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СОДЕРЖАНИЕ

С 2016 ГОДА СТАТЬИ В ЖУРНАЛ ПРИНИМАЮТСЯ ЧЕРЕЗ РЕДАКЦИОННУЮ ПЛАТФОРМУ:
http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

НОВЫЕ ПРАВИЛА ПУБЛИКАЦИИ АВТОРСКИХ МАТЕРИАЛОВ (2019):
http://www.medarhive.ru/jour/about/submissions#authorGuidelines

CONTENT

SINCE 2016, ARTICLES IN THE JOURNAL HAVE BEEN ACCEPTED THROUGH THE EDITORIAL PLATFORM:

http://www.medarhive.ru/jour/about/submissions#onlineSubmissions

NEW GUIDELINES OF PUBLICATION FOR AUTHORS OF ARTICLES (2019):

http://www.medarhive.ru/jour/about/submissions#authorGuidelines

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ПРОФЕССОР КУДРЕВЕЦКИЙ ВАСИЛИЙ ВАСИЛЬЕВИЧ — МАЛОИЗВЕСТНЫЕ ФАКТЫ БИОГРАФИИ

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Rostov State Medical University, Internal Medicine Department № 1, Rostov-on-Don, Russia

Professor Kudrevetski Vasily Vasilievich — Little Known Biography Facts

Резюме

Кудревецкий Василий Васильевич (1859-1937? гг.) — терапевт, доктор медицины, профессор, действительный статский советник. Профессиональная деятельность ученого была связана с Императорским Варшавским университетом, в котором он заведовал кафедрой факультетской терапевтической клиники (1895 по 1910 гг.), был деканом медицинского факультета и исполнял обязанности ректора (1909-1910 гг.).

Профессор Кудревецкий В.В. был учеником выдающегося ученого, академика Павлова И.П. Под его руководством в небольшой лаборатории клиники проф. С.П. Боткина они проводили первые фундаментальные исследования и экспериментальные работы, посвященные физиологии пищеварения. Накопленный опыт по этой теме позволил Кудревецкому в 1890 году защитить докторскую диссертацию, научным консультантом которой выступил сам Иван Петрович.

Результаты фундаментальных работ Кудревецкого В.В. легли в основу научных представлений о физиологии пищеварительной системы и не потеряли своей актуальности сегодня.

Ключевые слова: *Кудревецкий Василий Васильевич, Императорский Варшавский университет*

Конфликт интересов

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

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Abstract

The scientist's professional activities were associated with the Imperial University of Warsaw, where he headed the department of the faculty therapeutic clinic (1895-1910), was the dean of the medical faculty and acting as the rector (1909-1910).

Professor Kudrevetski V.V. was a scholar of an outstanding scientist, academician Pavlov I.P. Under his leadership in a small laboratory of the prof. S.P. Botkin clinic, they carried out the first fundamental research and experimental work on the physiology of digestion. The accumulated experience on this topic allowed Kudrevetski to defend his doctoral dissertation in 1890, the scientific consultant of which was Ivan Petrovich himself.

The results of fundamental works of V.V. Kudrevetski formed the basis of scientific ideas about the physiology of the digestive system and have not lost their relevance today.

Key words: *Kudrevetski Vasily Vasilievich, Imperial University of Warsaw*

Conflict of interests

The authors declare no conflict of interests

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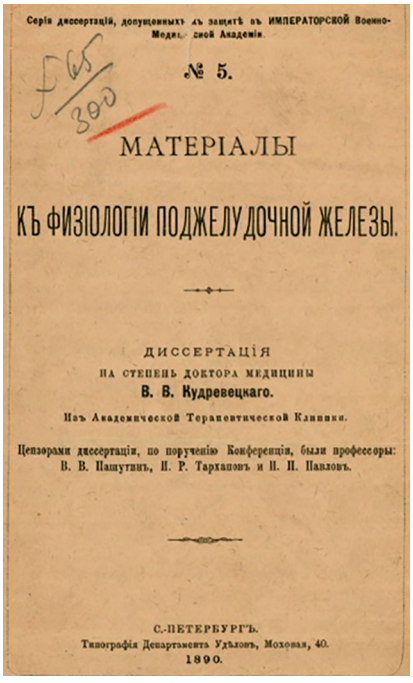
Vasily Vasilievich Kudrevetsky, the son of a priest, was born on January 21, 1859, in the village of Pochep, Chernihiv Region [2]. His path towards medicine turned out to be «tortuous and thorny». He got his secondary education at the Chernihiv Theological Seminary.

Figure 1. *Prof. Kudrevetski V.V. (1897)*

Having shown high learning abilities, after 4th grade, in 1878, he enrolled at the Imperial Novorossiysk University in Odessa, where he graduated from the Natural Sciences Department of the Faculty of Physics and Mathematics as a Candidate of Science in 1882 [3]. Then for two years, he attended lectures at the Mathematics Department of the same faculty. In his 2nd year, he moved to the Imperial Military Medical Academy (St. Petersburg). It was only in January 1885 that he enrolled as a 3rd-year student.

From that point, the search for his calling was complete. Student Vasily had chosen medicine. Despite his young age, at the age of 26, he had a broad outlook. He was an outstanding personality and had oratory skills. In 1887, Kudrevetsky graduated with a physician's degree with honors. After winning a competition, he was honored to remain at the Academy to undergo three-year advanced training [4]. To this end, he was assigned to the service as a physician at the Clinical Military Hospital and the resident physician at the therapeutic («Botkin») clinic, which was then headed by prof. L. V. Popov [5]. Without putting his clinical work on hold, Vasily Vasilievich worked on his dissertation titled «Materials on the Physiology of the Pancreas», which he submitted for defense on November 10, 1890. This work was written under the guidance of future Nobel Prize winner, world-famous scientist, Academician I. P. Pavlov. In the concluding remarks, Kudrevetsky noted: «This study was carried out by me at the suggestion and under the guidance of the highly respected Professor Ivan Petrovich Pavlov, whom I sincerely thank for all his work and the warm attention that he paid me in carrying out this work» [6].

Vasily Vasilievich was the first to quantify «fat and starch enzymes» in pancreatic juice, studied the effect of solar plexus extirpation on the secretory function of the pancreas, proved (using a degeneration method) the presence of secretory fibers in the sympathetic nerve, and suggested the presence of fibers that delay pancreatic secretion. Kudrevetsky's experimental work revealed that direct nerve irritation during vivisection caused the secretion of pancreatic juice, which was significantly rich in solid substances and enzymes compared with juice obtained in dogs with a constant fistula of the pancreatic duct in a chronic experiment. He also noted that protein enzyme can be contained in the active form in the «nerve» juice [7]. These experimental data laid the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МАТЕРІАЛЫ

КЪ ФИЗІОЛОГІИ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ.

ДИССЕРТАЦІЯ
НА СТЕПЕНЬ ДОКТОРА МЕДИЦИНЫ
В. В. Кудревецкаго.
Изъ Академической Терапевтической Клиники.

Цензорами диссертаціи, по порученію Конференціи, были профессоры: В. В. Пашутинъ, И. Р. Тархановъ и И. П. Павловъ.

С.-ПЕТЕРБУРГЪ.
Типографія Департамента Удѣловъ, Моховая, 40.
1890.

Figure 2. *A copy of the cover of V.V. Kudrevetski's dissertation (1890*

groundwork for future research in this area and formed the basis of modern scientific ideas about the physiology of the digestive system.

Vasily Vasilievich always spoke warmly of his teacher. To this day, the records of his work with Academician I. P. Pavlov at the S. P. Botkin Clinic have been kept, which were published on the 150th anniversary of his birth.

«I remember Ivan Petrovich, like all his many students, with a feeling of deep admiration and gratitude. I was lucky to work under the guidance of Pavlov in the initial period of his research on the physiology of digestion. This was almost 50 years ago, when Ivan Petrovich worked in the modest laboratory of the Prof. Botkin Clinic. It was a small two-roomed wooden house that was located in a separate part of the clinic's garden. Both the house itself and the whole atmosphere were extremely modest. For example, a «thermostat» designed by Ivan Petrovich himself was made of a sardine tin box attached to an iron rack and heated by a small kerosene lamp. Many of his works on the physiology of digestion were conducted in this laboratory. This laboratory was intended for the experimental development of clinical, mainly pharmacological, topics proposed by S. P. Botkin to his residents, which allowed Ivan Petrovich to carry out such work. The resident who received the task turned for help and guidance to the actual chief of the laboratory — Ivan Petrovich, who usually did not refuse such requests. Not only that, if he became interested in the subject, he would work on it with his enormous enthusiasm, devoting a lot of effort and time to such work. Sometimes, he would even develop a special new technique for a particular case. All this resulted in substantial research papers published as dissertations for the Doctor of Medicine degree. Thanks to this confluence of circumstances, Pavlov, the physiologist, acquired the reputation of an outstanding experimenting pharmacologist. When there was a vacancy at the Department of Pharmacology at the Military Medical Academy, he was offered the position. He remained in this department for five years before moving to the Department of Physiology» [9].

Prof. Kudrevetsky noted that in some of these dissertations — when they appeared in print — it was not sufficiently emphasized that Ivan Petrovich was their main inspirer and leader. «It turned out to be the expropriation of his merits in some way as we, his students, told him with indignation. But Ivan Petrovich answered with warmth, «This is all not important, the main thing is that the truth be found». And he showed such unworldly self-forgetfulness in his further scientific work. He was the same with respect to all kinds of worldly benefits.

«Although many years have passed since then, I vividly recall both the general picture and small episodes of the work that was taking place in this small laboratory. In the morning, at a certain hour, we (only three of us regularly worked at that time) are already in our places; each of us has his own task for this day, we are waiting for Ivan Petrovich. But he did not keep us waiting for long. He comes, after a long way with his quick energetic gait (he lived far from the laboratory), cheerful and friendly. Before starting the next work, he tells us his thoughts on the results of recent experiments, and always listens carefully to our opinions; sometimes even a dispute arises over a particular issue. This manner of discussing all the material obtained in the laboratory, with his students as with employees, created a particularly pleasant atmosphere. We had «secular» talks in our minutes of leisure, but it was obvious that he was of little interest in it, although he was sometimes witty, and laughed merrily», recalled Vasily Vasilievich.

Despite being easy to talk to, when it came to work, Academician I. P. Pavlov was strict and demanding of his students, caused them a lot of grief, for example, when asked to repeat each experiment many times. Pavlov taught that we should strive to ensure that the physiological experiment is reproduced with the same constancy and accuracy as any physical experiment and that only then could we validate the conclusion.

«Ivan Petrovich brought great excitement to the work in the laboratory with his particular enthusiasm and even fervor, with which he dealt with the questions he posed. This was especially noticeable when a new fact was outlined in a particular experiment. And in the cycle of his research of many new things, this was a frequent occurrence. If one of his students stayed in the laboratory until late at night to finish studies on a particular digestive juice obtained during another experiment, Ivan Petrovich came to the laboratory at night to find out the final results of the experiment, without waiting until morning» [9].

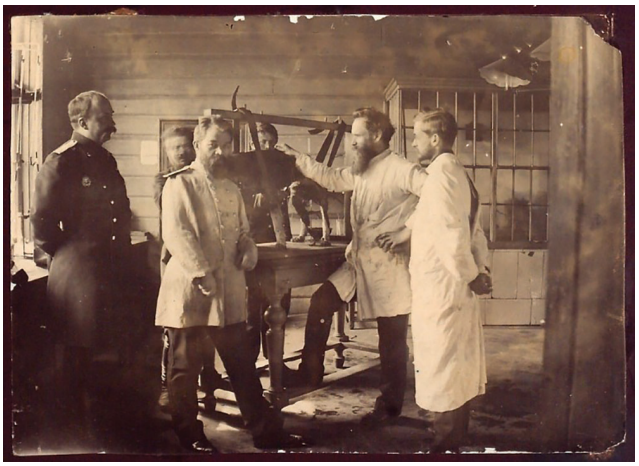


Figure 3. *In the laboratory of Professor S.P. Botkin (1880s). From left to right: Professors Smirnov G.A., Kudrevetski V.V., Pavlov I.P. and Verkhovsky B.V.*

Figure 4. *«Laboratory at the Villiers Clinic, 1889th year. E.O. Shumova-Simanovskaya, I. Pavlov, V. Kudrevetski and N. Ketcherg. My first great independent school», — written on the back of the photo by the hand of Ivan Petrovich [8]*

Ivan Petrovich demonstrated such enthusiasm for work by willingly sharing his laboratory experience with anyone, even if the person was not from his laboratory. One little-known story can serve as an example of his enthusiasm for work and an intense desire to interest others with something that was interesting to him. Once Ivan Petrovich organized a competition for the best prediction of the results of an experiment on how the infusion of alkaline solution into a dog's stomach would affect the separation of hydrochloric acid. To do this, he sent a sheet to all laboratories of the Institute of Experimental Medicine, and each participant also contributed 20 kopecks. Vasily Vasilievich wrote that «it turned out to be an extremely interesting and fun contest, with all chiefs of all laboratories and their students as participants». He also recalled how everyone who visited the laboratory had tea at break time. «Tea was brewed in a glass flask and served to guests in large beakers, and glass rods that were used in chemical experiments were used for stirring» [9].

Such a working and simultaneously friendly environment created by Academician I. P. Pavlov in his laboratories had a beneficial effect on the young scientists, who were making their first steps in research.

After defending his dissertation, Vasily Vasilievich worked as an intern in the same therapeutic clinic. For special success in his training, in 1891, he was sent for an internship abroad «for scientific purposes». At that time, it was a mandatory condition of the Conference of the Imperial Military Medical Academy for a professorship presentation. Visiting the laboratories of famous European medical scientists of that time, Kudrevetsky acquired state-of-the-art knowledge, added to his scientific and clinical experience, and established new professional contacts [10].

Figure 5. *Group of the first residents of the Institute of Experimental Medicine. Top row 2nd from the left A.N. Mokeev; middle row: in the center of acad. I.P. Pavlov, 2nd from left — G.S. Shubenko, 1st from the right — Kudrevetski V.V., 3rd from the right — Shumova-Simanovskaya E.O.; bottom row — in the center — Dolinsky I.L. (1893)*

Figure 6. *Photo collage dedicated to the activities of the Russian Medical Society at the University of Warsaw. Above — a photo of the next meeting of the society, below — a photo of the chairman of the society — prof. Kudrevetski V.V., as well as works published by members of the society (1913)*

In those years, issues of diagnosis and management of infectious diseases and vaccinations were especially relevant, which we can see from his research papers. After the internship, he published «Über Tuberkulose des Pankreas» (translated from German: «On Pancreatic Tuberculosis», 1892), «Zur Lehre von der durch Wirbelsäulentumoren bedingten Compressionserkrankung des Rückenmarkes» (translated from German: «On the theory of spinal cord compression disease caused by spinal tumors», 1892), «Recherches experimentales sur l'immunization contre la diphtérie» (translated from French: «Experimental studies on immunization against diphtheria», 1893), etc.

However, success in his homeland did not keep him waiting for long, and he was soon awarded the title of privat-docent at the Military Medical Academy of Internal Medicine, and then that of professor. By the Highest Order for the Civil Department (April 21, 1895), he was appointed, first, an extraordinary professor, and then (December 4, 1899) an ordinary professor at the Imperial University of Warsaw at the Department of Therapeutic Clinic [11, 12].

He highly appreciated the trust of the medical faculty and set to work with great enthusiasm. In those years, the department received new equipment that allowed to conduct not only clinical but also research work and experiments. The department was located at the Holy Spirit Hospital in Warsaw. In a report on the faculty clinic for the year 1900, the professor reported giving lectures to students, conducting practical classes, 2841 outpatients and 844 inpatients treated on 50 beds by the department staff [13].

The educational process at the department was inextricably linked with clinical work and was built on «patient-book-patient» principle. Each student in the clinic monitored his patient (from 3 to 5 during the year). He had to examine the patient daily and monitor the course of the disease, treatment prescribed, keep medical history and then report about it. This monitoring was conducted under the guidance and control of resident physicians and professors. Once a week, the professor himself with the students of the whole clinic did a round; each student reported his observations for the week, and the students discussed the most interesting clinical

cases. Students were also divided into groups, and in the evening, arranged rounds in the clinic with resident physicians. This approach, along with clinical lectures, allowed students to monitor everything that happened in the hospital throughout the year and contributed to the formation of clinical thinking, and gradually accustomed them to independent practice [14]. In the clinical laboratory, students conducted various chemical, microscopic and bacteriological studies required for the diagnosis of diseases of patients monitored by each student. During their training, they got acquainted with all the methods of clinical research and put these skills to practice when learning the subject. Students were actively involved in the study of outpatients and practiced collecting medical history and complaints, examination and physical examination under the supervision of resident physicians, and once a week — of the professor. They also attended clinical autopsies, where they compared the pathological findings they found with the intravital symptoms and manifestations of diseases they had previously observed in the hospital [15].

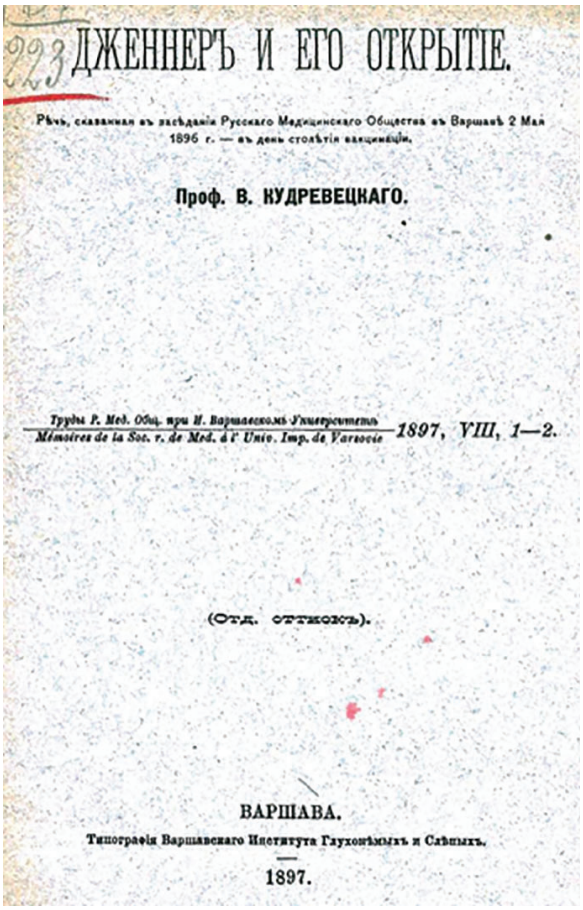
During the summer vacation period from 1900 to 1908, Vasily Vasilievich annually traveled abroad «for scientific purposes», where he spent a lot of time in clinics and laboratories, expanding his scientific horizons and speaking at scientific forums. He continued to develop topics on immunization against diphtheria, smallpox. He studied the management of tuberculosis and implemented the results of his work and observations into hospital practice.

While conducting his primary job, Vasily Vasilievich was also involved in social work. In 1896, he was elected by the Warsaw City Council as a member of the commission to conduct competitive tests for the position of resident physician at the Jesus Child Hospital. According to the University Council election, in 1902, he was approved as a judge of the professorial disciplinary court by the Trustee of the Warsaw School District. From 1905, he served as the dean of the Faculty of Medicine for five years. And from 1906, he actively participated in the work of the Russian Medical Society at the university, first as a fellow chairman and then chairman [16]. Vasily Vasilievich was heavily involved in drawing up the agenda of the meetings. He argued that the topics discussed should match urgent issues facing medical science of that time. Thanks to his work, the Russian Medical Society united physicians of various specialties, shared current knowledge in internal medicine, and also developed measures for the management and prevention of diseases.

The authority of Prof. Kudrevetsky was unquestioned. He spoke convincingly and in a well-argued manner. He had good erudition and experience, a unique scientific and clinical mind. He was an excellent organizer.

From 1894 to 1910, Vasily Vasilievich was promoted to the civil rank, starting with a college assessor and ending with an active state councilor. The ranking table introduced by Peter the Great in 1722 defined only 14 classes of civil servants, where the position of the active state councilor corresponded to the civil rank of class 4. Employees of this level were to be addressed as «Your Excellency!» At the same time, this title gave an important advantage — the right to hereditary nobility. Active state councilors could have senior management positions, which enabled Prof. Kudrevetsky to head a large structural unit, for example, a university.

In pre-revolutionary Russia, all job transfers were recorded in a special document — an official list that was the prototype of the modern-day employment record book. The professor's list indicated that on January 10, 1909, he was approved by the Minister of Public Education as «Acting Rector of the University of Warsaw» [4]. Such an appointment was recognition of his merits and a sign of high confidence from colleagues and the Ministry.



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ВАРШАВА.
Типографія Варшавскаго Института Глухонѣмыхъ и Слѣпыхъ.
1897.

Figure 7. *Speech by prof. Kudrevetski V.V., dedicated to the 100th anniversary of the use of the first vaccine against smallpox, developed by the English physician Edward Jenner (meeting of the Russian Medical Society in Warsaw, 1896)*

However, this fact did not become critical in the future life of the scientist. In 1909, Prof. Kudrevetsky was 50 years old, which allowed him to resign from service and retire. And, «according to his petition dated December 31, 1910, by the Highest Order for the Civil Department, he was dismissed and had the right to wear the uniform of an ordinary professor» [17]. This was the last official entry in the document on his working activity that summarized his professional career.

He handed over the reins of the university to the dean of the Law Department, Professor Ivan Nikolayevich Trepitsyn. His department was then headed by Professor Alexander Iosifovich Ignatovsky, a young but serious scientist who had already achieved significant success in research [18]. Due to the outbreak of the First World War, A. I. Ignatovsky had to organize the evacuation of the department from Warsaw to Rostov-on-Don and its subsequent establishment at the Nikolayev City Hospital [19, 20]. But this is another story.

Prof. Kudrevetsky remained chairman of the Russian Medical Society in Warsaw for several years. We do not know the reason for his early retirement, whether it is poor health, political motives, or, maybe, other plans. It remains a mystery. In the book by D. G. Kvasov (1967), it appears that before the occupation of Warsaw by German troops in 1915, Prof. Kudrevetsky had no time to leave with the university. And after the revolution, he lived in Zagreb (Yugoslavia), from where he wrote letters to Russia, to his teacher, Academician I. P. Pavlov [7]. Then he continued his career as a senior physician and teacher in the Don Cadet Corps, which was evacuated from Novorossiysk to Egypt at the end of 1921 [21]. Unfortunately, we could not find any other information regarding his life and professional activity after that.

For his impeccable civil service and personal contribution to the development of the Russian Empire in 1896, Vasily Vasilyevich was awarded the Highest Decree «silver medal for wearing on his chest on the Alexander ribbon» in memory of the reign of Emperor Alexander III. He was also the Knight of the Order of St. Anne grade 3 (1900), St. Stanislav grade 3. (1904), St. Anne grade 2. (1907).

The exact date of his death is not known. However, his last hand-written letters date back to 1936 [4].

Professor Kudrevetsky was single and had no children. He devoted all his time to his department, students and the university. His energy, bright mind, and keen intellect brought together talented scientists and brilliant clinicians.

V. V. Kudrevetsky's achievements in the study of the physiology of digestion cannot be overstated. His work with I. P. Pavlov at the end of the century before the last became fundamental in understanding the functioning of the gastrointestinal tract.

Figure 8. *Silver medal worn on the chest on the Alexander ribbon in memory of the reign of Emperor Alexander III*

This article contains a large amount of information about the life and work of Prof. V. V. Kudrevetsky It was gathered from the archives, libraries and museums of our country. The authors hope that the professor's life will not only serve as a striking example for the young generation of physicians but will also shed light on unknown pages of the history of Russian medicine.

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ФИБРИЛЛЯЦИЯ ПРЕДСЕРДИЙ ПРИ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИИ

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Atrial Fibrillation in Hypertrophic Cardiomyopathy

Резюме

В настоящем обзоре представлены современные сведения об особенностях фибрилляции предсердий у лиц с гипертрофической кардиомиопатией. Приводятся данные о распространенности, патогенезе и осложнениях фибрилляции предсердий. В статье представлены современные клинические рекомендации авторитетных научных медицинских сообществ по обсуждаемой проблеме. Подробно освещаются факторы риска возникновения фибрилляции предсердий на фоне гипертрофической кардиомиопатии с демонстрацией результатов различных исследований, посвященных изучению взаимосвязи между факторами риска и вероятностью развития аритмии. Описываются методы выявления, клинические проявления и течение фибрилляции предсердий у больных с гипертрофической кардиомиопатией. Представлены современные литературные данные, посвященные тактике ведения пациентов с фибрилляцией предсердий, рассматриваются подходы к лечению с использованием антикоагулянтов, антиаритмических препаратов, показания для проведения радиочастотной транскатетерной аблации и результаты исследований, посвященные долгосрочной эффективности процедуры. Обсуждается ведение больных в случае невозможности восстановления и поддержания синусового ритма.

Ключевые слова: *гипертрофическая кардиомиопатия, нарушения ритма сердца, фибрилляция предсердий, факторы риска, антикоагулянтная терапия, антиаритмическая терапия, обструкция выносящего тракта левого желудочка, катетерная аблация*

Конфликт интересов

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

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Abstract

The current information about features of atrial fibrillation in patients with hypertrophic cardiomyopathy is presented in this review. The data about prevalence, pathogenesis and its various complications in these patients are disclosed. The article contains updated clinical recommendations of authoritative medical societies on the discussing problem. There is detailed discussion of risk factors of atrial fibrillation onset in setting of hypertrophic cardiomyopathy with demonstration of results of different studies concerning to investigation of relationship between risk factors and probability

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of the arrhythmia development. There is description of detection methods, clinical manifestations, and the course of atrial fibrillation in patients with hypertrophic cardiomyopathy. The contemporary literature data are presented regarding to the management of patients with atrial fibrillation with use of anticoagulants, antiarrhythmic drugs, indications for performing of radiofrequency ablation and results of studies concerning long-term efficacy of such procedure are demonstrated. The discussion on the management of the patients in cases of sinus rhythm restoration or maintenance failure is described.

Key words: *hypertrophic cardiomyopathy, cardiac arrhythmias, atrial fibrillation, risk factors, anticoagulant therapy, antiarrhythmic therapy, left ventricular outflow tract obstruction, catheter ablation*

Conflict of interests

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ACC/AHA — American College of Cardiology / American Heart Association, AF — atrial fibrillation, ECG — electrocardiography, EF — ejection fraction, ESC — European Society of Cardiology, HCM — hypertrophic cardiomyopathy, HF — heart failure, HM — Holter monitoring, HR — heart rate, LA — left atrium, LGE — late gadolinium enhancement, LV — left ventricle, LVOT — left ventricular outflow tract, MRI — magnetic resonance imaging, NYHA — New York Heart Association, OSA — obstructive sleep apnea syndrome, Pmax — maximum P wave duration, PWD — P wave dispersion, RD — rhythm disturbances, SCD — sudden cardiac death

Introduction

Hypertrophic cardiomyopathy (HCM) is a disease with morphological expression only in the heart; it is primarily characterized by left ventricular (LV) hypertrophy with no other cardiac, systemic or metabolic diseases that can cause severe hypertrophy in a particular patient with sarcomere mutation that causes this disease, or with genetic etiology that remains unclear [1–5].

HCM prevalence is quite high and is approximately one case per 500 individuals [2–3, 6]. By some accounts, the prevalence of this disease in the United States is even higher, reaching a ratio of 1:200 [4]. HCM is an autosomal dominant disease; its causes include mutations of genes that encode regulatory, contractile and structural proteins of cardiac sarcomeres [7–9]. To date, at least 13 genes with more than 1,500 mutations expressed mainly or exclusively in heart tissues have been found in patients with HCM [5, 9–11].

Various clinical manifestations of HCM due to the severe hypertrophy of heart walls, obstruction of LV outflow tract (LVOT), mitral valve insufficiency and microvascular pathology include various rhythm disturbances (RD) [12–15]. Almost all types of arrhythmias are detected in association with HCM, particularly atrial fibrillation (AF), other supra- and ventricular RD, extrasystoles, Wolff–Parkinson–White syndrome and, to a lesser extent, bradyarrhythmia [11, 16].

Arrhythmias usually aggravate the clinical picture of cardiomyopathy, increase the risk of stroke and overall mortality and contribute to the progression of heart failure (HF) [17–19]. AF is the most frequent persistent cardiac RD in patients with HCM that contributes to the worsening of the symptoms of the underlying disease and the quality of life [17, 20, 21].

The objective of this review was to summarize literature data on epidemiology, pathogenetic features, clinical manifestations, screening methods and management of AF associated with HCM.

1. Epidemiology and Relevance

AF is the most common persistent arrhythmia in patients with HCM found in 14–28% of cases [3, 14, 17, 21–27]; its incidence in people aged 70+ reaches 40% [25]. AF is found 4-6 times more often in patients with cardiomyopathy than in patients of the same age in the general population [5, 28]. In patients with non-valvular AF, HCM is detected in 1.1% of cases [29]. AF in patients with hypertrophic cardiomyopathy is hard to manage; its course is worse than in patients without this pathology since diastolic filling during the development of AF with HCM is even more disturbed; so, there is increased filling pressure and LV diastolic dysfunction due to the thickening and rigidity of myocardial walls [30]. Besides the absence of atrial systole, increased frequency of ventricular response in AF reduces the time of LV diastolic filling. Therefore, AF leads to decreased cardiac output, afterload and arterial hypotension, which, in turn, can contribute to LV myocardial hypercontractivity. As a result, the pressure gradient in LVOT increases, and, despite hypotension, LV filling pressure remains high, further aggravating diastolic dysfunction and symptoms of HF [28].

Diagnosing HCM in most cases precedes arrhythmia development; therefore, pathophysiological disorders such as diastolic dysfunction, myocardial ischemia and autonomic dysregulation predispose to AF [18, 21]. Patients with HCM and AF have an elevated risk of cardiovascular complications due to thromboembolic episodes, HF, as well as general and sudden cardiac death (SCD) [18, 28, 31]. The prevalence of thromboembolic complications in patients with HCM and AF reaches 30%, with an annual frequency of 3.75% per 100 patients per year. Patients with AF more often have acute cerebrovascular accidents than patients with sinus rhythm do (13.4% and 6.7%, p = 0.019) [18]. A systematic review that included 51 studies with a total of more than 20,000 patients with HCM showed that AF is associated with an elevated risk of thromboembolic complications seven times, HF — 2.8 times, SCD — more than 1.7 times, and death from other causes — 2.5 times [5]. In general, patients with HCM and AF have an unfavorable prognosis, especially in combination with LVOT obstruction and age below 50 years [24, 25].

2. Risk Factors

Size, volume and function of left atrium (LA). Increased size and volume of LA are directly related to the onset or relapse of AF [5, 21, 23, 32-35]. Increased LA size and increased ventricular dysfunction, associated with HCM, lead to an elevated risk of thrombosis in atria and, consequently, the risk of thromboembolic events. In a pooled cross-sectional study of patients with HCM and sinus rhythm, the mean LA diameter was 38 mm compared with 45 mm in patients with AF [18, 26]. However, it is still not clear whether LA increases before AF or dilation is secondary to arrhythmia [17].

LA remodeling associated with HCM represents a typical pattern with the impairment of all three atrial functions: reservoir, conduit (passing blood from pulmonary veins to LV) and pumping that increase as HCM progresses, which was demonstrated by Kowallick J. T. et al. (2017): LA dysfunctions are associated with the presence and severity of LV fibrosis but not with its hypertrophy [36]. Numerous studies with echocardiography and magnetic resonance imaging (MRI) of the heart revealed that the increased volume and impaired function of LA are independent and more reliable predictors of AF than the size of LA [37, 38].

In a prospective study of 427 patients with HCM, 41 of whom subsequently developed AF after enrollment in the study, LA ejection fraction (EF) and its end-diastolic volume were important markers of predisposition to AF [39]. End-diastolic volume of LA ≥118 ml and EF of LA ≤38% obtained via cardiac MRI independently predicted a new onset of AF with a negative predictive value of 95%. It is noteworthy that in 59% of patients with HCM and with AF first detected during the average 5-year follow-up period, LA diameter was <45 mm, which, in accordance with modern recommendations, is considered a factor related to low risk of AF [40]. Patients with LA size <45 mm and newly diagnosed AF had high values of LA volume and a more significant disturbance of its function compared with patients without AF [28].

Several reasons for the increased LA size and volume are considered. In particular, LV diastolic dysfunction typical for HCM leads to an increase in filling pressure, which, in turn, is accompanied by remodeling and dilatation of LA [41, 42]. Increased filling pressure in LV leads to increased pressure in LA, which is required to maintain adequate diastolic filling. This pathophysiological mechanism contributes to remodeling and increase of LA, creating a substrate for the development of arrhythmia and the formation of blood clots due to blood stagnation in LA. According to Zegkos T. et al. (2017), AF is the consequence of the progression of the underlying disease and severe impairment of LV diastolic function, which, in addition to its clinical manifestations, is a key event in the development of arrhythmia [18]. Also, increased LA size with HCM is due to primary sarcomere myopathy of LA myocardium, LVOT obstruction, increased myocardial stiffness, mitral regurgitation and other RD. Considering the established role of increased LA size and its dysfunction in the development of AF with HCM, it is recommended to annually monitor LA parameters and re-examine in case of new symptoms for all stable patients with this disease [28].

Atrial ischemia and myocardial infarction with HCM are caused by calcium metabolism disorders that lead to increased trigger activity due to delayed postdepolarization, hypertrophy of myocardial sleeves (myocardial fibers located outside the pulmonary vein transition zone in LA), which is responsible for triggers from pulmonary veins to LP, microvascular coronary dysfunction, and other causes [5].

AF associated with HCM worsens coronary blood flow reserve, and the imbalance between myocardial oxygen supply and demand leads to the specific activation of redox signaling pathways and the formation of reactive oxygen forms, which, in turn, causes oxidative stress that plays a key role in ventricular remodeling. These mechanisms contribute to stable AF since myocardial ischemia creates a substrate for maintaining arrhythmia [43].

Myocardial fibrosis. In 2001, a small morphological study was conducted to analyze fragments of heart tissue in 10 patients with HCM (5 patients with AF and 5 with no arrhythmia) [44]. It was found that the extent

of fibrosis and the grade of stenosis in intramyocardial small arteries were more pronounced in the group of patients with AF. In patients with HCM, AF develops as a result of progressive atrial remodeling and fibrosis due to increased stretching of LA caused by LVOT obstruction, which leads to atrial myopathy [5]. The condition of "atrial standstill" is a severe form of atrial cardiomyopathy representing an arrhythmogenic substrate for AF. Atrial standstill can be associated with heterozygous mutations of SCN5A and connexin-40 genes [45].

With the latest advances in imaging diagnostic methods, cardiac MRI results dedicated to the identification of additional risk factors of AF were obtained. The detection of late gadolinium enhancement (LGE) in MRI indicates foci of myocardial fibrosis [46, 47]. To study the features of localization and extensiveness of LV myocardial fibrosis, cardiac MRI was performed in 67 patients with HCM, 17 of them with AF [48]. Results of this study revealed that AF was more often observed in patients with signs of LV myocardial fibrosis compared with individuals without it (42.1% and 3.4%, respectively). In a comparative study of two groups of patients with HCM with paroxysmal AF (n = 18) and without it (n = 27), Sivalokanathan S. et al. (2019) found the LGE phenomenon in the posterior LV wall when performing MRI in all patients with cardiomyopathy [47]. However, patients with paroxysmal AF had a greater LA volume, lower LA EF and larger LGE zones compared with the group of patients without AF.

Electrical remodeling of LA. Structural and functional remodeling of LA leads to its electrical instability and creates conditions for the development of various atrial arrhythmias, mostly AF.

Notably, in expanded LA, maximum diastolic potential decreases due to high pressure, and myocyte depolarization occurs faster, increasing susceptibility to arrhythmia. Interstitial fibrosis increases simultaneously with LA remodeling, changing the structure and function of the atria. Fibrosis impedes pulse conduction due to the interruption of the electrical integrity of myocytes, which leads to longer intra- and interatrial conduction time, and heterogeneous distribution of sinus impulses [49].

Predictors of AF in patients with HCM detected during electrocardiography (ECG) are being introduced into modern clinical practice and can help identify individuals with a high risk of AF. Maximum P wave duration (Pmax) and its dispersion (PWD) are easily calculated based on the standard ECG. Pmax reflects prolonged intra- and interatrial conduction. PWD is the difference between the longest (Pmax) and the shortest P (Pmin) wave according to ECG in 12 leads and reflects the heterogeneity of atrial conduction [28].

$$PWD = Pmax — Pmin$$

where PWD is P wave dispersion, ms; Pmax is the duration of the widest P wave, ms; Pmin is the duration of the narrowest P wave, ms

Ozdemir O., et al. (2004) analyzed ECG parameters in 27 patients with HCM and AF paroxysms compared with 53 patients selected by gender and age with no history of AF episodes [50]. Pmax of >134.5 ms and PWD of >52.5 ms determine AF with sensitivity of 92% and 96% and with specificity of 89% and 91%, respectively.

Köse S., et al. (2003) compared the morphological characteristics of P wave in 22 patients with HCM and history of AF and in 26 individuals without arrhythmia and found that PWD of >46 ms predicts AF with a sensitivity of 76% and a specificity of 82% [51]. In a study of 70 patients with HCM, 18 of whom developed AF in about 4.5 years, the authors found that PWD of >47.5 ms predicts AF with a sensitivity of 78% and a specificity of 72% [38].

Cardiac markers. It was previously found that highly sensitive cardiac troponin T (cTnT) has a predictive value for adverse outcomes with HCM [52, 53]. A small study demonstrated that cTnT levels were independent predictors of the presence and severity of AF [54]. The mechanism responsible for cTnT increase in such patients is not fully understood and requires further study. It is believed that it is based on pathological events such as remodeling of the heart, cardiomyocyte necrosis and atrial fibrosis. However, there is limited available information regarding cardiac marker value in assessing the relationship between AF and HCM [28].

It was shown that increased levels of B-type natriuretic peptide (BNP) with HCM are associated with AF [25]. N-terminal pro-BNP of 720 pg/ml predicts AF with a sensitivity of 72% and a specificity of 60% [38]. Overall, natriuretic peptides have a weak predictive power in relation to AF associated with this disease. Available data on using cardiac troponin and BNP levels to predict AF with HCM are insufficient. Therefore, most scientists do not recommend their clinical use for risk stratification in such patients [28].

LV hypertrophy and LVOT obstruction. The effect of LVOT obstruction on the development of AF is not fully understood since data from earlier studies are very contradictory. Moreover, the assessment of the presence and severity of LVOT obstruction in patients with HCM and heart RD can be very difficult. A positive correlation was confirmed by some studies [55, 56] but not found in others [21, 23]. Interesting results were obtained in a study of the relationship between the localization and severity of LV hypertrophy in patients with HCM with

clinical characteristics, a variant of RD, and the disease outcome during an average follow-up period of 6.1 years [57]. In the group of patients with more pronounced hypertrophy of the interventricular septum when hypertrophy covered more than half of the septum length from the heart apex to the base, various RD were observed significantly more often than in patients with local LV hypertrophy (50.1 % and 27.6%, respectively). AF was associated with a high incidence of interventricular septum lesion regardless of LVOT obstruction.

Obstructive Sleep Apnea Syndrome (OSAS) is the most common type of respiratory failure during sleep and is characterized by recurring episodes of upper airway obstruction, leading to hypopnea or apnea associated with periods of hypoxia, activation of the sympathetic nervous system with increased heart rate, increased blood pressure and awakening.

The prevalence of OSAS among patients with AF is extremely high — approximately 50%. When OSAS is associated with HCM, it worsens the severity of the underlying disease and increases mortality due to a 2-4-fold increase in AF incidence, increased diastolic dysfunction, LA dilatation, a more severe functional class of HF according to the classification of the New York Heart Association (NYHA), and deterioration in the quality of life despite optimal therapeutic management of patients [58]. Numerous studies demonstrated a higher prevalence of AF among patients with HCM and OSAS compared with subjects without it, as well as a larger LA and worse diastolic function with increased severity of OSAS [28, 58].

The pathophysiological mechanisms underlying the association of OSAS and HCM are likely to be associated with catecholaminergic activation observed in OSAS, which increases arrhythmogenicity, LV hypertrophy, filling pressure, reduces cardiac output, potentially initiating or worsening LVOT obstruction gradient and mitral regurgitation [28].

Other factors affecting the development of AF with HCM include the severity of LV hypertrophy, certain genetic mutations, insulin resistance, female gender, more severe NYHA class of HF, LVEF, severe mitral regurgitation, history of syncope, etc. [30, 34, 35, 46, 59–61].

3. Detection of Atrial Fibrillation

ECG is an available and informative method of detecting AF, especially in cases of long-term monitoring (24-48 hours) [62].

According to recommendations of the European Society of Cardiology (ESC) for the diagnosis and management of HCM [3], patients with sinus rhythm and anteroposterior LA size ≥45 mm should undergo 48-hour Holter monitoring (HM) ECG every 6-12 months. As per the recommendations of the American College of Cardiology / American Heart Association (ACC/AHA)-2011, one-time 24-hour outpatient ECG monitoring for adult patients with HCM should be carried out to detect asymptomatic flutter or AF [2]. According to the Russian clinical guidelines for HCM, ECG (in 12 leads) is recommended during the initial examination of all patients with suspected HCM and during follow-up. HM ECG (optimally for 48-72 hours) is recommended during the initial clinical examination and every 12-24 months. According to the comments to this paragraph, indications for HM ECG include the patient's complaints of palpitations and/or dizziness [63].

According to retrospective analysis, daily HM ECG allowed to detect AF in 9% of patients among the elderly population, who had severe HF and increased LA compared to the patients with sinus rhythm [12].

In late 2020, updated ACC/AHA recommendations [4] were issued with proposals in the «Assessment of heart rhythm» section that are given in Table 1.

Table 1. *ACC/AHA 2020 guidelines for the assessment of heart rhythm in patients with hypertrophic cardiomyopathy*

COR	LOE	Recommendations
I	B-NR	In patients with HCM who develop palpitations or lightheadedness, extended (>24 hours) electrocardiographic monitoring or event recording is recommended, which should not be considered diagnostic unless patients have had symptoms while being monitored
2a	B-NR	In patients with HCM who have additional risk factors for atrial fibrillation (AF), such as left atrial dilatation, advanced age, and NYHA class III to class IV heart failure (HF), and who are eligible for anticoagulation, extended ambulatory monitoring is reasonable to screen for AF as part of initial evaluation and periodic follow-up (every 1 to 2 years)
2b	B-NR	In adult patients with HCM without risk factors for AF and who are eligible for anticoagulation, extended ambulatory monitoring may be considered to assess for asymptomatic paroxysmal AF as part of initial evaluation and periodic follow-up (every 1 to 2 years)

Abbreviations: COR — class of recommendation; LOE — level of evidence; B-NR — moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, meta-analyses of such studies; ECG — electrocardiography; HCM — hypertrophic cardiomyopathy; AF — atrial fibrillation; HF — heart failure; NYHA — New York Heart Association. Adapted from S.R. Ommen et al. [4]

The accompanying text to this section includes the following: «Although some studies show that the incidence of asymptomatic AF can be as high as 50%, it remains unclear whether asymptomatic episodes, especially short ones, have an effect on an adverse outcome. AF predictors include LA dilatation, elderly age, HF grade III–IV according to NYHA. Therefore, patients with these characteristics should be examined more often, including extended ECG screening on an outpatient basis» [4].

According to Zegkos T. et al. (2017), who noted a smaller LA size among individuals with AF, there is no reliable indicator of the size of LA, which is important for screening patients with HCM for arrhythmia and timely administration of anticoagulant agents [18]. In this context, physicians should bear in mind the possibility of AF in any patient with HCM, even in an asymptomatic patient without risk factors for this atrial arrhythmia.

In recent years, with the development of digital and portable devices, it has become possible to use new mobile systems designed primarily to detect AF paroxysms. Table 2 shows sensitivity and specificity values of some devices for AF screening considering ECG in 12 standard leads as the «gold standard» [19].

Table 2. *Sensitivity and specificity of various AF screening tools*

Screening tools	Sensitivity	Specificity
Pulse taking	87-97 %	70-81 %
Automated BP monitors	93-100 %	86-92 %
Single lead ECG	94-98 %	76-95 %
Smartphone apps	91,5-98,5 %	91,4-100 %
Smartwatch	97-99 %	83-94 %

Notes: BP — blood pressure; ECG — electrocardiogram. Adapted from G. Hindricks et al. [19]

When determining AF using modern mobile and portable devices, an ECG should be recorded in one (≥30 sec) or 12 leads with the interpretation of results by a physician experienced in interpreting heart RD in order to make a final diagnosis [19].

4. Clinical Manifestations and Course

AF in some patients with HCM may not be accompanied by any complaints or symptoms, and in such cases, arrhythmia is detected during routine ECG. In some patients, AF is manifested by a variety of complaints of palpitations, pre- and syncopal conditions, onset or intensification of pain in the left half of the chest, shortness of breath at rest or during physical activity; there may be decreased exercise tolerance or blood pressure [62, 64].

According to the study by Zegkos T. et al. (2017), patients with HCM and AF had more pronounced clinical manifestations of HF than patients with no AF did [18]. In the study conducted by Siontis K., et al. (2014), a significant decrease in the functional ability of patients with HCM and AF was registered during a cardiopulmonary exercise test [25]. This was because LV diastolic dysfunction is initially observed in the cases of HCM, and, with the onset of AF, i.e., the loss of coordinated atrial systole, LV filling worsens significantly, which aggravates HF, especially during physical exertion. Thus, both AF and increased HF can be the result of progressive structural and functional impairment due to HCM. Therefore, ESC experts consider it appropriate to include a cardiopulmonary exercise test in the initial assessment program of such patients [2].

According to the current hypothesis, decreased cardiac output due to atrial systole loss and decreased stroke volume are taken into consideration in relation to the mechanisms by which AF is associated with decreased exercise tolerance in patients with HCM. Although, according to Azarbal F. et al. (2014) [65], who found that the paroxysmal form of AF is significantly associated with decreased exercise tolerance in patients with sinus rhythm at the time of the study and with no active hemodynamic consequences of arrhythmia, there are probably other non-arrhythmogenic causes of physical exercise intolerance. Diastolic dysfunction, ventricular remodeling, atrial enlargement, systemic vasodilation, or decreased intravascular volume predisposing to arterial hypotension, as well as increased adrenergic tone, are considered possible causes of decreased exercise tolerance in patients with HCM and AF [65].

The most common complication of AF associated with HCM is systemic thromboembolism [29, 31]. In particular, this arrhythmia increases the risk of ischemic stroke eightfold [21]. It should be noted that the increased risk does not depend on the form of arrhythmia (paroxysmal/persistent for a long time/permanent) or the number of AF paroxysms.

5. Management

Modern methods of managing AF with anticoagulants, antiarrhythmic agents, catheter ablation, and maze procedure have demonstrated their high efficiency, which has helped reduce the mortality rate of patients with HCM and AF to the level of patients with no AF [28, 31].

Anticoagulant therapy. AF in a patient with HCM is a direct indication for oral anticoagulant therapy. According to the ESC-2014 [3], ACC/AHA 2014 [66] and 2019 recommendations [67], the CHA_2DS_2-VASc scale is

not recommended for stroke risk assessment. According to Alphonse P. et al. (2020), based on the results of a meta-analysis and taking into consideration the multifold increase in the risk of thromboembolic complications, HCM itself should be included in the CHA_2DS_2-VASc scale as an independent risk factor [5].

The ACC/AHA 2011 guide for the diagnosis and management of HCM offers recommendations for anticoagulant therapy with oral anticoagulants, including vitamin K antagonists with a target range of the international normalized ratio of 2.0–3.0 [2] for patients who developed paroxysmal, persistent or permanent AF. Unfortunately, there are currently no randomized clinical trials of anticoagulant therapy in patients with this form of cardiomyopathy [5]. However, numerous retrospective studies demonstrated a decrease in the level of embolic complications in patients taking warfarin. Therefore, anticoagulant therapy is justified if AF persists for more than 48 hours or if there is a high probability of its relapse [2, 21]. Warfarin should be prescribed literally after the first AF episode [21].

Direct oral anticoagulants — direct thrombin inhibitor (dabigatran) and direct factor Xa inhibitors (rivaroxaban and apixaban) — can be successfully used in patients with HCM and AF [46, 63, 68]. According to the Russian recommendations on HCM, in the cases of side effects of warfarin or the inability to reach target INR, dabigatran etexilate, or rivaroxaban, or apixaban is recommended. In all cases of HCM complicated by AF, life-long therapy with warfarin (INR 2–3.0) or direct anticoagulant agents is recommended, even if sinus rhythm has been restored [63]. Patten M. et al. (2018) [64] recommend life-long oral anticoagulant therapy in cases of documented AF regardless of the individual score according to CHA_2DS_2-VASc in order to reduce the risk of stroke.

Antiarrhythmic therapy. Relative benefits of rhythm control compared with heart rate (HR) control in the management of AF in patients with HCM are not yet clear [30, 69]. This is partly because there are very limited data on the safety and efficacy of drug therapy for AF rhythm control in individuals with HCM. However, in some patients, especially with severe LVOT obstruction and increasing severity of HF and ventricular tachysystole, restoration of sinus rhythm is justified. Clinical guidelines of the Ministry of Health of the Russian Federation on AF and atrial flutter recommend restoration of sinus rhythm by electric or pharmacological cardioversion to improve symptoms for all patients with HCM and onset of symptomatic AF for the first time [62].

Currently, amiodarone is the most effective agent that reduces the frequency of AF paroxysms [17, 46, 63]. Amiodarone is recommended for patients with recent AF (<48 h) [63]. The minimum effective dose of this drug is 200 mg 5-7 times a week with regular monitoring of thyroid, hepatic and pulmonary functions [70, 71]. In one study involving 52 patients with HCM and AF, amiodarone was associated with more rare episodes of AF and embolic events compared with class I antiarrhythmic drugs [72]. In patients who initially received standard therapy (including digoxin, β blockers, calcium channel blockers, quinidine and disopyramides), sinus rhythm maintenance was achieved in 22 out of 38 (58%) compared with 7 out of 8 (87%) patients on amiodarone. Over time, 20 (39%) patients receiving conventional treatment switched to amiodarone, which significantly reduced the number of cardioversions [72]. Despite the high effectiveness of amiodarone in preventing AF relapse, this antiarrhythmic drug is considered not ideal for the group of patients with HCM due to the need for long-term use and high frequency of side effects [17, 46]. According to the results of another study with 98 participants, 19.1% of patients taking amiodarone developed side effects, which was the reason for the discontinuation of the drug, once again confirming the limited use of amiodarone among patients, especially young ones. At the same time, amiodarone was found to be highly effective in rhythm control: the drug was discontinued due to inefficiency (no sinus rhythm along with amiodarone intake) in 8.5% of patients [30]. The probability of taking amiodarone after 1 and 3 years was 51.4% and 29.2%, respectively, indicating poor tolerability of this drug in most patients.

Sotalol and disopyramide are alternative antiarrhythmic drugs for managing AF in patients with HCM. [30, 73–75]. Besides a direct antiarrhythmic effect, disopyramide also has a negative inotropic effect, which is especially important in cases of LVOT obstruction [19]. According to a retrospective analysis, using disopyramide was not associated with an increased risk of ventricular arrhythmia or SCD in patients with HCM [74]. Considering that monotherapy with disopyramide is potentially dangerous due to increased atrioventricular conduction, which accelerates ventricular response in AF [3], this agent is mainly used in emergency care. In such cases, disopyramide is administered simultaneously with rhythm control drugs along with continuous monitoring of the QTc interval [2]. When the QTc interval value reaches ≥480 ms, the dose of the drug should be immediately reduced, or the drug should be completely withdrawn [3]. Along with this, other drugs that extend QT interval should be avoided. The small number of examined patients with HCM does not provide a complete picture of the efficacy and safety of disopyramide and dofetilide in this population [30].

Sotalol, as a class III antiarrhythmic drug, demonstrated its efficacy in patients with structural heart diseases.

A recent study by Miller C. A. S. et al. (2019) showed that sotalol is effective for rhythm control with AF (27.2% of patients had to stop taking sotalol due to its inefficiency) [30]. At the same time, the probability of taking sotalol after 1 and 3 years was 74.4% and 50%, respectively, which indicates good tolerability of this drug. Based on the results of the then-largest study of the group of patients with HCM and AF who were taking sotalol (45 patients observed for 2.3 ± 2.3 years), the authors believe that sotalol may be the drug of choice in the treatment of such patients considering the absence of serious side effects [30].

In the study, there were no cases of SCD and no serious side effects among patients receiving amiodarone and sotalol. In the group of patients taking disopyramide, three cases of side effects were registered: anaphylaxis in one patient, stable form of ventricular tachycardia in one patient and QTc prolongation according to ECG data in one patient as well [30]. Three patients who received dofetilide developed side effects: symptomatic bradycardia in one patient and syncope in two patients. In one case, stable ventricular tachycardia was detected in a 50-year-old patient with HCM who received disopyramide. Due to a family history of SCD, a cardioverter-defibrillator was implanted for secondary prevention. During the administration of disopyramide (200 mg twice a day), the patient received three shocks of a cardioverter-defibrillator due to polymorphic ventricular tachycardia [30].

Experts from the ACC/AHA Working Group for the study of HCM in 2011 assigned amiodarone and disopyramide class IIa as agents for rhythm control (Fig. 1) [2].

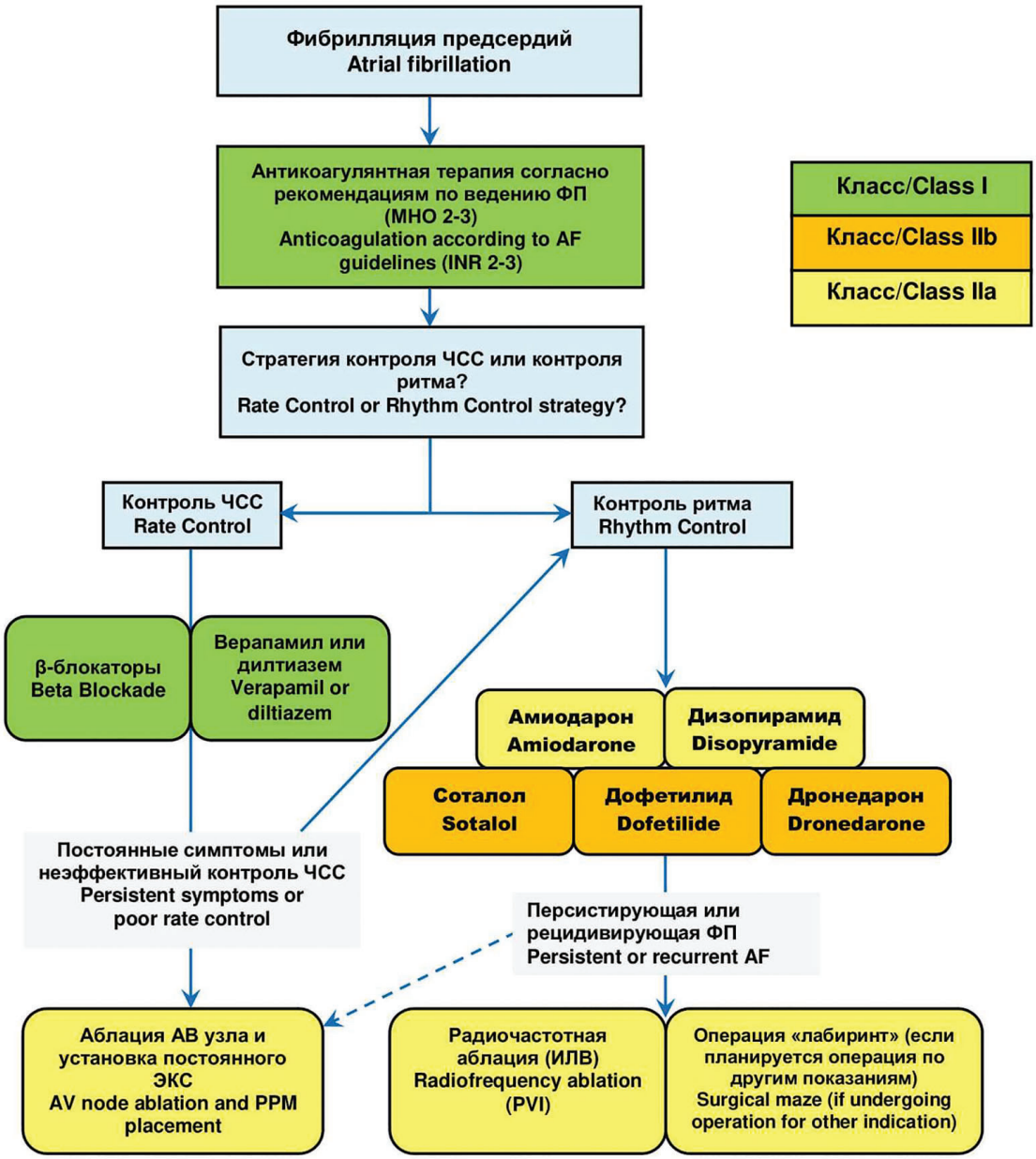

Figure 1. *Management of atrial fibrillation in hypertrophic cardiomyopathy*

Table 3. *ACC/AHA 2020 guidelines for the management of atrial fibrillation in patients with hypertrophic cardiomyopathy*

COR	LOE	Recommendations
I	B-NR	In patients with HCM and clinical AF, anticoagulation is recommended with direct-acting oral anticoagulants as first-line option and vitamin K antagonists as second-line option, independent of CHA2DS2-VASc score
I	C-LD	In patients with HCM and subclinical AF detected by internal or external cardiac device or monitor of >24 hours' duration for a given episode, anti-coagulation is recommended with direct-acting oral anticoagulants as first-line option and vitamin K antagonists as second-line option, independent of CHA2DS2-VASc score
I	C-LD	In patients with AF in whom rate control strategy is planned, either beta blockers, verapamil, or diltiazem are recommended, with the choice of agents according to patient preferences and comorbid conditions
2a	C-LD	In patients with HCM and subclinical AF detected by internal or external device or monitor, of >5 minutes' but <24 hours' duration for a given episode, anticoagulation with direct-acting oral anticoagulants as first-line option and vitamin K antagonists as second-line option can be beneficial, taking into consideration duration of AF episodes, total AF burden, underlying risk factors, and bleeding risk
2a	B-NR	In patients with HCM and poorly tolerated AF, a rhythm control strategy with cardioversion or antiarrhythmic drugs can be beneficial with the choice of an agent according to AF symptom severity, patient preferences, and comorbid conditions.
2a	B-NR	In patients with HCM and symptomatic AF, as part of an AF rhythm control strategy, catheter ablation for AF can be effective when drug therapy is ineffective, contraindicated, or not the patient's preference
2a	B-NR	In patients with HCM and AF who require surgical myectomy, concomitant surgical AF ablation procedure can be beneficial for AF rhythm control

Abbreviations: COR — class of recommendation; LOE — level of evidence; B-NR — moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies, meta-analyses of such studies; C-LD — randomized or nonrandomized observational or registry studies with limitations of design or execution, meta-analyses of such studies, physiological or mechanistic studies in human subject; HCM — hypertrophic cardiomyopathy; AF — atrial fibrillation.
Adapted from S.R. Ommen et al. [4]

Sotalol, dofetilide, and dronedarone belong to class IIb and can be used in the rhythm control strategy in patients with HCM [66, 67], but with the note that their use should be carefully considered in patients with implanted cardioverter-defibrillators. Flecainide and propafenone are undesirable due to possible proarrhythmic effects and hemodynamic deterioration [2, 3].

Thus, to date, the exact risks and benefits of using antiarrhythmic agents in patients with HCM and AF are unclear. Therefore, the decision on the choice of rhythm control tactics should be made in each case individually with discussion between the physician and the patient [30].

There are interesting recent recommendations for the management of patients with HCM and AF developed by AHA/ACC and published in 2020. [4].

If sinus rhythm cannot be maintained, β blockers or calcium channel blockers (verapamil, diltiazem) are prescribed to control the frequency of ventricular response [2, 62, 63]. Atenolol, nadolol, metoprolol succinate are justified in cases of preserved LV EF, and bisoprolol or carvedilol — in cases of systolic dysfunction. Verapamil or diltiazem should be used only with preserved LV EF [70]. Digoxin is actually not used for AF in patients with "classical" HCM. However, its use can be considered for patients with severe LV dysfunction in order to control heart rate. The Russian Guidelines for HCM recommend considering the use of digoxin in low doses for patients with non-obstructive HCM with persistent AF and chronic NYHA functional class II-IV with EF <50% in order to control ventricular contraction rate [63].

Catheter ablation. Indications for radiofrequency catheter ablation include symptomatic AF that is refractory to drug treatment and intolerance to drug therapy [66, 67]. The procedure should be carried out as soon as possible after the onset of AF while the arrhythmogenic substrate remains pliable for external exposure [70]. The 2014 ACC/AHA/Heart Rhythm Society guidelines include catheter ablation on the list of therapeutic methods for heart rate control [66]. However, most studies revealed a high frequency of repeated procedures to achieve long-term control AF [76]. Rhythm restoration and relapse rate reduction can be achieved in 2/3 of patients with HCM in two years [77]. The lower efficiency of stopping AF in patients with HCM (varying from 45 to 82% in the long-term) is due to pronounced remodeling of LA — its hypertrophy/dilation [22] and the presence of fibrotic zones (Fig. 2) [17, 76].

The need for re-ablation often occurs in elderly people with a large LA and high functional class of HF, according to NYHA [77]. With paroxysmal AF, the probability of successful relief is higher (77%) than with its permanent form (50%) [78].

Therefore, AF is the most common persistent arrhythmia that complicates the course of HCM. AF leads to the aggravation of the clinical manifestations of the disease, progression of HF, and an elevated risk of cardiovascular complications and mortality. In this regard, patients

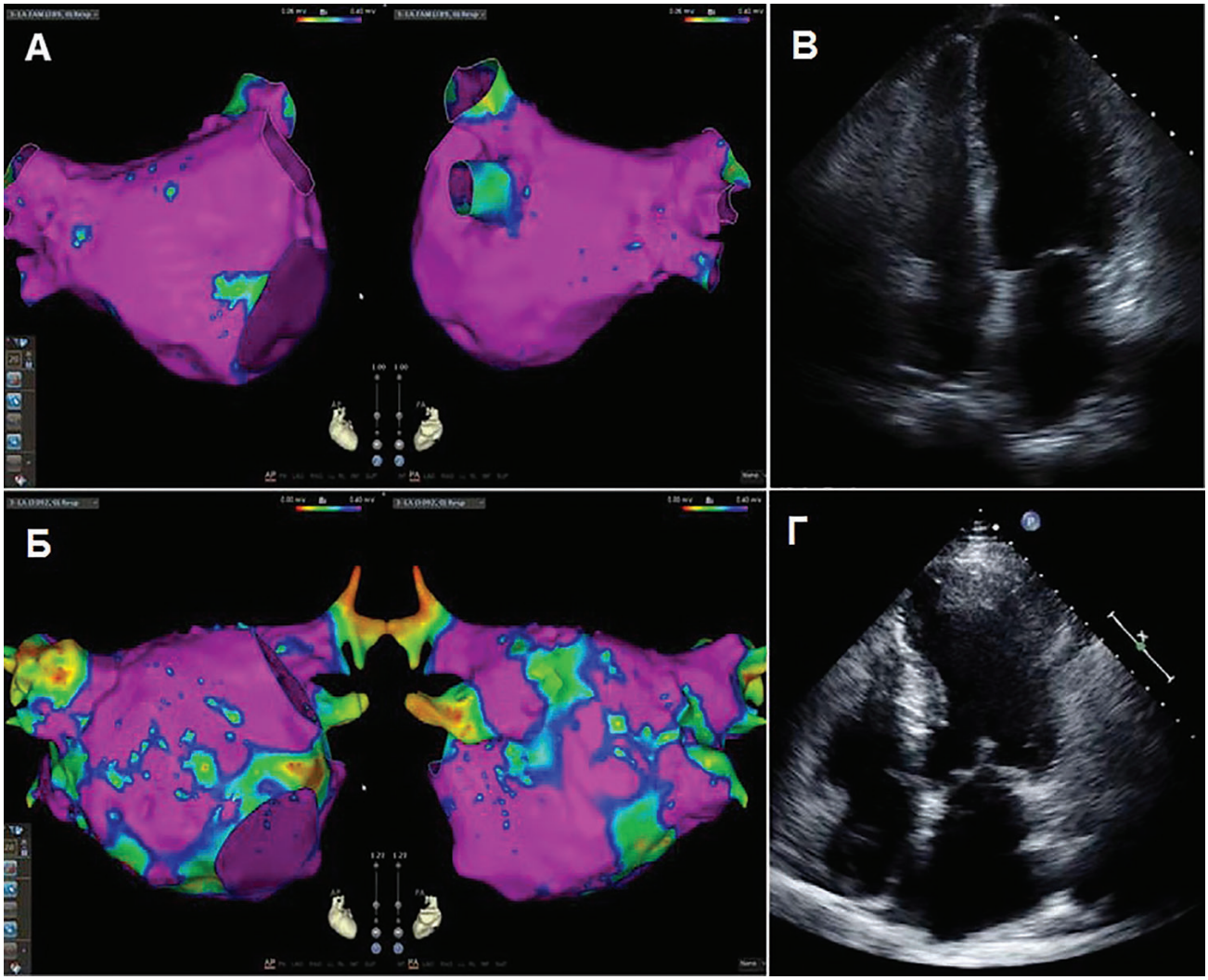

Figure 2. *Bipolar stress maps and echocardiographic data in patients with hypertrophic cardiomyopathy and atrial fibrillation*

with HCM should be examined for risk factors and AF. In the event of AF, a strategy for rhythm control or heart rate control should be carefully chosen based on existing experience with antiarrhythmic drugs and current recommendations. Anticoagulant therapy deserves special attention; its prescription is justified for all patients with HCM and AF in order to prevent thromboembolic complications.

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ПОСТ-КОВИДНЫЙ ПЕРИОД: СОВРЕМЕННЫЙ ВЗГЛЯД И КЛИНИЧЕСКИЕ ОСОБЕННОСТИ

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Post-COVID 19 Period: Modern State and Clinical Features

Резюме

Коронавирусная болезнь (COVID-19) рассматривается в качестве серьезной проблемы общественного здравоохранения, о чем свидетельствует неуклонный рост вновь зараженных пациентов.

Несмотря на то, что борьба с данной инфекцией длится более года, до сих пор недостаточно изучены малопрогнозируемые последствия COVID-19 в сочетании или без сочетания с сопутствующими хроническими заболеваниями, что несомненно является дополнительной нагрузкой на амбулаторное звено здравоохранения. Данная статья представляет собой обзор, современной доступной литературы, посвященной особенностям течения и длительности пост-ковидного периода. Проанализировано более 15 исследований, в которых авторы оценивали встречаемость симптомов в пост-ковидный период и его клинические характеристики.

Ключевые слова: *COVID-19, пост-ковидный период, одышка, усталость, амбулаторный этап*

Конфликт интересов

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

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Abstract

Coronavirus disease (COVID-19) has proven to be a major global public health crisis, as evidenced by the steady increase in re-infected patients. In spite of the fight against this infection going on for more than a year, the unpredictable consequences of COVID-19, with or without concomitant chronic diseases, are still insufficiently studied, which undoubtedly is an additional burden on the outpatient health care unit. This article is a review of the available modern literature on the features of the course and duration of the post-COVID period. More than fifteen studies have been analyzed, in which the authors evaluated the incidence of symptoms in post-COVID period and its clinical characteristics.

Key words: *COVID-19, post-COVID 19 period, shortness of breath, fatigue, outpatient stage*

Conflict of interests

The authors declare no conflict of interests

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Introduction

Due to the increase in the incidence of novel coronavirus disease (COVID-19), clinical features of this disease are being studied both in the acute period and in the recovery period after infection [1–5].

There is currently not enough reliable professional information on the medical rehabilitation of COVID-19 patients since this disease is new. The conventional method of obtaining the necessary data from studies was ineffective since the experience of treating patients with coronavirus disease is limited to several months [6].

In the Russian Federation, recommendations were developed on rehabilitation measures after COVID-19 [6]. Experts proposed a scale for determining individual rehabilitation routing of persons with and after COVID-19. This scale allows determining the possibility of rehabilitation measures for patients at different stages of medical care. However, given the ambiguity of the recovery period after a new infection, a comprehensive and personalized algorithm for managing such patients at the outpatient stage should be developed.

Since most complaints of patients are due to respiratory symptoms, the best time for rehabilitation is the first two or three months after the acute period of coronavirus disease. Priority objectives of providing medical care to patients who contracted a new infection as part of rehabilitation measures are to prevent complications and quickly return patients to their previous lifestyle. Post-COVID rehabilitation of patients should start as early as possible. Therefore, there is need for a careful assessment of the clinical and functional status of the patient and choosing a comprehensive treatment plan, with the focus on the restoration of functional activity and return to social life depending on the individual characteristics of a person.

As new information regarding the diagnosis, treatment, and follow-up of patients with COVID-19 becomes available, the approach to coding conditions changes. To record COVID-19 cases, on March 25, 2020, the World Health Organization (WHO) recommended diagnostic criteria and COVID-19 codes according to the International Classification of Diseases, Tenth Revision (ICD-10). These codes were adopted in the Russian Federation on April 08, 2020, by Order of the Ministry of Health of the Russian Federation No. 13-2/I/2-4335, of April 08, 2020, "On the Coding of Coronavirus Disease (COVID-19)" [7]. Later, WHO experts added to the ICD-10 a diagnosis of U09.0 Post COVID-19 condition [8].

Post-COVID Period

The severity of SARS-CoV-2 disease varies from asymptomatic to life-threatening clinical symptoms. According to current estimates, approximately 20 million people in the world have «recovered» [9]; however, many clinicians report persisting symptoms of varying severity, up to significant organ dysfunction. At present, there is indeed insufficient information on the true nature and incidence of post-COVID-19 symptoms in the so-called «post-COVID» period, and there is no consensus on the occurrence and length of this period.

Greenhalgh Trisha et al. (2020) were among the first to propose the term «long-COVID», which implies a set of symptoms after the disease that persist for more than three weeks from the onset — «post-acute (probably meaning sub-acute) COVID-19» and for more than 12 weeks — «chronic COVID-19» [10].

Based on the study of the incidence of COVID-19 symptoms that included more than 4 million people in the United States, Britain and Sweden, it is believed that «sub-acute» COVID-19 is the presence of symptoms lasting more than three weeks from the onset, and chronic COVID-19 — symptoms lasting more than 12 weeks [10].

Experts at the National Institute for Health and Care Excellence the Scottish Intercollegiate Guidelines Network of General Practitioners define «post-COVID syndrome» as «a combination of symptoms that develop within 12 weeks after recovery and are not explained by the presence of other diseases» [11]. This document indicates the importance of follow-up in the post-COVID period taking into consideration multisystem disorders associated with COVID-19, which requires:

- Assessment of the general condition, the presence of fatigue and neurological symptoms;
- Assessment and management of persistent dyspnea, concomitant chronic conditions, if any;

- Assessment of the need for oxygen and its delivery;
- Assessment of the need for rehabilitation and its subsequent development;
- Psychosocial assessment (depression, anxiety disorders, post-traumatic stress disorders and subsequent referral to specialists to provide assistance according to indications);
- Assessment of cognitive impairment;
- Diagnosis of previously unverified diagnosis of venous thromboembolism.

The presence of «post-COVID syndrome» is quite natural since any infectious disease has certain consequences of varying duration and severity.

Post-COVID Period Clinical Signs

Long-term effects of COVID-19 are currently being studied, although the results of these studies include few data indicating the persistence of symptoms after the acute period in a certain number of patients (Table 1).

The above data indicate that dyspnea and increased fatigue are the leading symptoms in the post-COVID period and develop in most (up to 70%) patients. Cognitive impairments and headaches are detected in almost one in three (up to 36%) patients. The most analyzed studies provided no information on the time when the symptoms regressed and patients fully returned to their previous lifestyle, which does not allow us to estimate the true average duration of the recovery period after COVID-19. The incidence of COVID-19 symptoms in acute and recovery periods is presented in Table 2.

In one study conducted in Italy, which evaluated the persistence of COVID-19 in 143 patients aged 19 to 84 years (mean age 56.5 years), 53 (37%) were female, 90 (63%) were male, discharged from the hospital, only 18 (12.6%) patients had absolutely no symptoms associated with COVID-19 60 days after the onset of the first symptoms. Among all subjects, arterial hypertension was found in 50 (35%), thyroid diseases — in 26 (18.2%), autoimmune diseases — in 16 (11.2%), chronic obstructive pulmonary disease — in 13 (9.1%), chronic heart failure — in 7 (4.9%) patients [13].

Table 1. *The incidence of symptoms after COVID-19 infection in the recovery period*

Author, source	Number of patients, gender, age	Symptoms	Observation period
Arnold et al. 2020 [12]	n=110 median age 60, 49 women (44%) 61 male (56%)	Dyspnea (39%) Fatigue (39%) Insomnia (24%) Myalgia (22%) Anosmia (11%) Arthralgia, headache, abdominal pain, diarrhea (<5%) Combination of multiple symptoms 74%	Median of 83 days after hospital discharge
Carfi et al. 2020 [13]	n=143 median age 56,5 53 women (37,1 %) 90 male (62,9%)/	Fatigue (53,1%) Dyspnea (43,4%) Arthralgia (27,3%) Chest pain (21,7 %) Cough, sputum, joint pain, anosmia, rhinitis, taste disturbance, loss of appetite, Sikki syndrome, redness of the eyes, headache, dizziness, myalgia, diarrhea (< 20%) Combination of 1-2 symptoms — 32% 3 symptoms — 55%	Mean of 60 days after hospital discharge
Cirulli et al. 2020 [14]	n=233 median age 56 148 women (63,6 %) 85 male (36,4%)	Concentration and memory problems, anosmia, ageusia, dyspnea, headache, heart palpitations, chest pain, tachycardia, and cough: - 42,3% - 33,8% - 24,1%	 Symptom lasting for >30 days Symptom lasting for >60 days Symptom lasting for >90 days
Lu et al. 2020 [15]	n=60 median age 45,9	Memory loss (28,3 %) Myalgia (25%) Mood changes (16,7%) Fatigue (6,7%) Numbness in extremities (6,7 %) Combination of symptoms 55%	3 months after hospital discharge
Mandal et al. 2020 [16]	n=384 median age 59,9 146 women (38%) 238 male (62%)	Fatigue (69%) Dyspnea (53%) Cough (34%) Depression (15%)	Median of 54 days after hospital discharge

Author, source	Number of patients, gender, age	Symptoms	Observation period
Miyazato et al. 2020 [17]	n=63 median age 48,1 21 women (33,3 %) 42 male (66,7 %)	Dyspnea (17,5%) Dysosmia (16,1%) Fatigue (15,9%) Cough (7,9%) Dysgeusia (4,8%)	60 days after symptom onset
		Fatigue (9,5%) Cough (6,3%) Dysosmia (9,7%) Dysgeusia (1,6%)	120 days after symptom onset
Paterson et al. 2020 [18]	n=180 median age 39,9 98 women (54%) 82 male (46%)	Fatigue (28,9%) Anosmia (27,2%) Ageusia (15,6%) Joint pain (11,1%) Rhinorrhea (8,9%) Dyspnea (8,3%) Headache (7,2%) Myalgia (7,2%) Nausea (6,1%) Chest tightness (6,1%) Chills (4,4%) Cough (4,4%) Diarrhea (4,4%) Combination of symptoms 55%	125 days after symptom onset
Shah et al. 2020 [19]	n=60 median age 67 20 women (32%) 40 male (68%)	Dyspnea (20%) Cough (20%)	12 weeks after symptom onset
Sollini et al. 2020 [20]	n=10 median age 58 7 women (70%) 3 мужчины/male (30%)	Dyspnea (70%) Fatigue (70%) Ageusia (20%) Joint pain (20%) Chest pain (10%) Headache (10%) Trembling hands (10%)	>30 days after hospital discharge
Stavem et al. 2020 [21]	n=434 median age 49,8 244 women (56 %) 190 male (44%)	Dyspnea (15%) Smell dysfunction (12%) Taste dysfunction (10%) Arthralgia (9%) Myalgia (8,5%) Headache (6%) Dry cough (6%) Sore throat, chills, runny nose, vision disturbance, skin rash, conjunctivitis, ear pain, cramps, wheeze, confusion, gastrointestinal symptoms (<5%)	1,5 — 6 months after symptom onset
Surde et al. 2020 [22]	n=4 182 median age 42,8 2 991 women (71,5 %) 1 191 male (29,5 %)	Symptom lasting for >4 weeks (13,3%) Symptom lasting for >8 weeks (4,5%) Symptom lasting for >12 weeks (2,3%) Symptoms: fatigue, headache, dyspnoea, and anosmia	12 weeks after symptom onset
Townsend et al. 2020 [23]	n=128 median age 49,5 70 women (54%) 58 male (46%)	Fatigue (52,3%)	Median of 10 weeks after symptom onset
Van den Borst et al. 2020 [24]	n=124 median age 59 50 women (40%) 74 male (60%)	Decreased quality of life (72%) Fatigue (69%) Cognitive or mental impairments (36%)	3 months after hospital discharge
Wong et al. 2020 [25]	n=78 median age 62 29 women (36%) 49 male (64%)	Worsened quality of life (51%) Dyspnea (50%) Cough (23%) Combination of symptoms 76%	3 months after symptom onset
Y.M. Zhao et al. 2020 [26]	n=55 median age 47,5 23 women (41,8 %) 32/male (58,2 %)	Gastrointestinal symptoms (30,91%) Fatigue (16,36%) Headache (18,18%) Dyspnoea (14,55%) Cough and sputum (1,81%)	3 months after hospital discharge

Table 2. *Symptoms of COVID-19 in the acute and post-infectious periods*

Symptom	Occurrence in the acute period	Occurrence in the recovery period
Fatigue	about 80%	53,1%
Dyspnea	about 70%	43,4%
Arthralgia	about 56%	27,3%
Chest pain	about 40%	21,7%
Cough, sputum, joint pain	about 60%	<20%
Anosmia, rhinitis, taste disturbance	30-50%	<20%
Loss of appetite, Sikki syndrome, redness of the eyes, headache, dizziness, myalgia, diarrhea [13]	40-60%	<20%
Dyspnea	about 70%	39%
Fatigue	39%	39%
Insomnia	<10%	24%
Myalgia	30%	22%
Anosmia	40-50%	11%
Arthralgia, headache, abdominal pain, diarrhea	about 30%	<5%
Fever [12]	about 75%	<5%
Memory loss	13,3%	28,3%
Myalgia	15%	25%
Mood changes	41,7%	16,7%
Повышенная утомляемость/Fatigue	26,7%	6,7%
Impaired mobility [15]	11,7%	6,7%
Fatigue	67,3 — 76,9%	69%
Dyspnea	54,8 — 63,3%	53%
Cough	32,2 — 46,2%	34%
Depression [16]	61,1 — 93,3%	15%
Dyspnea	42,9%	17,5%
Dysosmia	40,3%	16,1%
Fatigue	55,6%	after 60 days — 15,9%, after 120 — 9,5%
Cough	63,5%	after 60 days — 7,9%, after 120 — 6,3%
Dysgeusia [17]	43,5%	after 60 days — 4,8%, after 120 — 1,6%
Dyspnea	57%	15%
Smell dysfunction	64%	12%
Taste dysfunction	68%	10%
Arthralgia	47%	9%
Myalgia	62%	8,5%
Headache	68%	6%
Dry cough [21]	67%	6%

In a telephone survey conducted by the Center for Disease Control and Prevention on a random sample of 292 individuals aged 18+ with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 performed on an outpatient basis, fatigue (71 %), cough (61%) and headache (61%) were the most common symptoms. The authors noted that 26% of persons aged 18–34 years (n = 85), 32% of those aged 35–49 years (n = 96), and 47% of those aged 50 years and above (n = 89) had symptoms that persisted for more than two weeks [27].

Mandal S. et al. (2020) presented data on the incidence of symptoms after novel coronavirus disease [16]. This study included 384 patients (62% — men, 38% — women) with average age of 59.9 years. Patients were observed at three major London clinics for novel coronavirus disease. Changes in their condition were monitored by phone or in person during examination 4–6 weeks after discharge from the hospital. The severity of dyspnea was assessed by the 11-point rating scale of dyspnea (Shortness of Breath Numerical Rating Scale), where a higher score (0–10) indicated serious pathological changes. Patients with abnormal blood tests or significant changes in X-ray examination at discharge were invited for re-examination. X-ray was evaluated using the platform of the British Society of Thoracic Imaging [28]. The severity of depression was established according to the results of the Patient Health Questionnaire-2 (PHQ-2) consisting of two questions and assessing the presence/absence of feelings of depression, hopelessness, interest in activities that previously gave pleasure. The follow-up period averaged 54 (from 47 to 59) days after discharge from the hospital. The average duration of hospital stay was 6.5 days (4–10.75); 14.5% of patients underwent treatment in the intensive care unit. Results of this study revealed that 53% of patients had persistent dyspnea, 34% had cough, 69% reported fatigue, and 14.6% of

subjects had depressive disorders. Out of 273 patients, 7.3% who received treatment in the hospital had persistent lymphopenia in the recovery period; 30.1% of 229 patients had an elevated D-dimer level, and 9.5% of 190 patients had increased C-reactive protein.

At the time of the first visit to the hospital, chest X-ray was performed for 333 of 384 (87%) patients. No pathological or infiltrative changes in lungs were found in 15%; 56% of patients had pathological changes typical for the acute period of disease; 29% had no identified pathology or had pathology not typical for COVID-19. Control X-ray was performed for 66% of patients: 151 (62%) had results consistent with the physiological picture; 66 (27%) showed significant improvement; the signs in 4 (2%) patients remained unchanged; 23 (9%) patients showed a significant deterioration on X-ray associated with pulmonary fibrosis.

Halpin S. et al. (2021) in January 2021, for the first time in the UK, provided data on the incidence of post-COVID-19 symptoms [29]. This study included 100 patients who were discharged from the largest university clinic (Leeds Teaching Hospitals NHS Trust) in Europe, with a capacity of about 1,800 beds. A telephone survey was conducted with recovering patients 4–8 weeks after discharge from the clinic, using the adapted questionnaire EQ-5D that included five questions and assessed subjective sensations of the patient's physical and mental state (mobility, personal care, daily activities, pain/discomfort, anxiety/depression). Patients were followed-up by a multidisciplinary team of specialists: physiotherapists, therapists, rehabilitation therapists, neuropsychologists. Follow-up period averaged 48 ± 10.3 days (from 29 to 71 days) after discharge from the hospital. The patients were divided into two groups. Group 1 included 32 patients (59.4% men) aged 58.5 (34–84) years who underwent intensive care; group 2 included 68 patients (51.5% men) aged 70.5 (20–93) years who received conventional therapy.

The most common symptoms during recovery were fatigue (in 72% of patients of group 1 and in 60.3% of group 2); dyspnea (in 65.6% and in 42.6% of patients, respectively) and psychological disorders (in 46.9% and in 23.5% of patients, respectively). According to the EQ-5D questionnaire, a clinically significant drop in quality of life was observed in 68.8% of patients in the intensive care group and in 45.5% in the conventional therapy group. Therefore, fatigue, shortness of breath and psychological stress associated with this disease were reported on average seven weeks after discharge from the hospital, which led to a significant drop in quality of life. These symptoms were present in patients regardless of intensive care, with a higher frequency in individuals of group 1.

As for the persistence of symptoms during the recovery period after COVID-19, these symptoms lasted longer than symptoms after community-acquired pneumonia. Wootton D. et al. (2017) showed that, on average, 97% of patients after pneumonia recovered by the 10-11th day of the disease [30]. Wyrwich K. et al. (2015) confirmed that dyspnea disappears, on average, 14 days after the onset of the first symptoms of pneumonia, and fatigue — after 20 days in a group of 201 patients (mean age 62.4 years, 45% men). The hospitalization period averaged 6.8 days, 91.4% of patients were hospitalized on the first day of the onset of pneumonia symptoms. The authors noted that chills, sweating and fever lasted less than a week, and fatigue, weakness and shortness of breath — less than three weeks. Other symptoms (headache, decreased appetite, dizziness, dyspepsia, body aches, sleep disturbance) persisted for 1-2 weeks [31]. The results indicate a longer period of symptoms after novel coronavirus disease compared with that of pneumonia, which requires further study of the post-COVID-19 recovery period.

Need for Individual Post-COVID Recovery Program

There are currently no approaches to consistent monitoring of the functional state of patients after novel coronavirus disease [10]. Of course, the lack of reliable information on the management of patients in the recovery period, specifically in the first three months of the disease, creates certain challenges in assessing dynamic changes in the clinical picture and in the development of therapeutic and preventive measures for physicians who work in outpatient health care.

The workload on the primary care unit requires rational approaches to the management of patients in the post-COVID period, given that, according to the World Health Organization, as of December 27, 2020, more than 79.2 million cases of the diseases had been registered in the world, and over 1.7 million were fatal [32].

Klok F. et al. (2020) proposed a scale for assessing the functional state of patients after COVID-19 [33] (Fig. 1).

This scale can be used to assess the effect of symptoms on the functional state of a person and allows assessing the changes in the post-COVID-19 recovery period. This scale is intended for use at various stages of the post-COVID period, which allows assessing the functional status and changes in the patient's recovery [33].

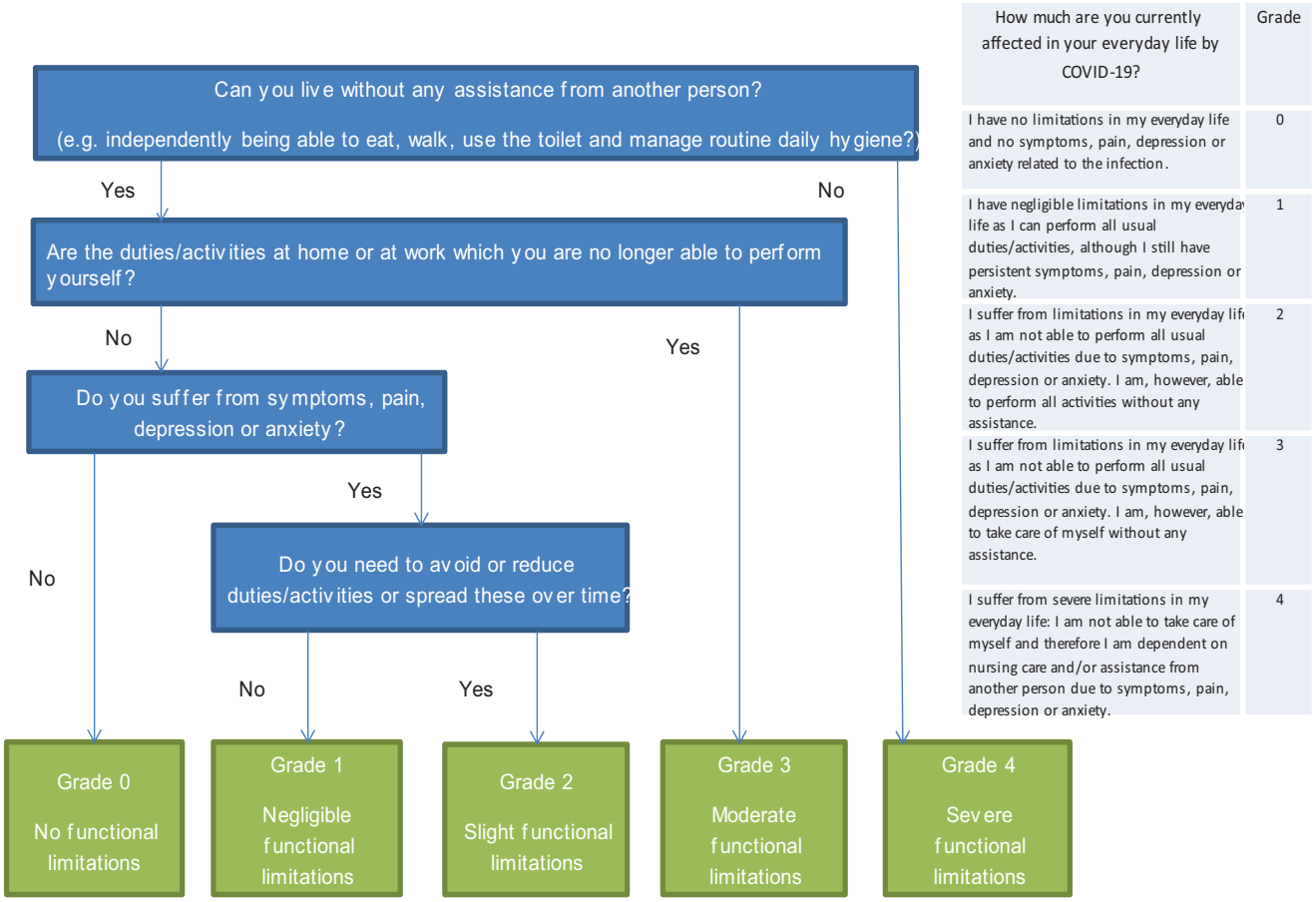

Figure 1. *The Post-COVID-19 Functional Status (PCFS) Scale (Klok et al., 2020)*

The main objective in the early days of the pandemic was the treatment and follow-up of patients in the acute period of the disease. Given that most patients are followed up on an outpatient basis, there is currently a need for management algorithms since many patients have residual symptoms after infection. Clear algorithms for the management of patients during the post-COVID period will surely not only reduce the burden on the outpatient unit but will also help reduce the number of re-hospitalizations, avoiding the complications associated with COVID-19 and improving the quality of life.

The Authors' Opinion on the Principles of Rehabilitation and Treatment of Patients after COVID-19

From our point of view, planning rehabilitation programs (rehabilitation treatment plan) should start during hospitalization (or in the acute period in the case of outpatient treatment) in order to further monitor the clinical condition of recovering patients and optimize their functional recovery. The continuity of hospital and outpatient stages plays a critical role in this process. Post-COVID-19 rehabilitation at the outpatient stage should start as early as possible and should include the following aspects:

- restoration/maintenance of functional status *(aimed at regression of clinical symptoms and their consequences)*,
- monitoring the course of chronic non-communicable diseases *(if any)*,
- maintaining mobility and mental health *(especially in elderly people)*,
- vaccine prophylaxis of acute infectious respiratory diseases.

When examining a patient at the outpatient stage after coronavirus disease, the general condition, respiratory symptoms and their severity, anthropometric and hemodynamic parameters, exercise tolerance *(possibly using a six-minute walk test)*, bad habits, risk factors, and the level of adherence to a healthy lifestyle should be assessed.

Depending on the severity of the condition, it is necessary to resolve the issue of dispensary follow-up of the patient on an individual basis. One should take into

consideration the reluctance to follow the physician's recommendations and poor adherence to a healthy lifestyle *(non-compliance with the principles of healthy nutrition, active lifestyle, and behavioral risk factors)* of outpatients of working age due to their formal attitude to preventive examinations and delayed response to examination results due to the lack of time because of work.

In the recovery period, it is important to recommend physical activity of any type depending on the individual characteristics of the person — breathing exercises, walking, exercise therapy. Aerobic exercises for 20-30 minutes are indicated at least three times a week for 8-12 weeks, taking into consideration weather conditions, the patient's condition and physical capabilities. Patients should be trained to monitor the effectiveness and safety of physical exertion, to know the "red flags" [5]. It is recommended to provide the patient with a leaflet/booklet containing recommendations on a healthy lifestyle, dietary habits, aerobic exercises, breathing exercises, etc. The set of measures should include a fixed date for the next follow-up visit to the physician or health center. Because the long-term consequences of new infections are still being studied, the determination of the frequency and indications for consultations with specialists (physiotherapy physician, rehabilitation physician, dietitian, physiotherapist, etc.) seems promising at the outpatient stage.

Conclusion

Literature and clinical data show a variety of clinical manifestations in the post-COVID period in both young and elderly people. On average symptoms persist for about 2-3 months, which physicians in the management of outpatients should consider.

Almost all authors emphasize the need for thorough monitoring and analysis of the clinical picture during the post-COVID period. Colleagues abroad suggest the gradation of this period by the duration of symptoms, dividing it into post-acute (sub-acute) and chronic. Considering that the pathogenesis of this disease is not fully understood, the exact duration and features of the post-COVID period require further study.

It is extremely important that the provision of medical care to this vulnerable group of patients be based on an interdisciplinary approach and the continuity of the inpatient and outpatient stages. Moreover, this approach will allow to effectively and consistently implement therapeutic measures to improve the physical and mental health of most patients recovering from COVID-19.

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АРТЕРИАЛЬНАЯ ЖЕСТКОСТЬ И СОСУДИСТОЕ СТАРЕНИЕ: ПОСЛЕДСТВИЯ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Arterial Stiffness and Vascular Aging: Effects of Hypertension

Резюме

В настоящем обзоре освещены вопросы взаимосвязи возраста и артериальной гипертензии, наблюдаемой в процессе старения организма. Проанализированы основные структурно-функциональные изменения, лежащие в основе повышения сосудистой жесткости. Отмечено сходство сосудистых изменений при старении и при артериальной гипертензии. Рассмотрено негативное влияние повышенного центрального артериального давления на органы-мишени. Уделено внимание анализу артериальной жесткости, как маркеру сосудистого старения. Отдельно освещены показатели каротидно-феморальной скорости распространения пульсовой волны, сердечно-лодыжечного сосудистого индекса (CAVI), лодыжечно-плечевого индекса, пальце-плечевого индекса и индекса аугментации. Рассмотрена прогностическая и клиническая ценность параметров сосудистой ригидности. Также отмечена независимая диагностическая и прогностическая ценность показателя сердечно-лодыжечного сосудистого индекса (CAVI).

Ключевые слова: *артериальная гипертония, старение, скорость пульсовой волны, центральное аортальное давление, индекс аугментации, эластичность артерий, артериальная жесткость, сосудистая жесткость*

Конфликт интересов

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

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Abstract

This review highlights the relationship of age and arterial hypertension observed in the aging process. The main structural and functional changes underlying the increase in vascular stiffness are analyzed. The similarity of vascular changes in aging and arterial hypertension was noted. The negative effect of increased central blood pressure on target organs is considered. Attention is paid to the analysis of arterial stiffness as a marker of vascular aging. The parameters of the carotid-femoral pulse wave propagation velocity, the cardio-ankle vascular index (CAVI), the ankle-brachial index, the finger-brachial index, and the augmentation index were examined separately. The prognostic and clinical value of the parameters of vascular

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stiffness is considered. In particular, the clinical guidelines for arterial hypertension report the need to use arterial stiffness indicators to improve the accuracy of cardiovascular risk stratification, especially in medium-risk patients. Measurement of vascular stiffness and central aortic pressure should be recommended as one of the methods for stratifying cardiovascular risk in patients with intermediate SCORE risk, as well as in those whose target organ damage was not detected by routine methods. The article also notes the independent diagnostic and prognostic value of the CAVI.

Key words: *arterial hypertension, aging, pulse wave, central aortic pressure, augmentation index, arterial elasticity, aortic rigidity, vascular stiffness*

Conflict of interests

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AH — arterial hypertension, AI — augmentation index, BP — blood pressure, CAVI — cardio-ankle vascular index, LV — left ventricle, PWV — pulse wave velocity, SBP — systolic BP

Introduction

The elderly and senile population is rising [1]. Arterial hypertension (AH) is the main factor contributing to the risk of cardiovascular complications and mortality in this age group [2].

The relationship between age and AH observed during the aging process is of great practical importance [3]. This is accompanied by a number of changes in the vascular system, particularly endothelial dysfunction, increased vascular stiffness, vascular wall remodeling and inflammation, defined as the so-called «vascular phenotype» of AH [4]. Such changes in blood vessels in young individuals with arterial hypertension suggest «premature» or «early» vascular aging [5].

Structural and Functional Changes in Blood Vessels During Aging

Physiological changes in the vascular wall are progressive and develop throughout life [6, 7]. Subclinical thickening of the intima-media complex is associated with aging and is also a predictor of future cardiovascular events [8].

Physiological aging affects elastic type vessels more than muscle type vessels; changes develop regardless of the progression of atherosclerosis [9]. The main changes during arterial remodeling affect the intima and middle layer [10]. Along with morphological rearrangement due to atherosclerosis, age-related involution of structural proteins — elastin, fibulin, collagen — is observed in the arterial medial layer and, as a result, thinning, splitting, and fragmentation of elastic fibers develop [7]. Their degeneration is associated with increased collagen, decreased elastin and calcium deposition [11]. Calcification of vascular media is a sign of vascular aging. Endothelial cells of the intima change their size and shape; their function progressively worsens [12]. There is a thickening of the subendothelial layer, separation of endothelial cells from smooth muscle cells, and an increase in the amount of connective tissue [13]. In the end, functional changes progress in the form of endothelial dysfunction [12]. In particular, endothelium-dependent vasodilation decreases due to less production of biologically active substances with a vasodilating effect by endothelial cells, i.e., endothelin-1 and nitric oxide (NO) [14]. Nitric oxide is also known to have an anti-atherosclerotic effect [15]. Decreased vascular elasticity leads to the reduced release and bioavailability of nitric oxide, which is the trigger for the formation of atherosclerotic plaques and may result in a further increase in arterial stiffness [16].

Parallels Between Vascular Changes in Hypertension and Aging

Many mechanisms associated with vascular changes during aging are also activated in hypertension leading to impaired rheological properties of blood, endothelial dysfunction, vascular inflammation, remodeling and increased arterial stiffness [7, 17]. In individuals with risk factors due to genetic, environmental, or intrauterine determinants of fetal development, the processes of vascular changes are accelerated; they lead to early vascular aging, which predisposes to cardiovascular diseases [18]. Numerous risk factors such as smoking, hypercholesterolemia, hypertension, type 2 diabetes mellitus intensify arterial aging processes, partly due to increased oxidative stress, activation of pro-inflammatory mechanisms and changes in the regulation of the renin-angiotensin-aldosterone

system [19]. Association, mainly with diabetes, significantly increases the risk of micro- and macrovascular complications and cardiovascular morbidity [20]. As with aging, in case of arterial hypertension, there is decreased endothelium-dependent vasodilation, decreased bioavailability of NO, breakdown of NO synthase, increased oxidative stress, and development of endothelial dysfunction [21]. In large arteries, these molecular and cellular processes are manifested as increased arterial stiffness, which causes elevated central blood pressure, leading to isolated systolic hypertension, which is common in the elderly population [22]. However, the exact mechanisms causing these cellular and vascular events are not entirely clear, and it is quite difficult to differentiate the "age-related effect" from the "blood pressure effect". Vascular properties are thought to depend on the effect of several interdependent factors that change along with body aging throughout life [23].

Arterial Stiffness in Terms of Cardiovascular Disease Continuum

Mechanical changes associated with structural and functional disorders are characterized by decreased compliance, elasticity/extensibility and increased stiffness of the vascular wall [24]. Narrowing of the arterial lumen due to the destruction of elastic fibers in the middle layer and collagenous remodeling leads to increased pulse pressure in the aorta and increased pulse wave velocity (PWV) [24, 25]. Increased aortic stiffness causes changes in the functioning of the cardiovascular system as a whole. A less extensible aorta cannot effectively dampen blood volume ejected into the systole by the left ventricle, leading to increased central systolic blood pressure (SBP), thereby increasing the afterload on the left ventricle (LV) and contributing to its hypertrophy [26]. Since the efficiency of cardiac output is determined by the global contractile function of the LV, the elasticity of main arteries, and general peripheral resistance, it is the central and not peripheral BP that determines the level of the afterload on LV walls during systole [27]. High aortic SBP for a given stroke volume requires a large amount of energy in LV systole, which ultimately reduces the efficiency of cardiac output [28]. Reduced coronary blood flow due to increased central pulse BP in vessels with increased stiffness can pathogenetically determine LV diastolic dysfunction in patients with AH and may ultimately lead to heart failure [29]. This hypothesis is confirmed by the fact that the risk factors for heart failure include AH, atherosclerosis, and age, which are also associated with increased arterial stiffness and central BP. Early detection of heart failure without reduced ejection fraction is an urgent problem; functional diagnostic methods are actively used for its management [30, 31]. Therefore, the analysis of the elastic properties of blood vessels from the perspective of a comprehensive assessment of the effect of cardiovascular risk factors on the prognosis may be promising.

Assessment of Vascular Stiffness

Assessment of arterial stiffness was proposed as a marker of vascular aging. Since invasive assessment of arterial wall elasticity during vascular catheterization is quite laborious and not economically viable for screening, non-invasive methods, particularly volumetric sphygmography, dopplerography, and magnetic resonance imaging (MRI), are used widely. One of the primary methods for assessing arterial stiffness is the determination of pulse wave velocity (PWV) using sphygmography [32]. A value of carotid-femoral PWV of more than 10 m/s may indicate an increased risk of adverse cardiovascular events [33]. Modern devices with various tranducers are used to determine PWV. The Complior System (Colson, Les Lilas, France) includes a mechanical tranducer; methods based on applanation tonometry (for example, a «conventional» SphygmoCor device, AtCor Medical, West Ryde, NSW, Australia) include a Millar piezoelectric «tonometer». Devices such as the VP1000, Omron Healthcare (Kyoto, Japan), VaSera — N1000 (Fukuda Denshi, Japan) are based on the oscillometric method (Fig. 1).

VaSera — N1000 (1500) volumetric sphygmography devices enables to measure PWV on the ankle-brachial segment; the cardio-ankle vascular index (CAVI), ankle-brachial index (ABI), finger-brachial index (FBI) and augmentation index (AI) are automatically calculated based on the measurement [34] (Fig. 2, 3).

It should be noted that as a derivative of cardiopulmonary PWV, the CAVI index can be considered a parameter of "true arterial stiffness" that is less dependent on intravascular BP [35]. Table 1 shows threshold CAVI values in different age groups of the Russian population [34].

Besides the assessment of arterial stiffness based on PWV, analysis of aortic pulse pressure and augmentation index (AI) may be important for describing the state of the cardiovascular system since they characterize the elasticity, which has an effect on the formation of reflected vascular waves [31, 36].

Local vascular stiffness using imaging methods can be determined by analyzing the diameter of superficial and deep arteries in systole and diastole. Examples of the assessment of local aortic stiffness include MRI and ultrasound echo tracking [25, 32].

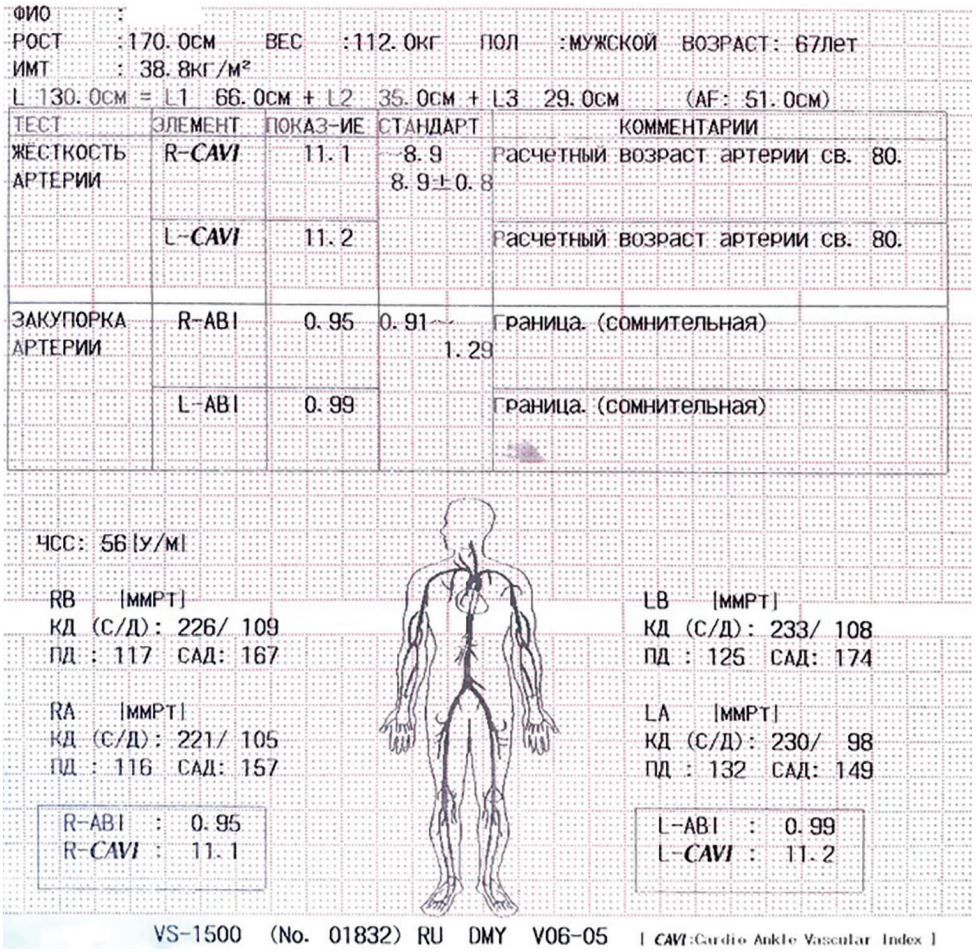

Figure 1. *CAVI evaluation Protocol. The figure shows (from top to bottom) ECG curves, phonocardiograms, plethysmograms from the right and left upper and lower extremities*

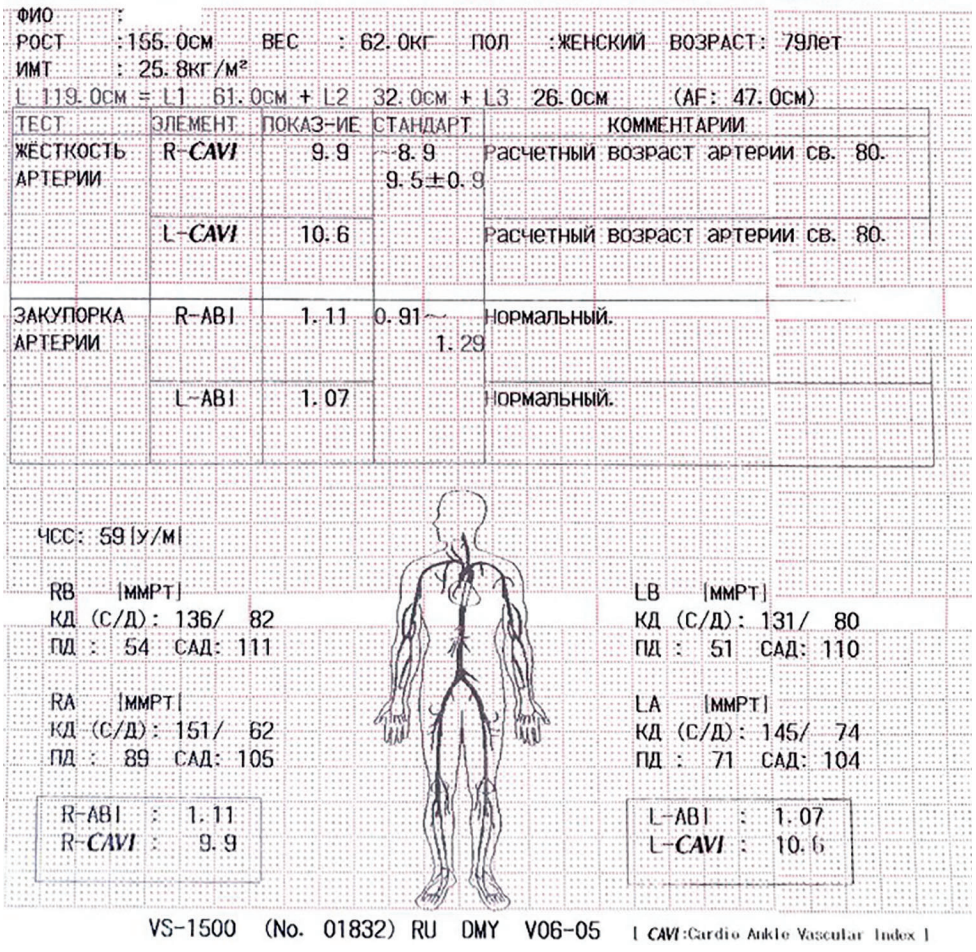

Figure 2. *CAVI evaluation Protocol, continued. The table shows the indicators of the cardio-ankle-vascular index (CAVI) on the right and left-top and the ankle-shoulder index (ABI) on the right and left-bottom, measured in a 79-year-old woman. The indicators presented in the table correspond to the age norm*

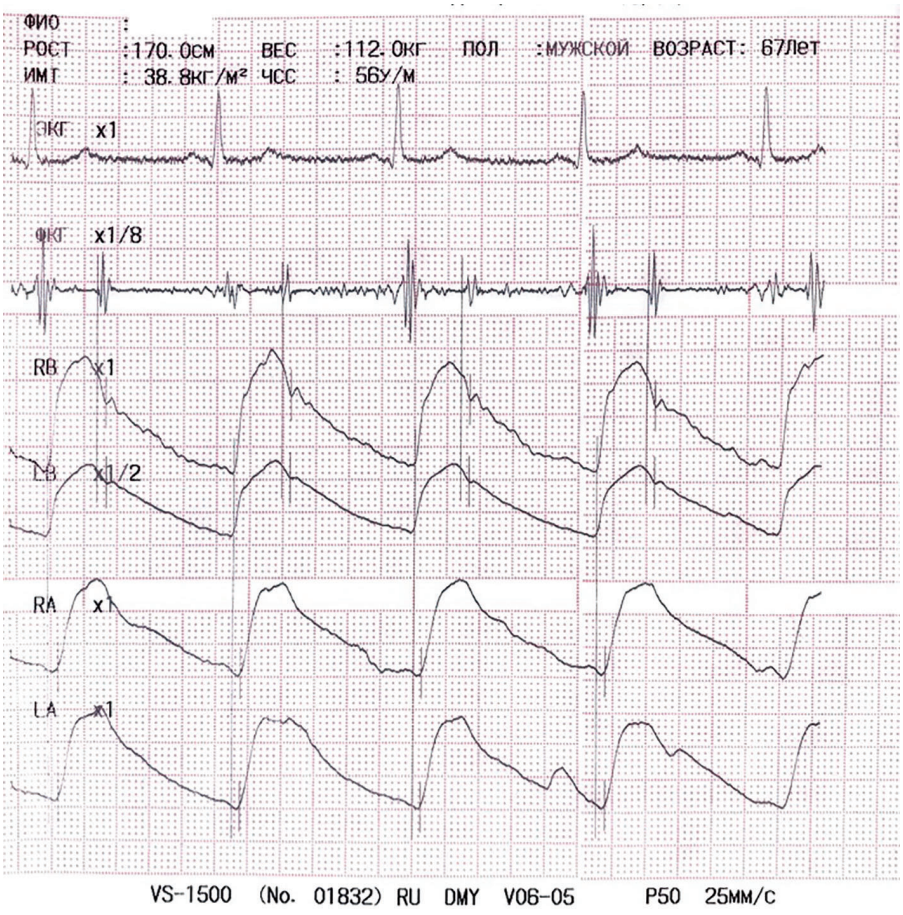

Figure 3. *CAVI evaluation Protocol, continued. The table shows the indicators of the cardiovascular-ankle-vascular index (CAVI) on the right and left-top and the ankle-shoulder index (ABI) on the right and left-bottom, measured in a 67-year-old man. Indicators (CAVI, ABI) presented in the table above the age norm (the upper limit of the norm for CAVI is 10, for ABI-0.9)*

Table 1. *CAVI indicators depending on age according to research data in the Russian population (M±SD) [34]*

Age	<20 years	21-30 years	31-40 years	41-50 years	51-60 years	61-70 years	>70 years
Indicator CAVI	6,7±0,76	7,2±0,61	7,4±0,63	7,55±0,7	8,0±0,67	8,5±0,64	9,8±1,51

Arterial Stiffness Application in Prediction

Assessment of arterial elasticity is important from a clinical point of view, since it correlates with the pathogenesis of a wide range of cardiovascular and cerebrovascular diseases, in particular, such as AH, cerebrovascular accident, vascular cognitive impairment [34, 37–39]. Improving knowledge and early detection of vascular aging can help improve the prevention of cardiovascular and cerebrovascular diseases. Cardiovascular diseases are known be asymptomatic for a long time since multiple organ lesions are based on a subclinical decrease in elasticity and an increase in arterial stiffness of main arteries [39]. Therefore, patients with subclinical lesions are at higher risk of developing a symptomatic disease compared with patients with traditional risk factors [39]. European (2018) and Russian (2020) clinical guidelines on AH allow using arterial stiffness parameters to increase the accuracy of cardiovascular risk stratification, especially in patients with moderate risk [40, 41]. The measurement of vascular stiffness and central aortic pressure should be recommended as one of the methods of cardiovascular risk stratification in patients with moderate risk on the SCORE scale (Systematic COronary Risk Evaluation), and if lesions of target organs are not detected by routine methods [27, 28]. There are data suggesting that central BP is a more reliable prognostic factor for death from cardiovascular diseases and all causes than BP in the brachial artery [29].

Several studies revealed the independent diagnostic and prognostic value of CAVI [41, 42]. According to some experts, CAVI may be useful for screening, ongoing monitoring and evaluation of the effect of treatment [34].

Conclusion

Remodeling of blood vessels during the aging of the human body is based on pathogenetic mechanisms that play an important role in the development of arterial hypertension. Assessment of stiffness in the main arteries is of great interest for the development of non-invasive diagnostic methods for pathophysiology, pharmacology,

and general practice, and is important for assessing cardiovascular risk and determining the prognosis for existing cardiovascular or cerebrovascular disease.

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АСПИРАЦИОННЫЙ ПНЕВМОНИТ ПРИ НАЗАЛЬНОЙ ЛИКВОРЕЕ. ОБЗОР ЛИТЕРАТУРЫ

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Aspiration Pneumonitis with Nasal Liquorrhea. Literature Review

Резюме

Повреждение мозговых оболочек в сочетании с наличием дефекта костных структур основания черепа и формированием сообщения с полостью носа или околоносовыми пазухами являются необходимыми условиями назальной ликвореи. Существует целый ряд осложнений назальной ликвореи различного происхождения: инфекционные (менингит, абсцесс мозга), пневмоцефалия, аспирационный пневмонит и гастрит. Проведен обзор литературы, относящейся к аспирационному пневмониту при назальной ликвореи. Было отобрано 4 статьи с описанием 9 случаев. Проведен анализ демографических показателей пациентов, клинических данных, особенностей лечения. Исходя из анализа литературы, аспирационный пневмонит является редким осложнением назальной ликвореи. Для проведения дифференциальной диагностики с другими видами пневмонита необходимо опираться на дополнительные клинические данные, такие как односторонние выделения прозрачной жидкости из носа при наклоне головы, ухудшение состояния и усиление симптомов в горизонтальном положении, отсутствие синдрома системного воспалительного ответ, неэффективность антибактериальной терапии, рецидивирующий характер течения. Антибактериальная терапия не приводит к излечению пациента от пневмонита. Для лечения этой патологии необходимо прежде всего устранить причину аспирации — выполнить пластику дефекта основания черепа при отсутствии противопоказаний со стороны анестезиологического пособия.

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

Конфликт интересов

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

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Abstract

Damage to the meninges in combination with the presence of a defect in the bone structures of the base of the skull and the formation of communication with the nasal cavity or paranasal sinuses are necessary conditions for nasal liquorrhea. There are a number of complications of nasal liquorrhea of various origins: infectious (meningitis, brain abscess), pneumocephalus, aspiration pneumonitis and gastritis. A review of the literature related to aspiration pneumonitis in nasal liquorrhea has been carried out. 4 articles were selected with descriptions of 9 cases. The analysis of demographic indicators of patients, clinical data, treatment characteristics was carried out. Based on the analysis of the literature, aspiration pneumonitis is a rare complication of nasal liquorrhea. For differential diagnosis with other types of pneumonitis, it is necessary to rely on additional clinical data, such as unilateral discharge of clear fluid from the nose when tilting the head, worsening of the condition and intensification of symptoms

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in a horizontal position, absence of systemic inflammatory response syndrome, ineffectiveness of antibiotic therapy, recurrent the nature of the flow. Antibiotic therapy does not cure the patient from pneumonitis. For the treatment of this pathology, it is first of all necessary to eliminate the cause of aspiration — to perform plastic surgery of the skull base defect in the absence of contraindications from the side of anesthetic aid.

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

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BMI — body mass index, CPAP — constant positive airway pressure, CT — computed tomography

Introduction

CSF rhinorrhea occurs only if damage to the meninges, skull base fracture and a leakage into the nasal cavity or paranasal sinuses are combined [1]. The most common causes of this state include traumatic brain injuries (traumatic CSF leak), as well as endoscopic and neurosurgical interventions (iatrogenic CSF leak). Also, CSF leak can be of idiopathic origin (spontaneous CSF leak); it is often associated with increased intracranial pressure, metabolic and endocrine disorders [2, 3].

Abundant watery nasal discharge may inconvenience the patient with CSF rhinorrhea but poses no direct threat to life and cannot lead to the complete emptying of cisterns and cerebrospinal fluid spaces. Due to compensatory mechanisms, CSF rhinorrhea results in increased production and decreased reabsorption of cerebrospinal fluid [4]. However, CSF rhinorrhea has a number of complications of various origin. These include infectious complications (meningitis, brain abscess), pneumocephalus, aspiration pneumonitis and gastritis [5].

Pneumonitis is a disease with pathogenesis based on damage to the walls of alveoli and lung parenchyma, which results in their scarring and fibrotic changes. Pneumonitis can be induced by autoimmune diseases, exposure to chemicals, infectious agents, radiation or aspiration [6]. Aspiration pneumonitis develops when the contents of the oropharynx or stomach enter the lower respiratory tract. Risk factors for aspiration include conditions with impaired consciousness, traumatic brain injuries, and diseases with symptoms of dysphagia [7].

In 2016, Justin Seltzer et al. [8], for the first time, described a case of aspiration pneumonitis in a 44-year-old woman with CSF rhinorrhea. In previous series analyzing skull base defect management, authors focused on the diagnosis and surgical methods for CSF rhinorrhea [9]. Aspiration pneumonitis associated with cerebrospinal fluid leak is underestimated in clinical practice.

Patients with profuse CSF rhinorrhea often complain of coughing at night because, when they are in supine body position, cerebrospinal fluid enters the lower respiratory tract through the nasal cavity and nasopharynx and irritates the mucous membrane of the larynx and pharynx [10].

Objective: review of articles on aspiration pneumonitis with CSF rhinorrhea to identify patterns of development of this complication and develop optimal management for patients.

Materials and Methods

A review of articles from the Pubmed database published between 2000 and 2021 was carried out. Literature was searched using the following keywords: “CSF rhinorrhea”, “skull base damage”, “aspiration pneumonitis”, “complications of CSF rhinorrhea”. Inclusion criteria: articles in English and Russian reporting on aspiration pneumonitis with CSF rhinorrhea and mentioning diagnosis and the approach to the management of this complication. Exclusion criteria: articles with no mention of lung damage associated with CSF rhinorrhea or with insufficient data. We found four articles describing nine cases. Analysis of demographic parameters (gender, age, body mass index (BMI)), clinical data (symptoms, etiology of CSF leak, X-ray data), treatment features (previous conservative therapy, type of approach, plastic surgery materials, use of lumbar drainage) was carried out.

Results

According to the analysis, the average age of patients was 51 years (range 33–76 years). Most of patients were

female — eight (88.9%); male — one (11.1%). Seven (77.8%) patients were overweight, and five (55.6%) had grade 3 obesity. The most frequent complaints included nasal discharge, cough, and shortness of breath. Increased body temperature and typical signs of intoxication were found in two (22.2%) cases. X-ray of the chest in most cases revealed ground-glass opacity pattern. There was no relationship between the damaged side of the skull base and the affected lung; bilateral airiness disorders were often found. According to brain computed tomography (CT), in four (44.4%) cases, the defect was localized in the ethmoid roof, in three (33.3%) cases — in the cribriform plate, in one (11.1) case — in the sphenoid sinus, and in one (11.1) case — in the petrous pyramid of the temporal bone. Demographic and clinical data of patients are shown in Table 1.

The authors used different treatment methods. In their description of the first six cases, Maya Or et al. [11] performed plastic surgery for cerebrospinal fluid fistula without management of pneumonitis during pre- and postoperative periods. Endoscopic endonasal approach was used in five patients, and postaural approach — in one patient (in case of a defect of the petrous pyramid of the temporal bone). Deep fascia of thigh and pedicled nasoseptal flap were used for the correction of defects. Further, patients underwent average follow-up of 20.5 months in the center with the subsequent CT of the chest. The authors report the complete postoperative resolution of pneumonitis after eliminating its causes.

Justin Seltzer et al. [8] report that their patient underwent several courses of antibiotic therapy. However, therapy was ineffective, and she was prescribed symptomatic treatment with glucocorticosteroids, adrenergic agonists and antitussive agents. The patient was referred to a thoracic surgeon who performed a biopsy of the upper lobe of the right lung. However, nothing was revealed apart from signs of acute bronchopneumonitis.

Table 1. *Demographic and clinical indicators of patients*

№, Author	Gender	Age	Etiology	BMI	Complaints	X-ray / CT of the lungs	Defect localization
1 [Maya Or] [11]	F	76	Spontaneous	37	Rhinorrhea on the right, shortness of breath, cough	Central and peribronchial ground-glass opacities in all lobes	Right ethmoid region
2 [Maya Or] [11]	F	51	Spontaneous	36	Rhinorrhea on the right, intermittent cough, meningitis	Bilateral ground-glass opacities with bronchial wall thickening	Right lateral sphenoid
3 [Maya Or] [11]	F	44	Spontaneous	37	Recurrent rhinorrhea on the right, shortness of breath on exertion, cough, hoarseness	Bilateral patchy opacities in lower lobes (left > right)	Right cribriform plate
4 [Maya Or] [11]	F	54	Spontaneous	41	Rhinorrhea on the left, headache	Ground-glass opacities in all right lobes	Left ethmoid region
5 [Maya Or] [11]	F	36	Spontaneous	31	Rhinorrhea on the left, cough, shortness of breath, wheezing	Ground-glass opacities in both upper lobes + left lower lobe	Left ethmoid region
6 [Maya Or] [11]	M	64	Spontaneous	21	Rhinorrhea on the left	Ground glass opacities bilaterally, bronchial wall thickening, borderline bronchiectasis	Left tegmen mastoideum
7 [Justin Seltzer] [8]	F	44	Spontaneous	36,5	Rhinorrhea on the right, cough, shortness of breath on exertion, hoarseness	Bilateral violation of the airiness of the lungs in the lower lobes	Right ethmoid region
8. [Mark G Jones] [12]	F	33	Spontaneous	N/a	Discharge from the nose, cough, heaviness and pain in the chest, fever	Bilateral ground-glass opacities	Cribriform plate
9 [Wasgewatta] [13]	F	53	Spontaneous	35	Discharge from the nose, cough, fever	Bilateral ground-glass opacities in the lower lobes	Right cribriform plate

Note: BMI — Body mass index, X-ray — Roentgen examination, CT — computed tomography

The patient was then referred to an ENT specialist who noticed the constant nasal discharge and prescribed a test to determine β2-transferrin in nasal secretion. The patient was referred to the neurosurgical department, where endoscopic endonasal plastic surgery of the skull base defect was performed. During surgery, lumbar drainage was placed and fluorescein sodium was used. The authors report an uneventful postoperative period. CT of the lungs in 11 months revealed no signs of lung tissue damage. This case demonstrates the late diagnosis of CSF rhinorrhea after unsuccessful management of pneumonitis and confirms the conclusion that the cause of aspiration should be eliminated.

Mark G. Jones et al. [12] reported a similar case. Nasal discharge in this case was described as occasional. The patient repeatedly underwent antibiotic therapy for bilateral pneumonia. However, her clinical picture included signs of intoxication (fever, neutrophilia, swollen lymph nodes). Bronchoscopy revealed *Haemophilus influenzae*. A two-week course of amoxicillin/clavulanate and azithromycin helped improve the patient's condition. However, later on, symptoms of pneumonia recurred since the discontinuation of antibiotics led to worsening. As in the previous case, the patient also underwent a biopsy, but its results revealed nothing but bronchiolitis. Aspiration pneumonitis was suggested, and brain magnetic resonance imaging revealed a defect in the region of the cribriform plate. After the plastic surgical correction of this skull base defect, symptoms of pneumonitis regressed.

Sanjiwika Lalanjani Wasgewatta et al. [13] reported a case of spontaneous CSF rhinorrhea and pneumonia during CPAP-therapy (CPAP — Constant Positive Airway Pressure, mode of mechanical ventilation with constant positive pressure) for obstructive sleep apnea syndrome. After the treatment course, the patient began to complain of coughing, headache, nasal discharge and fever. The patient was prescribed acetozalomide (diacarb), after which the patient noted a decrease in headaches and nasal discharge. Another patient underwent endoscopic endonasal plasty of skull base defect and ventriculoperitoneal shunting. The authors reported that a week after this surgery, a second CT of the chest revealed no signs of lung tissue damage.

Discussion

Aspiration is defined as the accidental transfer of oropharyngeal or gastric contents (endogenous factors) or fluid and particulate matter (exogenous factors) into the lower respiratory tract. Clinical response to aspiration depends on the nature of the aspirated material, airway microbiocenosis, and colonization by pathogenic organisms [14].

With profuse CSF rhinorrhea, CSF can enter bronchi and alveoli, which may lead to irritation in the respiratory tract. Although patients with skull base defects often complain of coughing in supine body position, cases of pneumonitis as a complication of CSF rhinorrhea have not been adequately described in the literature.

All patients in this study had spontaneous CSF rhinorrhea, which is more common in menopausal women with obesity. There are studies that prove the relationship between obstructive sleep apnea syndrome and spontaneous CSF rhinorrhea [15, 16]. According to a meta-analysis conducted by Bakhsheshian J. et al. (2015), the risk of CSF rhinorrhea is 4.73 times higher in patients with obstructive sleep apnea syndrome than in the control group [17]. However, we found in the literature only a handful of reports of cases of spontaneous CSF rhinorrhea after the start of CPAP therapy [18, 19]. The mechanism of this complication is believed to be associated with changes in intracranial pressure and venous pressure of cerebrospinal fluid [20].

X-ray is used for the diagnosis of pneumonitis (radiography, chest CT). The most common symptom in patients was ground-glass opacity, which is an indicator of lung tissue density and a sign of interstitial infiltration. Ground-glass opacity is represented by a certain area with moderately reduced lung tissue airiness.

This phenomenon is caused by the thickening of interalveolar septa and their partial filling [21]. Differential diagnosis with other types of pneumonitis should be based on additional clinical data, such as unilateral discharge of clear liquid from the nose when the head is tilted, state worsening and intensification of symptoms in a lying position, the frequent absence of systemic inflammatory signs (according to SIRS: fever >38.0 °C or hypothermia <36.0 °C, tachycardia >90 beats per minute, tachypnea >20 breaths per minute, leukocytosis $>12\times10^9$/l or leukopenia $<4\times10^9$/l), absence of a response to antibiotic therapy, and a recurrent disease course. In our country, CSF rhinorrhea is diagnosed based on a laboratory test to determine glucose in nasal secretions, endoscopic examination, CT cisternography, and high-resolution CT [22].

All authors reported that antibiotic therapy was ineffective since lung damage was caused not by infectious agents but by aspiration. Symptoms quickly regressed after successful reconstruction of cerebrospinal fluid fistula. These data suggest that the resolution of pneumonitis depends primarily on the management of the underlying cause (chronic aspiration); antibiotic therapy has no effect on the outcome. Therefore, at the stage of differential diagnosis of lung damage associated with CSF rhinorrhea, it is very important to pay attention to additional clinical signs, such as unilateral nasal discharge of

clear liquid, increased coughing in lying position, and no signs of intoxication.

This analysis is limited by the small number of publications, cases, and retrospective study design. To obtain reliable results, a large-scale prospective study is required.

Conclusion

Aspiration pneumonitis is a rare complication of CSF rhinorrhea that is associated with chronic nasal cerebrospinal fluid leakage via CSF pathways due to skull base defects. This type of aspiration pneumonitis is resolved only after eliminating the cause of CSF rhinorrhea.

Differential diagnosis with other types of pneumonitis should be based on additional clinical data, such as unilateral discharge of clear liquid from the nose when the head is tilted, state worsening and intensification of symptoms in a lying position, no systemic inflammatory signs, no response to antibacterial therapy, and recurrent course of disease. This disorder should be managed, first of all, by eliminating the cause of aspiration, i.e., performing plastic surgery of skull base defect if there are no contraindications for anesthesia.

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КОРОНАВИРУСНАЯ ИНФЕКЦИЯ У ПАЦИЕНТА С ОЖИРЕНИЕМ (ОБЗОР ЛИТЕРАТУРЫ)

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Coronavirus Infection an Obese Patient (Literature Review)

Резюме

В современном мире проблема ожирения на фоне пандемии новой коронавирусной инфекции приобрела особую опасность. С одной стороны, распространенность ожирения среди населения неуклонно растет, с другой — доказано, что лица с ожирением относятся к группе наиболее уязвимых в аспекте повышенного риска заражения и неблагоприятного прогноза. Это связано с наличием и особенностями развития различных патологических механизмов у данной категории больных. К ним относятся высокая экспрессия ангиотензинпревращающего фермента 2, высокая вероятность развития «цитокинового шторма», поддержание хронического воспалительного процесса в жировой ткани, изменение активности фермента дипептидилпептидазы-4, которые приводят к усугублению нарушения метаболизма в жировой ткани, а также нарушению иммунной протекции. Тяжесть состояния больных с ожирением, госпитализированных с COVID-19 (COronaVIrus Disease 2019), обусловлена наличием полиморбидности. Мировая врачебная практика в борьбе с пандемией COVID-19 показывает, что больные коронавирусной инфекцией на фоне ожирения чаще требуют госпитализации в отделения реанимации и интенсивной терапии и подключения к аппаратам искусственной вентиляции легких. В настоящее время продолжают изучаться особенности течения коронавирусной инфекции на фоне ожирения. К их числу относятся наличие тяжелой дыхательной недостаточности, высокий риск развития респираторного дистресс-синдрома, тромбозов и тромбоэмболических осложнений, а также ухудшение течения хронических сердечно-сосудистых заболеваний, что приводит к развитию полиорганной недостаточности и смерти. Разработка лекарственных препаратов учитывает механизмы проникновения вируса в клетку, особенности его патофизиологии и взаимодействия с организмом человека.

Ключевые слова: *ожирение, коронавирусная инфекция, ангиотензинпревращающий фермент, цитокиновый шторм, респираторный дистресс-синдром*

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Abstract

In the modern world the problem of obesity in combination with new coronavirus infection has acquired a special danger. On the one hand, the prevalence of obesity among the population is steadily increasing, on the other-it has been proven that obese people are among the most vulnerable in terms of increased risk of infection and a serious prognosis. This is due to the presence and peculiarities of the development of various pathological mechanisms in this category of patients. These include: high expression of angiotensin-converting enzyme 2, a high probability of a «cytokine storm» developing, maintenance of a chronic inflammatory process in adipose tissue, changes in the activity of Dipeptidyl peptidase-4 enzyme. All these processes lead to an aggravation of metabolic disorders in adipose tissue and violation of immune protection. The world medical practice in the fight against the COVID-19 pandemic shows that patients with coronavirus infection against the background of obesity more often need hospitalization in intensive care units and connection to artificial ventilation equipment. Currently, many features of the course of coronavirus infection against the background of obesity have been identified and continue to be studied. These include: the presence of severe respiratory failure, a high risk of developing respiratory distress syndrome, thrombosis and thromboembolic complications, as well as worsening of the course of chronic cardiovascular diseases. All this eventually leads to the development of severe multiple organ failure, which is often the cause of death in this category of patients.

Key words: *obesity, coronavirus infection, angiotensin converting enzyme, cytokine storm, respiratory distress syndrome*

Conflict of interests

The authors declare no conflict of interests

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ACE-2 — angiotensin-converting enzyme 2, AT — adipose tissue, ATI — adipose tissue inflammation, AH — arterial hypertension, ARDS — acute respiratory distress syndrome, BMI — body mass index, BP — blood pressure, CHD — coronary heart disease, CVI — coronavirus infection, DM — diabetes mellitus, DM 2 — type 2 diabetes mellitus, DPP-4 — dipeptidyl peptidase-4, IL — interleukin, IR — insulin resistance, MS — metabolic syndrome, MV — mechanical ventilation, OB — obesity, TNFα — tumor necrosis factor α

Introduction Coronavirus Pandemic in the Setting of Obesity Epidemic

The problem of obesity (OB) existed before the COVID-19 (COronaVIrus Disease 2019) pandemic. Today, obesity (OB) is regarded as one of the most critical diseases that lead to early disability and high mortality [1]. According to the World Health Organization (WHO, 2016), approximately 13% of the world's adult population is obese (11% of men and 15% of women) [2].

A study titled «Cardiovascular Epidemiology in Russian Federation» (ESSE-RF) revealed the prevalence of obesity among adults in 2014 of 29.7 ± 0.3% (30.8 ± 0.4% in women, 26.6 ± 0.5% in men) [3]. Today, about half (51.7% of women and 46.5% of men) of the Russian population has excess body weight and OB [4], while the number of patients with this disorder is constantly increasing [5]. An essential feature of our country is a significant increase in the prevalence of OB in men of working age; it is of great importance due to the increased cardiovascular risk.

Patients with OB proved to be most susceptible to the risk of various severe infectious diseases [2]. Examination of 268 patients hospitalized for influenza A (H1N1) in California demonstrated that 58% of them were diagnosed with OB; morbid obesity (body mass index (BMI) ≥40 kg/m^2) was associated with death. In another Mexican study, a higher risk of hospitalization in cases of OB was also confirmed — not only in the setting of influenza but also with other viral diseases such as parainfluenza, rhinovirus and metapneumovirus infections, as well as coronavirus disease [6].

The problem of OB combined with novel coronavirus infection (CVI) is of particular importance these days. The COVID-19 epidemic started in December 2019 in Wuhan (China) and spread rapidly across almost all countries. It was caused by the new SARS-CoV-2 coronavirus that induces severe acute respiratory syndrome (Severe Acute Respiratory Syndrome Coronavirus 2).

The current COVID-19 pandemic swept over Europe and North America, where the prevalence of OB is so high that it can be considered the «non-infectious epidemic of the 21st century» [7].

According to the World Health Organization, in May 2020, more than four million confirmed cases of COVID-19 were registered worldwide, including 280 thousand deaths. According to the official electronic information resource https://coronavirus-monitor.info, as of January 2021, the coronavirus disease (COVID-19) pandemic had affected 96 million patients and caused two million deaths. In Russia, as of that date, there were 3.6 million patients and 67 thousand fatal outcomes.

Pathophysiology of Severe Coronavirus Disease in Cases of Obesity

One of the reasons for the increased risk of CVI consequences with underlying OB is the activity of angiotensin-converting enzyme 2 (ACE2) [8, 9]. It was established that overweight triggers the expression of the parts of genes responsible for ACE-2 protein production [10, 11]. This protein is the «site of entry» for the SARS-CoV-2 virus into a cell. ACE-2 is involved in blood pressure (BP) regulation due to the inhibition of the activity of the renin-angiotensin system, vasodilation, increased natriuresis and suppression of the inflammatory process. ACE-2 is also a SARS-CoV-2 receptor that interacts with amino acid transporters and integrins [11]. Expression of ACE-2 occurs mainly in smooth muscle cells, endothelial cells, pancreatic acini, renal tubular epithelium, and adipocytes [12-14]. In adipose tissue, adipocytes themselves and other cells (stromal cells, endothelial cells, macrophages and lymphocytes) can be the targets for viruses [15]. Analysis of the risk of infection with various viruses in the population demonstrated a low prevalence of SARS-CoV-2 in cases of OB [16]. However, considering the high affinity of target cells, including adipocytes, for receptors, we can assume a hematogenous route of distribution in adipose tissue, which increases the risk of disease in this group of patients.

It is notabe that male individuals are characterized by higher ACE-2 expression. This feature determines the increased risk of COVID-19 due to the higher actual body fat percentage in cases of OB [17]. According to the literature, among 41 patients hospitalized for verified COVID-19 in China, 73% of cases were male patients [18]. Analysis of the gender ratio of patients in the USA demonstrated the same pattern, with males dominating (12.2%) among patients with severe coronavirus disease (16%).

Increased risk of severe COVID-19 consequences in individuals with OB is also determined by the higher possibility of a «cytokine storm». A cytokine storm is an uncontrolled and non-protective response of the body's immune system that affects healthy tissues. Today, the term «cytokine storm» has no generally accepted definition; it just means a hyperactive immune response characterized by excessive production of interferons, interleukins, chemokines, tumor necrosis factor, colony-stimulating factor and some other mediators that are part of the immune response required for effective counteraction of the causative agents of infectious diseases. This uncontrollable increase of the synthesis of pro-inflammatory mediators is also called hypercytokinemia and cytokine cascade [19, 21].

It was established that OB and metabolic syndrome are accompanied by the production of proinflammatory cytokines and increased acute-phase proteins, leading to chronic inflammation. Patients with OB have higher activity of nuclear transcription factor-kappa B (NF-κB) and intensive production of proinflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin-1 (IL-1) and interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), plasminogen activator inhibitor (PAI-1); all these are factors actively synthesized by adipocytes in cases of OB [20]. OB is characterized by impaired congenital and acquired immunity, central and peripheral meta-inflammation (chronic systemic inflammation). Cellular hypoxia, mechanical stress of adipocytes, and excessive free fatty acids and lipopolysaccharides are the primary initiators of meta-inflammation [22, 23].

A cytokine storm involves a wide range of various clinical and laboratory abnormalities that are the features of a generalized systemic inflammatory response. In the respiratory tract, this can be manifested by severe pneumonitis, pulmonary edema, acute respiratory distress syndrome (ARDS), and severe hypoxemia. Severe cytokine storms may cause renal and hepatic failure, cholestasis, and cardiomyopathy. The combination of renal failure, death of endothelial cells and hypoalbuminemia can lead to a systemic increase in capillary permeability and edematous syndrome. Neurological toxic effects of a cytokine storm are often delayed and manifest as encephalopathy of different severity [21, 24].

SARS-CoV-2 leads to the activation of monocytes, macrophages and dendritic cells and the release of IL-6, which activates cis-acting signals and pleiotropic effects of the immune system. A randomized multicenter study demonstrated that IL-6 is a strong independent predictor of death in cases of COVID-19. By its nature, adipose tissue is the main source of IL-6 and its receptor, IL-6R [25]. The ability of coronavirus to "cling" to IL-6 and its receptors was established; it ensures cascade transmission of viral signals and effects.

A large amount of adipose tissue is by itself a constant source of pro-inflammatory cytokines synthesized both by adipocytes themselves and by macrophages migrating into adipose tissue, leading, as already mentioned, to the development and sustenance of a chronic slow inflammatory process in the body. In turn, pathological secretion of adipokines in adipose tissue (IL-1, IL-6, TNFα) in combination with increased C-reactive protein, leptin-to-adiponectin ratio and decreased protective factors (adiponectin, anti-inflammatory cytokine IL-10) are accompanied by a deteriorated immune response and adverse effects for all organs and tissues, including pulmonary parenchyma and bronchi [26, 27]. It was established that the increase in pro-inflammatory biomarkers

is in direct proportion to the severity of OB. Disorders of endocrine function in abdominal OB with the accumulation of visceral fat, including pericardial and perivascular fat, create conditions for the development of the inflammatory process that plays a significant role in comorbid pathology (see Fig. 1).

Local and systemic pathological changes caused by adipose tissue inflammation (ATI) are primarily due to intracellular inflammatory changes. The most significant processes in adipose tissue (AT) cells are: activation of kinase inhibitor (Inhibitor of kappa B kinase — IKK), c-Jun N-terminal kinase (JNK), endoplasmic reticulum enzymes, protein kinase-C (PK-C), as well as oxidative stress — impaired relationship between reactive oxygen species and antioxidant protective factors [27]. Activation of IKK, JNK, PK-C in cytosol leads to the release of nuclear transcription factor NF-κB (nuclear factor kappa B) that migrates to the cell nucleus and stimulates the transcription of genes of numerous regulatory substances, including adipokines, TNFα, IL, chemokines, inhibitors and activators of apoptosis, etc. Mechanisms that induce these reactions in adipocytes are not yet fully established. The prevailing idea suggests the leading role of cytokines secreted by activated pro-inflammatory macrophages in AT and, possibly, by other substances. Cytokines, primarily TNFα, induce a number of inflammatory changes in adipocytes, which, in turn, causes their intracellular hyperproduction, including TNFα, thus developing a kind of a «vicious circle». This fact was the basis for the idea that once initiated, ATI progresses without the help of additional factors [28].

The main systemic consequence of ATI is the development of the following diseases: atherosclerosis, type 2 diabetes mellitus (DM 2), metabolic syndrome (MS), non-alcoholic steatohepatitis, and arterial hypertension (AH). Each of these conditions may exacerbate the severity of COVID-19.

Special attention should be paid to the assessment of the immunity components in fat cells and their physiological role [24]. Innate immunity receptors, toll-like receptors (TLRs), primarily TLR4, were found in fatty cell membranes. TLRs recognize the molecular components of bacteria, viruses, fungi and other pathogens and activate pro-inflammatory signaling pathways. Lipopolysaccharide (LPS) from the wall of gram-negative bacteria is a specific TLR4 ligand. The source of LPS in healthy individuals is intestinal microorganisms. Activation of TLR4 stimulates intracellular kinases, which ultimately translocates the NF-κB nuclear factor into the cell nucleus, followed by stimulation of the transcription of many pro-inflammatory genes that encode the synthesis of inflammatory regulatory substances including cytokines, chemokines, adipokines. In particular, the

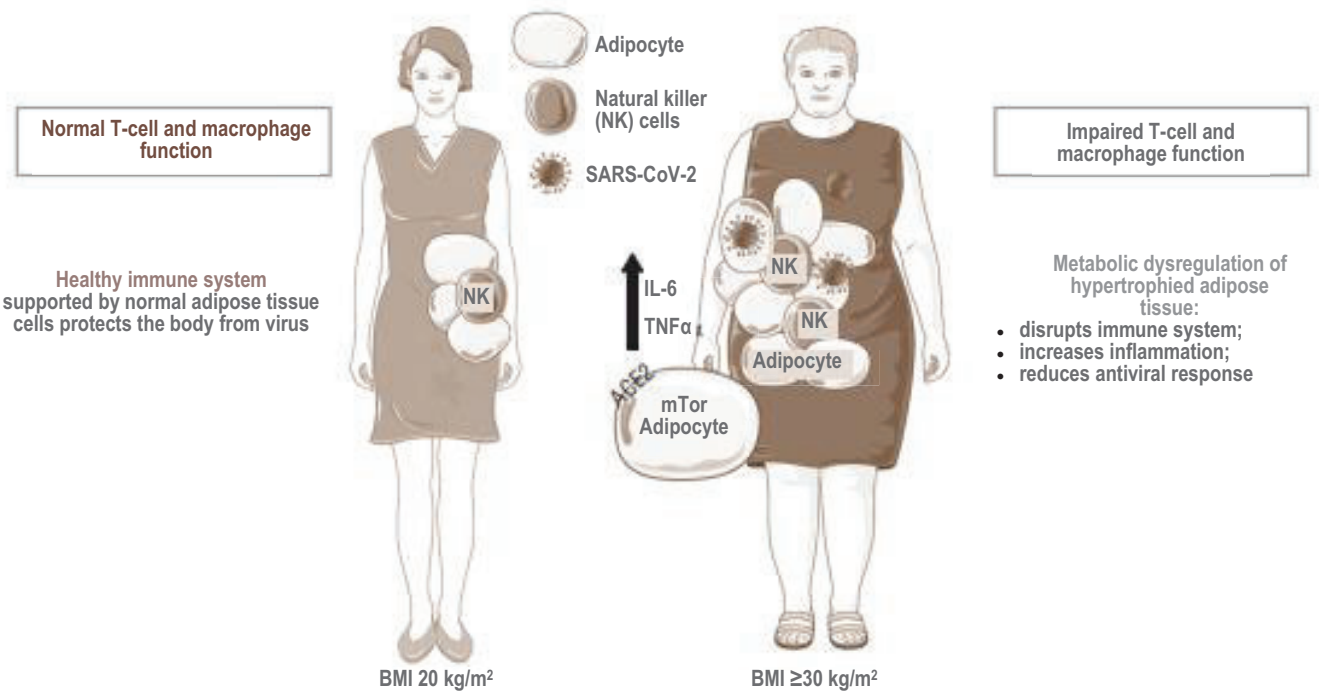

Figure 1. *Features of the pathogenesis of the severe course of coronavirus infection in obesity. Th e activity of immune cells and the secretion of proinfl ammatory cytokines increase in adipose tissue — this leads to hyperinfl ammation and the development of a «cytokine storm» [18]*

stimulation of TLR4 in isolated adipocytes increases the secretion of IL-6, TNFα, resistin and decreases adiponectin level [29]. The combination of these reactions causes the development of insulin resistance (IR), not only in adipocytes but also in hepatocytes and muscle cells. The activation of TLRs also increases lipolysis. Studies on rodents revealed that TLR4 is a necessary condition for the development of adipose tissue inflammation due to its infiltration by macrophages. Consequently, the activation of TLRs in AT causes a complex of changes typical for ATI [30].

Viral infections, particularly coronavirus infection, enhance the effect of cytokines, generalizing non-specific inflammation. Adipose tissue can act as a reservoir for a number of viruses, such as influenza, HIV and cytomegalovirus; according to recent data, COVID-19 can also be activated in it. An unexpected feature of coronavirus in cases of OB is its ability to quickly spread from the affected organ to the surrounding fatty tissue, affecting vital organs [31]. As a result, patients carry and spread coronavirus longer. This determines the specific features of the therapeutic approach to such patients, among other things — longer isolation and inpatient treatment.

Another factor of deterioration in COVID-19 patients with OB is the change in the activity of the dipeptidyl peptidase-4 (DPP-4) enzyme. This enzyme is a type II transmembrane glycoprotein produced in many tissues, including cells of the immune system. Functions of DPP-4 are not yet well understood, but we know that it is involved in the degradation of various hormones and proteins [32], particularly incretins. The cleavage of incretins (glucagon-like peptide 1 and insulinotropic peptide) determines the important role of DPP-4 in the metabolism of insulin and glucose. In patients with visceral OB, which is often coupled with type 2 DM, increased production of DPP-4 in AT leads to increased ATI, increased IR, decreased insulin secretion, and metabolic impairment in AT itself [36], which, in turn, results in the activation of catalytic enzymes and decreased activity of immune mechanisms. It was also established that one of the components of coronavirus, the so-called spike protein (hCOV-EMC), has an affinity for DPP-4 [33,34]. In vitro studies revealed that antibodies to DPP-4 are able to inhibit hCOV-EMC infection in bronchial epithelial cells and Huh-7 cells [34] and interfere with the development of immune response. It was found that MERS-coronaviruses use the DPP-4 enzyme to enter cells while SARS-CoV-2 virus uses ACE-2 for the same purpose. The study of the mechanisms of how coronavirus enters cells and ways of inhibiting these mechanisms is promising for the development of COVID-19 treatment methods [35].

Study Data on the Course of Coronavirus Disease in Obesity

It is well known that OB, particularly severe OB, is associated with a twofold risk of type 2 DM and a tenfold risk of cardiovascular death compared with individuals with normal body weight [36]. Therefore, a severe course of COVID-19 is most often observed in patients with comorbidities such as DM, OB, and cardiovascular diseases [36].

This was confirmed by observations demonstrating a high prevalence of OB in individuals with COVID-19 and a significant association of disease severity with the presence and grade of OB. In particular, a specific feature of patients with severe COVID-19 is polymorbidity. OB is the second most common comorbidity (48.3%) after AH (49.7%) [37]. In the 18-49 age group, OB was observed more often than chronic lung diseases and DM. A similar pattern was also determined in the 50-64 age group and in elderly patients (≥65), AH was the most common comorbidity.

A study performed by Chinese scientists, which involved 1,099 hospitalized patients and outpatients with COVID-19 (median age 47 years, majority (58%) — male subjects), demonstrated that AH (14.9%), DM (7.4%) and CHD (2.5%) were the most common comorbidities [38].

The observation carried out by British researchers, which included almost two million individuals, revealed that severe OB was the risk of increased mortality in individuals with COVID-19 only if they had two or more comorbid conditions [39].

According to current data, OB coupled with CVI in men leads to an extremely severe course of the disease, which requires mechanical ventilation (MV) [47]. French studies have shown that the frequency of mechanical ventilation used in intensive care units for the management of severe CVI is more than seven times higher for patients with BMI >35 kg/m^2 compared with patients with BMI <25 kg/m^2 [40]. Among 124 COVID-19 patients at one French hospital (CHU Lille), 47.6% were obese, while 28.2% had a BMI higher than 35 kg/m^2. The prevalence of OB in the group of patients who required mechanical ventilation was 68.6%. In all cases, the need for mechanical ventilation was due to a critical decrease in respiratory function with severe hypoxia. The number of patients requiring mechanical ventilation increased with the increased severity of OB, reaching maximum values at BMI ≥35 with significant association with the male gender. Interestingly, there was no link between the severity of the infectious disease with age, DM, or AH [41] in this study.

Today, we have accumulated evidence about the association of OB and its related conditions (such as DM, AH)

with a more severe course of COVID-19 and death [42, 43]. It is also known that CVI is associated with the risk of hyperglycemia, especially in elderly patients aged 60+ with DM [44].

Mechanisms that aggravate the course of COVID-19 and worsen the prognosis in patients with OB include impaired immune regulation, critical deficiency of cardiac and respiratory reserve with underlying chronic cardiovascular diseases and chronic obstructive pulmonary disease (COPD) [45]. As a result, all these factors lead to multiple organ failure, which is the cause of death in this category of patients [46]. Obese individuals are at increased risk of COVID-19 infection and poor prognosis [47].

There is a proven direct relationship between the severe course of COVID-19 and the high incidence of disseminated intravascular coagulation (DIC) syndrome, as well as venous thromboembolism. These complications are most often reported in patients with OB, which is an independent risk factor for thrombosis and thromboembolism [48].

Activation of ACE-2 expression in cases of CVI can also be one of the mechanisms of acute myocardial damage with the development of fulminant myocarditis [49].

It should be noted that abdominal OB itself is associated with worsened pulmonary ventilation, which significantly reduces blood oxygen saturation [50]. Pulmonary ventilation disorders and associated respiratory failure are the common cause of emergency hospitalization of obese patients. It was also proved that most patients with severe OB have more severe manifestations of obstructive sleep apnea compared with individuals with normal body weight [50]. Therefore, severe respiratory failure, which is typical for patients with COVID-19 and underlying OB, is a consequence of two mutually aggravating factors: viral pneumonia on the one hand and hypoventilation syndrome due to OB on the other hand.

Lessons from past coronavirus epidemics demonstrate the development of acute coronary syndrome, arrhythmias, decompensation of heart failure, thromboembolic complications primarily due to the combination of significant systemic inflammatory response and localized inflammation of the vascular wall. COVID-19 is no exception: it worsens the clinical course of comorbidities in cases of obesity, leading to the development of life-threatening complications. It should be noted that during epidemics, including COVID-19, most patients die from cardiovascular diseases [51].

Conclusion

Therefore, the current problem of obesity amid the coronavirus pandemic is of particular importance. On the one hand, the prevalence of OB among the population is steadily increasing. On the other hand, it was proven that obese individuals are at risk of infection and severe COVID-19. This is due to the high expression of angiotensin-converting enzyme 2, possible development of a «cytokine storm», chronic inflammatory process in adipose tissue, and changes in the activity of dipeptidyl peptidase-4; all these factors lead to impaired metabolism in adipose tissue and impaired immune mechanisms of antiviral defense.

Obese COVID-19 patients are more often hospitalized in the intensive care unit and more often require mechanical ventilation.

Many typical features of the course of coronavirus disease in cases of obesity have been identified. These include: severe respiratory failure, high risk of respiratory distress syndrome, thrombosis and thromboembolic complications, as well as worsening of chronic cardiovascular diseases. All these factors ultimately lead to severe multiple organ failure, which is the cause of death in this category of patients.

The issues of drug treatment, taking into account mechanisms of virus entry into cells, especially its pathophysiology and interaction with the human body, are of particular relevance in this situation.

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МИКРОБИОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА БИОЦЕНОЗА КИШЕЧНИКА АМБУЛАТОРНЫХ ПАЦИЕНТОВ, ИМЕЮЩИХ ПОВЕДЕНЧЕСКИЕ ФАКТОРЫ РИСКА ХРОНИЧЕСКИХ НЕИНФЕКЦИОННЫХ ЗАБОЛЕВАНИЙ

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Microbiological Characteristics of Intestinal Biocenosis of Ambulator Patients Having Behavioral Risk Factors for Chronic Non-Communicable Diseases

Резюме

Наиболее ранняя коррекция поведенческих факторов риска хронических неинфекционных заболеваний позволит снизить показатели преждевременной смертности населения. В настоящее время недостаточно изучена взаимосвязь измененного спектра микрофлоры кишечника при различных показателях субоптимального статуса здоровья и индекса массы тела. Находясь в состоянии субоптимального статуса здоровья, пациенты считают себя здоровыми и длительно не обращаются к врачу, что затрудняет реализацию ранних профилактических мероприятий у данной группы пациентов. **Цель.** Определить качественный и количественный состав микрофлоры кишечника до и через 1 месяц после приема метапребиотического комплекса, содержащего пищевые волокна (инулин) и олигосахариды (олигофруктозу), у амбулаторных пациентов, имеющих поведенческие факторы риска хронических неинфекционных заболеваний. **Материалы и методы.** Проведено обследование амбулаторных пациентов (114 чел.: 36 мужчин, 78 женщин в возрасте от 18 до 72 лет). Проведено обследование, включающее расспрос с детализированным активным сбором жалоб (в том числе с помощью международного опросника SHSQ-25) и анамнеза и тщательный физикальный осмотр с антропометрическим исследованием. Методом MALDI-ToF масс-спектрометрии определены степень микробиотических нарушений, структура микрофлоры кишечника с идентификацией выделенных из фекалий микроорганизмов до приема и после приема курса метапребиотического комплекса при различных показателях субоптимального статуса и индекса массы тела. **Результаты.** Получены новые данные о биоценозе кишечника пациентов, считающих себя здоровыми, при различных уровнях субоптимального статуса. При применении метапребиотического комплекса, содержащего инулин и олигофруктозу, обнаружено улучшение состава микрофлоры кишечника за счет снижения частоты выделения грамотрицательных микроорганизмов (медиана степени

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обсемененности: от 0,45 (0,3-0,98) до 0,3 (0,21-0,7) при низких показателях субоптимального статуса и от 0,5(0,7-1,7) до 0,31(0,2-1,3) при высоких), и повышения частоты выделения энтерококков (медиана степени обсемененности: от 5,58 (4,16-7,0) до 6,3 (4,8-7,8) при низких показателях субоптимального статуса и от 4,5 (2,8-6,3) до 5,1 (3,8-6,4) при высоких). **Заключение.** Доказана значимость изучения микробиотического комплекса кишечника при повышении показателей субоптимального статуса здоровья и индекса массы тела у пациентов, считающих себя здоровыми, что позволит проводить наиболее раннее выявление и рациональную индивидуальную профилактику хронических неинфекционных заболеваний.

Ключевые слова: *метапребиотики, факторы риска заболеваний, микробиоценоз кишечника*

Конфликт интересов

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

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Abstract

The earliest correction of behavioral risk factors for chronic non-communicable diseases will reduce the rates of premature mortality of the population. Currently, the relationship between the altered spectrum of intestinal microflora in various indicators of suboptimal health status and body mass index is not sufficiently studied. When they are in a state of suboptimal health status, patients consider themselves healthy and do not go to the doctor for a long time, which makes it difficult to implement early preventive measures in this group of patients. Goal. To determine the qualitative and quantitative composition of the intestinal microflora before and 1 month after taking a metaprebiotic complex containing dietary fiber (inulin) and oligosaccharides (oligofructose) in outpatient patients who consider themselves healthy, have behavioral risk factors for chronic non-communicable diseases or chronic non-communicable diseases in remission, and/or do not consult a doctor within the last 3 months. **Materials and methods.** Outpatient patients were examined (114 people: 36 men, 78 women aged 18 to 72 years). A survey was conducted, including a detailed active collection of complaints (including using the international SHSQ-25 questionnaire) and anamnesis, as well as a thorough physical examination with an anthropometric study. Using the MALDI-ToF mass spectrometry method, the degree of microbiotic disorders, the structure of the intestinal microflora was determined with the identification of microorganisms isolated from feces before and after taking the course of the metaprebiotic complex with various indicators of suboptimal status and body mass index. **Results.** New data were obtained on the intestinal biocenosis of patients who consider themselves healthy at different levels of suboptimal status. When using a metaprebiotic complex containing inulin and oligofructose, an improvement in the composition of the intestinal microflora was found due to a decrease in the frequency of release of conditionally pathogenic enterobacteria and other gram-negative microorganisms (median degree of contamination: from 0.45 (0.3-0.98) to 0.3(0.21-0.7) at low suboptimal status and from 0.5(0.7-1.7) to 0.31 (0.2-1.3) at high) and increase the frequency of enterococcal excretion (median degree of contamination: from 5,58 (4,16-7,0) to 6,3 (4,8-7,8) at low suboptimal status and from от 4,5 (2,8-6,3) to 5,1 (3,8-6,4) at high). **Conclusion.** The importance of studying the microbiotic complex of the intestine in increasing the indicators of suboptimal health status and body mass index in patients who consider themselves healthy is proved, which will allow for the earliest detection and rational individual prevention of chronic non-communicable diseases.

Key words: *metaprebiotics, disease risk factors, the intestinal microbiota*

Conflict of interests

The authors declare no conflict of interests

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CNCDs — chronic noncommunicable diseases, MPC — meta-prebiotic complex, RF — risk factors, SHS — suboptimal health status

Introduction

Socially significant chronic noncommunicable diseases (CNCDs) lead in the structure of morbidity, early disability and premature mortality in Russia and other developed countries [1]. Socially significant CNCDs include cardiovascular (hypertensive disease, myocardial infarction, stroke) and gastrointestinal diseases (gastric ulcer, pancreatitis, hepatitis, dysbiosis, dysfunction of small and large intestines), oncological, neuropsychiatric, respiratory and metabolic diseases (atherosclerosis, overweight, obesity) [1]. They are caused by the following risk factors (RF): unhealthy lifestyles, economic hardships and an adverse environment [2]. Many RF of CNCDs are interrelated and enhance each other, increasing the likelihood of these diseases [3]. The relationship between the altered spectrum of the species and the quantitative composition of gut microbiota with RF of CNCDs was proved [4–6]. Various representatives of normal microflora actively and steadily interact with a body, and changes in their composition are often secondary and reflect changes in the balance of microbiocenosis. Disorders of gut microbiota are manifested by an imbalance of the quantitative and qualitative composition of normal microflora that creates conditions for the excessive development of micromycetes, opportunistic and pathogenic flora [7]. These changes induce and support a «pro-inflammatory» environment, which is typical for pathological processes at the preclinical stage of diseases [3, 5]; they are manifested by the suboptimal health status (SHS) and cause functional dyspepsia and other diseases [8]. Patients with SHS consider themselves healthy and do not seek medical attention [9].

Early diagnosis and reversal of gut microbiota changes can be an additional tool to improve the quality of life of outpatients at the preclinical stage of disease. Probiotic agents (containing bifidobacteria and lactobacilli) were found not effective enough to correct microflora [10, 11]; not more than 0.0001% of probiotic microorganisms survive in the gastrointestinal tract of animals, and no more than 0.000000008% of lactobacilli survive in the human gastrointestinal tract [12]. The competition for the nutritious substrate between probiotic bacteria and their microbiota was proved, especially when prescribing drugs without considering the features of its species composition [13, 14]. Prescribing probiotics after treatment of patients with antibiotics does not always contribute to the restoration of their microbiota; sometimes, it even impedes it [15]; this may be due to the strain specificity of the species of microorganisms in the ecosystem of a particular patient. A more effective method for correcting gut microbiota disorders is the creation of a favorable environment for their habitation and good nutrition, using substances containing exometabolites (calcium lactate) and fruit polysaccharides (inulin and oligofructose) that are a growth medium.

This article presents the results of a dynamic study of the qualitative and quantitative composition of gut microbiota (culture) of outpatients who consider themselves healthy when using a meta-prebiotic complex (MPC) containing dietary fiber (inulin) and oligosaccharides (oligofructose) (STIM Lax, OOO V-MIN+, Russia).

Objective

To determine the qualitative and quantitative composition of gut microbiota one month before and after taking meta-prebiotic complex containing dietary fiber (inulin) and oligosaccharides (oligofructose), in outpatients with behavioral risk factors for chronic noncommunicable diseases.

Material and Methods

The study included the following outpatients: 114 individuals (36 male, 78 females aged 18 to 72 years). Inclusion criteria: patients who consider themselves healthy and/or who have not visited a physician during the last three months, who have behavioral RF of socially significant CNCDs or socially significant CNCDs in remission, who came to the clinic for any reason and/or were invited by the attending general practitioner for a routine examination. Exclusion criteria: clinically significant health disorders (acute diseases, acute CNCDs or decompensated conditions associated with CNCDs, infectious or oncological diseases) and/or visiting a physician during the last three months. In accordance with the Helsinki Declaration (1975, 1983, 1989), the participants were acquainted with the objectives and general provisions of the study and signed voluntary informed consent for this study. The Bioethics Committee of the Samara State Medical University (protocol No. 200 of May 22, 2019) approved the study protocol.

A routine clinical examination was performed, which included detailed questioning with active gathering of complaints (also using the SHSQ-25 international questionnaire) [9] and medical history, and thorough physical examination with anthropometric measures (measurement of height, body weight, waist circumference and hip circumference). BMI and waist/hip ratio were calculated for all patients depending on gender, age and suboptimal health status. Other RF of CNCDs were not taken into consideration in this part of the study. In order to identify and evaluate the relationship between RF of CNCDs and present functional

diseases of the gastrointestinal tract that are not currently considered in the prevention of CNCDs, the species composition of the gut microbiota was defined with the identification of microorganisms isolated from feces using MALDI-ToF mass spectrometry. Two to three grams of feces were delivered to the laboratory in a sterile vial with no preservative within two hours of sampling. Culturing was carried out using an extended list of artificial nutrient media under aerobic and anaerobic conditions. Primary isolation of the material was carried out on 5% blood agar, bismuth-sulfite agar, SS agar, selective medium for the isolation of obligate anaerobic microorganisms, universal chromogenic medium, mannitol agar, medium for selective isolation of clostridia, lactobacilli, bifidobacteria, Saburo medium (HiMedia, India). Anaerobic conditions were created using gas generating pouches (Anaerogaz, Russia). Cultures were identified using a Microflex LT device (Bruker Daltonik GmbH, Germany). The study group included «conditionally healthy» patients with suboptimal health status. The comparison group included «conditionally healthy» patients with no suboptimal health status. The extent of microbiotic disorders was determined [«Protocol of Patient Management. Intestinal Dysbiosis» OST 91500.11.0004-2003]; relative values (presence or absence) were compared for particular groups of microorganisms for 1 g of intestinal contents, as well as microbial diversity in patients with low and high suboptimal health status depending on the duration of MPC intake. The specified parameters were determined before taking MPC and in 78 individuals one month after the course (with a dose of three tablets per day for two months) of MPC. Depending on the duration of intake of the meta-prebiotic STIM Lax complex, patients were divided into three groups: group 1, 61 subjects with full course of MPC (two months), group 2, 32 subjects with an incomplete course (from 1 to 2 months), and group 3, 21 subjects with a course of less than one month. The duration of IPC intake was in accordance with the desire of the patients. Partial or complete refusal to take MPC was associated with the following reasons: feeling of well-being (patients considered themselves healthy); active social life and unwillingness to visit outpatient clinics, change lifestyle and take drugs; economic reasons. The parameters of suboptimal health status were calculated (SHS: total score of SHSQ-25 equal to 13 or more indicated a suboptimal health status that requires further examination of the patient) [9] and body mass index (BMI according to the formula: body weight, in kg/height, in m^2; obesity grade was assessed according to WHO criteria, 1997); quantitative parameters of gut microbiota diversity and its microbial load. Statistical analysis was carried out using Microsoft Office Excel 2010 and Statistica 13.3 software package (Statsoft, USA) with an assessment of the normality of distribution. The required number of observations was calculated by the following formula: $N = t^2 \times \sigma^2 / \Delta^2$, where N is the number of observations, t is the confidence coefficient depending on the given level of probability (p = 95%) of the final result, σ is the standard deviation, and Δ is the margin of error. The normality of distribution was checked using the Shapiro–Wilk test; differences between groups were evaluated using nonparametric analysis (Mann–Whitney, Kruskal–Wallis tests) at a significance level of $p < 0.05$. This clinical study was consistent with the principles of the Law on the Circulation of Medicines No. 61, of April 12, 2010, and the principles of Good Clinical Practice.

Results

Table 1 presents general characteristics of patients. In accordance with the goals and objectives of the study, BMI and waist/hip ratio were calculated for the entire cohort of patients depending on their gender and age. Other RF of CNCDs were not taken into consideration in this part of the study. A high BMI was more often observed in women than in men (39 individuals, 34.1% and 14 individuals, 12.3%, respectively), along with high suboptimal health status (women with high SHS — 33 individuals, 28.9%; women with low SHS — 19 individuals, 16.7%). There were no significant differences in the groups according to the waist/hip ratio. It is known that the better the person's well-being, the lower the value of suboptimal health status determined by the SHSQ-25 scale. A significant proportion of patients (65 patients, 57.0%) who considered themselves healthy had high suboptimal health status values and were part of the observation group. Patients with high suboptimal health status values were older and had high BMI ($p < 0.05$).

Parameters of the microbial load in the studied groups of patients are presented in Table 2. An initial examination of the patients revealed a reduced quantitative composition of the populations of microorganisms. When comparing the microbial composition before and after taking MPC, depending on the suboptimal status, significant differences were found in the groups of gram-negative flora, represented by non-enzymatic gram-negative bacteria and enterococci.

Data on differences in microbial diversity in groups of patients depending on the duration of MPC intake (Table 3) were obtained; the data did not depend on parameters of suboptimal health status. As early as the diagnosis stage, patients could be divided into three groups comparable in clinical characteristics: patients fully complying with the physician's recommendations;

Table 1. *General characteristics of patients*

Sign	SHS n=114*		Reliability**	Overweight n=114*		Reliability**
	Comparison group, SHS <13 Mean + Std n=49 (Me(IQR))	Observation group, SHS ≥13 Mean + Std n=65 (Me(IQR))		<24,9 n=61	≥25,0 n=53	
Age (Me(IQR)) n=114	42,0 (25,3-47,4) n=49	46,1 (34,4-62,7) n=65	**z=4,15; p=0,003**	47,0 (31-57) n=61	43,5 (35-57) n=53	**z=3,3; p=0,007**
Male age (Me(IQR)) n=62	42,5 (32,0-58,0) n=30	48,0 (29,0-52,1) n=32	**z=3,8; p=0,028**	41,0 (31,0-47,0) n=48	45,6 (33,0-48,0) n=14	**z=0,71; p>0,05**
Women age (Me(IQR)) n=52	35,1 (23,0-49,0) n=19	44,0 (38,5-56,5) n=33	**z=4,003; p=0,0004**	38,5 (30,0-48,0) n=13	43,2 (24,0-51,0) n=39	**z=4,74; p=0,045**
Waist-hip ratio in men (Me(IQR)) n=62	0,85 (0,83-0,92) n=30	0,94 (0,91-0,96) n=32	**u=6,0; z=0,0; p=1,0**	0,83 (0,80-0,87) n=48	0,93 (0,90-0,95) n=14	**u=0,0; z=0,0; p=1,0**
Waist-hip ratio in women (Me(IQR)) n=52	0,77 (0,75-0,89) n=19	0,82 (0,79-0,91) n=33	**u=0,0; z=0,0; p=1,0**	0,75 (0,67-0,79) n=13	0,95 (0,88-0,99) n=39	**u=0,0; z=0,0; p=1,0**

Note:
*n — number of observations
** u — the Mann-Whitney test; z — the number of standard deviations from the average value of the data point; p- the level of statistical significance

Table 2. *Microbial composition (median degree of contamination) before and after taking Mc*, depending on the suboptimal status*

Признак/ Attribute		Всего/ Total n=114 (100%)*			
		Группа сравнения / Comparison group, SHS <13 n=49 (43,0%)		Группа наблюдения / Observation group, SHS ≥13 n=65 (57,0%)	
		До приема МПК/ Before taking Mc** Mean + Std (Me(IQR))	После приема МПК/ After taking Mc** Mean + Std (Me(IQR))	До приема МПК/ Before taking Mc** Mean + Std (Me(IQR))	После приема МПК/ After taking Mc** Mean + Std (Me(IQR))
Bifidobacteria	p>0,05***	3,1 (2,8-3,89)	3,4 (3,1-3,9)	3,0 (2,6-3,3)	3,23 (2,5-3,34)
Lactobacilli	p>0,05	5,3 (4,8-5,6)	5,8 (5,4-6,7)	5,5 (4,8-5,4)	5,6 (5,2-6,1)
Lactic acid streptococcus	p>0,05	0,1 (0,05-0,11)	0,12 (0,06-0,14)	0,08 (0,05-0,1)	0,06 (0,04-0,09)
Clostridium	p>0,05	0,09 (0,03-0,1)	0,2 (0,1-0,5)	0,4(0,2-0,45)	0,6(0,4-0,9)
Escherichia	p>0,05	4,1(3,3-4,3)	5,2(3,4-6,1)	4,6(4,1-5,2)	5,3(3,9-5,4)
Opportunistic flora	p>0,05	0,8 (0,56-1,7)	0,6 (0,4-1,2)	0,9 (0,6-1,84)	0,8 (0,5-1,4)
Gram-negative flora	**p<0,05**	**0,45 (0,3-0,98)**	**0,3 (0,21-0,7)**	**0,5(0,7-1,7)**	**0,31(0,2-1,3)**
Staphylococcus aureus	p>0,05	0,3(0,15-0,45)	0,0	0,54(0,3-0,9)	0,0
Other staphylococci	p>0,05	0,2(0,0-1,1)	0,3(0,0-0,05)	0,1(0,0-1,3)	0,2(0,1-0,9)
Enterococci	**p<0,05**	**5,58(4,16-7,0)**	**6,3(4,81-7,79)**	**4,5(2,75-6,25)**	**5,1(3,75-6,44)**
Yeast	p>0,05	0,4(0,0-0,81)	0,3(0,0-0,5)	0,7(0,0-1,4)	0,4(0,0-1,36)
Mold fungi	p>0,05	0,2(0,0-0,43)	0,0	0,31(0,0-0,81)	0,0

Note:
*n — number of observations
**Mc — Metaprebiotics complex
***p — the level of statistical significance

Table 3. Microbial diversity of intestinal biocenosis depending on the duration of Mc intake*

Indicator	Before taking Mc* n=114**			After taking Mc* n=114**			Reliability***		
	Group 1. n=26	Group 2 n=28	Group 3 n=60	Group 1. n=26	Group 2 n=28	Group 3 n=60	Group 1. n=26	Group 2 n=28	Group 3 n=60
Microbial diversity Mean + Std (Me(IQR))	7,8 (7,2-8,8)	9,1 (8,5-9,4)	9,2 (7,3-9,6)	8,1 (7,2-9,1)	9,45 (8,5-9,73)	9,78 (8,62-11,3)	**z=0,1; p=0,93**	**z=4,73; p=0,042**	**z=4,12; p=0,003**

Note:
*Mc — Metaprebiotics complex
**n — number of observations
*** z — the number of standard deviations from the average value of the data point; p — the level of statistical significance

*Table 4. Differences in suboptimal status indicators before and after the course intake of Mc**

Подгруппа/ Subgroup	SHS до курса МПК/ SHS before the Mc course Mean + Std (Me(IQR))	SHS после курса МПК/ SHS after the Mc course Mean + Std (Me(IQR))	Достоверность/ Reliability***
All patients n=114	19,3 (10,8-25,6)	11,2 (7,4-16,9)	p <0,0001
Women n=78	19,1 (11,4-25,8)	11,8 (8,3-17,1)	p <0,0001
Men n=36	13,5 (5,9-19,7)	9,2 (7,7-14,2)	p=0,0004
Patients under 30 years of age n=22	14,8 (9,6-17,3)	11,2 (8,7-14,6)	p=0,0052
Patients over 30 years of age n=91	19,5 (14,3-22,4)	11,6 (10,9-19,8)	p <0,0001
Receiving Mc less than 1 month n=22	14,9 (12,5-16,8)	14,6 (12,1-16,4)	p=0,23**
Receiving MC from 1 month to 2 months n=30	18,6 (12,7-23,4)	12,1 (8,2-15,9)	p <0,0001
Admission of Mc full course (2 months) n=61	17,9 (11,8-26,1)	9,7 (6,7-13,9)	p <0,0001

*Mc — Metaprebiotics complex
** no significant difference
*** p — the level of statistical significance

patients partially following the recommendations, and patients not following the recommendations for various reasons. For patients who took the full course of MPC, improved microbiological parameters lasted even after the completion of the course.

Differences in the parameters of suboptimal health status before and after the course of MPC are presented in Table 4. Significant differences in all groups of patients were revealed: the general parameter of suboptimal health status decreased in all age groups, which indicates an improvement in the health parameters of the subjects. At the same time, the best values were obtained with the full course of MPC in two months.

Discussion

Mortality from CNCDs can be at least halved via the early diagnosis, identification and correction of individually significant behavioral RF [1–3] on an outpatient basis. A significant group (57%) of patients who were invited by the physician who considered themselves healthy and/or did not visit the physician had RF of CNCDs and had suboptimal health status. It was proven that increased body weight is one of the most important RFs of CNCDs that increase the probability of metabolic syndrome [2, 3]. Numerous studies proved the impact of changes in the quantitative and qualitative composition of gut microbiota on the utilization of nutrients and protection against aggressive environmental effects by increasing or reducing the risks of metabolic syndrome and comorbid pathology [4–6]. Many (45.6%) patients in our study had a high BMI with altered quantitative and qualitative parameters of gut microbiota. The studies showed that the composition of the gut microbiota can play a critical role in the development of obesity [4-6], and the microbiological phenomenon of dysbiosis is the initial stage of many concomitant diseases, which aggravates the course of the main pathological process [15]. There are contradictory reports about the relationship between group differences in the structure of the gut microbiota (for example, the presence of Bacteroidetes and Firmicutes) and the BMI of the host. However, taxonomic profiles have different patterns for obese and thin patients [4–6]. Our study found differences in the microbiotic status of outpatients depending on their body weight and the presence of suboptimal health status, as well as differences between normal gut microbiota and

the accepted standards. The total number of microorganisms in excess of 10^7 (R. V. Epstein-Litvak, F. L. Vilshanskaya, 1970) or more than 10^8 (V. M. Bondarenko et al., 1995) is considered the reference range for intestinal flora. Most of our patients (57%) with suboptimal health status, according to these criteria, were characterized by insufficient total microflora (less than 10^7). MPC helped obtain positive results of the correction of intestinal biocenosis and improve the parameters of suboptimal health status.

Conclusion

The results revealed qualitative and quantitative changes in the gut microbiota of outpatients who consider themselves healthy and/or have not visited a physician in the last three months. The hypothesis about the possible role of the gut microbiota in the regulation of human gene expression (including genes associated with lipid metabolism, obesity and inflammation) enabled to conduct studies that revealed the participation of microbiota in the pathogenesis and sanogenesis of major noncommunicable human diseases [16]. The above data proved the relationship between differences in the microbiota composition of outpatients and their body weight and the presence of suboptimal health status. This determines the need for the earliest possible individual evaluation of gut microbiota during active screening for RF of CNCDs and the need to determine the criteria of microbiota changes in patients with socially significant CNCDs. The importance of developing up-to-date guidelines for gut microbiota evaluation is discussed in literature [16]. The representativeness of the sample of participants suggests that such standards are especially relevant for the category of patients with suboptimal health status. Our study proved the importance of the full course of MPC for the long-term maintenance of a high population level of normal microflora in cases of microbiome disorders as part of the complex correction of behavioral risk factors associated with suboptimal health status, which will prevent obesity and associated diseases in this category of patients.

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All authors made a significant contribution to the preparation of the work, read and approved the final version of the article before publication and agree to take responsibility for all aspects of work

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ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ ТЕРАПИИ АДАЛИМУМАБОМ И СЕКУКИНУМАБОМ ПАЦИЕНТКИ С ПСОРИАТИЧЕСКИМ АРТРИТОМ

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Description of the Clinical Case of Adalimumab and Secukinumab Therapy of a Patient with Psoriatic Arthritis

Резюме

В данной статье рассмотрена актуальность лечения псориатического артрита генно-инженерными препаратами (адалимумабом и секукинумабом), а также проведен ретроспективный анализ истории болезни пациентки, получавшей данную терапию.

Ключевые слова: *Псориатический артрит, генно-инженерная терапия, адалимумаб, секукинумаб*

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

This article considers the relevance of treating psoriatic arthritis with genetically engineered drugs such as adalimumab and secukinumab. Also, it conducts retrospective analysis of the medical history of the patient, who had this therapy.

Key words: *psoriatic arthritis, genetically engineered drugs, adalimumab, secukinumab*

Conflict of interests

The authors declare no conflict of interests

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ADA — adalimumab, GEBD — genetically engineered biological drugs, IL — interleukin, LF — leflunomide, MT — methotrexate, PsA — psoriatic arthritis, TNF-α — tumor necrosis factor alpha

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Introduction

Today, genetically engineered biological drugs (GEBD) play an important role in the management of rheumatic diseases, especially when it comes to severe patients with poor response to conventional therapy with disease-modifying anti-inflammatory drugs. Psoriatic arthritis (PsA) is a complex immuno-inflammatory disease that affects the spine, joints and entheses [1]. It significantly worsens the quality of life of patients and the fact is that one person often may have several immuno-inflammatory diseases. For example, according to the literature, PsA is observed in about 30% of patients with psoriasis. This is because these disorders have similar genetic and immunological factors of development, specifically, genetic polymorphism of interleukin (IL) 23R, which determines the IL 12/23 signaling pathway of immunopathogenesis. This is the same reason why PsA and psoriasis may be concomitant with many other immuno-inflammatory diseases, in particular, inflammatory bowel diseases, thereby worsening the quality of life of patients and their prognosis for both work and life. Along with late detection and incorrect therapy, all this leads to a high level of disability among these patients [2]. Inhibitors of tumor necrosis factor alpha (TNF-α) are widely used in the management of PsA [3]. However, as mentioned above, entheses are often involved in the process in the cases of PsA. The activation of the IL 23/IL 17 axis is known to play a critical role in the development of enthesitis. It should be noted that the enthesitis of certain localities, for example, calcaneal enthesitis, seriously limits motor activity, and therapy with synthetic disease-modifying anti-inflammatory drugs in these conditions has shown to be ineffective. In such cases, an IL-17A inhibitor — secukinumab — is successfully used [4]. As for TNF-α inhibitors, it should be noted that immunogenicity is a property of proteins affecting immune response manifested in the formation of antibodies to the drug (ABD) and/or immune complexes. Decreased immunogenicity in cases of combination therapy with TNF-α inhibitors and methotrexate (MT) is observed in comparison with GEBD monotherapy, while the administration of a therapeutic dose of MT allowed reducing to a greater extent the incidence of antibodies to TNF-α inhibitors. As for adalimumab (ADA), in a number of studies, immunogenicity against ADA was observed at the early stages of treatment: in 67% of cases in patients positive for ABD, it developed in the first 280 weeks of therapy [5].

Objective

To evaluate the effectiveness of therapy with genetically engineered biological drugs in a female patient with psoriatic arthritis.

Materials and Methods

A retrospective analysis of the patient's medical records was carried out, as well as follow-up in the genetic engineering biological therapy room of the rheumatology center of Voronezh Regional Clinical Hospital No. 1.

Patient K, female, 22, was on an outpatient visit at the rheumatology center of VRCH No. 1 with a diagnosis of: Psoriatic arthritis, chronic asymmetric polyarthritis of the joints of hands, Rg stage 1–2; of feet, Rg stage 2; erosive, bilateral sacroiliitis, Rg stage 2 on the left, 1–2 on the right; coxarthrosis, Rg stage 1; arthritis, secondary arthrosis of right elbow joint, Rg stage 2–3; flexion contracture of right elbow joint, activity 2–3 on CEBD (adalimumab). Functional disorders 2–3. Psoriasis, remission.

The patient complained of constant pain in all joints, numbness of fingers, feet, swelling of 1, 3 left metacarpophalangeal joints, pain in cervical and lumbosacral spine, inability to move without assistance, morning stiffness that does not stop without taking non-steroidal anti-inflammatory drugs (NSAIDs). At the time of examination, she could move on her own with difficulty.

Medical history revealed that she considers herself ill since 2013 when the first symptoms of disease appeared. Psoriasis since 2012. In November 2012, she was diagnosed with juvenile chronic (psoriatic) oligoarthritis. Until the age of 18, she underwent regular inpatient treatment at Voronezh Regional Children's Clinical Hospital No. 1. From 2012 to 2016, she received methotrexate (MT) at a dose of 15 mg per week. Significant deterioration since January 2017, when pain and swelling in the joints intensified, and pronounced morning stiffness appeared. NSAIDs did not reduce the activity of disease, significant pain and joint dysfunction persisted. In March 2017, due to MT intolerance (severe nausea, vomiting after administration), she was switched to leflunomide (LF) at a dose of 20 mg per day. In April 2017, sulfasalazine (SF) was added to the treatment at a dose of 2 g per day. From 9 to 18 October 2017, she was hospitalized in the rheumatology department at VRCH No. 1. It was recommended that the patient should be referred to a commission for the selection of treatment with genetically engineered biological drugs (GEBD). On November 28, 2017, based on the decision of the medical commission of VRCH No. 1, taking into account the high activity of psoriatic arthritis and the ineffectiveness of the previous disease-modifying therapy (MT, LF, SF), as well as generalized enthesopathy, the patient was prescribed adalimumab (ADA) at a dose of 40 mg once every 2 weeks subcutaneously. Treatment was adjusted: ADA 40 mg once every 2 weeks, SF 2.0 g/day before the first administration of ADA, LF 20 mg/day for a long time. In February 2018, at the visit to rheumatologist, the

patient complained of the absence of a positive effect of ADA. In May, July, and September, during planned outpatient appointments, the patient also noticed no positive changes from the therapy.

Physical examination results: General condition is satisfactory. There are multiple tattoos on skin, psoriatic rashes on scalp. On auscultation, vesicular breathing over lungs, no crackles. Respiratory rate 15 per min. Heart rate is regular, 68 beats/min, blood pressure 110/70 mm Hg on both hands. Abdomen was soft and painless during palpation. Liver is not enlarged. Stool was regular and formed. Urination was without abnormalities. Status localis: pain on palpation and moderate deformity of wrist joints, swelling of 1, 2 metacarpophalangeal joint on the right. Movement in wrist joints is limited. A positive symptom of lateral compression of hands and feet. Palpation of right elbow is painful. Pain on palpation of the sacroiliac joints on both sides. Flexion contracture of the right elbow up to 30 degrees. Flexion in the right elbow is also limited. Range of motion in the spine, in hip joints in full. 4th and 5th toes of the left foot are painful and hammer-shaped, it is painful to stand on toes. Achilles tendons swollen, painful on palpation.

The patient was recommended to take a referral to a medical commission to resolve the issue of further treatment approach. On October 09, 2018, a commission was convened at VRCH No. 1. Given the high activity of the process, the ineffectiveness of treatment with ADA at a dose of 40 mg s/c once every 2 weeks and disease-modifying drugs (MT, LF, SF), it was recommended to switch the patient to an interleukin-17 inhibitor — secukinumab — at a dose of 150 mg s/c once a month (including induction treatment at a dose of 150 mg s/c on week 0-1-2-3-4). On January 09, 2019 — maintenance treatment at a dose of 150 mg s/c once a week.

On October 03, 2019, patient K. visited the rheumatology center of VRCH No. 1 on an outpatient basis to assess the effectiveness of therapy with secukinumab. The patient noted a stable state of health, morning stiffness for 5–10 minutes, pain in hip joints during exercise, when the weather changes, more on the left, periodic numbness in the neck in the morning. Physical examination: The condition is satisfactory. She moves on her own, without support. Palpation of right elbow joint, left sacroiliac joint is painful. Other joints are painless. Flexion contracture of the right elbow up to 30 degrees. Flexion in the right elbow is also limited. 4th and 5th toes on the left foot are hammer-shaped. Achilles tendons are painless on both sides, not swollen. Blood tests on September 30, 2019: hemoglobin 130 g/l (120–140 g/l), erythrocyte sedimentation rate (ESR) 6 mm/h (0–11 mm/h), C-reactive protein (CRP) 2.26 mg/l (0–5 mg/l). It is recommended to continue the ongoing therapy.

Discussion

In this clinical case, the tactic of replacing a genetically engineered biological drug from the group of tumor necrosis factor alpha inhibitors — adalimumab with an interleukin 17 inhibitor — secukinumab, was chosen. As a result of the therapy, the patient saw positive changes. In the clinical picture: stable state of health, morning stiffness for 5–10 minutes, severity of peripheral arthritis decreased, range of motion in the spine increased, pain in the hip joints during exercise and when the weather changed, more on the left, periodic numbness in the neck in the morning. There are no psoriatic rashes at the time of examination. The number of painful joints (NPJ) decreased from six to one, the number of swollen joints (NSJ) from four to one; there is a decrease in the disease activity score (Disease Activity Score 28 — DAS 28) — from 5.3 points to 2.2 (which corresponds to low disease activity). Laboratory parameters returned to normal: ESR — from 48 mm/h (September 03, 2018) to 6 mm/h (September 30, 2019), CRP — from 11.9 mg/l (September 03, 2018) to 2.26 mg/l (September 30, 2019). An effective and quick response to therapy was observed: after the first injection of secukinumab, the patient felt improvement (during the following week, she did not take NSAIDs). Quick response to therapy in this patient matches the data of randomized controlled trials [6]. It should be emphasized that for ten months of treatment, no adverse reactions that would require interruption of therapy were observed. The lack of effect on therapy with TNF-α inhibitor adalimumab may be associated with both primary and secondary inefficiency [7]. Risk factors for primary inefficiency are the following: female gender, prevalence of other inflammatory cytokines in the pathogenesis of the disease, pharmacokinetic characteristics of the drug, genetic predisposition. Mechanisms of secondary inefficiency include immunogenicity that depends on the state of the body's immune system. Due to MT intolerance in this patient, it was impossible to prescribe combination therapy with MT+ and TNF-α, and it should be noted that the apparent ability of methotrexate to prevent the formation of ABD was not found in leflunomide, which is indirectly confirmed in this case by the absence of effect from combination therapy LEF + ADA. Given the patient's medical history, young age, high activity of the disease, as well as the presence of enthesitis, it was decided to switch the patient not to another drug from the TNF-α-i group but to a drug from the group of IL 17 inhibitors. This approach had a positive result: the activity of the disease decreased, the patient's quality of life improved significantly, and her ability to work was restored. Secukinumab demonstrates a favorable safety profile in actual clinical practice in patients with psoriatic arthritis, and in clinical studies. According to the literature, in patients with PsA, secukinumab

provides a rapid clinical effect after the first week of treatment, prevents the progression of structural damage to joints, and promotes active regression of enthesitis [8].

Conclusion

This case demonstrates compliance with the golden rule in modern rheumatology «treat to target» — treatment to achieve the goal. The presented clinical case demonstrated high clinical efficacy of secukinumab in the treatment of patients with severe PsA, who are resistant to standard methods of treatment with disease-modifying drugs and the ineffectiveness of monoclonal antibodies to TNF-α. Results of this clinical case indicate the positive effect of secukinumab on the primary signs of PsA: arthritis, enthesitis, dactylitis, functional abilities, skin manifestations. An important condition for the development of such a treatment strategy is a timely response to the ineffectiveness of therapy, as well as obtaining information about the immunogenicity of various TNF-α inhibitors and improving test systems for determining the concentration of the drug and antibodies to the drug (ABD) and/or immune complexes.

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КЛИНИЧЕСКИЙ СЛУЧАЙ НАСЛЕДСТВЕННОГО ТРАНСТИРЕТИНОВОГО АМИЛОИДОЗА

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A Clinical Case of the Hereditary Transthyretin Amyloidosis

Резюме

Введение: транстиретиновый (ATTR) амилоидоз является тяжелым редким заболеванием с широким спектром неспецифических проявлений, в т.ч. поражением периферической нервной системы и сердца. Клинический случай: пациентку 60 лет в течение 2 лет беспокоили парестезии и слабость в дистальных отделах нижних конечностей, затрудняющая ходьбу. Первоначально симптомы рассматривались как проявление дегенеративного стеноза поясничного отдела позвоночника, выполнена декомпрессионная ламинэктомия, несмотря на которую симптоматика сохранялась. На основании данных клинического и электронейромиографического обследований, диагностирована аксональная сенсомоторная полиневропатия. При генетическом тестировании 4 членов семьи (пациентки, ее старшей сестры с сыном и дочерью) выявлен вариант нуклеотидной последовательности в четвертом экзоне гена транстиретина (*Chr18: 29178562, rs148538950, NM_000371.3:c. G368A:p. Arg123His*) в гетерозиготном состоянии. При исследовании нативных препаратов жировой клетчатки живота при окраске Конго красным и исследовании в поляризованном свете в единичных полях зрения выявлены микродепозиты амилоида, grade CR 1+ (минимальные отложения). При эхокардиографии выявлено утолщение стенок левого желудочка с нормальными конечнодиастолическим размером и объемом и сохраненной фракцией выброса, дилатацией левого предсердия, умеренной легочной гипертензией и диастолической дисфункцией типа 1. Пациентке рекомендовано начать специфическую антиамилоидную терапию — тафамидис. Заключение. У больных с поражением периферической нервной системы и утолщением стенок левого желудочка неясной этиологии необходимо комплексное обследование для своевременной диагностики и адекватной терапии амилоидной полинейропатии и кардиомиопатии.

Ключевые слова: *амилоидная кардиомиопатия, амилоидоз сердца, транстиретин, транстиретиновая семейная амилоидная полинейропатия, TTR-FAP, ATTR амилоидоз, ATTP-амилоидоз*

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Abstract

Introduction: Transthyretin (ATTR) amyloidosis is a severe rare disease with wide range of characters without specific symptoms including the damage to the peripheral nervous system and cardiac involvement. Case report: A 60-year-old female patient represented with weakness and paresthesia in the distal parts of the lower limbs, impeding walking for 2 years. Initially, symptoms were considered as a manifestation of degenerative stenosis of the lumbar spine, decompressive laminectomy was performed but the symptoms after surgical treatment persisted. Based on data from clinical and electroneuromyographic examinations, axonal sensorimotor polyneuropathy was diagnosed. Genetic testing of the patient, her elder sister, son and daughter using the Sanger sequencing method detected a variant of the nucleotide sequence in the fourth exon of the transthyretin gene (*Chr18: 29178562, rs148538950, NM_000371.3: c.G368A: p. Arg123His*) in the heterozygous state. A subcutaneous fatty tissue biopsy of abdominal wall with a Congo red stain and polarized light examination revealed amyloid microdeposits, grade CR 1+ (minimal deposits), confirmed the diagnosis of familial ATTR-amyloidosis. Echocardiography revealed concentric left ventricular wall thickening with normal end diastolic size and volume, preserved ejection fraction, left atrial enlargement, pulmonary hypertension and type 1 diastolic dysfunction. Specific anti-amyloid therapy — tafamidis was prescribed. Conclusion: In patients with peripheral polyneuropathy and left ventricular hypertrophy of unknown etiology, a complex examination is necessary for the timely detection and treatment of amyloid polyneuropathy and cardiomyopathy.

Key words: *asymptomatic cardiomyopathy, cardiac amyloidosis, transthyretin, transthyretin familial amyloid polyneuropathy, TTR-FAP, ATTR amyloidosis*

Conflict of interests

The authors declare no conflict of interests

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ATTR — transthyretin amyloidosis, BP — blood pressure, ECG — electrocardiogram, EchoCG — echocardiography, GFR — glomerular filtration rate, CHF — chronic heart failure, CHFpEF — CHF with preserved LVEF, HR — heart rate, LV — left ventricle, LV EF — left ventricle ejection fraction, TAVI — transcatheter aortic valve replacement

Introduction

Amyloidoses are a group of diseases with the specific feature of extracellular deposition of a specific glycoprotein (amyloid) in tissues and organs [1]. Amyloid infiltration of tissues and organs can result in their enlargement, damage/death of their cells and impaired functioning [2].

For clinical purposes, local and systemic (generalized) types of amyloidosis can be identified. Local types of amyloidosis are characterized by the involvement of one organ. Systemic types are characterized by the involvement of many organs and systems [3].

Modern classification of amyloidosis is based on the principle of the specificity of the main fibrillar protein of amyloid (36 different types of amyloidosis are known today). In the name of an amyloid type, the first letter is the capital letter A, which stands for “amyloid”, followed by the designation of a specific amyloid fibrillar protein — A (amyloid A protein), L (immunoglobulin light chains), TTR (transthyretin), etc. [2, 4].

Transthyretin (TTR) is a carrier protein of thyroxine (T4) and complex retinol-binding protein/vitamin A. Transthyretin is a tetramer; it consists of four identical subunits. About 95% of transthyretin is produced in the liver. Less than 5% of transthyretin is synthesized in the vascular plexus of the brain and retinal pigment epithelium. Less than 1% of thyroxine in serum is transported by transthyretin protein (99% of thyroxin is transported by thyroxine-binding globulin and albumin). Most of circulating transthyretin is unconjugated [5–7].

ATTR amyloidosis is a type of amyloidosis with pathogenesis based on the destabilization (improper folding) of transthyretin tetramer and deposition of incorrectly folded transthyretin monomers in tissues [8]. ATTR amyloidosis includes familial (mutant, hereditary) amyloidosis, which is inherited in an autosomal dominant manner with incomplete penetrance, and systemic senile amyloidosis ("wild", i.e., its phenotype most frequently observed in the natural population; its signs are determined by "normal" (non-mutant) alleles; it is called "cardiac Alzheimer's disease") with no mutations in transthyretin gene [2].

"Wild" ATTR amyloidosis affects 20–30% of people aged 80+, which suggests the existence of age-related triggers of amyloidosis; it is often found in patients with chronic heart failure (CHF) with preserved left ventricular ejection fraction (LV EF — CHFpEF) and degenerative aortic stenosis [9].

Hereditary ATTR amyloidosis is the result of a mutation in the gene (located on 18q chromosome and consisting of 4 exons) that encodes transthyretin, which leads to the replacement of amino acids in its molecule [10]. Today, there are more than 140 different mutations in the transthyretin gene; most of them are amyloidogenic, and only about ten are not [10, 11]. Most patients are heterozygotes; therefore, they have not only mutant but also normal non-mutant transthyretin. The phenotype of ATTR amyloidosis can be predominantly neurological, or predominantly cardiological, or mixed. Val-30Met mutation is the most frequent cause of amyloid polyneuropathy; however, its late onset may be manifested by cardiomyopathy. The most common mutation in ATTR amyloidosis in the world is *Val122Ile*, with predominating cardiological symptoms; it is observed in 3–4% of African Americans with different clinical manifestations, 10% of African Americans aged 60+ develop CHF. Patients with *Thr60Ala* mutation have a mixed phenotype; it is found in 1% of the population of the North-West of Ireland [6, 12–15]. A. Ya. Gudkova et al. examined 257 patients with CHF in the North-West region of Russia, where a relatively high mutation rate (4.6%) in the transthyretin gene was detected [10]. Only half of the cases, specifically of ATTR-Val30Met amyloidosis, have a typical clinical picture [10].

For a long time, hereditary ATTR amyloidosis was considered an endemic disease (in Portugal, Japan, Sweden, Brazil), with a prevalence of 1/1,000. Over time, reports of ATTR amyloidosis began to come from many countries outside of the endemic areas [16]. The number of patients in the world is currently about 50,000 [17].

Damage to the nervous system in cases of ATTR amyloidosis is represented by symptoms of peripheral neuropathy and autonomic dysfunction [3]. Clinical signs of neuropathy are caused by the degeneration of the myelin sheath of nerves and the compression of the nerve trunks by amyloid deposits and ischemia as a result of amyloid deposits in the walls of blood vessels. In most cases, there is a symmetric distal neuropathy with steady progression. The debut of nervous system impairment includes mainly sensory disturbances, primarily pain and temperature sensitivity, later vibrational and positional sensitivity, then motor disorders. Trophic disorders are manifested by weight loss. The earliest symptoms of neuropathy are paresthesias or painful dysesthesias (numbness). Lower limbs are involved in the pathological process more often than upper limbs and often cause problems with walking [3]. Dysfunctions of the autonomic nervous system often manifest with orthostatic arterial hypotension, sometimes with fainting, diarrhea, impaired bladder function, impotence in men [3]. There may also be signs of damage to the central nervous system: progressive dementia, headache, ataxia, seizures, spastic paresis, stroke-like episodes [17].

Cardiac damage with ATTR amyloidosis starts with amyloid depositions in the myocardium, continuously progresses to CHF, and leads to a progressive decrease in LVEF and patient death [7, 18]. Cardiac amyloidosis can cause various rhythm and conduction disturbances: atrial fibrillation, supraventricular tachycardia, ventricular pre-excitation syndrome, heart blocks, and sinus node weakness syndrome [19]. Amyloid can deposit on heart valves and lead to regurgitation or valve stenosis. The highest prevalence of amyloid was found in patients with aortic valve stenosis (74%); less often, amyloid was found in cases of mitral stenosis and insufficiency (28.6 and 29.2%, respectively), even less often — with aortic regurgitation (10.5%) [20].

Renal damage is also observed in patients with hereditary ATTR amyloidosis [3]. Amyloid nephropathy usually has clinical manifestations of isolated proteinuria and is characterized by a steadily progressive course with successively changing stages: proteinuric, nephrotic, chronic renal failure. Nephrotic syndrome and large kidneys persist even with the development and progression of renal failure. In the cases of nephrotic syndrome, antithrombin III deficiency is often observed along with the increased risk of thrombosis [3].

Damage to the gastrointestinal tract is often associated with amyloidosis; it can be manifested by nausea, vomiting, early satiety, diarrhea, constipation, alternating diarrhea and constipation, inadvertent weight loss due to secondary malabsorption. The following can be possible causes of diarrhea: 1) amyloid infiltration of the intestinal wall, including villi, and 2) intestinal autonomic plexus dysfunction [3].

A rare manifestation of amyloidosis described for ATTR types is eye damage (opacification of the vitreous body that leads to a gradual loss of vision; obstruction of the lacrimal canal that can lead to chronic open-angle glaucoma, conjunctival vascular anomalies, pupil abnormalities) [3].

Urogenital disorders are rare but can develop with ATTR-amyloidosis and manifest in men in the form of erectile dysfunction [3].

Since hereditary and "wild" ATTR amyloidosis are considered rare and usually manifest with heterogeneous symptoms similar to those of other more common diseases, their diagnosis presents a challenge. The primary sign of amyloidosis on the ECG is low QRS voltage (<0.5 mV in limb leads and/or <1.0 mV in precordial leads) [21]. A combination of low voltage on the ECG and echocardiographic signs of a large mass of myocardium is considered a typical diagnostic sign. It is believed that there is a true myocardial hypertrophic response to transthyretin infiltration that is not observed in AL amyloidosis (LV hypertrophy only due to amyloid deposition — pseudohypertrophy) [18]. QS complex, at least, in two chest leads without specific changes in repolarization ("pseudo-infarction pattern") can be observed in some patients [3]; T inversion or ST segment depression in lateral chest leads is rare but is sometimes recorded. HM ECG can help detect episodes of ventricular and supraventricular arrhythmias in many asymptomatic patients. Another sign is a decrease or absence of heart rhythm variability, which indicates autonomic nervous dysfunction [21].

Echocardiography (EchoCG) is considered the best method for detecting signs of amyloid cardiomyopathy; it can be used to diagnose symmetrical thickening of ventricular walls (>12 mm) with no reason for LV hypertrophy, especially thickening of the free wall of RV, normal LV size in diastole, increased size in systole. LV wall thickness >15 mm is rare in hypertensive disease. Therefore, if patients have thickened ventricular walls for no apparent reason, or severe LV hypertrophy, even with AH, a mismatch between increased LV mass and low QRS voltage on ECG should raise suspicion of cardiac amyloidosis. Echocardiography also reveals atrial dilatation, thickening of valves with blood regurgitation, effusion in the pericardial cavity, signs of diastolic myocardial dysfunction (the most typical restrictive type of diastolic dysfunction with E/A ratio of more than 2), diffuse or local LV hypokinesis [22]. Myocardial granularity or luminescence is quite common (26%) but may not be constant in the same patient; LV EF is often within normal, but it can significantly decrease in the terminal stage of the disease [3, 22]. ECG and EchoCG parameters independently have low sensitivity and specificity, which raises the question of the combination of various parameters of these methods for the diagnosis of cardiac amyloidosis. Caroll J. D et al. suggested using the ratio of the voltage sum to the cross-sectional area of the heart as a criterion for screening amyloid cardiomyopathy, which enabled the diagnosis of amyloid cardiomyopathy with a higher probability. This ratio also correlates well with clinical symptoms and death outcomes. [23]. Reference values of this parameter are to be determined.

Scintigraphy, single-photon emission computed tomography (99mTc pyrophosphate, 3,3-diphosphono-1,2-propane dicarboxylic acid (DPD) and hydroxymethylene diphosphonate — HMDP) are non-invasive methods with very high specificity (>99%) and sufficient sensitivity (86%); they can be used to diagnose ATTR amyloidosis and eliminate the need for endomyocardial biopsy [5, 24, 25].

Genetic testing in patients with clinical symptoms and family history is enough to diagnose ATTR-amyloidosis. Precise identification of the mutation via genetic testing helps to assess the prognosis and effectiveness of treatment [24, 26]. A biopsy with immunohistochemistry test with anti-transthyretin antibodies may also be used to confirm the diagnosis.

In cases of amyloidosis, there may be an increase in the levels of troponin T/I and N-terminal pro-brain natriuretic peptide (NT-proBNP); they are not specific, but the degree of increase correlates with the severity of cardiac amyloidosis [3].

Cardiac ATTR amyloidosis is often not diagnosed or is misdiagnosed as hypertrophic CMP, or CHFpEF with unknown etiology. The true prevalence of cardiac ATTR amyloidosis is unclear and probably higher than previously thought. Some recent studies demonstrate a higher prevalence: in 13% of patients with CHFpEF, a "wild" type of ATTR amyloidosis was confirmed [27], in 5% of patients with hypertrophic cardiomyopathy — a mutant type of ATTR amyloidosis [28]. Among 101 patients aged 86 ± 5 years (43% male subjects) with severe symptomatic aortic stenosis who underwent transcatheter aortic valve replacement (TAVI), 13.9% had ATTR amyloidosis [29]. According to Castano A. et al., 16% of patients undergoing TAVI (151 patients, 84 ± 6 years) had ATTR amyloidosis [30]. The figure was 6% in patients aged 65+ with aortic stenosis who underwent surgical replacement of the aortic valve [31].

Colleagues from Heart Failure Bridge Clinic (J. Hopkins Clinic) proposed and implemented screening criteria for cardiac amyloidosis in patients with CHF, as well as its diagnostic algorithm:

1. Age 50+ years
2. Thickness of interventricular septum (T_{IVS}) ≥1.2 cm
3. BMI ≤30 kg/m^2
4. Low voltage on ECG
5. Central or peripheral neuropathy, carpal tunnel syndrome

If a patient has ≥2 of these criteria, the diagnostic procedure should be started in order to exclude/confirm cardiac amyloidosis (**Fig. 1**) [32].

For timely diagnosis of ATTR amyloidosis in patients with peripheral polyneuropathy, it is recommended to use the algorithm shown in Figure 2.

The average life expectancy after the onset of the clinical symptoms of ATTR amyloidosis is 6–12 years; the common cause of death is heart damage. Hereditary ATTR amyloidosis was previously considered an incurable disease. In the 1990s, liver transplantation was used for the management of ATTR amyloidosis; then, stabilizers of transthyretin tetramers (diflunisal, tafamidis) were introduced into clinical practice; agents affecting mRNA (patisiran, inocerten) have recently been studied. In this regard, early diagnosis and timely initiation of therapy become extremely relevant in the cases of ATTR amyloidosis.

Here is a description of a patient with hereditary ATTR amyloidosis that debuted in the form of peripheral polyneuropathy with subsequent asymptomatic heart damage.

Patient N., female, a resident of Perm Krai, felt paresthesias from the age of 58; within two years, weakness in the distal parts of lower extremities increased, making walking difficult**.** Past diseases included just childhood infections. She denied having arterial hypertension, diabetes mellitus, acute cerebrovascular accident, history of acute myocardial infarction, smoking, alcohol abuse, and allergic reactions. There were no signs of autonomic dysfunction. Height 168 cm, weight 90 kg, stable over the past 5 years. The symptoms were initially considered a manifestation of degenerative stenosis of the lumbar

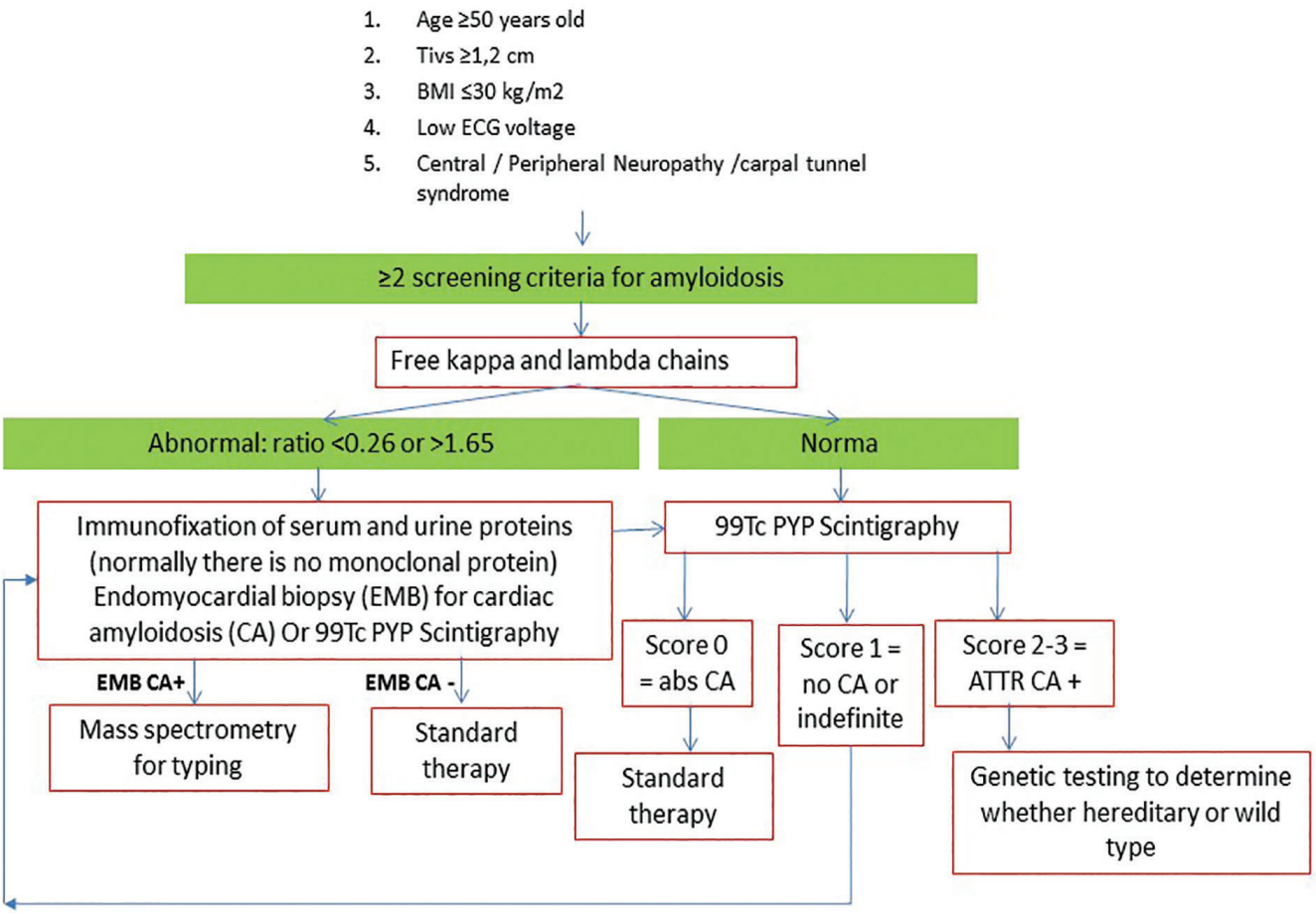

Figure 1. *Algorithm for the diagnosis of heart amyloidosis in CHFsPV*

CHFsFV — chronic heart failure with preserved ejection fraction; CA EMB: endomyocardial biopsy for cardiac amyloidosis; 99mTc-PYP- 99mtechnetium pyrophosphate [Fajardo J, Cummings A, Brown E, et al. (2019) Clinical pathway to screen for cardiac amyloidosis in heart failure with preserved ejection fraction. Amyloid 26:166–167. doi: 10.1080/13506129.2019.1583178]

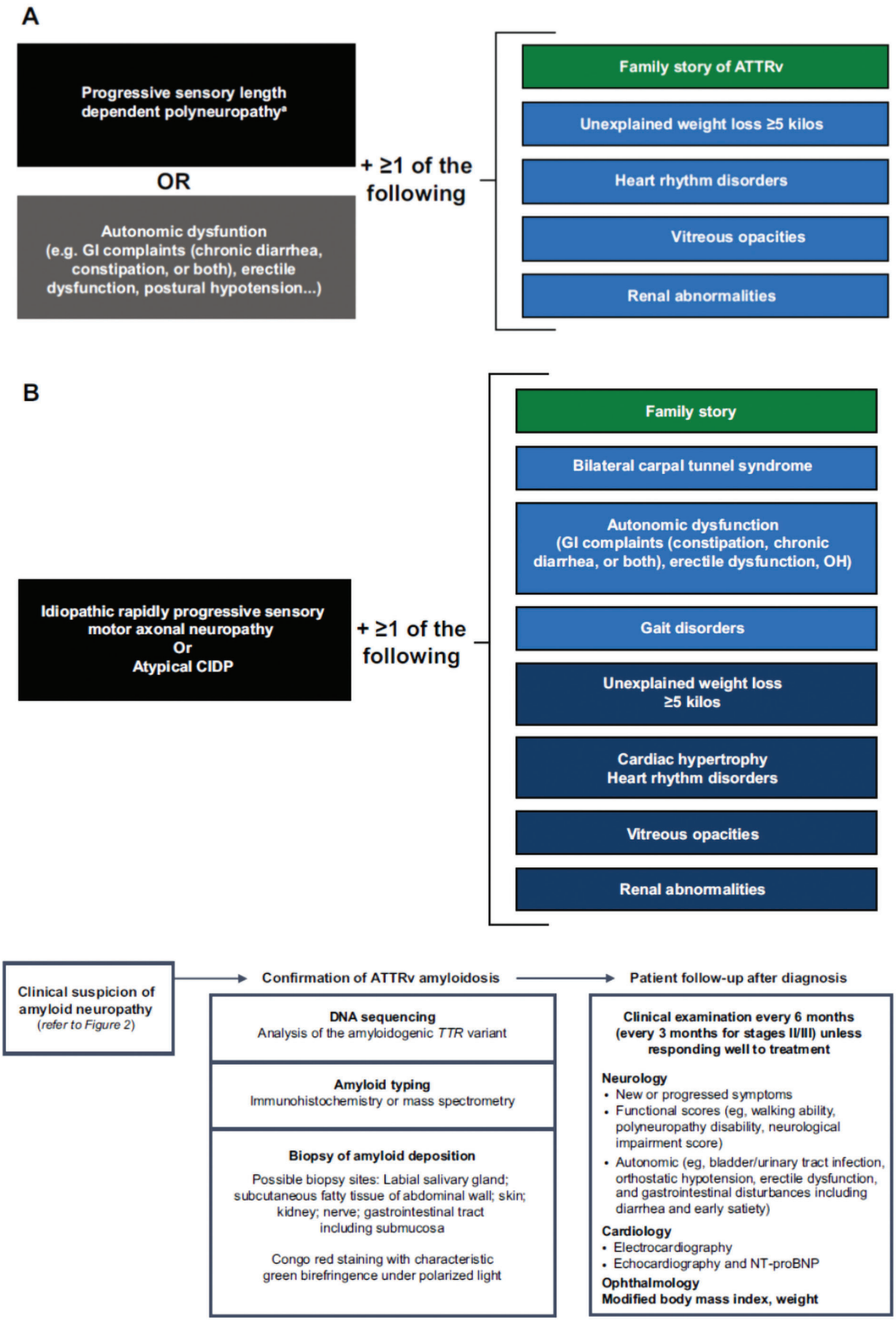

Figure 2. *Suspicion index for diagnosis of ATTRv amyloidosis with PN*

A — in endemic areas, B — in nonendemic areas. ATTRv hereditary transthyretin amyloid amyloidosis, CIDP chronic inflammatory demyelinating polyneuropathy, GI gastrointestinal, OH orthostatic hypotension. aNo diabetes, no alcohol abuse, vitamin B12 deficiency [15, 33]

spine; decompression laminectomy was performed. As symptoms remained after surgical treatment, the patient was referred to the Regional Neurological Center. Neurological status demonstrated signs of lower peripheral, predominantly distal, paraparesis (gait disturbance of "steppage" type — from French "steppage" — trotting, peroneal gait, atrophic changes, decreased tonus and muscle strength to 4 points in the proximal and to 3 points in the distal muscles of lower extremities), sensitive disorders of polyneural type (symmetrical superficial and deep hypesthesia in the distal parts of lower extremities, inhibition of deep reflexes, severe atactic syndrome with a sensitive component). Based on the clinical data and electroneuromyographic examination results, the diagnosis of axonal sensorimotor polyneuropathy was established.

Genetic testing was conducted in the patient and then her relatives to exclude the amyloid etiology of polyneuropathy. **Genetic testing** in the patient, her elder sister, son and daughter using the Sanger sequencing method revealed the nucleotide sequence variant in the fourth exon of the transthyretin gene in the deoxyribonucleic acid test sample (*Chr18: 29178562, rs148538950, NM_000371.3:c.G368A:p. Arg123His*) in heterozygous state (**Fig. 3**).

Histological results: Biopsy specimens from different parts of the gastrointestinal tract stained with red Congo and examined in polarized light revealed no amyloid deposits. Biopsy specimens of abdominal subcutaneous adipose tissue stained with red Congo and examined in polarized light revealed amyloid microdeposits, CR 1+.

ECG (**Fig. 4**) showed sinus rhythm, heart rate (HR) of 68 beats per minute, normal position of QRS axis and normal voltage of QRS complex (above 5 mm in leads from extremities and above 10 mm in precardial leads), abnormal Q wave in lead III lasting for 40 ms, amplitude 0.3 mV = ½ R.

Holter ECG monitoring revealed sinus rhythm with frequency; average heart rate of 79 beats/min during daytime, 67 beats/min at night and 75 beats/min for the whole measurement period; maximum heart rate of 145 beats/min, minimum — 51 beats/min; 8 ventricular extrasystoles, 10 supraventricular extrasystoles, including 3 of bigeminia type, 1 paired, 1 run of supraventricular tachycardia of 3 complexes. No pauses registered. During the monitoring, painless episodes of horizontal and oblique ST segment depression were registered, up to –0.12 mV lasting for 78 seconds, during daytime.

Daily monitoring of blood pressure (BP): Mean systolic BP 115 and 112 mm Hg, mean diastolic BP 75 and 73 mm Hg in daytime and at night, respectively; degree of night decrease in systolic blood pressure is 2%, in diastolic blood pressure — 3% (non-dipper).

Complete blood count: Hemoglobin concentration 127 g/l, red blood cell count 4.45×10^{12}/l, platelet count 303×10^{9}/l, WBC 6.7×10^{9}/l, erythrocyte sedimentation rate 12 mm/h.

Biochemical blood test: Aspartate aminotransferase — 21 IU/l (5~34), alanine aminotransferase — 16 IU/l (0~32), total creatine phosphokinase — 138 IU/l (21~215), its MV fraction — 14.30 IU/l (0,00~25.00), total lactate dehydrogenase — 613 IU/l (225~450), gamma glutamyl transpeptidase — 20 IU/l (9~39), alkaline phosphatase — 148 IU/l (64~306), alpha-amylase — 76 IU/l (0~220), total protein — 67 g/l (65~85), albumin — 42 g/l (35~55), albumin — 61.34% (54.40~69.66), alpha 1-globulin — 3.20% (2.63~5.03), alpha 2-globulin — 6.44% (4.87~10.48), beta 1-globulin — 7.08% (5,35~9.19), beta 2-globulin — 6.37% (2.38~7.11), gamma-globulin — 15.57% (9.69~18.90), uric acid — 332 mmol/l (184~464), urea — 4.80 mmol/l (2.50~8.33), creatinine — 58 μmol/l (53~88), iron — 21.5 μmol/l (9.0~30.4), OZHSS — 51.5 μmol/l (44.7~80.6), sodium — 141.0 mmol/l (130.5~156.6), potassium — 4.30 mmol/l (3.44~5.30),

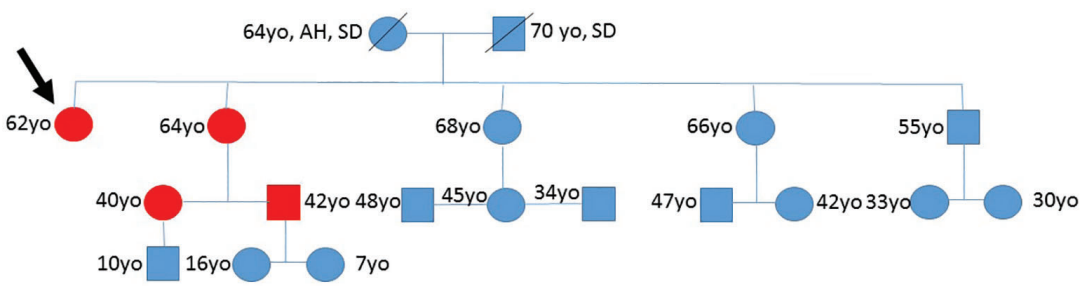

Figure 3. *Pedigree of the patient. Women are indicated by a circle, men by a square. Family members with an identified mutation are shown in red, and unexamined family members are shown in blue (examination is planned). The numbers indicate the age. AH — a history of arterial hypertension, SD — sudden death, yo — years old*

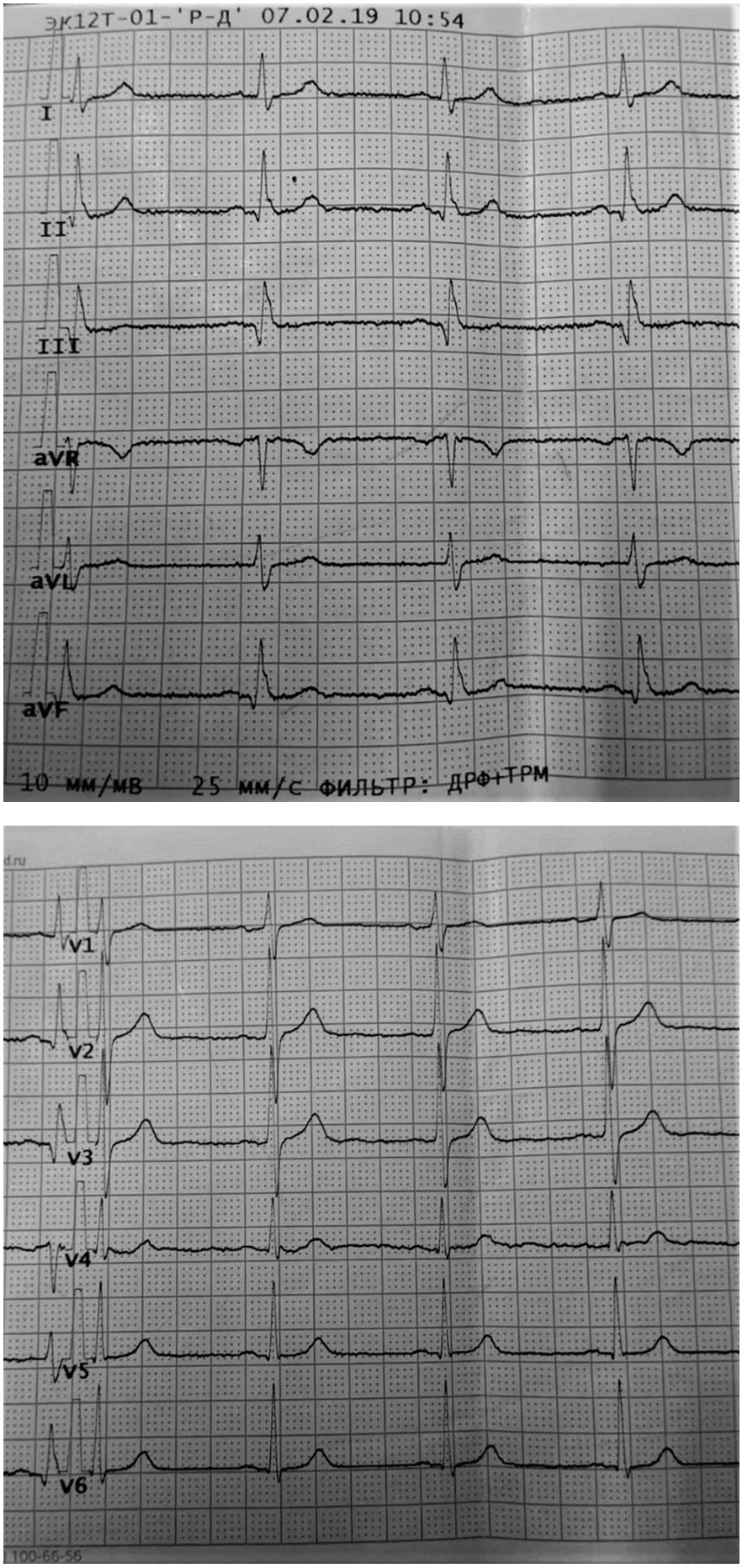

Figure 4. *Patient's Electrocardiogram*

calcium — 2.04 mmol/l (1.90~2.75), chlorides — 107 mmol/l (95~110), phosphorus — 1.20 mmol/l (0,78~1.65), total bilirubin — 9.0 μmol/l (1.7~20.5), direct bilirubin — 2.00 μmol/l (0.86~5.00), c-reactive protein — 0.9 mg/l (0.1~7.0), d-dimer — 152.0 ng/ml (64.0~550.0), fibrinogen — 2.26 g/l (1.80~3.50), prothrombin according to Quick — 103.50% (70.00~130.00), international normalized ratio — 0.980 (0.850~1.150), thrombin time — 20.8 sec (14.0~21.0), activated partial thromboplastin time — 31.20 sec (26.00~36.00).

Estimated glomerular filtration rate (GFR, CKD-EPI) was 96.2 ml/min/1.73 m^2.

Clinical urine test results are within normal.

Ultrasound examination of abdomen and retroperitoneal space: diffuse changes in enlarged liver (craniocaudal size of left lobe 120 mm, its thickness — 74 mm, vertical oblique size of right lobe — 172 mm, its thickness — 130 mm), pancreas, calculi (up to 6 mm) in gallbladder; spleen is not enlarged, 96 × 40 mm; diffuse changes in the parenchyma of both kidneys, cyst of the renal sinus of left kidney; hypoechoic (8 × 5 mm) lesion of the right lower parathyroid gland; diffuse changes in thyroid gland; enlarged cervical lymph nodes on both sides up to 13 mm, with reduced echogenicity, with a thickness of cortical layer 1 mm, with no signs of hypervascularization during color Doppler mapping.

Despite the fact that the patient had no history of AH and there were no reasons for overloading heart chambers with volume and/or pressure, **echocardiography** showed left ventricular concentric hypertrophy with interventricular septum thickness of 13.8 mm, posterior wall of 13.8 mm, preserved ejection fraction (55%), left atrial dilatation (35 ml/m^2), pulmonary hypertension (systolic pressure in pulmonary artery 38 mm Hg) and diastolic dysfunction of type 1 (E/A in transmissible flow = 0.76), mitral regurgitation grade 2, tricuspid regurgitation grade 2, pulmonary regurgitation grade 1.

The patient was prescribed specific anti-amyloid therapy with tafamidis.

Discussion

In this clinical case, the disease onset was with neurological symptoms. The diagnosis was clinically suspected and confirmed by molecular genetic analysis of the transthyretin gene, which revealed c.G368A:p.Arg123His mutation, and by amyloid biopsy samples of abdominal subcutaneous adipose tissue. A similar mutation was detected in the sister and two nephews of the patient. This revealed an autosomal dominant type of inheritance. The father and mother of the patient died at 70 and 64 years, respectively. In connection with living in a rural area of one of the regions of the Russian Federation, no intravital examination of parents was carried out; there are no accurate autopsy data on diseases and causes of death. It is recommended to examine two more sisters and a brother of the patient for timely diagnosis of possible amyloidosis and the beginning of treatment.

Cardiac amyloidosis should be diagnosed both with the detection of amyloid infiltration by endomyocardial biopsy and with a thickening of the left ventricular wall >12 mm in the absence of AH or other reasons for left ventricular hypertrophy if amyloid extracardiac localization is detected [2]. Cardiological examination of the described patient revealed thickening of LV myocardium wall, single ventricular and supraventricular extrasystoles, including these of bigeminia type, paired, run of supraventricular tachycardia, painless episodes of ST segment depression. Unfortunately, no cardiac magnetic resonance imaging and DPD scintigraphy were performed for technical reasons. It is recommended to carry out these procedures in the future, with an assessment of the parameters during therapy. This requires the widespread implementation of these examination methods throughout the Russian Federation and the inclusion of these methods in state guarantee programs for patients with amyloidosis. Nonetheless, even the available data are sufficient to diagnose cardiac amyloidosis in the presented patient.

Hereditary ATTR amyloidosis is one of the most serious hereditary polyneuropathies with onset in adulthood and a progressive course. In non-endemic areas, the diagnosis is usually established within 3-4 years. In our patient, about two years passed from the onset of clinical manifestations to the diagnosis.

The c.G368A:p.Arg123His mutation found is extremely rare. There were no patients with this mutation in the THAOS registry of patients with ATTR amyloidosis [6, 14, 33]. This mutation was detected in one out of 298 patients with thickening of LV myocardium in France, but there was no evidence of amyloid deposition in biopsy specimens of salivary glands, nerves and kidneys, and scintigraphy, and the patient refused endomyocardial biopsy [28]. This was the first description of the mutation in this patient described by us (http://amyloidosismutations.com). Prior to this, another amyloidogenic mutation in the given position of transthyretin was described — c.Arg123Ser [34].

Conclusion

A case of transthyretin-related familial amyloid polyneuropathy and cardiac amyloidosis associated with a rare c.G368A:p.Arg123His mutation was presented. For the timely diagnosis and adequate management of

this disease, a kind of "amyloid alertness" is required. Implementation of modern approaches to the diagnosis and management of amyloidosis will improve the quality and increase the life expectancy of patients with this disease.

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