiveness but has a better safety profile. The advantage of the parenteral route of administration is only in the rapid effect. However, the effect lasts only in the first days of treatment [5]. In real-life clinical practice, more than a third of examined patients used different routes of administration, including unjustifiably frequent and long parenteral use, or simultaneous use of different routes of administration and different NSAIDs, which significantly increases the risk of adverse events.

This study revealed that 62% of patients taking NSAIDs had to take these agents at least once a week. In total, a third of urgently admitted patients took NSAIDs regularly and frequently. In addition, most patients took the drugs for more than three years.

It should also be noted that 40% of patients took NSAIDs on their own, without the recommendation of their physician. This is crucial, given the low awareness of the possible side effects of NSAIDs among patients. The lack of patient awareness of the nosology for taking such agents was also revealed. Most of the examined patients who took NSAIDs also required proton pump inhibitors. This is because additional gastroprotective therapy is recommended during the combined use of antiplatelet agents and/or anticoagulants with NSAIDs [5]. However, only half of the patients who required proton pump inhibitors took them before hospitalization.

In our view, the lower hemoglobin level established in patients taking NSAIDs compared with those who did not take these agents one month before hospitalization is an important fact. There was no significant difference in the incidence of anemia among patients in the two groups, possibly due to the small number of patients.

Our study has several limitations. Firstly, we had to analyze information obtained from a relatively small group of patients since the study was suspended due to the COVID-19 pandemic. Secondly, the development of adverse events associated with NSAIDs was due to various reasons. However, we did not perform multivariate analysis in this paper. It will be performed in subsequent papers. The reason for taking NSAIDs — inflammatory disease, severity of inflammation, nociceptive or neuropathic pain, etc. — is certainly an important aspect. Differentiated analysis and the possibility of finding a relationship between NSAIDs and the destabilization of cardiovascular diseases and the development of emergency conditions require a large sample. We hope to resume this study.

Conclusion

Almost half of the patients admitted to the Emergency Cardiology Department took NSAIDs during the previous month before hospitalization. Most patients had to take NSAIDs frequently and regularly. Considering the plurality of medications taken for managing the underlying cardiovascular disease, the age of patients and comorbidities, NSAID use in this group of patients should not be uncontrolled. The possible use of NSAIDs in patients with cardiovascular comorbidity needs clarification since patients are poorly informed of the possible risks of adverse events when taking NSAIDs; they underestimate the danger and think it is unnecessary to inform physicians about the use of these drugs. Patients often take medications on their own, using different agents and different routes of administration simultaneously, thus increasing the risk of adverse events.

Вклад авторов:

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

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

Тяпкина М.А. (ORCID ID: https://orcid.org/0000-0002-1860-3171): концепция и дизайн исследования, получение данных, анализ и интерпретация данных, написание статьи, утверждение итогового варианта текста рукописи

Кошелева Н.А. (ORCID ID: https://orcid.org/0000-0001-5585-946X): концепция и дизайн исследования, получение данных, анализ и интерпретация данных, утверждение итогового варианта текста 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

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

Tyapkina M.A. (ORCID ID: https://orcid.org/0000-0002-1860-3171): research concept and design, obtaining data, analyzing and interpreting data, writing articles, approving the final version of the publication

Kosheleva N.A. (ORCID ID: https://orcid.org/0000-0001-5585-946X): research concept and design, obtaining data, analyzing and interpreting data, approving the final version of the publication

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DOI: 10.20514/2226-6704-2021-11-1-11-21

С.В. Тополянская*[1], Т.А. Елисеева[2], Н.А. Балясникова[2], О.Н. Вакуленко[2], Л.И. Дворецкий[1]

[1] — ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения РФ (Сеченовский Университет), кафедра госпитальной терапии № 2, Москва, Россия
[2] — ГБУЗ «Госпиталь для ветеранов войн № 3», Москва, Россия

ОСОБЕННОСТИ КОМПОЗИЦИОННОГО СОСТАВА ТЕЛА У ДОЛГОЖИТЕЛЕЙ С ИБС

S.V. Topolyanskaya*[1], T.A. Eliseeva[2], N.A. Balyasnikova[2], O.N. Vakulenko[2], L.I. Dvoretski[1]

[1] — I.M. Sechenov First Moscow State Medical University (Sechenov University), RF Health Ministry, Hospital Therapy Department № 2, Moscow, Russia
[2] — War Veterans Hospital N3, Moscow, Russia

Features of Body Composition in Centenarians with Coronary Artery Disease

Резюме

Цель исследования: изучение композиционного состава тела у больных ишемической болезнью сердца (ИБС) старше 90 лет (долгожителей) и анализ взаимосвязей между содержанием жировой, тощей ткани и минеральной плотностью костной ткани (МПКТ). **Материал и методы.** Данная работа — одномоментное («поперечное») исследование, в которое было включено 200 пациентов старше 90 лет (140 женщин и 60 мужчин, средний возраст 92,4 ±2,3 года), госпитализированных с диагнозом ИБС. Композиционный состав тела анализировали посредством двухэнергетической рентгеновской абсорбциометрии. **Результаты.** Избыточная масса тела или ожирение диагностированы у 139 (69,5%) больных. Скелетно-мышечный индекс оставался в пределах нормальных значений у 145 (72,5%) больных и был ниже нормы у 55 (27,5%). Снижение минеральной плотности костной ткани (Т-критерий) менее -2,5 SD выявлено у 81 (40,5%) больных, нормальные значения МПКТ — у 60 (30,0%) пациентов. Наименьшие значения МПКТ обнаружены в ребрах, наибольшие — в позвоночнике и нижних конечностях. Найдена положительная корреляция между индексом массы тела (ИМТ) и минеральной плотностью костной ткани во всех участках скелета (p <0,0001 для всех областей). Выявлена существенная прямая корреляция между содержанием жировой ткани во всех участках тела и МПКТ, особенно значимая между МПКТ ребер и содержанием жировой ткани в туловище (r=0,85; p <0,0001). Установлена прямая корреляция между содержанием тощей ткани и МПКТ; наиболее достоверная –между МПКТ верхних конечностей и содержанием тощей ткани в верхних конечностях (r=0,69; p <0,0001). Между содержанием жировой и тощей ткани найдена отрицательная корреляция, наиболее значимая между тощей и жировой тканью в нижних конечностях (r=-0,46; p <0,0001). **Заключение.** Полученные результаты свидетельствуют об особенностях композиционного состава тела у долгожителей. Отмечена достаточно высокая доля больных с избыточной массой тела, но с нормальными показателями МПКТ и содержания тощей ткани. Подтверждены значимые взаимосвязи между костной, жировой и тощей тканью.

Ключевые слова: *состав тела, мышечная масса, минеральная плотность костной ткани, жировая ткань, двухэнергетическая абсорбциометрия, долгожители*

*Контакты: Светлана Викторовна Тополянская, e-mail: sshekshina@yahoo.com
*Contacts: Svetlana V. Topolyanskaya, e-mail: sshekshina@yahoo.com
ORCID ID: https://orcid.org/0000-0002-4131-8432

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 06.11.2020 г.

Принята к публикации 21.01.2021 г.

Для цитирования: Тополянская С.В., Елисеева Т.А., Балясникова Н.А. и др. ОСОБЕННОСТИ КОМПОЗИЦИОННОГО СОСТАВА ТЕЛА У ДОЛГОЖИТЕЛЕЙ С ИБС. Архивъ внутренней медицины. 2021; 11(1): 11-21. DOI: 10.20514/2226-6704-2021-11-1-11-21

Abstract

Purpose. To investigate the body composition in patients over 90 years old (long-livers) with coronary artery disease (CAD), and analyzed the relationships between the fat and lean tissues, as well as bone mineral density. **Material and Methods**. A cross-sectional study of 200 patients over 90 years old (140 men and 160 women, mean age 92,4±2,3 года) who were hospitalized with a diagnosis of CAD was conducted. The body composition was analyzed by dual-energy X-ray absorptiometry (DXA). **Results**. Overweight or obesity were diagnosed in 139 (69.5%) patients. The musculoskeletal index remained within normal values in 145 (72.5%) patients and was below normal in 55 (27.5%) patients. Decrease of total BMD (T-score) below -2.5SD was detected in 81 (40,5%), and normal total T-score — in 60 (30.0%) patients. The smallest values of BMD were found in the ribs, the largest — in the spine and in lower extremities. A positive correlation was registered between body mass index and bone mineral density in all areas of the skeleton ($p < 0.0001$). A significant positive correlation was found between BMD and the fat mass in all parts of the body, especially significant between BMD of the ribs and the trunk adipose tissue ($r = 0.85$; $p < 0.0001$). A positive correlation has been established between the lean mass and BMD; the most significant between the BMD and the lean mass in the upper extremities ($r = 0.69$; $p < 0.0001$). A negative correlation was found between the fat and lean mass; the most significant between lean and adipose tissue in the lower extremities ($r = -0.46$; $p < 0.0001$). **Conclusion**. The study results indicate some features of body composition in long-livers. The proportion of overweight patients with normal indices of BMD and lean mass was relatively high. Significant relationships between the bone, adipose and lean tissues were confirmed.

Key words: *body composition, muscle mass, bone mineral density, adipose tissue, dual-energy X-ray absorptiometry, centenarians*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 06.11.2020

Accepted for publication on 21.01.2021

For citation: Topolyanskaya S.V., Eliseeva T.A., Balyasnikova N.A. et al. Features of Body Composition in Centenarians with Coronary Artery Disease. The Russian Archives of Internal Medicine. 2021; 11(1): 11-21. DOI: 10.20514/2226-6704-2021-11-1-11-21

BMD — bone mineral density, BMI — body mass index, IHD — ischemic heart disease, M — mean, SD — standard deviation

Introduction

The process of aging is associated with numerous changes in body composition. Aging inevitably leads to a decrease in muscle mass and strength, along with an increase in body fat and a decrease in bone mineral density, which often contributes to the so-called osteosarcopenic obesity [1, 2]. To a certain extent, these changes are associated with the imbalance between energy intake and expenditure due to an increasingly sedentary lifestyle. Some disorders also depend on the age-related rearrangement of the endocrine system and metabolic processes.

Increasing fat mass and its redistribution by central type in the senile population are associated with risk factors for diabetes mellitus and cardiovascular diseases [3]. Decreasing bone density is a key risk factor for fractures that lead to significant disability and increased mortality in the senile population. In turn, sarcopenia also leads to different functional disorders and disability in elderly individuals [1].

Age-associated changes in bone, adipose and muscle tissues are usually not isolated — they are combined with each other. Therefore, the same pathogenetic factors can underlie the decrease in bone and muscle tissue with aging: subclinical inflammation, deficiency of hormones and nutrients, as well as a decrease in physical activity [2]. The relationship between bone and muscle tissue can be also explained by other factors. A decrease in muscle mass leads to a decrease in bone loading, which contributes to a decrease in bone density [4]. Muscles

also perform an endocrine function by synthesizing biologically active molecules (myokines) that can have an effect on bone tissue regulation [2].

There are also certain correlations between adipose and bone tissue. This primarily includes the positive effect of mechanical stress that stimulates the formation of bone tissue by reducing apoptosis and increasing proliferation and differentiation of osteoblasts and osteocytes [4]. Also, the relationship between adipose and bone tissue can be mediated by various biologically active substances, particularly leptin and estrogens synthesized by adipocytes, as well as by sclerostin and osteocalcin produced by osteoblasts and stimulating the secretion of adipokines and insulin [2, 4].

Although the specific features of body composition in different groups of patients only recently attracted closer attention, there are now plenty of studies concerning this problem in elderly and senile patients and patients with several chronic diseases. However, only a few have studied body composition in long-living persons [5–6]. Among the available literature sources, we did not find any studies with dual-energy X-ray absorptiometry as a method to study the characteristics of body composition in long-livers; the above studies were carried out using a less sensitive technique called bioelectrical impedance analysis. Considering the above, it seems interesting (both from a scientific and a practical point of view) to analyze body composition in individuals over 90 years old.

The **objective of this study** was to assess body composition in patients over 90 years old (long-livers) with IHD and analyze possible relationships between the amount of fat mass and lean tissue and bone mineral density.

Materials and Methods

This was a one-stage (cross-sectional) study performed on the clinical base of the State Budgetary Healthcare Institution "Hospital for War Veterans (HWV) No. 3" (Moscow). Two hundred patients over 90 years old were involved in this study (140 women and 60 men, mean age 92.4 ± 2.3 years); they were hospitalized for a diagnosis of "ischemic heart disease" (IHD). This study included patients with confirmed IHD. Diagnosis of IHD was carried out in accordance with the European Society of Cardiology Guidelines for the diagnosis and management of chronic coronary syndromes (2019) [7].

Exclusion criteria: any diseases that can definitely cause changes in body composition (active malignant neoplasms, chronic obstructive pulmonary diseases, malabsorption syndrome, rheumatoid arthritis and other chronic inflammatory diseases, chronic kidney disease stage IV–V).

Standard methods of examination of patients with IHD were used to assess the condition of the patients. Also, the body weight and height of patients were determined and body mass index (BMI) was calculated. Normal parameters included body weight with BMI from 18.5 to 24.9; body weight with BMI from 25 to 29.9 was considered as overweight; obesity was diagnosed with BMI of more than 30 kg/m^2 [8].

Body composition was analyzed with dual-energy X-ray absorptiometry using the Lunar Prodigy Advance device (General Electric, USA). Analysis of body composition included the assessment of fat mass (in grams and as a percentage), lean tissue mass (in grams), bone mineral component (in grams), and total body weight (in kilograms). This analysis was performed in the left upper limb, left lower limb, left half of the trunk and in total in the left half of the body, right upper limb, right lower limb, right half of the trunk, and in total, in the right half of the body, in both upper limbs, both lower limbs, trunk, and in total, the whole body. Based on the results of body composition analysis, we further calculated the so-called appendicular skeletal muscle mass (ASMM) and musculoskeletal index. Appendicular skeletal muscle mass is the sum of lean tissue in the two upper and two lower limbs, and musculoskeletal index is the ratio of ASMM to body height squared. Sarcopenia was diagnosed in participants with musculoskeletal index less than 6.0 kg/m^2 in women and less than 7.0 kg/m^2 in men [9].

Senile asthenia syndrome was diagnosed according to Senile Asthenia Clinical Guidelines [10]. Screening diagnosis of senile asthenia syndrome was carried out using the "Age is no disqualification" questionnaire [10].

This study was conducted in accordance with international and Russian ethical standards, as well as the provisions of the Helsinki Declaration. All study participants signed an informed consent form. As part of a large research project, this study was approved on 14 JUN 2017 by the Independent Ethical Committee of Sechenov First Moscow State Medical University of the Ministry of Health of Russia (Resolution No. 05-2017).

The results obtained were analyzed using Statistica software (version 13.0, StatSoft Inc., USA). The sample was checked for normal distribution using Kolmogorov — Smirnov and Shapiro — Wilk tests. Descriptive statistics methods (mean values, standard deviation, minimum, maximum for quantitative variables; number and proportion for qualitative variables) were used to describe the obtained information. When the distribution of variational series did not meet the "normality" criteria, nonparametric statistics were used; the median (Me), quartiles (Q1–Q4) and interquartile range (from 25% to 75%) were determined. Groups were compared using parametric and nonparametric methods (Mann — Whitney or Kruskal — Wallis test, chi-square test or Fisher's exact test); correlation analysis was conducted using Spearman's rank correlation coefficient.

Results

In the group of patients, multiple comorbidity was registered in addition to IHD, which was quite typical for individuals of this age (in particular, arterial hypertension, atrial fibrillation, etc.) (Table 1).

In the group of long-livers, overweight or obesity was diagnosed in 139 (69.5%) individuals. Obesity was observed in 58 (29.0%) participants; most of them (45; 77.6%) had class 1 obesity, while class 2 obesity was registered only in 13 (22.4%) patients. Only one patient (0.49%) was diagnosed with body mass deficiency. Mean body mass index was 27.6 ± 4.5 kg/m^2 (with fluctuations from 18.2 to 38.8 kg/m^2) (Table 2).

Women demonstrated a higher proportion of adipose tissue in all parts of the body compared to men. The most obvious differences between women and men were related to adipose tissue of upper and lower limbs (Table 3).

Table 1. *Comorbid pathology in patients included in the study*

Diseases	Number of patients	
	n	%
History of myocardial infarction	48	23,8
Chronic heart failure	41	20,3
Atrial fibrillation	67	33,7
History of acute cerebrovascular accident	30	14,9
Arterial hypertension	200	100
Diabetes mellitus / impaired glucose tolerance	31	15,3

Table 2. *General characteristics of patients*

Parameters	Men n=60 (M±SD)	Women n=140 (M±SD)	p
Age, years	92,6±2,8	92,3±2,1	0,5
Body mass index, kg/m^2	27,3±3,8	27,6±4,8	0,6
Weight, kg	73,0±10,6	64,0±11,8	**0,000001**
Height, cm	165,3±14,6	152,1±6,8	**<0,000001**
Bone mineral density (total), mg/cm^3	1130,6±136,2	957,6±107,6	**<0,000001**
T-score, SD	-0,8 (-2,2; 0,5) *	-2,4 (-3,1; -1,3) *	**0,000004**
Z- score, SD	0,65 (-0,9; 1,9) *	-0,2 (-1,1; 0,65) *	**0,008**
Fat mass (total):			
g	21493±7690	23725±8451	0,08
%	29,9±8,0	37,1±8,3	**<0,000001**
Lean mass (total), g	48845±6326	38454±4653	**<0,000001**
Frail, %	44,4	74	**<0,000001**
Pre-frail, %	44,4	25,2	**0,0002**
Robust, %	11,1	0,8	**0,0003**

Note: * Me — median, Q25 and Q75 — 25% and 75% quartiles, respectively

Table 3. *The amount of fat mass in different body parts in men and women*

Parameters	Women n=140 (M±SD)	Men n=60 (M±SD)	p
Total fat mass, g	21493±7690	23725±8451	0,08
Total fat mass, %	37,1±8,3	29,9±8,0	**<0,0001**
Trunk fat mass, g	12949±5316	13561±5270	0,4
Trunk fat mass, %	37,5±9,5	33,6±9,1	**0,006**
Arms fat mass, g	2149±952	1577±751	**<0,0001**
Arms fat mass, %	35,5±8,9	23,3±8,3	**<0,0001**
Legs fat mass, g	7857±2748	5803±2021	**<0,0001**
Legs fat mass, %	39,4±8,1	27,3±7,3	**<0,0001**

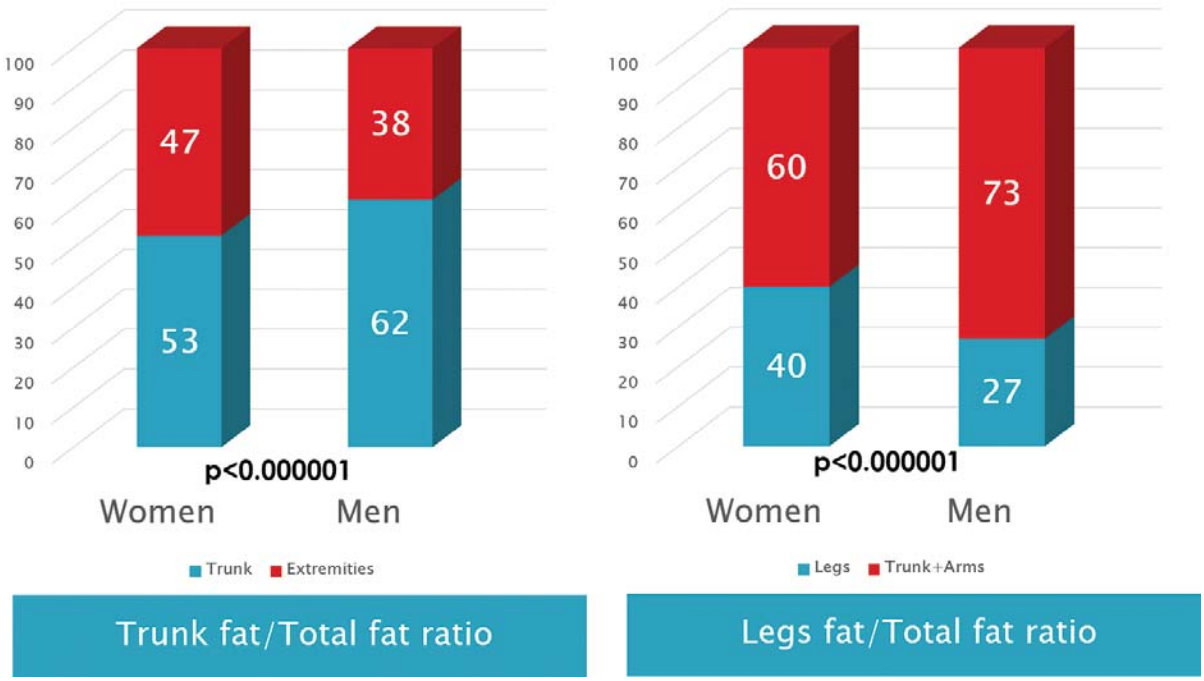

Figure 1. *Fat mass distribution in men and women*

Figure 1 shows the differences in the distribution of adipose tissue in men and women. The average ratio of fat mass in the trunk to the total fat mass was 0.53 ± 0.06 in women and 0.62 ± 0.05 in men (**p < 0.0001**). The average ratio of fat mass in lower limbs to the total fat mass reached 0.40 ± 0.77 in women and 0.27 ± 0.05 in men (**p < 0.0001**). The average ratio of fat mass in limbs to the fat mass in the trunk was 0.83 ± 0.23 in women and 0.56 ± 0.14 in men (**p < 0.0001**).

Average bone mineral density reached 1,008 ± 140 mg/cm^3, and T-test showed −1.7 SD. BMD reduced by no more than 1 SD is considered normal; BMD reduced by more than 1 SD but not reaching −2.5 SD corresponds to osteopenia; values below −2.5 SD reveal osteoporosis. The lowest BMD values were registered in ribs (626 ± 85 mg/cm^3), the highest — in the spine and lower limbs (Figure 2).

All bone mineral density parameters were significantly lower in women than in men; the greatest differences were observed in lower and upper limbs (Table 4).

The amount of lean tissue in women and men is presented in Table 5. The musculoskeletal index stayed within normal (more than 6.0 kg/m^2 in women and 7.0 kg/m^2 in men) in 145 (72.1%) patients. A decrease in this index was observed in 35 (25%) women and 20 (33%) men.

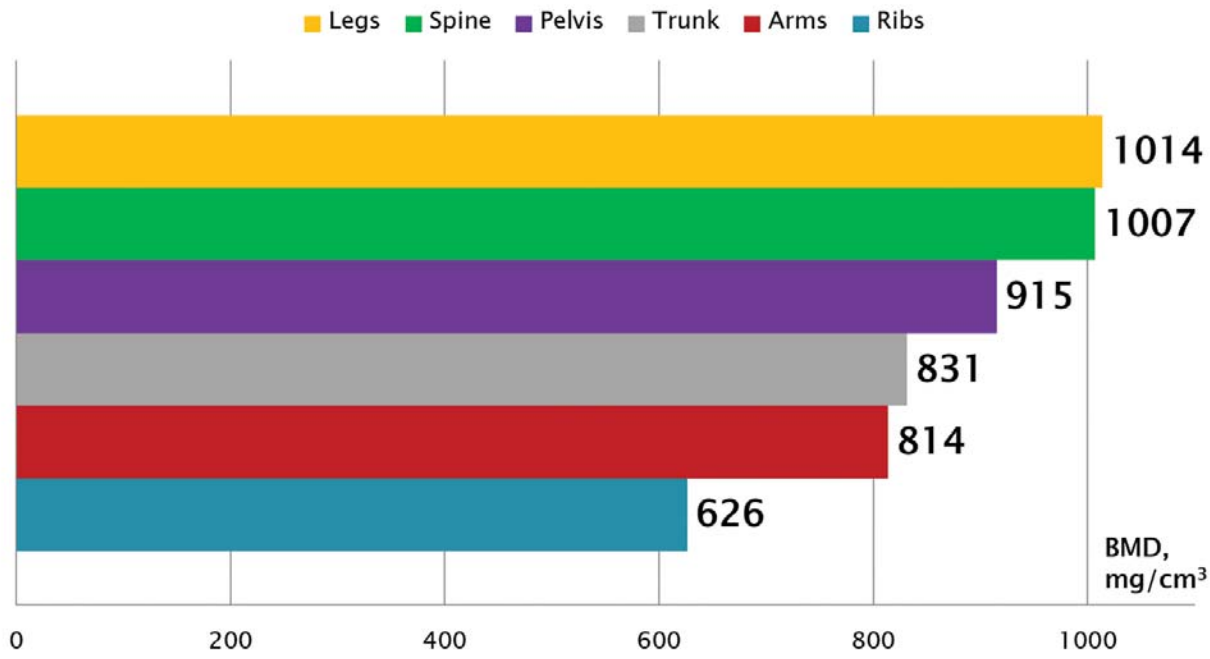

Figure 2. *Bone mineral density in different skeleton parts*

Table 4. *Bone mineral density in women and men*

Bone mineral density	Women n=140 (M±SD)	Men n=60 (M±SD)	p
Total BMD (mg/cm³)	**957**±107	**1130**±136	**<0,0001**
Arms BMD (mg/cm³)	**730** (673; 791) *	**981** (896; 1090) *	**<0,0001**
Legs BMD (mg/cm³)	**929**±147	**1212**±176	**<0,0001**
Trunk BMD (mg/cm³)	**803**±95	**897**±123	**<0,0001**
Ribs BMD (mg/cm³)	**603**±75	**682**±83	**<0,0001**
Pelvis BMD (mg/cm³)	**879**±133	**1000**±149	**<0,0001**
Spine BMD (mg/cm³)	**962**±163	**1114**±214	**<0,0001**

Note: * Me — median, Q25 and Q75 — 25% and 75% quartiles, respectively

Table 5. *Lean mass in women and men*

Parameters	Women n=140 (M±SD)	Men n=60 (M±SD)	p
Total lean mass, g	38453±4653	48845±6326	<0,0001
Trunk lean mass, g	20302±2729	25592±3379	<0,0001
Legs lean mass, g	11634±1780	14785±2588	<0,0001
Arms lean mass, g	3668±630	4965±697	<0,0001
Skeletal-muscle index, kg/m²	6,6±0,8	7,3±0,9	<0,0001

Correlation analysis revealed a significant direct correlation between the body mass index of patients and their fat mass (Fig. 3).

There was also a significant direct correlation between BMI and bone mineral density in all parts of the skeleton ($p < 0.0001$ for all areas); the strongest correlation was observed for the bones of the trunk ($r = 0.5$; $p < 0.0001$) and ribs ($r = 0.5$; $p < 0.0001$).

A highly reliable direct correlation was found between the fat mass in all parts of the body (both in grams and percentage) and BMD (both in total and in each separate part of the skeleton); the most reliable values were established for the correlation between BMD of ribs and fat mass of the trunk ($r = 0.85$; $p < 0.0001$) (Table 6).

There was a significant direct correlation between the mass of lean tissue and BMD (both in total and in

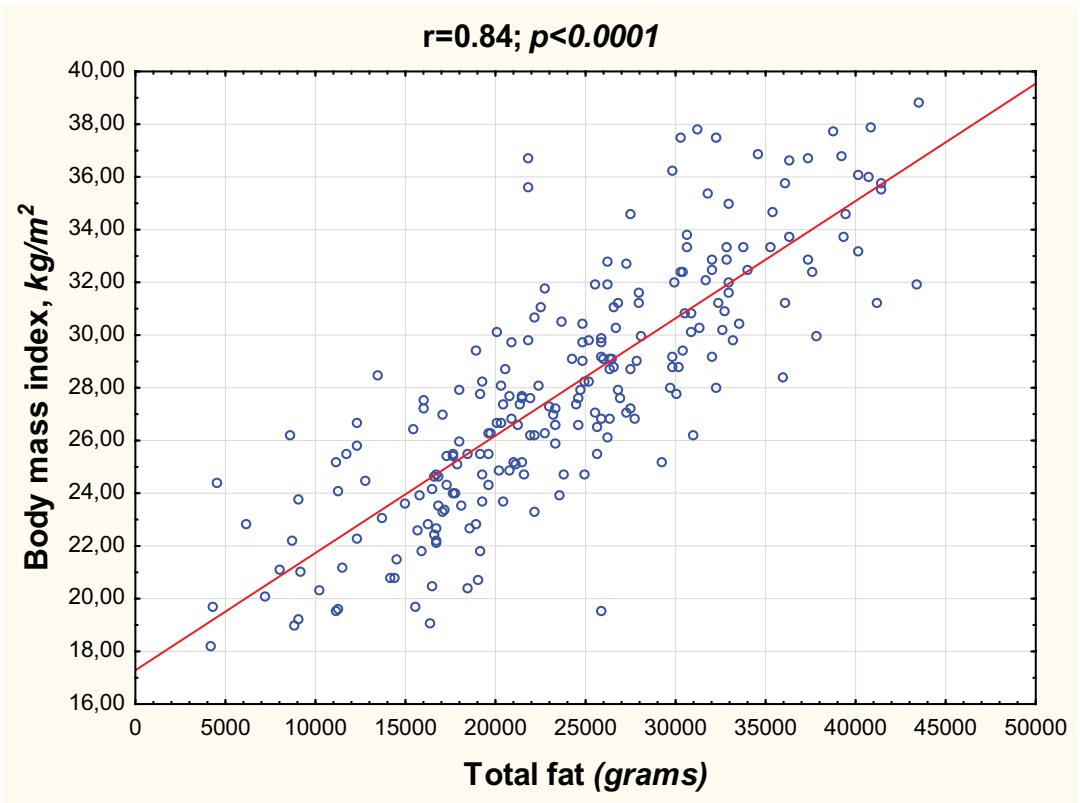

Figure 3. *Correlations between body mass index and fat mass*

Table 6. *Correlations between bone mineral density and trunk fat mass*

Bone mineral density	Trunk fat mass (g) r; p	Trunk fat mass (%) r; p
Total BMD (mg/cm³)	0,43; <0,000001	0,25; 0,0004
Total BMD (T-score)	0,46; <0,000001	0,33; 0,000003
Total BMD (Z-score)	0,2; 0,007	0,13; 0,06
Arms BMD (mg/cm³)	0,33; 0,000003	0,1; 0,08
Legs BMD (mg/cm³)	0,37; <0,000001	0,18; 0,01
Trunk BMD (mg/cm³)	0,59; <0,000001	0,4; <0,000001
Ribs BMD (mg/cm³)	0,85; <0,000001	0,4; <0,000001
Pelvis BMD (mg/cm³)	0,56; <0,000001	0,38; <0,000001
Spine BMD (mg/cm³)	0,51; <0,000001	0,36; <0,000001

Table 7. Correlations between bone mineral density and lean mass

Bone mineral density	Total lean mass r; p	Trunk lean mass r; p	Arms lean mass r; p	Legs lean mass r; p
Total BMD (mg/cm³)	0,57;<0,000001	0,52;<0,000001	0,64;<0,000001	0,49;<0,000001
Total BMD (T-score)	0,45;<0,000001	0,4;<0,000001	0,51;<0,000001	0,37;<0,000001
Total BMD (Z-score)	0,2; 0,003	-0,17; 0,01	0,31; 0,00001	0,15; 0,04
Arms BMD (mg/cm³)	0,6; <0,000001	0,57; <0,000001	0,69;<0,000001	0,56;<0,000001
Legs BMD (mg/cm³)	0,6; <0,000001	0,54; <0,000001	0,66;<0,000001	0,51;<0,000001
Trunk BMD (mg/cm³)	0,56;<0,000001	0,51; <0,000001	0,56;<0,000001	0,48;<0,000001
Ribs BMD (mg/cm³)	0,55;<0,000001	0,52; <0,000001	0,53;<0,000001	0,49;<0,000001
Pelvis BMD (mg/cm³)	0,55;<0,000001	0,52; <0,000001	0,54;<0,000001	0,43;<0,000001
Spine BMD (mg/cm³)	0,52;<0,000001	0,47; <0,000001	0,54;<0,000001	0,45;<0,000001

all parts of the body); the most reliable relationship was between BMD of upper limbs and lean tissue mass in upper limbs ($r = 0.69$; $p < 0.0001$) (Table 7).

An inverse correlation was observed between fat mass and lean tissue; the most significant one was for lower limbs ($r = -0.46$; $p < 0.0001$).

In the studied group of long-livers, sarcopenic obesity was found in 3 (1.5%) patients, along with absolutely normal bone mineral density, and in 10 (5%) patients — along with osteopenia. Osteosarcopenic obesity (a combination of osteoporosis, sarcopenia and obesity in one patient) was found in 4 (2%) patients, and a combination of osteoporosis with obesity was found in 17 (8.7%) patients. Normal BMD values combined with the absence of sarcopenia and obesity were registered in 33 (16.5%) patients, and isolated osteoporosis (with normal fat and muscle tissue) — in 41 (20.5%) patients.

Discussion

According to the available medical literature, our study is one of a few studies concerning body composition in long-livers [5, 6, 11]. Most other publications presented the results of studies of body composition in the elderly population and their comparison with younger individuals. It should be noted that we found no results of studying the body composition of long-livers using dual-energy X-ray absorptiometry in the available literature sources; a few studies of long-livers used a less sensitive technique of bioelectrical impedance analysis [5, 6, 11].

The results revealed a large number of overweight and obese 90-year-old patients (70%). As is known, fat mass increases with age; this fact is also obvious in the results of our work [2]. It should be emphasized that class 1 obesity was the most common, while there were no cases of class 3 obesity. Most of the examined patients had body mass index in the optimal range since, in senile age, the lowest mortality is observed in individuals with body mass index corresponding to overweight or class 1 obesity [12]. Adipose tissue is believed to have a protective effect in senile individuals, and the so-called "obesity paradox" means that the prognosis in overweight elderly patients is better than in individuals with normal or low body weight [13, 14]. Information obtained during this study supports this "obesity paradox," at least, in relation to long-livers.

In the studied group of patients, the ratio of fat mass in the trunk to the total fat mass was 0.53 in women and 0.62 in men. In other words, half of fat mass in women and more than half in men was distributed in the trunk (mainly in the abdominal area). These results confirm the well-known types of distribution of adipose tissue in men (more in the upper part, "apple-shaped") and in women (more in lower limbs, «pear-shaped»), although with aging, adipose tissue in women accumulates in the abdominal area too [15].

However, female long-livers demonstrated a higher proportion of adipose tissue; the most significant differences between women and men were in the adipose tissue of limbs. It is known that there are significant differences in women and men in the incidence of obesity, distribution of fat mass and fat metabolism [15]. Women generally have a higher proportion of adipose tissue than men, and they have more subcutaneous fat and fat in lower limbs; men are more prone to visceral fat deposition [15]. Sex hormones have a significant effect on adipose tissue. However, the level of estrogens in postmenopausal women decreases, leading to the excessive

accumulation of visceral fat in women. Postmenopausal women have a higher fat mass and its percentage than pre- and perimenopausal women. The more time passes after the start of menopause, the higher the increase in body weight, body mass index and the proportion of adipose tissue [15]. Menopause in all women in our study began at least 40 years ago.

The somewhat unexpected results of this study include a significant proportion of patients with normal bone mineral density, although a steady decrease in bone density with aging is usually observed [16]. For the clinical interpretation of these results, the following concept can be proposed: individuals with higher bone mass density are characterized by maximum life expectancy and, therefore, lower risk of fractures, while patients with severe osteoporosis die at an earlier age, primarily after femoral neck fractures. Other studies and our paper demonstrated that a decrease in bone mineral density was significantly more often observed in women [15]. It should be noted that gender differences in regard to osteoporosis persisted in patients over 95 years old. Despite their senile age, 5 out of 11 (45.5%) men over 95 had normal BMD values; this parameter in women amounted to 18.2%, which once again confirmed a greater predisposition to osteoporosis in women, even among super-long-livers.

Another unforeseen result of our study that allowed us to take a fresh look at the health status of long-livers is the relative preservation of muscle mass in the patients we observed. The musculoskeletal index stayed normal in almost three-quarters of patients, while a decrease in this index was found in 20 (33%) men and 35 (25%) women.

However, it should be noted that the total amount of lean tissue in the examined men was more than 10 kg higher than that in women (48 and 38 kg, respectively). As is known, muscle mass in men is initially higher due to the anabolic effect of testosterone, and its reduction with aging, in contrast to women, is less noticeable and more gradual [15].

In long-livers, significant relationships between bone, adipose, and lean tissues were established. There was a direct correlation between body mass index, fat mass in all parts of the body and BMD; the most reliable values were found for the correlation between BMD of ribs and fat mass in the trunk. Similar results were obtained in other studies that demonstrated a direct relationship between adipose tissue and BMD [4]. A meta-analysis with more than 20 thousand people enrolled in 44 studies revealed the most significant relationship between bone and adipose tissue in postmenopausal women of the Caucasian race (most of the patients in our study were of this type) [4].

It should be noted that all the effects of adipose tissue on the state of BMD are not fully understood; they can vary (from positive to negative) depending on fat mass and distribution — subcutaneous or visceral [2, 17]. According to some authors, an increase in body fat over 35–40% can have an adverse effect on BMD, while its smaller amount has a positive effect [18]. According to our data, no decrease in BMD, along with an increase in body fat to 40% or more, was detected, with the exception of BMD of upper limbs with an average value of 777.8 mg/cm^3 in obese individuals and 828.9 mg/cm^3 in patients with body fat less than 40% ($p = 0.03$).

In our study, as expected, a definite positive correlation was revealed between lean tissue mass and bone mineral density. This relationship between lean tissue in upper and lower limbs and BMD in the corresponding areas was more significant than the effect of fat on BMD in limbs. Similar results were obtained in other studies [4, 11]. According to a large meta-analysis by Ho-Pham L.T. et al. (2014), the effect of lean tissue on BMD is significantly greater than that of fat, especially in men as well as in pre-menopausal women [4].

This study established the expected inverse correlation between fat mass and lean tissue. With aging, fat mass increases and muscle tissue decreases, which is called sarcopenic obesity [2, 17]. However, it is not clear whether adipose tissue replaces the empty space remaining after the death of muscle fibers, or whether the number and size of muscle cells decrease due to fatty infiltration of muscle fibers [17]. Our data support the concept of substitution; it is no coincidence that the most significant negative correlation was found between the relative amount of adipose and lean tissue in lower limbs; body fat (in grams) and total fat mass (in grams), on the contrary, positively correlated with lean tissue amount. Other studies also describe the inverse relationship between fatty tissue and muscle mass; it is significant that the decrease in muscle mass was not accompanied by a corresponding change in body mass index since fat seemed to replace lost muscle tissue [19].

A typical decrease in muscle mass and bone density, along with an increase in fat mass with aging, is more often referred to as “osteosarcopenic obesity” [2, 17]. It should be noted that osteosarcopenic obesity was

found only in 4 (2%) patients enrolled in this study, and sarcopenic obesity was found in 10 (5%) participants. At the same time, 33 (16.5%) patients had normal BMD and muscle tissue with no obesity. The following could offer a possible explanation for this low incidence of osteosarcopenic obesity: our group of patients included a sufficient number (one-third) of men, and, as is known, men are less subject to a decrease in bone mineral density. Only a quarter of men had osteoporosis, and only one (1.7%) of them had both sarcopenia and obesity.

Conclusion

- The results can help to describe the body composition in long-living persons.
- A relatively high proportion of overweight patients, but with normal BMD and lean tissue mass, was found.
- Significant correlations between bone, adipose and lean tissues were confirmed.

Вклад авторов:

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

Тополянская С.В. (ORCID: http://orcid.org/0000-0002-4131-8432): концепция и дизайн исследования, сбор, анализ и интерпретация данных, написание рукописи

Елисеева Т.А., Балясникова Н.А., Вакуленко О.Н.: сбор и анализ данных

Дворецкий Л.И. (ORCID: http://orcid.org/0000-0003-3186-0102): концепция исследования

Contribution of authors

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

Topolyanskaya S.V. (ORCID: http://orcid.org/0000-0002-4131-8432): concept and design of the study, collection, analysis and interpretation of study, writing the manuscript

Eliseeva T.A., Balyasnikova N.A., Vakulenko O.N.: collection and analysis of data

Dvoretski L.I. (ORCID: http://orcid.org/0000-0003-3186-0102): study concept

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DOI: 10.20514/2226-6704-2021-11-1-22-33

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

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

РЕСПИРАТОРНАЯ РЕАБИЛИТАЦИЯ ПОСТ-COVID-19 ПАЦИЕНТОВ.

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

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

Respiratory Rehabilitation for Post-Covid-19 Patients

Резюме

В представленном клиническом обзоре нами оценены возможности лекарственных и немедикаментозных стратегий устранения и предотвращения патофизиологических изменений респираторной системы пост-COVID-19 пациентов. Предлагаются актуальные реабилитационные алгоритмы, основанные на оценке тяжести клинических проявлений новой коронавирусной инфекции (COVID-19), возможностях реабилитационных методик и персональной приверженности пациента к их выполнению.

Ключевые слова: *дыхательная гимнастика, экспираторные дыхательные тренажёры, мотивирующие вдох спирометры, интрапульмональная перкуссионная вентиляция лёгких, откашливатели, CPAP-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 06.11.2020 г.

Принята к публикации 23.12.2020 г.

Для цитирования: Малявин А.Г., Бабак С.Л., Горбунова М.В. РЕСПИРАТОРНАЯ РЕАБИЛИТАЦИЯ ПОСТ-COVID-19 ПАЦИЕНТОВ. Архивъ внутренней медицины. 2021; 1(1): 22-33. DOI: 10.20514/2226-6704-2021-11-1-22-33

Abstract

In the presented clinical review, we evaluated the possibilities of drug and non-drug strategies for eliminating and preventing pathophysiological changes in the respiratory system of post-COVID-19 patients. We offer up-to-date rehabilitation algorithms based on the assessment of the severity of clinical manifestations of COVID-19, the possibilities of rehabilitation techniques and the patient's personal compliance with their implementation.

Key words: *breathing exercises, expiratory breathing simulators, incentive spirometer, intrapulmonary percussion ventilation, coughing devices, CPAP, LTOT, oPEP*

Conflict of interest

The authors declare that this work, its subject, subject and content do not affect competing interests. Source of financing

Sources of funding

The authors claim that there is no funding for the study

Article received 06.11.2020.

Accepted for publication 23.12.2020

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

For citation: Malyavin A. G., Babak S. L., Gorbunova M. V. Respiratory rehabilitation for post-COVID-19 patients. The Russian Archives of Internal Medicine. 2021; 11(1): 22-33. DOI: 10.20514/2226-6704-2021-11-1-22-33

ACBTh — active cycle of breathing technique with huffing, BiPAP — bi-level positive airway pressure ventilation, CPAP — continuous positive airway pressure ventilation, FiO2 — fraction of inspired oxygen, IPV — intrapulmonary percussive ventilation, InS — incentive spirometer, LAAC — long-acting anticholinergics, LABA — long-acting b2-agonists, LTOT — long-term oxygen therapy, MI-E — mechanical insufflation/exsufflation devices, oPEP — oscillatory positive expiratory pressure breathing simulator, PAH — pulmonary arterial hypertension, PEEP — techniques with positive end-expiratory pressure, PR — pulmonary rehabilitation, RF — respiratory failure, RR — respiratory rate, SpO2 — arterial oxygen saturation

Introduction

The rehabilitation of post-COVID-19 patients should be comprehensive and take into consideration the following [1]:

- pathological changes in organs and systems, whose severity is determined by disease severity and the extent of tissue damage;
- iatrogenic lesions associated with side effects of medications (for example, cardiotoxicity, hepatotoxicity) and medical procedures (for example, tracheostomy, intubation);
- concomitant diseases (comorbidities);
- psychological constitution of the patient.

Therefore, it is almost impossible to develop a universal rehabilitation regimen. A patient-specific syndromic and pathogenetic approach that provides the maximum effectiveness of each rehabilitation technique depending on pathological changes present in the patient is preferable [2]. Obviously, pulmonary rehabilitation (PR) methods should be modified for such patients. Pulmonary rehabilitation should be understood as a complex intervention based on a thorough assessment of the patient's condition, followed by selecting personalized treatment that allows the patient [3]:

- to keep fit (physiotherapy);
- to change lifestyle and behavior through learning in order to improve physical and psychological state;
- to maintain commitment to healthy behavior.

There are two main types of PR: 1) pulmonary/drainage methods (PDM); 2) respiratory/ventilation methods (RVM). The former — PDM — are aimed at restoring mucociliary clearance and are based on: extrapulmonary vibration exposure and postural drainage; intrapulmonary percussion; optimizing coughing (huffing) and breathing practices; vacuum massage and bronchoalveolar lavage. The latter — RVM — are aimed at strengthening respiratory muscles and normalizing gas exchange and are based on: respiratory muscle training; optimization of phases of the breathing cycle; improvement of mechanical properties of lungs, normalization of standard lung volumes [4].

The development of rehabilitation programs should be based on the indications/contraindications of specific techniques, their possible interaction and avoiding excessive drug treatment. The main pathological changes (general and respiratory) in patients after COVID-19 are listed below, in relation to possible rehabilitation techniques (Table 1).

In most cases, COVID-19 patients have multiple lesions, which is why they need additional laboratory and diagnostic tests at the rehabilitation stage, in addition to medical history and clinical examination [5].

1. PULMONARY/DRAINAGE REHABILITATION METHODS

The choice of rehabilitation methods should be based on present indications/contraindications; comorbidities; clinical evaluation of the positive/negative effects of techniques. More detailed mechanisms of action, indications and contraindications are presented in the clinical recommendations for the medical rehabilitation of COVID-19 patients [6].

1.1. Physical activity

Objective: stimulation of blood/lymph circulation in muscles. *Action:* long aerobic exercises with light loads and low respiratory rate (RR) (not higher than 100/min). *Preferred types of activity*: Nordic walking, rowing machine, breaststroke swimming.

1.2. Chest massage

Objective: stimulation of blood/lymph circulation in muscles. *Action:* massage of the neck and collar zone and chest. *Preferred types of activity*: compression and vibration massage in combination with postural drainage.

1.3. Exercises with positive end-expiratory pressure

Objective: increasing the uniformity of lung ventilation. *Mechanism of action:* positive air pressure and high airflow velocity during forced expiratory maneuvers in cases of airway instability are accompanied by dynamic compression of airways (expiratory collapse, EC), which causes partial emptying of alveoli and mucus retention in small bronchi. To prevent EC, if there are no expiratory simulators, the simplest respiratory techniques can be used to create positive end-expiratory pressure (PEEP). For this purpose, inflatable low-resistance elastic items (condoms, medical gloves, balloons) are often used. It should be noted that the patient should perform the exhalation maneuver without significant

Table 1. *Pathological changes and possible rehabilitation methods*

Parameter	Rehabilitation techniques
General pathological changes	
Asthenic syndrome	Halotherapy, psychotherapy, therapeutic nutrition, vitamins, magnesium preparations, thyroxine replacement therapy
Muscle weakness	Massage, light physical training, thyroxine replacement therapy
Subfebrile condition	Paracetamol, low doses of steroid hormones while maintaining radiological manifestations of interstitial lung damage, antibiotics for confirmed bacterial infection
Depression	Halotherapy, psychotherapy, antidepressants
Obstructive sleep apnea	CPAP therapy
Sleep disorder	CPAP therapy, sedatives, sleeping pills
Respiratory disorders	
Hypoxemia	LTOT, InS, oPEP, IPV, CPAP therapy
Hypoxemia with hypercapnia	BiPAP therapy
Pulmonary hypertension (PH)	Drug therapy according to indications, mild to moderate PH: LTOT, oPEP, IPV
Bronchoobstructive syndrome	Inhaled bronchodilators (LABA/LAMA), halotherapy, IPV, CAD
Difficulty in expectoration	Mucolytics, halotherapy, IPV, CAD, postural drainage, chest vibration massage, ACB-H
Shortness of breath not associated with bronchial obstruction *(exclude manifestations of heart failure)*	Breathing exercises of full breath (pranayama), InS, breathing exercises with PEEP, oPEP, IPV, halotherapy, psychotherapy
Irregular ventilation and ventilation-perfusion disorders	Complete breathing exercises (pranayama), ACB-H, InS, breathing exercises with PEEP, oPEP, IPV

Note: CPAP — continuous positive airway pressure; LTOT — long-term oxygen therapy; InS– incentive spirometer; oPEP — oscillating positive expiratory pressure device; IPV — intrapulmonary percussive ventilation; BiPAP — bilevel positive airway pressure; LABA — long-acting b2 agonists; LAMA — long-acting M-anticholinergic agent; CAD — cough assist devices (insufflation/exsufflation); ACB-H — active cyclic breathing with huffing (rapid exhalation maneuver with clearing of throat); PEEP — positive end expiratory pressure

engagement of accessory respiratory muscles due to the risk of pulmonary barotrauma. In addition, uncontrolled resistance and its significant variation during the exhalation process are considered shortcomings of this technique. The effectiveness of such breathing exercises remains doubtful [7].

1.4. Respiratory gymnastics and postural drainage

Objective: stimulation of mucociliary and cough clearance in cases of a large amount of hard-to-remove sputum. *Mechanism of action:* these procedures are required in patients with destructive processes in lungs or with traction bronchiectasis with severe pneumosclerosis. A set of respiratory exercises is determined by the localization of the purulent production process. When performing drainage exercises, the pulmonary zone with a lesion should be located above the tracheal bifurcation, allowing to create a fluid outflow from the affected bronchi/cavities (postural drainage). Preliminary applications of warming materials (therapeutic mud, paraffin, ozokerite) and exposure of lungs to decimetric electromagnetic waves that dilute sputum and stimulate peripheral hemodynamics can increase the effectiveness of postural drainage [8].

1.5. Sound respiratory gymnastics

Objective: respiratory muscle training, increasing the uniformity of lung ventilation. *Mechanism of action:* exercises with the pronunciation of certain sounds and/or their combinations in a strictly defined manner transmits the vibration of vocal cords to the smooth muscles of bronchi/lungs and chest, causing the relaxation of spasmodic muscles. Airflow strength when pronouncing certain sounds depends on the frequency of vibration. This technique can be used to train respiratory muscles, and therefore, the diaphragm (the largest respiratory muscle) [8].

1.6. Breathing gymnastics (pranayama)

Objective: increasing the uniformity of lung ventilation, developing the correct breathing pattern. *Mechanism of action:* taking a "full breath" combined with the development of the correct breathing pattern (category of yoga breathing exercise "pranayama"). This exercise is based on consistent and maximum ventilation of different lung sections with the possible normalization of the ventilation/perfusion ratio. *Preferred type of exercise* [8, 9]:

1. Starting position — sitting on a chair with back straight and resting on the chair back, hands on knees, head not bowed ("proud posture").
2. Before starting this exercise, relax the chest by lifting shoulders and then lowering them relaxed backward.
3. Breathing in through the nose with a slightly strained nasopharynx (breathing in as if sniffing).
4. During the first phase of inspiration, the lower parts of lungs are ventilated. To this end, the anterior abdominal wall moves forward when the diaphragm is contracted and lowered.

5. Then the upper parts of the lungs are ventilated smoothly and without delay. To this end, the chest expands due to the work of the intercostal muscles in the second phase of inspiration. Maximum inspiration, if possible, should be carried out without noticeable efforts of accessory respiratory muscles.
6. Exhalation should be not forced but passive, using the weight of the chest, through pursed or puckered lips ("punctured tire" effect).
7. Make 20–30 breaths three times a day.

1.7. Forced expiration technique with huffing

Objective: increasing the uniformity of lung ventilation, stimulation of cough clearance with hard-to-remove sputum, re-expansion of atelectasis. *Preferred type of exercise* [10]:

1. After 3–5 slow deep breathing movements, take a deep breath through the nose. Using diaphragmatic breathing, breathe out through closed lips (single maneuver).
2. Take a deep breath and hold the breath for 1–3 seconds; expire a medium/low lung volume (to remove secretion from the peripheral part of the bronchial tree).
3. Take a normal breath; then, during exhalation, squeeze the air out of the lungs using abdominal and chest muscles, with an opened glottis, pronouncing "ha-af-fa" sound (sounds like a forced breath). Repeat several times (3–4 times).
4. When feeling that there is secretion in the upper respiratory tract, expire a large/medium lung volume (to remove sputum from proximal bronchi). Repeat this maneuver 2–3 times.
5. Perform several relaxation diaphragmatic maneuvers before the next cough effort.

1.8. Active cycle of breathing technique (ACBT)

Objective: increasing the uniformity of lung ventilation, stimulation of cough clearance with hard-to-remove sputum, re-expansion of atelectasis. *Mechanism of action*: based on the combination of three breathing techniques: breathing control, chest expansion control, forced expiratory method with huffing (Fig. 1) [10, 11].

Breathing Control (BC) is the technique of the diaphragmatic control of calm inspiration/expiration to relax the respiratory tract and muscles. When performing BC, the patient controls the upper part of the chest, breathes with his/her usual tidal volume (TV) with the usual respiratory rate (RR). This technique is considered effective with the subjective sensation of the so-called "distention" around the waist during inspiration associated with a falling diaphragm; this sensation disappears when expiring. BC is essentially the connective basis between active cycles of breathing techniques (ACBT).

Chest expansion control (CEC) is the technique of slow deep/full inspiration with brief breath-holding (1–2 seconds) and subsequent resting expiration. CEC allows air to spread to the most distal parts of the patient's bronchial tree. In addition, CEC increases airflow in the peripheral respiratory tract (RT), which significantly increases air volume for mobilizing tracheobronchial secretion. Performing 3–4 cycles of CEC is considered sufficient — it prevents muscle fatigue and hyperventilation.

Forced expiratory technique with huffing (FET-H) is a technique of two consecutive forced expirations with an opened glottis and mouth and with an "HA-A-A-A-FA" sound (hence the name "huffing"). FET-H can cause expectoration (coughing up); therefore, this technique usually completes the cycle of breathing techniques (Fig. 1).

Patients with hypersecretion or production of a large volume of sputum with no bronchial hyperreactivity, atelectasis, significant mucoid impactions/occlusions of small bronchi should perform a cycle of BC + CEC + BC + 2-FET-H, repeat 4–6 times in the course of ACBT. Patients with bronchospasm/airway obstruction are recommended to perform more BC repetitions (> 4/cycle), while patients with atelectasis or restrictive pathology (lung compression) require more CEC repetitions (> 6/cycle). An obvious measure of the effectiveness of ACBT is the improvement of lung auscultatory parameters. However, the advantages of this strategy (ACBT) in various groups of patients with respiratory pathology remain difficult to understand [11].

2. DRAINAGE REHABILITATION METHODS WITH SIMULATORS

In some cases, rehabilitation measures, especially those associated with the restoration of drainage function, are impossible without special medical devices — breathing simulators (BS) — that can significantly increase the effectiveness of the procedure and the patient's compliance with it. The most common BS can be divided into: 1) incentive (inspiration inducing) spirometers (InS); 2) positive end-expiratory pressure devices (PEEP/PEP); 3) oscillating positive expiratory pressure devices (oPEP) [13].

2.1. Hyperinflation (volume expanding) therapy with InS

Intermittent pressure hyperinflation (volume expanding) therapy (IPHT) is a variant of the physiotherapeutic effect on the lungs by inspiration of an excessive volume / with excessive pressure that re-expands atelectases and trains the patient's inspiratory muscles. In practice, IPHT is impossible without inspiratory air control devices referred to as "incentive spirometers" (InS). InS devices produce an effect on the distal parts

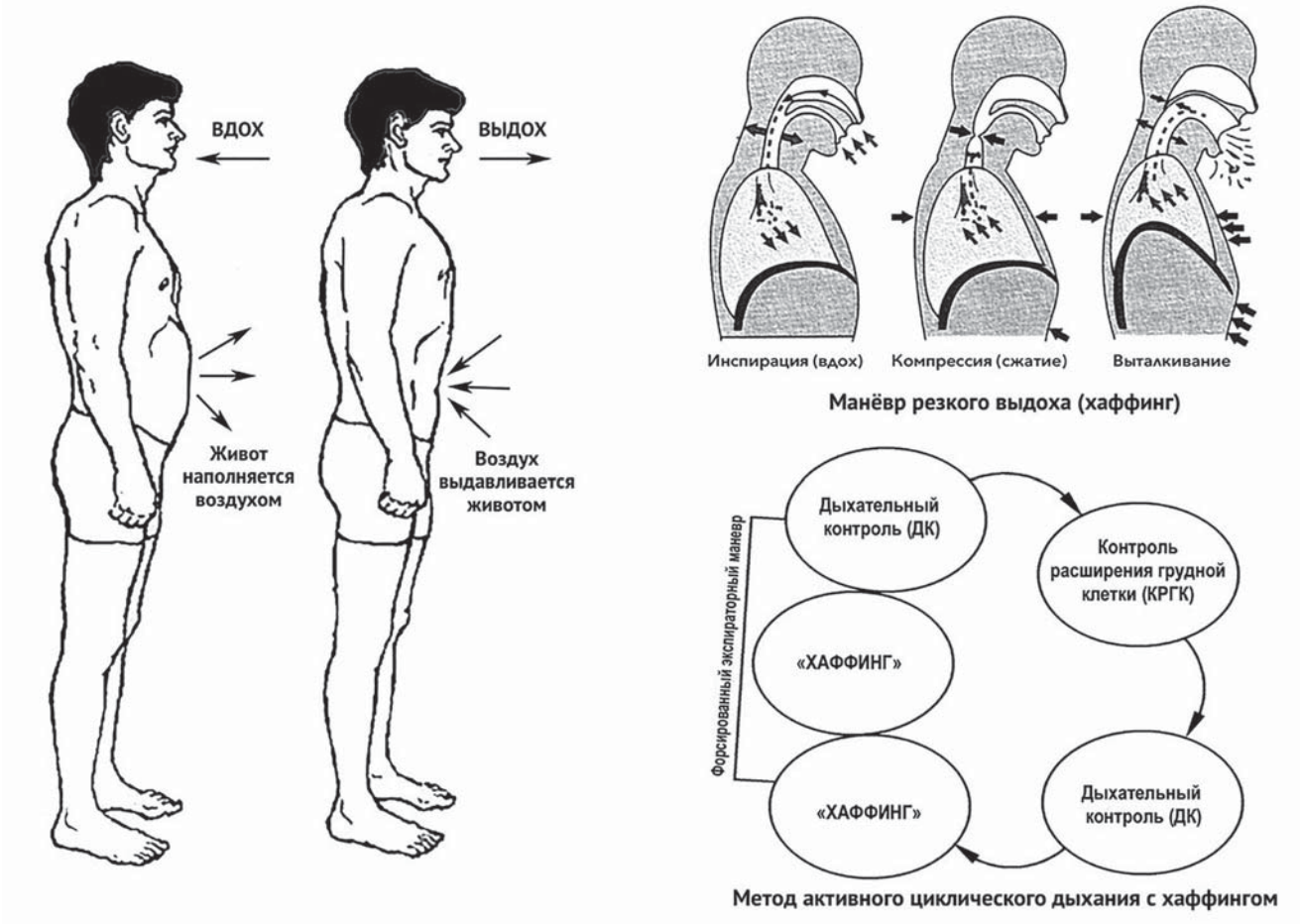

Figure 1. *Schematic representation of active cycle of breathing technique with huffing. The explanation in the text (adapted from: Fink JB. Respir Care. 2007; 52(9): 1210–21, [12])*

of the patient's lung apparatus and are divided into the following types: 1) with inhaled flow control (flow InS or FInS); 2) with inhaled volume control (volume InS or VInS) [14].

Treatment objective: respiratory muscle training, increasing the uniformity of lung ventilation, recruitment of poorly ventilated areas. *Mechanism of action*: based on a combination of re-expansion/opening of narrowed/obstructed airways, increased collateral ventilation, and "alveoli opening" time. IPHT therapy primarily allows to eliminate "air trapping", prevent/re-expand pulmonary atelectasis, and mobilize/expectorate accumulated tracheobronchial secretion. In other words, IPHT therapy is associated with a "load" that stimulates an increase in O_2 and CO_2 gas exchange, which increases "alveolar stratification" (diffusion changes in gas/blood phase) and perfusion (blood flow). In addition, increased collateral ventilation/blood flow will significantly reduce alveolar collapses and increase the duration of "alveoli opening". Such an effect is called a "recruitment maneuver" — a deliberate measure that increases dynamic transpulmonary pressure for the complete opening of unstable/airless (collapsed) alveoli [15].

2.2. Positive pressure therapy with PEEP/PEP simulators

Respiratory support with positive airway pressure should be performed in patients with instability/variability of the airway lumen. It is most often performed with the help of positive end-expiratory pressure (PEEP/PEP) devices. *Objective:* mobilization and evacuation of tracheobronchial secretion by increasing intrathoracic pressure of distal lungs; increasing collateral ventilation and training of respiratory muscles. *Mechanism of action*: based on physiological effects of elimination of alveolar collapse, longer "alveoli opening" time, increased collateral ventilation/blood flow. The following are the main indications for PEEP/PEP therapy [17]:

- recurrent sputum not responding to spontaneous cough;
- pulmonary diseases with hypersecretion/secretion accumulation, previously successfully treated by postural drainage technique (including chest procedures);
- air trapping and lung atelectasis that should be eliminated;

- optimization of aerosol distribution during bronchodilator therapy.

PEEP/PEP devices can be delivered as separate modules or as nebulizer valves. The latter allow to perform PEEP/PEP therapy simultaneously with drug delivery. In such cases, the PEEP/PEP valve generates high expiratory pressure of 20–90 mbar. Obviously, such pressure significantly limits/trains expiration; this determines a good combination of PEEP/PEP valves with small volume mesh nebulizers. If low pressure (10–20 mbar) is to be used in patients with impaired "respiratory drive" (respiratory failure with a normocapnic pattern), separate modules with a PEEP/PEP pressure gauge should be used, which can be connected with a face unit (mask or mouthpiece) [10].

2.3. Positive pressure therapy with oPEP simulators

Positive pressure respiratory support can be combined with oscillatory effects on the lung component. It is most often performed with the help of oscillatory positive expiratory pressure (oPEP) devices. *Objective:* mobilization and evacuation of tracheobronchial secretion by increasing intrathoracic pressure of distal lungs; increasing collateral ventilation and training of respiratory muscles, cough stimulation. *Mechanism of action*: based on physiological effects of expiration against positive pressure with rapidly changing/oscillating resistance; it allows to stabilize/open airways (expansion effect), eliminate air trappings (expansion effect), dilute and mobilize secretion (thixotropic effect), stimulate mucociliary clearance (resonant frequency effect with the ciliary epithelium at a frequency of 12–15 Hz). oPEP therapy is highly safe since small portions of air cannot dramatically increase pressure and cause barotrauma. In addition, the operating pressure of oPEP therapy is considered low, in the range of 15–20 mbar. The main indications for oPEP therapy are the same as those for PEEP/PEP therapy [18]. oPEP devices can be made as separate modules connected with the endotracheal or tracheostomy tube. *The following method is preferred* after basic treatment procedures (basic therapy) or additional bronchodilator therapy [10]:

1. The patient in the sitting position, with a straight back and head stretched up, performs the relaxed breathing control technique.
2. The patient makes full inspirations (2–3 times deeper than usual), with breath holding at maximum inspiration for 2–3 seconds; at least 3 repetitions should be done.
3. The patient breathes in and out with effort (expiration flow is 2–3 times more intense than usual) through the mouthpiece of the flutter (oPEP device), for more than 6 seconds, avoiding unproductive cough at the beginning of expiration; the oPEP device should be placed horizontally to achieve the most effective vibrations; 15–20 repetitions should be done.
4. A "forced expiratory technique with huffing" (FET-H) or similar is performed to stimulate cough and expectoration; at least 2 repetitions should be done.

3. MECHANICAL VENTILATION METHODS FOR REHABILITATION

3.1. Intrapulmonary percussive ventilation (IPPV)

Intrapulmonary percussive ventilation (IPPV) is a hybrid method of high-frequency ventilation support when pneumatic diffusive convective "percussions" are inflated into the patient's airways with a certain frequency, thus developing the tidal volume (TV) required to maintain gas exchange [19]. The primary component of the PERCUSSIONAIRE device (Percussionaire Corporation, USA) is the Phasitron — a special frequency chopper developed based on the original idea of medical engineer Forrest M. Bird in 1980 in Idaho, USA. *Objective:* stimulation of mucociliary and cough clearance, increasing collateral ventilation, stimulation of pulmonary microcirculation, normalization of the ventilation/perfusion ratio, prevention of air trapping and collapses of small airways [20]. *Mechanism of action is «simple and ingenious»*. Firstly, the Phasitron is powered by compressed air (4–6 atmospheres) from a gas cylinder (mobile option) or an air compressor (high-pressure port, resuscitation console). Therefore, this device is universal, i.e., it is independent of an electrical power supply, which is crucially important when transporting the patient. Secondly, the Phasitron does not require spontaneous breathing of the patient, unlike most devices for noninvasive ventilatory support. Compressed gas moves the internal piston of the Phasitron back and forth, «cutting» airflow into «percussions» with a certain frequency. Percussion frequency can be adjusted in a wide range (from 100 to 1000 Hz). Percussions move progressively and create their own "tunnel/channel" (like, for example, a rotating bullet), which allows to deliver a portion of air/gas to the alveolar area. This delivery does not depend on the patient's participation in respiration. The "tunnel" does not allow a portion of moving air to exert pressure ("Pr") on the patient's airways, ensuring the creation of TV at zero «Pr» values (Fig. 2) [20].

Thirdly, the original solution to maintaining a constant TV required by the patient was the idea of an "open breathing circuit" that allows to get an additional portion of air from the outside, if necessary (required fraction of inspired oxygen, FiO_2, is maintained), or "expire" a portion of air (no resistance on expiration). In practice, this enables to avoid using oxygen blenders/mixers completely, enables to humidify air, dramatically reduces the consumption of "working gas", and allows combination with a nebulizer for timely delivery

of the drug substance. Also, according to Newton's third law (action and reaction law), translational percussions reaching the alveolar zone cause reverse pneumatic shocks and air movement outside (named "Bird flows" after the inventor of this idea). This helps enhance the drainage of tracheobronchial secretion and sputum, activates regular contractions of the ciliary epithelium, which restores/normalizes mucociliary clearance (Fig. 3) [20].

The fourth unique property of the Phasitron is the biological "patient-device" feedback achieved via automatic "resistance/pressure" adjustment. The system, which is based on the law of energy conservation, automatically increases the flow rate when pressure falls and reduces it when pressure rises. This completely prevents barotrauma in areas with high resistance ("high narrowness"), making this device very safe even in newborns, when other methods of noninvasive ventilation support are almost impossible. In addition, this facilitates high "recruitment" of alveoli in gas exchange and stimulates the perfusion of previously quiet zones of lungs. Thus, the main mechanisms of action of IPPV therapy are associated with the following [21]:

- involvement of pulmonary structures in gas exchange, or "lung recruitment";
- mobilization and expectoration/coughing up of tracheobronchial secretion;
- increased diffusion capacity of lungs;
- improvement of bronchial blood flow and pulmonary microcirculation;
- restoration of air flow and elimination of «air trappings».

The procedure is preferably performed as follows [10]:

1. The patient in a sitting position performs relaxed breathing in the usual rhythm.
2. The patient breathes in and out at the usual rate through the mouthpiece of the Phasitron, avoiding unproductive cough at the beginning of expiration; the basic percussion frequency well tolerated by the patient should be adjusted using a controller; this stage should not be longer than 5 minutes.

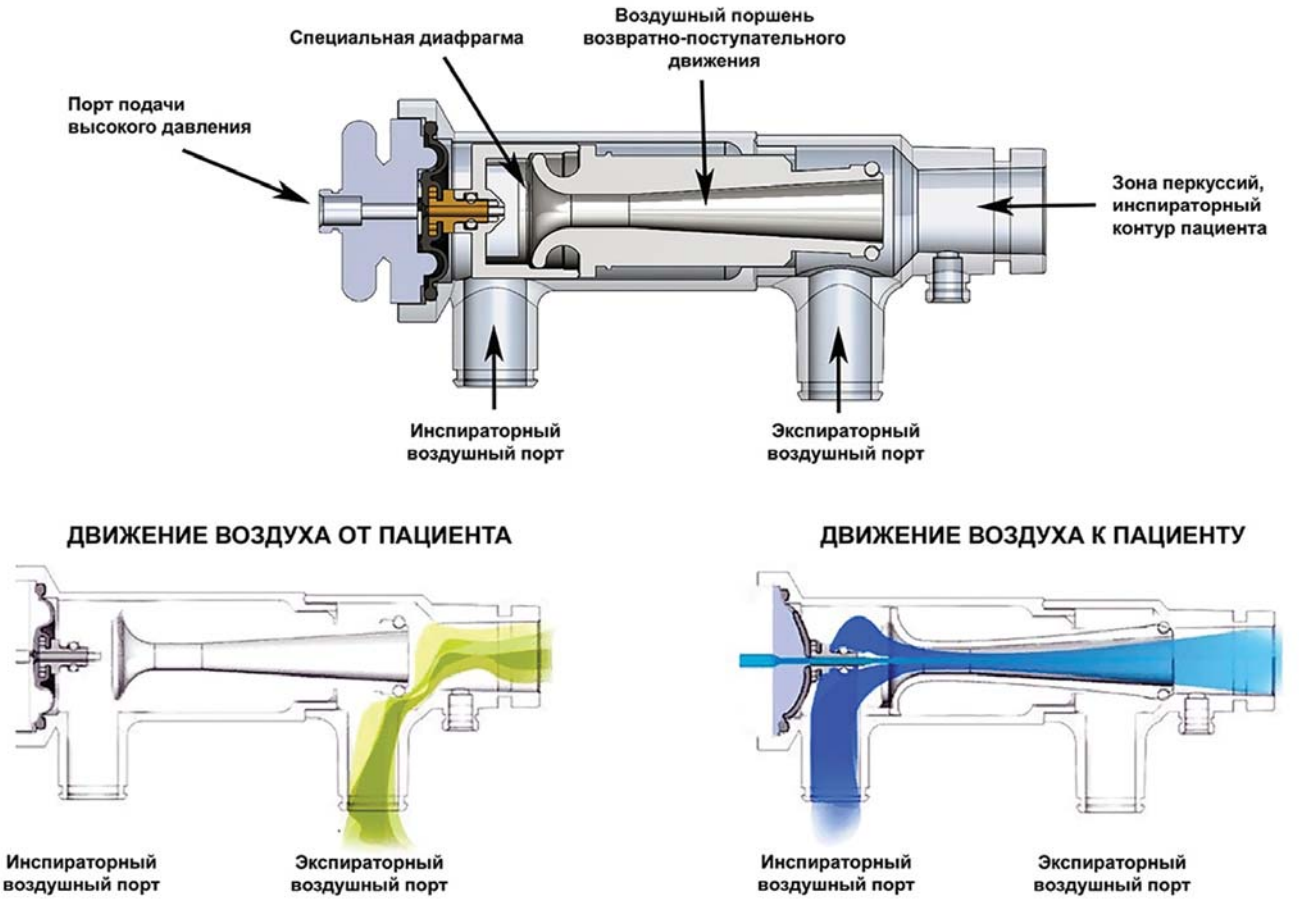

Figure 2. *Device diagram of the «Phasitron» block. Vertical section. The explanation in the text. (Source: Percussionaire Corp., Sandpoint, Idaho 83864 USA. [Electronic resource]. URL: https://percussionaire.com/products/phasitron. (date of the application: 22.12.2020))*

3. The patient continues breathing in/out through the mouthpiece of the Phasitron; the percussion frequency is doubled with the help of the controller; if a productive cough appears, coughing up is possible; this stage should not be longer than 15 minutes.
4. The patient continues breathing in/out through the mouthpiece of the Phasitron; the percussion frequency is lowered to the «basic» frequency with the help of the controller; if a productive cough appears, coughing up is possible; this stage should not be longer than 5 minutes.

The total duration of this procedure should not exceed 30 minutes; it can be repeated up to 4 times a day since premature fatigue of patient is possible.

3.2. Mechanical insufflation/exsufflation with oscillations

The idea of mechanical support of the patient's cough reflex is implemented in mechanical insufflation/exsufflation (MI-E) devices. An MI-E device is an air insufflator/exsufflator that allows to create a pressure drop in the patient's airways in a short time, which is consistent with the inspiratory/expiratory phase. This stimulates a cough reflex and enhances mucociliary clearance with expectoration. As a result, such devices were called «coughing machines» [22]. *Objective:* stimulation of mucociliary and cough clearance, respiratory muscle training. *Mechanism of action*: based on cough stimulation during a sharp drop in airway pressure. A 10 Hz oscillation is applied to the patient circuit for stabilizing the airway lumen to prevent barotrauma during insufflation (up to +60 mbar) and early expiratory collapses of small bronchi during exsufflation (up to –60 mbar) (Fig. 4). One of the most interesting MI-E devices is the Cough Assist E70 (Philips Respironics, USA) [23].

Absolute contraindications to MI-E [24]: 1) bullous pulmonary emphysema; 2) history of pneumothorax and barotrauma; 3) uncontrolled suffocation attack; 4) severe hypotension and/or pulmonary hemorrhage; 5) complete collapse of the upper RT (silent lung).

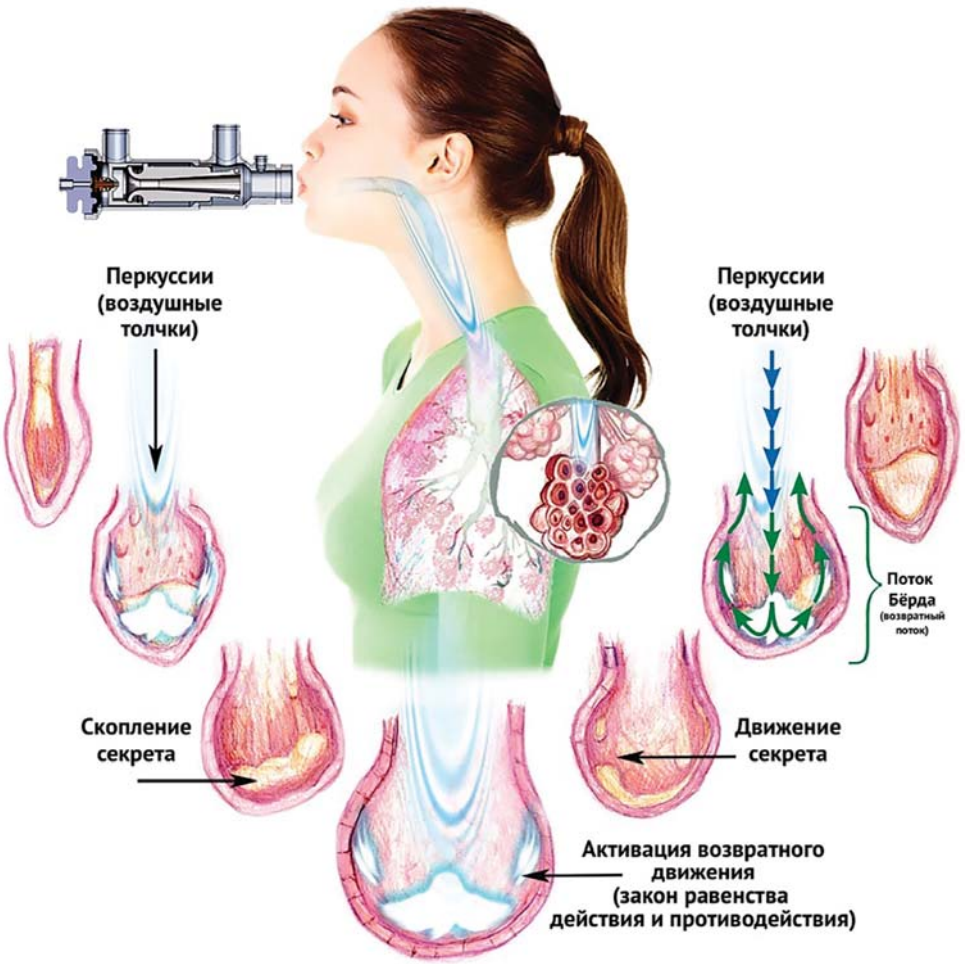

Figure 3. *Schematic representation of the "Byrd flow" formation mechanism. The explanation in the text. (Source: Percussionaire Corp., Sandpoint, Idaho 83864 USA [Electronic resource]. URL: https://percussionaire.com/products/travel-air. (date of the application: 22.12.2020))*

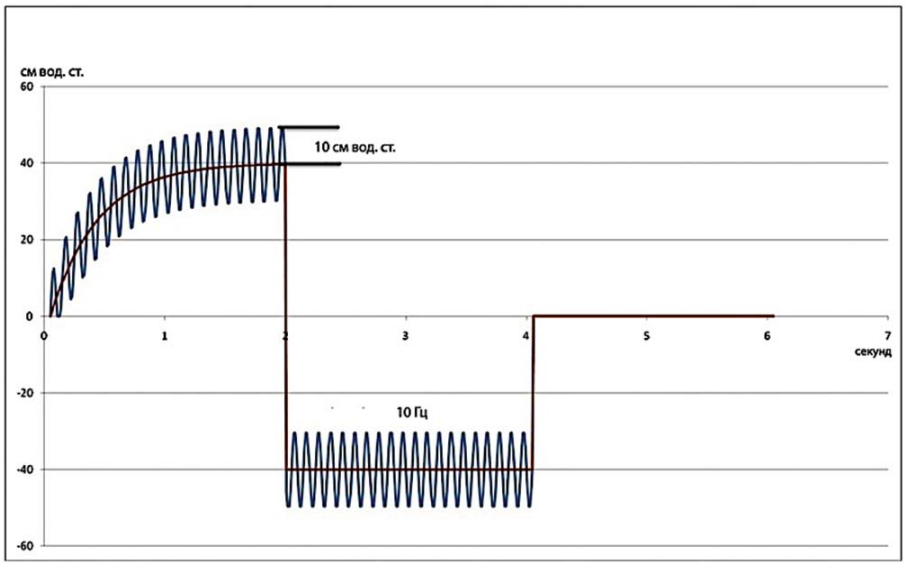

Figure 4. *Diagram of the insufflation/exufflation mechanism with oscillations. The blue line shows the pressure curve (+40 cm H_2O / -40 cm H_2O) at 10 Hz oscillations in the inhale/exhale phase lasting 2 seconds. (Adapted By: CoughAssist E70. Philips Respironics. [Electronic resource]. URL: https://philipsproductcontent.blob.core.windows.net/assets/20170908/b932adc03e96f6f21f2b8512458fa06f.pdf (date of the application: 22.12.2020))*

Patients in the following circumstances require particular attention and monitoring: 1) when carrying out the procedure after eating; 2) with gastroesophageal reflux; 3) with a sharp increase in RR; 4) with hemodynamic instability; 5) with severe bronchospasm; 6) with severe chest pain. *The procedure is preferably performed as follows* [10]:

1. The patient is in a sitting position and performs relaxed breathing in the usual rhythm.
2. The patient makes a 2–3 second inspiration through a mask (parameters should be preset in «automatic» mode, inspiration duration 0–5 seconds, with a 0.1 interval and oscillation frequency 10 Hz), avoiding unproductive cough at the beginning of inspiration.
3. The patient makes a 2–5 second expiration through a mask (parameters should be preset in «automatic» mode, expiration duration 0–5 seconds, with a 0.1 interval and oscillation frequency 10 Hz), avoiding unproductive cough at the beginning of expiration.
4. Repeat the inspiration/expiration cycle through a mask; a well-tolerated frequency of 1–20 Hz should be adjusted with the help of an oscillation controller; if a productive cough appears, coughing up is possible.

The total duration of this procedure should not exceed 30 minutes; it can be repeated up to 4 times a day since premature fatigue of patient is possible.

3.3. Long-term low-flow oxygen therapy

Long-term low-flow oxygen therapy (LTOT) is a method of restoring gas exchange function in cases of significant resting hypoxemia, defined as PaO_2 £ 55 mm Hg (7.3 kPa), or proven chronic hypoxemia PaO_2 56–59 mm Hg (7.4–8.0 kPa) in patients with pulmonary heart disease, polycythemia, pulmonary hypertension. The LTOT criterion in patients with physiological hemoglobin level is arterial blood oxygen saturation (SpO_2) less than 88% [6, 25]. *Objective:* elimination/minimization of respiratory failure (RF), stimulation of mucociliary clearance. *Mechanism of action*: based on the ability of oxygen with moderate concentration (21% < FiO_2 < 60%) and low flow (< 5.0 l/min) to stimulate metabolic processes in tissues, mucociliary clearance and to maintain physiological constancy of oxygen tension in arterial blood (PaO_2)). To perform LTOT at home, oxygen concentrators — portable medical devices that divide air (FiO_2 = 21%) into nitrogen (N_2) and oxygen (O_2) fractions — are used. With its maximum compliance for the patient and effective delivery of gas mixture, the nasal canula is regarded as the optimal device for performing LTOT at home. It should be noted that the actual value of FiO_2 depends on the geometry of the nasopharynx, oral breathing, minute ventilation, respiratory pattern (tidal volume and minute lung ventilation) [10].

The procedure is preferably performed as follows [25]:

- The duration of LTOT should exceed 15 hours/day; LTOT for 24 hours may yield additional benefits.
- LTOT is started at a flow of 1.0–1.5 l/min and is titrated stepwise (step of 0.5 l/min) until SpO_2 > 93% is reached.
- In patients who remain physically active, LTOT should be combined with additional oxygen therapy, especially during exercise.

- LTOT should be controlled every three months by analyzing arterial blood gas composition to assess the further effectiveness of the procedure.
- Control visits at the 6th and 12th month of LTOT should be carried out by a clinician with special training in respiratory medicine.

4. DRUG REHABILITATION THERAPY

A specific feature of drug rehabilitation therapy is its effect on the patient, depending on the patient's comorbidities. In the case of low comorbidity, the effectiveness of drug rehabilitation therapy is doubtful [6, 26, 27].

4.1. Bronchodilator therapy (combined bronchodilators)

Combined bronchodilator therapy should be performed in patients with proven airway obstruction of different severity. In patients with no obstructive disorders, such therapy is directly associated with side and undesirable effects from the cardiovascular system, especially in the case of drug overdose in individuals receiving it for the first time. If necessary, a rational combination of short-acting beta-2 agonists (SABA) and anticholinergics (SAAC) with their retard forms is possible. In post-COVID-19 patients with chronic obstructive pulmonary disease (COPD), the possibility of severe COPD exacerbation increases significantly. Such cases require a rational combination of long-acting beta-2 agonists (LABA) and long-acting anticholinergics (LAAC), which are the basic treatment for COPD with nebulized delivery of SABA + SAAC in high doses for 2–6 weeks. Post-COVID-19 patients with bronchial asthma (BA) may experience an increase in bronchial hyperreactivity and/or moderate exacerbation of BA. In such cases, ramping up treatment for BA with high doses of inhaled corticosteroids (ICS) and nebulized delivery of SABA + SAAC in high doses for 4–8 weeks is preferable [6, 26].

4.2. Mucolytic therapy

Most post-COVID-19 patients may develop impaired mucociliary clearance because novel coronavirus SARS-CoV-2 has a strong negative effect on bronchopulmonary segments (edema, inflammation, hypersecretion of tracheobronchial secretion, increased bronchial obstruction) [28], which makes long-term administration (> 1 month) of mucoactive agents relevant. Mucolytic therapy is most advisable in patients with chronic cough (> 8 weeks) and hard-to-remove sputum. The group with "peripheral action" (levodropropizine), which suppresses the release of neuropeptides and histamine, is usually identified among "anti-tussive medications". These agents have no negative effect on the central nervous system and mucociliary transport. In cases of a "debilitating" unproductive cough, non-codeine central-acting drugs (butamirate) that reduce the excitability of the cough center can be prescribed. However, detoxifying mucolytics (carbocysteine, N-acetylcysteine, erdosteine) and mucolytics that stimulate the motor and secretory function of the respiratory tract (ambroxol) are essential in that context.

4.3. Systemic corticosteroid therapy

The administration of systemic glucocorticosteroids (SGC) to patients after COVID-19 remains difficult to understand and debatable. Obviously, morphological changes in lungs of post-COVID-19 patients («ground-glass opacity» revealed by chest multispiral computed tomography (MSCT)) may persist for a long time (more than 90 days), which demonstrates the existence of a late slow phase of exudative changes; signs of «general inflammatory reaction» (weakness, asthenia, low-grade fever, loss of appetite) without evidence of bacterial infection may persist, raising the prospect of SGC therapy. At the same time, well-known side effects of such therapy (hyperglycemia, arterial hypertension, gastropathy, bacterial superinfection, osteoporosis) make a strong case against this treatment strategy [29]. However, post-COVID-19 patients with «ground-glass opacity» after day 90 of the disease are recommended to start low-dose SGC therapy with methylprednisolone (4–8 mg) for 1.5–3.0 months. Arguments for such treatment strategy are based on the extreme similarity of pulmonary MSCT findings in post-COVID-19 patients with radiological signs of «pulmonary vasculitis» that are effectively managed by SGC therapy. High-dose SGC therapy, monoclonal, anti-interleukin-6 (tocilizumab) therapy, including for the elimination of the «cytokine storm», is not relevant at the post-COVID-19 rehabilitation stage [6, 29].

4.4. Other drug rehabilitation therapy

Mild pulmonary arterial hypertension (PAH) (< 50 mm Hg) in post-COVID-19 patients requires no additional drug use and is resolved spontaneously by day 90 of the disease. However, if clinical symptoms of PAH are persistent and severe, therapeutic doses of diuretics, amlodipine, sildenafil should be prescribed. The administration of bosentan and prostanoids is justified only in cases of progressive PAH. The anti-inflammatory pleiotropic effect of statins on small vessels and bronchi and the additive effect of low doses of selective β-adrenergic blockers («overregulation» effect) are proven in post-COVID-19 patients with cardiovascular comorbidity. On the other hand, the management of arterial hypertension (AH) in such patients requires high doses of angiotensin-converting enzyme inhibitors (ACE inhibitors) due to their effect on angiotensin II (the most important component of inflammatory response in cases of COVID-19) [6].

Conclusion

Modern medicine has a broad range of drug and non-drug methods for the rehabilitation of post-COVID-19 patients. In addition, selecting proper rehabilitation methods and patient-specific rehabilitation programs with consideration of the individual clinical situation allows to avoid/prevent functional disorders and restore the quality of life in post-COVID-19 patients.

Вклад авторов:

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

С.Л. Бабак (Scopus Author ID: 45560913500, ORCID: https://orcid.org/0000-0002-6571-1220): роль автора в обосновании и написании рукописи, вклад в разработку дизайна и метаанализа данных, ответственность за англоязычный перевод научного материала.

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

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

Author Contribution:

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

S.L. Babak (Scopus Author ID: 45560913500, ORCID: https://orcid.org/0000-0002-6571-1220): the role of the author in the justification and writing of the manuscript, contribution to the development of design and meta-analysis of data, responsibility for the English translation of scientific material.

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

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

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DOI: 10.20514/2226-6704-2021-11-1-34-42

Е.В. Ефремова*[1], А.М. Шутов[1], Е.В. Петрова[2]

[1] — Ульяновский государственный университет, Ульяновск, Россия
[2] — Пензенский государственный университет, Пенза, Россия

ЛИЧНОСТНЫЕ ОСОБЕННОСТИ И МЕХАНИЗМЫ АДАПТАЦИИ БОЛЬНЫХ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ И ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

E.V. Efremova*[1], A.M. Shutov[1], E.V. Petrova[2]

[1] — Ulyanovsk State University, Ulyanovsk, Russia
[2] — Penza State University, Penza, Russia

Personal Characteristics and Adaptation Mechanisms of Patients with Arterial Hypertension and Chronic Heart Failure

Резюме

Адаптационные процессы при хронических заболеваниях, в том числе при артериальной гипертензии (АГ) и хронической сердечной недостаточности (ХСН), зависят как от личностных особенностей пациента, так и от коморбидности (наличия у больного сопутствующих заболеваний) **Цель исследования:** изучить личностные особенности и механизмы адаптации больных с АГ и ХСН. **Материалы и методы:** Обследовано 122 больных (49 женщин и 73 мужчины, средний возраст 62,9±9,4 лет) с АГ и ХСН. Для диагностики АГ руководствовались рекомендациями по лечению артериальной гипертонии Европейского Общества Гипертонии и Европейского Общества Кардиологов (2013г.). ХСН определяли согласно рекомендациям по диагностике и лечению хронической сердечной недостаточности Общества специалистов по сердечной недостаточности (ОССН), Российского кардиологического общества (РКО) (2016г.). Для оценки коморбидности использовали индекс коморбидности (ИК) Чарлсона; коморбидность расценивали как высокую при ИК ≥6 баллов (60 больных). Для оценки личностных особенностей и общего психического статуса использовалась проективная методика — тест восьми влечений Сонди, опросник Мини-мульт (сокращенный вариант MMPI). Для оценки адаптационных психологических механизмов использовались «Индекс жизненного стиля» и «Копинг-тест». Проводилась оценка когнитивного статуса. **Результаты.** ИК составил 5,3 (IQR:4-7) баллов. Группа больных с АГ, ХСН и высокой коморбидностью отличалась выраженностью депрессивно-ипохондрического профиля по сравнению с пациентами с низкой коморбидностью. Схожие данные были получены при проективном исследовании: в группе с высокой коморбидностью был наиболее выражен фактор D– (депрессивное состояние) (1,7 (IQR:1-2) и 0,9 (IQR:0-1), баллов соотв., p=0,009) и фактор P– (параноидальность) (1,8(IQR:1-2,5) и 1,3(IQR:1-2) баллов соотв., p=0,01). Определены взаимосвязи, позволяющие говорить о единых адаптационных процессах больных с АГ и ХСН в зависимости от коморбидности: у больных с высокой коморбидностью неконструктивные копинг-стратегии («конфронтативный», «бегство-избегание») коррелировали с механизмами психологической защиты «регрессия» (r=0,41, p=0,003), и «замещение» (r=0,39, p=0,001). **Выводы.** Коморбидность оказывает негативное влияние на когнитивные и адаптационные возможности больных с АГ и ХСН, способствует возникновению депрессивно-ипохондрических состояний, сопровождающихся снижением мотивации и приверженности к лечению, что необходимо учитывать при междисциплинарном подходе к данной категории больных.

Ключевые слова: *артериальная гипертензия, хроническая сердечная недостаточность, личностные особенности, механизм адаптации*

*Контакты: Елена Владимировна Ефремова, e-mail: lena_1953@mail.ru
*Contacts: Elena V. Efremova, e-mail: lena_1953@mail.ru
ORCID ID: https://orcid.org/0000-0002-7579-4824

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 30.06.2020 г.

Принята к публикации 05.08.2020 г.

Для цитирования: Ефремова Е.В., Шутов А.М., Петрова Е.В. ЛИЧНОСТНЫЕ ОСОБЕННОСТИ И МЕХАНИЗМЫ АДАПТАЦИИ БОЛЬНЫХ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ И ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ. Архивъ внутренней медицины. 2021; 1(1): 34-42. DOI: 10.20514/2226-6704-2021-11-1-34-42

Abstract

Adaptation processes in chronic diseases, including arterial hypertension (AH) and chronic heart failure (CHF), depend both on the personality of the patient and on comorbidity. **Objective:** to study the characteristics of adaptation and mental functioning of patients with hypertension and heart failure with comorbidity (the patient has concomitant diseases). **Design and methods.** 122 patients (49 women and 73 men, average age 62.9 ± 9.4 years) with hypertension and heart failure were examined. AH was diagnosed and evaluated according to guidelines for the treatment of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology (2013). CHF was diagnosed in accordance with the guidelines for the diagnosis and treatment of chronic heart failure of the Society of Heart Failure Specialists, Russian Cardiology Society (2016). Charlson Comorbidity Index (IC) was used to evaluate comorbidity; comorbidity was regarded as high at IC ≥ 6 points (60 patients). To assess personal characteristics and mental status, a projective methodology was used — Sondi's test, a Mini-mult questionnaire (shortened version of MMPI). To assess the adaptive psychological mechanisms were used «Life Style Index» and «Copy Test». Cognitive functions and quality of life were evaluated. **Results.** IC was 5.3 (IQR:4-7) points. The group of patients with hypertension, heart failure and high comorbidity differed in the severity of the depressive-hypochondriacal profile compared with patients with low comorbidity. Similar data were obtained in a projective methodology: in the group with high comorbidity, the most pronounced factor is D– (depression) (1.7 (IQR: 1-2) and 0.9 (IQR: 0-1), points respectively, p = 0.009) and factor P– (paranoid) (1.8 (IQR: 1-2.5) and 1.3 (IQR: 1-2) points respectively, p= 0.01). Relationships have been identified that make it possible to talk about common adaptation processes in patients with AH and CHF depending on comorbidity: in patients with high comorbidity, non-constructive coping strategies («confrontational», «flight-avoidance») correlated with psychological defense mechanisms of the regression type (r=0.41, p=0.003) and replacement (r=0.39, p=0,001). **Conclusions.** Comorbidity has a negative impact on the cognitive and adaptive capabilities of patients with hypertension and heart failure, contributes to the emergence of depressive-hypochondriacal conditions, accompanied by a decrease in motivation and adherence to treatment, which must be taken into account with an interdisciplinary approach to this category of patients.

Key words: *arterial hypertension, chronic heart failure, psychological characteristics, adaptation mechanism*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 30.06.2020

Accepted for publication on 05.08.2020

For citation: Efremova E.V., Shutov A.M., Petrova E.V. Personal Characteristics and Adaptation Mechanisms of Patients with Arterial Hypertension and Chronic Heart Failure. The Russian Archives of Internal Medicine. 2021; 1(1): 34-42. DOI: 10.20514/2226-6704-2021-11-1-34-42

Introduction

Despite all the progress in diagnosis and therapeutic options, arterial hypertension (AH) management remains a challenge [1]. Poor adherence to therapy is currently considered one of the primary reasons for the low effectiveness of AH management [2]. Single-pill strategy (using fixed combinations as early as the beginning of treatment) is seen as one way to improve adherence to therapy [3]. Adherence to therapy is determined by many factors; personality traits of patients and their motivation are of great importance. Studies show that the cost of medications is not a critical factor, including in Russia [4].

Shaping an attitude towards one's disease is a long process that depends not only on the patient's personality but also on external environmental factors. Adaptation to the disease occurs in several stages, including awareness of this new condition, acceptance or rejection of the diagnosis, and, ultimately, reorganization of living space with the re-evaluation of personal values. The patient's motivation for treatment depends on his/her personality and his/her desire and deliberate decision to comply with the physician's recommendations. In addition, comorbidity, which is currently considered a pandemic by the World Health Organization, influences adherence to treatment [5]. There is an extensive ongoing discussion on the problem of comorbidity (present concomitant pathology), including in patients with hypertension. Comorbidity always causes poor adherence to therapy and an unfavorable prognosis in patients

with cardiovascular diseases. According to local studies, the polymorbidity index is 16.8% [6] higher in patients with arterial hypertension than in patients without AH. According to the literature, the combination of arterial hypertension and chronic heart failure is as high as 85.6%, and that of arterial hypertension and ischemic heart disease — 81.3% [7]. In addition, arterial hypertension is the main risk factor for high comorbidity, which, in turn, worsens the prognosis [8].

Cerebrovascular disease is the second most frequent cause of cognitive impairment (vascular cognitive impairment), which is why the analysis of cognitive functions should be performed as part of comprehensive diagnosis of patients with AH, especially in the elderly population [9]. Despite the contradictory data concerning the choice of the method for evaluating cognitive deficit, «Hypertension in adults» (2020) Clinical Guidelines of the Russian Cardiology Society recommend evaluation of cognitive function in elderly patients with the help of the MMSE test [10].

Comorbidity worsens the prognosis, raises the treatment cost, affects the quality of life, and leads to the consolidation of depressive reactions [11]. Arterial hypertension is associated with depression and anxiety. In addition, depression, hostility, and an increased level of anxiety have a negative effect on adherence to drug therapy in patients with arterial hypertension [12]. According to our previous studies, an obsessive-phobic attitude towards the disease and illness anxiety disorder worsen adherence to therapy in patients with CHF [13].

Particular attention is paid to the so-called cardiovascular comorbidity [14]. Chronic heart failure (CHF) as a component of cardiovascular comorbidity is an unfavorable prognostic factor. The prevalence of CHF is growing globally and within our country. In recent years, it increased to 8.8% [15]. However, the effect of comorbidity on the emotional and motivational components of the personality of the patient with arterial hypertension and chronic heart failure is under-investigated.

The **objective of the study** was to examine personality traits and adaptation mechanisms of patients with AH and CHF with the consideration of their comorbidity.

Materials and methods

A total of 122 patients (49 women and 73 men, mean age 62.9 ± 9.4 years) with arterial hypertension, stage 2–3, grade III (according to Russian Hypertension Classification) and chronic heart failure were examined. This study was approved by the Ethics Committee of Ulyanovsk State University; patients signed voluntary informational consent. Diagnosis of AH was established in accordance with the recommendations of the European Society of Hypertension and the European Society of Cardiology for the management of arterial hypertension (2013). [16]. European recommendations on arterial hypertension (2018) were considered when analyzing the data obtained. [3]. CHF was diagnosed in accordance with the recommendations for the diagnosis and management of chronic heart failure of the Society of Heart Failure Specialists (SHFS), Russian Cardiology Society (RCS) (2016). [17]. To evaluate comorbidity, we used the Charlson comorbidity index (CI); comorbidity was regarded as high for CI ≥ 6 points [13]. Comorbidity was defined as the combined manifestation of two or more chronic diseases related in pathogenesis or present simultaneously in one patient, regardless of the activity of each of them [18]. All patients were divided into two groups depending on the comorbidity grade: 62 patients with low comorbidity (CI < 6 points) and 60 patients with high comorbidity (CI ≥ 6 points). Table 1 presents clinical features of the examined patients with AH and CHF.

Personality traits and mental status were assessed using a projective technique — Szondi test (modified by L. N. Sobchik, 2002), and the Mini-Mult questionnaire (shortened version of MMPI) [19–20]. Adaptive psychological mechanisms were assessed using the Plutchik-Kellerman-Conte Life Style Index Questionnaire and Coping Test [21–22]. Cognitive status was assessed using the Mini-Mental State Examination scale (MMSE) [23]. Clinical Dementia Rating (CDR) scale was used for clinical evaluation of dementia severity. A multidisciplinary team, including different specialists, carried out evaluation.

This paper is a prospective cohort study with a follow-up period of 12 months. The total mortality rate was estimated as the primary endpoint. The study had the following exclusion criteria: acute myocardial infarction; acute cerebrovascular accident (stroke) within six months before inclusion in the study; mental disorders, severe cognitive disorders (moderate to severe dementia) that make it difficult to conduct psychological tests).

Statistical analysis was carried out using the StatSoft Statistica v.10.0.1011.6 software package. Shapiro-Wilk's W test was used to evaluate data distribution in variational series. Depending on the study result, data were presented as M ± SD, where M is the arithmetic mean, SD is standard deviation (with normal distribution), or Me (IQR), where Me is the median, IQR is interquartile range: 25 percentile — 75 percentiles (with distribution other than normal). Student's t-test and Mann-Whitney U test (with distribution other than normal) were used to compare groups. Analysis of categorical data was carried out using Fisher's exact test. A correlation analysis was performed. Differences were considered significant at $p < 0.05$.

Table 1. *Patients with hypertension and chronic heart failure*

Parameters	Patients with hypertension and CHF (n=122)	Patients with hypertension and CHF with low comorbidity (n = 62)	Patients with hypertension and CHF with high comorbidity (n = 60)	p*
Women (n, %)	49 (40,2%)	27 (43,5%)	22 (36,7%)	0,5
Men (n, %)	73 (59,8%)	35 (56,5%)	38 (63,3%)	0,5
Age (M ± SD, years)	62,9±9,4	58,1±8,2	67,9±7,9	<0,0001
The presence of hypertension (All patients had stage 3 hypertension) (n, %):	122 (100%)	62 (100%)	60 (100%)	
AH 2 degrees	61 (50%)	34 (54,8%)	21 (35%)	0,03
AH 3 degrees	61 (50%)	28 (45,2%)	39 (65%)	0,03
Duration of hypertension (M ± SD, years)	11,9 (5;16)	11,4(5;16)	12,4(6;18)	0,4
Duration of CHF (M ± SD, years)	4,4(2;6)	3,5(2;5)	5,5(2;7)	0,003
The presence of CHF (n, %):				
Functional class of CHF (n, %):	122 (100%)	62 (100%)	60 (100%)	
1 FC	7 (5,7%)	5 (8%)	2 (3,3%)	0,2
2 FC	61 (50%)	45(72,6%)	16 (26,7%)	<0,0001
3 FC	54 (44,3%)	12 (19,4)	42 (70%)	<0,0001
By LV ejection fraction (n, %)				
CHF with low EF (less than 40%) (n, %)	26(21,3)	10(16,2%)	16(26,7%)	0,11
CHF with intermediate EF (from 40% to 49%) (n, %)	30(24,7%)	16(25,8%)	14(23,3%)	0,45
CHF with preserved EF (50% or more) (n, %)	66(54%)	36(58%)	30(50%)	0,24
CAD, including	100 (81,9%)	46 (74,2%)	54 (90%)	0,02
myocardial infarction in history (n, %)	31 (25,4%)	7 (11,3%)	24 (40%)	0,0002
Atrial fibrillation (n, %)	18 (14,7%)	6 (9,7%)	12 (20%)	0,09
Atrial fibrillation (n, %)	13 (10,7%)	4 (6,5%)	9 (15%)	0,1
GFR (M±SD, ml/min/1.73 m^2)	63,9±16,2	72,7±13,6	55,9±12,8	<0,0001
BMI (M±SD, kg/m^2)	31,5±7,9	33,3±6,7	29,4±4,6	0,008

Note: AH — hypertension, CAD — coronary artery disease, BMI — body mass index, LV — left ventricle, GFR — glomerular filtration rate (according to the formula CKD EPI, 2011), EF — ejection fraction, FC — functional class, CHF — chronic heart failure
* — differences between the group of patients with low comorbidity and the group of patients with high comorbidity

Results

Charlson Comorbidity Index considering age was 5.3 (IQR: 4–7) points. Table 2 presents the structure of comorbidities in examined patients.

During 12 months of follow-up, 12 (9.8%) patients with AH and CHF died; all patients had high comorbidity.

Assessment of cognitive functions of patients with AH and CHF considering their comorbidities

In the study of the cognitive status of patients with AH and CHF, 68 (55.7%) patients with AH and CHF had predementia cognitive impairment, and one in four patients (30; 24.6%) had mild dementia. Results obtained with the Mini Mental Status Exam (MMSE) did not contradict the results obtained using the Clinical Dementia Rating scale for dementia in patients with AH and CHF.

Patients with AH and CHF performed tasks to assess orientation in time, place and perception — by 99%; attention — by 62%; memory — by 40%; speech and reading — by 90%. Memory (r = –0.41; p = 0.004) and attention (r = –0.45; p = 0.001) deteriorated with age. Also, with increasing comorbidity (dementia not included in this scale), deterioration of parameters indicating the level of attention (r = –0.50; p = 0.0001), memory (r = –0.42; p = 0.0002) and speech was observed (r = –0.40; p = 0.001).

Assessment of personality traits and mental status of patients with AH and CHF considering their comorbidities

Multidimensional diagnosis of personality traits of patients with AH and CHF was carried out using the Mini-Mult questionnaire. Values of all basic scales of the Mini-Mult questionnaire were in the range from 37.9 to 76.1 T-points. Results of this study showed high values of hypochondria, depression, hysteria and psychasthenia scales. According to the results of multivariate analysis, the averaged personality profiles of patients were different depending on their comorbidity (Fig. 1).

Compared with patients with low comorbidity, patients with AH and CHF with high comorbidity had high values on the hypochondria (76.7 ± 10.9 and 70.1 ± 11.3 T-points, respectively, p = 0.01), depression

Table 2. *Characterization of comorbidity in patients with hypertension and CHF*

Parameters	n (%)
Chronic kidney disease (GFR <60 ml/min/1.73 m^2)	60 (49,2%)
Dementia	30 (24,6%)
Type 2 diabetes, including with target organ damage	27 (22,1%) 12 (9,8%)
Peripheral vascular disease	18 (14,8)
Cerebrovascular accident in history, including hemiplegia	15 (12,3%) 2 (1,7%)
Chronic non-specific lung diseases	14 (11,5%)
Peptic ulcer	12 (9,8%)
Connective tissue diseases	10 (8,2%)
Moderate liver damage (viral hepatitis in history)	3 (2,5%)
Malignant tumors without metastases	3 (2,5%)

Примечание: АГ — артериальная гипертензия, СКФ — скорость клубочковой фильтрации (по формуле CKD EPI, 2011), ХСН — хроническая сердечная недостаточность
Note: AH — hypertension, GFR — glomerular filtration rate (according to the formula CKD EPI, 2011), CHF — chronic heart failure

(63.1 ± 11.7 and 56.4 ± 13.8 T-points, respectively, p = 0.004), and psychasthenia (67.5 ± 8.8 and 63.6 ± 11.1 T-points, respectively, p = 0.02) scales, which is typical for a depressive-hypochondriac profile.

The significant complex of hypochondriac depression in the clinical presentation included a pessimistic perception of somatic pathology with a hypertrophic evaluation of its consequences. Patients were dominated by anxiety-phobic emotions, fears of the recurrence of severe crises and heart attacks, long-term treatment with unfavorable outcome, negative social consequences, and futile treatment. In 50% of cases with high comorbidity, patients refused to follow medical instructions and sometimes followed their «own recovery program».

A projective technique — Szondi test — was used to analyze the key drives in the structure of motivation and personality traits of patients with AH and CHF. Key drives largely determine lifestyle, areas of social activity, and have a significant impact on the development of an individual hierarchy of values, which is an integral component in developing an attitude towards a chronic pathological condition. The averaged profile of key drives in patients with AH and CHF is presented in Fig. 2.

Test results revealed that patients with AH and CHF demonstrated average types of reaction without pathological personality traits. According to the obtained profile, patients with AH and CHF are characterized by high anxiety, unstable motivation, emotional lability, and adaptation difficulties [19]. In general, comorbidities did not significantly affect the profile of key drives in patients with AH and CHF. However, the D-factor (depressive state) was most pronounced in patients with high comorbidity compared to patients with low comorbidity: 1.7 (IQR: 1–2) and 0.9 (IQR: 0–1) points, respectively, p = 0.009. Patients with low comorbidity are characterized by optimism, search for new contacts, and high achievement motivation, which is lost in patients with high comorbidity. The P-factor (paranoid) is also

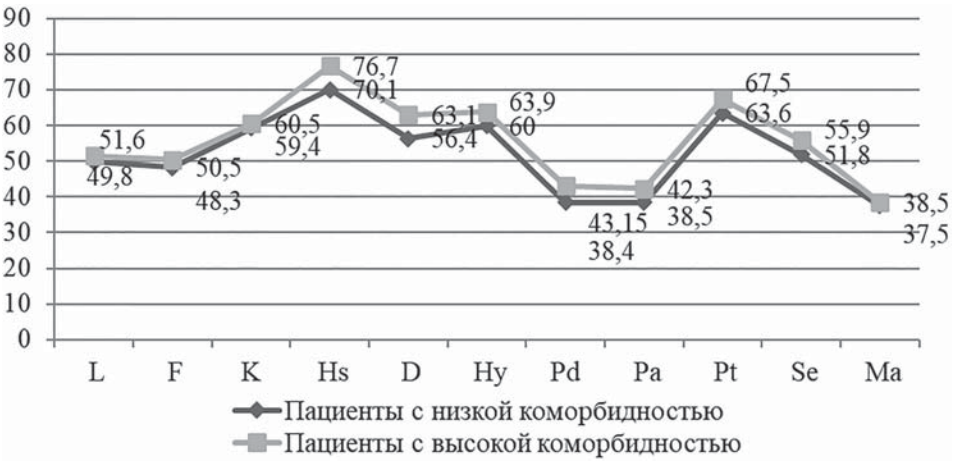

Figure 1. *Averaged personality profile of patients with hypertension and heart failure according to comorbidity*
Note. Scales: L — lies, F — reliability, K — correction, Hs — hypochondria, D — depression, Hy — hysteria, Pd — psychopathy, Pa — paranoia, Pt — psychasthenia, Se — schizoid, Ma — hypomania

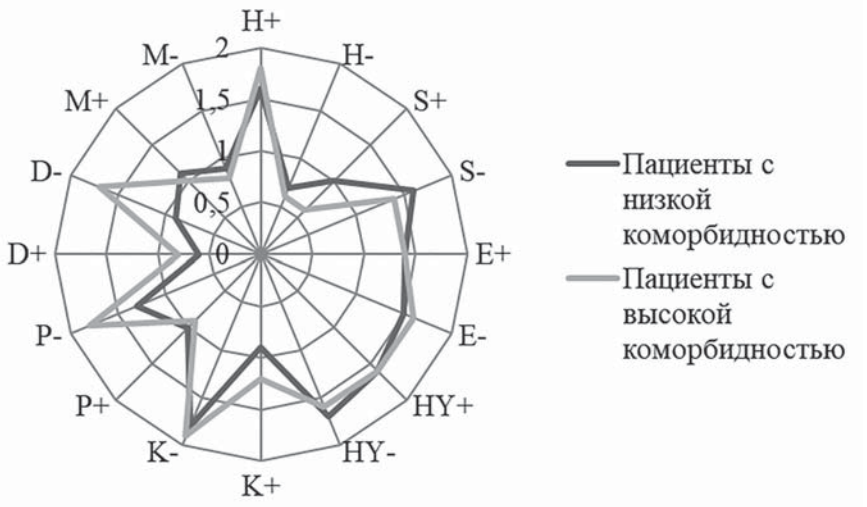

Figure 2. *Averaged profile of drives of patients with hypertension and heart failure according to comorbidity*
Note. Factors: H — sexual indifference; S — sadism-masochism; E — epileptoid tendencies; HY — hysterical tendencies; K — catatonic manifestations; P — paranoia; D — depressive state; M — manic manifestations

more intense in the group of patients with high comorbidity than in the group with low comorbidity: 1.8 (IQR: 1–2.5) and 1.3 (IQR: 1–2) points, respectively, p = 0.01. Patients with high comorbidity and paranoid traits are characterized by suspicion, hostility towards others, a tendency to dramatization and selectivity in contacts, which may influence their adherence to treatment.

Adaptation mechanisms of patients with AH and CHF considering their comorbidities

The severity of all protective mechanisms in patients with AH and CHF did not exceed 60 standard points (Fig. 3).

In general, patients with AH and CHF, regardless of comorbidity level, have the most intense psychological defense mechanisms of «projection» (49.3 (IQR: 33–67) %), «rationalization»" (37.1 (IQR: 25–50) %) and «denial» (35.1 (IQR: 18–45) %) types. The combination of psychological defense mechanisms of the «projection» and «rationalization» types indicates an awareness of the disease as a traumatic situation and its rational interpretation with suppressed emotions. However, the absence of proper emotional response leads to a psychological conflict and a decrease in the significance of traumatic moments [24].

In our study, the level of comorbidity in patients with AH and CHF had no significant effect on the severity of psychological defense mechanisms. There was a downward trend in almost all parameters of the severity of psychological defense mechanisms. A significant decrease in values on any scale of the questionnaire indicates the ineffectiveness of this type

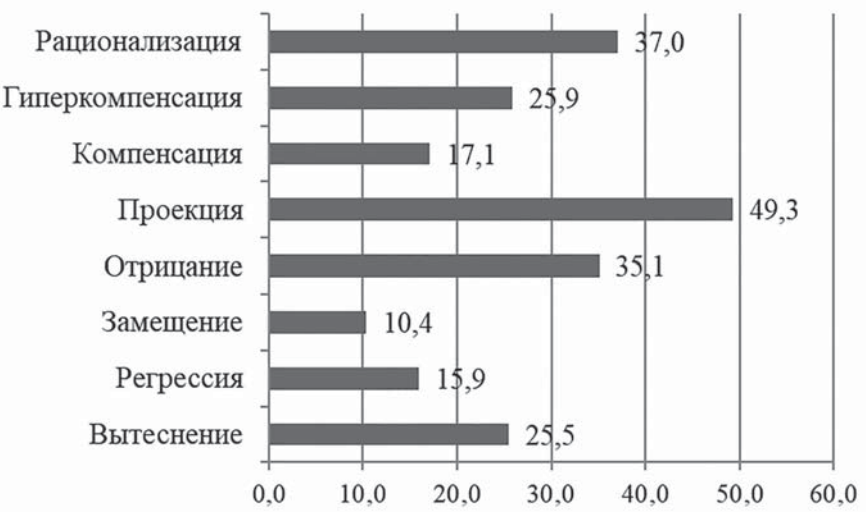

Figure 3. *The severity of the mechanisms of psychological defense in patients with hypertension and heart failure*
Note. The intensity of psychological defense mechanisms in %

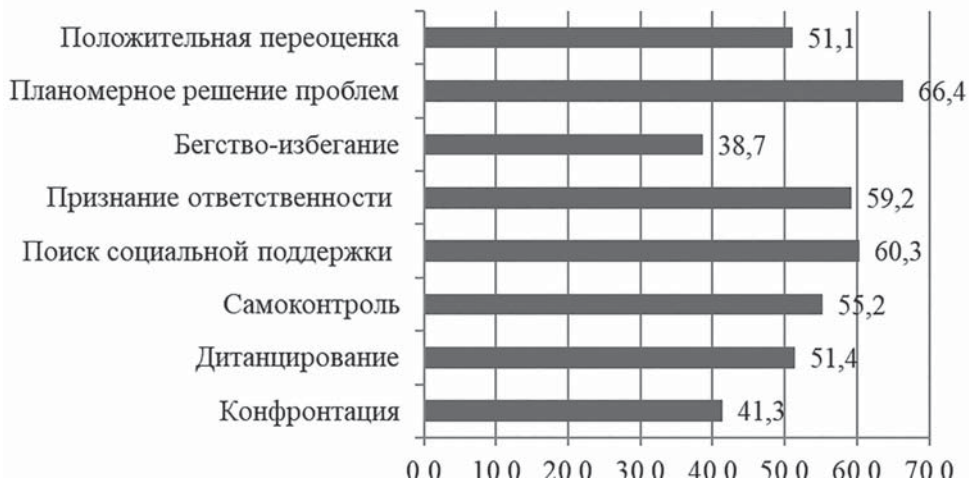

Figure 4. *Copying strategies of patients with hypertension and heart failure*
Note. The intensity of coping strategies in %

of psychological defense, which most likely leads to maladaptation.

The predominant types of coping strategies, regardless of the comorbidity level, in patients with AH and CHF were «systematic problem-solving» (66.4 (IQR: 56–83) points), «seeking social support» (60.3 (IQR: 50–72) points), «acceptance of responsibility» (59.2 (IQR: 42–75) points) (Fig. 4). These coping strategies can be described as relatively constructive and constructive. AH and CHF patients are characterized by active recognition of their role in the problem and the desire to have informational and emotional support from others.

Our study shows that the following constructive mechanisms are more pronounced in patients with low comorbidity than in patients with high comorbidity: «seeking social support» (63.6 (IQR: 50–72) % and 56.9 (IQR: 50–72) % respectively, $p = 0.03$) and «systematic problem-solving» (68.7 (IQR: 52–75) % and 59.8 (IQR: 52–75) %, respectively, $p = 0.02$), which characterize patients' adaptive abilities to use the resources of the external environment for obtaining information and for emotional support.

Direct relationships of non-constructive coping strategies («confrontation», «escape-avoidance») with psychological defense mechanisms of the «regression» ($r = 0.41$, $p = 0.003$) and «substitution» ($r = 0.39$, $p = 0.001$) types were revealed in patients with high comorbidity. For patients with low comorbidity, direct relationships of constructive coping strategies («systematic problem-solving», «seeking social support») with psychological defense mechanisms of the «rationalization» ($r = 0.44$, $p = 0.0004$), «hypercompensation» ($r = 0.40$, $p = 0.02$), and «denial» ($r = 0.39$, $p = 0.03$) types were revealed. The revealed relationships allow defining common adaptation processes in patients with AH and CHF depending on comorbidity.

Discussion

In our study, patients with arterial hypertension generally had comorbidity, including high comorbidity, with a Charlson comorbidity index of more than 6 points (49% of examined patients). Chronic kidney disease is observed in almost one in three patients with cardiovascular disease, including patients with arterial hypertension and chronic heart failure; it leads to poor prognosis, deterioration of quality of life, and higher treatment cost [25]. According to this study, all deceased patients had high comorbidity during the follow-up period. Half of the patients (49%) had chronic kidney disease, which is consistent with data in literature sources. The high prevalence of CKD in our study was also due to the age of the patients and their high comorbidity.

In this study, patients with arterial hypertension were characterized by a depressive-hypochondriac state, which was aggravated by high comorbidity. High level of anxiety complicates targeted efforts and attention focusing for a long time, making long-term compliance with medical recommendations harder. Depression and asthenic syndrome lead to irrational defense methods, a desire to withdraw from society, leading to more focus on somatic problems, and skepticism about the success of treatment. Patients may refuse to fulfill their needs and may not cope with their social roles.

Considering the conventional holistic approach to understanding personality and its studying in normal and pathological states, it becomes relevant to identify the features of psychological defense mechanisms in patients with AH and CHF, and the relationship between the severity of psychological defense and comorbidity [26]. Our study determined common adaptation mechanisms in patients with AH and CHF depending on the level of comorbidity according to the Charlson CI. In addition, patients with high comorbidity were characterized by maladaptation to their pathological state and

consolidation of primitive psychological defense mechanisms. In contrast, patients with low comorbidity used mature psychological defense mechanisms and constructive coping strategies.

Analysis of local studies on adaptation mechanisms showed that, compared to healthy individuals, patients with CHF were characterized by more intense psychological defense mechanisms, including «projection» and «denial» types [27]. Psychological defenses and coping strategies are usually considered as intrinsic ways of responding to stressful situations and forms of adaptation processes [28]. Coping strategies are the most advanced adaptive mechanism that provides a productive interaction between the personality and the environment in both typical and stressful conditions of chronic disease. Comorbidity in patients with AH and CHF negatively affects all components of relationships (cognitive, emotional, behavioral) and contributes to the aggravation of maladaptation to changed lifestyle [26, 29]. Mechanisms that reflect the relationship between high comorbidity and changes in mental life in cases of chronic diseases are diverse, which determines the patient-oriented approach to this category of patients and selection of targets to be modified, including those useful for promoting satisfactory adherence to therapy.

Conclusion

Patients with arterial hypertension and chronic heart failure are characterized by high comorbidity. In addition, high comorbidity aggravates the depression with hypochondriac state in patients with AH and CHF, has a negative effect on adaptive capabilities, which is accompanied by low motivation and adherence to treatment; this fact should be considered when taking an interdisciplinary approach to the treatment of this category of patients.

Вклад авторов:

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

Ефремова Е.В. (ORCID ID: https://orcid.org/0000-0002-7579-4824): дизайн, написание, редактирование текста и утверждение финального варианта статьи

Шутов А.М. (ORCID ID: https://orcid.org/0000-0002-1213-8600): дизайн, написание, редактирование текста и утверждение финального варианта статьи

Петрова Е.В. (ORCID ID: https://orcid.org/0000-0003-4117-7331): написание, редактирование текста и 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

E.V. Efremova (ORCID ID: https://orcid.org/0000-0002-7579-4824): design, writing, editing and approval of the final version of the article

A.M. Shutov (ORCID ID: https://orcid.org/0000-0002-1213-8600): design, writing, editing and approval of the final version of the article

Petrova E.V. (ORCID ID: https://orcid.org/0000-0003-4117-7331): writing, editing the text and approving the final version of the article

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DOI: 10.20514/2226-6704-2021-11-1-43-50

Я.М. Вахрушев, М.С. Бусыгина*, А.В. Воробьева, А.М. Фаррахов

ФГБОУ ВО «Ижевская государственная медицинская академия» Министерства здравоохранения РФ, кафедра пропедевтики внутренних болезней с курсом сестринского дела, Ижевск, Россия

КЛИНИКО-ФУНКЦИОНАЛЬНАЯ ХАРАКТЕРИСТИКА ХРОНИЧЕСКОЙ ДУОДЕНАЛЬНОЙ НЕДОСТАТОЧНОСТИ

Ya.M. Vakhrushev, M.S. Busygina*, A.V. Vorobyova, A.M. Farrakhov

«Izhevsk State Medical Academy» of the Ministry of Health of the Russian Federation, Department of Propaedeutics of Internal Medicine with a nursing course, Izhevsk, Russia

The Clinical and Functional Characteristics of Chronic Duodenal Insufficiency

Резюме

Цель: изучение клинического течения и особенностей нарушений моторно-эвакуаторной функции желудочно-кишечного тракта при хронической дуоденальной недостаточности. **Материалы и методы.** В исследование включено 40 пациентов с хронической дуоденальной недостаточностью (ХДН): 18 (48,2%) женщин, 22 (51,8%) мужчин, средний возраст 37,1±13,8 лет. Группа контроля состояла из 30 здоровых лиц: 10 (33,3%) женщин, 20 (66,7%) мужчин, средний возраст 40,5±13,47 лет. В обследовании пациентов использованы анамнестические и физикальные данные, результаты биохимических, рентгенологических и эндоскопических исследований, внутриполостной манометрии, электрогастроэнтерографии. Оценивали параметры, отражающие психоэмоциональное состояние и вегетативный статус. **Результаты.** У 19 (46,8%) пациентов с ХДН болевой синдром возникал после приема пищи, наиболее часто локализуясь в правом подреберье у 11 (29,0%) и в эпигастральной области у 18 (44,9%) больных. Пациенты с ХДН предъявляли те или иные диспепсические жалобы, которых не наблюдалось в контрольной группе: 22 (57%) отмечали отрыжку горечью, 31 (77,6%) — чувство горечи во рту, 21 (53%) — изжогу, метеоризм — 25 (53,3%) и кашицеобразный стул — 28 (71%). У пациентов с ХДН по сравнению с контрольной группой наблюдались снижение содержания общего белка (62,24±0,17 и 72,3±0,21 г/л, p=0,0002), триглицеридов (0,42±0,0021 и 1,5±0,04 ммоль/л, p=0,022), жирорастворимых витамина В12 (188,0±0,21 и 328,6±18,9 пг/мл, p=0,0048), 25-ОН витамина Д (26,87±0,12 и 64,7±1,25 нг/мл, p=0,018). При ХДН по сравнению с контролем выявлено существенное повышение гастрина (29,7 [25,7;32,5] и 19,2 [18,8;20,1] пмоль/л, p=0,0004) и кортизола (471,8±1,09 и 365,3±2,6 нмоль/л, p=0,0001). Уровень инсулина был существенно ниже показателей контрольной группы: (2,89 [2,5;3,0] и 3,8 [2,2;4,5] мкмоль/л, p=0,006). По данным гастроэнтероманитора в постпрандиальном периоде установлено нарушение пропульсивной моторики во всех отделах пищеварительной трубки, что доказывает снижение коэффициента ритмичности (K-ritm) двенадцатиперстной кишки, тощей и подвздошной кишки натощак в 1,5 раза в обе фазы исследования (p=0,000). Коэффициент отношения интрадуоденального давления к интрагастральному при ХДН составил 1,26 [1,19;1,32], что значительно ниже значений в контрольной группе (1,7 [1,0;2,4], p=0,00037) и свидетельствует о нарушении замыкательной функции привратника. Шкала тревоги Ч.Д. Спилбергера (адаптация Ю.Л. Ханина) показала повышение по сравнению с контрольной группой уровней ситуативной (57 [54;60] и 47,0 [45;50] баллов, p=0,0021) и личностной тревожности (25,1 [22,6;27,4] и 21,9 [19,5;23,9] баллов, p=0,003) у пациентов с ХДН. **Заключение.** В связи с неманифестированным течением и отсутствием специфических симптомов хронической дуоденальной недостаточности, в обследовании пациентов для постановки диагноза необходимо использовать помимо клинических данных, рентгенологические, эндоскопические, манометрические и электрофизиологические исследования.

Ключевые слова: *хроническая дуоденальная недостаточность, дуоденогастральный рефлюкс, электрическая активность желудка, электрическая активность двенадцатиперстной кишки, электрическая активность тонкой кишки, замыкательная функция привратника*

Конфликт интересов

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

*Контакты: Марина Сергеевна Бусыгина, e-mail: marina.busygina.login@gmail.com
*Contacts: Marina S. Busygina, e-mail: marina.busygina.login@gmail.com
ORCID ID: https://orcid.org/0000-0003-1740-2391

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 22.10.2020 г.

Принята к публикации 24.12.2020 г.

Для цитирования: Вахрушев Я.М., Бусыгина М.С., Воробьева А.В. и др. КЛИНИКО-ФУНКЦИОНАЛЬНАЯ ХАРАКТЕРИСТИКА ХРОНИЧЕСКОЙ ДУОДЕНАЛЬНОЙ НЕДОСТАТОЧНОСТИ. Архивъ внутренней медицины. 2021; 11(1): 43-50. DOI: 10.20514/2226-6704-2021-11-1-43-50

Abstract

Purpose: to study the clinical course and features of violations of the motor-evacuation function of the gastrointestinal tract in chronic duodenal insufficiency. **Materials and methods**. The study included 40 patients with chronic duodenal insufficiency (CDI): 18 (48.2%) women, 22 (51.8%) men, mean age 37.1 ± 13.8 years. The control group consisted of 30 healthy individuals: 10 (33.3%) women, 20 (66.7%) men, mean age 40.5 ± 13.47 years. In the examination of patients, anamnestic and physical data, the results of biochemical, X-ray and endoscopic studies, intracavitary manometry, and electrogastroenterography were used. Parameters reflecting psycho-emotional state and vegetative status were evaluated. Results. In 19 (46.8%) patients with CDI, the pain syndrome occurred after eating, most often localized in the right hypochondrium in 11 (29.0%) and in the epigastric region in 18 (44.9%) patients. Patients with CDF presented some dyspeptic complaints that were not observed in the control group: 22 (57%) noted belching with bitterness, 31 (77.6%) — a feeling of bitterness in the mouth, 21 (53%) — heartburn, flatulence — 25 (53.3%) and mushy stools — 28 (71%). In patients with CDI, compared with the control group, there was a decrease in the content of total protein (62.24 ± 0.17 and 72.3 ± 0.21 g / l, p = 0.0002), triglycerides (0.42 ± 0.0021 and 1.5 ± 0.04 mmol / L, p = 0.022), fat-soluble vitamin B12 (188.0 ± 0.21 and 328.6 ± 18.9 pg / ml, p = 0.0048), 25-OH vitamin D (26.87 ± 0.12 and 64.7 ± 1.25 ng / ml, p = 0.018). With CDI, compared with control, a significant increase in gastrin (29.7 [25.7; 32.5] and 19.2 [18.8; 20.1] pmol / L, p = 0.0004) and cortisol (471, 8 ± 1.09 and 365.3 ± 2.6 nmol / L, p = 0.0001). The insulin level was significantly lower than the values of the control group: (2.89 [2.5; 3.0] and 3.8 [2.2; 4.5] μmol / L, p = 0.006). According to the gastroenteromanitor in the postprandial period, impaired propulsive motility in all parts of the digestive tube was established, which proves a decrease in the rhythm coefficient (K-ritm) of the duodenum, jejunum and ileum on an empty stomach by 1.5 times in both phases of the study (p = 0.000). The ratio of intraduodenal pressure to intragastric pressure in chronic heart failure was 1.26 [1.19; 1.32], which is significantly lower than the values in the control group (1.7 [1.0; 2.4], p = 0.0004) and indicates a violation of the closure function of the gatekeeper. Alarm scale RH. Spielberger (adaptation of Yu.L. Khanin) showed an increase in comparison with the control group in the levels of situational (57 [54; 60] and 47.0 [45; 50] points, p = 0.0021) and personal anxiety (25.1 [22.6; 27.4] and 21.9 [19.5; 23.9] points, p = 0.003) in patients with CDI. **Conclusion**. In connection with the non-manifest course and the absence of specific symptoms of chronic duodenal insufficiency, in the examination of patients for the diagnosis, it is necessary to use, in addition to clinical data, X-ray, endoscopic, manometric and electrophysiological studies.

Key words: *chronic duodenal insufficiency, duodenogastric reflux, electrical activity of the stomach, electrical activity of the duodenum, electrical activity of the small intestine, pyloric closure function*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 22.10.2020

Accepted for publication on 24.12.2020

For citation: Vakhrushev Ya.M., Busygina M.S., Vorobyova A.V. et al. The Clinical and Functional Characteristics of Chronic Duodenal Insufficiency. The Russian Archives of Internal Medicine. 2021; 11(1): 43-50. DOI: 10.20514/2226-6704-2021-11-1-43-50

ANS — autonomic nervous system, CAR — coefficient of adaptation reserves, CDI — chronic duodenal insufficiency, CRG — cardiac rhythmography, DD — duodenum, GIM — gastrointestinal monitor, GIT — gastrointestinal tract, PA — personal anxiety, SA — situational anxiety, TI — tension index

The duodenum is located at the critical crossing between the stomach and small intestines, liver and pancreas, which determines its importance in the synchronization of digestive organs. Despite the long history of studying duodenal diseases, the problem remains relevant in modern gastroenterology. The significance of disorders in this segment of the gastrointestinal tract (GIT) is also determined by the absence of a decrease in the incidence of gastric, biliary and pancreatic diseases over the past decade, which is also due to duodenal diseases [1].

Clinical observations show that patients with a duodenal disorder develop a complex set of symptoms, including morphological inflammatory changes in the duodenal mucosa (duodenitis), impaired gastrointestinal motor function and duodenal hormonal insufficiency. In most cases, duodenal diseases are chronic and lead to chronic duodenal insufficiency (CDI).

Considering the range of problems, in 2018, we proposed the term «chronic duodenal insufficiency», which is rarely used in modern clinical practice [2]. Firstly, this is due to limited diagnostic approaches in clinical settings that allow to study the functional state of the duodenum. Secondly, CDI course is often subclinical due to comorbidities of GIT organs. Thirdly, general symptoms in patients with CDI often prevail over local symptoms due to impaired hormone-producing function of the duodenum [3].

The **objective of this work** is to study the clinical course and features of motor-evacuation disorders of the gastrointestinal tract in cases of CDI.

Materials and methods

This study included 40 patients diagnosed with chronic duodenal insufficiency (CDI): 18 (48.2%) women, 22 (51.8%) men, mean age 37.1 ± 13.8 years. The control group included 30 healthy individuals: 10 (33.3%) women, 20 (66.7%) men, mean age 40.5 ± 13.47 years. Comparability in the two groups was determined by age ($p = 0.104$) and by gender ($\chi^2 = 2.59$, $p = 0.114$). This was an open-label cohort study. Inclusion criteria: signs of CDI according to fibrogastroduodenoscopy (FGD) results and voluntary informed consent of patients to participate in this study. Exclusion criteria: diabetes mellitus, age under 18 and over 65, thyroid diseases, pregnancy and lactation, cancer and autoimmune diseases, chronic viral hepatitis, liver cirrhosis. This study was performed in two stages.

For CDI determination, medical history data and physical findings, results of X-ray and endoscopic examinations, intracavitary manometry were used [4]. Endoscopic criteria for CDI [5]: bile in stomach in fasting state, persistent duodenogastric reflux, dilated duodenum, pyloric sphincter incompetence, yellow-green color of mucous lake, yellowish gastric mucus, congestion of gastric contents, large amount of bile in the duodenum, antral gastritis, reflux esophagitis, erythematous gastropathy, and hyperplasia of gastric folds.

Total serum protein was analyzed using the biuret method with the "Total Protein Agat" reagent kit (manufactured by Agat-Med LLC, Russia). Vitamin B12 concentration was determined by enzyme-linked immunosorbent assay in blood serum using the «Ridascreen@Fast Vitamin B12» reagent kit (manufactured by Stylab Company LLC, Russia). Serum alpha-amylase activity was determined using the amyloclastic method (according to Karavey) using the «Alpha-Amylase Agat» reagent kit (manufactured by Agat-Med LLC, Russia). Serum transferrin level was analyzed by enzyme immunoassay using the «ADVIA Chemistry Transferrin Reagents» reagent kit (manufactured by Siemens Healthcare Diagnostics, Germany). The level of triglycerides in blood serum was analyzed by enzyme immunoassay using the «Triglycerides — UTS» reagent kit (manufactured by Ailiton LLC, Russia). The determination of 25-OH vitamin D was carried out by enzyme immunoassay using the "25-OH Vitamin D" kit (manufactured by Techsystems CJSC, Russia) [6].

Gastrin, insulin, and cortisol levels in peripheral blood were determined by electrochemiluminescence-based analysis. To determine cortisol level, we used a reagent-kit manufactured by Vector-BEST (Russia), reference number — X-3964, range of measured values declared by the manufacturer — 0–1200 nmol/l; for insulin — a reagent kit manufactured by DRG Instruments GmbH (Germany), reference number EIA2935, range of measured values declared by the manufacturer — 0.75–300 μmol/l; for gastrin — a reagent kit manufactured by Biohit (Finland), reference number 601035, range of measured values declared by the manufacturer — 0–52.3 pmol/l [7].

A histological examination of a biopsy specimen obtained during fibrogastroduodenoscopy (FGD) from the gastroduodenal zone was performed.

To determine the closing function of the pylorus, the ratio of intraduodenal to intragastric pressure was used, which was studied using the open-tip catheter manometry technique with Waldman's device [8].

The GEM-01 Gastroskan-GEM (Istok-Sistema, Fryazino) gastrointestinal monitor was used to assess the motor function of the gastrointestinal tract (GIT). The following parameters were evaluated: Pi, Pi/Ps(%), Pi/P(i+1), and C rhythm, where Pi is the electrical activity of each GIT organ; Pi/Ps is the percentage of the ratio of the frequency spectrum to the total spectrum; Pi/P(i+1) is the ratio of the electrical activity of the upper organ to the lower organ; and C rhythm is rhythm coefficient, which is the ratio of the length of the spectral envelope of the examined part to the width of its spectral section. These studied parameters were determined in fasting state and in postprandial period [9].

The Eysenck Personality Questionnaire (EPQ) was used to assess the type of personality. A score of up to 10 points indicates introversion, from 15 to 24 points — extroversion, from 11 to 14 points — ambiversion [10]. High average values (more than 16 points) on the neuroticism scale indicate high emotional instability. Personal (PA) and situational anxiety (SA) were determined using the Spielberger State-Trait Anxiety Inventory (adapted by Yu. L. Khanin). SA is an indicator of the intensity of feelings that arise in response to the current situation, PA is a person's tendency to perceive a wide range of situations as threatening. Interpretation of results: up to 30 points is a low level of anxiety, 31–44 points — moderate, 45 or more — high.

Heart rate variability analysis with the Varicard 2.51 (Yupacom Company, Russia) device was performed to study the functioning of the autonomic nervous system (ANS). The following parameters were used: Mo (mode) is the most common duration of R-R intervals; AMo (mode amplitude) is the number of cardio intervals that fall within the mode range as a percentage; ΔX of the variational range is the maximum amplitude of fluctuations in the values of cardiac intervals; TI (tension index) reflects the degree of heart rhythm control centralization. Vegetative reactivity (VR) is a reaction of the ANS to external and internal stimuli, which was determined

by the following formula: TI2/TI1, where TI1 is clinostatic position, TI2 is orthostatic position, first episode (minute 1) [11].

In cases of normal vegetative reactivity, the TI2/TI1 value is in the range from 0.7 to 1.5; with hypersympathicotonic — more than 0.5; with asympaticotonic — less than 0.7 [11]. The coefficient of adaptation reserves (CAR) was calculated using the TI3/TI2 formula, where TI3 is the orthostatic position from minute 5. Normal CAR is in the range from 0.33 to 3; insufficient — with CAR under 0.33; excessive — with CAR over 3 [12].

Statistical processing of the obtained data was carried out using Excel® 2016, IBM SPSS v. 17.0. The Kolmogorov-Smirnov test was used to check whether sign distribution was within normal. When deviating from the normal distribution, quantitative signs were expressed as the median and interquartile range (25th percentile — 75th percentile) — Me [IQR]]; when corresponding to the law of normal distribution — as the mean value with standard deviation (M ± σ). The following was used to assess intergroup difference depending on the nature of distribution: Mann-Whitney test (U), Student's t-test, Pearson's chi-square test (χ^2) to compare qualitative parameters. Differences were considered statistically significant at $p < 0.05$.

Patients were examined on the basis of voluntary informed consent, in accordance with order No. 390n of the Ministry of Health and Social Development of the Russian Federation of April 23, 2012, in compliance with ethical principles (resolution of the Ethics Committee of 25 June 25, 2013).

Results

The study of the social status of patients with CDI revealed that 30 (75.8%) of the examined individuals were employees with computer-related work, and only 10 (26.1%) of the patients were workers with an active lifestyle. 30 (75.8%) patients with CDI associated their state of health with negative emotional stress.

Concomitant pancreatitis was diagnosed in 30 (75.8%) patients with CDI, chronic acalculous cholecystitis — in 27 (66.8%), postcholecystectomy syndrome — in 25 (63.6%), gastroesophageal reflux disease — in 32 (80.2%).

Nineteen (46.8%) patients with CDI experienced pain after eating, most often localized in the right upper quadrant — in 11 (29.0%) patients, and in the epigastrium — in 18 (44.9%) patients. The painless variant was detected in 5 (12.3%) patients with CDI. Most patients had "aching" pain (32 (80%)).

Patients with CDI had certain complaints of dyspepsia that were not observed in the control group (Table 1): 22 (57%) of them had bitter eructation, 31 (77.6%) — bitter taste in the mouth, 21 (53%) — heartburn, 25 (53.3%) — flatulence, and 28 (71%) — loose stool. Asthenic syndrome was found in 25 (63.3%) patients of the study group ($\chi^2 = 54.8$, $p = 0.00037$), and was manifested by general weakness, irritability, apathy, insomnia.

General examination revealed dry skin with reduced turgor and elasticity in patients with CDI; 30 (74.3%) patients showed signs of roseola rash on the face, 17 (43.7%) — elements of pustular rash, 7 — (17.9%) signs of telangiectasias. On examination, the tongue was covered with white-yellowish fur in 31 (78.9%) patients, with herds of epithelial desquamation — in 7 (18.6%) patients. Most patients (34; 86.1%) had an asthenic body type with a lower body mass index compared with the control group (16.7 ± 0.27 and 24.3 ± 0.42 kg/m^2, $p = 0.025$).

Compared with the control group, patients with CDI showed a lower total protein level (62.24 ± 0.17 and 72.3 ± 0.21 g/l, $p = 0.00021$), which was probably associated with impaired absorption of protein in the duodenum. There was also a decrease in the level of triglycerides (0.42 ± 0.0021 and 1.5 ± 0.04 mmol/l, $p = 0.022$) and increase in amylase level (205.7 ± 12.9 and 126.9 ± 11.3 mmol/l, $p < 0.01$ mmol/l) compared with the control group (126.9 ± 11.3 mmol/l, $p = 0.00018$).

Table 1. *Characteristics of pain and dyspeptic syndromes in patients with CDI*

Parameter	n (%)	χ^2	p
Painless option	5(12,3%)	60,8	0,0022
Pain in the right hypochondrium	11 (29,05)	38,4	0,0017
Pain in the epigastric region	18 (44,9%)	36,3	0,025
Aching nature of pain	32(80%)	18,1	0,0039
Belching bitter	22 (57%)	51,8	0,0013
Feeling bitter in the mouth	31 (77,6%)	66,53	0,00217
Heartburn	21 (53%)	20,2	0,000122
Flatulence	25 (53,3%)	53,3	0,0014
Mushy stool	28 (71%)	60,2	0,0018

Note: CDI — chronic duodenal insufficiency, p — reliability, n — number of patients

A decrease in the levels of fat-soluble vitamin B12 (188.0 ± 0.21 and 328.6 ± 18.9 pg/ml, p = 0.0048) and 25-OH vitamin D (26.87 ± 0.12 and 64.7 ± 1.25 ng/ml, p = 0.018) also indicates duodenal malabsorption in patients with CDI compared with the control group.

The study of iron metabolism revealed a decrease in the transferrin saturation coefficient in patients with CDI compared with the control group (13.2 ± 0.12% and 34.7 ± 0.18%, p = 0.04).

A significant increase in the levels of gastrin (29.7 [25.7; 32.5] and 19.2 [18.8; 20.1] pmol/l, p = 0.0004) and cortisol (471.8 ± 1.09 and 365.3 ± 2.6 nmol/l, p = 0.000147) was also detected in patients with CDI compared with the control group. Insulin level was significantly lower than in the control group: (2.89 [2.5; 3.0] and 3.8 [2.2; 4.5] μmol/l, p = 0.006).

Besides signs of CDI, FGD revealed the following changes in patients: erythematic gastropathy in 37 (93.3%) patients, reflux esophagitis in 27 (66.6%) patients, atrophic gastritis in 17 (42.0%) patients, erosive and ulcerative lesions of the mucosa in 21 (53.3%) patients. According to the histological analysis of the biopsy specimen, patients with CDI developed atrophy in 16 (42.0%) cases, and intestinal metaplasia in 2 (5.6%) cases. All patients had morphological changes of the duodenal mucosa: lymphocytic infiltration, chronic inflammation; 28 (70%) patients had atrophy.

Intracavitary manometry in patients with CDI compared with the control group showed a significant increase in intragastric (119 [114; 126] and 70 [57; 74.8] mm Aq, p = 0.00012) and intraduodenal pressure (168 [165; 172] and 116 [111.9; 124] mm Aq, p = 0.000029). The ratio of intraduodenal to intragastric pressure in patients with CDI was 1.26 [1.19; 1.32], which was significantly lower than in the control group (1.7 [1.0; 2.4], p = 0.00037).

Table 2 presents changes in the myoelectric activity of GIT organs in patients with CDI. The significant increase in gastric Pi/Ps in the postprandial period (46.5 ± 5.8%) was probably due to compensatory hypertrophy of gastric smooth muscles in this group of patients. The increase in the ratio Pi/Pi+1 stomach/duodenum (17.43 ± 2.46) in patients with CDI was caused by the difficult passage of food through the duodenum. An inadequate response of the duodenum to food stimulation, represented by a decrease in the electrical activity of the duodenum (1.7 ± 0.07%), was observed. Normal values of the gastric rhythm coefficient (4.7 ± 2.42) before food stimulation decreased postprandially (3.9 ± 0.11). The low ratio of gastric rhythm was combined with the decrease in this parameter in the duodenum (0.72 ± 0.12 in fasting state; 0.3 ± 0.01 postprandially). There was no similar relationship with the rhythm coefficient in the jejunum.

The range of frequencies typical for the jejunum, ileum and colon revealed no differences in «Pi/Pi+1» and «Pi/Ps» parameters in fasting state between the group of patients with CDI and the control group. However, C rhythm in these parts of the intestine was significantly

Table 2. *Indicators of electrical activity of the gastrointestinal tract in patients with CDI according to (M ± σ)*

Indicators	Zone	Fasting		P	After meal		P
		Patients with CDI (n=40) (M±σ)	Control group (n=30) (M±σ)		Patients with CDI (n=40) (M±σ)	Control group (n=30) (M±σ)	
Pi/Ps (%)	Stomach	13,6 ±0,58	23,6±9,5	**0,000**	46,5±5,8	24,1±1,8	**0,000**
	Duodenum	4,4 ±1,02	2,1±0,68	**0,000**	1,7 ±0,07	2,18±0,17	**0,000**
	Jejunum	3,22±0,12	3,35±0,18	0,958	5,46±0,12	5,1±0,9	0,862
	Ileum	6,54±0,22	8,08±0,15	0,890	17,62±0,42	12,1±1,4	**0,015**
	Colon	69,01±4,14	64,04±3,16	0,622	39,62±2,45	76,2±8,2	**0,000**
Pi/P (i+1)	Relationship Stomach/ Duodenum	6,7 ±0,38	10,4±5,7	**0,000**	17,43 ±2,46	10,2±4,2	**0,000**
	Relationship Duodenum/ Jejunum	0,45±0,01	0,60±0,02	**0,000**	0,40±0,02	0,5±0,06	**0,000**
	Relationship Jejunum/ Ileum	0,46±0,04	0,40±0,01	0,425	0,36±0,08	0,32±0,12	0,874
	Ileum/ Colon	0,109±0,08	0,13±0,04	0,398	0,57±0,09	0,22±0,05	**0,000**
K ritm	tomach	4,7 ±2,42	4,85±2,1	0,883	3,9 ±0,11	4,71±0,18	**0,001**
	Duodenum	0,72 ±0,12	0,9±0,5	**0,013**	0,3±0,01	0,87±0,05	**0,000**
	Тощая Jejunum	2,26±0,51	3,43±0,18	**0,03**	1,519±021	3,26±0,11	**0,003**
	Ileum	3,077±1,39	4,99±0,29	**0,021**	2,44±0,08	5,11±0,21	**0,017**
	Colon	28,03±3,37	22,85±4,17	**0,004**	6,33±1,25	25,18±5,18	**0,000**

Note: signs obey the law of normal distribution (according to the Kolmogorov-Smirnov criterion), presented as M — arithmetic mean, σ — standard deviation), p — the significance of the reliability of differences between the observation group and control groups of patients (according to Student's t-test), n- number of patients.
Duodenal ulcer — duodenum, CDI — chronic duodenal insufficiency. Pi is the electrical activity of each organ of the gastrointestinal tract, Pi / Ps is the ratio of the frequency and total spectrum in percent, Pi / Pi + 1 is the ratio of the electrical activity of the overlying organ to the underlying one, K ritm is the rhythm coefficient, which is the ratio of the length of the envelope of the spectrum of the examined section to the width of the spectral section of this section

different in patients with CDI compared with the control group, which indicates impaired motor and evacuation function of the small intestine and colon in patients with CDI in fasting state. In the postprandial period, there was also impaired propulsive motility in all parts of the gastrointestinal tube, indicating a 1.5-fold decrease in the rhythm coefficient of the duodenum, jejunum and ileum in fasting state in both stages of this study (p = 0.000).

Analysis of the general diagram of the study of the myoelectric activity in the stomach, large intestine and small intestine in three-dimensional mode in patients with CDI showed an increase in signal strength from the stomach in the postprandial period and a decrease in signal strength from the duodenum and colon in comparison with fasting state.

Analysis of psychoemotional disorders revealed a higher level of situational (57 [54; 60] and 47.0 [45; 50] points, p = 0.0021) and personal anxiety (25.1 [22.6; 27.4] and 21.9 [19.5; 23.9] points, p = 0.003) in patients with CDI compared with the control group. Values on the «extraversion-introversion» scale in patients with concomitant CDI were below the control level (8.92 ± 0.29 points), suggesting their introversion tendency.

The study of ANS functioning (Table 3) based on the results of cardiac rhythmography (CRH) in patients with CDI compared with the control group revealed the predominance of the sympathetic division of ANS: Mode amplitude was 94.0% [92.5; 97.5] and 48.3% [45.5; 49.9], respectively, p = 0.00013; variational range (ΔX) was 0.03 [0.018; 0.043] and 0.24 [0.2; 0.3] respectively, p = 0.00022; and TI1 was 1110.4 [1077.5; 1129.3] conventional units and 115.0 [110.0; 121.0] respectively, p = 0.00019. Patients with CDI demonstrated an asympathicotonic

Table 3. *The functioning of the ANS in patients with HTN (Me [IQR])*

Parameters	Patients with CDI (n=40)	Control group (n=30)	p
AMo, %	94,0 [92,5;97,5]	48,3 [45,5;49,9]	0,00013
ΔX (c./s.)	0,03 [0,018;0,043]	0,24 [0,2;0,3]	0,00022
IN1 (con.unit)	1110,4 [1077,5;1129,3]	115,0 [110,0;121,0]	0,00019
IN2 (con. unit)	421,3 [396,5;459,2]	81,1 [80,9;81,2]	0,00054
IN3 (con. unit)	121,7 [107,23;131,4]	61,2 [61,1;61,4]	0,00059
IN2/IN1	0,58 [0,53;0,65]	1,1 [1,05;1,17]	0,024
IN3/IN2	IN3/IN2=0,34[0,2;0,5]	1,32[1,31;1,33]	0,0016

Note: traits do not obey the law of normal distribution (according to the Kolmogorov-Smirnov criterion), presented as Me-median and interquartile range (25th percentile — 75th percentile) — [IQR]., P — significance of differences between the observation group and the control group of patients (according to the Kruskal-Wallis criterion, n is the number of patients, duodenal ulcer, duodenal ulcer, chronic duodenal insufficiency, chronic duodenal insufficiency. range — the maximum amplitude of fluctuations in the values of cardiointervals, IN — stress index, IN2 / IN1 — an indicator of autonomic reactivity, IN1 — wedge position, IN2 — orthoposition the first episode (1st minute), IN3 / IN2- CRA- adaptation reserve coefficient, IN 3- Orthopositional second episode (5th minute)

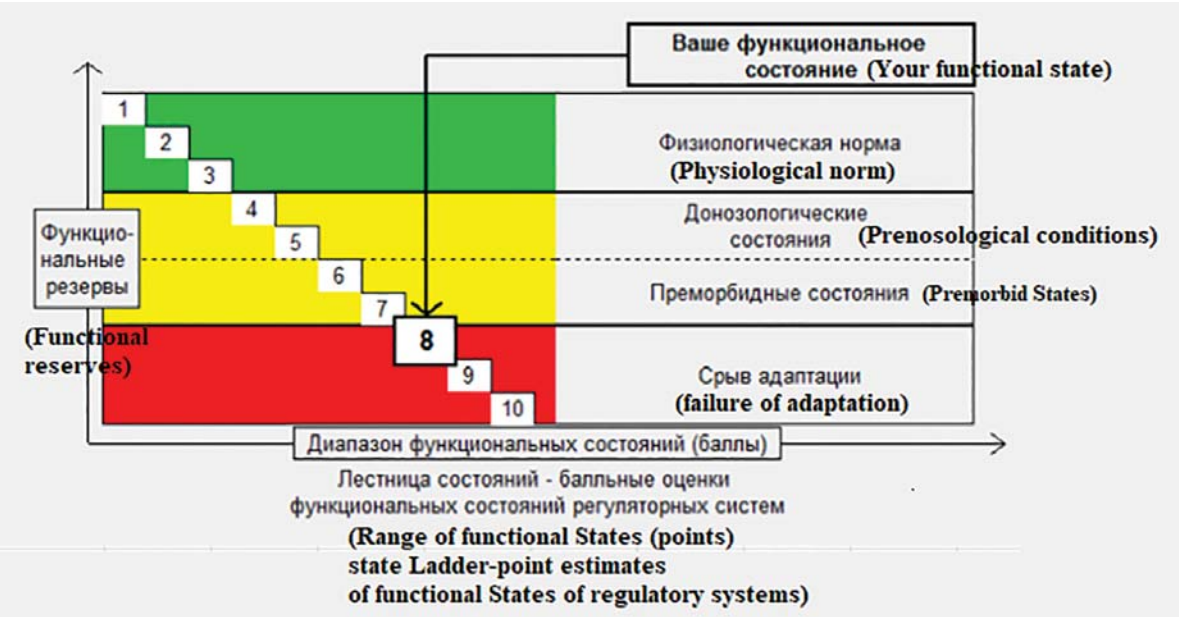

Figure 1. *Scoring of functional states of VNS in CDI*

type of autonomic reactivity in comparison with the control group (TI2/TI1 = 0.58 [0.53; 0.65] and 1.1 [1.05; 1.17] respectively, p = 0.024) and insufficient CAR (TI3/TI2 = 0.34 [0.2; 0.5] and 1.32 [1.31; 1.33] respectively, p = 0.0016). The obtained CRH data in Fig. 1 are presented in the form of a ladder of states and indicate that most patients with CDI (33 (83.5%)) are on the verge of ANS adaptation failure.

Direct correlation analysis demonstrated a moderate direct relationship (r = 0.447, p = 0.007) between Pi/Pi+1 (S/DD) and mode amplitude in patients with CDI, which indicates the regulatory effect of ANS on gastroduodenal motility.

Discussion

Epigastric pain in patients with CDI can be explained by concomitant gastrostasis caused by impaired gastric motor function. Through gastrography, gastric pain was previously attributed to a specific convulsive state of the stomach, characterized by a sharp increase in its tone, with frequent and rapid cramps (clonicotonus) at its peak [13]. This was confirmed during this study. Gastric and duodenal hypertension was observed based on the results of studying electrical activity in fasting state. In the postprandial period, impaired propulsive motility was observed in all parts of the gastrointestinal tract, contributing to pain [14]. The origin of numerous dyspeptic symptoms can be explained not only by the impaired functional state of the duodenum but also by comorbidities of the digestive system.

The secondary lesion of the celiac plexus caused by overexcitation of the sympathetic and parasympathetic divisions of the autonomic nervous system has a certain significance in the development of pain syndrome and its severity in patients with CDI [15].

Most patients have asthenia manifested by increased fatigue, irritability, apathy, sleep disturbance, in the occurrence of which the stagnation of duodenal contents is crucial [16]. The development of generalized symptoms can be interpreted as impaired absorption of vitamins, trace elements and proteins in the duodenum, which was also established in our study.

Many abnormal signs during the experiment after the removal of the duodenum are caused by the loss of the effect of duodenal hormones (gastrin, secretin, cholecystokinin, etc.) [17]. Also, disorders of the intestinal hormonal system have an effect not only within the gastrointestinal tract but also non-digestive (trophic) effect by interacting with pituitary and endocrine hormones[18]. In our study, the increase in gastrin level in patients with CDI was probably associated with the irritating effect of DGR on G cells in the antrum. Cortisol level can change as a result of any stressful effect, impaired body adaptation observed in patients with CDI in the form of increased anxiety level. The decrease in insulin level in patients with CDI compared with the control group may be due to the decrease in n. vagus tone, and the impaired production of the "insular hormone" that induces insulin production [19].

Conclusion

A specific feature of the clinical course of chronic duodenal insufficiency is the predominance of dyspeptic complaints over pain syndrome. The motor and evacuation function of the stomach, duodenum and small intestine is simultaneously impaired during periods of fasting and active digestion. It was found that neurohormonal factors, including the autonomic nervous system, psychoemotional state, and gastrointestinal hormones, are of great importance in regard to the impaired functional state of the duodenum. Due to the silent course and absence of specific symptoms of chronic duodenal insufficiency, X-ray, endoscopic, manometric and electrophysiological studies should be used, in addition to clinical data, in the examination of patients for diagnosis.

Вклад авторов

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

Вахрушев Я.М. (ORCID ID: https://orcid.org/0000-0001-9424-6316): разработка концепции и дизайна, интерпретация и критический анализ результатов, формулировка выводов, редактировании, окончательном утверждении для публикации

Бусыгина М.С. (ORCID ID: https://orcid.org/0000-0003-1740-2391): сбор и обработка материала, написание текста

Воробьева А.В. (ORCID ID: https://orcid.org/ 0000-0003-1459-2337): сбор материала

Фаррахов А. М. (ORCID ID: https://orcid.org/0000-0001-8472-9330): сбор материала

Contribution of authors

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

Vakhrushev Ya.M. (ORCID ID: https://orcid.org/0000-0001-9424-6316): concept and design development, interpretation and critical analysis of the results, formulation of conclusions, editing, final approval for publication

Busygina M.S. (ORCID ID: https://orcid.org/0000-0003-1740-2391): collecting and processing material, writing text

Vorobieva A.V. (ORCID ID: https://orcid.org/ 0000-0003-1459-2337): collection of material

Farrakhov A.M. (ORCID ID: https://orcid.org/0000-0001-8472-9330): collection of material

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DOI: 10.20514/2226-6704-2021-11-1-51-59

Е.Ю. Кудашкина*[1], Е.Г. Гавриленко[1], А.А. Якушев[2], Г.Г. Тотолян[1], Н.Н. Петренко[2], Л.Ю. Ильченко[1,2], И.Г. Федоров[1,2], И.Г. Никитин[1,3]

[1]— Кафедра госпитальной терапии № 2 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
[3]— Федеральное государственное автономное учреждение «Лечебно-реабилитационный центр» Минздрава России, Москва, Россия

ПЕРВИЧНЫЙ ГИПЕРПАРАТИРЕОЗ С ПРЕИМУЩЕСТВЕННЫМ ПОРАЖЕНИЕМ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

E.Yu. Kudashkina*[1], E.G. Gavrilenko[1], A.A. Yakushev[2], G.G. Totolyan[1], N.N. Petrenko[2], L.Yu. Ilchenko[1,2], I.G. Fedorov[1,2], I.G. Nikitin[1,3]

[1]— 2nd Department of hospital therapy, N.I. Pirogov Russian national research medical university, Moscow, Russia
[2]— Federal state autonomous institution «Centre of medical rehabilitation» ministry of healthcare of the Russian Federation, Moscow, Russia
[3]— State Clinical hospital named after V. M. Buyanov, Moscow, Russia

Primary Hyperparathyroidism with a Predominant Lesion of the Gastrointestinal Tract

Резюме

Первичный гиперпаратиреоз является достаточно распространенной патологией, однако, несмотря на это, врачи различных специальностей сталкиваются с трудностями при его диагностике. Многообразие клинических проявлений обуславливает длительный срок постановки диагноза и, как следствие, несвоевременность начала лечения. Описаны, с учетом патогенеза, основные симптомы данной патологии. Лабораторными маркерами гиперпаратиреоза служат стойкое повышение уровня паратиреоидного гормона и гиперкальциемия. Визуализирующие методы обследования используются для верификации заболевания. Прицельное ультразвуковое исследование паращитовидных желез необходимо проводить всем пациентам с подозрением на нарушение обмена кальция.

В данной статье представлен клинический случай первичного гиперпаратиреоза с преимущественной гастроинтестинальной симптоматикой. Пациентка дважды госпитализировалась в стационар с различными клиническими проявлениями поражения органов желудочно-кишечного тракта. Были установлены такие патологии как эрозивный гастрит, терминальный илеит, хронический панкреатит, желчекаменная болезнь.

Проводился дифференциальный диагноз с лимфомой тонкой кишки, болезнью Крона. Кроме того, имелась общемозговая симптоматика в виде заторможенности, быстрой истощаемости. Из-за тяжелых электролитных расстройств пациентка наблюдалась в реанимационном

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

отделении. В связи с развитием механической желтухи выполнена эндоскопическая ретроградная холангиопанкреатография с папиллосфинктеротомией. На основании гиперкальциемии, повышенного уровня паратиреоидного гормона, визуализации образования паращитовидной железы по данным ультразвукового исследования был установлен диагноз первичного гиперпаратиреоза. В хирургическом отделении проведена аденомэктомия левой нижней паращитовидной железы. Больная была выписана с положительной динамикой в виде улучшения общего самочувствия, прекращения болевого синдрома, рвоты, расширения двигательной активности. Своевременная диагностика и лечение первичного гиперпаратиреоза, на примере описанного случая, приводит к полному купированию симптомов и улучшению качества жизни пациентов.

Ключевые слова: *первичный гиперпаратиреоз, гиперкальциемия, паратиреоидный гормон*

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 08.10.2020 г.

Принята к публикации 17.11.2020 г.

Для цитирования: Кудашкина Е.Ю., Гавриленко Е.Г., Якушев А.А. и др. ПЕРВИЧНЫЙ ГИПЕРПАРАТИРЕОЗ С ПРЕИМУЩЕСТВЕННЫМ ПОРАЖЕНИЕМ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА. Архивъ внутренней медицины. 2021; 11(1): 51-59. DOI: 10.20514/2226-6704-2021-11-1-51-59

Abstract

Primary hyperparathyroidism is a common pathology, but it is fact that doctors of various specialties run against difficulties in diagnosinging. The variety of clinical manifestations causes a long period of diagnosis and, late start of treatment. The main symptoms of this pathology are described taking into account the pathogenesis. The most common laboratory markers of hyperparathyroidism are incrising level of parathyroid hormone and hypercalcemia. Imaging examination methods are used to establish primary hyperparathyroidism. Targeted ultrasound examination of the parathyroid glands should be performed in all patients with suspected calcium metabolism disorders.

This article presents a clinical case of primary hyperparathyroidism with predominant gastrointestinal symptoms. The patient was twice admitted to the hospital with various clinical manifestations of damage to the gastrointestinal tract. Erosive gastritis, terminal ileitis, chronic pancreatitis, and cholelithiasis were identified. A differential diagnosis was made with small intestine lymphoma and Crohn's disease. In addition, there were General cerebral symptoms in the form of lethargy, rapid exhaustion. Due to severe electrolyte disorders, the patient was observed in the intensive care unit. Due to the development of mechanical jaundice, endoscopic retrograde cholangiopancreatography with papillosphincterotomy was performed. Based on hypercalcemia, elevated parathyroid hormone levels, and visualization of parathyroid gland formation, the diagnosis of primary hyperparathyroidism was established based on ultrasound data. An adenomectomy of the left lower parathyroid gland was performed. in the surgical department. The patient was discharged with positive dynamics in the form of improvement in General health, cessation of pain, regress of vomiting, expansion of motor activity. Betimes diagnosis and treatment of primary hyperparathyroidism, on the example of the described case, leads to complete relief of symptoms and improvement of the quality of life of patients.

Key word: *primary hyperparathyroidism, hypercalcemia, parathormone*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

Sources of funding

The authors declare no funding for this study

Article received on 08.10.2020

Accepted for publication on 17.11.2020

For citation: Kudashkina E.Yu., Gavrilenko E.G., Yakushev A.A. et al. Primary Hyperparathyroidism with a Predominant Lesion of the Gastrointestinal Tract. The Russian Archives of Internal Medicine. 2021; 11(1): 51-59. DOI: 10.20514/2226-6704-2021-11-1-51-59

ALP — alkaline phosphatase, BP — blood pressure, CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration Formula, CNS — central nervous system, D-FIS — Daily Fatigue Investigation Scale, EGD — esophagogastroduodenoscopy, GFR — glomerular filtration rate, GIT — gastrointestinal tract, HR — heart rate, MEN — multiple endocrine neoplasia, MSCT — multispiral computed tomography, PHPT — primary hyperparathyroidism, PTH — parathyroid hormone, SD — standard deviation, US — ultrasound

Relevance

Primary hyperparathyroidism (PHPT) (fibrocystic osteodystrophy, Recklinghausen's disease, parathyroid osteodystrophy) is an endocrine disease caused by hyperproduction of parathyroid hormone (PTH) by pathologically changed parathyroid glands and characterized by impaired calcium and phosphorus metabolism [1].

Until recently, PHPT was considered a rare disease with a pronounced clinical presentation with

predominant damage to the bone system and kidneys. Primary epidemiological studies included only patients who were admitted to the hospital with severe clinical signs. However, screening determination of blood calcium level later performed in Western Europe and the USA revealed that the true level of morbidity is much higher and includes a significant number of mild and asymptomatic forms, and the clinical picture is characterized by damage to various organs and systems [2–5].

The prevalence of PHPT ranges from 0.4 to 18.8 cases per 10,000 people. Data variability is the result of the lack of large international studies with uniform diagnostic standards. Peak incidence occurs in patients aged 40–60. Women suffer from this disease 2–4 times more often than men, while most women suffer from it in the postmenopausal period [5].

Among etiological factors, parathyroid adenoma is the cause in 80–85% of cases; in 15–20% of cases, PHPT is caused by hyperplasia of several/all parathyroid glands; parathyroid cancer is the cause in 1–5% of cases. Adenoma usually affects one gland, usually the lower one, but hyperplasia can develop in one, two, three or all four parathyroid glands. PHPT is sporadic in most cases (90–95%) [5]. About 5% of PHPT cases are a part of multiple endocrine neoplasia (MEN), a syndrome caused by tumors or hyperplasia in two or more endocrine organs. The following hereditary variants were also described: hyperparathyroidism syndrome with a tumor of the lower jaw, familial hypocalciuric hypercalcemia, and familial isolated hyperparathyroidism [6].

The pathogenesis of the clinical signs of PHPT includes excessive PTH production with a decrease in the regulatory effect of calcium on parathyroid hormone production, leading to its excessive release, i.e., impaired negative feedback mechanism. In cases of hyperplasia of parathyroid glands, an increase in the number of PTH secreting cells is observed. Excessive PTH increases bone resorption by osteoclasts and mobilization of calcium and phosphorus from them. The stimulating effect of PTH on 1,25-(OH)2-D3 production by the kidneys enhances calcium absorption in the intestine, and its excretion decreases. Excessive parathyroid hormone also affects intracellular calcium homeostasis, thus stimulating the release of calcium ions from cells in the extracellular space. A decrease in intracellular calcium concentration leads to impaired calcium-dependent processes: muscle contraction, nerve impulse conduction, and blood coagulation. These mechanisms lead to hypercalcemia syndrome and calcium deposition in different organs and tissues [7].

Significant challenges in the diagnosis of this disease can be attributed to a variety of its clinical manifestations. The diagnosis is established based on laboratory tests, persistent increase in PTH, and hypercalcemia. However, routine blood biochemistry does not include the determination of calcium level; this fact complicates diagnostic search and means more time is required to establish the right diagnosis.

We will describe one case of PHPT for illustrative purposes.

Case report

Patient D., 56 y.o., female, teacher; in September 2019, she was urgently hospitalized in intensive care unit for sudden significant general weakness, nausea, repeated vomiting of gastric contents, pain in the upper abdomen.

The patient considers herself ill since June 2019, when she first experienced abdominal pain, stool with a tendency to constipation, and general weakness. During the next three months, she was twice urgently hospitalized in different hospitals in Moscow with suspected acute pancreatitis; this diagnosis was subsequently not confirmed. During examination, esophagogastroduodenoscopy (EGD) revealed erosive gastritis; endosonography demonstrated calculous cholecystitis, signs of papillitis, microcholecholithiasis, and diffuse changes in the pancreas. Endoscopic retrograde cholangiopancreatography, papillosphincterotomy, drainage of bile ducts were performed. However, abdominal pain persisted. Therefore, an additional examination was carried out, which revealed kidney stones according to ultrasound (US) results; lymph nodes enlarged to 7.8 mm in diameter and located medial to the cecum during computed tomography (CT) of the urinary system; multiple polygonal flat ulcers covered by fibrin (terminal ileitis) during colonoscopy. This morphological presentation was suspicious in regard to lymphoma. Biopsy specimens of the terminal ileum revealed deformed mucosal fragments with an uneven ulcerated surface, with dense diffuse infiltration of stroma by lymphocyte-like cells with a small amount of plasmocytes and neutrophils, angiomatosis, foci of granulation tissue; in circumscribed portions, there were fragments of the integumentary epithelium, in the depth of the tissue — single deformed crypts with no goblet cells. However, immunohistochemistry of specimens and cerebrospinal fluid yielded no data suggesting lymphoma.

The patient's general condition on admission to the intensive care unit was severe. The patient was obtunded, rapid exhaustion was observed. The patient was hardly cooperative, with cognitive impairments. Twenty-three points according to D-FIS (Daily Fatigue Investigation Scale). This scale includes eight questions regarding the signs of fatigue, with five possible answers ranging from sign absence to its significant severity (maximum score — 32). Speech is slow and quiet, hoarse voice. The patient moved with difficulty due to severe muscle weakness. Skin was pale, dry, no peripheral swelling. Lymph nodes were not enlarged. Contours of the neck without changes, thyroid gland was not enlarged. Musculoskeletal system without visible abnormality. Vesicular breathing in lungs, respiratory rate — 18 per minute. Cardiac rhythm is regular, with heart rate 109 bpm. Heart tones are clear, blood pressure (BP) 130 and 100 mm Hg on both arms. Tongue is dry, covered with a whitish-yellow fur. Abdomen of regular shape, soft, moderately painful in the periumbilical area. Liver along the edge of the costal arch. Bowel sounds were auscultated. Stool with a tendency to constipations, type 2 and 3 according to the Bristol scale, formed, and brown without pathological impurities. No costovertebral angle tenderness on both sides. Urination is free, painless.

Complete blood count revealed mild normochromic normocytic anemia (hemoglobin — 90 g/l, RBC — 3.06×10^{12}/l, hematocrit — 27.1%).

Blood biochemistry: hypokalemia up to 2.4 mmol/l (3.44–5.3 mmol/l), aspartate aminotransferase — 76 IU/l (5–34 IU/l), alanine aminotransferase — 43 IU/l (0–32 IU/l), gamma-glutamyltranspeptidase — 180 IU/l (9–39 IU/l), lactate dehydrogenase — 728 IU/l (225–450 IU/l), creatine phosphokinase — 64 IU/l (33–211 IU/l), total bilirubin — 15.1 μmol/l (1.7–20.5 μmol/l), urea — 5.2 mmol/l (2.5–8.33 mmol/l), creatinine — 66 μmol/l (53–88 μmol/l), alpha-amylase — 96 IU/l (0–220 IU/l), glucose — 6.1 mmol/l (3.8–6.1 mmol/l), alkaline phosphatase — 135 IU/l (64–306 IU/l).

Ultrasound of the hepatobiliary system revealed diffuse changes in the liver, pancreas, and gallbladder calculi. Brain CT showed no abnormalities. According to echocardiography — local and global systolic contractile function of myocardium retained, left ventricular hypertrophy. Abdominal X-ray — moderate pneumatosis of the colon; no changes were found during the passage of barium suspension through the small intestine.

A differential diagnosis was made with lymphoma of the small intestine, Crohn's disease, neurological pathology (stroke, myasthenia, Guillain-Barre syndrome, focal pathology of the central nervous system (CNS)). Considering the non-specific clinical presentation and polysystemic nature of the disorder, PHPT was suspected.

Increased levels of serum PTH up to 300.4 pg/ml (15–65 pg/ml) and calcium — up to 3.57 mmol/l (1.9–2.75 mmol/l) were found, as well as decreased levels of 25-OH vitamin D down to 10.71 ng/ml (30–40 ng/ml) and magnesium — down to 0.62 mmol/l (0.66–1.07 mmol/l). Urine biochemistry showed a decrease in potassium to 10.2 mmol/l (20–80 mmol/l) and sodium — to 34 mmol/l (40–220 mmol/l) and an increase in calcium — to 10.55 mmol/l (2–6.4 mmol/l). Glomerular filtration rate (GFR) — 90 ml/min/1.73 m^2 (according to CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), 2011).

Ultrasound of the thyroid gland revealed thyroid nodules: in the middle segment, there was an isoechoic lesion 19 × 9 mm, with an inhomogeneous structure, with sharp and smooth contours; in the upper segment — several hypoechoic lesions up to 7 mm; posteriorly to the middle and lower segments of the left thyroid lobe — hypoechoic lesion 51 × 27 × 30 mm of the left lower parathyroid gland.

The patient was examined by an endocrinologist who confirmed PHPT. The following clinical diagnosis was established: PHPT with end-organ damage, severe course. Adenoma of the left lower parathyroid gland. Complications: Vitamin D deficiency Gallstone disease. Papillitis. Microcholecholithiasis. Papillosphincterotomy, drainage of bile ducts on August 19, 2019. Urolithiasis. Severe water-electrolyte imbalance (hypokalemia, hyponatremia, hypercalcemia). Comorbidities: Mild normochromic normocytic anemia. Hypertensive disease stage II, grade I, high risk (according to the Russian Hypertension Classification).

Adenomectomy of the left lower parathyroid gland was performed in the surgical department of the hospital. Morphological examination revealed a lesion of solid-trabecular structure, from parathyroid cells with eosinophilic cytoplasm, hemorrhages, thin fibrous capsule (parathyroid adenoma).

The patient was discharged with positive changes — cessation of pain and vomiting, increased general activity. The D-FIS fatigue score on discharge was 12 points. The recommendation included intake of vitamin D,

calcium (under control), spironolactone; laboratory tests over time; follow-up by an endocrinologist at the place of residence.

Currently (at the time of writing this paper), the patient's condition is satisfactory, PTH level 82 pg/ml (15–65 pg/ml).

Discussion

PHPT often has no typical clinical presentation and can mimic various diseases. However, there are specific changes that may lead the attending physician to suggest the possibility of PHPT accompanied by increased bone resorption, hypercalcemia and calcium deposition in different organs [7].

PTH releases calcium from the main depot, resulting in decreased bone density — parathyroid osteodystrophy with joint damage and development of chondrocalcinosis. This can be manifested by pain syndrome of different severity and pathological fractures. However, since patients with PHPT are postmenopausal women, these changes can be mistaken for postmenopausal or age-related osteoporosis. Without additional laboratory and diagnostic tests, such patients can be treated with calcium supplements, which will further exacerbate hypercalcemia and aggravate the course of disease [7].

Hypercalcemia leads to nephrolithiasis and nephrocalcinosis [8]. Single stones, multiple stones, calculi in both kidneys consisting of oxalates or calcium phosphates can be found. Surgical removal of stones does not lead to complete recovery. Calculi re-appear, also in the treated kidney. There is evidence of urolithiasis regression after surgical management of PHPT [9, 10]. In this case, the development of chronic kidney disease with reduced glomerular filtration leads to irreversible changes.

An increase in calcium in the extracellular space causes transmembrane imbalance of ions, impaired formation of resting membrane potential, and a decrease in the rate of transmission of nerve impulses [7]. This is manifested by slowness of thought (bradyphrenia), rapid fatigue, slow speech, and muscle weakness as a result of neuromuscular transmission disorders.

There has been an intense debate over the impact of PHPT on cardiovascular risks in recent times. This may be due to the direct action of PTH and calcium. Various forms of arrhythmia may develop. There is evidence that the normalization of calcium and PTH levels does not always make other risk factors return to normal after parathyroidectomy. Arterial hypertension is believed to remain unchanged after parathyroidectomy in patients with manifested PHPT [11].

Gastrointestinal symptoms are found in almost half of patients with PHPT [12]. Patients may have complaints of lack of appetite, constipation, nausea, flatulence, weight loss. The development of erosive and ulcerative lesions of the gastrointestinal tract (GIT) is associated with hypercalcemia and increased secretion of gastrin and hydrochloric acid, which returns to normal after removal of the substrate of PTH level increase. The course of peptic ulcers in cases of PHPT is characterized by a more pronounced clinical picture, more frequent exacerbations, bleedings; it is hard to manage, unlike peptic ulcers caused by other factors [12]. The lesion of the gastrointestinal mucosa can also be a consequence of hypergastrinemia due to MEN syndrome. GI motility is impaired, which leads to nausea, vomiting, weakened peristalsis in the stomach and intestine, constipation, and abdominal pain syndrome.

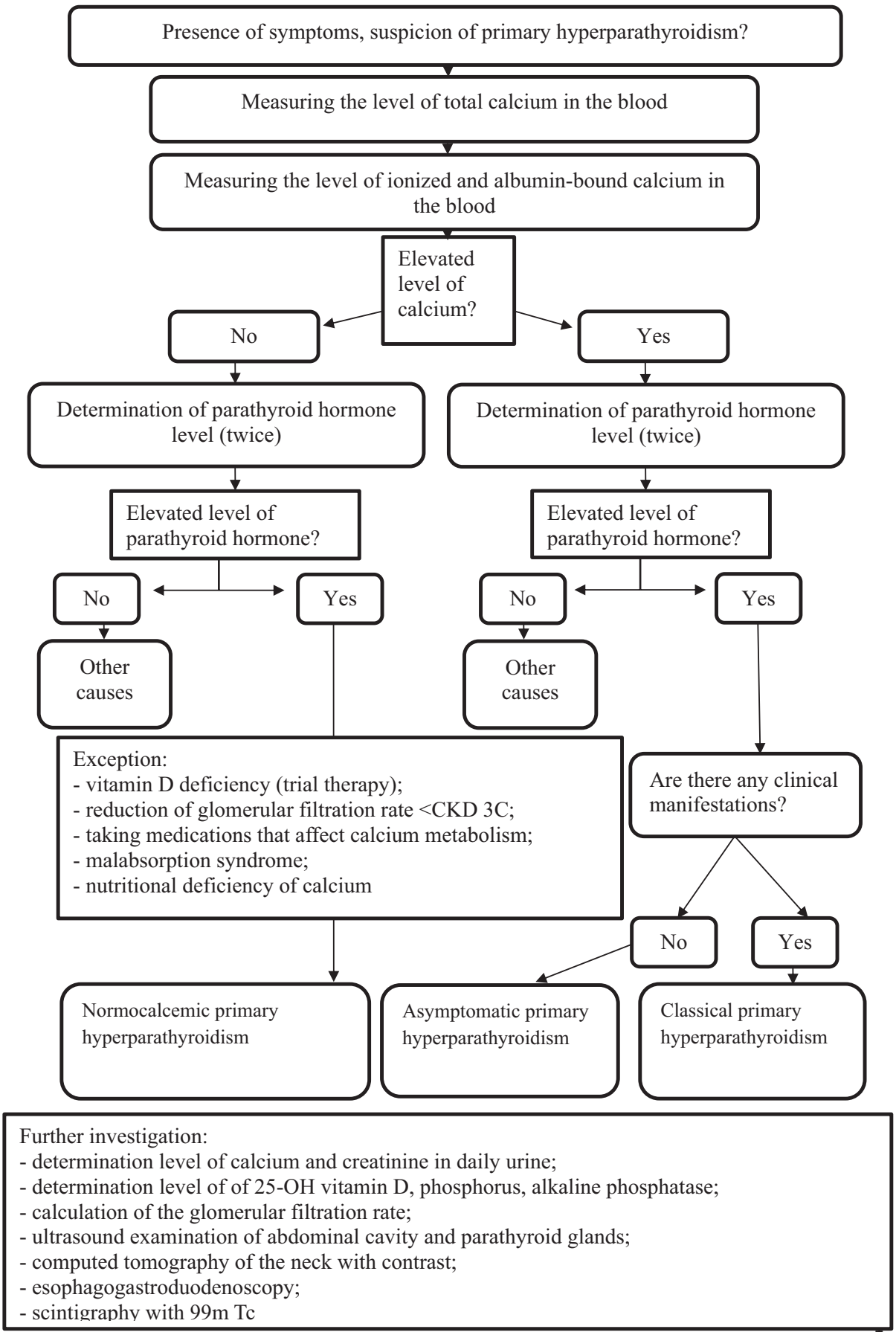
Experimental studies showed that hypercalcemia contributes to pancreatic stones, which causes the obstruction of ducts and recurrent pancreatitis. Hypercalcemia can trigger the conversion of trypsinogen to trypsin [13]. An increase in calcium concentration also leads to the formation of gallstones, choledocholithiasis with possible development of obstructive jaundice.

In the abovementioned clinical case, gastroenterological and neurological symptoms were predominant in the presence of polysystemic lesions. Erosive lesions of the upper gastrointestinal tract and intestine also developed. The revealed changes required the exclusion of other diseases (in particular, lymphoma of the small intestine, Crohn's disease), which complicated differential diagnosis and required more time for diagnostic search.

Cholelithiasis and signs of exacerbation of chronic pancreatitis led to repeated hospitalizations of the patient in the surgical department, demonstrating the challenges in establishing the right diagnosis.

Neurological symptoms required the exclusion of the pathology of the central and peripheral nervous system.

The normocalcemic variant of PHPT also poses certain diagnostic challenges [14]. Normal calcium levels in cases of PHPT may be due to the low specificity of determination of total blood calcium, hemodilution, malabsorption syndrome, vitamin D deficiency. For further examination, it is recommended to determine the level of ionized and albumin-bound calcium, as these parameters have greater sensitivity [1].



Scheme. *Algorithm for the diagnosis of primary hyperparathyroidism (ad. Russian assosiation of endocrinologists. Primary heperparathyroidism. Clinical trials, 2016 [1])*

Vitamin D (25(OH)D) deficiency is often observed in patients with PHPT, which exacerbates the manifestations of hyperparathyroidism accompanied by bone destruction and an elevated risk of postoperative hypocalcemia (hungry bone syndrome) [14].

In the differential diagnosis of the normocalcemic variant of PHPT with vitamin D deficiency with secondary hyperparathyroidism with vitamin D deficiency, pharmacological tests are used, i.e., experimental replacement therapy [14]. The intake of vitamin D by patients with PHPT will lead to hypercalcemia with increased PTH level, and in patients with secondary hyperparathyroidism, it will reduce/normalize PTH level with normocalcemia.

Many researchers consider different types of PHPT to be manifestations of different stages of this disease. Follow-up monitoring of patients with the normocalcemic variant demonstrated an increase in calcium level above reference values in 30% of individuals after 6–24 months [15].

Ultrasound is the basic screening method — and in most cases, the only method of imaging changed parathyroid glands. However, its sensitivity amounts ranges 36 to 90% [16]. The results largely depend on the experience of the specialist, the volume of parathyroid glands and the size of the lesion. During a non-localized examination, the specialist may not see or suspect any pathology. This method is also non-informative with atypical localization of parathyroid glands. In addition, lower parathyroid glands migrate with the thymus from the third gill pouch and can be ectopic. According to J. M. Ruda et al., 2005, the informative value of ultrasound in cases of multiple adenomas is significantly lower than with solitary adenomas, and amounts to 16–30% [16].

Accurate preoperative topical diagnosis helps to best plan the subsequent surgical intervention, which can be done using several imaging methods, for example, ultrasound and scintigraphy (see scheme).

The method of choice for PHPT management is surgical treatment — removal of pathologically changed parathyroid glands. According to the consensus of the European Society of Surgery [17], and Russian clinical guidelines [1], indications for surgical treatment are the following:

- serum concentration of total calcium 0.25 mmol/l (1 mg %) higher than normal;
- GFR reduction less than 60 ml/min/1.73 m^2;
- visceral manifestations of PHPT;
- daily calcium excretion of more than 400 mg per day;
- decrease in bone mineral density in radial, femoral or vertebral bones less than –2.5 SD (standard deviation) by T-test;
- history of fractures and/or fractures of vertebral bodies confirmed by X-ray;
- age under 50 years.

Intraoperative determination of PTH level as a marker of effective surgical treatment is recommended. A criterion for effective management is a decrease in PTH level by at least 50% from the baseline, 10 minutes after removal of parathyroid adenoma [18].

Conservative treatment of patients with PHPT with no indications for surgical treatment (mild types) includes diet with restriction of calcium intake, antiresorptive drugs (bisphosphonates, denosumab) and calcimimetics (cinacalcet).

Conclusion

Today, PHPT is a common disease, which can be encountered by any type of physician. The variety of clinical symptoms makes it difficult to establish the right diagnosis. Cases of atypical course of gastroenterological diseases (gastric and duodenal ulcer, chronic pancreatitis, gallstone disease, erosions and ulcers of the intestine) require considering the probability of parathyroid gland pathology and examining the patient according to the abovementioned algorithm (scheme).

Long-lasting PHPT leads to persistent organ damage. However, timely diagnosis and surgical treatment result in a favorable prognosis for the patient and significant regression of symptoms.

Вклад авторов:

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

Е.Ю. Кудашкина (Orcid ID: https://orcid.org/0000-0002-8819-8511): описание случая, создание блок-схемы

Е.Г. Гавриленко (Orcid ID: https://orcid.org/0000-0003-1079-1902): описание случая

А.А. Якушев (Orcid ID: https://orcid.org/0000-0003-1265-5090): редактирование текста

Г.Г. Тотолян (Orcid ID: https://orcid.org/0000-0002-9922-5845): систематизация данных обзора

Н.Н. Петренко: оценка морфологической картины биоптатов

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

И.Г. Федоров (Orcid ID: https://orcid.org/0000-0003-1003-539X): поиск литературных источников

И.Г. Никитин (Orcid ID: https://orcid.org/0000-0003-1699-0881): 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

E.Yu. Kudashkina (Orcid ID: https://orcid.org/0000-0002-8819-8511): describing the clinical case and creating of flowcharts

E.G. Gavrilenko (Orcid ID: https://orcid.org/0000-0003-1079-1902): describing the clinical case

A.A. Yakushev (Orcid ID: https://orcid.org/0000-0003-1265-5090): editing the paper

G. G. Totolyan (Orcid ID: https://orcid.org/0000-0002-9922-5845): systematization of review

N.N. Petrenko: Morphological describing of biopsy

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

I.G. Fedorov (Orcid ID: https://orcid.org/0000-0003-1003-539X): search for literature

I.G. Nikitin (Orcid ID: https://orcid.org/0000-0003-1699-0881): design and approval of the final version of the article

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DOI: 10.20514/2226-6704-2021-11-1-60-66

Г.А. Игнатенко[1], Г.Г. Тарадин*[1,2], А.Э. Багрий[1], И.В. Ракитская[1], К.Э. Могилевская[1], В.И. Меркурьев[3], А.Л. Христуленко[1]

[1] – ГОО ВПО «Донецкий национальный медицинский университет им. М. Горького», Донецк, Украина
[2] — ГУ «Институт неотложной и восстановительной хирургии им. В.К. Гусака», Донецк, Украина
[3] — КУ «Центральная городская клиническая больница № 1», Донецк, Украина

СЛУЧАЙ БРАДИКАРДИИ, РАЗВИВШЕЙСЯ НА ФОНЕ ГИПЕРКАЛИЕМИИ У ПАЦИЕНТКИ ОТДЕЛЕНИЯ АМБУЛАТОРНОГО ГЕМОДИАЛИЗА

G.A. Ignatenko[1], G.G. Taradin*[1,2], A.E. Bagry[1], I.V. Rakitskaya[1], K.E. Mogilevskaya[1], V.I. Merkuriev[3], A.L. Khristulenko[1]

[1] — State Educational Organization of Higher Professional Education «M. Gorky Donetsk National Medical University», Donetsk, Ukraine
[2] — State Institution «V.K. Gusak Institute of Urgent and Recovery Surgery», Donetsk, Ukraine
[3] – Clinical Institution «Central City Clinical Hospital № 1», Donetsk, Ukraine

The Case of Bradycardia Occured in the Setting of Hyperkalemia in a Patient in Ambulatory Hemodialysis Department

Резюме

В статье представлено клиническое наблюдение развития брадикардии у 64-летней пациентки с хроническим заболеванием почек, находящейся на лечении в отделении амбулаторного гемодиализа. При регистрации электрокардиограммы была зафиксирована аритмия в виде ритма из атриовентрикулярного соединения. Характерные изменения на электрокардиограмме, наличие факторов риска, данные дополнительно собранного анамнеза позволили предположить развитие опасного состояния — гиперкалиемии. Диагноз подтвердился после определения уровня сывороточного калия. Приведенный случай иллюстрирует необходимость рассматривать вероятность гиперкалиемии у пациентов с хроническим заболеванием почек, включая находящихся на гемодиализе. При возникновении характерных клинических проявлений и изменений на электрокардиограмме необходимо как можно быстрее определить сывороточное содержание калия для своевременной и адекватной коррекции электролитного нарушения.

Ключевые слова: *брадикардия, узловой ритм, нарушения ритма сердца, гиперкалиемия, калий, факторы риска, хроническое заболевание почек, гемодиализ*

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 01.10.2020 г.
Принята к публикации 13.01.2021 г.

Для цитирования: Игнатенко Г.А., Тарадин Г.Г., Багрий А.Э. и др. СЛУЧАЙ БРАДИКАРДИИ, РАЗВИВШЕЙСЯ НА ФОНЕ ГИПЕРКАЛИЕМИИ У ПАЦИЕНТКИ ОТДЕЛЕНИЯ АМБУЛАТОРНОГО ГЕМОДИАЛИЗА. Архивъ внутренней медицины. 2021; 11(1): 60-66. DOI: 10.20514/2226-6704-2021-11-1-60-66

*Контакты: Геннадий Геннадьевич Тарадин, e-mail: taradin@inbox.ru
* Contacts: Gennady G. Taradin, e-mail: taradin@inbox.ru
ORCID ID: https://orcid.org/0000-0003-3984-8482

Abstract

The presented article contains the clinical observation of bradycardia development in 64-year-old patient with chronic kidney disease who was in ambulatory treatment at the hemodialysis department. During electrocardiogram recording an arrhythmia was detected as a junctional rhythm. The specific changes on electrocardiogram, presence of risk factors, and data of additional collection of history disease allowed purposing the development of dangerous condition — hyperkalemia. The diagnosis was confirmed after detection of the serum potassium level. This case illustrates the necessity to consider the possibility of hyperkalemia in patients with chronic kidney diseases including those who undergoing hemodialysis treatment. Relevant clinical manifestations and changes on the electrocardiogram require the urgent assessment of the serum potassium level for timely and adequate correction of the electrolyte disorder.

Key words: *bradycardia, junctional rhythm, cardiac arrhythmias, hyperkalemia, potassium, risk factors, chronic kidney disease, hemodialysis*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

Sources of funding

The authors declare no funding for this study

Article received on 01.10.2020

Accepted for publication on 13.01.2021

For citation: Ignatenko G.A., Taradin G.G., Bagry A.E. et al. The Case of Bradycardia Occured in the Setting of Hyperkalemia in a Patient in Ambulatory Hemodialysis Department. The Russian Archives of Internal Medicine. 2021; 11(1): 60-66. DOI: 10.20514/2226-6704-2021-11-1-60-66

AH — arterial hypertension, AV — atrioventricular, BP — blood pressure, CKD — chronic kidney disease, ECG — electrocardiogram, HR — heart rate, K^+ — potassium, MV — mitral valve

Introduction

Hyperkalemia is often among electrolyte disorders that develop in cases of chronic kidney disease (CKD); it is diagnosed at serum potassium concentration (K^+) above the upper normal limit (> 5.5 mmol/l) [1, 2]. Severe hyperkalemia is a critical condition that requires emergency interventions due to its ability to cause life-threatening rhythm and conduction disorders, even cardiac arrest and death. Electrocardiogram (ECG) is an affordable diagnostic tool for the detection of hyperkalemia. Based on the concepts of clinical significance, the type of ECG changes is a more important predictor of the outcome than the actual K^+ blood level [3].

Some chronic diseases increase the risk of hyperkalemia, especially progressive CKD, chronic heart failure, type 2 diabetes mellitus, and arterial hypertension [4]. Several agents also increase serum K^+ levels, particularly renin-angiotensin-aldosterone system inhibitors, angiotensin II receptor antagonists, potassium-sparing diuretics and non-steroidal anti-inflammatory drugs [5, 6]. Irrational intake of K^+ with foods with its high content, even in the cases of normal K^+ concentration in serum, can also be accompanied by adverse cardiovascular and renal events [7]. Risk factors for hyperkalemia are presented in the following table 1 [5].

Clinical manifestations of severe hyperkalemia, such as arterial hypotension, shock, severe weakness to complete inability to move the limbs, and cardiac arrest can easily be mistaken for a worsening of the underlying disease [3]. In such cases, ECG changes help establish the correct diagnosis before measuring serum K^+ level [3, 8].

Severe hyperkalemia slows down the rate of conduction in the His — Purkinje system, which can be manifested by different conduction disorders. ECG may reveal significant bradycardia or sinus arrest with the appearance of substitutive junctional or idioventricular rhythms, various atrioventricular (AV) conduction disorders, even complete transverse blockade [3, 9, 10]. Our observation describes one of such rhythm disorders in a patient with CKD.

Table 1. *Risk factors for the development of hyperkalemia**

Clinical Risk Factors	Medication Exposure
Male gender	Potassium supplements
Caucasian	Penicillin G
Diabetes mellitus	Digoxin
Cardiovasular diseases	Nonsteroidal anti-inflammatory drugs
Chronic heart failure	Angiotensin-converting enzyme inhibitors angiotensin receptor blocker
Acute kidney injury	Mineralocorticoids receptor antagonist
Chronic kidney disease	β-adrenergic blockers
Acidosis	Heparin
Urinary tract obstruction	Amiloride, triamterene, trimethoprim, pentamidine

* **Note:** Adapted from J.R. Montford et al. [5]

Case report

Patient K., female, 64, since 2013 has been undergoing outpatient treatment in the Hemodialysis Department for CKD stage V as the outcome of chronic mesangial proliferative glomerulonephritis, chronic tubulointerstitial nephritis, renal replacement therapy with hemodialysis since 10 JUL 2013; nephrogenic anemia; symptomatic AH grade 3.

The patient has glomerulonephritis since 1976, when proteinuria of up to 1 g/l was first detected; since 1985, occasional swelling on legs to the knee level — the patient asked for medical help, was examined, consulted with a nephrologist. In 1985, she was diagnosed with chronic glomerulonephritis with retained renal function, received treatment (heparin, dipyridamole, delagil, ascorutin).

In 1990, puncture biopsy of kidney was performed. Conclusion: chronic mesangial proliferative glomerulonephritis with moderate tubulointerstitial component, in combination with chronic tubulointerstitial nephritis.

Since 1990, AH has been registered at home, with blood pressure (BP) 180–220/100–120 mm Hg; antihypertensive agents were prescribed. At that time, serum urea and creatinine levels were within normal.

For a long period of time — until 2011 — the patient did not visit a nephrologist, was not examined, levels of creatinine, urea and electrolytes were checked extremely rarely; we found no available data. In January 2011, azotemia was revealed during planned hospitalization: serum urea — 15 mmol/l, creatinine — 0.28 mmol/l, glomerular filtration rate (GFR) — 16 ml/min/1.73 m^2 (CKD-EPI). After discharge from the hospital, the patient did not visit a nephrologist for one year.

However, according to the patient, her condition began to deteriorate: in January 2012, nausea, vomiting, severe weakness, shortness of breath at rest appeared, AH could not be corrected (the patient does not remember the agents used). Laboratory tests (05 MAR 2012) revealed urea level of 36.0 mmol/l, creatinine — 1.02 mmol/l, GFR — 3 ml/min/1.73 m^2 (CKD-EPI), K^+ — 4.6 mmol/l. In May 2012, live-saving renal replacement therapy with program hemodialysis was started, and the condition significantly improved: nausea, weakness, dyspnea decreased, blood pressure decreased to 140/80 mm Hg, urea (to 25 mmol/l) and creatinine (to 0.6 mmol/l). K^+ level during routine tests ranged from 3.1–5.4 mmol/l. According to the records in the Hemodialysis Department, no previous episodes of clinically significant hyperkalemia were observed in this patient.

Additional examinations during a visit to the Hemodialysis Department:

24 JUL 2020: Echocardiography revealed additional transverse trabeculae of left ventricle (in apex area), left ventricular myocardial hypertrophy (left ventricular myocardial mass 257.68 g, left ventricular myocardial mass index 154.3 g/m^2), moderate dilation of left atrium (LA diameter 4.8 cm), satisfactory myocardial contractility (contractility 36%, ejection fraction according to Teichholz 64.6%). Pulmonary pressure was 24 mm Hg. Mild mitral insufficiency was also found (MV leaflet sclerosis with fibrotic foci, calcification (grade 1–2) of the posterior MV leaflet, some limited excursion of MV leaflets). No signs of local contractility disorder were found.

28 JUL 2020: 24h ECG monitoring in the presence of sinus rhythm revealed the following disorders: single supraventricular extrasystole — 175 per day; group (3–4 complexes) supraventricular extrasystole — 4 per day; single monomorphic ventricular extrasystole — 3 per day. Average heart rate (HR) during daytime — 82 bpm, minimum — 57 bpm, and maximum — 132 bpm; average HR during night sleep — 60 bpm, minimum — 51 bpm, and maximum — 82 bpm. No diagnostically significant changes in repolarization processes were found in the course of examination.

Laboratory test results (Table 2) 18 AUG 2020

No ECG was registered during the patient's last visit to the Hemodialysis Department when K^+ level of 5.4 mmol/l was recorded.

The patient regularly takes moxonidine 0.2 mg twice a day, carvedilol 12.5 mg twice a day, and amlodipine 10 mg/day for her AH.

On 25 AUG 2020, the patient felt unwell before her next hemodialysis session: severe weakness, drowsiness, dizziness, increasing nausea, vomiting with gastric contents (once). However, the patient went for the hemodialysis procedure. On the way to Hemodialysis Department, BP increased to 160/100 mm Hg; the patient took a combined tablet of captopril 50 mg and hydrochlorothiazide 25 mg.

In the Hemodialysis Department, after connecting to the device at 08:10 a.m., bradycardia was registered on the monitor, with HR 30–32 bpm and BP 90/60 mm Hg. Medical help was provided (08:15 a.m.): atropine 2 mg i/v, mesatone 10 mg i/v — with no significant effect. ECG (08:15 a.m.): rhythm from AV connection with simultaneous excitation of atria and ventricles, HR 44 bpm, low voltage of the ECG in standard and amplified leads with maximum R wave amplitude in lead I — 4 mm. High pointed symmetrical positive T waves registered in leads V_2–V_4, QRS — 0.11 s, QT (abs.) — 0.58 s, QT (corr.) — 0.49 s (Fig. 1).

At 08:30 a.m., a joint examination was conducted by physicians of the Hemodialysis Department and an employee of the Prof. A.I. Dyadyk Department of Therapy of the Faculty of Internship and Postgraduate Education.

Objective findings: general state of moderate severity. The patient is awake, contact is limited, eyes are closed, the patient is obtunded. Skin with no rash, with high moisture content, pale. By percussion — symmetrical

vesicular resonance above the lungs, by auscultation — vesicular breathing in lungs, no wheezing or crepitus, respiratory rate 18 per min. Cardiac activity is rhythmic, muffled heart sounds, loud second heart sound above the aorta, systolic murmur at the apex. HR 32–40 bpm (cardiomonitor data throughout the examination period), BP 120/90 mm Hg. On palpation, abdomen is soft, painless, some regions of the intestine with normal properties. Swelling of lower legs.

Upon speaking with the patient, it turned out that she had eaten a watermelon, tomato salad with greens (parsley) the day before.

Table 2. *Results of laboratory tests*

Parameter	Results on 18.08.2020	Units	Normal range*
Red blood cells	3,15	10^{12}/L	3,70-4,70
Hemoglobin	95	g/L	115-145
Cell-color ratio	0,9	–	0,85-1,05
White blood cells	3,3	10^{9}/L	4,00-10,00
Platelets	166	10^{9}/L	170,00-400,00
ESR	24	mm/h	3,00-20,00
Band neutrophils	3	%	1,00-6,00
Segmented neutrophils	56	%	47,00-72,00
Eosinophils	1	%	1,00-5,00
Monocytes	5	%	3,00-12,00
Lymphocytes	35	%	19,00-37,00
Calcium	2,09	mmol/L	2,20-2,55
Inorganic phosphorus	2,06	mmol/L	0,81-1,45
Serum iron	19,2	μmol/L	10,70-32,20
Ionized calcium	1,06	μmol/L	1,10-1,30
K^+	5,4	mmol/L	3,50-5,50
Total blood protein	77	g/L	64,00-83,00
Blood urea	20,1	mmol/L	3,50-7,20
Creatinine	0,779	mmol/L	0,044-0,08
Blood glucose	5,3	mmol/L	4,10-6,10
Total bilirubin	12,1	μmol/L	5,00-21,00
Indirect bilirubin	12,1	μmol/L	calculated unit
Alanine aminotransferase	34	U/L	7-56
Aspartate aminotransferase	18	U/L	5-40

***Note:** normal values are given in accordance with the reference values of the laboratory in which the clinical and biochemical parameters of this patient were determined.
ESR — erythrocyte sedimentation rate; K^+ – potassium

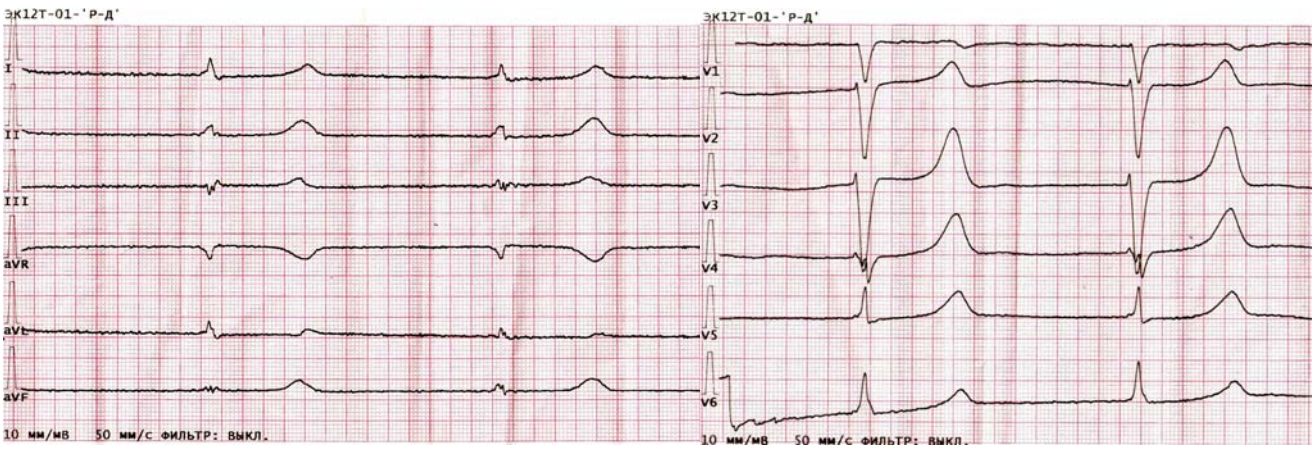

Figure 1. *Patient's electrocardiogram recorded during an episode of bradycardia, heart rate 44 beats/min.*

Based on complaints (severe weakness, drowsiness, nausea, vomiting), medical history (low-potassium diet violation), specific ECG data (new-onset junctional rhythm, high pointed symmetrical T waves in leads V_2–V_4, prolonged QT), hyperkalemia was suggested.

Blood test for K^+ (blood sample was taken urgently at 08:15 a.m., the result was obtained at 08:35 a.m.) — 7.2 mmol/l.

It was decided to continue the hemodialysis procedure. Treatment started: calcium gluconate 10% 30 ml i/v, metoclopramide 2 ml i/v, furosemide 20 mg i/v, glucose 20% 30 ml i/v. The patient was left under the care of physicians in the department; the required resources for cardiopulmonary resuscitation, if necessary, were provided.

Bicarbonate hemodialysis was performed for 3 hours. Composition of dialysis fluid: Na^+ — 136 mmol/l, HCO_3^- — 34 mmol/l; dialysate temperature was 37.5°C. Blood flow rate was 150 ml/min, dialysate flow rate was 300 ml/min.

At the 75th minute of the hemodialysis procedure, bradycardia resolved according to the monitor data. The hemodialysis session was 3 hours long. The patient's condition was considered satisfactory.

At 09:30 a.m., another ECG was registered, with positive changes: sinus rhythm was restored, regular, with HR 75 bpm, the voltage of QRS ventricular complex waves increased to 8 mm, QRS duration was 0.08 s, QT interval was normalized: QT (abs.) — 0.40 s, QT (corr.) — 0.44 s, PQ interval — 0.22 s (Fig. 2).

Repeated blood test for K^+ (result obtained at 10:00 a.m.) — 5.8 mmol/l. The patient felt satisfactory, no complaints. On 25 AUG 2020 at 02:00 p.m., the patient went home with recommendations to keep a low potassium diet and to take sodium polystyrene sulfonate 15 g three times a day.

27 AUG 2020 serum K^+ level — 5.2 mmol/l.

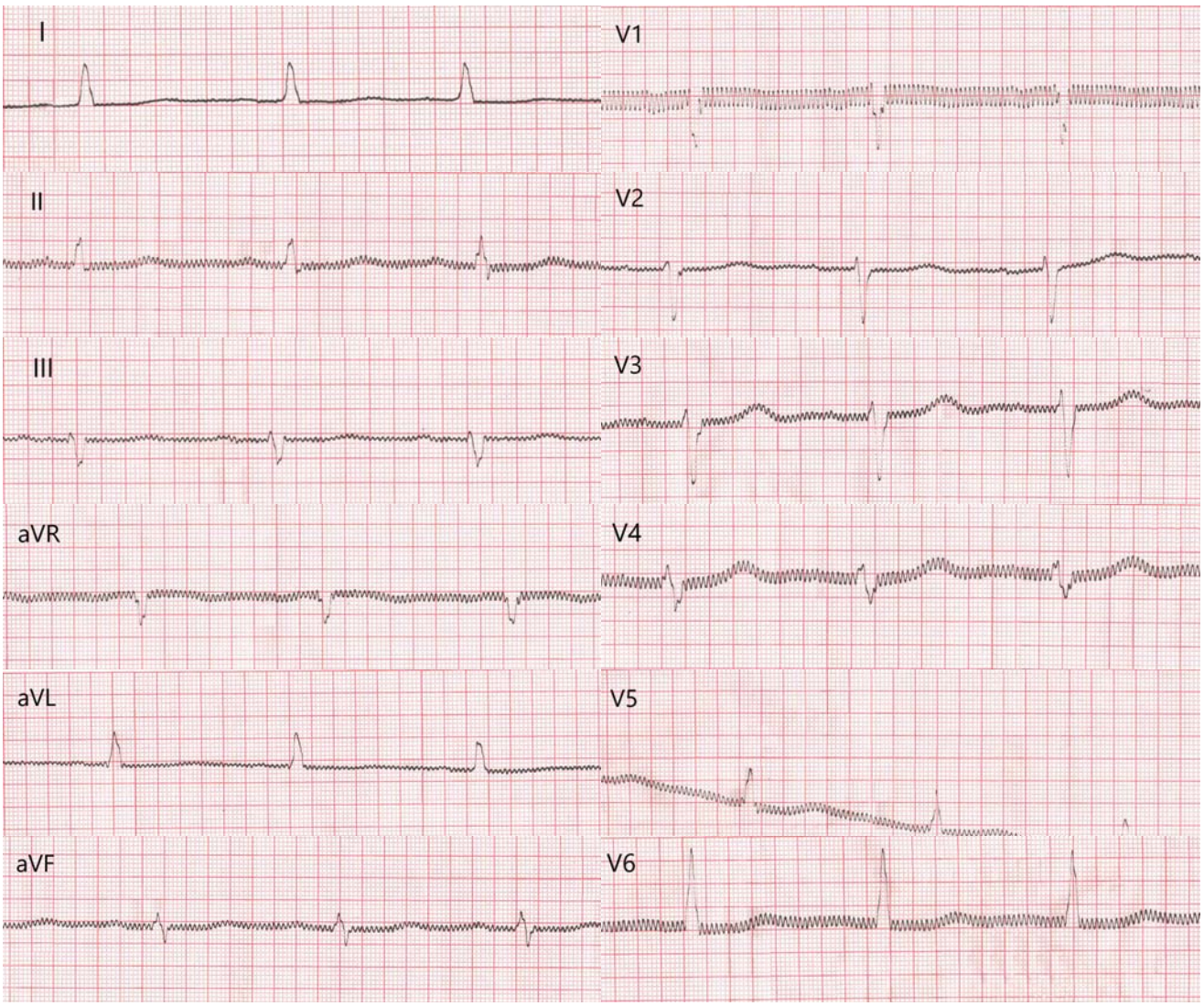

Figure 2. *The patient's electrocardiogram recorded after urgent medical care provided (02:00 p.m.), heart rate 73 beats/min.*

Discussion and conclusion

In our opinion, this case is interesting due to the fact that hyperkalemia manifested as junctional bradycardia, which was detected on the ECG during the hemodialysis session. In order to clarify the cause of the registered arrhythmia, a more detailed history was collected and serum K^+ level was determined, which allowed finding a life-threatening condition — hyperkalemia.

K^+ is a key element in maintaining the electrical potential of the cell membrane. On the ECG, early signs of hyperkalemia look like "sharp-pointed" T waves, more visible in precordial leads (V_2–V_4) [5]; they were also observed in our patient. A significant increase in the concentration of K^+ leads to delayed conduction in the AV node and His — Purkinje system due to the shortening of action potential and lengthening of phase IV of diastolic depolarization. On the ECG, this is visible as a prolonged PQ interval, decreased amplitude and enlargement of the P wave, as well as the prolonged QRS complex [5]. In our case, QRS width was 0.11 s.

In addition, the following is possible in cases of hyperkalemia: changes in the ST segment and axis position, new episode of conduction disorder (or aggravation of any of them), atrial fibrillation, ventricular tachycardia, ventricular fibrillation, asystoles. It should be noted that there are many reports of a normal or close to normal ECG in patients with severe hyperkalemia [11–13]. In the observed patient, we managed to register nodal rhythm with typical bradycardia (HR 30–44 bpm).

The prevalence of hyperkalemia among patients with end-stage renal failure is 5–10% [14]. Kidneys play a key role in maintaining potassium homeostasis. Normally, 80–90% of filtered K^+ is reabsorbed in proximal tubules and the loop of Henle, with total excretion of K^+ with urine determined primarily by its secretion into the lumen of the distal tubules of nephrons. Kidneys can increase K^+ excretion if it is in excess [15]. For this reason, patients with end-stage renal failure and significantly reduced glomerular filtration rate have an acute and/or chronic impaired K^+ excretion with the constant risk of hyperkalemia [16]. Such patients have a higher risk of adverse effects of hyperkalemia, general mortality rate, as well as mortality from cardiovascular causes [13, 17].

According to the results of a systematic literature review by E. Palaka et al. [4] that included 67 studies, the main risk factors for hyperkalemia were CKD or impaired renal function. Figure 3 shows the most common risk factors for hyperkalemia according to the systematic review [4].

Patients on dialysis for terminal renal failure deserve special attention because the risk of hyperkalemia can increase, in addition to the underlying renal pathology, due to various parameters of dialysis therapy, simultaneous intake of medical agents, or specific dietary features [12, 18].

Therefore, this case demonstrates the development of hyperkalemia in a patient with CKD on hemodialysis. Considering the high prevalence and severity of rhythm and conduction disorders due to increased serum K^+, physicians who treat patients with risk factors for hyperkalemia should pay special attention to dietary recommendations, careful selection and dosage of medical agents. If patients develop rhythm disorders, including bradycardia, it should be remembered that ECG changes in such patients may be the only manifestations of hyperkalemia, which should be considered during differential diagnosis of ECG-found changes and for providing adequate medical care.

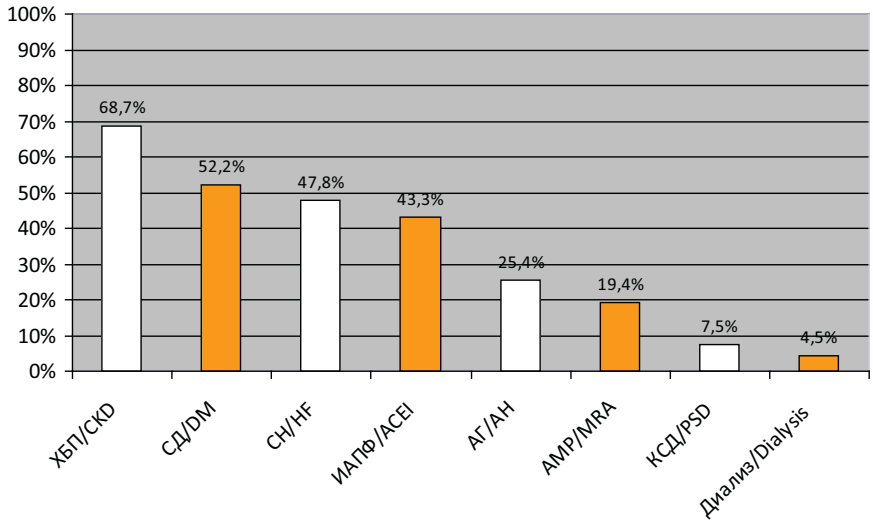

Figure 3. *The most common risk factors for hyperkalemia*

Notes: CKD — chronic kidney disease; DM — diabetes mellitus; HF — heart failure; ACEI — angiotensin-converting enzyme inhibitors; AH — arterial hypertension; MRA — mineralocorticoid receptor antagonist; PSD — potassium sparing diuretics. Adapted from E. Palaka et al. [4]

Вклад авторов:

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

Игнатенко Г.А. (ORCID: https://orcid.org/0000-0003-3611-1186): создание идеи и концепции рукописи, утверждение окончательного варианта

Тарадин Г.Г. (ORCID: https://orcid.org/0000-0003-3984-8482): написание введения, обзорной части, окончательное редактирование рукописи

Багрий А.Э. (ORCID: https://orcid.org/0000-0002-0295-3724): создание дизайна рукописи, критический обзор материала, окончательное редактирование рукописи

Ракитская И.В. (ORCID: https://orcid.org/0000-0003-2694-6614): сбор и анализ литературных данных, написание обзорной части и заключения рукописи, редактирование рукописи

Могилевская К.Э.: сбор, анализ и подача клинико-лабораторных данных больной

Меркурьев В.И.: написание анамнеза, клинических данных и результатов исследований; описание пребывания больной в отделении гемодиализа

Христуленко А.Л. (ORCID: https://orcid.org/0000-0002-9954-4715): написание обсуждения и заключения

Contribution of Authors:

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

Ignatenko G.A. (ORCID: https://orcid.org/0000-0003-3611-1186): generating the idea and the concept of the manuscript, approval of the final version

Taradin G.G. (ORCID: https://orcid.org/0000-0003-3984-8482): writing of the introduction, the review part, final editing of the manuscript

Bagry A.E. (ORCID: https://orcid.org/0000-0002-0295-3724): creating the article design, editing a manuscript

Rakitskaya I.V. (ORCID: https://orcid.org/0000-0003-2694-6614): collection and analysis of literature data, writing the review and conclusion of the manuscript, editing of the manuscript

Mogilevskaya K.E. — collection, analysis and presentation of clinical and laboratory data of the patient; investigation results

Merkuriev V.I. — writing of the history disease, clinical data and research results; description of staying of the patient in the hemodialysis department

Khristulenko A.L. (ORCID: https://orcid.org/0000-0002-9954-4715): writing of discussion and conclusion

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DOI: 10.20514/2226-6704-2021-11-1-67-71

А.В. Ягода[1], А.В. Рыбас*[1], Е.Н. Данилова[2], Ю.В. Громова[2]

[1] — Кафедра госпитальной терапии ФГБОУ ВО «Ставропольский государственный медицинский университет» Минздрава России, Ставрополь, Россия
[2] — Государственное бюджетное учреждение здравоохранения Ставропольского края «Ставропольская краевая клиническая больница», Ставрополь, Россия

ПАРАНЕОПЛАСТИЧЕСКИЙ ВАСКУЛИТ У БОЛЬНОЙ С АСТРОЦИТОМОЙ ГОЛОВНОГО МОЗГА

A.V. Yagoda[1], A.V. Rybas*[1], E. N. Danilova[2], Yu. V. Gromova[2]

[1] — Department of Hospital Therapy of Stavropol State Medical University, Stavropol, Russia
[2] — Stavropol Regional Clinical Hospital, Stavropol, Russia

Paraneoplastic Vasculitis in a Patient with Astrocytoma of the Brain

Резюме

Представлено клиническое наблюдение паранеопластического васкулита на фоне астроцитомы головного мозга. Паранеопластический васкулит — редкая разновидность паранеопластического синдрома, частота его выявления у онкологических больных составляет 0,01-5%, причем в 70% случаев манифестация васкулита наблюдается задолго до клинических проявлений первичной опухоли. Васкулитом, как правило, сопровождаются медленно прогрессирующие опухоли, такие как рак молочной и предстательной желез. Васкулит развивается на фоне рака желудка, легкого, аденокарциномы почек, эпителиомы, саркомы, холангиокарциномы, других солидных опухолей, множественной миеломы, неходжскинской лимфомы. Из нозологических форм паранеопластических васкулитов (васкулопатий) указываются узелковый полиартериит, геморрагический васкулит, гранулематоз Вегенера, неспецифический аортоартериит, синдром идиопатической легочной гипертензии, тромбоваскулиты, протекающие под масками болезни Винивартера-Бюргера, синдрома Мошковиц, а также аллергический геморрагический васкулит, кожный васкулит, системный некротизирующий васкулит с повышением титра антител к антигенам цитоплазмы нейтрофилов (ANCA). В описанном наблюдении пациентка страдала паранеопластичеким васкулитом, морфологически напоминающим узелковый полиартериит, с развитием вторичного амилоидоза сосудов, тканей, вторичной артериальной гипертензии. Прогрессирование сосудистого процесса привело к поражению артерий мозга и сердца, к развитию ишемического инсульта и гемодинамически значимому стенозу коронарных артерий, развитию острого (повторного) инфаркта миокарда, осложнённого острой сердечной недостаточностью, послужившими причиной смерти. Клиническая значимость наблюдения заключается в описании не представленного в научной литературе паранеопластического васкулита, развившегося на фоне астроцитомы головного мозга с формированием вторичного амилоидоза.

Ключевые слова: *паранеопластический васкулит, паранеопластический синдром, астроцитома, острый инфаркт миокарда*

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 15.11.2020 г.
Принята к публикации 10.12.2020 г.

*Контакты: Анна Викторовна Рыбас, e-mail: rybasdoc@mail.ru
*Contacts: Anna V. Rybas, e-mail: rybasdoc@mail.ru
ORCID ID: https://orcid.org/0000-0001-5360-0913

Для цитирования: Ягода А.В., Рыбас А.В., Данилова Е.Н. и др. ПАРАНЕОПЛАСТИЧЕСКИЙ ВАСКУЛИТ У БОЛЬНОЙ С АСТРОЦИТОМОЙ ГОЛОВНОГО МОЗГА. Архивъ внутренней медицины. 2021; 1(1): 67-71. DOI: 10.20514/2226-6704-2021-11-1-67-71

Abstract

Clinical case of paraneoplastic vasculitis associated a brain tumor was presented. Paraneoplastic vasculitis is a rare type of paraneoplastic syndrome. The frequency of detection of paraneoplastic vasculitis in cancer patients is 0.01-5%. In 70% of cases, the manifestation of vasculitis is observed long before the clinical manifestations of the tumor. Most studies report so-called leukocytoclastic vasculitis (allergic) or allergic angiitis. Vasculitis is usually accompanied by slowly progressing tumors such as breast and prostate cancer. It also develops with of stomach cancer, lung cancer, kidney adenocarcinoma, epithelioma, sarcoma, cholangiocarcinoma, other solid tumors, multiple myeloma, non-Hodgkin's lymphoma. The nosological forms of paraneoplastic vasculitis include called polyarteritis nodosa, hemorrhagic vasculitis, Wegener's granulomatosis, non-specific aortoarteritis, idiopathic pulmonary hypertension syndrome, thrombovasculitis, allergic hemorrhagic vasculitis, cutaneous vasculitis, systemic necrotizing vasculitis with increased ANCA titer. The patient suffered from paraneoplastic vasculitis with the development of amyloidosis of vascular tissues and arterial hypertension. The progression of the vascular process led to damage of the arteries of the brain and heart, the development of ischemic stroke and hemodynamically significant stenosis of the coronary arteries, the development of acute myocardial infarction complicated by acute heart failure, which caused death. The clinical significance of the case lies in the fact that paraneoplastic vasculitis, which was developed due to a brain astrocytoma with the formation of amyloidosis was firstly described.

Key words: *paraneoplastic vasculitis, astrocytoma, acute myocardial infarction*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 15.11.2020

Accepted for publication on 10.12.2020

For citation: Yagoda A.V., Rybas A.V., Danilova E.N. et al. Paraneoplastic Vasculitis in a Patient with Astrocytoma of the Brain. The Russian Archives of Internal Medicine. 2021; 1(1): 67-71. DOI: 10.20514/2226-6704-2021-11-1-67-71

ECG — electrocardiogram, MR — magnetic resonance, PNV — paraneoplastic vasculitis

Introduction

Paraneoplastic vasculitis (PNV) and vasculopathies are among the most challenging diseases for management in clinical practice. The paraneoplastic vascular lesion of the vasculitis type is a very rare phenomenon. According to different sources, the detection rate of PNV in cancer patients is 0.01–5%, while in 70% of cases, vasculitis manifests long before the clinical signs of the primary tumor; this fact should be considered when planning the examination for a patient with an "atypical" course of the vascular process.

Most studies report the so-called leukocytoclastic vasculitis (hypersensitive, allergic vasculitis, or allergic angiitis), which is often observed with secondary forms of lesions, including tumors — hairy cell leukemia, non-Hodgkin's lymphoma, lymphogranulomatosis, myeloma [1, 2].

Vasculitis is usually accompanied by slowly progressive tumors, such as breast and prostate cancer. PNV can also develop in patients with gastric, lung or renal adenocarcinoma, epithelioma, sarcoma, cholangiocarcinoma, other solid tumors, multiple myeloma, and non-Hodgkin's lymphoma [2, 3], with the predominance of blood tumors (hemoblastoses) in the etiology of PNV [1].

Nosological forms of paraneoplastic vasculitis and vasculopathies include the following: polyarteritis nodosa, hemorrhagic vasculitis, Wegener's granulomatosis, nonspecific aortoarteritis, idiopathic pulmonary arterial hypertension, thrombovasculites with the course simulating Vinivarter-Buerger disease or Moscowitz syndrome, allergic hemorrhagic vasculitis, cutaneous vasculitis, systemic necrotizing vasculitis, etc. The predominant clinical varieties of PNV include cutaneous forms of the purpura type, maculopapular, urticarial, petechial rash, and ulcers with different elements in one patient as one of the criteria for this type of vasculitis. The type of skin rashes is not related to the type of tumor or its localization [2–4].

Currently, there is no single theory of PNV pathogenesis. Most researchers discuss the autoimmune mechanism of development with the participation of cytokines and adhesion molecules with the deposition of immune complexes in the walls of blood vessels of various calibers and the subsequent development of inflammation and necrosis. The determination of a high titer of autoimmune antibodies (antineutrophilic cytoplasmic, antinuclear, antiphospholipid) in patients with PNV is evidence of the autoimmune nature of PNV [1].

Proponents of non-immune theories of PNV pathogenesis attribute inflammation in vessel walls to the exposure of the endothelial layer to mediators and substances produced by the tumor itself [1].

Tumor-associated vasculitis can occur in complicated forms, with a negative effect on the course of the tumor and the prognosis as a whole.

Case report

Patient P., 44 y.o., female, was hospitalized in the cardiology department of a regional clinical hospital. She was urgently transported for interventional treatment from the hospital, where she was examined and treated for ischemic heart disease (IHD) due to acute coronary syndrome (severe retrosternal pain and ST segment elevation on ECG in V_2–V_5) and clinical signs of nascent pulmonary edema.

Medical history revealed that the first symptoms of ischemic heart disease (retrosternal pain) appeared six years before hospitalization; stable exertional angina of functional class II was established. About six months ago, she suffered an acute cerebrovascular event (ischemic stroke). For more than six years, she noted increased blood pressure (BP), occasionally up to 200/110 mm Hg. Paroxysms of atrial fibrillation-flutter were registered, for which the patient regularly takes sotalol (80 mg). There is a family history of myocardial infarction (father).

Prior to hospitalization, the following results of outpatient and inpatient examinations of the patient were obtained.

Complete blood count: RBC — 3.95 × 10^{12}/l, hemoglobin — 118 g/l, hematocrit — 35.9%, WBC — 6.1 × 10^9/l (segmented neutrophils — 58%, stab neutrophils — 3%, lymphocytes — 28%, monocytes — 9%, eosinophils — 2%), platelets 183 × 10^9/l, erythrocyte sedimentation rate (ESR) — 22 mm/h. Common urinalysis: protein — 193 mg/dl, WBC — 15–20 per field of vision. Lipid profile: total cholesterol — 5.21 mmol/l, high density lipoproteins (HDL) — 1.71 mmol/l, low density lipoproteins (LDL) — 3.35 mmol/l, triglycerides (TG) — 1.20 mmol/l, atherogenic index (AI) — 2.0. Blood biochemistry: electrolytes within normal, aspartate aminotransferase — 13 U/l, alanine aminotransferase — 11 U/l, lactate dehydrogenase — 255 U/l, C-reactive protein — 4.8 mg/l, creatinine — 113 μmol/l, urea — 8.9 mmol/l. Total protein, bilirubin, blood glucose — without changes. Troponin T — 0.08 ng/ml, myoglobin — 54.72 ng/ml, creatine phosphokinase MB — 2.7 ng/ml. Hepatitis B surface antigen (HBsAg) and total antibodies to hepatitis C virus (anti-HCV) — not found. Coagulogram within normal. High level of brain natriuretic propeptide (NT-proBNP) — over 9000 pg/ml — is noteworthy.

Magnetic resonance (MR) imaging. Signs of ischemic stroke in the circulation zone of the right middle cerebral artery. Study over time — MR signs of poststroke cerebrospinal fluid cyst in the right frontal lobe.

Duplex imaging of brachiocephalic arteries. No structural changes or hemodynamically significant disorders of the blood flow in carotid arteries at the extracranial level were found. Deformed course of the third segment of both vertebral arteries with multifocal compensated stenosis up to 40%. Hypoplasia of the right vertebral artery. Asymmetric blood flow in vertebral arteries, 30–40% due to the relative decrease on the right.

Consultation with a neuro-ophthalmologist: retinal angiopathy of both eyes.

ECG: sinus rhythm with heart rate (HR) 90 per minute, QRS axis in horizontal position. Cicatricial changes in the anterior-septal-apical area of the left ventricle — LV (QS V_1–V_3, qV_4), signs of LV myocardial hypertrophy with hemodynamic overload.

24 hours Holter ECG monitoring: sinus rhythm with HR from 69 to 123 (mean 81, daytime — 92, nighttime — 74) per minute, single ventricular extrasystoles — VES (495), paired VES (6), ventricular extrasystole grade 5 (Lown), short unstable paroxysms (2) of ventricular tachycardia (duration up to 10 seconds), long QT syndrome, transient AV block grade 1. With increase in heart rate, downsloping ST segment depression and inverted T wave in leads II, III, aVF, V_5–V_6 were occasionally observed, accompanied by subjective feelings (heart pain, malaise, palpitations) with a total duration of 10 minutes 24 seconds.

Echocardiography with color flow mapping: left ventricle — end-diastolic dimension (EDD) 4.8 cm; end-systolic dimension (ESD) 3.3 cm; LV posterior wall in diastole (LVPWd) 1.1 cm; interventricular septum in diastole (IVSd) 1.3 cm, left ventricular myocardial mass index (LVMMI) 138 g/m^2, concentric hypertrophy, ejection fraction 60% (Teicholz). Systolic pressure in pulmonary artery — 35 mm Hg (normal up to 30 mm Hg). No evidence for myocardial motion disorders found. No separation of pericardial layers. Dilation of both atria, marginal thickening and fibrosis of the cusps of mitral and aortic valves, mitral and tricuspid regurgitation grade 1–2, pulmonary valve dysfunction. Additional chord in the cavity of the left ventricle.

Esophagogastroduodenoscopy: superficial gastritis.

Chest radiography: cardiac border expanded to the left.

On admission to the Regional Vascular Center: the general condition of the patient is severe; skin is pale, acrocyanosis, position — orthopnea. By auscultation — decreased vesicular breathing in the lower parts of lungs, large number of moist rales, respiratory rate — 22 per minute. Sinus rhythm with HR 100 per minute, heart tones are muffled. BP — 90/60 mm Hg. Abdomen is soft, non-tender. No swelling.

ECG at admission — sinus rhythm with HR 80 per minute, focal changes in anterior-septal-apical-lateral area of the left ventricle in the form of ST elevation.

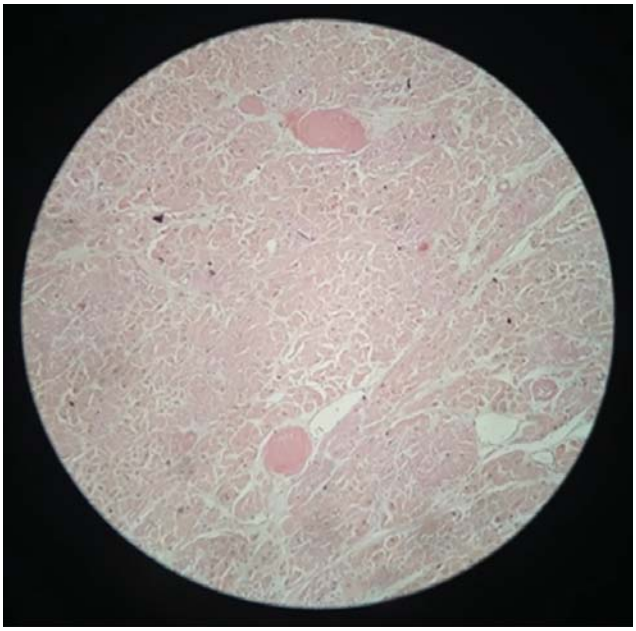

Figure 1. *Heart. Amyloid in a vessel wall. Complete obliteration of the lumen. Congo red stain, ×100*

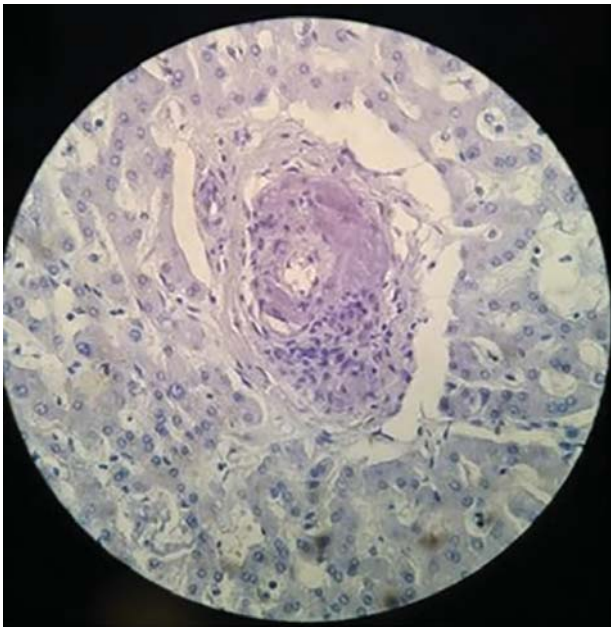

Figure 2. *Liver. Productive periarteritis. Hematoxylin stain, ×100*

The patient underwent emergency coronary angiography, with the following results: right-dominant circulation, coronary arteries normally positioned. Occlusion in the middle third of the anterior interventricular artery was found. Balloon angioplasty in the middle third of the anterior interventricular artery with a 2.5 × 25 mm balloon catheter was performed; TIMI 2 blood flow (contrast enhancement of the vessel with delayed filling of distal flow) along the entire length of the artery; there were no residual stenosis, dissections or extravasation.

After angioplasty, the patient's condition suddenly worsened, signs of respiratory and heart failure appeared, and cardiogenic shock developed. The patient received vasopressor and inotropic support and was transferred to mechanical ventilation. According to ECG — electromechanical dissociation of heart. Resuscitation measures had no effect. The patient died two hours after admission to the hospital.

Autopsy study: dense mottled myocardium with areas of yellowish and dark red color — in anterior and partially posterior-lateral walls throughout the whole thickness of the heart muscle. At the mouth of the left coronary artery — atherosclerotic plaque, 0.4 cm, flat. Arteries with dense whitish walls. LV cavity was enlarged. Histology: parenchymal myocardial dystrophy, foci of cardiosclerosis, zones of cardiac muscle necrosis of trasmural type in macroscopically described areas. Heart vessels along their entire length with significantly thickened sclerosed walls, with disorganization of all layers and deposits of amorphous lumpy eosinophilic masses, developing aneurysms in the form of nodules with significantly narrowed lumens, in some places — to complete narrowing, with lymphocytic infiltration — signs of periarteritis. Examination with Congo red stain and in polarized light revealed amyloid deposits in the walls of blood vessels, the stroma, and epicardium (Fig. 1).

Similar changes in the walls of arterial vessels are observed when examining lungs, kidneys, adrenal glands, spleen, uterus, its appendages, pancreas, and liver (Fig. 2).

On the basal surface of the brain, between pons and cerebral peduncles, there was a superficial dense rounded lesion, 1 cm in diameter, of grayish-white color, in the pia mater, the basilar artery was under this lesion. Histology revealed a nodular form of diffuse astrocytoma (Fig. 3).

Tumor nodules of fibrous white tissue, 3 and 4.5 cm in diameter, were found in the uterine body — interstitial-subserous leiomyoma.

Pathological diagnosis:

Main: Paraneoplastic vasculitis (polyarteritis nodosa) with predominant heart lesion, sclerotic phase in addition to diffuse astrocytoma of pons.

Complications: acute transmural myocardial infarction of the anterior-lateral wall of left ventricle. Acute heart failure: pulmonary edema. Cerebral edema. Symptomatic arterial hypertension (LV myocardial hypertrophy 1.6 cm). Secondary amyloidosis with predominant damage to the vessels of the heart, lungs, kidneys, liver, spleen. Acute heart failure: venous congestion and fibrosis of internal organs, right-sided hydrothorax (100 ml). Secondary pulmonary hypertension. Chronic cor pulmonale: RV myocardial hypertrophy 0.6 cm.

Comorbidity — interstitial-subserous leiomyoma of the uterine body.

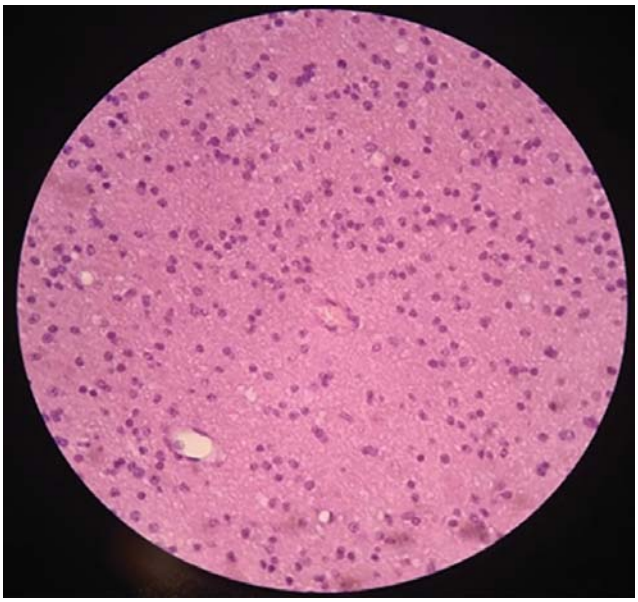

Figure 3. *Diffuse astrocytoma. Hematoxylin and eosin stain, ×400*

Discussion

Therefore, it was found (incidentally) that the patient had an astrocytoma (malignant glial tumor), which was not previously listed among the neoplasms that cause a systemic vascular lesion.

Coexistent vasculitis and tumors, the non-specificity of clinical findings and laboratory results, manifestation of vasculitis prior to the clinical manifestations of the brain tumor, and the generalized nature of the lesion suggest the paraneoplastic nature of the vascular process.

The patient suffered from paraneoplastic vasculitis with secondary vascular amyloidosis and secondary arterial hypertension. The progression of the vascular process led to damage to the brain and heart arteries, ischemic stroke and hemodynamically significant stenosis of coronary arteries, and acute (repeated) myocardial infarction, complicated by acute heart failure, which caused death. Despite a histological picture that resembles that of polyarteritis nodosa (aneurysms, nodules), we do not think this term can be used in this case, not only due to the incomplete range of morphological signs but also due to the lack of clinical criteria for this form of systemic vasculitis.

Amyloid deposits in tissues and in affected vessels do not contradict the theory of paraneoplastic vasculitis. In addition, systemic amyloidosis (Lubarsch-Pick syndrome) can be found — although quite rarely — as a paraneoplastic process: solid tumors make up about 7% of the causes of systemic amyloidosis [5].

The clinical significance of this observation lies in that it was the first described case of PNV that developed in association with brain astrocytoma with the development of secondary amyloidosis; it expands the range of causative tumors for this type of vasculitis and demonstrates new possibilities for its diagnosis in cases with simultaneous amyloidosis.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией, согласны быть ответственными за все аспекты работы.

А.В. Ягода: (ORCID: 0000-0002-5727-1640): разработка концепции, анализ и интерпретация данных, проверка содержания, окончательное утверждение рукописи для публикации

А.В. Рыбас: (ORCID: 0000-0001-5360-0913): анализ и интерпретация данных, разработка дизайна, оформление обзора, обоснование и написание рукописи

Е.Н. Данилова: сбор клинического материала, анализ, интерпретация данных

Ю.В. Громова: сбор и анализ гистологического материала, интерпретация данных

Author Contribution:

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

A.V. Yagoda: (ORCID: 0000-0002-5727-1640):): development of the concept, analysis and interpretation of data, validation of content, final approval of the article for publication

A.V. Rybas: (ORCID: 0000-0001-5360-0913): analysis and interpretation of data, research concept and design, design review, study and writing of the article

E.N. Danilova: data collection and processing, analysis, data interpretation

Yu.V. Gromova: collection and analysis of histological material, data interpretation

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DOI: 10.20514/2226-6704-2021-11-1-72-75

Е.Н. Харламова*, Ю.Ю. Карпенко

ФГБОУ ВО ВГМУ имени Н.Н. Бурденко Минздрава России,
кафедра госпитальной терапии и эндокринологии, Воронеж, Россия

ОЦЕНКА ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ РИТУКСИМАБОМ ПРИ СИСТЕМНОЙ СКЛЕРОДЕРМИИ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

E.N. Harlamova*, Ju.Ju. Karpenko

State Budgetary Educational ln-stitution of High Professional Education «Voronezh State Medical University n.a. N.N. Burdenko» of the Ministry of Health of the Russian Federation, Department of Hospital Therapy and Endocrinology, Voronezh, Russia

Evaluation of the Efficiency of Treatment with Rituximab for Systemic Scleroderma (A Case Report)

Резюме

В статье описан клинический случай прогрессирующей формы системной склеродермии у мужчины 39 лет. У пациента наблюдалось острое течение и быстрое прогрессирование заболевания со значительным исходным снижением форсированной жизненной ёмкости легких; с признаками неблагоприятного прогноза, такими как диффузная форма, высокий кожный счет (>14 по Rodnan), мужской пол, высокая позитивность по антителам к Scl-70 (антитела к топоизомеразе I). В связи с неэффективностью стандартной терапии глюкокортикоидами и иммуносупрессантами на ранней стадии болезни был рассмотрен вариант лечения генно-инженерными препаратами (ритуксимабом). В результате проводимой терапии отмечена положительная динамика.

Ключевые слова: *системная склеродермия, ритуксимаб, неблагоприятный прогноз*

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 15.10.2020 г.

Принята к публикации 11.11.2020 г.

Для цитирования: Харламова Е.Н., Карпенко Ю.Ю. ОЦЕНКА ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ РИТУКСИМАБОМ ПРИ СИСТЕМНОЙ СКЛЕРОДЕРМИИ (КЛИНИЧЕСКИЙ СЛУЧАЙ). Архивъ внутренней медицины. 2020; 10(6): 72-75. DOI: 10.20514/2226-6704-2021-11-1-72-75

Abstract

The article describes a clinical case of a progressive form of systemic scleroderma in a 39-year-old man. The patient has an acute course and rapid progression of the disease with a significant initial decrease in the forced vital capacity of the lungs, with signs of an unfavorable prognosis, such as a diffuse form, a high skin count (> 14), male sex, and high positivity for antibodies to Scl-70. In connection with the ineffectiveness of standard therapy with glucocorticoids and immunosuppressants at an early stage of the disease, the option of treatment with genetically engineered drugs (rituximab) was considered. As a result of the therapy, a positive trend was noted.

Key words: *systemic scleroderma, rituximab, poor prognosis*

*Контакты: Евгения Николаевна Харламова, e-mail: evgenya.harlamova@yandex.ru
* Contacts: Evgenija N. Harlamova, e-mail: evgenya.harlamova@yandex.ru
ORCID ID: https://orcid.org/0000-0001-8864-7623

Conflict of interests
The authors declare that this study, its theme, subject and content do not affect competing interests

Sources of funding
The authors declare no funding for this study

Article received on 15.10.2020
Accepted for publication on 11.11.2020

For citation: Harlamova E.N., Karpenko Ju.Ju. Evaluation of the Efficiency of Treatment with Rituximab for Systemic Scleroderma (A Case Report). The Russian Archives of Internal Medicine. 2020; 10(6): 72-75. DOI: 10.20514/2226-6704-2021-11-1-72-75

ANF — antinuclear factor, GC — glucocorticoids, GEBT — genetically engineered biologic therapy, ILD — interstitial lung disease, RTM — rituximab, SSc — systemic sclerosis

Relevance

Systemic sclerosis (SSc) is a chronic autoimmune disease that affects the skin, joints and internal organs (heart, lungs, kidneys, digestive tract); it includes immune system and microcirculation disorders, inflammatory changes, and generalized fibrosis. Lung injury is a very common manifestation of SSc. The frequency of pulmonary localization of the sclerotic process is 65–80% [1]. Interstitial lung disease (ILD) in systemic sclerosis is characterized by inflammation in alveoli with excessive proliferation of fibroblasts in the interalveolar septa, vascular walls, perivascular, peribronchial, subpleural and basal areas. ILD contributes to poor prognosis and is the leading cause of mortality in SSc. The treatment of patients with ILD associated with SSc has not been sufficiently studied. A number of studies demonstrate the effectiveness of monoclonal antibodies against B cells (rituximab) [2]. The significance of B cells in SSc pathogenesis is well known: they intensify fibrosis due to the production of fibroblast-activating autoantibodies; B cells can also directly intensify fibrosis by direct intercellular contacts with fibroblasts, and via cytokines (interleukin-6) [3]. Studies show that rituximab (RTM) can improve lung function and reduce the severity of skin fibrosis in patients with SSc [4].

Objective of the study: description of a clinical case with a progressive form of systemic sclerosis that is refractory to standard treatment with glucocorticoids and immunosuppressants.

Materials and methods

A retrospective analysis of the medical record of a patient with systemic sclerosis was carried out.

Male patient, 39, with a diffuse form of systemic sclerosis, with a rapidly progressing course, high activity, with lesions of the skin (hyperpigmentation, sclerodactyly), blood vessels (Raynaud syndrome of upper and lower limbs, auricle necrosis, small digital ulcers), joints (polyarthritis of hands, X-ray stage III, periarticular fibrosis with the formation of contractures), lungs (basal pulmonary sclerosis), gastrointestinal tract (esophageal hypotension, esophageal stricture 0.8–0.9 cm), muscles (history of myositis), heart (myocarditis with rhythm disorders, atrial fibrillation paroxysms, painless myocardial ischemia, chronic heart failure stage 1, FC 1), kidneys (proteinuria), immune disorders (antibodies against topoisomerase I (Scl-70) "+++", antinuclear antibodies (ANF "+") in combination with secondary osteoarthritis of knee joints (X-ray stage I), feet (X-ray stage II). Duodenal peptic ulcer without exacerbation.

At the time of examination (15 Sep 2020), the patient complained of pain in the small joints of hands, dense swelling of fingers, the lower third of forearms, feet, the lower third of lower legs, limited hand mobility, numbness in fingers, whitening and blueing of hands, small ulcers on the tips of fingers and toes, muscle pain, and occasional loose stools.

Medical history: The patient considers himself sick from the beginning of September 2016, when the swelling of ankle joints appeared, then pains in hand joints, elbows, knees, muscles of hips, whitening and blueing of fingers, general weakness, morning stiffness in joints for about an hour. Examination revealed increased acute-phase parameters: C-reactive protein — 10.73 mg/l (normal to 5 mg/l); immunological parameters: ANF "+", AT Scl-70 "+++". The presence of Scl-70 antibodies indicates a diffuse form of disease, a rapidly progressive course and a high risk of severe ILD.

The patient received the following treatment in the Rheumatology Department of the City Hospital: pulse therapy with glucocorticoids (GC) (methylprednisolone 1,000 mg), vascular treatment, immunosuppressive treatment (methotrexate 10 mg/week). The treatment had a short-term effect. From 14 to 31 August 2017, the patient was hospitalized in the Rheumatology Department of the Regional Hospital for disease progression and no effect of treatment. The following therapy was carried out: prostanoids for intravenous administration (iloprost), GC (prednisolone 10 mg), calcium antagonists, pentoxifylline, nonsteroidal anti-inflammatory drugs with slight positive changes. Recommendations included prednisolone with dose reduction from 10 to 5 mg/day,

cyclophosphamide 50 mg/day, PDE5 inhibitor (sildenafil). In December 2017, the patient's condition worsened, muscle and joint pains increased, which required the use of narcotic analgesics for pain relief. The patient was referred to the V. A. Nasonova Federal State Budgetary Research Institution "Research Institute of Rheumatology" (Moscow) to get medical advice in order to determine further treatment strategy. It was recommended to start genetically engineered biologic therapy (GEBT) with rituximab due to the ineffectiveness of standard therapy with GC and immunosuppressants; at the early stage (first 3 years of disease) with signs of poor prognosis, such as the diffuse form, high skin score (> 14 according to the Rodnan scale), male gender, rapid progression with a significant initial decrease in forced lung capacity; high positivity of antibodies against Scl-70.

Combined use of rituximab with GC and mycophenolate mofetil was recommended.

Treatment with rituximab (500 mg) was started in December 2017. Subsequently, RTM infusions (500 mg) were performed every three months. Planned infusion in March 2020 was delayed due to the unfavorable epidemiological situation associated with novel coronavirus disease; infusion was performed in June, the next one is scheduled for late September.

The last hospitalization in the Rheumatology Department was in November 2019.

The patient regularly takes methylprednisolone (8 mg/day), mycophenolate mofetil (2,000 mg/day), antiplatelet agents, angiotensin-converting enzyme inhibitors (perindopril), mineralcorticoid receptor antagonists, calcium antagonists (diltiazem), proton pump inhibitors, non-steroidal anti-inflammatory drugs if necessary.

Patient's life history: No family history of rheumatological diseases. Comorbidities: duodenal peptic ulcer (at the age of 19), fracture of the forearm and left calcaneus, concussion during childhood. Unremarkable history of allergies. Denies contracting tuberculosis, hepatitis B, C, HIV, typhoid, paratyphoid, diabetes mellitus, psoriasis, and cancer. No blood transfusions performed. Denies smoking and drinking alcohol. No contact with infectious patients. Person with group 2 disability since 2016.

Objectively: General condition of the patient is satisfactory. The state of consciousness was normal. Normosthenic body type. Undernourished (height 182 cm, weight 54 kg, body mass index 16 kg/m^2)). Skin with foci of "salt and pepper" hyperpigmentation. Visible mucosae of normal color. Dense swelling of hands, feet, lower third of lower legs, lower third of forearms. Digital ulcer on the thumb (large), healing ones — on 4 fingers of the right hand, on the distal finger of the left hand, on the first toe of the left foot. Muscles are developed satisfactorily, with normal tone. Lymph nodes are not enlarged.

Respiratory system: normosthenic form of the chest. Respiratory rate 16 per minute. No shortness of breath during exercise. Auscultatively: vesicular breathing in lungs throughout all pulmonary fields, somewhat weakened in the lower parts on both sides, no rales.

Circulatory system: heart area with no visible abnormalities. Apex beat in 5 intercostal space along the left midclavicular line. Relative heart dullness: right — along the right edge of sternum, left — along the left midclavicular line, upper — rib 3. Heart sounds are muffled, no murmurs heard. Cardiac rhythm is abnormal, with heart rate of 80 pm. Blood pressure 130/90 mm Hg.

Digestive system: lips of normal color. Tongue is dry, covered with white fur. No visible peristalsis. Tone of abdominal muscles is normal. Abdomen is soft and nontender. Liver is palpated along the edge of costal arch. Spleen is not enlarged.

Urinary system: no swelling in kidney area. Costovertebral angle tenderness was absent on both sides. Stool with a tendency to loose, urination — according to the patient, within normal.

Joint condition: movement in fingers is limited due to swelling and contractures. Palpation of paravertebral points of lumbosacral spine is painless. Palpation of knee joints is moderately painful.

Laboratory test results:

Complete blood count from 04 Sep 2020: hemoglobin 159 g/l, RBC 4.4×10^{12}/l, WBC 5.9×10^{9}/l, platelets 302×10^{9}/l, ESR 7 mm/h. C-reactive protein — negative.

Blood biochemistry on 04 Sep 2020: glucose 4.80 mmol/l, alanine aminotransferase 19 U/l, aspartate aminotransferase 19 U/l, creatinine 79.0 μmol/l, total cholesterol 4.3 mmol/l, total protein 77 g/l, urea 5.0 mmol/l, uric acid 203.0 μmol/l.

Common urinalysis on 04 Sep 2020: color — straw-yellow, transparency — slightly turbid, reaction — acidic, specific gravity 1010, protein — negative, WBC — 1–2 per field of vision.

Immunogram on 28 Nov 2019: immunoglobulin G > 24.000 mg/ml (4.8–16.0 mg), immunoglobulin M 2.200 mg/ml (0.48–2.0 mg), rheumatoid factor 10.6 IU/ml (less than 15), anticentromere antibodies (ACA) 0.1 U/ml (0–10), antibodies against Scl-70 more than 200 U/ml (0.0–25.0).

Diagnostic test results:

Electrocardiogram on 25 Oct 2019: sinus rhythm. Complete left bundle branch block. LV hypertrophy with changes in myocardium of posterolateral wall. Supraventricular extrasystole, ventricular extrasystole. Heart rate 75 bpm. QRS axis in horizontal position.

Echocardiography on 27 Nov 2019: dilated left heart chambers. Aorta, cusps of aortic and mitral valves (MV) are indurated. MV regurgitation grade 1. LV contractile function is reduced (Teicholz EF 51%).

Computed tomography of the chest on 20 Aug 2020: signs of diffuse changes in lungs — pulmonary sclerosis, pulmonary fibrosis, emphysema, calcifications in both

lung apices. Pattern of chronic obstructive pulmonary disease.

Pulmonary function test on 28 Aug 2019: lung capacity and bronchial patency within normal.

Abdominal ultrasound on 18 Dec 2018: signs of moderate diffuse changes in the liver.

Ultrasound of the kidneys on 17 May 2019: no abnormalities were revealed.

X-ray of the hands on 21 Jan 2019: osteoarthrosis grade III.

X-ray of the feet on 21 May 2019: osteoarthrosis grade II, polyarthritis grade I.

Chronometry of esophagus on 18 Dec 2018: barium passing through the esophagus is slowed down. Incompetence of cardia, gastroesophageal reflux. Esophageal hypotension.

Discussion

In response to well-tolerated therapy with rituximab, the patient's condition after three years was stable, disease activity decreased. The clinical picture showed decreased joint pain, decreased skin density, no dyspnea during exercise. According to laboratory tests, the following positive changes are observed: ESR decreased to 7 mm/h, C-reactive protein is negative, hemoglobin level increased to 157 g/l. Spirometry parameters stabilized: lung capacity and bronchial patency within normal. However, severe Raynaud syndrome persists.

Standard treatment with immunosuppressants that is currently used is not effective enough to improve the prognosis of SSc. Therefore, the task of studying and adopting new approaches to treatment remains relevant [5]. Since B-cells are highly significant in SSc pathogenesis, they should be considered as a high-potential therapeutic target. Some clinicians regard RTM as an alternative to immunosuppressants for the management of ILD, and 69% of Canadian SSc experts share this opinion [6]. The latest Russian clinical recommendations concerning SSc also note the advisability of using RTM when standard treatment with immunosuppressants is ineffective or impossible [7].

Conclusions

This clinical observation demonstrates the advisability of prescribing RTM, especially at the early stages of the disease. However, further study of using RTM in controlled trials is required.

Вклад авторов:

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

Е.Н. Харламова (ORCID ID: https://orcid.org/0000-0001-8864-7623): вклад в разработку концепции и дизайна, роль автора в сборе, анализе и интерпретации данных, согласие автора быть ответственным за все аспекты работы

Ю.Ю. Карпенко (ORCID ID: https://orcid.org/0000-0003-4757-2738): роль автора в обосновании и написании рукописи, в проверке критически важного интеллектуального содержания, в окончательном утверждении для публикации 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

E.N. Harlamova (ORCID ID: https://orcid.org/0000-0001-8864-7623): contribution to the development of the concept and design, the author's role in the collection, analysis and interpretation of data, the author's consent to be responsible for all aspects of the work

Ju.Ju. Karpenko (ORCID ID: https://orcid.org/0000-0003-4757-2738): role of the author in substantiating and writing the manuscript, in reviewing critical intellectual content, in the final approval for publication of the manuscript

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DOI: 10.20514/2226-6704-2021-11-1-76-80

А.Е. Шкляев[1], А.М. Хисамутдинова*[1], А.Г. Бессонов[2], О.В. Муравцева[2], А.В. Кобелев[2], С.Н. Стяжкина[1]

[1] — ФГБОУ ВО «Ижевская государственная медицинская академия Минздрава России», Ижевск, Россия
[2] — БУЗ УР «Первая Республиканская клиническая больница МЗ УР», гастроэнтерологическое, хирургическое отделение, Ижевск, Россия

ПЕРВИЧНЫЙ ГИПЕРПАРАТИРЕОЗ ВСЛЕДСТВИЕ АДЕНОМЫ ПАРАЩИТОВИДНОЙ ЖЕЛЕЗЫ: КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

A.E. Shklyaev[1], A.M. Khisamutdinova*[1], A.G. Bessonov[2], O.V. Muravtseva[2], A.V. Kobelev[2], S. N. Styazhkina[1]

[1] — Izhevsk state medical Academy, Izhevsk, Russia
[2] — Republican clinical hospital, gastroenterological Department, Izhevsk, Russia

Primary Hyperparathyroidism Due to Parathyroid Adenoma: Clinical Case

Резюме

Первичный гиперпаратиреоз — эндокринное заболевание, характеризующееся избыточной секрецией паратиреоидного гормона при верхне-нормальном или повышенном уровне кальция крови вследствие первичной патологии околощитовидных желез. Первичный гиперпаратироз в зависимости от клинических проявлений может протекать в нормокальциемической, мягкой и манифестной формах. В данной статье представлен клинический случай развития манифестной формы по типу висцеральных нарушений, которые проявились в виде патологии желудочно-кишечного тракта. Данная форма заболевания является показанием к оперативному лечению и дальнейшей коррекции кальций-фосфорного обмена.

Ключевые слова: *первичный гиперпаратиреоз, хронический панкреатит, аденома паращитовидных желез*

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 26.10.2020 г.
Принята к публикации 07.12.2020 г.

Для цитирования: Шкляев А.Е., Хисамутдинова А.М., Бессонов А.Г. и др. ПЕРВИЧНЫЙ ГИПЕРПАРАТИРЕОЗ ВСЛЕДСТВИЕ АДЕНОМЫ ПАРАЩИТОВИДНОЙ ЖЕЛЕЗЫ: КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ. Архивъ внутренней медицины. 2021; 11(1): 76-80. DOI: 10.20514/2226-6704-2021-11-1-76-80

Abstract

Primary hyperparathyroidism (PGPT) is an endocrine disease characterized by excessive secretion of parathyroid hormone (PTH) in upper — normal or elevated blood calcium levels due to primary parathyroid gland pathology (osch). Primary hyperparathyrosis, depending on the clinical manifestations, can occur in the normocalcemic, mild and manifest form. This article presents a clinical case of the development of the manifest form by the type

*Контакты: Арина Михайловна Хисамутдинова, e-mail: arinahis2508@gmail.com
* Contacts: Arina M. Khisamutdinova, e-mail: arinahis2508@gmail.com
ORCID ID: https://orcid.org/0000-0001-8482-7336

of visceral disorders. Which appeared in the form of pathology of the gastrointestinal tract. This form of the disease is an indication for surgical treatment and further correction of calcium-phosphorus metabolism.

Key words: *Primary hyperparathyroidism, chronic pancreatitis, adenoma of the parathyroid glands*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

Sources of funding

The authors declare no funding for this study

Article received on 26.10.2020

Accepted for publication on 07.12.2020

For citation: Shklyaev A.E., Khisamutdinova A.M., Bessonov A.G. et al. Primary Hyperparathyroidism Due to Parathyroid Adenoma: Clinical Case. The Russian Archives of Internal Medicine. 2021; 11(1): 76-80. DOI: 10.20514/2226-6704-2021-11-1-76-80

BMI — body mass index, CL — cholelithiasis, FGD — fibrogastroduodenoscopy, GIT — gastrointestinal tract, NSAIDs — non-steroidal anti-inflammatory drugs, PHPT — primary hyperparathyroidism, PTG — parathyroid glands, PTH — parathyroid hormone, US — ultrasound

Introduction

Primary hyperparathyroidism (PHPT) is an endocrine disease characterized by excessive secretion of parathyroid hormone (PTH) in patients with abnormal or elevated blood calcium levels due to primary pathology of parathyroid glands. PHPT is manifested by a multisymptomatic clinical presentation involving various organs and systems in the pathological process, which leads to a significant decrease in the quality of life, disability of patients, and increased risk of premature death [2].

Depending on the severity of clinical symptoms, there are normocalcemic, mild and manifesting types of PHPT [1]. Depending on the variety of lesions in various systems and organs, the manifesting type is characterized by an intense clinical picture of bone lesions and/or visceral disorders and the risk of hypercalcemic crisis.

Damage to the gastrointestinal tract (GIT) is found in half of patients with PHPT. Patients have complaints of anorexia, constipation, nausea, flatulence, and weight loss. Gastric and/or duodenal peptic ulcers develop in 10–15% of cases, pancreatitis — in 7–12%; pancreatolithiasis and pancreatic calcinosis are less frequent [2]. The development of a gastric ulcer in cases of hypercalcemia is associated with increased secretion of gastrin and hydrochloric acid, which returns to normal after removal of parathyroid adenoma. The course of the gastric ulcer in cases of PHPT is characterized by a more intense clinical picture (frequent exacerbations with severe pain, perforations are possible) than in cases of a gastric ulcer caused by other factors. In this clinical case, we will observe the manifestation of the visceral type of disease, which is characterized by gastrointestinal lesions.

Case report

Patient K., 49 y.o., female, was admitted to the Gastroenterology Department on October 16, 2019 with complaints of severe general weakness, nausea during daytime, and vomiting bile up to four times a day (with relief), bitter taste in the mouth. There were no abdominal pains at the time of admission. Stool is formed, "pellet-like", sometimes with blood streaks, regular, up to three times a day (sometimes every other day), without mucus. No appetite. No skin itching. Low-grade body temperature occasionally in the evening. Fast satiation. Chewing within normal. Swallowing and food passage through the esophagus within normal.

The patient considers herself ill since 2015 when she was incidentally diagnosed with cholelithiasis (CL) during an ultrasound examination (US) of abdominal organs; no treatment was carried out. She started experiencing occasional aching pains in the epigastrium at night; she received outpatient treatment (proton pump inhibitor (omeprazole) with a positive effect). In 2015, there were three exacerbations; the patient was treated on an outpatient basis (omeprazole) with improvement. There were no GIT complaints until 2019. Worsening since February 2019, in the form of constant aching pain in the right upper quadrant, worsening at night. The patient took a non-steroidal anti-inflammatory drug (NSAID) up to several tablets per day. After two weeks, she visited a local therapist, was treated on an outpatient basis with a positive effect (proton pump inhibitor (omeprazole). In May 2019 — relapse of abdominal pain, again stopped by conservative treatment. At the beginning of August 2019 — relapse of pain; on August 16, 2019 a laparoscopic cholecystectomy was performed. Two days after discharge, the patient experienced repeated vomiting and epigastric pain; she was hospitalized with a diagnosis of "postcholecystectomy syndrome", was discharged with improvement. On October 4, 2019, she was again hospitalized for repeated vomiting bile and epigastric pain. The patient received treatment (infusion therapy, antiemetics, antibacterial therapy, proteolysis inhibitors, enzymes, proton pump inhibitors) with a slight improvement (less frequent vomiting, pain syndrome subsided). Considering persistent complaints, cancer alertness, weight loss of 20 kg over the past two months, the patient was transferred to the Gastroenterological Department

of the First Republican Clinical Hospital (Izhevsk) for examination and treatment.

Objectively on admission: general condition is satisfactory. Clear consciousness. Active position. Asthenic body type, hypotrophy (BMI 21.0 kg/m^2). Skin is pale, dry, of normal temperature, decreased turgor. Nails and hair are dull and brittle. Atrophic limb muscles. No peripheral edema. Respiratory rate 16 per minute. Vesicular breathing in the lungs, no rales. Regular heart rhythm with HR 84 per minute. Heart tones are clear. Rhythmic pulse of satisfactory filling. BP 100/70 mm Hg on both arms. Tongue is moist, with dense yellow fur. Abdomen of normal shape. On palpation, soft, painful in epigastrium and Shofar zone. Liver does not protrude from the edge of costal arch. Size according to Kurlov 11 × 8 × 7 cm. Gallbladder removed. Spleen not palpable. Kidneys not palpable. No CVA tenderness on percussion.

Laboratory and diagnostic test results

On admission on October 16, 2019: WBC — 7.47 × 10^9/l, RBC — 2.80 × 10^{12}/l, hemoglobin — 85 g/l, platelets — 232 × 10^9/l, ESR — 26 mm/h. Total protein — 56.7 g/l, albumin — 31.71 g/l, alpha$_1$ globulins — 2.72 g/l (1.4–3.0); alpha$_2$ globulins — 5.43 g/l (5.6–9.1); beta$_1$ globulins — 4.43 g/l (5.4–9.1); beta$_2$ globulins — 2.96 g/l (3.2–6.5); gamma globulins — 9.45 g/l (8.1–17.0); urea — 3.41 mmol/l, creatinine — 68.53 μmol/l, alkaline phosphatase (ALP) — 697.18 U/l, gamma-glutamyltranspeptidase (GGT) — 20.94 U/ml (7.0–32.0), aspartate aminotransferase (AST) — 9.3 U/l, alanine aminotransferase (ALT) — 5.30 U/l, sodium — 138.00 mmol/l, potassium — 3.00 mmol/l, glucose — 5.68 mmol/l, lipase — 16.78 U/l (0.0–60.0), alpha-amylase — 37.86 U/l (25.0–94.0), total bilirubin — 6.84 μmol/l, direct bilirubin — 2.20 μmol/l. Prothrombin index (PTI) — 95.0%; prothrombin time — 13.9 seconds; fibrinogen — 2.64 g/l; activated partial thromboplastin time (APTT) — 26.4 seconds.

Considering anemia, blood tests for serum iron, vitamin B$_{12}$ and folic acid were performed. Folic acid deficiency component of anemia was diagnosed (folic acid — 4.94 nmol/l (6.0–39.0)).

Urinalysis: specific gravity — 1004; pH — 6.5; protein — 0.1 g/l; glucose — 2.8 mmol/l; WBC — 0; RBC — 0; bacteria — 0. Urine amylase — 86.4 U/l (10.0–500.0).

Fecalysis: macroscopic examination — formed, brown, occult blood (++++); digestible muscle fibers +; indigestible fiber ++; neutral fat +. Stool culture for opportunistic flora: no growth of typhoid-paratyphoid-dysenteric bacteria was found.

Fibrogastroduodenoscopy (FGD) was performed: indirect signs of pancreatic pathology. Significant reflux — gastroduodenitis. Biliary duodenogastric reflux grade 3. Rough cicatricial-ulcerative deformation of duodenal bulb. Achalasia cardiae. Chronic reflux-esophagitis. Erythematous papillitis, moderate.

According to the biopsy — chronic atrophic gastritis of mild activity. Focal colonic metaplasia.

Colonoscopy: endoscopic signs of ischemic colitis in erosive stage, with damage to the blind, ascending, transverse, descending, sigmoid colon. Ileocecal valve dysfunction. Histological study revealed a picture of chronic nonspecific colitis with areas of stromal edema, reactive proliferation of glandular crypt epithelium, presence of neutrophil accumulations in the lumen of separate crypts, activity grade 1–2.

According to abdominal ultrasound, there were signs of diffuse changes in pancreatic parenchyma, with increase in size due to body and tail; calculus of left kidney.

Angiography of abdominal aorta and its branches to exclude ischemic origin of total erosive colitis: no data for stenotic-occlusive pathology of abdominal vessels were obtained.

On day 12 of therapy, negative clinical changes were observed (vomiting increased to 4–5 times a day) along with increase in alkaline phosphatase level to 837.0 mmol/l. In order to stop vomiting, a selective 5HT3 receptor antagonist was prescribed (ondansetron 8 mg/day).

Schwartz test revealed decompensated pyloric stenosis and slow passage of the contrast agent through the small intestine. Consultation with surgeon: at the time of examination, data for decompensated pyloric-bulbar stenosis are doubtful; no absolute indications for surgical treatment.

Considering persistent multiple vomiting, the daily dose of ondansetron was increased to 16 mg per day, potassium chloride was added to correct electrolyte disorders.

On day 18 of treatment, vomiting increased to 10 times a day, irrespective of food intake. To exclude the central origin of vomiting, magnetic resonance imaging (MRI) of the brain was performed: atrophic process of brain substance was revealed. Consultation with neurologist: no data for focal neurological pathology at the time of examination.

A multidisciplinary team meeting was held in connection with the negative changes; it was decided to adjust infusion therapy, monitor daily urine, review the pituitary gland on brain MRI, review adrenal glands on abdominal CT, perform ultrasound of the thyroid gland, blood test for calcium, thyroid hormones (thyroid stimulating hormone (TSH), free triiodothyronine ($T_{3)}$, free thyroxine (fT_4)), parathyroid hormone.-

Test results: TSH — 0.745 μIU/ml (0.4–5.5), free T_4 — 14.5 pmol/l (9.0–23.0), PTH — 2048 pg/ml (9.5–75.0 pg/ml), calcium — 2.53 mmol/l (2.10–2.55), phosphorus — 2.03 mmol/l (0.87–1.45). Ultrasound of thyroid and parathyroid glands revealed signs of parathyroid adenoma located on the back border of the lower pole on the right; the structure of the thyroid gland echographically

with slight changes. Consultation with endocrinologist: the patient was diagnosed with «primary hyperparathyroidism, adenoma of parathyroid glands», surgical treatment is recommended.

The following treatment was performed in the Gastroenterology Department: infusion therapy, antispasmodics, enzymes, H_2 blockers, antimicrobials (metronidazole, rifamixin), glucocorticoids, selective 5HT3 receptor antagonist (ondansetron), bismuth agents, folic acid, anti-inflammatory (mesalazine), laxatives, gastroprotectors, and enteral nutrition.

During the patient's stay in the Gastroenterology Department, laboratory parameters improved slightly: WBC — 8.73×10^9/l, RBC — 3.59×10^{12}/l, hemoglobin — 107 g/l, platelets — 234×10^9/l, alkaline phosphatase — 478.74 U/l, lipase — 11.24 U/l, alpha-amylase — 23.36 U/l.

In connection with the diagnosed primary hyperparathyroidism with underlying parathyroid adenoma, which caused indomitable vomiting with secondary water-electrolyte disorders, the patient was transferred to the Surgical Department for surgical treatment of parathyroid adenoma.

On November 20, 2019, a right-sided parathyroidectomy was performed. According to biopsy results, no neoplasm elements were found.

The postoperative period was characterized by a significant decrease in levels of hemoglobin, calcium, potassium (laboratory test results from November 25, 2019: WBC — 7.80×10^9/l, RBC — 2.04×10^{12}/l, hemoglobin — 59 g/l, platelets — 140×10^9, total calcium — 1.37 mmol/l; potassium — 2.73 mmol/l).

Transfusion of RBC concentrate was performed, with positive effect. The decrease in calcium level to less than 1.9 mmol/l was an indication for intravenous administration of calcium gluconate [1]. After three days, blood calcium level increased to 2.25 mmol/l, along with the improved general state of the patient. Conservative treatment in the Surgical Department: infusion therapy, calcium gluconate, RBC concentrate, alfacalcidol. On day 14 after surgical treatment, the wound healed by primary intention, scar is competent. The patient was discharged for outpatient treatment.

Final clinical diagnosis: Primary hyperparathyroidism with adenoma of the right lower parathyroid gland (condition after right-sided parathyroidectomy), gastrointestinal type, newly diagnosed, complicated by gastropathy in the form of indomitable vomiting, secondary erosive-ulcerative enterocolitis with symptoms of transient dynamic small bowel obstruction. Nutritional deficiency grade 2. Water-electrolyte disorders of moderate severity. Background disease: Chronic biliary-dependent pancreatitis, parenchymal type, recurrent course, dyspeptic form, exacerbation phase. Exocrine pancreatic insufficiency grade 1. Postcholecystectomy syndrome (condition after laparoscopic cholecystectomy due to cholelithiasis from August 16, 2019). Duodenal ulcer, newly diagnosed, remission phase. Cicatricial deformation of the duodenal bulb with compensated pyloric-bulbar stenosis. Urolithiasis.

Diet recommendations (calcium-, potassium-rich) were given on discharge. Limited physical activity for 2–3 months. Alfacalcidol + calcium carbonate (0.25 μg + 500 mg) — 2 capsules in the morning and 1 capsule in the evening. Control of complete blood count, total and ionized calcium.

Discussion

In the presented clinical case, the patient suffered from nausea, indomitable vomiting, and epigastric pain persisting after cholecystectomy due to cholelithiasis. The treatment prescribed to relieve chronic biliary-dependent pancreatitis had no effect. During examination of the patient, parathyroid adenoma was found. Clinical manifestations corresponded to the picture of the visceral type of primary hyperparathyroidism, which was an absolute indication for surgical treatment. Surgical treatment is the most radical and effective method of managing this pathology [3]. The postoperative period can be characterized by hypocalcemia (up to 50% of cases), which is caused by long suppression of the normal function of parathyroid glands by active parathyroma, postoperative edema of the remaining parathyroid glands, or by "hungry bone" syndrome [2]. During the postoperative period, serum calcium level in this patient dropped to 1.37 mmol/l, which was an indication for intravenous administration of calcium gluconate [2]. The patient was discharged with a significant improvement during follow-up by a local therapist and endocrinologist, with recommendations to continue taking calcium and the active form of vitamin D on an outpatient basis.

Conclusion

The diagnosis of primary hyperparathyroidism with visceral signs is a challenging task for physicians of most specialties. Timely diagnosis and surgical treatment can significantly improve the prognosis and patient's quality of life. Analysis of clinical cases that are difficult to diagnose is important to improve the effectiveness of primary care physicians since they can bring the experience of clinical treatment of patients with rare pathologies into their practice [5].

Вклад авторов:

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

А.Е. Шкляев (ORCID: https://orcid.org/0000-0003-4479-508X): разработка концепции — формирование идеи; формулировка ключевых целей и задач. Подготовка и редактирование текста — составление

черновика рукописи. Утверждение окончательного варианта — принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант.

А.М. Хисамутдинова (ORCID: https://orcid.org/0000-0001-8482-7336): разработка концепции — развитие ключевых целей и задач. Проведение исследования — сбор данных, анализ и интерпретация полученных данных. Подготовка и редактирование текста — составление черновика рукописи, участие в научном дизайне. Утверждение окончательного варианта — принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант.

А.Г. Бессонов: разработка концепции, подготовка и редактирование текста, ресурсное обеспечение исследования, утверждение окончательного варианта — принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант

О.В. Муравцева: разработка концепции, подготовка и редактирование текста, ресурсное обеспечение исследования, утверждение окончательного варианта — принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант

А.В. Кобелев: разработка концепции, подготовка и редактирование текста, ресурсное обеспечение исследования, утверждение окончательного варианта — принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант

С.Н. Стяжкина: разработка концепции, подготовка и редактирование текста, ресурсное обеспечение исследования, утверждение окончательного варианта — принятие ответственности за все аспекты работы, целостность всех частей статьи и ее окончательный вариант

Author Contribution:

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

A.E. Shklyaev (ORCID: https://orcid.org/0000-0003-4479-508X): concept development — formation of an idea; formulation of key goals and objectives. Preparation and editing of the text — drafting of the manuscript. Approval of the final version — taking responsibility for all aspects of the work, the integrity of all parts of the article and its final version

A.M. Khisamutdinova (ORCID: https://orcid.org/0000-0001-8482-7336): concept development — development of key goals and objectives. Research — data collection, analysis and interpretation of the data obtained. Preparation and editing of the text — drafting of the manuscript, participation in scientific design. Approval of the final version — taking responsibility for all aspects of the work, the integrity of all parts of the article and its final version

A.G. Bessonov: development of the concept, preparation and editing of the text, resource support of the research, approval of the final version-taking responsibility for all aspects of the work, the integrity of all parts of the article and its final version

O.V. Muravtseva: concept Development, drafting and editing text, resource support of the research, the approval of the final option — taking responsibility for all aspects of the work, the integrity of all parts of an article and its final version

A.V. Kobelev development of the concept, preparation and editing of the text, resource support of the research, approval of the final version-taking responsibility for all aspects of the work, the integrity of all parts of the article and its final version

S.N. Styazhkina: development of the concept, preparation and editing of the text, Resource support of the research, approval of the final version-taking responsibility for all aspects of the work, the integrity of all parts of the article and its final version

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