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107076, Москва, ул. Короленко, д.3А, офис 18Б
Тел.: (495) 777-41-17
E-mail: info@medarhive.ru

ГЕНЕРАЛЬНЫЙ ДИРЕКТОР
Чернова Ольга Александровна
o_chernova@medarhive.ru

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

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

Отдел распространения и рекламы
Бабяк Алина
reklama@medarhive.ru

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FOUNDER AND PUBLISHER
«SYNAPSE» LLC
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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

MEDICAL EDITOR
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PAGE-PROOFS
Kotov Vitaly

ADVERTISING
Babiak Alina
reklama@medarhive.ru

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В.Н. Ларина*, Т.А. Гайдина, А.С. Дворников, К.Е. Назимкин

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

ВОЗМОЖНОСТИ ОБСЛЕДОВАНИЯ ПАЦИЕНТОВ С ПОДОЗРИТЕЛЬНЫМИ НА МЕЛАНОМУ НОВООБРАЗОВАНИЯМИ КОЖИ, ВПЕРВЫЕ ВЫЯВЛЕННЫМИ В ПЕРВИЧНОМ ЗВЕНЕ ЗДРАВООХРАНЕНИЯ

V.N. Larina*, T.A. Gaydina, A.S. Dvornikov, K.E. Nazimkin

N.I. Pirogov Russian National Research Medical University, Moscow, Russia

The Principles of Examination of Patients with Detected Melanoma Suspected Skin Neoplasm in the Primary Health Care Stage

Резюме

В настоящее время в структуре смертности населения в Российской Федерации и ряда других странах онкологические заболевания занимают ведущие позиции среди других причин. Меланома кожи является одной из наиболее агрессивных злокачественных опухолей, с быстрым прогрессированием, нередко приводящим к летальному исходу в достаточно короткие сроки. Раннее выявление и рационально организованная маршрутизация пациентов с первично выявленной меланомой кожи в первичном звене здравоохранения направлена на снижение заболеваемости и смертности от злокачественных заболеваний, улучшение качества жизни пациентов. Результаты исследований предполагают, что увеличение заболеваемости меланомой кожи обусловлено как гипердиагностикой, так и настороженностью врачей и населения по отношению к пигментным новообразованиям кожи. В статье обсуждаются факторы риска развития меланомы кожи. Уделяется внимание современным клиническим методам прогнозирования течения меланомы кожи, поскольку данное заболевание является потенциально обратимым. Рассматриваются компьютерные методы скрининга и диагностики меланомы кожи, применимые в условиях первичного звена здравоохранения. Отдельный раздел посвящён дерматоскопии или эпилюминесцентной микроскопии, которая относится к исследованию пигментных поражений кожи с использованием поверхностной микроскопии. Представлен перечень исследований при подозрении на злокачественное новообразование кожи/меланому кожи у пациента, обратившегося за медицинской помощью в лечебно-профилактическое учреждение. Обсуждается значимость критериев алгоритма ABCDE, алгоритма «Арджензиано» в исследовании пигментных поражений кожи с дальнейшим анализом результатов искусственным интеллектом для принятия решения.

Ключевые слова: *злокачественное новообразование, меланома, дерматоскопия, первичное звено здравоохранения*

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*Контакты: Вера Николаевна Ларина, e-mail: larinav@mail.ru

*Contacts: Vera N. Larina, e-mail: larinav@mail.ru

ORCID ID: https://orcid.org/0000-0001-7825-5597

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Abstract

Currently, in the structure of mortality in the Russian Federation and a number of other countries, oncological diseases occupy a leading position among other causes. Melanoma of the skin is one of the most aggressive malignant tumors, with rapid progression, often leading to death in a fairly short time. Early detection and rationally organized refferral of patients with diagnosed skin melanoma in primary health care settings is aimed at reducing morbidity and mortality from malignant diseases, and improving the quality of life of patients. Research results suggest that the increased incidence of skin melanoma is due to both overdiagnosis. and an increase in the alertness of doctors and the population in relation to pigmented skin formations. The article discusses the proven risk factors for the development of skin melanoma, since this disease is potentially reversible. Attention is paid to modern clinical methods for predicting the course of skin melanoma. The review article examines computer-based methods for screening and diagnosing skin melanoma, applicable in primary health care settings. A separate section is devoted to dermatoscopy or epiluminescence microscopy, which refers to the study of pigmented skin lesions using surface microscopy. A list of studies is presented in case of suspicion of a malignant neoplasm of the skin / melanoma of the skin in a patient who sought medical help at a medical and prophylactic institution. The significance of the criteria of the ABCDE algorithm, the "Argenziano" algorithm in the study of pigmented skin lesions with further analysis of the results by artificial intelligence for decision-making is discussed.

Key words: *malignant tumors, melanoma, skin, dermatoscopy, primary health care settings*

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ABCDE — **a**symmetry of tumor, irregular **b**orders, irregular **c**oloration, **d**iameter 6 mm or more and morphological changes, i.e. **e**nlargement, CDKN2A — cyclin-dependent kinase inhibitor 2A, CI — confidence interval, CNN — convolutional neural network, CPRs — Complex Regional Pain Syndrome, MN — melanocytic nevus, OR — odds ratio, SM — skin melanoma

In recent decades, the incidence of skin melanoma (SM) in most developed countries has been steadily increasing, much faster than other types of cancer [1, 2]. According to statistics, in 2018 in the Russian Federation (RF), the skin was the leading localization in cancer morbidity for both men and women (12.6% — without melanoma; 14.4% — with melanoma) [3]. At the end of 2019, in local cancer institutions in the Russian Federation, the skin remained the leading localization in the incidence of malignant neoplasms for both men and women (without melanoma — 13.1%, with melanoma — 15.0%) [4].

From 2008 to 2018, mortality due to SM in men and women in our country increased by 11.19% [3]. The increase in the incidence of melanoma is due to both overdiagnosis and the vigilance of medical personnel and the general population in regard to pigmented skin neoplasms.

The life expectancy of patients with SM depends primarily on the stage of the tumor process when the treatment was started; disappointing statistics in the Russian Federation suggest the underdevelopment of early diagnosis of SM. Despite the increase in the rate of active detection of patients with SM in the Russian Federation in 2017, only one in three patients was actively detected. In 2016–2017, the neglect rate in regard to SM remained at 19.0%, which is unacceptably high in case of visually localized tumors [5].

An increase in the incidence of melanoma by 4–6% per year in elderly patients with fair skin has been reported in many countries, including Australia, the United States and most parts of Europe [6–8]. At the same time, there is a significant increase in the overall five-year survival of patients with SM, which is largely associated with early diagnosis and detection of tumors at initial stages [9]. The prognosis for some patients with melanoma may be favorable. However, the disease has a significant impact on the quality of life [10] and health care costs [11].

SM is a potentially preventable tumor because it has proven risk factors for its development. The most significant risk factor for SM is skin exposure to ultraviolet radiation [12]. Other risk factors include sunburn in childhood, Fitzpatrick skin phototypes I and II, CDKN2A genetic mutation, ten or more dysplastic nevi or more than 100 multiple melanocytic skin nevi, history of SM, familial melanoma [13, 14].

Early detection, well-organized routing of initially identified patients with SM and timely treatment significantly improve the prognosis. The diagnosis of SM in primary health care is difficult because physicians are not sufficiently qualified to conduct a differential assessment of the nature of pigmented skin lesions [15]. Considering the current situation, physicians of outpatient departments have to improve their skills in diagnosing SM [16].

Diagnosis of Skin Melanoma

To differentiate SM from benign pigmented skin lesions, a number of clinical prediction methods (CPRs — Complex Regional Pain Syndrome) and computer diagnostic methods have been developed.

The UK National Institute of Clinical Medicine (NICE) does not recommend the routine use of computer-assisted diagnostic tools in the initial assessment of skin lesions. However, it recommends a seven-step diagnostic algorithm in primary care for the diagnosis of SM. During the diagnosis of SM by dermatologists, some CPRs clinical prediction methods have demonstrated high sensitivity and specificity [9].

When examining a skin neoplasm, dermatologists most often use an ABCDE algorithm, which evaluates the following criteria: **a**symmetry of tumor, irregular **b**orders, irregular **c**oloration, **d**iameter 6 mm or more and morphological changes, i.e. **e**nlargement. If two criteria are met, the sensitivity and specificity of the ABCDE algorithm is 89.3% and 65.3%; if three criteria are met — 65.5% and 81% [9].

Skin neoplasms may have their own unique elements. However, there are common features that are typical for a particular neoplasm, so illustrations can be used in primary care as one of the clinical prediction methods. CPRs can be used alone for clinical (i.e. naked eye examination) examination of a skin lesion, or in combination with dermoscopy.

Dermoscopy

Dermoscopy, or epiluminescence microscopy, refers to the examination of pigmented skin lesions using surface microscopy [17]. The use of dermoscopy, primarily by dermatologists, improves the accuracy of diagnosis compared to naked eye examination, since it allows visualization of specific features that are not visible to the naked eye [18]. In their work, Kittler H. et al. (2002) demonstrated a higher diagnostic accuracy of dermoscopy than when no dermoscopy is used to detect SM (OR 4.0 [95% CI 3.0–5.1] vs OR 2.7 [95% CI 1.9–3.4]; p = 0.001) [19].

However, the effectiveness of dermoscopy depends on the clinical experience and professionalism of the specialist. Dermatologists with extensive experience and training in dermoscopy have higher rates of detecting SM than inexperienced dermatologists or primary care physicians [20]. According to D. Piccolo et al. (2002), the sensitivity of diagnosing SM via dermoscopy was higher for an experienced dermatologist (92%) and lower — for an inexperienced dermatologist (69%); specificity was also higher for the experienced (99%) than the inexperienced professional (94%). The authors cited an interesting fact that computer analysis showed more false results (26%) than an experienced (0.6%) and inexperienced (5.5%) dermatologist [21].

Software for computer analysis of malignancy of skin neoplasms is being improved. This is critical during a pandemic when patients want to get a "second opinion" remotely.

In recent years, new methods for assessing the pigmentation of skin neoplasms and detecting melanoma have emerged, including spectrophotometric intracutaneous analysis, or SIAscopy, optical coherence tomography, confocal microscopy, multiphoton tomography, electrical impedance spectroscopy etc.; all these methods should be more actively implemented in general clinical practice [22].

Primary care physicians often deal with skin lesions with suspicions of malignancy; they are difficult to differentiate from true malignant neoplasms when the patient should be immediately referred to a specialist for verification of diagnosis and treatment. At the same time, a primary care physician should be informed about benign skin neoplasms that can be observed when working in an outpatient department [15].

In the Russian Federation, particularly the Moscow Healthcare Department, one of the priorities in recent years has been delivering preventive medical care to the public, including early diagnosis of oncological diseases and timely start of treatment. New algorithms and educational projects for the early diagnosis of malignant neoplasms and routing of patients with suspected or newly diagnosed cancer are being developed and implemented. One of the regulations governing the organization of oncological medical care in the Moscow Healthcare Department is the order of the Moscow City Healthcare Department No. 16 of January 15, 2020 "On the Provision of Medical Care in the Field of Oncology in Medical Organizations of the State Healthcare System of the City of Moscow" [17].

This order approved a list of examinations for patients with complaints or signs typical for an oncological disease, as well as the timing of examination and the timing consulting oncologist when the preliminary diagnosis of a malignant neoplasm is confirmed (3 and 5 days, respectively). One of the sections of this order includes a list of complaints/signs of skin malignant neoplasm/melanoma and a list of examinations for suspected skin malignant neoplasm/melanoma.

The list of complaints/signs of skin malignant neoplasm/skin melanoma requiring further examination of patients is given below:

1. Pigmented lesion with rapid growth.
2. Pigmented lesion with changing configuration of its boundaries.
3. Pigmented lesion with different coloration.
4. Itching in the area of pigmented lesion.
5. Burning sensation in the area of pigmented lesion.
6. Indolent skin ulcer.
7. Painful and bleeding ulcers, induration, crusts on the skin surface (especially on the scalp, neck).
8. Induration of skin area.
9. Red border around any mass lesion.

If the patient has any complaint, they should be examined according to the list given in Table 1.

To meet the requirements of this order and improve the quality of medical care for the early diagnosis and

Table 1. Checklist for suspected skin malignancy / skin melanoma

N	Investigation	Importance	Additional condition
1.	Clinical blood test	Yes, if it was not performed during the last 14 days	No
2.	Activated partial thromboplastin time	Yes	No
3.	Prothrombin (thromboplastin) time	Yes	No
4.	Antibodies to the Hepatitis C virus in blood	Yes	No
5.	Hepatitis B virus antigen (HBsAg) in blood, qualitative study	Yes	No
6.	Antibodies to the Treponema pallidum in blood test	Yes	No
7.	Human immunodeficiency virus test	Yes	No
8.	Consultation with an oncologist	Yes	No

treatment of oncological diseases, the Personal Assistant project was implemented in the work of primary health care facilities in Moscow [23]. This project is intended to provide consultative and logistical assistance to patients from the moment of suspicion of a malignant neoplasm and examination to confirm the diagnosis to registration with an oncologist for regular medical check-ups and treatment.

At present, for the early diagnosis of SM, primary care physicians of the Moscow Healthcare Department can use clinical research methods (naked eye) and improvised low-magnification optical systems (loupes). The latter were approved in the mandatory list of devices for primary care physicians and have been widely used only in the last five years with the addition of general practitioners to the staff of local clinics. In recent years, general practitioners have also been using dermoscopes in their routine practice. An illustrative example is dermoscopy performed by a primary care physician/general practitioner in the case of suspicious skin neoplasms as part of a comprehensive examination of patients in "Zdorovaya Moskva" pavilions.

Despite that recently, at the primary care stage in Russian health care, special attention has been paid to the early diagnosis of malignant skin neoplasms, the incidence of neglected SM remains high [5].

This is primarily due to primary care physicians not being sufficiently skilled in the field of skin neoplasms. Insufficient time devoted to oncodermatology during the initial training and postgraduate education of primary care physicians/general practitioners, little experience in working with SM patients — all this affects the timely verification of malignant skin tumors [24].

Diagnosis of Skin Neoplasms Using the Example of Examination of a Patient in Primary Health Care

Below is an example of patient examination, which indicates the possibility of timely diagnosis of skin neoplasms in primary health care with subsequent routing to provide immediate specialized treatment.

During examination in the course of periodic medical check-up at a Moscow clinic, a mass lesion was revealed on the skin of the back of patient N., 7 mm in diameter, with a round shape, distinct boundaries, light brown in color, with slight polychromy, an uneven surface, rising above the surface of unchanged skin.

Consultation was conducted with an associate professor of the Department of Outpatient Therapy of the Medical Faculty of the N.I. Pirogov Russian National Research Medical University. During the visit, a macro photo of the skin neoplasm was taken (Fig. 1, A), as well as a dermoscopic micro photo (Fig. 1, B) using a Handyscope optical device with 20x magnification (FotoFinder; Germany) connected to a smartphone with the Handyscope3 mobile application. Artificial intelligence in this application is a convolutional neural network (CNN), which is trained based on more than 100,000 micro photos of skin neoplasms with a histologically confirmed diagnosis; it is the optimal option for screening diagnostics in primary health care [25]. CNN is able to develop its own decision-making algorithms during image analysis and demonstrates better specificity and sensitivity compared to dermatologists with initial (up to 2 years) and intermediate (up to 5 years) experience in dermoscopic evaluation [25]. Handyscope is a convenient portable device that allows to not only take high-quality images of skin neoplasms and analyze them with CNN, but also e-mail them through the Handyscope3 application for prompt discussion of a clinical case with competent subject matter experts, which is critical for primary care physicians and the development of telemedicine in general.

In patient N., computer analysis by CNN in the Handyscope3 mobile application showed a high risk of neoplasm malignancy (red zone 0.93) (Fig. 1, C). The patient was referred to an oncologist to determine further treatment tactics.

Amid the ongoing Covid-19 pandemic, the option to take a photo of a skin melanocytic nevus (SMN) with the subsequent entry of macro and dermoscopic micro photos into an electronic patient record for further analysis and remote consultation is especially relevant. Our foreign colleagues widely use the opportunities for teledermoscopic consultations. In a pilot study, Zink A. et al.

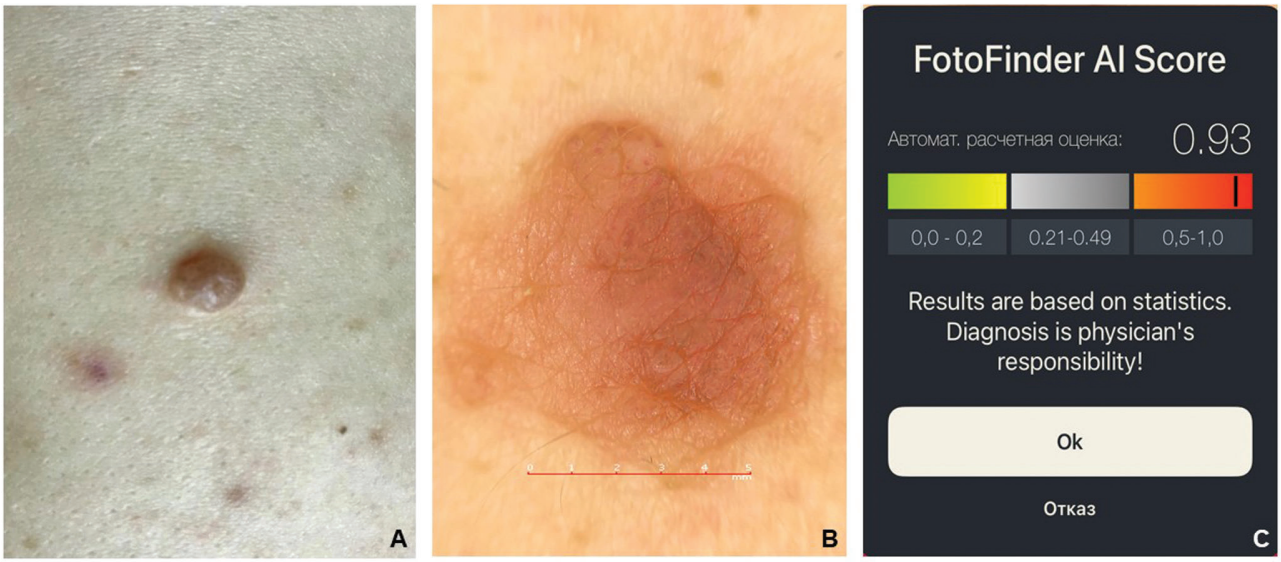

Figure 1. *A — macro view of a neoplasm on the back skin*
B — dermatoscopic micrograph of a neoplasm on the back skin
C — assessment of a dermatoscopic micrograph of the neoplasm by artificial intelligence

compared the accuracy of the results of teledermoscopic consultations with subsequent SMN histology. Macro and dermoscopic micro photos of SMNs were taken by five medical residents in 26 patients using a mobile phone and a Handyscope optical system, and the images were analyzed by an experienced dermatologist. As a result of remote teleconsultation, it was decided to excise and histologically examine 23% of SMNs from those examined. There was a 92.3% match of diagnoses made remotely using macro photos and dermoscopic microimages with histological examination. It is important that macro photos and dermoscopic microimages of SMNs can be taken not only by subject matter experts but also by primary care physicians. And the analysis of the obtained images can be used both for screening for SM and for remote consultations on further tactics of patient management. Mobile teledermoscopy may be an alternative to a clinical examination by a subject matter expert [26].

Undoubtedly, entering macro photos and dermoscopic microimages of SMNs into an electronic patient record for subsequent computer analysis by CNN and/or for remote telemedicine consultations can be a good instrument for early diagnosis of SM by primary care physicians.

Prospects for Improving the Diagnosis of Skin Melanoma in Primary Health Care

Particular attention should be paid to improving the equipment of primary care physicians' offices with dermoscopes and guidance materials (illustrations of skin neoplasms, clinical guidelines, clinical prediction methods) [27].

Optimization of the routing of patients with suspected malignant neoplasms, including SM, has a significant impact on the timely establishment of diagnosis, speeds up diagnosis, improves its accuracy and enables to start treatment earlier [23].

If SM is suspected, primary care physicians often refer patients to a dermatologist and not an oncologist in order to determine further tactics for examining the patient, which delays diagnosis and treatment. Referral for a biopsy only after consultation with an oncologist and the inability to take a biopsy from a patient with suspected SM directly at the district cancer detecting center at the patient's place of residence also delay diagnosis and are often the key challenges. Using the example of delivering cancer care at the Moscow Healthcare Department under the new Moscow Standard for the provision of cancer care, such challenges can be resolved by setting up multidisciplinary cancer centers with a full range of clinical capabilities. These centers enable the diagnosis, surgical treatment, medication therapy and regular medical check-up of patients with oncological diseases. Each center receives patients from one or two administrative districts of Moscow. In this way, all stages of specialized care are carried out within one medical facility [23].

Overdiagnosis of SM is an equally important problem [28]. On the one hand, referral of a patient with any skin neoplasm for consultation with an oncologist with further biopsy to confirm the diagnosis will not be helpful. On the other hand, it requires additional resources of the cancer department and leads to emotional stress in case of a wrong diagnosis of skin cancer and referral to an oncologist, as well as in the case of an unjustified biopsy. Therefore, training primary care physicians in the field of dermatooncology and equipping the workplace with modern diagnostic instruments is justified and necessary.

Using computer information systems in routine practice could significantly improve the diagnosis of SM. For example, the presence of a dermoscopy report in the patient's electronic record with the option to enter data in accordance with the criteria of various algorithms (ABCDE, Argenziano 7-point checklist, etc.) with further analysis by artificial intelligence, obtaining a result and making a decision.

The option to take photos of skin neoplasms with their transfer to an electronic record will allow to visually assess changes in the skin neoplasms. If dermoscopy is not accompanied by photographic evidence, i.e. dermoscopic images — and this is precisely the state of affairs in Russian primary health care — then, when observing a patient over time, it is difficult to compare the results of the current and previous dermoscopy examinations, especially if they are carried out by different specialists. This is also because there is no standardized protocol for recording the detected dermoscopic signs using a certain sequence and unified terminology for their description, depending on the particular dermoscopic algorithm used [23, 28].

An image (photo) of a skin neoplasm in the patient's electronic record will also allow remote diagnosis and double-checking by experts or a computer similar to the "artificial intelligence" of the X-ray department of the Moscow Healthcare Department [29–31].

The use of SM clinical prediction methods in actual clinical practice by primary care physicians requires additional time during examination, which is currently not provided for these procedures and, according to the standard, averages 15–18 minutes [32].

Conclusion

Today, more and more attention is paid to the problem of early diagnosis of malignant skin neoplasms. New clinical prediction methods are being developed, and the existing ones are being improved. Workplaces are beginning to be equipped with new diagnostic instruments; new innovative methods for diagnosing SM are being applied, such as "smartphone optical systems", etc. [33–39]. However, there are several issues that have not been fully resolved, such as the competence of primary care physicians in the field of dermatooncology, the full equipment of workplaces with diagnostic instruments and guidance material and the improvement of routing patients with suspected skin malignancy and additional time for diagnostic procedures. Solving these issues will reduce not only the frequency of underdiagnosis of SM but also its overdiagnosis, which leads to unjustified biopsies, surgical interventions that affect the quality of life of patients, as well as additional financial costs. A well-functioning system of providing medical care to patients with suspected skin cancer will enable the timely verification of the diagnosis of SM, the placement of such individuals under care, their monitoring and treatment and extending the life expectancy and improving the quality of life of such patients.

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

Гайдина Т.А. (ORCID ID: https://orcid.org/ 0000-0001-8485-3294): сбор, анализ и интерпретации данных, подготовка рукописи, ответственный за все аспекты работы

Дворников А.С. (ORCID ID: https://orcid.org/ 0000-0002-0429-3117): сбор, анализ и интерпретации данных, подготовка рукописи, ответственный за все аспекты работы

Назимкин К.Е. (ORCID ID: https://orcid.org/ 0000-0001-5343-4847): сбор, анализ и интерпретации данных, подготовка рукописи, ответственный за все аспекты работы

Author Contribution

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

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

Gaydina T.A. (ORCID ID: https://orcid.org/0000-0001-9002-7749): collection, analysis and interpretation of data, preparation of the manuscript, responsible for all aspects of the work

Dvornikov A.S. (ORCID ID: https://orcid.org/ 0000-0002-0429-3117): collection, analysis and interpretation of data, responsible for all aspects of the work

Nazimkin K.E. (ORCID ID: https://orcid.org/ 0000-0001-5343-4847): collection, analysis and interpretation of data, preparation of the manuscript, responsible for all aspects of the work

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Р.Н. Мустафин

ФГБУЗ «Башкирский государственный медицинский университет»,
Уфа, Россия

КЛИНИЧЕСКИЕ МАСКИ НЕЙРОФИБРОМАТОЗА 1-ГО ТИПА

R.N. Mustafin

Bashkir State Medical University, Ufa, Russia

Clinical Masks of Neurofibromatosis Type 1

Резюме

Нейрофиброматоз 1-го типа является самым распространенным аутосомно-доминантным опухолевым синдромом, встречающимся с частотой 1 на 3000 населения. Особенностью клинических проявлений болезни является постепенное появление признаков и выраженный клинический полиморфизм от стертых и атипичных форм до тяжелых классических проявлений. В данном обзоре рассмотрены заболевания, симптомы которых значительно схожи с нейрофиброматозом 1-го типа, в связи с чем важным методом для дифференциальной диагностики является молекулярная диагностика болезни. Поскольку 10% случаев заболевания обусловлены крупными делециями локуса 17q11.2, помимо секвенирования гена *NF1* необходимо проведение зависимой от лигирования мультиплексной амплификации зонда. В большинстве случаев начальными проявлениями нейрофиброматоза 1-го типа являются множественные пигментные пятна, которые на протяжении многих лет могут быть единственными внешними признаками болезни. В связи с этим могут быть ошибочно установлены диагнозы, для которых характерны данные пигментные изменения: синдромы Блума, LEOPARD, Карнея, Костелло, Коудена, Легиуса, Ниймеген, Нунан, Пейтца-Егерса, Сильвера-Рассела, кардио-фацио-кожный синдром. Обнаружение подкожных нейрофибром может стать основанием для неверной диагностики схожих по клинике синдромов Легиуса и множественной эндокринной неоплазии. Кроме того, множественные липомы являются специфическими проявлениями липоматозов Маделунга или Деркума, семейного ангиолипоматоза, этиология которых считается неизвестной. Сделано предположение, что эти заболевания являются атипичными формами нейрофиброматоза 1-го типа, поскольку ряд авторов описали идентификацию мутаций в гене *NF1* у пациентов со множественным липоматозом. Поэтому важное значение имеет широкое внедрение в клиническую практику возможности молекулярно-генетической идентификации болезни для выявления случаев нейрофиброматоза 1-го типа, не соответствующих принятым NIH (National Institute of Health) критериям диагностики. Наиболее перспективно создание панели с исследованием всех генов, мутации в которых могут вызывать схожие с нейрофиброматозом 1-го типа проявления. Ранняя диагностика заболевания необходима для своевременного начала лечения и предотвращения тяжелых проявлений, поскольку в клиническую практику внедряются эффективные методы противоопухолевой терапии, такие как ингибиторы митоген-активируемой киназы.

Ключевые слова: *ген NF1, дифференциальная диагностика, липоматоз, мутации, нейрофиброматоз 1-го типа, секвенирование*

Конфликт интересов

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

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*Контакты: Рустам Наилевич Мустафин, e-mail: ruji79@mail.ru
*Contacts: Rustam N. Mustafin, e-mail: ruji79@mail.ru
ORCID ID: https://orcid.org/0000-0002-4091-382X

Abstract

Neurofibromatosis type 1 is the most common autosomal dominant tumor syndrome. The prevalence of the disease is 1 in 3000 people. Neurofibromatosis type 1 is characterized by the gradual appearance of signs of the disease and pronounced clinical polymorphism from erased and atypical forms to severe classical manifestations. The review is devoted to the consideration of diseases, the manifestations of which are significantly similar to neurofibromatosis type 1, and therefore, molecular diagnosis of the disease is an important method for differential diagnosis. To make a diagnosis of neurofibromatosis type 1, it is necessary to find mutations in the *NF1* gene using sequencing. In 10% of cases, neurofibromatosis type 1 is caused by large deletions of the 17q11.2 locus, therefore, multiplex ligation-dependent probe amplification is also necessary. Typically, the initial manifestations of neurofibromatosis type 1 are multiple café-au-lait spots, which may be the only external signs of the disease for many years. Therefore, patients with neurofibromatosis type 1 may be mistakenly diagnosed with diseases for which these pigmentary changes are characteristic: Bloom, LEOPARD, Carney, Costello, Cowden, Legius, Nijmegen, Noonan, Peitz-Jägers, Silver-Russell, cardio-facio-cutaneous syndromes. The detection of subcutaneous tumors can become the basis for an incorrect diagnosis of the clinically similar Legius syndrome and multiple endocrine neoplasia. In addition, multiple lipomas are specific manifestations of Madelung or Dercum lipomatosis, familial angiolipomatosis, the etiology of which is considered unknown. Therefore, I assume that these diseases are atypical forms of neurofibromatosis type 1, since a number of authors have described the identification of mutations in *NF1* gene in patients with multiple lipomatosis. Therefore, it is important to widely introduce into clinical practice the possibility of molecular genetic identification of the disease in order to identify cases of neurofibromatosis type 1 that do not meet the diagnostic criteria adopted by the NIH. It is promising to create a panel for the study of all genes, mutations in which can cause manifestations similar to neurofibromatosis. Early diagnosis of the disease is necessary for timely initiation of treatment and prevention of severe manifestations, since effective methods of antitumor therapy of neurofibromatosis type 1, such as inhibitors of mitogen-activated kinase, are being introduced into clinical practice.

Key words: *NF1 gene, differential diagnosis, lipomatosis, mutations, neurofibromatosis type 1, sequencing*

Conflict of interests

The authors declare no conflict of interests

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AMP — adenosine monophosphate; NF1 — neurofibromatosis type 1

Introduction

Neurofibromatosis type 1 (NF1) is the most common hereditary tumor syndrome with autosomal dominant inheritance pattern. The global average incidence of NF1 is 1 per 3,000 people [1]. NF1 is caused by germline heterozygous mutations in the *NF1* gene, which is located at 17q11.2 and includes 280,000 bp and 57 exons. Mature mRNA of this gene is 11,000 bp long and is translated into the tumor suppressor protein neurofibromin [2]. The *NF1* gene is characterized by increased mutability, therefore, 50% of NF1 cases are sporadic due to *de novo* mutations in the germ cells of parents [3].

Neurofibromin regulates RAS-cyclic AMP (cyclic adenosine monophosphate) pathway, MAPK/ERK kinase cascade, adenylate cyclase and cytoskeletal assembly. The main domain of this protein is GRD (GAP (GTP-ase activating protein) related domain) that converts GTP-bound RAS oncogenes into GDP-bound (inactivated) forms [4]. The pathogenesis of NF1 is caused by the effect of neurofibromin deficiency (due to *NF1* mutations) on the hyperactivation of RAS oncogenes that increase AKT (RAC-alpha serine/threonine-protein kinase)/mTOR (mammalian target of rapamycin) and RAF (rapidly accelerated fibrosarcoma)/MEK (mitogen-activated protein kinase) signaling. As a result, the risk of developing tumors increases [2].

NF1 is characterized by complete penetrance by the age of five [5], when specific signs of the disease develop. These include café-au-lait macules (CALM), freckles, Lisch nodules, neurofibromas, optic nerve gliomas, and specific skeletal anomalies (sphenoid wing dysplasia, thinning of cortical bone, congenital pseudarthrosis). Diagnosis of NF1 is clinically confirmed by the presence of two of these signs or one sign in the case of first-degree blood relatives with NF1. These criteria are established by the National Institutes of Health (NIH) [1].

Specific features of NF1 include the development of new symptoms with age, as well as a pronounced variability of clinical presentations even in patients with an identical mutation and in members of the same family [1, 2, 6, 7], with the exception of monozygotic twins who have coinciding manifestations of NF1 even in the development of malignant neoplasms [8]. CALM are detected in 98% of NF1 patients [9], specific cutaneous or subcutaneous neurofibromas in 95%, plexiform neurofibromas

in 50% [10], spinal neurofibromas in 35%, and optic nerve gliomas in 18% [9]. NF1 patients are characterized by high risk of malignant neoplasms (MNs), especially of aggressive type such as MPNST (malignant peripheral nerve sheath tumor), that develops in 13% of patients, most often degenerating from plexiform neurofibromas [11]. Moreover, on average, in 10% of cases, somatic mutations in the *NF1* gene in individuals without NF1 cause sporadic MNs that are resistant to standard pharmacotherapy [4].

Differential diagnosis of pigment spots in neurofibromatosis type 1

CALM are detected in 3% of healthy newborns [12]. Since the average incidence of NF1 is 0.033% [1], CALM in most cases are not associated with a germline mutation in the *NF1* gene, which can lead to a wrong diagnosis of NF1 in children. There are a number of diseases with clinical signs similar to NF1, for which CALM are a typical symptoms or may develop in some patients. For the purposes of differential diagnosis, hereditary tumor syndromes with similar signs have to be considered above all. Clinical signs of NF1 are similar to those of neurofibromatosis type 2, patients with NF2 also develop CALM, however, in smaller size and numbers (Figure 1). This disease is caused by mutations in the *NF2* gene (that encodes schwannomin and is located at 22q12.2) [13]. The clinical presentation in Legius syndrome (NF1-like syndrome) is also very similar to that of NF1: multiple CALM or freckling, macrocephaly, facial dysmorphism, cognitive and behavioral disorders. This disease develops due to the mutations in the *SPRED1* gene that includes 7 exons and is localized at 15q3.2. The gene product (like neurofibromin) works as a negative regulator of RAS-MAPK signaling pathways [14].

In addition to NF1 and neurofibromatosis type 2, multiple CALM were described in cases of other RASopathies: Noonan syndrome (mutations in the *PTPN11* tyrosine phosphatase gene, localization 12q24.3), Costello syndrome (mutations in *HRAS* oncogene localized at 11p15.5), cardiofaciocutaneous syndrome (mutations in *BRAF* genes (encodes BRAF oncogene, locus 7q34)), *MAP2K1* (encodes mitogen-activated protein kinase, locus 15q22.31), *MAP2K2* (locus 19p13.3), *KRAS* (encodes KRAS oncogene, locus 12p12.1) [12]. RASopathies include LEOPARD syndrome (Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, Deafnes) when multiple lentigines (brown spots) on the face (Figure 2) are caused by mutations in the *PTPN11* (protein-tyrosine phosphatase non-receptor 11) gene. More than 65% of patients with LEOPARD syndrome have major missense mutations in the *PTPN11* gene — Tyr272Cys and Thr468Met. Like in NF1, the signs of LEOPARD syndrome also include skeletal anomalies, neuroblastomas, and hemoblastoses [15].

CALM and sun-sensitive butterfly-shaped facial rash are typical for Bloom's tumor syndrome that is caused by mutations in the *BLM* gene (locus 15q26.1), whose product has helicase activity [16]. Multiple CALM are also found in patients with other hereditary tumor syndromes: Fanconi anemia (affected *FANCA* gene (Fanconi anemia complementation group, locus 16q24.3)),

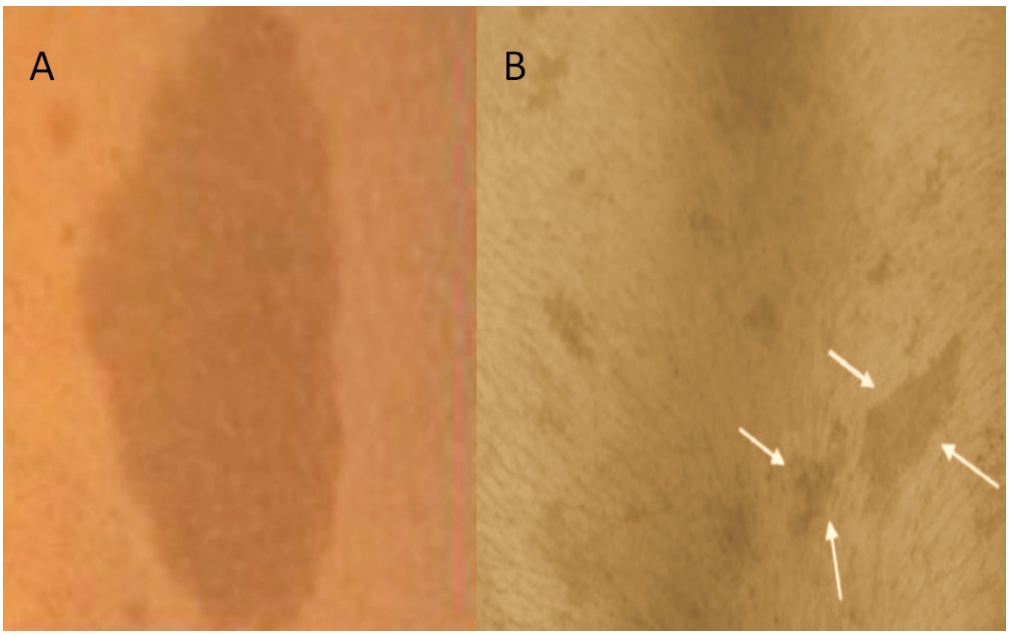

Figure 1. *Comparative characteristics of café-au-lait spots in neurofibromatosis type 1 (A) and neurofibromatosis type 2 (B) [13]*

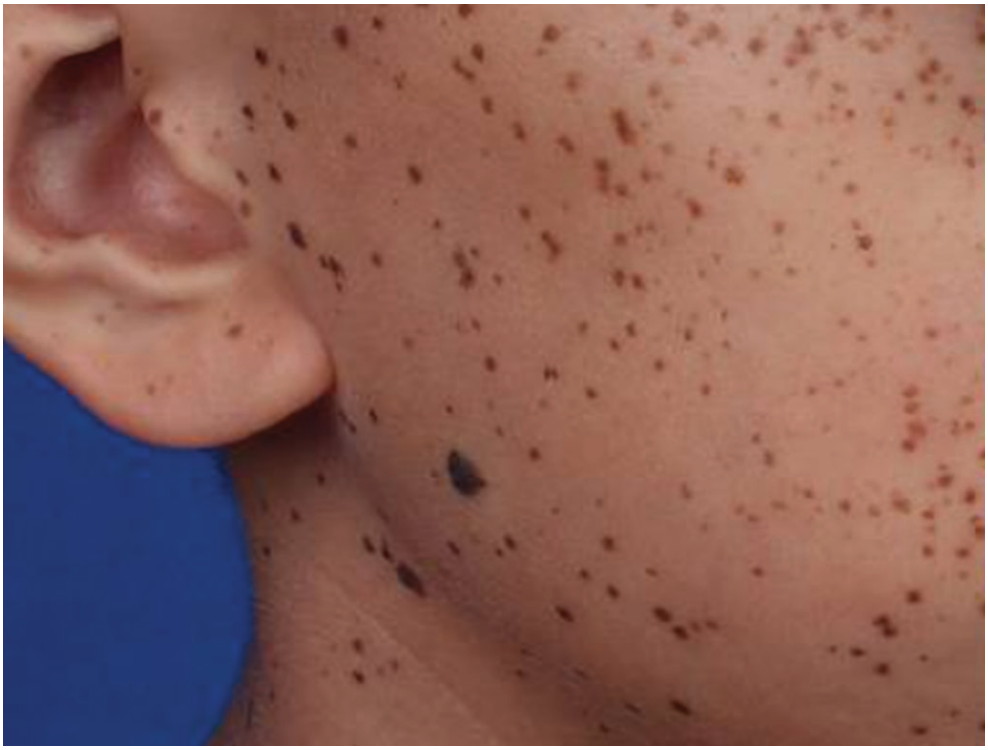

Figure 2. *Typical brown pigmented spots on the face in LEOPARD syndrome [15]*

Nijmegen syndrome (*NBN* gene (Nijmegen breakage syndrome, 8q21.3)) [17], Lynch syndrome (*MSH2* (mutS homolog 2, 2p21); *MSH6, MLH1, PMS2* genes) [18], Cowden syndrome (*PTEN* gene, 10q23.31) [19], Peutz-Jeghers syndrome (*STK11* gene encodes tumor suppressive serine-threonine kinase 11, locus 19p13.3) [16], Gorlin-Goltz syndrome (*PTCH1* gene, 9q22.32) [20]. CALM are also detected in 84% of cases of ataxia-telangiectasia (Louis-Bar syndrome), which is caused by mutations in the *ATM* gene (localization 11q22.3) that encodes serine-threonine protein kinase [21]. In cases of tuberous sclerosis, CALM are also detected in addition to typical depigmented spots [20]. Tuberous sclerosis is caused by mutations in tumor suppressor genes *TSC1* (localization 9q34) or *TSC2* (16p13.3) and its incidence is 1:6000 people [22].

Multiple CALM are typical signs of McCune-Albright-Braytsev syndrome (caused by a mutation in the *GNAS* gene (Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide, localization 20q13.32) [12]), Silver-Russell syndrome (caused by hypermethylation of the *H19* gene (11p15.5, tumor suppressor long non-coding RNA) [23], Carney syndrome (*PRKAR1A* gene, protein kinase cAMP-dependent type 1 regulatory subunit, 17q24.2) [20]. A familial case of the development of multiple CALM was described; the lesion was caused by a germline mutation in the *MAP2K2* gene that encodes mitogen-activated protein kinase involved in neurofibromin regulatory pathways [24]. Mutations in the *MAP2K2* gene are typical for Costello syndrome [12]. However, in the case described by the authors, CALM was the only sign of the disease [24]. CALM can also be found in patients with Marfan syndrome (fibrillin-1 gene, *FBN1*, 15q21), Gaucher's disease (glucosylceramidase beta gene, *GBA*, 1q22) and Hunter disease (iduronate sulfatase gene, *IDS*, Xq28) [16]. Since sporadic skin or subcutaneous tumors that can be confused with neurofibromas and lead to the diagnosis of NF1 cannot be excluded in any individuals with the diseases described above, a differential diagnosis is required, which is based on molecular genetic identification of a germline mutation in DNA isolated from blood WBC.

Differential diagnosis of tumors in neurofibromatosis type 1

Tumors that are similar to NF1 both in appearance and in pathogenesis develop in cases of type 2 neurofibromatosis. They can include NF1-like cutaneous neurofibromas, nodular schwannomas from peripheral nerves, and specific plaques (irregular, pigmented lesions circumscribed from the surrounding skin (Figure 3)). A characteristic difference between neurofibromatosis type 2 and NF1 is the development of schwannomas of acoustic nerves [25]. In tuberous sclerosis, facial angiofibromas (many reddish papules in the area of the chin, cheeks, nose, and nasolabial folds), gingival fibromas, subungual fibromas, and shagreen plaques on the skin

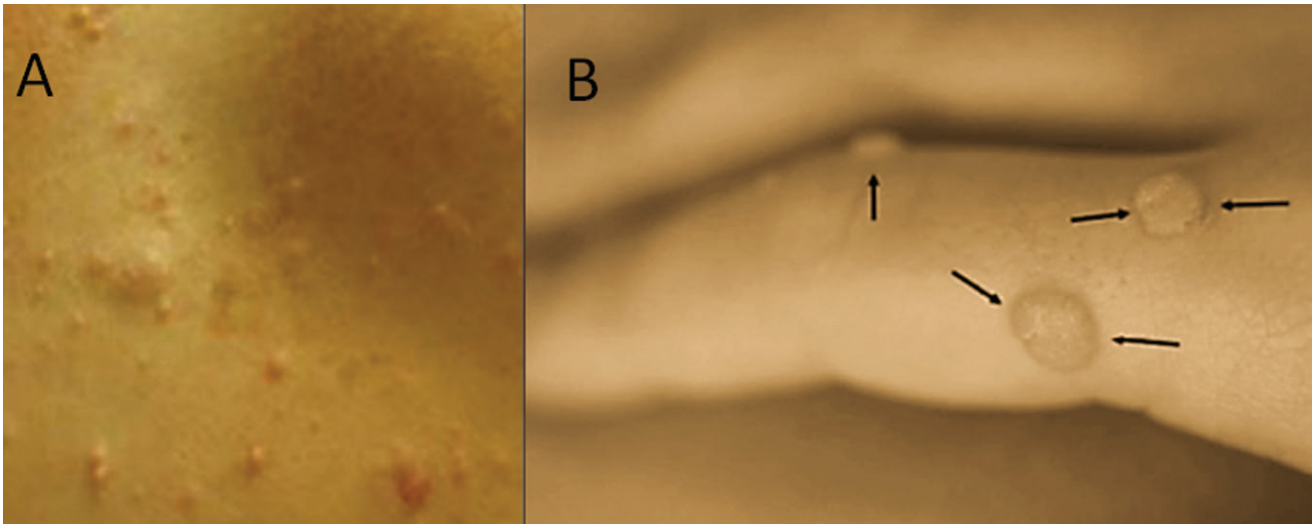

Figure 3. *Cutaneous neurofibromas in neurofibromatosis type 1 (A) [12] and classic cutaneous plaques in neurofibromatosis type 2 (B) [13]*

can also be confused with signs of NF1 [26]. In addition to CALM, Carney syndrome is characterized by pigmented tumors on the skin that may resemble pigmented neurofibromas [20]. In cases of Legius syndrome, multiple lipomas develop that are similar to subcutaneous neurofibromas [14].

NF1 types with subcutaneous neurofibromas depending on the location of the lesion may resemble the clinical presentation of different lipomatoses. In patients with Madelung's disease, lipomas are typically located on the lower body, legs and neck (proximal form), thighs, hands and knee joints (distal form), forearms, lower body, thighs and lower legs (central form) [27]. Like NF1, Madelung's disease can be also accompanied with polyneuropathy [28, 29] and cognitive impairment [30]. Multiple painful subcutaneous lipomas are also typical for Dercum's disease, which was described as early as 1892 and has an autosomal dominant pattern of inheritance, similar to NF1. This disease is subdivided into diffuse, generalized nodular, localized nodular, and periarticular types [31].

In addition to Dercum's disease, a number of authors describe familial angiolipomatosis with an autosomal dominant inheritance with no accurate identification of the genetic causes of this disease. It is assumed that they are based on NF1 [32, 33]. It can be assumed that Madelung's and Dercum's diseases are also atypical forms of NF1. This is evidenced by information on the role of mast cells in the development of angiolipomas in Dercum's disease [34] and familial angiolipomatosis [35], since mast cells are also important in the development of neurofibromas [36].

Other hereditary tumor syndromes can also cause multiple lipomas. Familial multiple lipomatosis (FML) with the incidence of 1:50,000 people [37] may be caused by atypical hereditary retinoblastoma. A family was described with a splice site mutation in the *RB1* gene (encodes the tumor suppressor protein RB, locus 13q14.2) accompanied by the development of many lipomas with incomplete penetrance in regard to retinoblastoma [38]. FML is also found in cases of multiple endocrine neoplasia with loss of heterozygosity of the *MEN1* gene (locus 11q13.1, encodes the tumor suppressor protein menin) in some tumors [39]. A recent publication describes a case of genetically confirmed Cowden syndrome (mutation c.195C>A (p.Y65*) in the *PTEN* gene) with multiple CALM and subcutaneous lipomas. Immunohistochemical results revealed no loss of heterozygosity for the *PTEN* gene in tumors [19].

Therefore, since the genetic basis of a number of lipomatoses has not yet been established, but an autosomal dominant type of inheritance was determined, it can be assumed that they are one of the types of NF1 and other hereditary tumor syndromes. To confirm this assumption, mutations in the *NF1* gene and other tumor suppressor genes in all patients with multiple lipomas should be searched for. At the same time, there are cases when no mutations in the *NF1* gene are found with a typical NF1 clinical presentation with CALM, freckles, neurofibromas, and Lisch nodules [40], as well as cases of familial lipomatosis with an autosomal dominant type of inheritance and with the absence of mutations in *NF1, SPRED1,* and *PTEN* genes [41]. This suggests the need to develop a full panel of molecular genetic tests for differential diagnosis of various diseases with signs similar to NF1. Table 1 includes the characteristics of all the abovementioned diseases with a clinical presentation characterized by the presence of CALM and/or tumor syndrome. To develop a differential diagnostic panel for NF1, molecular genetic testing of genes is required that can be affected by mutations causing these diseases (Table 1).

Table 1. *Neurofibromatosis type 1 differential diagnoses*

Disease (mutated gene, localization)	Pigmented cutaneous manifestations (difference from NF1*)	Tumors and tumor-like formations (difference from NF1)
Familial angiolipomatosis (unknown)	not typical	multiple lipomas (histologically angiolipomas)
Ataxia-telangiectasia (*ATM*, 11q22.3)	CALM**	leukemias, carcinomas
Bloom's syndrome (*BLM,* 15q26.1)	CALM, a rash on the face of the "butterfly" type	leukemias
Gorlin-Golts syndrome (*PTCH1,* 9q22.32)	CALM	basal cell skin cancer, medulloblastoma
Gaucher disease (*GBA,* 1q22)	CALM	not typical
Dercum disease (unknown)	not typical	multiple painful lipomas (histologically angiofibrolipomas)
Cardio-facio-cutaneous syndrome (*BRAF*-7q34, *MAP2K1*-15q22.31, *MAP2K2*-19p13.3, *KRAS*-12p12.1)	multiple CALM	not typical
Carney syndrome (*PRKAR1A*, 17q24.2)	CALM on the face	pigmented skin tumors, heart myxomas, pituitary adenomas
Costello syndrome (*HRAS,* 11p15.5)	multiple CALM	skin papillomas
Cowden syndrome (*PTEN,* 10q23.31)	CALM	skin trichilemmomas (on the face and ears), thyroid and breast cancer, endometrial cancer, hamartomas, intestinal polyps, multiple lipomas
Lynch Syndrome (*MSH2,* 2p21)	multiple CALM	colon cancer, endometrial and ovarian cancer
Legius syndrome (*SPRED1*, 15q3.2)	multiple CALM or freckles	multiple lipomas (histologically lipomas)
Madelung disease (unknown)	not typical	multiple subcutaneous lipomas with specific localization (not neurofibromas histologically)
McCune-Albright-Braitse syndrome (*GNAS*, 20q13.32)	large CALM	not typical
Marfan syndrome (*FBN1*, 15q21)	CALM	not typical
Multiple endocrine neoplasia (*MEN1,* 11q13.1)	not typical	multiple lipomas (lipomas histologically)
Neurofibromatosis type 2 (*NF2,* 22q11.2)	CALM (fewer and smaller spots)	NF1-like cutaneous neurofibromas (fewer), nodular schwannomas (from large nerve trunks), plaques (pigmented)
Nijmegen syndrome (*NBN*, 8q21.3)	multiple CALM	rhabdomyosarcoma, lymphoma, leukemias
Noonan syndrome (*PTPN11*, 12q24.3)	multiple CALM	neuroblastoma, leukemias
Peutz-Jeghers syndrome (*STK11*, 19p13.3)	CALM, pigmented spots on the lips and oral mucosa	polyps and hamartomas of the gastrointestinal tract, colon cancer, pancreas cancer, breast and ovary cancer
Hereditary retinoblastoma (*RB1,* 13q14.2)	not typical	multiple lipomas (histologically lipomas), retinoblastoma (retina malignant tumor)
Silver-Russell syndrome (*H19,* 11p15.5)	multiple CALM	not typical
Tuberous sclerosis (*TSC1*-9q34, *TSC2*-16p13.3)	depigmentation spots along with CALM	angiofibromas (localized on the face), fibromas (located on the gums and under the nails), internal organs hamartomas
Fanconi anemia (*FANCA,* 16q24.3)	CALM multiple CALM	squamous cell carcinoma, leukemias, Wilms' tumor and brain tumors
Hunter syndrome (*IDS,* Xq28)	CALM CALM	not typical
LEOPARD**** syndrome (*PTPN11,* 12q24.3)	multiple lentigines	neuroblastoma (malignant tumor, unlike benign neurofibromas)

Note: NF1* — neurofibromatosis type 1; CALM — café-au-lait macules, LEOPARD**** — Lentigines, Electrocardiographic conduction abnormalities, Ocular hypertelorism, Pulmonic stenosis, Abnormal genitalia, Retardation of growth, Deafnes)

Identification of atypical forms of neurofibromatosis type 1

Results of histological examinations of subcutaneous tumors in NF1 revealed the presence of atypical signs of the disease in the form of liponeurofibromas. For example, analysis of 130 neoplasm samples from various NF1 patients demonstrated that the microscopic pattern in 24.6% of cases can be described as liponeurofibromas. These changes are most often found in patients of advanced age and in female patients. At the same time, intratumoral fat deposits differ in morphology and size in comparison with subcutaneous tissue during light microscopy [42]. Histological results also demonstrated atypical neurofibromas consisting of cells with hyperchromic nuclei, with a large number of recurrent chromosomal aberrations including deletion of the 9p21.3 locus that includes *CDKN2A/B* genes. It should be noted that 9p21.3 deletion is a specific sign of MPNST, therefore, these atypical neurofibromas [11] are characterized by frequent malignant transformation [43].

Due to the possibility of detection the mutations in the *NF1* gene, clinical signs of NF1 that do not meet the NIH diagnostic criteria are described. NF1 patients with multiple lipomas are described [44, 45]. In 2021, sequencing of the *NF1* gene in two patients from the same family with lipomatosis and CALM revealed the missense mutation c.3445A>G (p.Met1149Val) [46]. Earlier in 2020, missense mutations leading to the replacement of methionine in position 1149 of neurofibromin (p.Met1149) were described in 62 NF1 patients with mild clinical course of the disease, mainly with CALM and with no visible plexiform neurofibromas and gliomas [47]. In 2019, 135 NF1 patients from 103 unrelated families were described; they had identical three-nucleotide deletion of c.2970_2972del resulting in methionine depletion in neurofibromin (p.Met992del). All patients are characterized by atypical clinical presentation with no cutaneous, subcutaneous, or spinal neurofibromas, as well as optic nerve gliomas. However, 38.8% of patients had cognitive impairments, and 4.8% had brain tumors not related to optic nerves [1]. In 2019, Trevisson E. et al. identified the missense mutation c.3112A>G (p.Arg1038Gly) in 7 NF1 patients with CALM as the only sign of the disease [48].

In 2009, Upadhyaya M. et al., while examining NF1 patients with spinal plexiform neurofibromas, determined the association of missense and splicing mutations in the *NF1* gene in patients with scarce clinical signs of the disease that did not meet the NIH diagnostic criteria [49]. In 2015, Pinna V. et al. examined 786 NF1 patients and found among them 6 unrelated patients with identical missense mutation c.5425C>T (p.Arg1809Cys) with a mild course of the disease with characteristic CALM and freckling, but with no skin or plexiform neurofibromas, no Lisch nodules, skeletal anomalies, or gliomas of optic nerves [50]. There were cases of NF1 with inapparent clinical signs with no visible skin or plexiform neurofibromas, with a three nucleotide deletion in exon 17 of the NF1 gene (c.2970-2972 delAAT) that results in the loss of one amino acid, methionine (p.Met991) in neurofibromin [5]. A missense mutation with an arginine amino acid substitution in an identical position (p.Arg1809) in 136 patients with NF1 causes one typical feature of NF1 such as only multiple CALMs, with no visible skin or plexiform neurofibromas. These patients were characterized by Noonan-like syndrome (25%); they also had increased risk of developing pulmonary artery stenosis and short stature [3]. It is noteworthy that multiple pigmented spots, short stature, and pulmonary artery stenosis are also specific for LEOPARD syndrome [51].

Genophenotypic correlations in NF1 were also determined for microdeletions of the 17q11.2 locus together with the *NF1* gene and its flanking neighboring genes that are detected in 10% of all NF1 patients. These patients have more pronounced signs of the disease with cognitive deficiency and facial dysmorphism [7], as well as early manifestation of tumors [52]. The 3 most common types of microdeletions are the following: type 1 as 1.4 megabases in size, flanked proximally by NF1-REPa and distally by NF1-REP-c; type 2 as 1.2 megabases in size, with deletion of *NF1*, *SUZ12* and *SUZ12P* genes; type 3 as 1.0 megabases in size, with breakpoint regions in paralogous areas in the middle of NF1-REP-b and distally of NF1-REP-c [53]. Type 1 is detected in 70–80% of cases, type 2 in 10–23%, and type 3 in 1–4%. The reason is non-allelic homologous recombination (NAHR) between low copy repeats during meiosis (types 1 and 3) or mitosis (type 2) [7]. More severe manifestations of NF1 with extended deletions of the entire *NF1* gene with neighboring loci [53] may indicate the impact of the loss of genes located in the area of the microdeletion on the pathogenesis of NF1. In particular, in cases of type 1 microdeletion, the *HCA66* gene is lost, which has a protein product that interacts with the tumor suppressor Apaf-1 (apoptic protease activating factor-1). Therefore, when *HCA66* is inactivated, cells become less susceptible to apoptosis, which contributes to the exacerbation of the tumor syndrome in NF1 [54].

Current diagnostic approaches and management of neurofibromatosis type 1

Since the clinical manifestations of NF1 may not meet the criteria established by NIH, one of the most important methods of diagnosing this disease is the molecular genetic test for the mutation that should be performed in all suspected cases. Since the disease is caused by germline heterozygous mutations in the *NF1* gene, DNA isolated from peripheral blood WBC is used to find said mutations. Subsequently, the detection of intragenic mutations is carried out using next-generation sequencing with Integrative genomics viewer software [55] and

confirmation of results via Sanger sequencing [56]. Since 10% of NF1 cases are caused by microdeletions at the 17q11.2 locus [7], multiplex ligation-dependent probe amplification (MLPA) is used to detect them with analysis of results by means of Coffalyser MLPA analysis software [57].

The identification of mutations in the *NF1* gene is important for the development of treatment for NF1 patients, since, in cases of nonsense mutations (up to 20% of all types of changes in NF1 [58]), the technique of terminating the translation of premature termination codons in the reading frame can be used. To this end, pseudouridylation, inhibition of nonsense-mediated mRNA decay, and suppressor tRNAs are used [59]. Management of cystic fibrosis with aminoglycosides demonstrated that the use of gentamicin in low doses in cases of nonsense mutations in the CFTR gene (formation of a stop codon at amino acid residues 542 and 553 of protein product) contributes to the translation of a protein of normal length in the amount of 25–35% of normal. This effect is associated with closely related mismatch of aminoacyl-tRNA with a premature termination codon [60]: deoxystreptamine ring of aminoglycosides connected to several amino sugars connects to the decoding center of the ribosome (acts as a proofreader for attaching only related aminoacyl-tRNAs to the peptidyl transferase center of ribosome). The effectiveness of gentamicin in restoring normal protein expression in the presence of a premature termination codon was proven in experiments on mice regarding the Duchenne muscular dystrophy, nephrogenic diabetes insipidus, hemophilia, retinal degeneration, *APC*-mediated colon cancer, Hurler syndrome. Other antibiotics that cause translational termination of premature termination codons include negamycin (binds to the small ribosomal subunit), spiramycin, josamycin, and tylosin. Suppression of translation of premature termination codons in mammalian cells without affecting translation termination in normal termination codons is caused by PTC124, known as ataluren. This agent demonstrated its effectiveness in restoring the translation of normal proteins in models of various monogenic diseases [59]. Antitumor activity is also demonstrated by tetracycline group antibiotics that inhibit protein synthesis in tumor mitochondria, thus causing a cytotoxic effect. Further, the analysis of a culture of MPNST cells from an NF1 patient demonstrated that doxycycline in combination with photodynamic effect caused by 5-aminolevulinic acid had a pronounced cytotoxic effect on tumor cells [61]. The suppression of translation of premature termination codons has been shown to be effective against tumor suppressor genes in other hereditary tumor syndromes [59], however, no such studies were conducted for NF1. However, in cases of deep intron mutations in the *NF1* gene that cause insertions of latent exons in mRNA, experimental studies on fibroblast and lymphocyte lines demonstrated the effectiveness of antisense oligomers in the restoration of normal splicing. These molecules specifically bind to new 5' splice sites required for insertion of latent exons and suppress them, preventing the formation of mutant mRNA [58, 62].

Currently, the only agent approved by the FDA (Food and Drug Administration) for the targeted therapy of NF1 is the ATP-independent inhibitor of mitogen-activated protein kinase (MEK) selumetinib [63]. This agent is recommended at a dose of 25 mg per 1 m^2 of body surface area. Back in 2016, the results of treatment of 24 NF1 pediatric patients with selumetinib were published. There were rare side effects in the form of acne, asymptomatically increased level of creatine kinase, and lesions of the gastrointestinal tract (GIT). After a course of treatment with 28-day cycles, 71% of children demonstrated a decrease in the size of neurofibromas [64]. The effectiveness of selumetinib in combination therapy with LDN-193189 (inhibitor of BMP2 receptor of type 1) was proven in vitro on MPNST (NF1-/-) cell line, while the isolated use of LDN-193189 gave no proper antiproliferative effect. Based on the results obtained, it is expected that selumetinib can be used in the complex chemotherapy of MPNST [65]. In 2020, Baldo F. et al. examined 17 children with plexiform neurofibromas during one year of treatment with selumetinib and observed a decrease in size (more than 20% of volume) of tumors in 16 out of 17 patients with NF1 [66]. In 2020, Santo V.E. et al described the effectiveness of selumetinib in the management of plexiform neurofibromas in 18 out of 19 patients with NF1 (95%) during the first 60–90 days of treatment [67]. In 2020, Gross A.M. et al., in a phase 2 open-label clinical trial of selumetinib on a continuous schedule (28-day cycles) in children with NF1, described a persistent decrease in the size of inoperable neurofibromas in 70% of patients (35 of 44) [68]. Selumetinib has been shown to be effective in the management of brain tumors in cases of NF1: in 36% (9 of 25) of patients with grade 1 pilocytic astrocytoma and in 40% (10 of 25) of patients with low-grade glioma [69]. Treatment with selumetinib (12 cycles) in 24 NF1 patients with spinal neurofibromas demonstrated 75% efficacy [70].

Gene therapy may become a promising technique for NF1management. The insertion of a full-length normal *NF1* gene using recombinant adeno-associated virus (rAAV) containing an expression cassette to replace mutant alleles and to restore neurofibromin function is difficult due to the large size of cDNA (8500 bp). Therefore, the use of truncated variants of *NF1* gene that retain functional domains is more favourable [58]. A panel of AAV vectors was used in vitro on MPNST cell lines and human Schwann cell lines to restore the Ras-GTPase activity of neurofibromin. As a result, significant restoration of the ability to suppress RAS oncogenes using neurofibromin domain was determined [71]. Partial restoration of their normal tumor suppressive function was demonstrated on cell lines of neurofibromas, upon

transfection of isolated domains GRD, CSRD, LRD, CTD of the *NF1* gene into their genomes. These recombinant transgene sequences can be designed to encode truncated functional proteins that can be easily packaged into viral vectors [72].

Conclusion

Neurofibromatosis type 1 is the most common hereditary tumor syndrome. A number of authors have described atypical manifestations of NF1, including those with multiple lipomas, as well as those that do not meet NIH criteria. Since no genetic etiology was established for a number of familial lipomatoses, it was suggested that they may be atypical signs of NF1 and other hereditary tumor syndromes. It is evidenced by the data of the results of the papers by different authors, presented in this review. To confirm this assumption, a standardized panel should be developed to search for mutations in tumor suppressor genes that are involved in diseases characterized by the development of multiple lipomas and/or CALM. Modern medicine requires wide implementation of methods available for patients for molecular genetic confirmation of NF1 diagnosis into clinical practice. It will allow early identification of the disease and the use of effective treatment methods with mitogen-activated protein kinase inhibitors.

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И.Т. Муркамилов*[1,2], И.С. Сабиров[2], В.В. Фомин[3], Ж.А. Муркамилова[2], И.О. Кудайбергенова[1], Ф.А. Юсупов[4]

[1] — Кыргызская государственная медицинская академия имени И.К. Ахунбаева, Бишкек, Кыргызстан
[2] — ГОУ ВПО Кыргызско-Российский славянский университет, Бишкек, Кыргызстан
[3] — ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова (Сеченовский Университет), Москва, Россия
[4] — Ошский государственный университет, Ош, Кыргызстан

ХРОНИЧЕСКАЯ БОЛЕЗНЬ ПОЧЕК И ЗЛОКАЧЕСТВЕННЫЕ НОВООБРАЗОВАНИЯ: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ

I.T. Murkamilov*[1,2], I.S. Sabirov[2], V.V. Fomin[3], Zh.A. Murkamilova[2], I.O. Kudaibergenova[1], F.A. Yusupov[4]

[1] — I.K. Akhunbaev Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan
[2] — SEI HPE Kyrgyz Russian Slavic University, Bishkek, Kyrgyzstan
[3] — FSAEI HE First Moscow State Medical University named after I.M. Sechenov (Sechenov University), Moscow, Russia
[4] — Osh State University, Osh, Kyrgyzstan

Chronic Kidney Disease and Malignant Neoplasms: The Current State of the Problem

Резюме

Хроническая болезнь почек является фактором риска заболевания других органов. Больные с патологией почек имеют повышенный риск развития и смерти от сердечно-сосудистых заболеваний, кроме того, есть также свидетельства того, что риск рака и смертность от рака могут быть увеличены у людей с хронической болезнью почек. Хроническая болезнь почек и злокачественные новообразования взаимосвязаны в обоих направлениях: рак может вызывать прямое поражение почечной ткани или косвенное через побочные эффекты лечения онкологического процесса. В свою очередь хроническая болезнь почек, наоборот, может быть фактором риска развития злокачественных новообразований. Кроме того, оба патологических процесса могут иметь общие факторы риска. Хроническая болезнь почек может возникнуть в результате применения химиотерапевтических средств. Многие из существующих и недавно разработанных химиотерапевтических агентов против рака нефротоксичны и могут способствовать дисфункции почек, которая часто проявляется на терминальных стадиях рака. На сегодняшний день терапевтические вмешательства в борьбе с прогрессирующим ростом онкологических заболеваний может ускорить развитие хронической болезни почек. В статье приводятся данные о взаимовлиянии хронической болезни почек и развития злокачественных новообразований. Рассмотрены нефрологические аспекты клинической картины онкологических заболеваний. Обсуждаются механизмы негативного влияния на почечную ткань противоопухолевых препаратов — цисплатина, ифосфамида, метотрексата и циклофосфамида. Учитывая связь между заболеванием почек и развитием, а также и лечением рака, в обзорной статье подчеркивается важность междисциплинарного сотрудничества между онкологами и нефрологами для прогнозирования и предотвращения нефротоксичных эффектов проводимой противоопухолевой химиотерапии, а по мере внедрения новых методов лечения злокачественных новообразований требуется надлежащая диагностика и лечение возникающих в ходе терапии новых почечных токсических эффектов.

Ключевые слова: *хроническая болезнь почек, злокачественные новообразования, нефротоксичность, канцерогенное действие лекарств, цисплатин, ифосфамид, метотрексат, циклофосфамид*

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

Конфликт интересов

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

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Abstract

Chronic kidney disease is a risk factor for other organ disease. People with kidney disease have an increased risk of developing and dying from cardiovascular disease, and there is also evidence that the risk of cancer and cancer mortality may be increased in people with chronic kidney disease. Chronic kidney disease and malignant neoplasms are interconnected in both directions: cancer can cause damage to the kidney tissue directly or indirectly through the side effects of cancer treatment. In turn, chronic kidney disease, on the contrary, can be a risk factor for the development of malignant neoplasms. In addition, both pathological processes can share common risk factors. Chronic kidney disease can result from the use of chemotherapy drugs. Many of the existing and recently developed cancer chemotherapeutic agents are nephrotoxic and can contribute to renal dysfunction, which often manifests itself in terminal cancer. To date, therapeutic interventions to combat the progressive growth of cancer can accelerate the progression of chronic kidney disease. The article provides data on the interaction of chronic kidney disease and the development of malignant neoplasms. The nephrological aspects of the clinical picture of oncological diseases are considered. The mechanisms of the negative effect on the renal tissue of anticancer drugs — cisplatin, ifosfamide, methotrexate and cyclophosphamide — are discussed. Given the link between kidney disease and the development and treatment of cancer, the review article highlights the importance of interdisciplinary collaboration between oncologists and nephrologists to predict and prevent nephrotoxic effects of cancer chemotherapy, and as new treatments for malignant neoplasms are introduced, proper diagnosis and treatment of emerging malignancies is required. new renal toxic effects.

Key words: *chronic kidney disease, malignant neoplasms, nephrotoxicity, carcinogenic effect of drugs, cisplatin, ifosfamide, methotrexate and cyclophosphamide*

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AKI — acute kidney injury, CF — cyclophosphamide, CKD — chronic kidney disease, GFR — glomerular filtration rate, GLN — glomerulonephritis, HD — hemodialysis, MNs — malignant neoplasms, NS — nephrotic syndrome, PS — paraneoplastic syndrome, WHO — World Health Organization

Introduction

Risk factors of malignancies, as well as of other chronic non-communicable diseases, including chronic kidney disease (CKD), are largely similar. The incidence of malignant neoplasms (MNs) has undoubtedly increased progressively everywhere in recent years. The increasing incidence of malignant neoplasms in the general population is due to a higher life expectancy, urbanization, new carcinogenic factors, hereditary burden, improved diagnosis of cancer, etc. [1]. According to the World Health Organization (WHO), cancer is the second leading cause of death in the world [2]. In 2018, 9.6 million people died from neoplasms [2]. Cancer causes almost one in six deaths worldwide [2]. N.F. Bakalets et al. (2016) reported that more than 10 million new cases of neoplasms are recorded annually in the world, and this number is growing every year [3]. According to the Republican Medical Information Center in Kyrgyzstan, malignant neoplasms rank second among the causes of death. In 2018 alone, 4.1 thousand deaths from neoplasms were registered, which is 12.6% of the total number of deaths. Among those who died from oncological diseases, mortality among people of working age amounted to 1,800, or 43.3% of the total number of deaths from this cause, and among elderly groups — 2,300 deaths, or 54.7%. It should also be noted that MNs accounted for 10.1% of the causes of primary disability.

According to the literature, MNs increase the risk of kidney diseases, and the presence of MNs has a negative impact on the general prognosis [4]. At the same time, patients with CKD at the stage of renal failure have a higher risk of developing malignant neoplasms of different localizations [5]. Therefore, CKD is an independent predictor of the development of MNs. In addition, individuals with kidney tumors have a higher risk of

developing and progressing CKD associated with therapeutic and diagnostic measures for kidney cancer [4].

Colon and rectal cancer is the third most common cancer and the second leading cause of cancer-related deaths worldwide [6]. The high risk of developing colorectal cancer in patients with CKD was shown in a meta-analysis conducted by Komaki Y. et al. in 2018 [7]. Survival rates of patients with CKD and colon and rectal neoplasms were significantly lower [7].

A population-based cohort study revealed that the relative risk of developing cancer in men with glomerular filtration rate (GFR) of less than 55 mL/min is significantly higher, while the risk of developing cancer increases by 29% for every 10 mL of GFR decrease. The incidence of non-Hodgkin's lymphoma, Kaposi's sarcoma, and lip, colon, and thyroid cancer was significantly higher in patients with CKD [8]. It should be said that the risk of MNs is also high in individuals on long-term hemodialysis (HD) [9]. In this regard, some researchers recommend regular screening for MNs in patients on long-term HD for more than 3 years, which can increase their life expectancy [9]. Meanwhile, other researchers believe that, despite the increased risk of developing malignant neoplasms in patients receiving chronic HD, routine screening for all individuals is not recommended [9]. Regular screening should be individualized according to the patient's life expectancy and the possibility of kidney transplantation in the future [8,9,10]. It should be noted that the incidence and nature of MNs in individuals with CKD may vary in different geographical areas. A meta-analysis performed by Leeaphorn N. et al. (2014) demonstrated that the prevalence of MNs in patients with membranous glomerulonephritis (GLN) in most residents reaches up to 10% [11]. It is significant that this meta-analysis pooled the results of six studies, with a total of 785 patients; the average age of participants with membranous GLN and cancer was 67±7 years, and in 20±6.8% of cases, the diagnosis of cancer preceded the diagnosis of membranous GLN [11]. Lung and prostate cancer account for the vast majority of tumors associated with membranous GLN. Hematological malignancies should also be considered one of the potential types of cancer associated with membranous GLN [11].

According to Heaf J.G. et al. (2019), hypertensive nephropathy is associated with an increased risk of skin and kidney cancer [12]. The risk of developing MNs in cases of CKD is thought to be associated with proteinuria and GFR value. Later, a population-based study performed by Ahn S.Y. et al. (2020) demonstrated the relationship between proteinuria and an increased risk of developing neoplasms [13]. Various types of MNs were associated with GLN, or were identified during the diagnosis of GLN [14]. Ryu J. et al. (2019) analyzed the clinical and laboratory data of 1,155 patients with GLN after nephrobiopsy [15]. The age of participants was 49,7±17,3 years. Individuals with IgA nephropathy accounted for 37.9% of those examined, while patients with membranous GLN accounted for 13.5% [15]. The incidence of MNs was three times higher in patients aged 50+ with GLN compared with the general population [15]. Amyloidosis was the most common type of GLN associated with MNs (20.7%) [15]. Compared with other types of GLN, MNs were observed in patients with amyloidosis almost 28 times more often than in the general population [15].

The development of CKD in patients with malignant neoplasms may be due to the risk factors and the effect of treatment that potentiates oncogenesis. In 2014, I.B. Kolina and I.N. Bobkova published an article on the problems of kidney damage in MNs [5]. The authors identify the following types of nephropathies in cases of MNs depending on the mechanism of development [5]:

- Lesions caused by the mechanical impact of the tumor.
- Lesions caused by tumor management.
- Paraneoplastic nephropathies.
- Lesions caused by metabolic factors.

Long-term hormonal therapy is accompanied by changes in the metabolism of lipids, carbohydrates and purines, leading to an increased risk of development and progression of atherosclerosis [16]. Also, several oncological agents used in the management of malignant neoplasms can induce vascular damage, even if there are no other risk factors [16]. In particular, cisplatin, paclitaxel, L-asparaginase, methotrexate, 5-fluorouracil cause endothelial dysfunction and can lead to kidney diseases [16]. Damage to renal glomeruli in cases of MNs is rare and morphologically heterogeneous [17, 18]. Sudden deterioration of kidney function and tumor lysis syndrome were described in detail in the published work by I.B. Kolina and I.N. Bobkova [5].

Paraneoplastic Syndromes

Paraneoplastic syndrome (PS) refers to non-specific syndromes of malignant growth. According to present-day information, PS includes various pathological manifestations due to the indirect influence of the tumor process on metabolism, immunity, and functional activity of different organs [18]. The term "paraneoplastic syndrome" has been used in the medical vocabulary since 1948. In 2010, in the 3rd issue of the "Clinical Nephrology" journal, an editorial was published under the title "E.M. Tareyev and the doctrine of nephritis (for the 115th anniversary)" [19]. It describes a variety of clinical and morphological variants of kidney damage in connection with paraneoplastic and paratuberculous syndromes [19]. In the case of PS with the same malignant tumor (for example, nephrocarcinoma or lymphogranulomatosis), one patient may develop GLN (more often membranous GLN, although other morphological variants of GLN are possible), and another may develop

amyloidosis [19]. It is difficult to predict the variant of kidney damage since, in this situation, as in the case of "cold", drug-induced, and finally infectious factors, nephritis is a manifestation of individual hypersensitivity [19]. The emphasis made by E.M. Tareev in this argument is very important to understand his view on the theoretical concepts of the pathogenesis of nephritis and especially on approaches to the classification of kidney diseases [19].

In 1922, Galloway introduced the concept of paraneoplastic glomerulopathy [20]. However, the first original study that established the relationship between cancer and nephrotic syndrome (NS) was published in 1966 by Lee J.C. et al [21]. In the Russian-language literature, the interest in PS was primarily aroused by the works of E.M. Tareev and his scholarly tradition, which, for the first time, described nonspecific reactions in patients with malignant neoplasms of different localizations [22–24].

The published work by L.I. Anikonova et al. (2016), lists criteria for PS-related glomerulopathy: 1) chronological relationship between the diagnosis of glomerular syndrome and the tumor; 2) parallel evolution of the tumor and of the syndrome of achieved specific cytotoxic therapy; 3) existence of a pathogenetic relationship between glomerulopathy and the tumor [25]. If we consider certain types of neoplasms, then the relationship between NS and chronic lymphocytic leukemia was established as early as 1957 [30]. Researchers at I.I. Mechnikov North-West State Medical University (St. Petersburg) described a clinical case where a patient developed severe NS with acute kidney injury (AKI) six years after the diagnosis of chronic lymphocytic leukemia, and the results of nephrobiopsy revealed focal segmental glomerulosclerosis and acute tubular lesions [25]. According to the researchers, in up to 50% of cases in clinical practice, the development of paraneoplastic NS precedes tumor manifestations, often contributing to its detection; parallelism between tumor relapses and renal syndrome is not always observed [25].

Excessive production of growth factors, pro-inflammatory cytokines, and various antigens in cases of MNs is accompanied by kidney damage [5]. Tumor cells can produce cytokines and lymphokines that cause podocyte dysfunction, which is accompanied by impaired permeability of the glomerular filter. Glomerular injury can be caused by direct exposure to cryoglobulin-producing tumor cells followed by complement activation via an alternative pathway. There is formation of intracapillary thrombi, which consist of cryoglobulin precipitates. There is also massive infiltration of glomeruli by macrophages and monocytes, which contributes to kidney damage in PS [26]. In addition, the independent role of tumor tissue antigens in the development of certain morphological types of glomerulopathies is currently being actively studied [26]. Hyperproduction of antibodies under intensive tumor growth leads to the formation of immune complexes, which enter kidneys from the systemic circulation and accumulate in subepithelial space [26]. Renal manifestations of oncological disease progress and are clinically manifested by hematuria, proteinuria, hypo- and dysproteinemia, hyperfibrinogenemia [5, 22, 23]. In their work, Zafar-Mohtashami A. et al. (2020) described the development of paraneoplastic NS in a 65-year-old patient with carcinoma of unknown primary site [27]. According to the researchers, NS was completely resolved with chemotherapy. In another observation, the development of nephrotic level proteinuria was observed in a 55-year-old woman with ovarian cancer. As a result of surgical removal of tumor and glucocorticoid therapy, NS remission and preserved kidney function were observed [28].

The most common type of paraneoplastic nephropathy in malignant neoplasms is membranous GLN [24]. Paraneoplastic membranous GLN is often resistant to standard immunosuppressive regimens, although sometimes an initial decrease in proteinuria and other signs of NS can be observed [18]. Patients with MN may develop mesangiocapillary GLN and minimal change disease, although these types of kidney damage are more typical for lymphoproliferative diseases [23]. Mesangiocapillary GLN was described in patients with Wilms' tumor, malignant melanoma, and also as part of PS in lung cancer [23]. Minimal change disease has been described in cases of different carcinomas. Combinations of minimal change nephropathy with rectal cancer are known; in this context, hyperproduction of vascular endothelial growth factor was found [23]. Minimal change disease can develop in cases of pleural mesothelioma [23]. There are reports of completely resolved NS after surgical removal of tumor [28]. However, the small number of observations does not allow to make a conclusion about a causal relationship between MN and this type of kidney damage [24].

Liu X. et al. observed a 59-year-old man with lung adenocarcinoma and membranous GLN that was manifested by the swelling of lower limbs, hypoproteinemia, and proteinuria [29]. It is noteworthy that therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (erlotinib) led to the stable remission of paraneoplastic membranous GLN associated with lung adenocarcinoma [29]. The development of membranous GLN in cases of lung cancer is associated with a mutation of the gene that encodes EGFR (epidermal growth factor receptor). It should be noted that according to world statistics, lung cancer remains the most common type of cancer (1.6 million new cases annually). Approximately 70–80% of membranous GLN is due to primary kidney diseases; secondary forms develop due to autoimmune diseases, infections, drug exposure, or MNs [30]. The aspects of GLN associated with MNs are being actively studied [30]. Higashihara T. et al. (2020) report on a case of NS in a patient with squamous cell lung cancer and the effectiveness of chemoradiotherapy in relation to proteinuria

and tumor growth [31]. The patient had a morphological pattern of proliferative GLN with deposits of monoclonal immunoglobulin λ-chain. In the above study, the authors note that literature describes more than 130 patients with renal damage associated with lymphocytic leukemia who underwent nephrobiopsy due to NS or unclear renal dysfunction [31].

Other potential causes of renal dysfunction in patients with MNs are tumor lysis syndrome, chemotherapy toxicity, ureteral obstruction by enlarged lymph nodes [5]. Among chemotherapy agents, cisplatin (10–80%), ifosfamide (1.4–30%), methotrexate (1.8–12%) and carboplatin (0–25%) have the greatest nephrotoxic effect [32]. Cisplatin is one of the most widely used agents in the management of MNs (tumors of ovaries, testicles, head, neck) and is known to be one of the most nephrotoxic drugs. Cisplatin causes severe tubular damage, predominantly in proximal tubules, electrolyte imbalance, AKI, and thrombotic microangiopathy [33]. In connection with long-term treatment, arterial hypotension as a result of hyponatremia and decreased circulating blood volume are often observed. This may create a premorbid background for the development of AKI or the progression of CKD, especially in elderly patients. Nephrotoxicity is more dependent on the dose of cisplatin used. A single injection of the medication at a dose of less than 50 mg/m^2 rarely causes AKI [34]. The role of cisplatin in the development of CKD was established in a number of experimental studies where the molecular and cellular mechanisms of cisplatin nephrotoxicity were summarized [35]. Cisplatin-induced AKI is based on increased expression of biomarkers of tubular injury, increased oxidative stress, inflammation, apoptosis, and necrosis of tubular epithelium [35]. All patients treated with cisplatin have magnesium deficiency [34]. There are reports that the initial magnesium deficiency in the blood of MN patients increases the risks of AKI associated with cisplatin, and the correction of magnesium-deficient conditions, or the administration of magnesium to MN patients during their treatment with cisplatin significantly reduces its nephrotoxicity [36]. In literature, the role of oxidative stress is discussed, which is caused by mitochondrial dysfunction and intracellular accumulation of reactive oxygen intermediates, which is an important feature of cisplatin-induced AKI [37]. In proximal tubules, after receptor-mediated endocytosis, cisplatin is hydrolyzed into a positively charged molecule [38]. Also, Klotho protein is thought to play a protective role in the development of AKI in patients with cisplatin-induced malignant neoplasms [39]. According to researchers, approximately 30–60% of children treated with cisplatin develop severe tubular and/or glomerular damage [32]. In adults, high doses of cisplatin can cause significant cardio-, nephro- and cerebrotoxic effect. Neurological manifestations of decreased magnesium level in blood serum can include headaches, dizziness, fainting, feeling of shortness of breath, hyperacusis, increased fatigue, poor tolerance to bright light, seeing dark spots in one's vision, crawling sensation, impaired memory and concentration, hyperactivity, fear, depression, irritability, sleep disturbances. In some cases, cardiac manifestations of hypomagnesemia (severe cardiac arrhythmias, arterial hypotension) can induce kidney dysfunction [40].

Another medication with a negative effect on proximal tubules is ifosfamide, which has structure and action similar to cyclophosphamide (CF). Ifosfamide induces damage to proximal tubules by metabolites and leads to energy depletion of tubular cells. The above study noted that ifosfamide can damage the distal tubules, leading to nephrogenic diabetes [34]. Some researchers highlight the delayed nephrotoxic effect of ifosfamide in the form of decreased GFR as a result of glomerular damage, hypophosphatemia, hypokalemia, hypomagnesemia, hyperaminoaciduria, glucosuria, and hyperphosphaturia due to the tubular toxicity of this agent [40]. Young age and a cumulative dose of the drug of 45 g/m^2 are the main risk factors for the development of nephrotoxicity; the toxic cumulative dose of this drug is 60–72 g/m^2 [40]. In 2004, Rogowska E. and Woźniak W. described a case of Fanconi syndrome in a 13-year-old patient with skin cancer treated with high doses of ifosfamide [41]. One year later, another case was described when a 58-year-old woman with MN, after five cycles of chemotherapy with ifosfamide, developed tubular proteinuria, glycosuria, and microhematuria [42]. Three months after another cycle of treatment with ifosfamide (treatment cycle 6), the patient had general weakness and nocturia, and HD sessions were started due to azotemia [42]. Another observation described a case of Fanconi syndrome 17 months after the administration of ifosfamide for the management of Burkitt lymphoma in a two-year-old child [43]. It is worth noting that about 30% of children treated with ifosfamide have tubular damage [32]. In 18–28% of cases, AKI and CKD develop during the administration of ifosfamide [34]. The risk of ifosfamide nephrotoxicity increases significantly with age and in the presence of comorbid pathologies. Considering that the course of ifosfamide nephrotoxicity is often asymptomatic, careful laboratory monitoring is necessary, with a focus on renal tubular function.

In the mid-20th century, American pediatrician Farber S. (09/30/1903–03/30/1973) founded the Pediatric Cancer Research Foundation and investigated the effectiveness of various medications [44]. Farber's most famous achievement was the agent named "methotrexate", which was synthesized at his request by the brilliant chemist Yellapragada Subba Row (01/12/1895–08/08/1948). This medication is still one of the key anticancer chemotherapy drugs. Methotrexate is a cytotoxic drug from the group of antimetabolites, folic acid antagonists. Methotrexate has significant

Table 1. *Anticancer drugs associated with acute kidney injury [50]*

Medication	Mechanism of action	Renal histopathologic features	Clinical nephrotoxic effects
Cisplatin	Cross-linking and interference with DNA replication	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi syndrome, NDI, sodium and magnesium wasting
Ifosfamide	Nitrogen mustard alkylating agent; inhibition of DNA synthesis through DNA strand-breaking effects	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi syndrome, NDI
Pemetrexed	Antifolate agent; inhibition of dihydrofolate reductase, thymidylate synthase, and glycinamide ribonucleotide formyltransferase	Acute tubular injury and acute tubular necrosis	Acute kidney injury, proximal tubulopathy, Fanconi syndrome, NDI
Methotrexate	Antifolate agent; inhibition of dihydrofolate reductase	Crystalline nephropathy and acute tubular injury	Acute kidney injury
Pamidronate	Pyrophosphate analogue; associated with moderate FPPS inhibition	Focal segmental glomerulosclerosis, acute tubular injury	Nephrotic syndrome, acute kidney injury
Zoledronic acid	Pyrophosphate analogue; associated with potent FPPS inhibition	Acute tubular injury and acute tubular necrosis	Acute kidney injury

immunosuppressive effect, even at relatively low doses that have no noticeable hematological toxicity. As a result, methotrexate is widely used in comparison with other cytostatics. Methotrexate is more active against rapidly growing cells and is excreted by the kidneys [34]. High doses of methotrexate under acidic urine reaction conditions lead to the precipitation of metabolite crystals inside the tubules [34]. Approximately 47% of patients show signs of nephrotoxicity during the administration of high doses of this drug; they are accompanied by decreased GFR [45]. Adequate hydration and urine alkalinization are standard parts of the program when using high doses of methotrexate [34]. Methotrexate often causes electrolyte disturbances, particularly hypokalemic acidosis and hypocalciuria [34]. Also, methotrexate tends to accumulate in tissues, causing toxic liver damage and myelodepression. Previous studies demonstrated the independent role of high doses of methotrexate in the development of CKD in cases of MN in the pediatric population [46]. High doses of methotrexate lead to a persistent decrease in GFR and may cause proteinuria several years after the end of treatment [46]. Factors that increase the risk of nephrotoxicity are high doses of methotrexate, reduced GFR, elderly age, male gender, and polypharmacotherapy (antibiotics and proton pump inhibitors) [47].

Cyclophosphamide (CF) has a wide spectrum of antitumor activity. CF has significant immunosuppressive effect with predominant inhibition of Blymphocytes. Antitumor activity is achieved directly in cells of the malignant tumor, where CP is biotransformed under the action of phosphatases, forming an active metabolite with an alkylating effect. E.I. Dorokhina et al. (2016) report that CF has a direct damaging effect on the urinary system and can cause hemorrhagic cystitis [40]. The nephrological risk of CF is that this drug causes hyponatremia, which manifests within one hour after administration and disappears in two days. Hyponatremia is caused by impaired excretion of water by the kidneys. Hyponatremia is probably associated with the effect of CF on distal tubules. Hyponatremia usually develops in acute form and resolves after discontinuation of the medication. Trisenox (arsenic trioxide) is one of the main cytotoxic agents used in the management of cancer. Nephrotoxic effects are manifested in the form of tubulointerstitial nephritis and rhabdomyolysis [48]. Besides anticancer agents, nephrotoxic antibiotics, antiviral and antifungal drugs used to manage infectious complications can also induce changes in the kidneys [34, 40, 48, 49].

Basic variants of nephropathies caused by anticancer agents are presented in tables according to the KDIGO conference (2018) on onconephrology dedicated to the study of kidney damage in cases of malignant neoplasms of solid organs [50].

Therefore, it can be noted that there are different mechanisms for the realization of the nephrotoxicity of anticancer drugs, as well as various forms of its clinical and laboratory manifestations. Summing up, it should be emphasized that risk factors for the development of kidney damage in cases of MNs and during their management are the cumulative dose of the chemotherapy agent, the total dose of the agent accumulated over all received courses of chemotherapy, drug administration regimens, the combination of several nephrotoxic medications, hypovolemia, anemia, presence of comorbid pathologies, as well as concomitant diseases of the urinary tract and tumor infiltration.

Вклад авторов:

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Муркамилов И.Т. (ORCID ID: https://orcid.org/0000-0001-8513-9279): интерпретация и критический анализ результатов, формулировка выводов

Сабиров И.С. (ORCID ID: https://orcid.org/0000-0002-8387-5800): редактирование текста

Фомин В.В. (ORCID ID: https://orcid.org/0000-0002-2682-4417): разработка концепции и дизайна

Муркамилова Ж.А. (ORCID ID: https://orcid.org/0000-0002-7653-0433): сбор и анализ первичных клинических данных

Кудайбергенова И.О. (ORCID ID: https://orcid.org/0000-0003-3007-8127): разработка концепции и дизайна

Юсупов Ф.А. (ORCID ID: https://orcid.org/0000-0003-0632-6653): сбор и анализ первичных клинических данных

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

Murkamilov I.T. (ORCID ID: https://orcid.org/0000-0001-8513-9279): interpretation and critical analysis of the results, formulation of conclusions

Sabirov I.S. (ORCID ID: https://orcid.org/0000-0002-8387-5800): editing

Fomin V.V. (ORCID ID: https://orcid.org/0000-0002-2682-4417): concept and design development

Murkamilova Zh.A. (ORCID ID: https://orcid.org/0000-0002-7653-0433): collection and analysis of primary clinical data

Kudaibergenova I.O. (ORCID ID: https://orcid.org/0000-0003-3007-8127): concept and design development

Yusupov F.A. (ORCID ID: https://orcid.org/0000-0003-0632-6653): collection and analysis of primary clinical data

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А.Ю. Крапошина[1,2]*, Е.А. Собко[1,2], И.В. Демко[1,2], А.Б. Кацер[1], О.В. Казмерчук[1], Ю.И. Абрамов[1]

[1] федеральное государственное бюджетное образовательное учреждение высшего образования «Красноярский государственный медицинский университет имени профессора В.Ф. Войно-Ясенецкого» Министерства здравоохранения Российской Федерации, Красноярск, Россия
[2] Краевое государственное бюджетное учреждение здравоохранения «Краевая клиническая больница»

СОВРЕМЕННОЕ ПРЕДСТАВЛЕНИЕ О ТЯЖЕЛОЙ БРОНХИАЛЬНОЙ АСТМЕ

A.Yu. Kraposhina[1,2]*, E.A. Sobko[1,2], I.V. Demko[1,2], A.B. Katser[1], O.V. Kazmerchuk[1], Yu.I. Abramov[1]

[1] Prof. V.F. Voino-Yasenetsky Krasnoyarsk State Medical University, Krasnoyarsk, Russian Federation
[2] Regional Government-Owned Publicly Funded Healthcare Institution "Regional Clinical Hospital"

Modern Understanding of Severe Bronchial Asthma

Резюме

В обзоре приведены современные данные о тяжелой бронхиальной астме. Частые обострения астмы значимо снижают качество жизни пациентов, становятся причиной потери трудоспособности, инвалидизации и летального исхода. Гетерогенность тяжелой бронхиальной астмы укладывается в понятия фенотипа и эндотипа, идентификация которых в клинической практике имеет ограничения, но является необходимой для персонализированной терапии. Анализ литературы, отражающей опыт в ведении данных пациентов, необходим для формирования целостных представлений о тяжелой бронхиальной астме и разработки путей оптимизации терапии.

Ключевые слова: *фенотип, эндотип, тяжелая бронхиальная астма*

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Abstract

The review provides data on severe bronchial asthma. Frequent exacerbations of asthma significantly reduce the quality of life of patients, cause disability, disability and death. The heterogeneity of severe bronchial asthma fits into the concepts of phenotype and endotype, the identification of which in clinical practice has limitations, but is necessary for personalized therapy. Analysis of the literature reflecting experience in patient data management is needed to form holistic perceptions of severe bronchial asthma and develop ways to optimize therapy.

Key words: *phenotype, endotype, severe bronchial asthma*

*Контакты: Ангелина Юрьевна Крапошина, e-mail: angelina-maria@inbox.ru
*Contacts: Angelina Yurievna Kraposhina, e-mail: angelina-maria@inbox.ru
ORCID ID: https://orcid.org/0000-0001-6896-877X

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AV — artificial ventilation, BA — bronchial asthma, BMI — body mass index, COPD — chronic obstructive pulmonary disease, CT — computed tomography, FAO — fixed airflow obstruction, FEV_1 — forced expiratory volume in 1 second, FVC — forced vital capacity, GCs — glucocorticosteroids, GERD — gastroesophageal reflux disease, PFT — pulmonary function test, SBA — severe bronchial asthma.

Introduction

Despite considerable progress in medication treatment, uncontrolled bronchial asthma (BA) remains the main challenge in managing patients with this disease. Patients with severe bronchial asthma (SBA) make up a special group among patients with no disease control. GINA Steps 4 and 5 therapy is ineffective despite high compliance with treatment, correct inhalation technique and management of comorbidities. Therefore, a thorough analysis of the pathogenesis and clinical features of BA course is required. The analysis of literature sources reflecting the experience in managing these patients is essential to form a comprehensive idea of SBA and develop methods to improve treatment.

Epidemiology and socio-economic burden of SBA

Frequent BA exacerbations significantly reduce the quality of life of patients, resulting in labor capacity loss, disability and death [1–3]. Management of patients with BA in developed countries accounts for about 2% of public health costs [4]. In particular, 12% of patients admitted to the emergency room of large hospitals are the patients with BA exacerbation. The socio-economic burden of BA increases in proportion to the severity of this disease. It is known that more than half of the funds (according to some data, over 80%) allocated for BA management overall are spent on treating patients with severe BA [2]. The numerous studies devoted to the pharmacoeconomic search for SBA control methods also highlight the existing problem. However, the amount of financial contributions is not a guarantee of their effectiveness [4].

There is evidence that socio-economic consequences of SBA in Japan are lower than in European countries [5]. This is due to healthcare organization and the geographical features of the country that allow providing access to specialized medical care equally for the entire population of the country. In the United States, epidemiological studies are being conducted to analyze environmental and social factors that affect the prevalence of asthma, as well as its racial features [6]. The number of attacks in adults was found to depend on income: the patients with an income of 250% of the poverty datum line were more likely to report the onset of symptoms than the patients with an income of 450% of the poverty datum line.

According to the Federal State Statistics Service (Rosstat), more than 1 million people were diagnosed with bronchial asthma in the Russian Federation in 2014; the mortality rate was 1.3% [7]. About 6.9% of adults and 10.9% of children in our country suffer from this disease [2]. In 2014, a national register of patients with SBA was created. The analysis of information in this register allows optimizing the management of such patients. According to a clinical trial conducted in Russia, patients with SBA constituted 14–20% of all patients who initially sought medical attention [2].

Elderly patients are undoubtedly a special group among patients with SBA. The severity of disease in this group of patients is associated with a large number of comorbidities and a long history of asthma. In one study, Joe G. Zein et al. (2015) suggested that the severity of asthma in elderly patients is associated primarily with age-related changes in the lungs [8]. The following was discovered: the dependence between the duration and severity of asthma was found in young patients, however, it was not identified in elderly patients; the risk of SBA increases by 7% every year between the age of 18 and 45; however, after the age of 45, no such correlation was observed. Gender-related differences were described: after the age of 45, the disease severity in men depends on BA duration, whereas such correlation is not characteristic for women of this age group. The authors attributed the differences to the fact that oxidative stress reactions in young individuals are more intense, accelerating age-related changes in the lungs, and the functional activity of inflammatory cells in elderly patients is significantly reduced. The authors emphasize that age-related characteristics of this disease should be analyzed due to the growing elderly population.

Uncontrolled and true severe bronchial asthma

The uncontrolled course of this disease has remained remains the main challenge in the management of patients with bronchial asthma (BA) for a long time. According to GINA-2020, uncontrolled asthma has one or both of the following signs [1]:

1) Poor control of symptoms.
2) Frequent exacerbations (≥ 2 per year) that require systemic glucocorticosteroids (SGCs), or one exacerbation that requires hospitalization.

Patients with uncontrolled asthma include both patients with difficult-to-treat asthma and patients with true severe asthma. It is critical to distinguish between these terms since the management of patients will be different depending on the particular group to which they belong. In the case of patients with difficult-to-treat BA, the disease course remains uncontrolled despite the treatment according to GINA Steps 4 and 5. The diagnosis of severe bronchial asthma (SBA) is a subgroup of difficult-to-treat BA and can be made in case of uncontrolled disease course despite appropriate therapy, high degree of compliance, correct inhalation technique, and the management of comorbidities.

The prevalence of SBA is 3–10% [1], while disease control is generally not achieved in about 50% of BA patients [2, 9]. In one study conducted in the Netherlands, the prevalence of difficult-to-control asthma that required treatment according to Steps 4 and 5 was 17.4%. However, only 20.5% of patients in this group complied with the correct inhalation rules and demonstrated good compliance. Therefore, they were classified as an SBA group that included only 3.6% of the entire patient population [10]. In other words, in most cases of uncontrolled asthma, modifiable factors can be found that can help improve the course of the disease.

It is confirmed by a trial conducted in Denmark, where only 12% of patients with difficult-to-control disease met SBA criteria [11]. The authors of this trial also emphasized that a clear distinction between SBA and difficult-to-control BA can be a major challenge in real clinical practice. The group of patients who could not be certainly referred to a particular category constituted 32% of patients with uncontrolled BA. This group included patients who performed inhalation procedures correctly and had good compliance with treatment. At the same time, the impact of trigger factors persisted, and no control of comorbidities was achieved. In addition, this "uncertain" group also included patients diagnosed with BA only based on clinical data with no objective evidence of airflow variability. The importance of multidisciplinary management of patients with difficult-to-control asthma is emphasized since the lack of control of comorbidities irreversibly worsens BA course. The authors raise the question of the need for consensus on the duration of managing comorbidities before starting biopharmaceuticals. SBA and difficult-to-treat BA should be distinguished primarily to justify targeted therapy [11].

The study of A-N. Van Der Meer et al. (2016) demonstrated that among the patients with severe BA admitted to a specialized center for BA management, only 17% of patients needed targeted therapy [12]. For 83% of patients, after a multidisciplinary and multivariate assessment, an individual management plan was drawn up and submitted to the attending pulmonologist. In one Belgian study [13], only 24% of patients treated with omalizumab met all SBA criteria, according to national guidelines. Those were the patients who regularly received basic treatment and had two severe exacerbations during such treatment over the previous year. It is noteworthy that omalizumab therapy was more effective in patients who met all SBA criteria. For example, the number of patients who needed GCs decreased by 22% in the group of SBA patients compared with 8% in the group of patients with difficult-to-treat BA. Similar results were obtained for the number of hospitalizations and admissions emergency care departments [13].

It should be noted that SBA is a retrospective diagnosis [1]. According to the ERS/ATS (The European Respiratory Society / American Thoracic Society) joint recommendations, a specialist should observe the patient for at least three months in order to adjust modifiable factors and verify the diagnosis definitively [14]. It is also important to take into consideration that the severity of disease can change; therefore, disease control in patients with BA should be assessed [1].

SBA is advisably diagnosed sequentially by answering the following questions [1, 15, 16]:

1. Is the diagnosis correct?
2. What is the severity of the disease?
3. Is the treatment optimal?

Then a multivariate assessment of the clinical case is required, which includes the identification and management of comorbidities, taking into consideration social conditions and environmental factors, determining asthma phenotype, and assessing the individual features of the patient [16]. All this results in an individual plan for the management of a BA patient.

For each patient not responding to high-intensity therapy, other diseases should be ruled out and the diagnosis of BA should be confirmed. According to various data, the frequency of an alternative diagnosis in SBA cases ranges from 12 to 50% [17]. Diseases with symptoms similar to those of asthma include chronic obstructive pulmonary disease (COPD), tracheobronchomalacia, central type lung cancer, obstructive sleep apnea, bronchiectasis, allergic bronchopulmonary aspergillosis, tuberculosis, cystic fibrosis, alpha-1 antitrypsin deficiency, vocal cord dysfunction, obliterative bronchiolitis, congestive heart failure, eosinophilic lung diseases [18]. In particular, 70% of BA patients reportedly have vocal cord dysfunction. Allergic bronchopulmonary aspergillosis is found in 2–32% of patients with asthma. Even

though most of these patients respond well to treatment with GCs, antifungal agents should be used in some cases of steroid resistance.

Disease history, age at BA onset, typical symptoms, their frequency, the severity of exacerbations, and association with comorbidities are subject to analysis. It is noteworthy that the risk factors for exacerbations differ depending on disease severity. In the 2018 study, Kang H-R. et al. demonstrated that, in contrast to moderate asthma, age and comorbidities (except for allergic rhinitis) in SBA did not affect the frequency of exacerbations [19]. Regardless of disease severity, the administration of GCs was a risk factor for exacerbations, and the frequency of hospitalizations in the previous year was more important for patients with SBA. This study also demonstrated the increasing role of compliance with medication treatment depending on disease severity.

Special questionnaires can help assess the patient's condition. However, according to an Australian study, their use in actual clinical practice is limited: for example, only 31% of physicians used a questionnaire to assess BA control [20]. The subjective evaluation of control by both the physician and the patient generally does not match the results of the asthma control test (ACT) in about a third of cases [21]. Notably, this value is higher among patients receiving treatment Steps 4 and 5 therapy: 41% of patients who received Step 4 therapy and 48% of patients who received Step 5 therapy considered their asthma to be controlled, despite the fact that ACT score was less than 20, which corresponded to uncontrolled asthma. The same trend is observed among health care professionals. Physicians tend to underestimate the severity of the condition of patients with severe and difficult-to-treat BA.

Questionnaires with sensitivity of 80–90% seem to be the most cost-effective method to evaluate comorbidities [15]. Therefore, it is possible to make an individual plan of patient's assessment, and recommend consultations on an interdisciplinary basis, to avoid excessive health care costs [15].

The variability of airflow obstruction is an integral part of the diagnosis, although it cannot always be proven in cases of SBA. Maximum doses of albuterol (4–8 inhalations) are considered justified in order to detect a 12% increase in forced expiratory volume in 1 second (FEV_1) [15].

When confirming the diagnosis of SBA, the optimality of the treatment should be evaluated. In several cases of SBA, additional therapy (tiotropium bromide, macrolides, antifungal therapy) is prescribed, right up to the use of expensive biological agents [20]. At this stage it is critical to evaluate inhalation technique and the degree of compliance to avoid unnecessary ramping up of treatment and lower the risk of adverse events.

Patients with SBA require a multidisciplinary approach, as well as comprehensive and systematic assessment. The task of an interdisciplinary team is to identify patients with a high risk of hospitalization, adjust risk factors, and provide long-term care. In the 2016 study, Hannah Burke et al. demonstrated that such an approach reduced the number and duration of hospitalizations in patients with frequent BA exacerbations [22]. Improved quality of life and disease control were also reported [16]. A multidisciplinary approach requires specific knowledge and skills. Phenotyping and prescription of targeted therapy in BA were implemented in practice relatively recently; therefore, special attention should be paid to the training of medical personnel [20].

Non-drug factors in the management of patients with SBA

Properly selected therapy does not ensure optimal disease control. BA management is a dynamic and complex process, where the active participation of both the physician and the patient is important [16, 23]. Medication treatment is the key in the management of BA patients. However, it is difficult to achieve success with no proper attention to educating the patient, developing the right ideas about the disease and the goals of treatment, as well as correcting other non-drug factors such as continued exposure to the trigger, untreated comorbidities, obesity and smoking [1, 9].

The importance of non-drug factors was demonstrated in the study conducted by Hedenrud T. et al. (2019). It revealed that BA patients face challenges throughout all stages of treatment [23]. In this study, patients were interviewed using a special questionnaire. Basic problems included the inaccessibility of medical care (difficulties in making an appointment with a physician, lack of required medicines in pharmacies), as well as the lack of proper awareness of patients about the signs of their disease and the goals of treatment. The forgetfulness of patients and difficulties in inhaling drug products also play a certain role. Future studies are expected to include quantitative evaluation to define the prevalence of certain factors in the population of BA patients and identify the relationship between these problems and the socioeconomic status of patients [23].

The most common problems hindering disease control are incorrect inhalation technique (80%) and poor compliance (50%). About 50% of patients make mistakes when using a dry-powder inhaler; this figure reaches 80% in metered-dose inhalers [24]. Proper inhalation technique minimizes side effects that may be caused by poor compliance [25]. For example, the study performed by A.S. Melani et al. (2013), which included more than 1600 patients, showed that at least one critical error in inhalation technique, regardless of the type of inhaler, was associated with increased emergency department visits, number of hospitalizations, and the prescription of SGCs [26]. There is a direct relationship between inhalation technique and treatment success and, therefore, the

patient's satisfaction and their sense of a positive effect of the treatment, which improves therapy compliance [26].

In a study conducted by Lia Jahedi et al. (2017), patients with correct inhalation technique had better awareness of their disease and motivation for treatment, which underlines the importance of awareness-raising when managing BA patients [27]. Unfortunately, only 28% of physicians regularly assess inhalation technique when seeing patients, although according to the literature, a physician should give instructions to the patient at least three times and clearly demonstrate all stages of inhalation [24]. It is regular assessment and adjustment of skills that can exactly improve the control of disease symptoms and the quality of life of patients [26].

SBA clinical profile and phenotypes

The group of patients with SBA is heterogeneous. While standard therapy is effective in most patients with mild to moderate asthma, the management of a patient with severe asthma requires a case-by-case approach [28]. Such patients require targeted therapy, taking into consideration the disease phenotype. Phenotype means visible features of an organism attirbutable to the interaction of its genetic component and environmental factors [29]. The Clinical Guidelines "Bronchial Asthma" of the Ministry of Health of the Russian Federation identify five SBA phenotypes [30]:

– allergic BA,
– BA with fixed airflow obstruction (FAO),
– non-allergic BA,
– late-onset BA,
– BA with obesity.

Each phenotype has its own specific clinical, functional and laboratory features. However, according to the study performed by Sergeeva G.R. et al. (2015), in 83% of cases one patient has the signs of two or more phenotypes [31]. In addition, a phenotype can change over time and transform into another one.

Allergic SBA is the most common and easily recognizable SBA phenotype. The prevalence of severe allergic asthma is about 40–80% [6, 31, 32]. Disease onset occurs in early childhood, with hereditary burden and allergic comorbidities in most cases. The most common comorbidity is allergic rhinitis. The main differences from non-allergic asthma are the following: positive skin reactions and dependence of symptoms on contact with an allergen. Such patients are often characterized by polysensitization. Monosensitization is found only in 16% of cases. The most common allergen is house dust mite; sensitization to it is found in 35–86% of patients [32]. This phenotype is characterized by eosinophilic inflammation; patients respond well to treatment with inhaled glucocorticosteroids (IGCs). However, the long course of the disease, polysensitization, constant contact with an allergen, and high IgE levels can contribute to the development of fixed airflow obstruction, which leads to significantly decreased results of pulmonary function test (PFR) [32].

Non-allergic SBA is more common in adults and is not associated with allergies. The profile of airway inflammation in patients with this phenotype may be eosinophilic, neutrophilic, mixed, or low granulocytic. Patients with non-allergic asthma may not respond to treatment with IGCs depending on the type of inflammation. Non-allergic asthma is more likely to have a severe course than allergic asthma, which deteriorates the quality of life [33]. Pathology of the upper respiratory tract and the skin is less common in the group of patients with non-allergic BA. However, the prevalence of these diseases is higher compared to the control group. Therefore, patients with non-allergic BA also have a systemic component of the disease that requires further analysis. FeNO (nitric oxide fraction) level in exhaled air increases in proportion to the prevalence of rhinitis and dermatitis in the group of these patients [33].

Late-onset SBA. Late onset of SBA is considered to be the onset of respiratory symptoms in patients over the age of 40 years with no previous history of asthma. However, the age range is not exactly defined. This phenotype is more common among women and is associated with several comorbidities, changes in psychological status (depression, anxiety, dementia), development of eosinophilic-neutrophilic inflammation with a predominance of the latter component. It should be mentioned that late-onset BA is heterogeneous in regard to causative factors [34]. Results of the comparative study performed by Daniel J. Tan et al. (2016) revealed no significant differences in the severity of asthma between patients with early and late onset despite the different duration of the disease. At the age of 44, no prevalence of these phenotypes was also distinguished [35]. The differences included etiological factors and the effect on pulmonary function. The duration of the disease plays the key role in the decrease of PFT results, whereas for patients with a late onset, such factors are smoking and age-related changes in lungs [34, 35].

SBA with fixed airflow obstruction (FAO). Fixed bronchial obstruction is characterized by FEV_1/FVC ratio of less than 0.7 after adequate bronchodilation (salbutamol 400 μg), with the diagnosis of COPD absent or ruled out for this patient. SBA criteria are met by 71.7% of patients with FAO [36]. FAO is the result of bronchial wall remodeling due to persistent inflammation, long disease history, frequent exacerbations, and steroid resistance [37]. FAO risk factors also include a history of atopic dermatitis, artificial ventilation (AV), contact with mold, and elderly age [37, 38]. In contrast to the patients with no obstruction, the FAO patients are characterized by a significant decrease in spirometric parameters, increased FeNO level, high eosinophil and neutrophil count in induced sputum, and significantly higher rate of eosinophilia (≥ 3%) [39].

SBA in obese patients. It is known that obesity not only increases the risk of BA, but also worsens disease course and may even contribute to steroid resistance [40]. Obesity leads to the development of comorbidities that aggravate the course of asthma (for example, GERD, type 2 diabetes mellitus, arterial hypertension), maintains chronic systemic inflammation, and also negatively affects lung volume [32]. A 15% reduction in body weight significantly improves asthma control, lung function and quality of life [41].

In a recent study, SBA phenotypes were divided based on the CT of the lungs [42]. The patients were divided into three groups according to the changes found. Group 1 was characterized by remodeling in large airways (lobar, segmental, subsegmental bronchi); basic pathological patterns included the thickening of the bronchial wall, mucus plugs, and bronchiectasis. Group 2 was characterized by changes in small airways; basic pathological patterns included emphysema, air trapping, and changes in subsegmental bronchi. Group 3 included patients with no apparent changes. It is noteworthy that CT demonstrated at least one pattern of pathological changes in 80% of patients with SBA. A relationship was found between the thickening of the bronchial wall and the count of eosinophils in peripheral blood, as well as between the presence of mucous plugs and the eosinophil level in sputum; these facts allow us to interpret these changes in proximal airways as an indicator of eosinophilic inflammation in SBA [42].

Group 1 was the largest and included 44% of all patients. Absolute and relative levels of peripheral eosinophils in this group were significantly higher than in groups 2 and 3. Group 2 was dominated by male patients, often with a history of smoking. Bronchial obstruction was most pronounced in this group: patients required more treatment compared to other groups. In general, group 2 can be described as an asthma: COPD combination, recently classified as a separate subtype of SBA. Patients of group 3 required oral GCs as maintenance therapy significantly less often than the other two groups.

Regarding clinical signs, such as the age of BA onset, body mass index (BMI), the presence of atopy, total IgE level, the number of exacerbations in the previous year, there were no correlations with CT changes, and no differences between groups were found.

Therefore, remodeling in airways may be based on various pathogenetic processes, and one specific SBA phenotype may be underlain by different endotypes [32, 43].

SBA endotypes

A disease endotype characterizes the pathogenetic features of inflammation in airways and is determined based on genetic and molecular parameters [43, 44]. In contrast to the disease phenotype, endotypes are more determinated subgroups of patients [44], although they can also change over time [45]. It seems reasonable to divide the variety of SBA immunopathological processes into two large groups: Th2-type inflammation and non-Th2-type inflammation.

Th2-type inflammation is found in half of patients with BA and in 37% of patients with SBA [44]. The trigger mechanism for Th2-type inflammation is the interaction of the respiratory tract epithelium with environmental factors and the subsequent synthesis of signal substances – alarmins – by epithelial cells. Alarmins include interleukin-33 (IL-33), interleukin-25 (IL-25), and TsLP (thymic stromal lymphopoietin) (Fig. 1). It was demonstrated that most BA patients have a deficiency of E-cadherin and claudin-18, which are responsible for the strength of bonds between epithelial cells. This results in easier penetration of allergens and microbial antigens through epithelial barrier [44]. It should be noted that the decreased expression of E-cadherin is associated with epithelial-mesenchymal transition, which underlies the remodeling of the bronchial wall [40]. The development of Th2-type immune response requires the synthesis of such key cytokines as interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13). Their main sources in airways are Th2 lymphocytes and type 2 innate lymphoid cells (ILC2). ILC2 are innate immune cells, and their activation does not require interaction with an antigen and its recognition. Therefore, ILC2 activation underlies non-allergic eosinophilic inflammation [43]. IL-33 and IL-25 play a leading role in ILC2 activation, while TsLP stimulates mainly antigen-presenting cells, specifically dendritic cells that interact with T and B cells and trigger allergic inflammation. It is notable that ILC2 synthesize IL-5 and IL-13 5–10 times more than Th2 lymphocytes, as well as a small amount of IL-4 [48]. IL-4, IL-5, and IL-13 have synergistic effects that cause the attraction of effector cells to the inflammation site, as well as structural and functional changes in the bronchial wall [43, 44].

IL-4 is crucial for the differentiation of naive Th lymphocytes into Th2 lymphocytes. Together with IL-13, it mediates subepithelial fibrosis, thereby participating in the processes of airway remodeling [43]. IL-13 is described as a key effector cytokine that plays an important role in many aspects of BA pathogenesis, including B cell switch to IgE production, mucus hypersecretion, goblet cell hyperplasia, and bronchial hyperreactivity. IL-5 is the main cytokine responsible for the recruitment and survival of eosinophils and, to a lesser extent, of mast cells and basophils. Eosinophils are the main effector cells of Th2-type inflammation; their degranulation and release of substances such as eosinophilic cationic protein and eosinophil-derived neurotoxin are associated with the development of fixed airflow obstruction that determines the severe course of the disease [46].

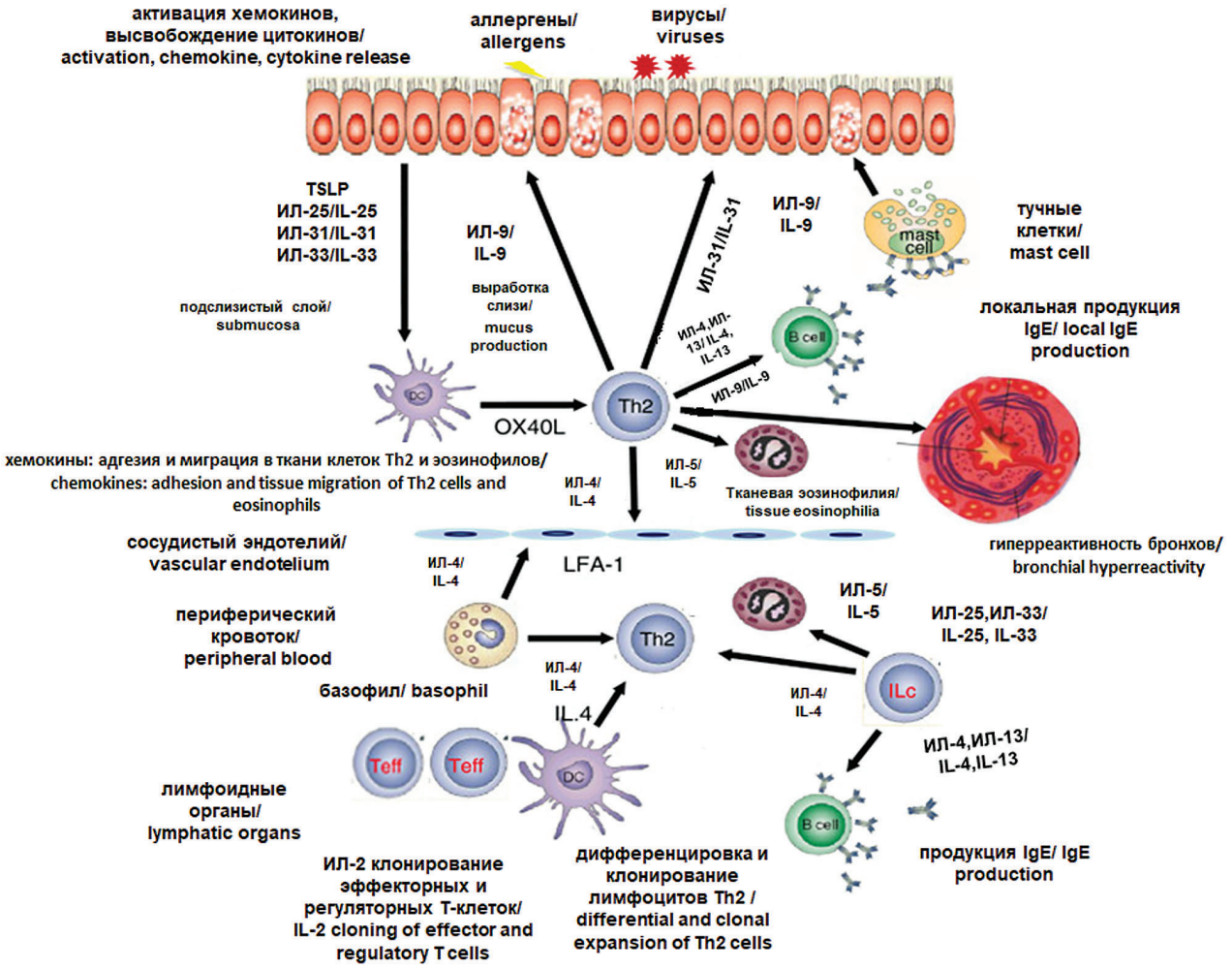

Figure 1. *Mechanisms of allergic inflammation in asthma [47].*
Note: B cell — B-lymphocyte, DC (dendritic cell) — dendritic cell, IgE — immunoglobulin E, ILc (innate lymphoid cell) — innate immunity lymphocyte, LFA-1 (lymphocyte function-associated antigen 1) — integrin LFA-1, OX40L — receptor ligand OX40 (CD252), Teff — T-effector, Treg — T-regulator, TSLP (thymic stromal lymphopoietin) — thymic stromal lymphopoietin

Non-Th2-type inflammation is characterized by the absence of signs of Th2-type inflammation in sputum and peripheral blood and is associated with molecules such as interleukin-1ß (IL-1ß), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-17A/F (IL-17A/F), interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) [45]. Various authors estimate the prevalence of non-Th2-type inflammation in all BA patients to be 40–70% [45]. In the structure of non-T2 asthma, neutrophilic and low granulocytic inflammation are distinguished depending on the detection of an inflammatory cell pool in induced sputum samples. Activation of Toll-like receptors leads to the differentiation of naive Th lymphocytes into Th1 and Th17 lymphocytes that produce IL-8, IL-1ß, IFN-γ, and TNF-α, facilitating the recruitment of effector cells, mainly neutrophils [45].

The role of neutrophils in SBA is diverse. However, their participation in oxidative stress reactions and ability to synthesize transforming growth factor beta (TGF-ß), a powerful inducer of epithelial-mesenchymal transition [40], are of special significance. IL-17, IL-6, and IL-8 are described as key non-Th2-type inflammatory cytokines. It is noteworthy that cytokines of the IL-17 family can promote both the migration of neutrophils into the respiratory tract and the induction of Th2-type immune response cytokines, thereby affecting the development of eosinophilia [47]. The role of cytokines of the IL-17 family in the pathogenesis of BA is multifaceted and ambiguous. However, there is evidence in the literature that an increased level of IL-17 is an independent risk factor for SAD, and the presence of single nucleotide polymorphisms in the IL-17 gene is associated with the development of allergic diseases [47].

Although low granulocytic inflammation is characterized by the absence of sputum eosinophilia and neutrophilia, an increased amount of inflammatory cells in patients with low granulocytic inflammation was demonstrated compared to relatively healthy individuals [44]. Bronchial hyperreactivity in patients with a low granulocytic type of inflammation is thought to be associated not only with exposure to inflammatory cytokines: it was demonstrated in animal models that treatment with nerve growth factor (NGF) induced bronchial hyperreactivity to the same extent as allergen sensitization [44].

Low granulocytic inflammation is thought to be most common in cases of well-controlled asthma and is associated with better pulmonary function parameters. However, about 20% of patients with low granulocytic inflammation have a severe course of the disease, which is refractory to ongoing therapy [48]. Signs of airway remodeling in this group of patients suggest the existence of mechanisms for the development of fixed airflow obstruction regardless of the severity of inflammation, which was also demonstrated in animal models. Smooth muscle cells play a leading role in airway remodeling in the cases of low granulocytic inflammation [48].

It should be noted that endotypes are closely related to disease phenotypes. Approximately 25% of patients with SBA have severe eosinophilic inflammation and late onset of the disease [49]. Allergic and aspirin-induced SBA are also phenotypes with Th2 endotype [44]. A recent cluster analysis revealed Th2 endotype in cases of late-onset eosinophilic asthma associated with chronic rhinosinusitis with nasal polyps, which was characterized by high expression of specific IgE to Staphylococcus aureus enterotoxin and high IL-5 levels [44]. This study demonstrated the possible presence of the association of Th2/Th17 cells in bronchoalveolar lavage, which was characterized by a more severe course of the disease compared to the separate presence of these lymphocytes [44]. Patients with non-Th2 endotype are also characterized by late onset of the disease [45]. According to the literature, the neutrophil level in sputum is higher in elderly patients with BA than in young and middle-aged patients [45]. Poor response to inhaled and systemic GCs is a typical sign of patients with non-Th2-type inflammation. It is known that IGCs induce apoptosis of eosinophils. However, they have the opposite effect on neutrophils [40]. The main trigger factors in the group of patients with non-Th2-type inflammation include intense physical activity, weather conditions (in particular, exposure to cold), exposure to smoking, pollutants, and infectious agents. Colonization with microorganisms such as *Moraxella*, *Streptococcus*, and *Haemophilus* was associated with higher neutrophil and IL-8 levels in BA patients. Association with obesity was established for both Th2- and non-Th2 endotypes [40, 44].

Therefore, it becomes obvious that the patients with SBA need personalized treatment with consideration to the specific pathogenetic symptoms of the disease. To distinguish between Th2- and non-Th2-type inflammation, biomarkers that play a key role in a particular clinical case should be identified. A perfect biomarker is a parameter with high sensitivity and specificity that characterizes the symptoms of the disease, allows choosing targeted therapy, monitoring its effectiveness, predicting the response to treatment. At the same time, it should be non-invasive and available in clinical practice [50]. Established markers of Th2-type inflammation include blood and sputum eosinophilia, increased total IgE, and increased FeNO in exhaled air. However, all of them have certain limitations [49].

It is difficult to discuss the predominant role of a particular type of inflammation in SBA pathogenesis [43, 44]. It is noteworthy that the relationship between the severity of inflammation and the number of exacerbations, as well as the impact on the prognosis of BA, were demonstrated for both eosinophilic and neutrophilic inflammation [40, 44, 45, 49]. Both sputum eosinophilia and neutrophilia are associated with decreased FEV_1 before the bronchodilation test. However, only sputum neutrophilia was associated with post-bronchodilation FEV_1 [40]. This supports the impaired immune response as the basis for the severe course of BA. Molecular biology methods can help conduct a thorough analysis of existing impairments, which is required for the development of targeted therapy and improved management of patients with SBA.

Conclusion

SBA is definitely a serious medical and socio-economic issue. Non-drug factors and a multidisciplinary approach are of particular importance in the management of such patients. The heterogeneity of SBA includes the concepts of phenotype and endotype. Their determination in clinical practice is limited but is necessary for personalized treatment. A severe course of this disease is due to impaired regulatory mechanisms of innate and acquired immunity. Interpretation of mechanisms that cause airway remodeling with no severe inflammation presents a challenge. Further molecular biology studies are required in order to explain the pathogenetic mechanisms underlying the severe course of this disease, as well as the search for new biomarkers that will allow diagnosing pathological processes in clinical practice.

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Крапошина А.Ю. (ORCID ID: https://orcid.org/0000-0001-6896-877X): написание текста, подготовка публикации

Собко Е.А. (ORCID ID: https://orcid.org/0000-0002-9377-5213): редактирование текста

Демко И.В. (ORCID ID: https://orcid.org/0000-0001-8982-5292): окончательное утверждение рукописи

Кацер А.Б. (ORCID ID: https://orcid.org/0000-0002-6649-8900): сбор материала

Казмерчук О.В. (ORCID ID: https://orcid.org/0000-0001-7999-4113): написание текста

Абрамов Ю.И. (ORCID ID: https://orcid.org/0000-0002-9937-1025): анализ полученных 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.

Kraposhina A.Yu. (ORCID ID: https://orcid.org/0000-0001-6896-877X): text writing, preparation of a publication

Sobko E.A. (ORCID ID: https://orcid.org/0000-0002-9377-5213): text editing
Demko I.V. (ORCID ID: https://orcid.org/0000-0001-8982-5292): final approval of the manuscript
Katser A.B. (ORCID ID: https://orcid.org/0000-0002-6649-8900): collection of material
Kazmerchuk O.V. (ORCID ID: https://orcid.org/0000-0001-7999-4113): text writing
Abramov Yu.I. (ORCID ID: https://orcid.org/0000-0002-9937-1025): analysis of the received data

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А.А. Жилина*, Н.В. Ларева, Е.В. Лузина, С.М. Цвингер, Е.И. Морозова

ФГБОУ ВО «Читинская государственная медицинская академия» МЗ РФ, кафедра терапии факультета повышения квалификации и профессиональной переподготовки, Чита, Россия

КЛИНИЧЕСКАЯ ЗНАЧИМОСТЬ ПОЛИМОРФИЗМА ГЕНА ЦИТОХРОМА P4502C19(681G/A) У ЖИТЕЛЕЙ ЗАБАЙКАЛЬСКОГО КРАЯ ПРИ ЛЕЧЕНИИ КИСЛОТО-ЗАВИСИМЫХ ЗАБОЛЕВАНИЙ

A.A. Zhilina*, N.V. Lareva, E.V. Luzina, S.M. Tsvinger, E.I. Morozova

Chita State Medical Academy, Chita, Russia

Clinical Significance of Cytochrome P4502C19 (681G/A) Gene Polymorphism in Residents of the Trans-Baikal Territory in Treatment of Acid-Dependent Diseases

Резюме

Цель исследования. Изучить полиморфизм CYP2C19(681A/G) среди населения Забайкальского края в сравнении с данными в других регионах мира и России. **Материалы и методы.** Проведено генетическое типирование CYP2C19(G681A) у 132 человек (81 женщина и 53 мужчины) проживающих на территории Забайкальского края, медиана возраста составила 47 (18; 72) лет. Отклонения распределений генотипов изученного полиморфного локуса от распределения Харди-Вайнберга оценено с использованием критерия хи-квадрат. Сравнительный анализ полученных данных проведен с помощью критерия Фишера. Различия считали значимыми при p <0,05. **Результаты.** Распространенность CYP2C19(681G/G) составила 105 человек (79,6%), CYP2C19(681G/A) — 25 лиц (18,9%) и CYP2C19(681A/A) — 2 участника (1,5%). Аллель А гена CYP2C19 в 681 положении встречался в 14,2%. Аллель А реже встречается в популяции Забайкальского края, по сравнению с азиатами (Китай p <0,001; Япония p=0,015) и не отличался в распространенности от коренных американцев, латиноамериканцев, афроамериканцев, жителей Московской, Воронежской, Иркутской областей и Саха-Якутии. CYP2C19(681A/A) чаще встречался в азиатской популяции, чем среди забайкальцев, p=0,003. Распространенность генотипа CYP2C19(681A/A) не отличалась между популяцией Забайкальского края афроамериканцами, европеоидами, населением Московской и Воронежской области. **Заключение.** Распространенность аллеля А полиморфного локуса 681G/A CYP2C19 в популяции Забайкальского края составила 14,2% и оказалась сопоставимой с европеоидами, но встречалась реже, чем у китайцев и в японской популяции. Распространенность генотипа CYP2C19(681A/A) составила 1,5%, что соответствовало мировым данным среди европеоидных популяций и встречалась реже, чем у азиатов.

Ключевые слова: *полиморфизм, цитохром P450, аллель, CYP2C19(681A/G)*

Конфликт интересов

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

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*Контакты: Альбина Александровна Жилина, e-mail: albina1228@yandex.ru
*Contacts: Albina A. Zhilina, e-mail: albina1228@yandex.ru
ORCID ID: https://orcid.org/0000-0002-4405-2975

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Abstract

Aims. To study the CYP2C19(681A/G) polymorphism among the population of the Trans-Baikal Territory in comparison with data in other regions of Russia and the world. **Materials and methods.** The study involved 132 people (81 women and 53 men). The median age was 47 (18; 72) years. Genotyping of the 681G/A polymorphic locus of the CYP2C19 gene was performed by polymerase chain reaction. **Results.** The prevalence of CYP2C19(681G/G) was 105 people (79.6%), CYP2C19(681G/A) — 25 people (18.9%) and CYP2C19(681A/A) — 2 participants (1.5%). Allele A of the CYP2C19 gene in position 681 was found in 14.2%. Allele A is less common in the population of the Trans-Baikal Territory, compared with Asians (China, p <0.001; Japan, p = 0.015) and did not differ in prevalence from Native Americans, Hispanics, African Americans, residents of Moscow, Voronezh, Irkutsk regions and Sakha-Yakutia. CYP2C19(681A/A) was more common in the Asian population than among the Transbaikalians, p = 0.003. The prevalence of the CYP2C19(681A/A) genotype did not differ between the population of the Trans-Baikal Territory, African Americans, Caucasians, and the population of the Moscow and Voronezh regions. **Conclusions.** The prevalence of the allele A in the population of the Trans-Baikal Territory was 14.2% and was comparable to the Caucasians, but less common than in the Asian population. The prevalence of the CYP2C19(681A/A) was 1.5%, which was consistent with world data among Caucasoid populations and was less common than in Asians.

Key words: *polymorphism, cytochrome P450, allele, CYP2C19(681A/G)*

Conflict of interests

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ADDs — acid-dependent diseases, CYP — cytochrome P450, GERD — gastroesophageal reflux disease, PPIs — proton pump inhibitors

One of the reasons for adverse drug reactions is the differences in the mechanisms of drug interactions mediated by various enzymes of the cytochrome P450 (CYP) family [2]. Cytochrome P450 is a superfamily of enzymes that catalyze the metabolism of medications and other substances. Genetic polymorphism in CYP is the main reason for individual differences in drug responses ranging from side effects to lack of efficacy. Of the 50 cytochrome P450 isoenzymes identified, more than 20 are functionally polymorphic (e.g., CYP2A6, CYP2C9, CYP 2C19, CYP2D9, CYP1B1 and CYP1A2). CYP2C19 is the most polymorphic member of the CYP2C subfamily. It catalyzes the metabolism of medications, including proton pump inhibitors [1]. One of the most common and potentially dangerous diseases today is gastroesophageal reflux disease (GERD); the prevalence of this disease tends to increase and significantly worsens the quality of life of patients. GERD is based on the reflux of stomach contents into the esophagus, i.e. gastroesophageal reflux. Proton pump inhibitors (PPIs) are the drugs of choice to relieve reflux symptoms and epithelialize erosions on the esophageal mucosa [2]. Despite that, these medications are far from "perfect" antisecretory agents, they have the most significant and long-term acid-suppressive capacity compared to antacids and H2 blockers of histamine receptors [2]. Cytochrome P450 2C19 (CYP2C19) plays a key role in PPI metabolism [3]. It particularly determines the rate of PPI metabolism, which varies in different ethnic groups due to the phenomenon of genetic polymorphism. There are currently 27 allele variants of CYP2C19; among them, CYP2C19*2, CYP2C19*3 and CYP2C19*17 alleles are described in the most detail [3]. The prevalence of mutant alleles in the population of patients with acid-dependent diseases can affect the outcome of treatment [4].

Genetic polymorphism of CYP2C19 results in individual differences in enzyme expression and metabolic activity. Allelic variation classifies the population according to CYP2C19 catalytic activity into slow, extensive and ultra-rapid drug clearance phenotypes [1]. Among all nonfunctional alleles, CYP2C19*2 (681G/A) is the most significant [3]. Patient genotyping for this gene can optimize the management of acid-dependent diseases (ADDs). It is known that the prevalence of polymorphic alleles varies in different populations [1]. To date, there are no data on the prevalence of the 681G/A polymorphic locus of CYP2C19 gene in the population of Trans-Baikal Territory, which does not allow us to assess the need for genotyping this gene in order to improve the quality of treatment for patients with acid-dependent diseases.

Objective of the Study

To analyze the prevalence of genotypes and alleles of the 681G/A polymorphic locus of the CYP2C19 gene among the population of Trans-Baikal Territory in comparison with data from other regions of Russia and the world; to assess the need for genotyping this polymorphic locus in clinical practice for patients with ADDs.

Materials and Methods

The study involved 132 subjects (81 females and 53 males). The study group included 79 patients with gastroesophageal reflux disease (30 males and 49 females), median age 44.5 (33; 57). The patients were examined and treated by a gastroenterologist at the diagnostic local clinic of the Federal State Budgetary Educational Institution of Higher Education Chita State Medical Academy of the Russian Ministry of Health from 2018 to 2020. GERD was diagnosed in patients based on the data of daily pH-impedancemetry and endoscopic examination of the upper gastrointestinal tract, according to the clinical guidelines of the Russian Gastroenterological Association (2017) [5].

We carried out a prospective single-center study. Patients with other chronic non-communicable diseases were excluded from the study. *It was decided to expand the cohort of participants based on a control group (apparently healthy individuals) who underwent a preventive medical examination at the diagnostic local clinic* — Federal State Budgetary Educational Institution of Higher Education Chita State Medical Academy of the Ministry of Health of Russia ═53 subjects (24 males and 29 females), age 45 (28; 62) because, as a result of statistical data processing, no differences were found in the prevalence of polymorphic variants of the CYP2C19*2 gene. All respondents who agreed to take part in the study were born and have lived in Zabaykalsky Krai for at least three generations and described themselves as Caucasians. Therefore, a group of 132 individuals (54 males and 78 females) was formed, median age was 47 (18; 62). This study followed the ethical principles of the Declaration of Helsinki. The study was approved by the local Ethics Committee at the Chita State Medical Academy, Chita, protocol No. 83, dated October 22, 2016.

Genotyping of the 681G/A polymorphic locus of the CYP2C19 gene was carried out by polymerase chain reaction. DNA samples isolated from peripheral venous blood WBC were the material for genetic analysis. Visualization of the amplification products was performed by electrophoresis in 3% agar gel with the addition of ethidium bromide with UV detection. We used standard kits for the studied SNPs manufactured by Litekh Research and Production Company (Moscow). Genetic tests were performed in the molecular genetics laboratory of the Research Institute of Molecular Medicine of the Chita State Medical Academy of the Ministry of Health of Russia.

Data were collected using MS Excel. Calculations were carried out using the online Hardy-Weinberg equilibrium calculator, Statistica 10.0. Statistical processing was carried out according to the principles of the International Committee of Medical Journal Editors (ICMJE) and the recommendations of "Statistical Analysis and Methods in the Published Literature (SAMPL)" [4]. Nominal data were described with the indication of absolute values and percentages in groups. Normality of the trait distribution was assessed using the Shapiro-Wilk test. In all cases, the hypothesis of normality was rejected. Therefore, the results are presented as a median and interquartile interval (Me (25%; 75%)). Assessment of the deviation in the distributions of genotypes of the studied polymorphic locus from the Hardy-Weinberg distribution was carried out using a modified Pearson's chi-square test. Comparative analysis of the data obtained was carried out using the Fisher test. Statistical significance of the relative odds was estimated based on the 95% confidence interval (95% CI). Differences were considered significant at $p < 0.05$.

Results

As a result of genotyping the 681G/A polymorphic locus of the CYP2C19 gene, three genotypes (G/G, G/A, A/A) were identified. The CYP2C19(681G/G) genotype had the highest prevalence — 105 (79.5%) individuals, the heterozygous variant of CYP2C19(681G/A) was less common — 25 (18.9%) respondents, and only 2 (1.5%) participants had the A/A genotype (see Table 1). It was established that the distribution of frequencies of genotypes and alleles of the polymorphic locus 681 G/A of the CYP2C19 gene corresponded to the distribution according to Hardy-Weinberg law, $p = 0.8843$ and $p = 0.1157$, respectively, suggesting the obtained results could be extrapolated to the population.

Table 1. *Frequency of genotypes and alleles of the CYP2C19 gene at the 681G/A position in the population of the Trans-Baikal Territory*

Genotypes and Alleles	Frequency (%)
G/G	79,6
G/A	18,9
A/A	1,5
G	85,8
A	14,2

A comparative analysis of the prevalence of the non-functional CYP2C19*2 allele in the population of Trans-Baikal Territory was carried out using world data and the results of studies performed by other Russian authors [2, 5, 6, 7, 8]. Statistically significant differences were obtained relative to Asian populations. In the Chinese population, the A allele was more prevalent than in the population of Trans-Baikal Territory (OR = 6.365, 95% CI 3.209; 12.625, $p < 0.001$). The prevalence of the non-functional CYP2C19 allele at position 681 in the Japanese population was also significantly higher than in our study (OR = 2.468; 95% CI 1.215; 5.012, $p = 0.015$). When comparing our data with the results obtained by other Russian authors, there were no statistically significant differences in the prevalence of this allele (see Table 2).

When analyzing the prevalence of the non-functional homozygous genotype of cytochrome P450, the CYP2C19(681A/A) genotype was found to be more common in Asians than the population of Trans-Baikal Territory (OR = 10.513, 95% CI 1.902; 58.106, $p = 0.003$) and did not differ from other populations in the world and in Russia ($p > 0.05$), see Table 3.

Table 2. Comparative analysis of the prevalence of the cytochrome P450 allele-A of the 681G/A polymorphic locus in populations around the world and in various regions of Russia

Population	Allele A (%)	p
Native Americans (n=1133) [8]	9,75	0,515
Hispanics (n=1898) [9]	10,77	0,67
Afro-Latinos (n=82) [9]	18,29	0,563
Argentine Ashken Jews (n=163) [9]	13,64	1,000
Chinese (n=267)[9]	51,3	0,001
Japanese (n=186)[4]	29	0,015
Russian Federation		
Moscow region, Caucasian nationality (n=1912) [10]	14,0	1,000
Voronezh region (n=580) [10]	11,4	0,67
Sakha-Yakutia (n=206) [11] Caucasians	13,49	1,000
Sakha-Yakutia (n=409) [11] Yakuts	14,54	1,000
Irkutsk region (n=89) [4]	11,3	0,67
Trans-Baikal Territory, own data (n=132)	14,2	-

Note: n — number of subjects; p — significance level

Table 3. Comparative analysis of the prevalence of the CYP2C19(681A/A) genotype in populations of the world and Russia

Population (n)	Allele A/A (%)	p
African American (n=966) [12]	3,7	0,683
Asians (n=573) [12]	13,8	0,003
Caucasians (n=1356) [12]	2,1	1,00
Russian Federation		
Moscow region, Caucasian nationality (n=971) [10]	1,4	1,00
Voronezh region (n=290) [10]	1,7	1,00
Own data (n=132)	1,5	-

Note: χ^2 — Pearson chi square, n — number of subjects; p — significance level

Discussion

The main tasks of pharmacogenetics are the search for an optimal drug for a particular patient, the determination of the required and sufficient dose, the optimization of side effects by analyzing the individual set of genes involved both in the implementation of the mechanism of drug action and in its metabolism.

PPI metabolism occurs with the participation of the CYP2C19 isoenzyme, and its genetic polymorphism impacts the antisecretory activity of these drugs [13]. Poor metabolizers are characterized by the decline in microsomal hydroxylation processes in the liver, leading to an increase in the area under the curve (AUC) by 5–12 times compared to extensive metabolizers. Individuals who are heterozygous for variant alleles demonstrate AUC values 2–4 times higher than those of extensive metabolizers. Enhanced pharmacokinetics leads to improved pharmacodynamics. Average 24-hour values of intragastric pH indicate the status of a metabolizer: the highest pH (and PPI effect) is in "poor" metabolizers, intermediate pH — in heterozygotes and lowest pH — in "extensive" metabolizers [14]. Patients with the CYP2C19(681G/G) genotype are defined as rapid metabolizers of proton pump inhibitors, and patients with the CYP2C19(681G/A) and CYP2C19(681A/A) genotype have slow drug metabolism [15]. In our study, about 80% of respondents had the CYP2C19(681G/G) genotype, indicating the predominance of "extensive" metabolizers in the population of Trans-Baikal Territory.

To improve the effectiveness of treatment of patients with GERD, it should be determined whether the genotype of a rapid metabolizer of cytochrome P450 2C19 is a risk factor for the failure of therapy with proton pump inhibitors [3]. In particular, the clinical efficacy of PPIs in eradication therapy for H. pylori-associated diseases and in the management of gastroesophageal reflux disease in "slow" metabolizers is more than double than that in "extensive" metabolizers. These differences primarily relate to omeprazole and lansoprazole, whose metabolism depends on CUPC19, and are not significant for rabeprazole and pantoprazole, which are metabolized to a lesser extent by this enzyme [13]. In a meta-analysis, Hitomi Ichikawa et al. (2016) showed that the effectiveness of PPI therapy in GERD, including reflux esophagitis and non-erosive reflux disease, was 56.4% (95% CI; 53.9–58.9%, 870/1543). Treatment response rates

varied significantly between genotypes: rapid — 52.2% (315/604); intermediate — 56.7% (298/526) and poor metabolizers — 61.3% (138/225), p = 0.047 [15]. Similar data were obtained in a study to analyze the endoscopic treatment of esophagitis eight weeks after the use of PPIs [16]. The effectiveness of therapy for poor metabolizers, heterozygotes and extensive metabolizers was 85–100%, 68–95% and 46–77%, respectively. In H. pylori-infected patients, the wild-type CYP2C19 genotype correlates with a lower response (20% lower cure rate) to combination therapy with a PPI and two antibacterials [1]. In 2006, Ariizumi, Ken et al. conducted a study on the efficacy of 10 mg rabeprazole per day in patients with reflux esophagitis depending on the CYP2C19 polymorphism. This study involved 103 patients who received 10 mg of rabeprazole daily. Treatment control was performed after 4 and 8 weeks using endoscopic examination of esophagus and stomach. Before therapy, a study of CYP2C19 polymorphism was carried out. Four weeks after treatment, the healing rate of esophageal mucosa in extensive, intermediate and poor metabolizers was 83.3% (15/18), 77.3% (17/22) and 88.9 (8/9), respectively. After eight weeks, mucosal healing rates were 86.1% (31/36), 92.0% (46.50) and 82.4 (14/17), respectively. There were no differences in mucosal healing in patients with reflux esophagitis among all three genotypes, either after four or eight weeks. The authors concluded that the effectiveness of rabeprazole to a lesser extent depends on the polymorphism of cytochrome P450 [17]. Considering the predominance of "extensive" metabolizers among the residents of Trans-Baikal Territory, rabeprazole is probably preferable in order to increase the effectiveness of managing acid-dependent diseases.

GERD is a chronic relapsing disease, so it is important to predict the exacerbation of the pathological process after stopping therapy. In the Japanese population, it was established that the recurrence of gastroesophageal reflux disease symptoms in extensive metabolizers of CYP2C19 is higher (38.5%) than in heterozygous extensive (10.9%) or poor (5.6%) metabolizers [1, 18]. Given the low prevalence of heterozygous (18.9%) and poor homozygous genotypes (1.5%) among people living in Trans-Baikal Territory, frequent relapses in patients with GERD can be assumed.

The clinical application of pharmacogenetics should be considered in cases when a genotype predicts side effects and/or non-response in patients; genotyping offers definite advantages over phenotyping; a drug has a narrow "therapeutic window"; an equivalent alternative drug is available; possible development of serious side effects or the consequences of a lack of response; there is a possibility of a negative effect/no response with a "marked" frequency; data from prospective studies demonstrating the benefits of genotyping have been accumulated [1]. The practical implication of genotyping for one in five Chinese or patients with variant CYP2C19 alleles is that standard doses of PPIs may be excessive. In European populations, there is a low prevalence of CYP2C19 polymorphisms, which makes genotyping clinically less significant for reflux esophagitis and peptic ulcer management [12]. Our comparative analysis of the prevalence of CYP2C19(G681A) genotypes yielded similar data. It was revealed that in Caucasian populations, including in Russia and in Trans-Baikal Territory, there is a low variability of the studied polymorphisms with a predominance of rapid metabolizers. This makes genotyping of this locus less significant in the management of reflux esophagitis and dictates the need for more frequent use of metabolically neutral PPIs for management of ADDs in the residents of Trans-Baikal Territory.

Conclusion

The frequency of the A allele of the 681G/A CYP2C19 polymorphic locus in the population of Trans-Baikal Territory was 14.2% and was comparable with Caucasians, but was less common than in the Chinese and Japanese populations ($p < 0.001$ and $p = 0.015$, respectively). The prevalence of the CYP2C19(681A/A) genotype was 1.5%, which matched world data among Caucasian populations; it was less common than in Asians ($p = 0.003$). Given the high prevalence of "extensive" metabolizers in Trans-Baikal Territory, with low variability of the CYP2C19(G681A) genetic polymorphism, it is advisable to use drugs that are less metabolized through this cytochrome without prior genetic testing.

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Жилина А.А. (ORCID: https://orcid.org/0000-0002-4405-2975): разработка концепции и дизайна, набор материала, статистическая обработка данных, написание статьи, автор согласен нести ответственность за все этапы работы

Ларева Н.В. (ORCID: https://orcid.org/0000-0001-9498-9216): разработка концепции и дизайна, проверка критически важного интеллектуального содержания, автор согласен нести ответственность за все этапы работы

Лузина Е.В. (ORCID: https://orcid.org/0000-0002-8282-3056): проверка критически важного интеллектуального содержания, автор согласен нести ответственность за все этапы работы

Цвингер С.М. (ORCID: https://orcid.org/0000-0003-2082-9839): проверка критически важного интеллектуального содержания, автор согласен нести ответственность за все этапы работы

Морозова Е.И. (ORCID: https://orcid.org/0000-0002-2481-5189): подборка литературы, автор согласен нести ответственность за все этапы работы

Author Contribution:

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

Zhilina A.A. (ORCID: https://orcid.org/0000-0002-4405-2975): development of the concept and design, a set of materials, statistical data processing, writing an article, the author agrees to be responsible for all stages of the work

Lareva N.V. (ORCID: https://orcid.org/0000-0001-9498-9216): development of the concept and design, verification of critical intellectual content, the author agrees to be responsible for all stages of the work

Luzina E.V. (ORCID: https://orcid.org/0000-0002-8282-3056): verification of critical intellectual content, the author agrees to be responsible for all stages of the work
Zwinger S.M. (ORCID: https://orcid.org/0000-0003-2082-9839): verification of critical intellectual content, the author agrees to be responsible for all stages of the work
Morozova E.I. (ORCID: https://orcid.org/0000-0002-2481-5189): a selection of literature, the author agrees to be responsible for all stages of the work

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Е.С. Мазур*, В.В. Мазур, Н.Д. Баженов, Ю.А. Орлов

ФГБОУ ВО Тверской ГМУ Минздрава России, кафедра госпитальной терапии и профессиональных болезней, Тверь, Россия

ПРЕДИКТОРЫ РАСТВОРЕНИЯ ТРОМБОВ В УШКЕ ЛЕВОГО ПРЕДСЕРДИЯ У БОЛЬНЫХ ПЕРСИСТИРУЮЩЕЙ НЕКЛАПАННОЙ ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ

E.S. Mazur*, V.V. Mazur, N.D. Bazhenov, Yu.A. Orlov

Tver State Medical University, Tver, Russia

Predictors of Thrombus Dissolution in the Left Atrial Appendage in Patients with Persistent Nonvalvular Atrial Fibrillation

Резюме

Цель работы — выявить факторы, влияющие на вероятность растворения тромба в ушке левого предсердия у больных персистирующей неклапанной фибрилляцией предсердий. **Материал и методы**. Повторное чреспищеводное эхокардиографическое исследование выполнено 88 больным персистирующей неклапанной фибрилляцией предсердий, у которых при первом исследовании был выявлен тромб в ушке левого предсердия. **Результаты**. При повторном исследовании, которое выполнялось в среднем через 30,0 (22,0; 40,0) дня после первого, растворение тромба в ушке левого предсердия было констатировано у 60 (68,2%) из 88 включенных в исследование пациентов. Анализ многофакторной логистической регрессии показал, что шансы растворения выявленного в ушке левого предсердия тромба возрастают в 5,789 (1,907–17,568) раза при размере тромба не более 25 мм, в 5,318 (1,325–21,353) раза при скорости кровотока в ушке левого предсердия не менее 20 см/с и в 3,687 (1,229–11,059) раза в случае использования прямых оральных антикоагулянтов, а не варфарина. При сочетании двух и более из указанных факторов вероятность растворения тромба достигает 89,6%. **Заключение**. Вероятность растворения тромба в ушке левого предсердия у больных персистирующей неклапанной фибрилляцией предсердий возрастает при небольшом размере тромба, высокой скорости изгнания крови из ушка левого предсердия и использовании прямых оральных антикоагулянтов.

Ключевые слова: *персистирующая фибрилляция предсердий, чреспищеводная эхокардиография, тромбоз ушка левого предсердия, пероральные антикоагулянты*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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*Контакты: Евгений Станиславович Мазур, e-mail: mazur-tver@mail.ru

*Contacts: Evgeniy S. Mazur, e-mail: mazur-tver@mail.ru

ORCID ID: https://orcid.org/0000-0002-8879-3791

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Abstract

The aim of this study is to identify factors influencing the likelihood of the thrombus dissolution in the left atrial appendage in patients with persistent nonvalvular atrial fibrillation. **Material and methods.** A repeated transesophageal echocardiography was performed in 88 patients with persistent nonvalvular atrial fibrillation and with the left atrial appendage thrombus at the first transesophageal echocardiography. **Results.** The second transesophageal echocardiography was performed on average 30.0 (22.0; 40.0) days after the first one, the thrombus dissolution in the left atrial appendage was revealed in 60 (68.2%) patients. The multivariate logistic regression analysis showed that the chances of the thrombus dissolution increased by 5.789 (1.907–17.568) times with the thrombus size not more 25 mm, by 5.318 (1.325–21.353) times with the left atrial appendage emptying flow velocity not less 20 cm/s and 3.687 (1.229–11.059) times when prescribing the direct oral anticoagulants, and not warfarin. Combination of two or more factors give the probability of the thrombus dissolution of more than 89.6%. **Conclusion.** The probability of the thrombus dissolution in left atrial appendage in patients with persistent nonvalvular atrial fibrillation increases with a small thrombus size, a high the left atrial appendage emptying flow velocity, and if direct oral anticoagulants were prescribed.

Key words: *persistent atrial fibrillation, transesophageal echocardiography, left atrial appendage thrombosis, oral anticoagulants*

Conflict of interests

The authors declare no conflict of interests

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AF — atrial fibrillation, ACT — anticoagulant therapy, DOACs — direct oral anticoagulants, LAA — left atrial appendage, TEC — transesophageal echocardiography, TVA — Thrombus-Velocity-Anticoagulant prognostic scale

Introduction

According to current recommendations [1, 2], if transesophageal echocardiography (TEC) reveals a thrombus in the left atrial appendage (LAA) in a patient with persistent atrial fibrillation (AF), the planned cardioversion should be postponed for at least three weeks, during which the patient should receive adequate anticoagulant therapy (ACT, recommendation class I). Before cardioversion, repeated TEC should be considered to confirm thrombus dissolution (recommendation class IIa). This issue can be considered while relying only on the assessment of the probability of thrombus dissolution by the time of cardioversion. A high probability of thrombus dissolution may serve as a basis for cardioversion without repeated TEC, while a low probability indicates the need for such examination.

Information in the literature on the frequency of dissolution of thrombi in LAA by the time of repeated TEC is scarce and fairly contradictory. According to the X-TRA study and the CLOT-AF register [3], after 6–8 weeks of taking rivaroxaban, complete dissolution of thrombus is observed in 41.5% cases, and after 3–12 weeks of treatment with vitamin K antagonists — in 62.5% cases. However, in a study conducted by A. Hussain et al. [4], thrombus dissolution during repeated TEC performed on average 67 days after the first study was reported in 77% of patients treated with direct oral anticoagulants (DOACs) and in 74% of patients treated with warfarin. A study by Saaed M. et al. [5] demonstrated that after four weeks of taking warfarin, dissolution of thrombus in LAA was observed in 90% of cases. Discussing the effectiveness of ACT in patients with AF, the participants of the Delphi Panel Discussion concluded that there is still not enough information to make detailed recommendations for the management of patients with identified atrial thrombosis [6]. Given the above, we considered it appropriate to analyze and present our own data on the frequency of LAA thrombus dissolution by the time of repeated TEC in patients with persistent AF.

Objective of the study was to identify factors that affect the possibility of LAA thrombus dissolution in patients with persistent non-valvular AF.

Material and Methods

The material for a single-center, retrospective cohort study was the register of TECs performed before the planned cardioversion in patients with persistent AF

from 2011 to 2021 by one of the authors of this article. Examinations were performed on Vivid E9 and Vivid S70 (GE, USA) devices with a transesophageal matrix multiplane phased transducer (2D/3D/4D) 6VT-D. The LAA was scanned from the midesophageal access in sections from 0 to 180° with a stepwise interval of 10–30°. Thrombi in the LAA were defined as discrete echopositive masses with a density that differs from the endocardium and pectineal muscles [7]. Information was entered into the register after the operator performed 50 transesophageal examinations with results that could formally be considered unreliable.

At the time of analysis, the registry contained information on 963 patients with persistent AF; in 149 (15.5%), a thrombus in the LAA was detected during the first TEC performed before the planned cardioversion. The study included 88 patients who underwent at least one repeated TEC after thrombus detection.

At the time of thrombus detection, all patients received ACT [1, 2], in accordance with the recommendations for preparing patients with persistent AF for planned cardioversion. However, its duration exceeded three weeks in only 44 (50.0%) of them. After detection of a thrombus in the LAA, 39 (44.3%) patients started or continued taking warfarin at doses that maintain the INR at the level of 2–3 U, 21 patients (23.9%) — rivaroxaban 20 mg once a day, 14 patients (15.9%) — apixaban 5 mg twice a day and 14 patients (15.9%) — dabigatran at a dose of 150 mg twice a day. Repeated TEC was performed on average 30.0 (22.0; 40.0) days after the first examination. It should be noted that in all patients treated with warfarin, INR before both the first and repeated TEC was within the target range. However, the overall duration of maintaining optimal anticoagulation was unknown.

Statistical analysis was carried out using IBM SPSS Statistics 22 software. For intergroup comparisons of means, the Mann-Whitney test was used. Means were presented as a median and an interquartile interval — Me (P_{25}; P_{75}). When comparing sample rates, the χ^2 criterion with Yates correction was used. Multiple logistic regression analysis was used to identify factors influencing thrombus dissolution. To determine the cut-off points and to assess the prognostic value of these factors, ROC analysis was performed. The cut-off point was the value of the maximum sum of test sensitivity and specificity. Results were considered statistically significant if the alpha error probability was less than 5% ($p < 0.05$).

Results

Out of 88 patients with persistent non-valvular AF with a thrombus in the LAA detected during the first transesophageal examination, its dissolution was established during re-examination in 60 (68.2%) patients. The groups of patients who dissolved and did not dissolve thrombus in the LAA were comparable in age, gender, range of comorbidities and clinical assessment of stroke risk. There were no intergroup differences in the average duration of paroxysm, the proportion of individuals with atrial flutter and the time of re-examination (Table 1). However, in patients who dissolved a thrombus, its initial size was, on average, smaller, and blood flow velocity in the LAA was higher than in patients with an undissolved thrombus. Also, the majority of patients who dissolved the thrombus received DOACs, and the majority of patients with an undissolved thrombus received warfarin. Therefore, thrombus size, blood flow velocity, and ACT features can be considered as potential predictors of thrombus dissolution by the time of echocardiographic re-examination.

All three variables were included in the multiple logistic regression analysis, with thrombus length and LAA flow velocity presented both in numerical terms and in binary form. According to ROC analysis, the points of separation of patients with a dissolved and undissolved thrombus are thrombus length of 26 mm and blood flow velocity of 20 cm/s. Data presented in Table 2 indicate that an increase in thrombus size by 1 mm is associated with a decrease in the chances of its dissolution by 1.098 times, and an increase in the velocity of blood ejection from the LAA by 1 cm/s is accompanied by an increase in the chance of thrombus dissolution by 1.084 times. The small size of thrombus (no more than 25 mm) increases the chances of its dissolution by 5.789 times, and the velocity of blood ejection from the LAA over 20 cm/s increases it by 5.318 times. Regardless of these factors, DOACs rather than warfarin increase the chances of thrombus dissolution by 3.687 times.

It should be noted that small thrombus size, high blood flow velocity in the LAA, and the use of DOACs have approximately the same effect on the chances of thrombus dissolution in the LAA, making it possible to assess the presence of any of these factors in a patient with 1 point. In this case, the minimum score that a patient can receive on the TVA scale (Thrombus ≤25 mm, Velocity ≥20 cm/s, Anticoagulant = DOAC) will be 0, and the maximum is 3.

According to the data presented in Figure 1, an increase in the total score on the TVA scale is accompanied by an increase in the number of cases of thrombus dissolution, and with a score of 2 or more, thrombus dissolution is observed in the overwhelming majority of patients. The area under the characteristic curve of the assessment on the TVA scale is greater than the area under the characteristic curves of all predictors included in this scale, although these differences do not reach the level of statistical significance (Fig. 2).

Data presented in Table 3 indicate that 1 point on the TVA scale does not statistically significantly affect the chance of thrombus dissolution compared to a zero

score on this scale. However, at 2 points, the chances of thrombus lysis increase by 18 times, and at 3 points — by 57 times.

Sensitivity of the TVA ≥2 criterion in relation to the dissolution of thrombus in the LAA is 71.7%, specificity is 82.1%, the predictive value of a positive and negative result is 89.6 and 57.5%. Therefore, the probability of thrombus dissolution in the LAA after 4–5 weeks of ACT is close to 90% if at least two of the following three conditions are met: thrombus size is not more than 25 mm, blood flow velocity in the LAA is not lower than 20 cm/s, a patient is taking DOACs.

Table 1. *Characteristics of patients with persistent nonvalvular AF*

Indicator	Total n = 88	LAA thrombus dissolved n = 60	LAA thrombus not dissolved n = 28	p
Age, years	62,5 (56,0; 67,0)	63,0 (56,5; 67,0)	61,0 (54,0; 65,5)	0,284
Men	48 (54,5)	36 (60,0)	12 (42,9)	0,203
Idiopathic AF	15 (17,0)	12 (20,0)	3 (10,7)	0,439
Hypertension	63 (71,6)	41 (68,3)	22 (78,6)	0,461
Coronary heart disease	12 (13,6)	9 (15,0)	3 (10,7)	0,832
Myocardial infarction history	8 (9,1)	5 (8,3)	3 (10,7)	0,972
DCMP	6 (6,8)	3 (5,0)	3 (10,7)	0,592
Heart failure	25 (28,4)	20 (33,3)	5 (17,9)	0,213
Diabetes	20 (22,7)	11 (18,3)	9 (32,1)	0,244
Stroke history	6 (6,8)	5 (8,3)	1 (3,6)	0,711
CHA_2DS_2-VASc, scores	2,00 (1,00; 3,00)	2,00 (1,00; 3,00)	2,00 (2,00; 3,00)	0,619
High stroke risk	53 (60,2)	36 (60,0)	17 (60,7)	0,865
ACT more than three weeks	44 (50,0)	29 (48,3)	15 (53,6)	0,819
Atrial flutter	11 (12,5)	8 (13,3)	3 (10,7)	1,000
Paroxysm, days	53,0 (30,0; 90,0)	49,5 (30,5; 72,5)	53,0 (27,5; 90,5)	0,542
Thrombus length, mm	18,8 (13,0; 27,0)	16,2 (12,0; 22,4)	27,0 (19,4; 29,0)	0,001
LAA emptying flow velocity, cm / s	15,5 (10,0; 20,0)	18,5 (11,0; 22,0)	12,5 (4,00; 18,0)	0,001
LAA area, cm^2	4,75 (4,22; 6,02)	4,70 (4,10; 5,88)	5,21 (4,40; 6,20)	0,233
Warfarin therapy	39 (44,3)	21 (35,0)	18 (64,3)	0,020
Rivaroxaban therapy	21 (23,9)	18 (30,0)	3 (10,7)	0,088
Apixaban therapy	14 (15,9)	10 (16,7)	4 (14,3)	0,978
Dabigatran therapy	14 (15,9)	11 (18,3)	3 (10,7)	0,551
Treatment time, days	30,0 (22,0; 40,0)	30,0 (22,0; 41,0)	31,5 (23,5; 35,5)	0,733

Note: Data are presented as median (25^{th}; 75^{th} percentiles) or as absolute and relative numbers — n (%)
ACT — anticoagulant therapy, DCMP — dilated cardiomyopathy, DOAC — direct oral anticoagulants, LAA — left atrial appendage, AF — atrial fibrillation, CHA_2DS_2-VASc — clinical stroke risk assessment scale

Table 2. *Some factors influence on the chances of a LAA thrombus dissolution*

Factor	OR	95% CI	p
Thrombus, mm	0,911	0,855–0,972	0,005
Flow velocity, cm/s	1,084	1,011–1,162	0,024
Thrombus ≤25 mm	5,789	1,907–17,568	0,002
Flow velocity ≥20 cm/s	5,318	1,325–21,353	0,018
Receiving DOAC	3,687	1,229–11,059	0,020

Note: CI — confidence interval, OR — odds ratio, DOAC — direct oral anticoagulants

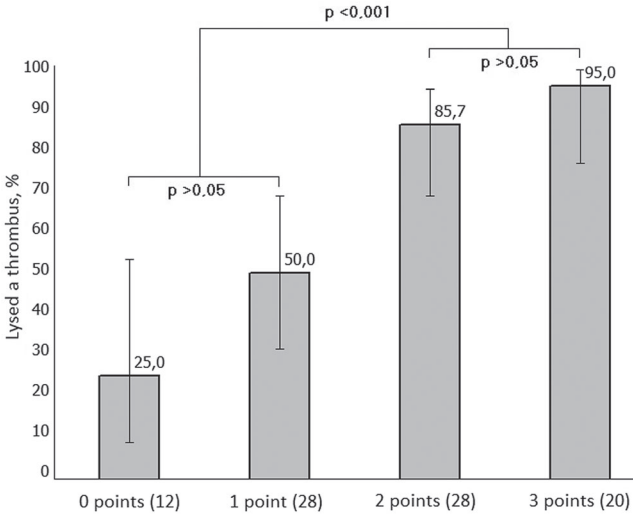

Figure 1. *Frequency of the left atrial appendage thrombus dissolution in patients with different sum of points on the TVA scale (Thrombus, Velocity, Anticoagulant). The number of patients with different sum of points is indicated in parentheses*

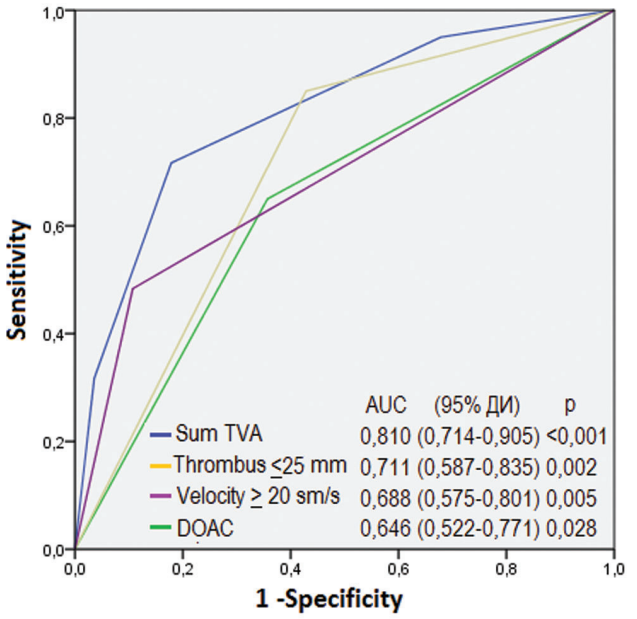

Figure 2. *Characteristic curves of the sum of points on the TVA scale and each predictor. TVA — Thrombus, Velocity, Anticoagulant, DOAC — direct oral anticoagulants, AUC — area under the characteristic curve*

Discussion

In the present study, three factors were identified that have an effect on the possibility of thrombus dissolution in the LAA in patients with persistent AF — thrombus size, blood flow velocity in the LAA, and the nature of anticoagulant therapy (warfarin or DOACs). Of 63 thrombi, the length of which did not exceed 25 mm, 51 (81.0%) had dissolved by the time of repeated TEC, and of the 25 larger thrombi — only 16 (36.0; p < 0.001). Therefore, the small size of the thrombus increases the chances of its dissolution by 5.789 (1.907–17.568) times.

We were unable to find published data on the effect of the size of the atrial thrombus on the probability of its dissolution. However, such data are available for thrombi in LV. A study conducted by B. Lattuca et al. [8] demonstrated that an increase in the area of a left ventricular thrombus reduces the probability of its dissolution (OR 0.66; 95% CI 0.45–0.96; p = 0.031). J.K. Oh et al. [9] reported the dissolution of the left ventricular apical thrombus in 23 (29.9%) of 77 examined patients one month after starting anticoagulant therapy. The initial size of the dissolved thrombi was less than that of the preserved thrombi: 10.7 ± 4.2 vs. 12.1 ± 5.5 mm, p = 0.046. According to the logistic regression analysis, an increase in the size of the apical thrombus by 1 mm reduces the chances of its dissolution by 1.06 (0.99–1.14) times, that is, by 6.2% (p = 0.053). According to the present study, an increase in the size of a thrombus in the LAA by 1 mm reduces the chances of its dissolution by 1.098 (1.029–1.170) times, that is, by 2.9–17.0% (p = 0.005). Therefore, the data obtained in this study on the effect of the LAA thrombus size on its dissolution are fully consistent with the data presented in the literature on the probability of dissolution of the left ventricular thrombi.

The effect of blood flow velocity in the LAA on the possibility of thrombus development and the risk of developing thromboembolic complications was first demonstrated in the SPAF-III study [10] and later confirmed in several other studies [11–14]. A decrease in the blood flow velocity in the LAA to 20 cm/s or less is considered critical for the development of a thrombus [10, 15, 16]. According to our data, at such a velocity of blood ejection from the LAA, the chances of thrombus dissolution decrease by 5.318 (1.325–21.353) times (p = 0.018). Of 32 patients with blood flow velocity in the LAA of at least 20 cm/s, thrombus dissolution was observed in 29 (90.6%) patients, and out of 56 patients with a lower

Table 3. *Changes in the chances of a thrombus dissolution depending on the TCA score*

TCA score	OR	95% CI	p
1 point	3,000	0,668–13,472	0,152
2 points	18,000	3,349–96,734	0,001
3 points	57,000	5,181–627,138	0,001

Note: CI — confidence interval, OR — odds ratio

blood flow velocity in the LAA — in 31 (55.4%, p = 0.002). The coincidence of critical blood flow velocity in the LAA, which predetermines the development and dissolution of a thrombus, is not accidental since these processes occur simultaneously, and the "fate" of a thrombus depends on the predominance of one of them.

Therefore, the relationship between the probability of thrombus dissolution and its size and blood flow velocity in the LAA revealed in this study is confirmed by literature data; the same cannot be said about the third of the identified predictors of successful thrombus dissolution, i.e. the use of DOACs. At present, there is no evidence in the literature of the advantage of DOACs over warfarin in dissolving thrombi in the LAA. The only randomized trial on this issue (X-TRA) demonstrated that rivaroxaban can be used to dissolve atrial thrombi but is not superior to warfarin [3]. Several non-randomized studies found no differences between DOACs and vitamin K antagonists in terms of the effectiveness of LAA thrombus dissolution [4, 5, 17]. In the present study, thrombus dissolution during repeated TEC was found in 21 (53.8%) of 39 patients treated with warfarin and in 39 (79.6%) of 49 patients treated with DOACs (p = 0.020). Given the non-randomized nature of this study, the relatively small number of patients enrolled, and the lack of data on the duration of the target range of INR in warfarin-treated patients, additional evidence is required for the greater effectiveness of DOACs in dissolving thrombi in the LAA.

Any of the predictors identified in this study enables us to predict the probability of thrombus dissolution by the time of repeated TEC. However, the combination of these predictors has the greatest prognostic value. If the patient has at least two of them, the probability of thrombus dissolution reaches 89.6%, which allows following clinical recommendations [1, 2] and avoiding control TEC before cardioversion.

Conclusion

In patients with persistent non-valvular AF, the chances of dissolution of a thrombus detected in the LAA in connection with ACT increase by 5.789 (1.907–17.568) times with a thrombus size of not more than 25 mm, by 5.318 (1.325–21.353) times with blood flow velocity in the LAA of at least 20 cm/s and by 3.687 (1.229–11.059) times with DOACs rather than warfarin. When two or more of these factors are combined, the probability of thrombus dissolution by the time of repeated TEC is 89.6%.

Вклад авторов:

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Мазур Е.С. (ORCID ID: https://orcid.org/0000-0002-8879-3791): разработка концепции и дизайна, сбор, анализ и интерпретации данных, проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации, ответственный за все аспекты работы

Мазур В.В. (ORCID ID: https://orcid.org/0000-0003-4818-434X): интерпретация результатов, проверка критически важного интеллектуального содержания, внесение в рукопись существенной правки

Баженов Н.Д. (ORCID ID: https://orcid.org/0000-0003-0511-7366): получение и анализ результатов

Орлов Ю.А. (ORCID ID: https://orcid.org/0000-0001-9114-0436): получение результатов, написание 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

Mazur E.S. (ORCID ID: https://orcid.org/0000-0002-8879-3791): concept and design development, data collection, analysis and interpretation, critical intellectual content validation, final approval of the manuscript for publication, responsible for all aspects of the work

Mazur V.V. (ORCID ID: https://orcid.org/0000-0003-4818-434X): analysis and interpretation of data, preparation of a manuscript, responsible for all aspects of the work

Bazhenov N.D. (ORCID ID: https://orcid.org/0000-0003-0511-7366): data collection, analysis and interpretation, responsible for all aspects of the work

Orlov Yu.A. (ORCID ID: https://orcid.org/0000-0001-9114-0436): data collection, preparation of a manuscript, responsible for all aspects of the work

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А.А. Маркова*[1], М.И. Барсукова[2]

[1]— ФГБОУ ВО «Саратовский государственный медицинский университет» им. В.И. Разумовского Минздрава России, кафедра госпитальной терапии лечебного факультета, Саратов, Россия
[2]— ФГБОУ ВО «Саратовский государственный медицинский университет» им. В.И. Разумовского Минздрава России, кафедра педагогики, образовательных технологий и профессиональной коммуникации, Саратов, Россия

ТАКТИКА СООБЩЕНИЯ ПЛОХИХ НОВОСТЕЙ В ПРОФЕССИОНАЛЬНОМ ОБЩЕНИИ ВРАЧА И ПАЦИЕНТА

A.A. Markova*[1], M.I. Barsukova[2]

[1]— Saratov State Medical University named after V.I. Razumovsky, Ministry of Health of Russian Federation, Department of the Internal Medicine, Saratov, Russian Federation
[2]— Saratov State Medical University named after V.I. Razumovsky, Ministry of Health of Russian Federation, Department of Pedagogics, Educational Technologies and Professional Communication, Saratov, Russian Federation

Tactics of Reporting Bad News in Professional Communication Between a Doctor and a Patient

Резюме

Статья посвящена развитию уровня коммуникативной компетентности будущих врачей и особенностям профессионального общения с пациентами. Основанием работы стали вопросы определения речевого поведения врача в одной из самых сложных коммуникативных ситуаций — ситуации сообщения плохих новостей. На материале реальных записей речи врачей проведен анализ рискогенных коммуникативных шагов в общении врача и пациента, определены максимально эффективные способы реализации речевых тактик врача в ситуации сообщения плохих новостей. Сделано заключение о необходимости повышения уровня профессиональной коммуникации врачей и обучения студентов медицинских вузов коммуникативным навыкам сообщения плохих новостей.

Ключевые слова: *речевая тактика, сообщение плохих новостей, врач, пациент, коммуникативные навыки*

Конфликт интересов

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

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Abstract

The article is devoted to the development of the level of communicative competence of future doctors and the peculiarities of professional communication with patients. The basis of the work were the questions of determining the speech behavior of a doctor in one of the most difficult communicative situations — the situation of delivering bad news. Based on the material of real recordings of doctors' speech, the analysis of risky

*Контакты: Анна Александровна Маркова, e-mail: markova-ann@yandex.ru
*Contacts: Anna A. Markova, e-mail: markova-ann@yandex.ru
ORCID ID: https://orcid.org/0000-0001-8561-2214

communicative steps in the communication between the doctor and the patient is carried out, the most effective ways of implementing the doctor's speech tactics in the situation of bad news are determined. Conclusions are drawn about the need to improve the level of professional communication of doctors and to train medical students in the communication skills of delivering bad news.

Key words: *speech tactics, delivering bad news, doctor, patient, communication skills*

Conflict of interests

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Introduction

Professional communication between a physician and a patient is the most important part of practical medicine. Physicians themselves, their patients and many researchers in this sector recognize the need and importance of the communicative aspect [1, 2]. As the adage goes: "The old doctor speaks Latin, the new doctor speaks English, the good doctor speaks the patient's language." Proper communication between a physician and a patient undoubtedly determines the patient's attitude towards the physician, the success of diagnosis and the management of the disease. The speech behavior of a physician and his/her communication skills help to find a common language with the patient.

Implementation of a new educational standard allowed the inclusion of the "Professional communication" course in the list of modules that are taught at the Department of Pedagogy, Educational Technologies and Professional Communication at V.I. Razumovsky Saratov State Medical University. The theoretical basis of professional communication and speech-behavioral models of various situations of medical discourse are honed in practical classes. Teaching staff performs a number of tasks: improve the general and communicative culture of future professionals; teach the basic tools of effective professional communication; develop the skills of conflict-free professional communication between a physician and a patient; study with students the practical methods of convincing patients and overcoming communication barriers that arise between a physician and a patient.

One of the most difficult issues to manage is the special situation in the interaction between the patient and the physician — delivering bad news to the patient. Insufficient exploration of this issue in domestic and foreign literature makes it relevant to study the communicative behavior of a physician when communicating with a patient in difficult life circumstances and presents a particular challenge in regard to the collection of information. In domestic medical, pedagogical, and psychological literature, this issue is usually addressed from the point of view of ethics and deontology [3–6]. Foreign studies describe several communication models tested in clinical practice [7, 8]. However, we should mention that many researchers only write that a physician should be more attentive, more tactful, etc., that is, he/she should comply with ethical standards. However, the analysis of specific speech and behavioral steps and the ways of their verbal and non-verbal expression are still not analyzed. Therefore, a physician can only guess what modes of communication will be appropriate and most effective and act according to his/her language habits.

According to the current legislation, a physician is obliged to provide a patient with complete information about the patient's disease [9]. Therefore, mastering the tactics of delivering bad news in different situations of institutional communication with patients becomes a mandatory professional skill for a physician.

A physician in his/her daily activities constantly has to face negative emotions of patients. The physician experiences enormous psychological stress when he/she has to deliver bad news to a patient.

In foreign literature, the term "bad news" means any information from a physician about the state of health that negatively and significantly changes the patient's idea of his/her future [10–12].

In Russian literature, bad news is divided into two types that seem relevant: actual bad news and unpleasant news [13]. *Bad news* is the news a physician has to deliver to patients, their partners and family members regarding a terminal illness, incurable disease, mutilation, sudden or predictable death. Bad news may include informing about serious illnesses with reversible processes (for example, syphilis, tuberculosis, etc.); fatal diseases with irreversible processes (for example, HIV, AIDS, leukemia, multiple sclerosis, metastatic malignant tumors, etc.); incurable diseases with severe or irreversible consequences (for example, diabetes mellitus, Down syndrome, hemophilia, schizophrenia, epilepsy, etc.); the patient's disability (for example, loss of limbs); informing relatives about the death of the patient, as a fait accompli. *Unpleasant news* means news that can make a patient experience such emotional reactions as fear, anxiety, worrying, sadness, grief. This may be informing a patient about upcoming surgery; a chronic disease (for example,

bronchitis, arterial hypertension, etc.); a limb fracture that causes an unpleasant experience in a patient (anxiety, fear, grief, etc.) [13].

The **SPIKES** model is the most developed and practically tested model for delivering bad news. This model includes six consecutive steps: **S** (setting) — preparing for a conversation, developing a plan for a conversation, creating a comfortable environment, allocating time for a conversation, ensuring confidentiality, determining the number of participants in a conversation. **P** (perception) — finding out what the patient already knows about his/her condition or disease, determining patient's expectations, his/her ideas about the current condition. **I** (invitation) — defining the information that the patient wants to hear; what is important for the patient to hear first of all; whether the patient wants to know all the details of the current situation. **K** (knowledge) — informing about the current condition and verbalization of the diagnosis: start with the fact that you have information about the current condition of the patient; do not underestimate, do not rush; provide information gradually; make sure the patient understands you; give support, express regret. **E** (emotion) — psychological support: provide time for the patient's emotional response; ask him/her how he/she feels; explain that his/her feelings are normal in this situation. **S** (strategy and summary) — development of a joint plan for further actions: discuss who can help and support the patient from his/her inner circle, from social organizations; warn the patient about possible unpredictable circumstances; let him/her know on what day and at what time he/she can contact you [7].

However, due to the lack of time, the conditions for creating a comfortable environment while talking with the patient, and other factors, it is hard to adhere to the above model in actual clinical practice. In light of this, it seems to us especially important and relevant to use verbal and non-verbal tactics when delivering bad news to a patient.

Objective of the study: to find the most effective ways to implement the tactics of delivering bad news.

Research problems: Analysis of challenging aspects in communication between a physician and a patient; analysis of the culture of delivering bad news in the practice of a physician, and describing communication errors in the speech behavior of a physician when implementing the tactics of delivering bad news using the example of real cases from the practice of a general practitioner.

Materials and Methods

This work is a single-center, cross-sectional study. This study was conducted in accordance with international and Russian ethical standards, the provisions of the Declaration of Helsinki, and was approved by the local Ethics Committee of V.I. Razumovsky Saratov State Medical University of the Ministry of Health of Russia. All patients and physicians signed informed consent for voluntary participation in the study. Inclusion criteria: presence of bad news that should be delivered to a patient, age 18+, signed informed consent.

Six female physicians took part in the conversation with patients; their work experience ranged from 3 to 10 years; they were general practitioners with an average age of 29 ± 4.3 years. The study involved 30 patients (20 females and 10 males, average age 54.3 ± 12.5 years).

Dialogs between a physician and a patient when delivering bad news to the patient were recorded and analyzed; they were collected via the participant observation method in the therapeutic departments of clinics in Saratov. Reasons for delivering bad news: newly diagnosed benign tumors and malignant tumors of internal organs. During the conversation, attention was paid to the physician's use of non-verbal ways of communicating with a patient. After recording the dialog, the attending physician clarified the details and features of the patient's clinical situation required for the full description of each specific case.

Results

In this article, to illustrate the issue under consideration, four clinical cases were selected, which demonstrate both the wrong speech behavior of a physician and the right choice of speech tactics and their verbal and non-verbal implementation.

Clinical Case No. 1

Let's consider a dialog between a physician and a patient.

Physician: *Ultrasound examination of abdominal organs revealed a mass in your liver.*

Patient (female): *What could it be? Is it serious?*

Physician: *We have to perform magnetic resonance imaging of the liver.*

Patient (female): *Could it be cancer?* (her expression changes.)

Physician: *Everything is possible.*

Was the behavior of the physician correct during this conversation? The patient definitely did not expect to receive such news. She was upset, began to worry about the news. Patients often lose appetite and stop sleeping, constantly thinking about their new problems; they worry and try to imagine possible outcomes. In this case, the etiology of the mass in the liver was not clear. It could be a liver cyst, hemangioma, nodular hyperplasia, adenoma. These lesions are benign and usually require follow-up. Could the patient be told that it could be cancer when the diagnosis is not confirmed? Of course, this news turned out to be "bad" for the patient because it

caused negative emotions and feelings. Every person might associate the very word "cancer" with an unfavorable prognosis. In our opinion, in this situation, the physician should have said that at present, we cannot say exactly what kind of mass it is. Further tests are required. The physician might have even reassured the patient that masses in the liver are more often benign, and examination methods sometimes can give inaccurate results (for example, magnetic resonance imaging of the liver could show no mass in the liver).

Clinical Case No. 2

Here is another example of how a physician should not talk to a patient. Patient I., male, 20. Examination revealed a malignant tumor of the colon, peritoneal carcinomatosis. Chemotherapy and extensive surgery are indicated. The patient inquired about his condition while the physician was doing her rounds. The physician replied that she would first speak with the patient's parents. After the physician left, the patient looked nervous. In the evening, the physician spoke to the patient's father, explained that the prognosis was unfavorable, and chemotherapy and several serious surgeries were required. What did the physician expect by talking first with the father but not with the patient himself? Apparently, deeply sympathizing with the patient, the physician tried to avoid an unpleasant conversation and tried to shift the responsibility for communicating the patient's diagnosis to the shoulders of his parents. Does a physician have the right to do such things? In accordance with current legislation — no. The patient is an adult. He wanted to know about his condition; he was worried and, of course, immediately understood that the physician was hiding something from him. And what about the patient's grief-stricken father, how well could he talk to his son? Will he be able to support his son in such a difficult time? When the patient sees his parents in distress, he would likely think that everything is very bad and could lose faith and hope for the future. In such a situation, the physician himself/herself should tell the patient about the diagnosis, methods of treatment, further prognosis, without hiding the truth from the patient. However, at the same time, the physician should give the patient some reassurance, making it clear that treatment exists and every effort should be made to combat the disease.

Delivering news to patients is a very difficult problem. After hearing a diagnosis with a poor prognosis from a physician, patients almost always ask: "How long do I have?" Despite that present-day medicine can determine the approximate life expectancy of patients with a particular pathology, no one, even the most experienced professional, can say how long the patient will live. This issue is undoubtedly very important for patients with severe diseases. After all, they try to imagine how to "build" their lives going forward, what to do with the time left. And if you say they have very little time? Unfortunately, many patients, in this case, lose hope, interest in life and die even faster than expected.

Clinical Case No. 3

Let's consider the behavior of a physician when communicating with a patient under follow-up for a long time for a malignant tumor of the pancreas with a poor prognosis. Patient, male, 51, was diagnosed with pancreatic adenocarcinoma. At the case conference, the tumor was regarded as unresectable. Median survival of such patients is six months [14]. During the first conversation, the physician clearly explained to the patient that life expectancy differs in different individuals with the same pathology and depends on many factors; she set the patient up to fight the disease. The patient was observed in the department for three years; the diagnosis was repeatedly confirmed; the patient was in constant contact with the attending physician, followed all the recommendations in a timely manner and felt good. This example demonstrates the longer life expectancy of a patient with cancer with a statistically low life expectancy; there was a trusting relationship between physician and patient and high adherence to therapy.

Clinical Case No. 4

This clinical case demonstrates correctly chosen tactics of speech behavior and the specific features of its implementation. Patient, male, 76. Examination revealed primary multiple malignant tumors of the colon and the stomach with severe concomitant pathology. On the case conference, tumors were regarded as unresectable. When speaking with the patient, the physician described the diagnosed pathology as follows:

Physician: Hello, I.M. (addresses by name and patronymic; takes a chair, sits next to the patient's bed). I.M., I have some not very good news to tell you (pauses). Based on the results of the examination, you have two tumors: in the stomach and the large intestines…unfortunately, you cannot be operated on…

Patient: So, life is over (doesn't look at the physician, stares ahead).

Physician: I.M., you know (puts his hand on the patient's forearm), the histological variant of tumors is not the worst. There are no metastases. I will tell you later what to do, what to eat, what drugs to take to treat anemia ... we will definitely deal with it and we will do our best to make you feel good...

The physician found the right words to encourage the patient, to inspire him with belief in the possibility of continuing to fight. At the level of speech implementation, the physician used the tactics of consolation, empathy and support, as well as the tactics of creating the line of thinking and explaining. Analysis of this material showed that the specific effective features included means

of harmonizing communication: "we" — which emphasized that the problem was shared (we will definitely deal with it and do our best); euphemisms demonstrating softening of categoricalness (not very good news). It should be noted that the patient's relatives played an important role in supporting him: they were very attentive, helped him feel needed and filled the patient's life with positive emotions and care; were constantly in contact with the attending physician and followed all the recommendations for treatment and care.

Discussion

The art of communication between a physician and a patient is a very complex and multifaceted process where a physician acts not only as a professional who uses his knowledge and experience for the treatment, rehabilitation and maintenance of the patient's health, but also as a person who analyzes the patient's treatment process in the context of moral, ethical, cultural, religious values. The art of communicating with a patient requires not only the desire of the physician but also the relevant knowledge. Future and practicing physicians usually master the skills of communicating with the patient based on their linguistic abilities during practice, adopting "a manner of speaking from clinicians or intuitively finding their own style, the success of which, however, may be in doubt" [2].

Physicians must be well versed in the principles of ethics and deontology in medicine, and have knowledge of communication psychology. Without sufficient knowledge in these areas, it is impossible to find the right individual approach to each patient.

The communicative culture of delivering bad news takes up a special niche in the physician's work. Despite that delivering bad news to a patient or his/her relatives is an integral part of the work of a practicing physician, it always causes tension in the emotional-volitional sphere. There is no doubt that the more severe and unfavorable a patient's prognosis, the more difficult it is for a physician to choose the right words and properly describe the problem. Not only young but also experienced professionals, deep down inside, do not want to deal with the negative emotions of patients. Such reluctance can lead to a situation where a physician either does not fully inform the patient about the diagnosis, trying to avoid unnecessary questions, or conveys it with detachment, hastily, not caring about the patient's mental state. Both scenarios of speech behavior, in this case, are risky and cannot be considered acceptable by a physician [15]. Of course, not only the patient experiences negative emotions while talking about the worsening of health. The physician also experiences anxiety and fear for the future of his/her patient. The physician understands that after this conversation, the patient's life will change and will never be the same.

A sick individual is very different from a healthy person in many ways: special physical condition during the period of illness, intensity of emotions, mental stress, belief in recovery, hope of returning to the family, labor

Table. *Verbal and nonverbal tactics when telling a patient bad news*

Verbal tactics
Consolation: "don't worry"; "we'll manage, we'll ease Your suffering"; "it could be worse"; "now you need to think about how to cope with the disease"
Support: "do not worry ahead of time, let's wait for the results of the study"; "You did the right thing, seeing the doctor just in time"; "first of all, You need to calm down"; "do not be afraid of this operation"; "don't worry, everything will go well"; "we are going to manage it, You are not alone, don't worry"
EEmpathy: "I know what you are going through"; "be patient a little, I understand that it hurts you, it will become much easier against the background of treatment"; "I understand that it is unpleasant to do this study, but it is necessary"
Nonverbal tactics
Touching, patting (takesika): touching the patient's forearm; shaking the hand; patting the shoulder to support the patient
Eye contact: making eye contact at the same eye level; do not turn away and do not avert your eyes during a conversation
Eye expression: kind, open, confident, warm, caring, soothing look
Facial expression (facial expressions): friendly, sympathetic, compassionate, but at the same time, encouraging and supportive facial expression
Pose (pantomime): straight back, slight tilt of the head or upper body towards the patient
Distance (distance to the interlocutor): the distance to the patient is about half a meter, sufficient for a confidential conversation; there are no barriers between the doctor and the patient (for example, a table)
Voice (intonation, volume, tone, rhythm): confidential intonation; soft speech, unhurried rhythm, semantic pauses in combination with visual contact

and social activity create a special atmosphere in relations between a physician and a patient. For many people, disease is a severe trauma that leads to noticeable mental changes: in the patient's attitude towards himself/herself, close ones, work, life. These psychoemotional changes in a person are due to physical suffering, disruption of their daily habits, the threat of various complications, dependence on others, worries and fear for the future [16].

Undoubtedly, how bad the news will be for the patient depends on his/her expectations, awareness of the illness, and how "sick" the person felt before receiving news about his/her state of health.

Knowledge of the laws of professional communication and ways to implement the tactics of delivering bad news will help physicians navigate a difficult situation, build the right communication strategy, support, and comfort the patient and significantly ease his/her negative response.

The table includes the most successful, in our opinion, verbal and non-verbal tactics that help physicians best deliver bad news to patients [17].

Conclusion

Knowledge of the laws of professional communication and the ability to choose the best speech tactics and ways of their verbal and non-verbal implementation are becoming critical in professional interaction between a physician and a patient when implementing the tactics of delivering bad news. Speech tactics required for delivering bad news include consolation, empathy, and support. It is recommended to include the "Professional Communication" course in the list of taught disciplines for students of medical institutions of higher professional education, for the specialty programs "General Medicine" and "Pediatrics". In practical classes, teaching staff should work out the basics of professional communication with students, pay special attention to the speech behavior of physicians in a difficult situation of interacting with a patient — delivering bad news. A graduate skilled in communicative behavior in various professional communication situations will fit the image of a physician, defined as the only possible in one of V.M. Bekhterev's principles: "If the patient does not feel better after talking with the physician, then this is not a physician".

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Маркова А.А. (ORSID ID: https://orcid.org/0000-0001-8561-2214): концепция и дизайн исследования, получение данных, анализ и интерпретация данных, написание статьи, утверждение итогового варианта текста рукописи

Барсукова М.И. (ORCID ID: https://orcid.org/0000-0001-5277-8090): концепция и дизайн исследования, получение данных, анализ и интерпретация данных, написание статьи, утверждение итогового варианта текста рукописи

Author Contribution:

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Markova A.A. (ORCID ID: https://orcid.org/0000-0001-8561-2214): research concept and design, obtaining data, analyzing and interpreting data, writing articles, approving the final version of the publication

Barsukova M.I. (ORCID ID: https://orcid.org/0000-0001-5277-8090): research concept and design, obtaining data, analyzing and interpreting data, writing articles, approving the final version of the publication

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М.С. Бычкова*[1], Е.В. Резник[1,2]

[1] — Федеральное государственное автономное образовательное учреждение высшего образования «Российский Национальный Исследовательский Медицинский Университет имени Н.И. Пирогова» Министерства здравоохранения Российской Федерации, кафедра госпитальной терапии № 2, Москва, Россия
[2] — ГКБ № 31 ДЗМ, Москва, Россия

ВЕДЕНИЕ ПАЦИЕНТА С ТЯЖЕЛОЙ АРТЕРИАЛЬНОЙ ГИПОТОНИЕЙ НА ФОНЕ ТЕРМИНАЛЬНОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ СО СНИЖЕННОЙ ФРАКЦИЕЙ ВЫБРОСА ЛЕВОГО ЖЕЛУДОЧКА

M.S. Bychkova*[1], E.V. Reznik[1,2]

[1] — N.I. Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation, department of Hospital Therapy № 2, Moscow, Russia
[2] — City Clinical Hospital № 31, Moscow, Russia

Management of a Patient with Severe Hypotension and Advanced Heart Failure with Reduced Left Ventricular Ejection Fraction

Резюме

Артериальная гипотония часто встречается при хронической сердечной недостаточности. Снижение артериального давления может быть обусловлено различными причинами, в том числе снижением насосной функции сердца, лекарственными препаратами, измененной вазореактивностью, связанной с сопутствующими заболеваниями (например, сахарным диабетом) и др. Единых критериев оценки тяжести артериальной гипотонии нет. Степень влияния ее на прогноз и течение заболевания окончательно не изучены. Сложность ведения пациентов с сердечной недостаточностью и артериальной гипотонией заключается в подборе и титровании рекомендованных лекарственных препаратов для компенсации заболевания без развития дополнительных побочных эффектов. На сегодняшний день разработаны поэтапные алгоритмы назначения и коррекции лекарственной терапии пациентам с артериальной гипотонией. В данной статье представлен клинический случай ведения пациента с тяжелой артериальной гипотонией на фоне хронической сердечной недостаточности со сниженной фракцией выброса левого желудочка.

Пациенту с врожденным пороком сердца (двустворчатым аортальным клапаном) в 25 лет было выполнено протезирование аортального клапана. Спустя 13 лет, после перенесенной вирусной инфекции, развилась декомпенсация хронической сердечной недостаточности со снижением фракции выброса левого желудочка до 19% с последующим сохранением клинической симптоматики на уровне III — IV функционального класса, несмотря на оптимальную медикаментозную терапию в течение года. При наличии у пациента показаний к сердечной ресинхронизирующей терапии была имплантирована система модуляции сердечной сократимости, после чего улучшения клинической симптоматики не отмечалось, наблюдались частые (до 4 в течение год) декомпенсации, требовавшие госпитализаций. С целью предотвращения прогрессирования заболевания и улучшения прогноза, несмотря на гипотензию, был назначен сакубитрил/валсартан в минимальных дозах, на фоне чего удалось компенсировать пациента и добиться стабильного течения хронической сердечной недостаточности без потребности в госпитализации в течение 9 месяцев. Данный клинический случай позволяет рассматривать необходимость

*Контакты: Мария Сергеевна Бычкова, e-mail: mashabichkova@gmail.com
*Contacts: Maria S. Bychkova, e-mail: mashabichkova@gmail.com
ORCID ID: https://orcid.org/0000-0002-3453-5914

проведения дополнительных клинических исследований для изучения возможности назначения малых доз сакубитрил/валсартана у пациентов с артериальной гипотонией на фоне сердечной недостаточности с целью уменьшения выраженности клинической симптоматики и улучшения прогноза.

Ключевые слова: *терминальная сердечная недостаточность, двустворчатый аортальный клапан, сердечная ресинхронизирующая терапия, трансплантация сердца, система модуляции сердечной сократимости, гипотония, сакубитрил/валсартан*

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Abstract

Hypotension is often in chronic heart failure patients. It has various reasons, including a decrease in the pumping function of the heart, medications, altered vasoreactivity associated with concomitant diseases (for example, diabetes mellitus). There are no universal criteria for assessing the severity of hypotension. Its prognosis significance has not been studied well. It is difficult to select and titrate the drugs recommended for treatment of heart failure, so that the prescribed therapy compensates the patient and does not cause the development of side effects. Step–by–step algorithms for prescribing and correcting drug therapy for heart failure patients with hypotension have been developed. This article presents a clinical case of management of a patient with severe hypotension and chronic heart failure with a reduced left ventricular ejection fraction.

Aortic valve replacement was performed the patient with congenital heart disease (bicuspid aortic valve) in 25 years. In 13 years, after a viral infection, there was a decompensation of chronic heart failure with reduced ejection fraction to 19%. Against the optimal drug therapy, heart failure persisted III– IV functional class with 4 hospitalization during a year. Despite the indications for cardiac resynchronization therapy, a system for modulating cardiac contractility was implanted, after which there was no improvement in clinical symptoms, there were frequent decompensations up to. In order to prevent the progression of the disease and improve the prognosis, despite hypotension, sacubitril/valsartan was prescribed, against which it was possible to compensate the patient and achieve a stable course of chronic heart failure without the need for hospitalization for 9 months. This case report suggest that additional clinical researches are necessary to study the possibility of prescribing of small doses of sacubitril/valsartan in patients with hypotension and heart failure to reduce the severity of clinical symptoms and to improve the prognosis.

Key words: *terminal heart failure, bicuspid aortic valve, cardiac resynchronization therapy, heart transplantation, cardiac contractility modulation, hypotension, sacubitril/valsartan*

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24h ECG — 24-Hour Holter monitoring, ACE inhibitors — angiotensin-converting enzyme inhibitors, ALT — alanine aminotransferase, ARB — angiotensin II receptor blocker, ARNI — angiotensin receptor-neprilysin inhibitor, ARVI — acute respiratory viral infection, AST — aspartate aminotransferase, AUS — ultrasound examination of abdominal organs, BMI — body mass index, BP — blood pressure, CHF — chronic heart failure, CKD — chronic kidney disease, CRTd — cardiac resynchronization therapy with a defibrillator, ECHO-CG — echocardiography, ECG — electrocardiography, EDV — end-diastolic volume, EGD — esophagogastroduodenoscopy, ESC — European Society of Cardiology, ESD — end-systolic dimension, FC — functional class, FDA — Food and Drug Administration, FS — fractional shortening, GFR — glomerular filtration rate, GGTP — gamma-glutamyl transpetidase, HF — heart failure, HFmrEF — heart failure with midrange LV ejection fraction, HFpEF — heart failure with preserved LV ejection fraction, HR — heart rate, IABP — intra-aortic balloon counterpulsation, INR — international normalized ratio, LA — left atrium, LBBB — left bundle branch block, LDH — lactate dehydrogenase, LVEF — left ventricular ejection fraction, MCS — mechanical circulatory support, MRA — mineralocorticoid receptor antagonist, NYHA — New York Heart Association, OM — omecamtiv mecarbil, RCT — randomized clinical trial, RV — right ventricle, sPAP — systolic pulmonary artery pressure, SV — stroke volume, T2DM — type 2 diabetes mellitus, QRS axis — electrical heart axis

Introduction

The management of chronic heart failure (HF) remains an extremely pressing issue today. In the Russian Federation, HF of functional class (FC) I-IV, according to the New York Heart Association (NYHA) classification, affects 7.9 million individuals [1]. Present-day advances in drug therapy can help improve the quality of life and increase life expectancy. However, they inevitably increase the number of patients with end-stage HF. End-stage HF is characterized by persisting severe clinical

Table 1. *Updated HFA–ESC criteria for defining advanced heart failure*

All the following criteria must be present despite optimal guideline–directed treatment:
1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by a reduced LVEF ≤30%, isolated RV failure (e.g., ARVC) or non–operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT–proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.
3. Episodes of pulmonary or systemic congestion requiring high–dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise

Note: BNP — B-type natriuretic peptid, NT–proBNP — N-terminal pro-BNP, HFpEF — heart failure with preserved ejection fraction, HFmrEF — heart failure with mid-range ejection fraction, ARVC — arrhythmogenic right ventricular cardiomyopathy, LV — left ventricular LVEF — left ventricular ejection fraction, NYHA — New York Heart Association, ESC — European Society of Cardiology, RV — right ventricular

symptoms despite optimal treatment (Table 1) [2]. There are reasons to establish the diagnosis of end-stage HF in 1–10% of all patients with HF [3].

Drug treatment currently plays a central role in preventing the progression of HF. According to modern approaches, patients with chronic heart failure (CHF) with decreased LV systolic function should receive the following if they have no contraindications [1, 4]:

1) Angiotensin receptor-neprilysin inhibitor (ARNI) OR, if it cannot be prescribed/is contraindicated/leads to intolerance, an angiotensin-converting enzyme (ACE) inhibitor OR, if an ACE inhibitor leads to intolerance and ARNI cannot be prescribed, an angiotensin II prescription blocker (ARB) [5–7].
2) Beta blocker (BB) [1, 6].
3) Diuretic (in the case of congestion) [6, 8].
4) If there is no effect from a three-component ongoing therapy and LV EF < 35%, a mineralocorticoid receptor antagonist (MRA) should be added [5, 6].
5) To improve the prognosis, all patients with CHFrEF are indicated to have sodium-glucose cotransporter-2 inhibitors (SGLT-2, "metabolic diuretics") added to their treatment.

If a patient takes ACE inhibitors/ARBs, BBs, MRAs and a diuretic and clinical symptoms persist, then, if there is sinus rhythm with HR > 70 bpm with the intake of a target dose of BBs or intolerance to them, the addition of If-channel blockers (ivabradine) is indicated. For patients with atrial fibrillation, oral anticoagulants should be prescribed, and for patients with HR > 70 bpm with the intake of a target dose of BB, digoxin should be added. If a patient takes ACE inhibitors/ARBs, BBs, MRAs and a diuretic and has systolic blood pressure (BP) > 100 mm Hg and clinical symptoms persist, an ACE inhibitor/ARB should be replaced with ARNI [5, 6].

In patients with end-stage CHF, the administration of these groups of medicinal agents is limited by the frequent development of severe arterial hypotension (synonym: hypotension).

Arterial hypotension is blood pressure more than 20% below normal values; in absolute terms, it is a decrease in systolic blood pressure < 90 mm Hg or mean BP < 60 mm Hg. [9]. According to randomized clinical trials (RCTs), arterial hypotension develops in 10–15% of patients with HF [2].

Arterial hypotension in cases of HF can be caused by decreased cardiac pumping function, medication-induced hypovolemia, vasodilation, impaired vasoreactivity (for example, in patients with diabetes mellitus) [3]. Arterial hypotension can be caused by high doses of loop diuretics, which remain the basis for managing congestion in patients with HF. Progression of heart failure is often accompanied by impaired renal function (development of chronic cardiorenal syndrome), which, in turn, is accompanied by resistance to diuretics [10, 11]. Chronic cardiorenal syndrome may have several mechanisms, including hemodynamic disturbances, neurohormonal activation, increased tubular sodium reabsorption, inflammation, oxidative stress and drug nephrotoxicity. Resistance to diuretics, in this case, usually develops due to a number of renal adaptations after the administration of diuretics ("braking phenomenon"), including hypertrophy and hyperfunction of nephron sites, as well as increased renin secretion. To manage the braking phenomenon, thiazide diuretics are used simultaneously with loop diuretics. However, there are no reliable RCT data regarding the effectiveness of this combination, and the combination may lead to the development/aggravation of arterial hypotension [3].

In patients with an inadequate response to treatment with oral diuretics, intravenous administration of diuretics is recommended, starting with a dose higher than for oral medications. However, this can also contribute to the development of arterial hypotension. If diuretic therapy has no effect, peritoneal dialysis can be prescribed [2]. Indications for dialysis include end-stage HF, fluid overload, progression of chronic kidney disease (CKD), and end-stage CKD [2].

Parenterally administered inotropic agents may improve hemodynamics in patients and delay deterioration in target organ function [2]. Inotropic agents can be conditionally divided into catecholamine derivatives (dopamine, dobutamine), positive inotropic agents with vasodilatory effect (levosimendan) and cardiac glycosides. These medications are indicated for CHF patients with persistent congestion, hypoperfusion, regardless of the administration of vasodilators or diuretics. Despite

the favorable effect on hemodynamics and severity of symptoms, long-term use of medications with positive inotropic effect (except digoxin) has a negative effect on the prognosis for CHF patients [12]: These agents increase myocardial oxygen demand and intracellular calcium concentration thereby increasing the risk of cardiac arrhythmia and death [12]. Therefore, such medications should be administered only during the acute period of hypoperfusion and hypotension that cannot be corrected with agents of other classes.

Levosimendan is a medication with three main properties: inotropic, vasodilatory and cardioprotective. Its half-life is 1–1.5 hours, and clinical effects are due to the formation of active metabolites OR-1855 and OR-1896, with the effect persisting for 7–9 days after the end of a 24-hour infusion. Its inotropic effect is due to the increased sensitivity of cardiomyocyte myofibrils to calcium, which leads to the binding of troponin C to calcium ions and the formation of a troponin C and calcium complex. This, in turn, leads to increased myocardial contractility without developing diastolic relaxation abnormalities. The vasodilatory effect is due to the opening of ATP-sensitive potassium channels on the membrane of smooth myocytes of the vascular wall, which reduces total peripheral and pulmonary vascular resistance and, therefore, pre- and afterload. The cardioprotective effect of levosimendan is also based on its effect on the opening of mitochondrial ATP-sensitive potassium channels [12].

The REVIVE and SURVIVE studies, the two largest studies to this date, showed that hypotension developed more frequently during treatment with levosimendan than with a placebo, but not with dobutamine. The incidence of atrial fibrillation in the levosimendan group was higher than in both comparator groups. Ninety percent of patients received levosimendan at a rate of 0.2 mg/kg/min during the first 2 hours; among them, 70–85% continued to receive the agent at the same rate over the next 24 hours. The main side effect of levosimendan was the development of hypotension (in 50% of subjects) and arrhythmias. Results of clinical trials indicate that levosimendan should be used with caution in patients with arterial hypotension, especially in cases of hypovolemia.

Inotropes may also be used in patients with end-stage HF prior to temporary mechanical circulatory support (MCS), long-term MCS or heart transplantation. Long-term treatment with inotropes is not recommended for patients awaiting transplantation. Long-term MCS is advisable in such cases. Long-term therapy with inotropes may be a palliative option for patients with no alternative treatment options [2].

Omecamtiv mecarbil (OM), a new selective oral inotrope, is a cardiac myosin activator that improves myocardial contractility in patients with CHF. The GALACTIC-HF study established the safety of OM, including the absence of adverse effects of OM on renal function, serum potassium levels, blood pressure or heart rate (HR) [13, 14]. The Food and Drug Administration (FDA) recently approved another new medication for the management of HF with reduced ejection fraction (HFrEF) — vericiguat, an oral soluble guanylate cyclase stimulator that increases the bioavailability of nitric oxide. The VICTORIA study, which included patients with LVEF < 45% after a recent hospitalization for decompensated HF or after receiving intravenous diuretics, revealed that this drug reduces mortality from cardiovascular events and the number of hospitalizations for HF [15].

The EMPEROR-Reduced trial demonstrated a lower risk of death due to cardiovascular causes or hospitalization for HF for 16 months due to the effect of empagliflozin at a dose of 10 mg per day compared with the placebo (1:1 ratio) in a group of 3,730 patients with HF with reduced LV ejection fraction ≤40% and increased NT-proBNP [16]. Empagliflozin reduced the risk of hospitalization for heart failure by 30% (HR 0.70; 95% CI 0.58–0.85; p < 0.001). In addition, the incidence of adverse renal events (required chronic hemodialysis or kidney transplantation or persistent reduction in estimated glomerular filtration rate) dropped by 50% in the empagliflozin group (HR 0.50; 95% CI 0.32–0.77; p < 0.01). BP in the empagliflozin and placebo group was 122.6 ± 15.9 and in the placebo group 121.4 ± 15.4 mm Hg, respectively; the proportion of patients with arterial hypertension was 1,349 (72.4%) and 1,349 (72.3%), respectively. No information was provided on the use of this medication in patients with arterial hypotension.

In the DAPA-HF study, the treatment of patients with HFrEF with and without T2DM with dapagliflozin led to a decrease in body weight (-0.7 kg after 4 months and –0.8 kg after 8 months, respectively, p = 0.14) and systolic BP (–1.6 mm Hg and –1.8 mm Hg after 4 months, respectively, p = 0.43) [17]. One of the key inclusion criteria in the DAPA-HF study was SBP ≥95 mm Hg. Baseline SBP in 1,205 patients was < 110 mm Hg, in 981 patients ≥110 < 120; in 1,149 patients ≥120 < 130; and in 1,409 patients ≥130 mm Hg. Placebo-adjusted SBP reduction from the baseline with up to 2 weeks of dapagliflozin administration was –2.54 (–3.33 to –1.76) mm Hg. Patients with the lowest SBP levels demonstrated more optimistic results in reducing the number of HF decompensations (per 100 person-years) [RR 20.6; 95% confidence interval (95% CI) 17.6–24.2] than patients with the highest SBP values (RR 13.8; 95% CI 11.7–16.4). The benefit and safety of dapagliflozin were similar throughout the SBP range (p = 0.78). The discontinuation of the study drug demonstrated no differences between dapagliflozin and placebo groups in the analyzed SBP categories. Dapagliflozin had little effect on SBP in patients with HFrEF, was superior to the placebo in HF stabilization and was well tolerated throughout the SBP range in patients enrolled in the DAPA-HF study [17].

Table 2. *Indications and contraindications to heart transplantation Patients to consider*

Indications	Contraindications
1. End–stage HF with severe symptoms, a poor prognosis, and no remaining alternative treatment options 2. Motivated, well informed, and emotionally stable 3. Capable of complying with the intensive treatment required postoperatively Contraindications	1. Active infection 2. Severe peripheral arterial or cerebrovascular disease 3. Pharmacologic irreversible pulmonary hypertension (LVAD should be considered with subsequent re–evaluation to establish candidacy) 4. Cancer (a collaboration with oncology specialists should occur to stratify each patient as to their risk of tumour recurrence) 5. Irreversible renal dysfunction (e.g. creatinine clearance 35 kg/m^2 (weight loss is recommended to achieve a BMI) 6. Systemic disease with multiorgan involvement 7. Other serious co– morbidity with poor prognosis 8. Pre– transplant BMI >35 kg/m^2 (weight loss is recommended to achieve a BMI 9. Current alcohol or drug abuse 10. Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting

Note: LVAD — left ventricular assistant device, BMI — body mass index, HF — heart failure

In general, SGLPT2 inhibitors do not increase the risk of arterial hypotension in patients with T2DM. Therefore, possible hypotension should be considered on a case-by-case basis, especially in patients with a history of low BP, long-term T2DM or comorbidities [18].

Intra-aortic balloon counterpulsation (IABP) can also be performed in patients with end-stage HF. A single-center study (n = 56) revealed that IABP provided clinical stabilization in 57% of patients before the implantation of the MCS system [2].

Despite the advances in medication management of end-stage HF, many of these patients require heart transplantation (Table 2). It significantly improves survival, quality of life and prognosis compared with drug treatment. If a patient's condition worsens, a short-term MCS may be required as a "bridge" to heart transplantation [2]. The main limitation of heart transplantation is the relatively small pool of donor hearts that varies from country to country.

According to the IRODAT registry for 2018, in Russia, the number of heart transplantations was 1.72 per 1 million of the population. Among patients with HF in Russia (2019), 900 individuals needed heart transplantation, and 337 transplantations were performed [18]. In 2020, the COVID-19 pandemic could not but have a negative impact on heart transplantation statistics. Since the prognosis for patients with end-stage HF is extremely poor, they often do not live to receive a heart transplant. In this regard, the issue of drug treatment for patients with end-stage HF while on the waiting list for heart transplantation is extremely urgent.

This article describes the case of managing a patient with end-stage HFrEF with severe arterial hypotension while on the waiting list for heart transplantation.

Description of Clinical Case

In 2003, the patient, 25, was diagnosed with congenital heart disease: bicuspid aortic valve disease with severe aortic regurgitation. The patient in severe state was hospitalized at the V. I. Burakovsky Institute of Cardiac Surgery of the A. N. Bakulev National Medical Research Center for Cardiovascular Surgery. On admission, BP was 105/50 mm Hg and HR — 90 bpm. Electrocardiography (ECG) results revealed sinus rhythm with HR 64 bpm, left QRS axis deviation, signs of LV hypertrophy, incomplete left bundle branch block (LBBB), diffuse changes in the myocardium. Echocardiography (ECHO-CG): LVEF 30%, left atrium (LA) 4.6 cm, LV end-systolic dimension (ESD) 8.4 cm, LV end-diastolic dimension (EDD) 9.9 cm, LV end-systolic volume (ESV) 384 mL, LV end-diastolic volume (EDV) 552 mL, LV stroke volume (SV) 168 mL. Leaflets of mitral valve were thin, mobile; anterior mitral leaflet was elongated. Aortic valve: 2 leaflets, with no coaptation, ascending aorta 35 mm, at the level of the sinus of Valsalva 51–52 mm, arch 30 mm, descending aorta 19 mm, fibrous ring (FR) 43–44 mm, aortic regurgitation III–IV. Ultrasound examination of abdominal organs (US of the abdominal cavity) revealed ascites, hepatomegaly (right lobe 143 mm, left lobe 55 mm). Aortic valve prosthetics with MIKS-27 was performed, as well as left atrial appendage ligation. Recommendations on discharge included warfarin 6.25 mg per day under the control of international normalized ratio (INR); perindopril 2 mg per day; spironolactone 50 mg per day; hydrochlorothiazide + triamterene 25 mg + 50 mg per week; as a result, a stable course of the disease was maintained for 12 years. LVEF increased to 47%, LV EDD decreased to 9.2 cm.

At the age of 38, after an acute respiratory viral infection (ARVI) with catarrhal symptoms and fever up to 39 ^{0}C, the following symptoms developed: shortness of breath with minimal physical exertion, at rest, when talking, and asthma attacks at night. Echocardiography revealed LVEF decrease to 23%.

From the age of 39, clinical symptoms increased; examination revealed an enlarged liver, elevated levels of alanine aminotransferase (ALT) up to 81 U/L, total bilirubin up to 34 μmol/L, creatinine up to 134 μmol/L, as well as decreased estimated glomerular filtration rate (eGFR) (CKD–EPI) to 61 mL/min/1.73 m^2. According to ECHO-CG data, the function of the prosthesis is

satisfactory, aortic regurgitation grade I, mitral regurgitation grade III, LV EDD 9.1 cm; LV EDV 458 mL, LVEF 19%, diffusely decreased left ventricular contractility, increased pulmonary hypertension (systolic pulmonary artery pressure sPAP — 66 mm Hg).

Despite drug treatment in accordance with clinical recommendations, there were complaints of shortness of breath with minimal physical exertion and at rest, weakness, low-productive cough; increased cytolysis (ALT increased to 111 U/L) and decreased renal function were observed for a year. Despite indications for cardiac resynchronization therapy (left bundle branch block, QRS — 160 ms, CHF stage IIB, NYHA class IV, low LVEF (19%) along with optimal drug treatment), a cardiac contractility modulation system was implanted as part of clinical testing. There was no subsequent improvement in clinical symptoms; blood pressure decrease to 85/65 mm Hg was often observed; decompensations became frequent, up to four times a year, and required hospitalization.

Nine months after implantation of the cardiac contractility modulation system, there were complaints of dull pain in epigastric and mesogastric areas, which worsened when eating, nausea, weakness; chronic gastroduodenitis, exacerbation of pancreatitis were suspected. The patient was hospitalized in Gastroenterology Department. The patient's state at admission was severe. Self-care was impossible due to shortness of breath. Body weight 64 kg, height 174 cm, BMI = 21.14 kg/m^2. Swelling of lower legs, up to the middle third. By auscultation: vesicular breathing, decreased in the lower parts on both sides, no rales, RR 16 per minute. Heart sounds are clear, the sounds of the prosthesis are heard. Regular rhythm with HR of 60 bpm, blood pressure 110/70 mm Hg. Dry tongue with whitish coating. Abdomen of normal shape. Abdomen was soft and painless on palpation. Peristalsis was heard. Stool is regular, formed, with no pathological admixtures. Liver is not enlarged, its lower edge of normal elasticity on palpation, rounded edge.

Complete blood count revealed no abnormalities. In blood biochemistry: increased total lactate dehydrogenase (LDH) — 492 IU/L (225–450), gamma-glutamyl transpetidase (GGTP) — 192 IU/L (9–39), alpha amylase — 268 IU/L (0–220), total bilirubin — 42.0 mmol/L (1.7–20.5), direct bilirubin — 19.00 mmol/L (0.86~5.00), creatinine 156.8 μmol/L (eGFR (CKD-EPI) — 46.88 mL/min/1.73 m^2), aspartate aminotransferase (AST) — 89 IU/L (5–34), ALT — 58 IU/L (0–32); INR 2.5. Ultrasound examination of the abdominal organs (US of abdominal cavity) revealed diffuse changes in liver, pancreas; cranio-caudal size of the left lobe of liver 104 mm, thickness — 53 mm, oblique vertical size of the right lobe — 148 mm, thickness — 105 mm, as well as normal size, increased echogenicity and heterogeneous structure of pancreas. Esophagogastroduodenoscopy (EGD) revealed a presentation of superficial gastritis, cardia insufficiency, esophageal candidiasis. Recto-, sigmo- and colonoscopy revealed no organic pathology of the colon.

According to the examination results, the following diagnosis was established: chronic pancreatitis, exacerbation. Chronic superficial gastritis, exacerbation. Subsequent laboratory tests after 14 days of treatment demonstrated decreased level of transaminases: ALT 81 U/L, AST 25 U/L, creatinine 134 μmol/L (eGFR (CKD-EPI) — 57.08 mL/min/1.73 m^2), total bilirubin 34.0 mmol/L, potassium 3.9 μmol/L.

On ECG during hospitalization in the Gastroenterological Department, sinus rhythm was registered with HR of 64 bpm, as well as sharp left deviation of QRS axis, ventricular extrasystole, left bundle branch block, repolarization disturbances in V5–6, probably due to the overload of the left ventricle (Fig. 1 A). Periodically, changes associated with the heart contractility modulation device were observed (Fig. 1 B).

А Б

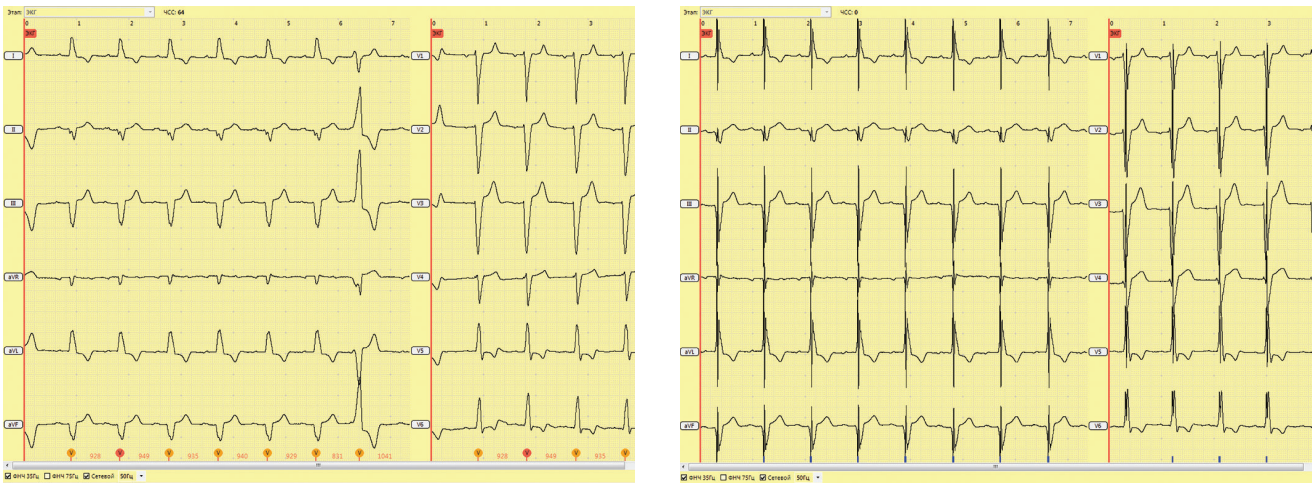
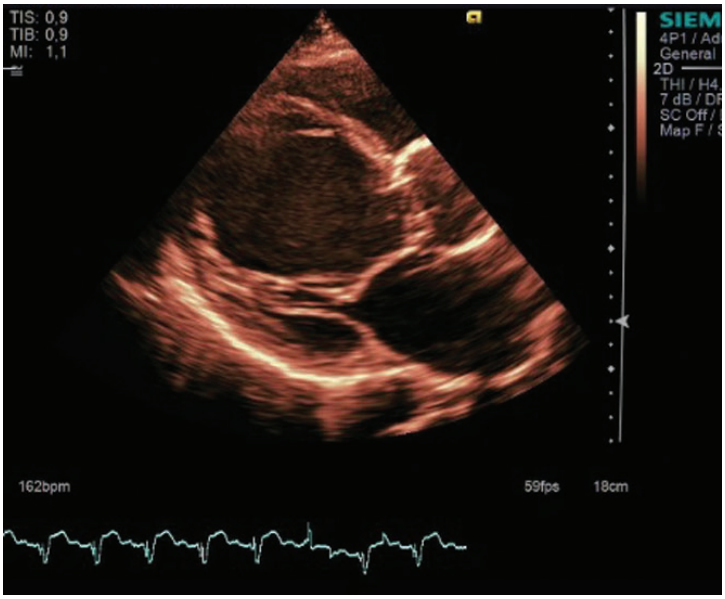
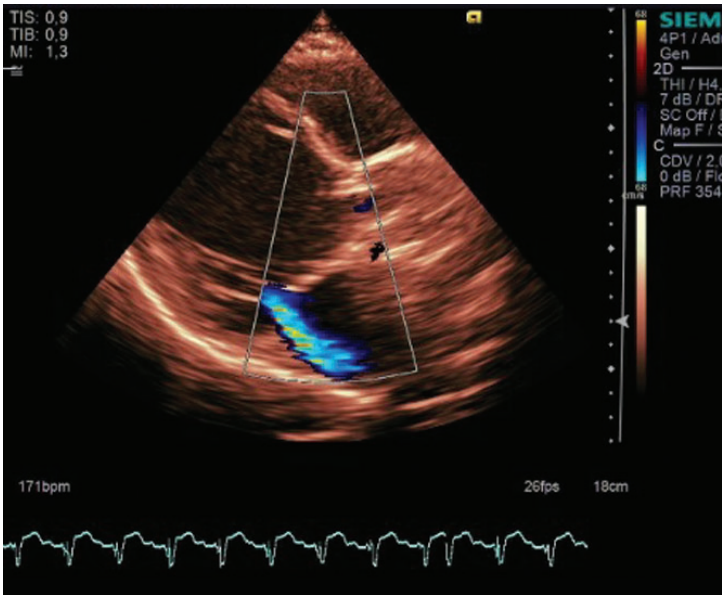


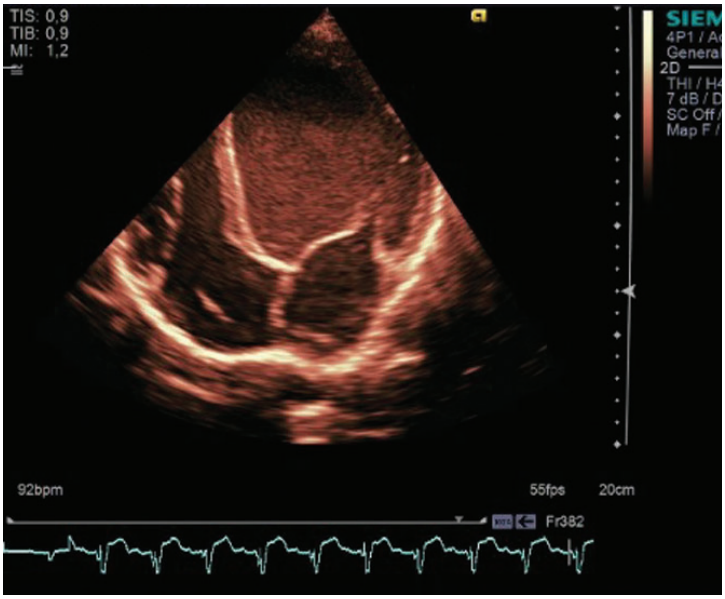
Figure 1. *Electrocardiogram*



A — parasternal position on the long axis

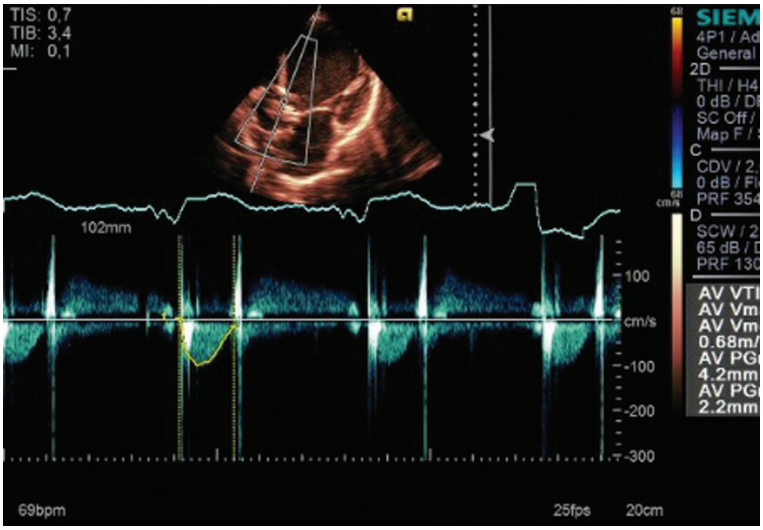


B — mitral regurgitation in the parasternal position along the long axis

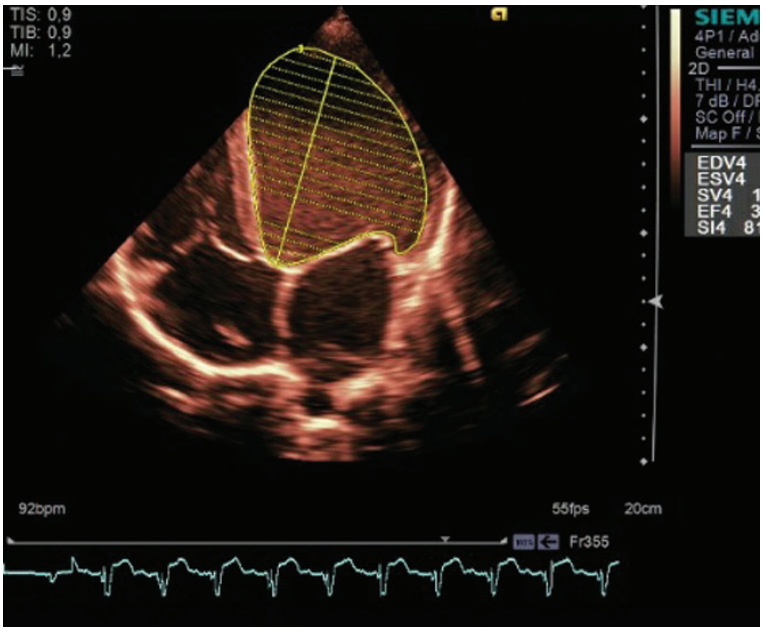


C — apical four-chamber position: dilatation of the left ventricle, the optimizer electrode in the right chambers

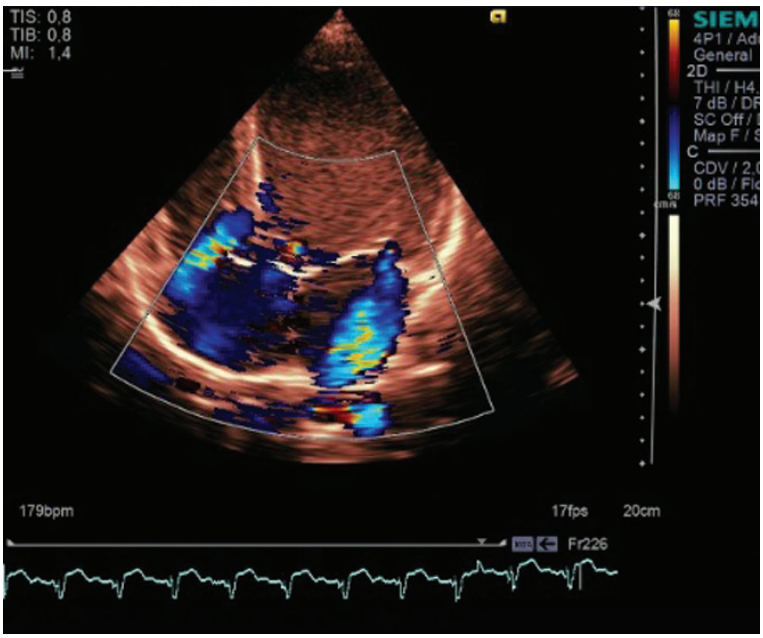
Figure 2 (A—C). *Echocardiograms from 2018*



D — gradient on the aortic prosthesis

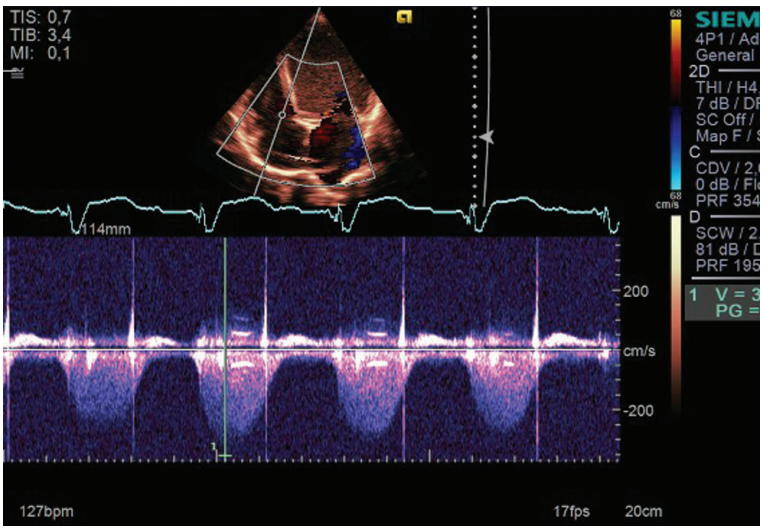


E — Left ventricular end diastolic volume

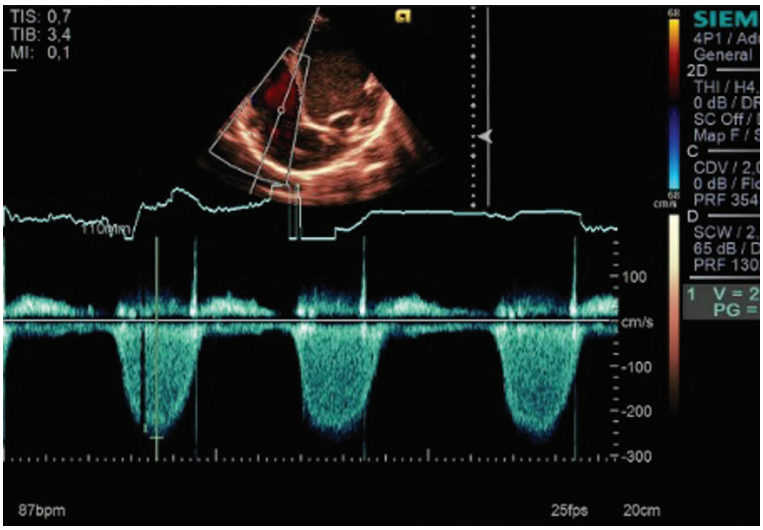


F — mitral and tricuspid regurgitation

Figure 2 (D—F). *Echocardiograms from 2018*



H — The maximal pressure gradient of tricuspid regurgitation is 50.71 mm Hg; systolic pressure in the pulmonary artery before taking sacubitril / valsartan is 70 mm Hg.



I — The maximal pressure gradient of tricuspid regurgitation is 27.47 mm Hg; systolic pressure in the pulmonary artery after 2 months sacubitril / valsartan treatment 32 mm Hg

Figure 2 (H—I). *Echocardiograms from 2018*

Holter ECG monitoring (24h ECG) revealed paroxysm of polymorphic ventricular tachycardia in the form of a 4-complex pirouette. Amiodarone, potassium asparaginate and magnesium asparaginate were added to the treatment, which aggravated weakness, yellowing of skin, nausea, vomiting. The medications were discontinued.

ECHO-CG revealed satisfactory function of the prosthesis, significant dilatation of heart chambers, decreased LV systolic function **(18%)**, relative insufficiency of atrioventricular valves.

Recommendations for outpatient treatment included warfarin 3.625 mg per day under the control of INR (target level 2.5–3.5), spironolactone 50 mg per day, carvedilol 6.25 mg per day, torasemide 20 mg per day, enalapril 2.5 mg per day. In the course of treatment, there was no significant improvement for two months.

Cardiac resynchronization therapy with a defibrillator (CRT-D) was considered. However, due to technical difficulties with the cardiac contractility modulation system, implantation of a resynchronization device was not performed.

Decompensation of HF with liver damage, development of hypoxic hepatitis, renal damage with the development of CKD stage C3aA1 were considered the symptoms that led to hospitalization in the Gastroenterology Department. There was a sharp deterioration two months after discharge, with dry cough, blood-streaked sputum. According to the results of ECHO-CG: sPAP 70 mm Hg, EF 19%, LV ESV 371 mL, LV EDV 458 mL (Fig. 2). The patient was examined by a transplantologist and was placed on the waiting list for heart transplantation. Considering the ineffectiveness of the treatment performed and four consecutive hospitalizations due to CHF decompensation during the previous year, enalapril was discontinued and, despite the tendency to arterial hypotension, sacubitril/valsartan 12.5 mg per day was prescribed [4, 5].

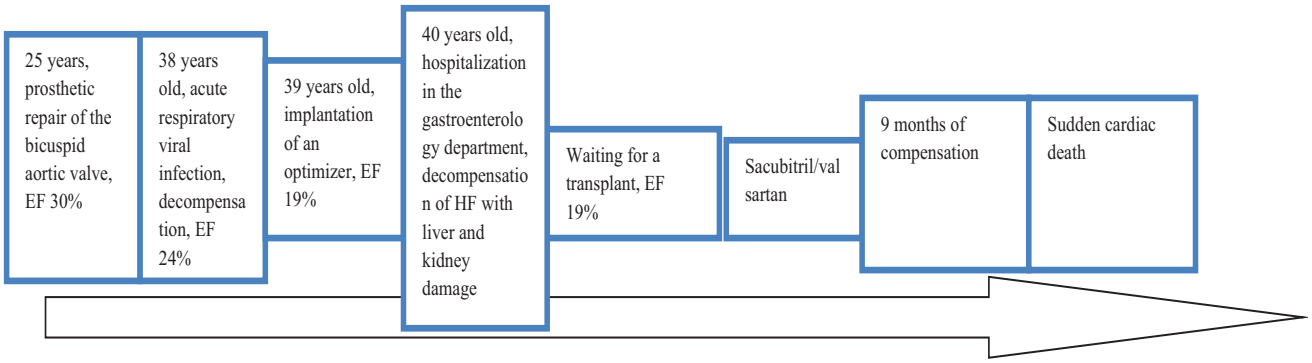


Figure 3. *Chronological sequence of the disease development*
Note: EF — ejection fraction

One month after this prescription, there was an improvement in general state, quality of life, increased exercise tolerance, regression of symptoms and signs of heart failure, and sPAP decreased to 53 mm Hg. Due to the decrease in blood pressure to 90/60 mm Hg, the dose of sacubitril/valsartan was reduced to 6.25 mg per day; the patient continued receiving carvedilol 6.25 mg per day, warfarin 4.375 mg per day under the control of INR, torasemide 20 mg per day, furosemide 120 mg per day; spironolactone was replaced with eplerenone 50 mg per day. A month later, hydrochlorothiazide 25 mg per day and acetazolamide 250 mg per day were added to therapy in order to achieve euvolemia. In the course of this treatment, HF was compensated, the patient started leading an active life, became in touch with friends and family and started tending to his garden.

Five months after starting sacubitril/valsartan, the transplantologist expressed doubts over the need for heart transplantation based on the clinical examination of the patient and the results of his clinical and biochemical tests. However, the patient remained on the waiting list for this intervention.

During nine months of treatment, the patient was stable, took care of himself, was in touch with his family, did chores and gardening. However, despite the ongoing therapy, the patient died suddenly (Fig. 3).

Discussion

Here is a case of HF progression in a patient after surgery for congenital heart disease (bicuspid aortic valve) during 16 years with a significant decrease in LV systolic function to 19% and increased FC.

The described clinical presentation was fully consistent with end-stage HF: the patient's state could not be stabilized, there were frequent episodes of HF decompensation that required four hospitalizations within 12 months despite treatment with ACE inhibitors, diuretics, MRAs.

Also, the patient tended to have arterial hypotension for a long time. Despite systolic blood pressure of less than 100 mm Hg, a drug from the ARNI group, sacubitril/valsartan, was prescribed as a "drug of last resort" at a minimum dose in order to improve the course of heart failure and the prognosis.

The effectiveness of sacubitril/valsartan in patients with HF was evaluated in the multicenter randomized phase III study PARADIGM-HF, which included 8,442 patients with HF II-IV FC and low LVEF that required no treatment with intravenous diuretics, with SBP above 100 mm Hg. Patients were randomized into groups taking enalapril 10 mg twice daily and sacubitril/valsartan 100 mg twice daily, with an increase to 200 mg twice daily. The study was terminated early due to a definite advantage of sacubitril/valsartan over the former drug of choice — enalapril — in the form of a 20% reduction in the relative risk of mortality and hospitalizations [1, 19].

The PIONEER-HF study demonstrated that the proportion of patients treated with ARNI and experiencing symptomatic hypotension was not significantly higher than in those treated with enalapril (15% vs 12.7%, $p = 0.95$). Switching from an ACE inhibitor to an ARNI had a significant beneficial effect on symptoms, morbidity and survival [1, 3].

Hypotension is an important factor limiting the titration of drugs for the treatment of HFrEF in routine practice [3]. There is evidence that sacubitril/valsartan has a modulating effect on blood pressure: it lowers BP in patients with initially high values and can increase it in patients with initially low BP [1]. Using sacubitril/valsartan for the treatment of patients with end-stage HF and severe hypotension was not studied in RCTs [19, 20]. In frail elderly patients, as well as in patients with systolic blood pressure of 100–110 mm Hg, an initial dose of ARNI 50 mg twice daily and slow titration (6–8 weeks) is recommended [3].

In this clinical case, despite indications for cardiac resynchronization therapy (CRT-D), the patient underwent implantation of a cardiac contractility modulation system. Five months later, instances of multiple organ failure increased, and LVEF did not increase.

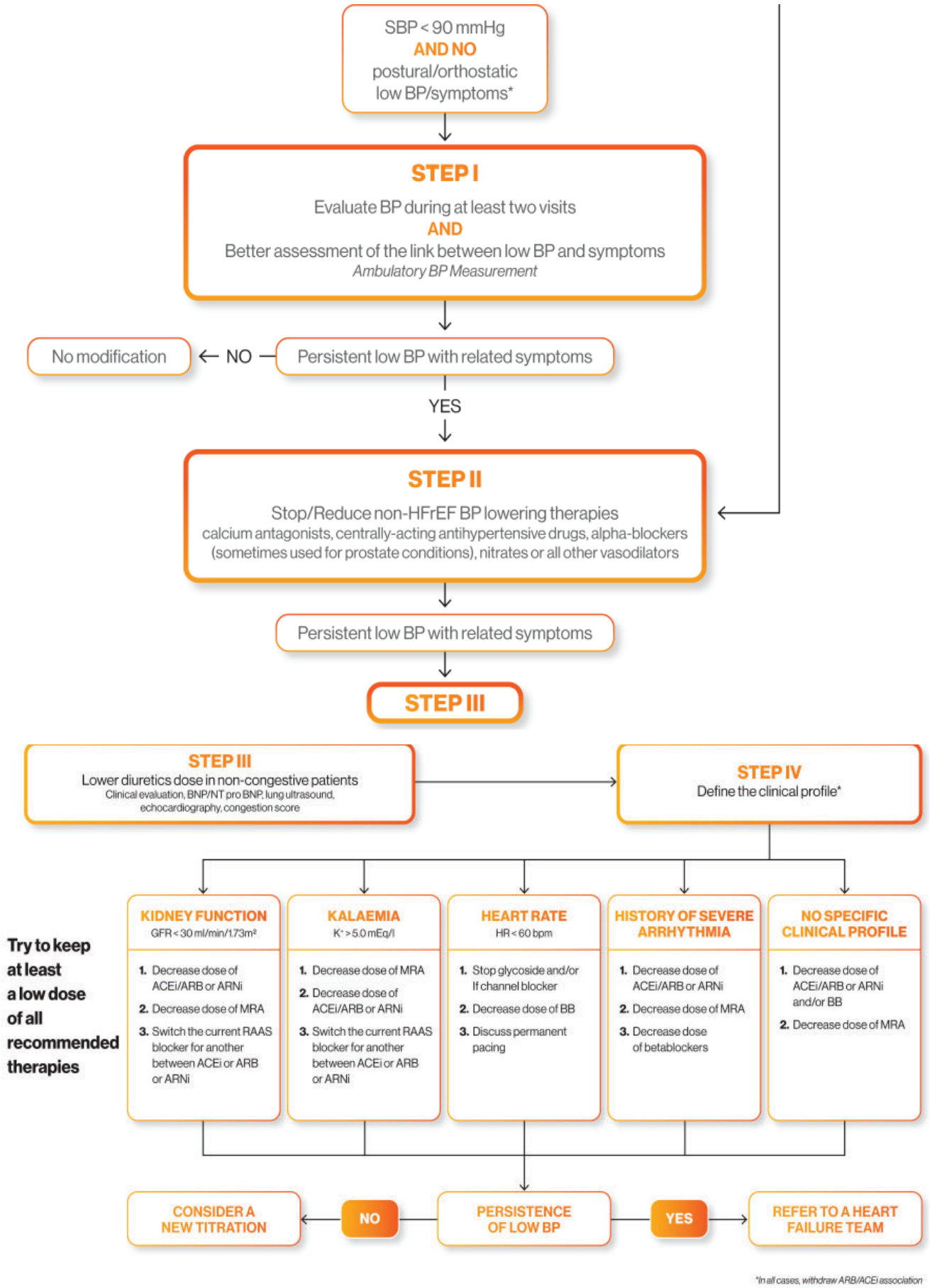


Figure 4. *Five–step algorithm for the management of patients with arterial hypotension [3]*

In this regard, the patient was on the waiting list for heart transplantation; the corresponding indication was end-stage HF (significant changes in hemodynamics and severe (irreversible) structural changes in target organs: heart, lungs, blood vessels, brain, kidneys).

The replacement of enalapril with sacubitril/valsartan in this case was a "treatment of last resort", which was prescribed despite the presence of arterial hypotension. Due to the "microdoses" (6.25 mg per day) of this agent, the patient's general state and quality of life improved; HF was compensated and hospitalizations for HF could be stopped. New oral inotropes, OM and vericiguat, were not recommended for this patient due to the unavailability of these agents in our country.

In 2020, the ESC working group developed a five-step algorithm for the drug treatment of patients with HFrEF in the presence of hypotension (Fig. 4). According to the algorithm, at the first stage, careful monitoring of BP and assessment of the relationship between low BP and clinical symptoms are recommended. At the second step, the discontinuation of several drugs in patients with HF and arterial hypotension, i.e. slow calcium channel blockers (SCCBs), alpha blockers, etc., taken for comorbid pathologies (glaucoma, benign prostatic hyperplasia, etc.) should be considered. At the third step, the dose of diuretics should be reduced. At the fourth step, dose reduction/withdrawal of the main groups of drugs for the treatment of CHF is considered depending on the clinical profile of the patient. For patients with GFR < 30 mL/min/1.73 m^2 and/or hyperkalemia, ACE inhibitors/ARA/ARNI/MRA should be discontinued. For patients with bradycardia, the BB, digoxin dose should be reduced/discontinued; the implantation of a pacemaker should be considered. At the fifth step, management of a patient should be discussed at a case conference [3].

There were no attempts to prescribe SGLPT2 inhibitors to the patient because, during the management of the patient, CHF was not indicated for them in our country.

Conclusion

Sacubitril/valsartan is the drug of choice for the treatment of patients with chronic HFrEF II-IV FC and should be used in combination with other agents (beta blockers, aldosterone antagonists) [1, 4, 21]. The discussed clinical case demonstrates the experience of prescribing sacubitril/valsartan for a patient with end-stage heart failure accompanied by severe arterial hypotension, which allowed to stabilize the patient's condition for nine months. In patients with failure of standard drug therapy for HF, careful dose titration of sacubitril/valsartan under close clinical and laboratory control may be performed; it may increase the chance of survival until surgery for patients on the waiting list for heart transplantation. RCTs should be conducted to investigate the possibility of prescribing low doses of sacubitril/valsartan for patients with hypotension associated with severe HF in order to reduce the severity of clinical symptoms and improve prognosis; this prescription can be performed simultaneously with new inotropes. Due to a large number of patients with arterial hypotension, the prescription of sacubitril/valsartan in low doses of 25, 12.5 and 6.25 mg is advisable.

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Резник Е.В. (ORCID ID: https://orcid.org/0000-0001-7479-418X): ведение пациента, идея представления клинического случая, предоставление материалов для написания, редактирование, утверждение текста рукописи

Бычкова М.С. (ORCID ID: https://orcid.org/0000–0002–3453–5914): написание рукописи текста, обзора литературы по теме

Author Contribution:

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

Reznik E.V. (ORCID ID: https://orcid.org/0000-0001-7479-418X): patient management, the idea of presenting a clinical case, providing materials for writing, editing, approving the text of the manuscript

Bychkova M.S. (ORCID ID: https://orcid.org/0000-0002-3453-5914): writing a manuscript of a text, a review of the literature on the topic

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О.Н. Денисов[1], Е.В. Ефремова*[2], А.А. Нафеев [3]

[1] — ГУЗ «Ульяновская областная клиническая больница», Ульяновск, Россия
[2] — ФГБОУ ВО «Ульяновский государственный университет», Ульяновск, Россия
[3] — ФБУЗ «Центр гигиены и эпидемиологии в Ульяновской области», Ульяновск, Россия

СЛУЧАЙ ПОЛНОЙ АВ-БЛОКАДЫ У ПАЦИЕНТА С КЛЕЩЕВЫМ БОРРЕЛИОЗОМ

O.N. Denisov[1], E.V. Efremova*[2], A.A. Nafeev[3]

[1] — Ulyanovsk Regional Clinical Hospital, Ulyanovsk, Russia
[2] — Ulyanovsk State University, Ulyanovsk, Russia
[3] — Center for Hygiene and Epidemiology in the Ulyanovsk Region, Ulyanovsk, Russia

A Case of Complete AV Blockade in Patient with Lyme Borreliosis

Резюме

Болезнь Лайма (клещевой боррелиоз) — инфекционное трансмиссивное природно-очаговое заболевание, имеющее наклонность к хроническому и рецидивирующему течению с преимущественным поражением кожи, нервной системы, опорно-двигательного аппарата и сердца. Миокардиальное повреждение проявляется, как правило, поражением проводящей системы в виде атриовентрикулярной блокады различной степени, внутрижелудочковой блокады, дисфункции синоатриального узла. При несвоевременной диагностике и отсутствии этиотропного лечения клещевого боррелиоза может возникнуть хронизация поражения проводящей системы сердца и потребоваться имплантация электрокардиостимулятора.

Ключевые слова: *болезнь Лайма, атриовентрикулярная блокада, клинический случай*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Lyme disease (tick-borne borreliosis) is an infectious vector-borne natural focal disease that tends to a chronic and recurrent course with a predominant damage to the skin, nervous system, musculoskeletal system and heart. Cardiac features is manifested, as a rule, by a involvement of the conducting system as varying degrees of atrioventricular block, Bundle–branch block, dysfunction of the sinoatrial node. In case of untimely diagnosis and etiotropic treatment of tick-borne borreliosis, chronic lesions of the cardiac conduction system may occurs and implantation of a pacemaker may be required.

Key words: *Lyme disease, atrioventricular block, clinical case*

Conflict of interests

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*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

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24h ECG — 24-Hour Holter monitoring, AV block — atrioventricular block, CPK — creatine phosphokinase, ECG — electrocardiography, EDD — end diastolic diameter, ESR — erythrocyte sedimentation rate, HR — heart rate, LDH — lactate dehydrogenase, LV — left ventricle, SA block — sinoatrial block, SHI — state health institution, TSH — thyroid stimulating hormone

Introduction

Lyme disease (tick-borne borreliosis, chronic erythema migrans) is an infectious vector-borne natural focal disease caused by gram-negative spirochetes of the Borrelia genus. Tick-borne borreliosis is characterized by predominant damage to the skin, nervous, cardiovascular and musculoskeletal systems [1, 2]. Not only Russia but the whole world has recently seen an increase in the incidence of Lyme disease [1–3].

Human infection is mostly the result of a bite by an infected ixodid tick (Ixodes persulcatus and Ixodes ricinus are of major epidemiological importance in our country) in the area of the neck, chest, armpits, inguinal folds, i.e. in areas with thin skin and abundant blood supply. In most cases, attachment to the human body goes unnoticed since tick saliva contains anesthetic, vasodilator and anticoagulant substances. A person starts feeling rawness and itching at the site of the bite in at least 6–12 hours. Early removal of ticks prevents human infection if there is an infection in the tick's gastrointestinal tract [2]. The causative agent of Lyme disease can be transmitted through tick feces when they come into contact with human skin. Cases of mechanical transmission during accidental crushing of ticks when removing them from animals, as well as the alimentary route — when drinking raw milk (primarily goat milk) or dairy products without heating — cannot be excluded [2, 3].

The causative agent migrates from the place of insertion with the flow of lymph and blood to internal organs, joints, lymph nodes, with possible involvement of meninges in the inflammatory process, and causes a cascade of immunopathological reactions. The causative agent can persist in the body for a long time (more than 10 years), mostly in the lymphatic system. Immunity in case of Lyme disease is non-sterile with possible re-infection after 5–7 years [1, 2]. Processes associated with the accumulation of specific immune complexes in the synovial membrane of the joints, dermis, kidneys, myocardium are critical in the pathogenesis of tick-borne borreliosis.

Today, 0.3% to 4% of Lyme disease cases develop with cardiac involvement, and its incidence in children can be as high as 30% [3, 4]. Myocardial damage usually manifests as damage to the conducting system in the form of atrioventricular (AV) block of different grades (in 49% of cases — grade 3 AV block), intraventricular block, dysfunction of the sinoatrial node, extended QT interval and nonspecific changes in the T wave. Myocarditis and pericarditis in Lyme disease are much less common [3–6].

In actual clinical practice, delayed organ damage in case of Lyme disease requires vigilance and differential diagnosis. We present a description of a clinical case of a patient with a newly diagnosed complete AV block, which was a manifestation of myocardial damage with Lyme disease.

Description of Clinical Case

Patient Sh., male, 24, was admitted on August 05, 2019 to the Department of Cardiac Surgery and Heart Rhythm Disorders of the Ulyanovsk Regional Clinical Hospital (URCH) with complaints of weakness, dizziness and syncope attacks. According to the history, from August 01, 2019, the patient noted dyspnea and rare pulse up to 34 bpm, headache, syncope — twice, vomiting and discomfort in the epigastric region, episodes of severe dizziness. With these complaints, the patient visited the State Healthcare Institution "Cherdaklinskaya Central District Hospital", where an electrocardiographic (ECG) study revealed complete AV block, and the patient was transferred to the URCH. The epidemiological history indicates a tick bite in May 2018 in the patient's area of residence (Cherdaklinsky district), which was found by chance during self-examination. The patient did not seek medical assistance; the tick was not sent for testing for Borrelia infection; the patient did not notice the development of erythema and fever.

Upon admission of patient Sh., examination revealed pale annular erythema on the skin of the right side of the abdomen (5 cm in diameter) and on the right forearm (6 cm in diameter) (Fig. 1). Lymph nodes were not palpable. Vesicular breathing in lungs, no rales. Respiratory rate 18 per minute. Heart tones were muffled, heart rate (HR) — 40 per minute, blood pressure — 130 and 80 mm Hg on both arms. Abdomen was soft and painless during palpation. No peripheral edema.

Complete blood count on August 05, 2019: hemoglobin — 134 g/L, RBC — 4.7×10^{12}/L, WBC — 9.2×10^{9}/L (neutrophils — 60.6%, lymphocytes — 25.6%, monocytes — 12.2%, eosinophils — 1.2%, basophils — 0.4%), platelets — 185×10^{9}/L, ESR — 34 mm/h (due to the ongoing infectious process). Blood biochemical test on August 05, 2019: total protein — 65 g/L, albumin — 36 g/L, urea — 4.8 mmol/L, creatinine — 86.1 μmol/L, alanine aminotransferase — 95 IU/L (more than two upper limits of the norm (< 41 IU/L) is not diagnostically significant), total bilirubin — 13 μmol/L, glucose — 4.84 mmol/L, total cholesterol — 3.72 mmol/L, potassium — 4.4 mmol/L, sodium — 140 mmol/L, lactate dehydrogenase (LDH) — 227 U/L (130–235 U/L), creatine kinase (CPK) — 94.7 U/L (24–195 U/L), CPK-MB — 8.5 U/L (< 171 U/L), troponin — negative. Coagulogram revealed no abnormalities: prothrombin time — 10.7 seconds, activated partial thromboplastin time — 35.7 s, international normalized ratio — 0.95, fibrinogen — 1.5 g/L.

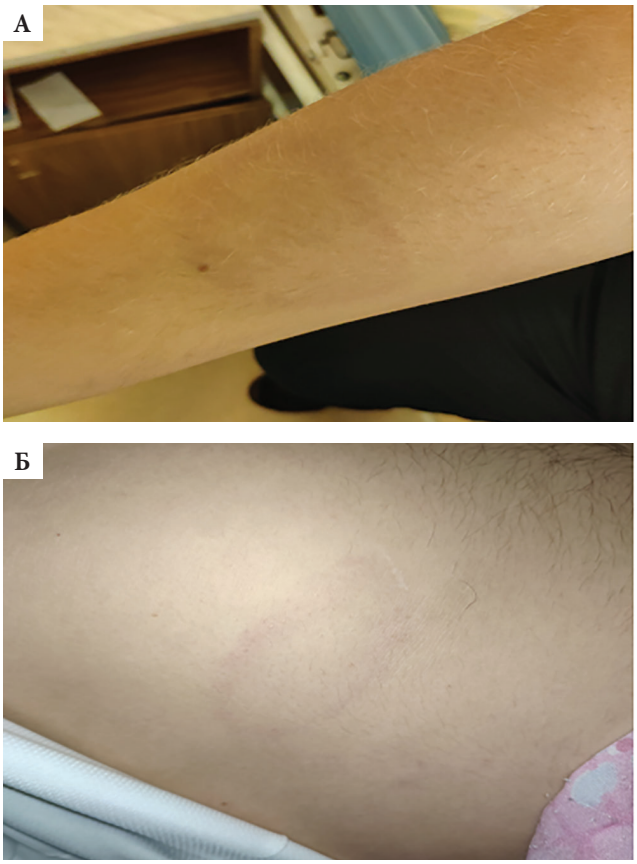

Figure 1. *Annular erythema (А — in the skin of the right forearm, Б — in the skin of the abdomen)*

Blood test for thyroid hormones on July 01, 2019 revealed no abnormalities: thyroid stimulating hormone (TSH) — 1.07 μIU/L (0.3–4.2 μIU/mL), free thyroxine (T4) — 14.93 pmol/L (10.8–22.0 pmol/L).

Test for C-reactive protein on August 05, 2019 showed an increase up to 24 mg/mL in connection with an infectious process. During treatment, C-reactive protein subsequently decreased to 5 mg/mL on August 13, 2019.

No antibodies to human immunodeficiency virus, total antibodies to hepatitis C virus (anti-HCV), hepatitis B virus surface antigen (HBs Ag) were found in the samples on August 06, 2019.

Blood serum test for antibodies to tick-borne borreliosis (Borrelia burgdorferi) on August 09, 2019 revealed positive titers of Ig G — 2.142 U/L and Ig M — 3.223 U/L (reference range of positive results — more than 1.11 U/L).

According to echocardiography results on August 05, 2019, no pathology was found: heart valves without changes, mean pulmonary arterial pressure — 15.7 mm Hg, diameter of ascending aorta — 28 mm, end diastolic diameter of the left ventricle (LV EDD) — 58 mm, LV posterior wall — 8 mm, interventricular septum — 8 mm, LV ejection fraction — 74%; pericardium without changes; local contractility is not impaired.

An ultrasound examination of abdominal organs and kidneys on August 05, 2019 revealed an enlarged liver due to the right lobe — 172 mm, left lobe — 62 mm; the structure was fine-grained, irregular echogenicity, a calcification up to 1 mm in segment 8; portal vein was not dilated. Gallbladder, pancreas, spleen, kidneys within normal.

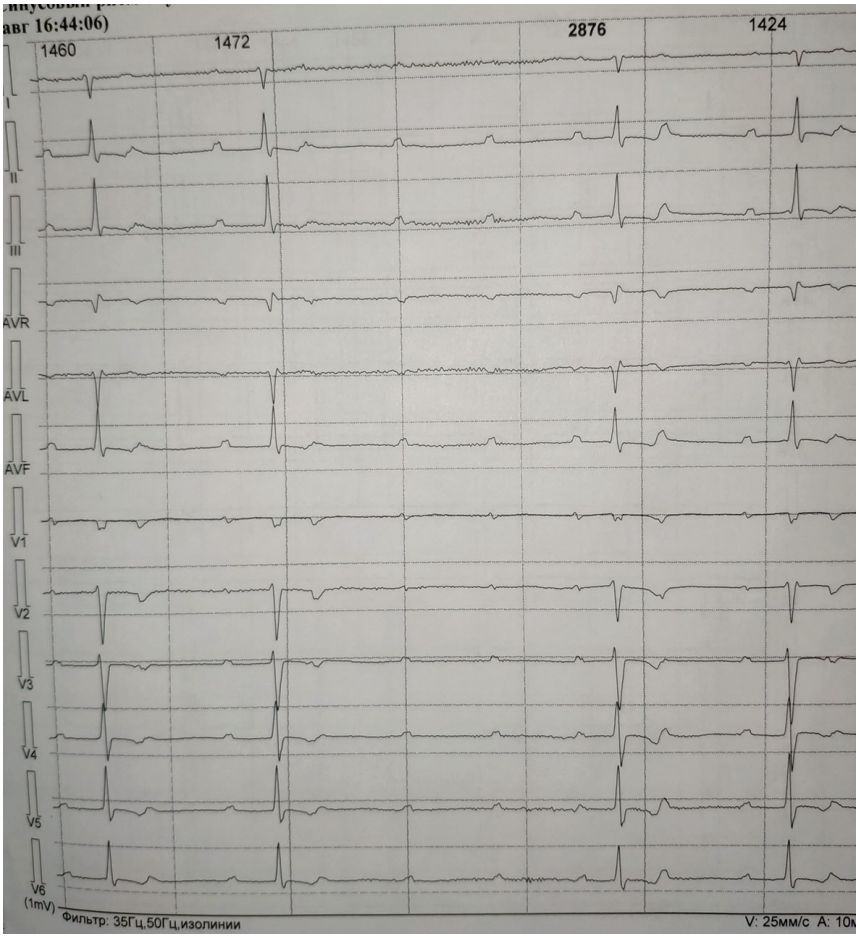

Figure 2. *Results of 24-hour ECG monitoring (08.05.2019). Sinus rhythm with complete AV block was observed with an average heart rate of 44 beats / min. (from 28 to 73 beats / min.) during the monitoring*

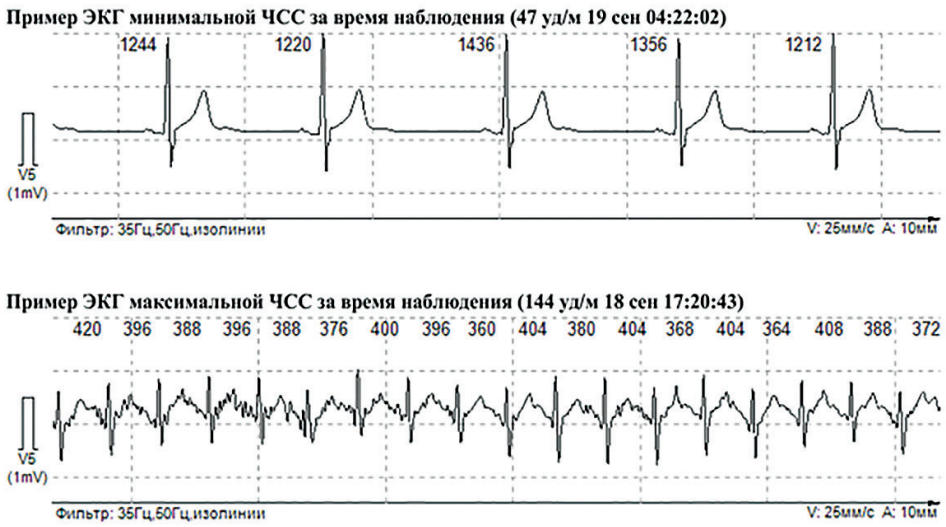

Figure 3. *Results of 24-hour ECG monitoring (19.09.2019). Sinus rhythm was observed with an average heart rate of 77 beats / min. during the day (52-144), at night 54 beats / min (47-75)*

Holter ECG monitoring (24h ECG) on August 05, 2019 showed that average HR during daytime was 44 bpm, at night — 45 bpm. Circadian index (CI) — 98%, decreased (< 120%), indicating "rigid rhythm". Minimum HR was 25 bpm while awake. During monitoring, sinus rhythm with complete AV block with average HR of 44 bpm was observed (28–73 bpm). A non-pathological number of ventricular extrasystoles was registered. There were 392 pauses with RR interval duration of up to 2.9 s. Average corrected QT interval per day was 416 ms (322–517 ms). No significantly prolonged corrected QT interval was registered (Fig. 2).

Follow-up 24h ECG on August 15, 2019 revealed sinus rhythm, average HR during daytime was 60 bpm (43–120), average HR at night was 45 bpm (39–66). 15 single ventricular extrasystoles, 26 single atrial extrasystoles, 4 paired atrial extrasystoles and 4 group atrial extrasystoles were registered. Maximum pause due to grade 2 sinoatrial (SA) block at night was 2,092 ms. During monitoring, grade 1 AV block was registered, maximum PQ interval was 232 ms during daytime and 212 ms at night.

The patient was examined by an infectious disease specialist (September 10, 2019); based on the complaints, history, examination data, laboratory tests and instrumental examinations, the clinical diagnosis of Lyme disease (tick-borne borreliosis) was established. Cardiac type, chronic recurrent course. Transient complete AV block with syncopal conditions. In accordance with the clinical guidelines [1], treatment with antibacterial agents (locally-manufactured doxycycline, 200 mg/day, 14 days) was prescribed.

During treatment, positive changes were registered: 24h ECG in a month revealed full restoration of AV conduction.

Follow-up outpatient 24h ECG on September 19, 2019 revealed sinus rhythm, average HR during daytime was 77 bpm (52–144), average HR at night was 54 bpm (47–75). There were 52 single ventricular extrasystoles, 1 paired monomorphic ventricular extrasystole, 5 single atrial extrasystoles, 4 pauses due to grade 2 SA blockade at night, maximum pause was 1,620 ms (Fig. 3).

In accordance with the clinical guidelines, the patient has been undergoing follow-up by an infectious disease specialist and general practitioner in the local clinic for three years.

Discussion

First manifestations of Lyme disease may develop several months or even years after infection when clinical signs and patterns typical for chronic infection are observed [1]. In the presented clinical case, organ damage appeared four months after the tick bite.

Diagnosis of Lyme disease can be considered justified in the presence of epidemiological data (being in an endemic region in the spring-summer period, the fact of a tick bite, duration of incubation period), migratory erythema around the tick bite, as well as features of the clinical presentation and development changes that are typical for this disease [1, 2]. Due to the significant clinical polymorphism and a significant percentage of non-erythema forms (46.4%) [7], the final diagnosis should be confirmed by immunological and/or molecular genetic tests [8]. Enzyme-linked immunosorbent assay is the method most widely used in clinical practice. It allows determining IgM and IgG antibodies to tick-borne borreliosis (in blood serum, cerebrospinal fluid, intraarticular fluid) [1, 2].

The patient in the described clinical case had an epidemiological history; on examination, annular erythema was observed; there were symptoms of myocardial damage in the form of conduction disorders. The diagnosis was also confirmed by a laboratory test — positive titers of antibodies to tick-borne borreliosis

Cardiac damage in case of Lyme disease in the form of AV block is usually reversible; the normal function of the conducting system is restored within a few days (up to a week) [9]. However, in case of late diagnosis and without etiotropic treatment, the process may become chronic, and damage to the cardiac conduction system may progress rapidly and require intensive treatment [4–6].

Etiotropic treatment for Lyme disease includes antibiotic therapy (tetracyclines, penicillins, cephalosporins) [1]. The earliest possible administration of agents is required to achieve maximum efficacy and prevent organ damage. In the chronic form of disease, repeated courses of antibiotic therapy are recommended [1, 10].

Differential diagnosis of the causes of AV block and antibiotic therapy in the presented clinical case prevented pacemaker implantation, which is often (up to 30%) required in the absence of timely etiotropic treatment for Lyme disease [4, 5, 11]. Attention should be given to the development of a scale that makes it possible to suspect "Lyme carditis" — The Suspicious Index in Lyme Carditis (SILC) score, which includes "constitutional symptoms" (fever, weakness, arthralgia, dyspnea), epidemiological history (being in an endemic region, tick bite), male gender, age under 50, presence of erythema migrans. According to the SILC, a serologic test for Lyme disease is performed at moderate to high risk, as well as empiric antibiotic therapy [4].

If there is organ damage, the follow-up of patients with confirmed tick-borne borreliosis should be carried out once every three months during the first year, once every four months during the second year and once every six months during the third year. According to clinical indications, consultations of specialist physicians or instrumental examination of patients should be performed [1]. In this case, considering Lyme disease of the cardiac type, the patient was recommended to undergo follow-up once every three months.

Conclusion

The presented clinical case demonstrates the need for the clinician's vigilance in diagnosing delayed organ damage in Lyme disease. The established diagnosis and treatment performed made it possible to avoid the implantation of a pacemaker in a young patient with Lyme disease of the cardiac type. However, considering the chronicity of this disease, follow-up is required.

Вклад авторов:

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Денисов О.Н. (ORCID ID: https://orcid.org/0000-0003-2216-5490): дизайн, написание, редактирование текста и утверждение финального варианта статьи

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

Нафеев А.А. (ORCID ID: https://orcid.org/0000-0003-3113-6018): 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

Denisov O.N. (ORCID ID: https://orcid.org/0000-0003-2216-5490): design, writing, editing of the text and approval of the final version of the article

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

Nafeev A.A. (ORCID ID: https://orcid.org/0000-0003-3113-6018): writing, editing the text and approval of the final version of the article

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