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Научно-практический журнал для работников здравоохранения

Включён в Перечень ведущих рецензируемых периодических изданий ВАК Минобрнауки РФ

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE

www.medarhive.ru

ДЕКАБРЬ 2020 (№ 6(56))

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Общество с ограниченной ответственностью «Синапс»
107076, Москва, ул. Короленко, д.3А, офис 18Б
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Бабяк Алина
reklama@medarhive.ru

Тираж 3000 экземпляров.

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

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

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

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

Контент доступен под лицензией
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Журнал включен в Российский индекс научного цитирования (РИНЦ)

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

Подписной индекс в каталоге «Почта России» 87732

DOI: 10.20514/2226-6704-2020-6

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THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE
www.medarhive.ru
DECEMBER 2020 (№ 6(56))

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Circulation 3000 exemplars

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

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

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

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

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

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

Subscription index in the catalogue «Russian Post» 87732

DOI: 10.20514/2226-6704-2020-6

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DOI: 10.20514/2226-6704-2020-10-6-407-413

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ЖИЗНЬ И ДЕЯТЕЛЬНОСТЬ РОБЕРТА КОХА

G.V. Maksimov[1], O.V. Lushina*[1,2], M.V. Pavlova[2], M.V. Veselova

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Robert Koch's Professional and Personal Life

Резюме

Пожалуй, всех творческих людей, чьи фамилии мы помним, объединяет такая черта характера, как увлеченность. И область творчества здесь не так уж важна — и в искусстве, и в технических науках, и в медицине для достижения результата необходимо полное погружение в исследование, некая одержимость.

Роберт Кох (1843–1910 гг) — великий исследователь, немецкий врач, микробиолог и гигиенист, примером своей жизни доказал, что четкая цель, сила духа и работоспособность побеждают все неблагоприятные обстоятельства. В нашей работе была рассмотрена жизнь и деятельность Роберта Коха на значительном отрезке времени — с окончания учебы до открытия туберкулина, анонсирования его как средства лечения туберкулеза и признания ошибочности этого утверждения. С точки зрения авторов работы, этот отрезок времени представляет огромный интерес. Мы видим Роберта Коха — ученого, обладающего незаурядными способностями и уникальным сочетанием свойств характера. Трудолюбие и высочайшая трудоспособность, требовательность к себе, четкая организация работы, умение не останавливаться при сложностях — предопределили успех его исследований.

Ключевые слова: *Роберт Кох, туберкулез, туберкулин, Эмми Фраац*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 14.08.2020 г.

Принята к публикации 26.10.2020 г.

Для цитирования: Максимов Г.В., Лушина О.В., Павлова М.В. и др. ЖИЗНЬ И ДЕЯТЕЛЬНОСТЬ РОБЕРТА КОХА. Архивъ внутренней медицины. 2020; 10(6): 407-413. DOI: 10.20514/2226-6704-2020-10-6-407-413

Abstract

All creative people, whose names we remember, are united by such a character trait as passion. And the field of creativity is not so important here — both in art, and in technical sciences, and in medicine, to achieve a result, complete immersion in research, some kind of obsession is necessary.

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Robert Koch (1843-1910) — a great researcher, a German physician, microbiologist and hygienist, proved by his own example that a clear goal, fortitude and efficiency overcome all unfavorable circumstances.
This work examined the life and work of Robert Koch over a significant period of time — from graduation to the discovery of tuberculin, its announcement as a treatment for tuberculosis and the recognition of the fallacy of this statement. From the point of view of the authors of the work, this period of time is of great interest. We see Robert Koch — a scientist with extraordinary abilities and a unique combination of character traits. Diligence and the highest ability to work, exactingness towards himself, a clear organization of work, the ability not to stop in the face of difficulties — predetermined the success of his research.

Key words: *Robert Koch, tuberculosis, tuberculin, Emmy Fraaz*

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

Sources of funding
The authors declare no funding for this study

Article received on 14.08.2020
Accepted for publication on 26.10.2020

For citation: Maksimov G.V., Lushina O.V., Pavlova M.V. et al. Robert Koch's Professional and Personal Life. The Russian Archives of Internal Medicine. 2020; 10(6): 407-413. DOI: 10.20514/2226-6704-2020-10-6-407-413

Robert Koch, a great scientist

Today, when the whole world continues struggling against tuberculosis, the biography of Robert Koch is shown in a new light. It would seem that Koch's time is behind nowadays in so many aspects: material and technical resources of laboratories, speed of communication, a great number of deeply erroneous and imperfect theories (that, however, were common among medical professionals).
Researcher Robert Koch seemed to work from the perspective of «what can I do for science and practical medicine?» He did not make demands like «give me laboratories, assistants, and a salary, then I will start working». No. Koch embarked on a very difficult yet the only possible course for him: first work, then conditions. Koch was also able to make space for himself. His first laboratory was a fenced-off corner in his own reception room; for a long time, his laboratory was equipped with an imperfect microscope and tableware borrowed from his wife. In such imperfect conditions, Koch conducted rigorously substantiated experiments and carried out diligent work.
This is probably the only way that discoveries are made: when one does not count hours of working time; when one does not compare the result and invested efforts; when material, physical and emotional costs have no special significance for the researcher for one reason — that the researcher cannot live and work in any other way. Trying to assess a creative process with a calculator in hands is the way to failure. Such a mathematical and practical approach is no good in this situation.
Koch got his results. These results and his name are now well known. We remember this man as an outstanding scientist with great talent.
However, researchers usually live with families and work with colleagues. It is impossible to talk about the biography of the genius without mentioning his family and relatives, teachers and schoolmates, and those who influenced him, helped with work or, on the contrary, hindered the course of his career. An individual in a thousand can be so restrained that his/her immediate family does not know if he/she has succeeded or failed. It is spouses, children and parents that have the difficult task of accepting and supporting. This is much more complicated than giving up on a spouse and concluding that the person is not fit for family life. Therefore, it is better to look for happiness elsewhere.
Of course, there are individualists by nature, but every adult at a certain age clearly realizes: parents grow old, colleagues and students are busy with their own work, and it is rather hard to be alone, to return every day to your empty house with no one to share your success or failure.
Family life with such a creative person also has its peculiarities. Family members should be empathic, supportive, able to endure hardships, and without discouragement. And they also have to decide not to use the very practical «calculator» to evaluate the ratio of labor and tangible benefits: money, position, «useful contacts», etc.

Everyone knows the names of Maria Sklodowska-Curie and Helena Roerich. Both women followed their spouses and found themselves in research. We do not remember the names of the wives of talented people, and we have to look them up when we need to. Usually, these wives made no discoveries of their own, wrote no books, or created their own paintings or magnificent melodies. Therefore, to the public, they remained a «shadow» of their talented spouses. Sometimes we unfairly forget that these «shadows» worked every day, providing their husbands with the opportunity to create. The work of wives is a daily routine, not historical events.

Emmy Koch was the wife of Robert Koch, the mother of his daughter. Her name is not associated with discoveries. It is hard to tell how successful this marriage was because it is obvious that the spouses had different plans for the future and even different ideas concerning here and now. However, one simple fact is revealing: Emmy shared with Robert the beginning of his medical and scientific career. She stayed with him, living on a very modest income and in conditions that did not meet her wishes. It seems that if she wanted to, Emmy could have returned to her parents (even without filing for divorce), leaving her husband to solve all the problems on his own, and then later raise the question of a reunion. She never did that. We can assume that there was no ultimatum like «family or science!». Later, we see the collapse of many years of marriage. Robert was wrapped up in science well before this divorce.

Robert Koch, a talented researcher

The beginning of Robert Koch's career was not trouble-free. Robert Koch started his education at the University of Goettingen (1862–1866) with lectures on natural sciences and botany. Since he had a keen interest in studying insects in childhood, his family indulged him in this hobby. In June 1865, Koch won the first prize, 80 thalers, in a student research competition. That year, he was appointed assistant to Prof. Krause, Director of the Pathology Institute. It was a great breakthrough for a student, a favorable beginning of a professional career. However, graduation was followed by a long period of instability because Koch could only apply for a teaching position. But he decided to go deeper into medicine: it was a relatable, honorable and lucrative profession.

In January 1866, Robert Koch earned his doctorate in medicine, and almost immediately, in February, he went to Berlin, to the famous Charité hospital where Rudolf Ludwig Karl Virchow worked. The name of this scientist was at that time well-known among scientists all over the world; with his theory of «cellular pathology», he was considered an authority beyond exception. This theory (later refuted by Koch) stated that diseases are caused by disorders in the normal activity of body cells. In other words, the origin and cause of diseases was sought (and found!) «inside» the body, and bacteriology as a science did not exist.

But at that time, Virchow was a legend, and Koch was travelling to Berlin to expand his knowledge. Just after four weeks, depressed and disappointed, he returned home to Clausthal. Koch could not «improve his knowledge» under the guidance of this distinguished scientist: when Virchow appeared at Charité and made patient rounds, he was always surrounded by a crowd of students, young physicians, assistants, colleagues. A personal meeting, conversation, request to explain an individual clinical case, all for what Koch came there, turned out to be impossible. Even Virchow's words were often difficult to hear in such a crowd.

Robert Koch was in a very difficult situation. It was almost impossible to get private practice: he was a young physician, a recent graduate, a «theoretician» with no experience of working alone. Then happenstance came to his aid — a cholera epidemic broke out. Physicians were needed urgently, and Koch was able to get a job in Hamburg. Ironically, at that time (in 1866), he was already looking at Vibrio cholerae in a microscope but considered this unimportant since he was working based on Virchow's theory. In 1884, Koch's impeccably substantiated report on the discovery of «cholera comma bacillus» would become a turning point: Virchow acknowledges bacteriology. But recognition and fame are in the distant future. The cholera epidemic is over, and Koch is jobless again.

It is only in September of 1866 that he got a position at the psychiatric hospital of Langenhagen village, near the city of Rakwitz. Honestly speaking, a position at a psychiatric hospital was very far from Koch's plans to become a physician on shipboard. However, after a long time of uncertainty, he now had a stable job and a salary. The young physician compared his dreams with reality and concluded that his long-time hopes could not be realized. He took up his duties

at the hospital and at the same time started looking for private practice. Now, when Koch's near future was clear and predictable, he could think about his own family. In 1867, Koch married Emmy Adolfine Josephine Fraatz, the daughter of a Hanoverian Superintendent General. A childhood friend, certified physician, was a «desirable alliance» for Emmy Fraatz. The spouse of a physician is a high status for a married lady, but the wedding was far from a magnificent celebration. It soon became clear that the young couple was going to live a modest life. Emmy Fraatz had expected more from her spouse.

The situation soon worsened: Koch's salary at the hospital was cut by half, income from private practice was small, and the couple was forced to return to Clausthal. Koch later found work in Niemegk. The family moved but was again in very modest financial circumstances. In 1868, their daughter Gertrude was born. Koch was confronted with reality: he had to find a stable job with a stable salary and to decide on his research work.

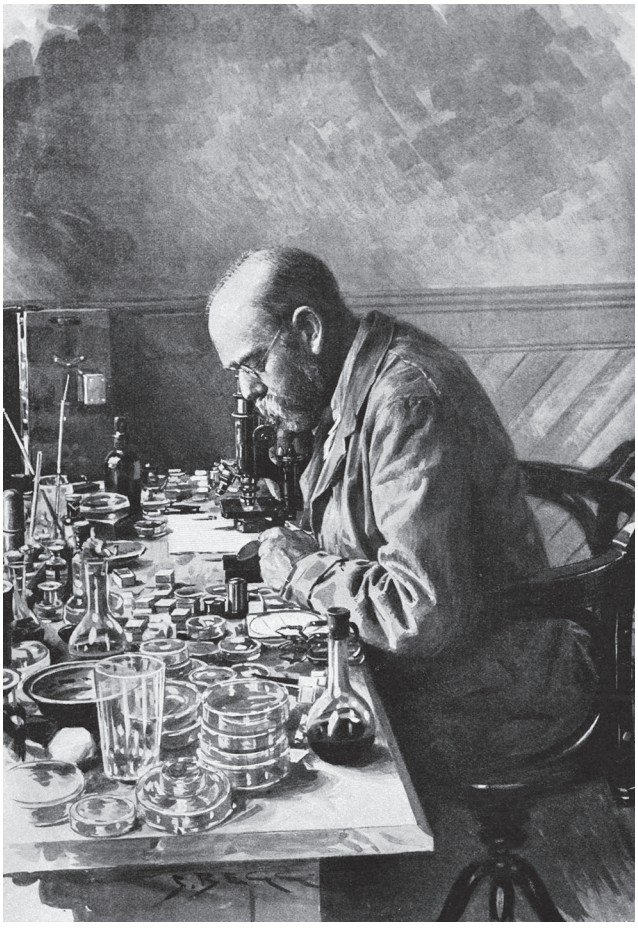

Figure 1. *Robert Koch at work (Photo from Paul de Kruif's book "Microbe Hunters", Orell Füssli, Zurich, 1927)*

The young physician moved to another place in the city of Rakwitz, Poznań province. He conducted private practice, and the local population eagerly sought his services. Hard work paid off.

In August 1870, Koch volunteered for the Franco-Prussian war and worked at a hospital. In March 1872, he was transferred to the position of district sanitary physician in Wollstein. It is with Wollstein that the beginning of Koch's research is associated.

The local population gave the new physician a warm reception. Robert Koch's life began to improve. Emmy gave her husband a gift that would be significant when Koch chose his future life path: on his 28th birthday, the physician received a microscope. Koch would spend many hours trying to find bacilli under this microscope.

In addition to his official duties, Koch conducted private practice and also put-up curtains in a corner in his reception room. This was his «laboratory» — a table with a microscope gifted to him by his wife and dishes from a table set (for lack of special laboratory equipment). In this «laboratory», Koch spent all his time free from his duties as a sanitary physician and private practice. The young researcher needed no leisure time. He forgot about the daily routine and did not count the hours spent looking through the microscope. He did not know what «spare time» was. All his time belonged to his work.

Emmy could hardly find her husband at home. Koch did not really seem concerned about improving the family's financial circumstances. He fulfilled his duties, but if there was a minute, he looked through his microscope. Emmy was left alone to deal with all household issues.

There was an outbreak of anthrax in the region of Wollstein. Nobody knew exactly why and how the epidemic broke out and ended. However, farmers noticed that not all of the grazing livestock was infected; part of the herd might become ill, but other animals in another part of the grazing field would be healthy. But these were just observations.

Koch took a blood sample of a sheep that had died from anthrax and placed the preparation under a microscope. The physician clearly saw mysterious «rods» and «clusters» that are absent in the blood samples of slaughtered healthy animals. The researcher transfused the blood of an infected sheep to a mouse (Koch had no syringes, so he made an injection with a sharp wooden stick). And when the mouse died, he took a sample of fluid from the spleen, placed the preparation under the microscope

and saw the same «rods» and «clusters». He tried to culture bacteria found on his plates on wet sand with a growth medium (a fragment of the spleen of the dead mouse and fluid from a bovine eye) but the experiment failed: there were too many foreign microorganisms. Koch needed a pure bacterial culture. How can one achieve that in «field conditions»? The researcher seemed to have absolutely nothing: no equipment, no conditions, and most importantly, he was alone, without assistants and colleagues. The letter would take a long time, and whom could he write? He had only one successful experiment with the mouse and one unsuccessful attempt to culture the «rods» and «clusters». There was a mysterious anthrax epidemic near his city.

Koch did not give up. His research in the «laboratory» were in full swing. To obtain a pure culture, he carried out technically exquisite work: he made a hollow in a glass, placed a growth medium and a drop of infected blood. He smeared the edges of the hollow with vaseline, covered the preparation with another glass and turned the resulting «sandwich». The drop was hanging without touching anything. Any airflow was excluded.

And the experiment was successful! Bacteria were cultured! For eight days, Koch made reinoculations to make sure.

He was once called for childbirth and forgot to remove the preparation from the microscope. Later, he returned and looked at it. The bacteria had spent several hours without food and heat and ... had formed spores. The riddle of anthrax was solved. The formation of spores explained everything: it is how bacteria exist in unfavorable conditions. While the cattle walked in infected areas of the pasture, there was no anthrax, but it «waited». In addition to describing the mechanism of spore formation, Koch also offered new methods of dealing with corpses of animals that had died from anthrax: burying them deep in the ground or burn.

Having finished his «Etiology of Anthrax», Robert Koch sought to make its presentation at the Ferdinand Cohn Institute of Plant Physiology in Breslau. Koch took to the presentation not only the preparations but also his microscope.

The scientist's speech was a huge success. Listeners were amazed by both the sensational results and the structure of the experiments: consistency, strict logic, accuracy and pedantry.

Robert Koch returned to Wollstein. This trip proved that it was necessary to look for ways of making photos of preparations because each one of them counts. While the researcher was experimenting with photos, his friends were looking for ways to transfer Koch to Breslau University. The conditions there were surely better than a corner in his own reception room.

Robert Koch found a way of making photos of preparations: the use of aniline dyes produces good photos. Therefore, there was no need to take glasses and worry about their safety because broken glasses would put the evidence base at risk. Koch would simply have nothing to demonstrate in support of his words. But now he could take photos. In addition, keeping a photo archive helped much in the organization of researches.

His friends succeeded in having Koch appointed a city sanitary physician in Breslau. He could combine his new duties with research work. The family moved but was met with challenges: the official salary was too small and Koch could not find private practice. There were enough physicians in the city.

After three months, Koch's family returned to Wollstein, where the scientist continued his research. For two years, he worked on the causes of purulent inflammation of wounds (he had seen enough practical examples during the «war episode» of his career), and the result was a paper on the etiology of wound infections published in 1878. This work outlined three basic requirements (Koch – Henle postulates) on the basis of which the relationship of disease with a specific microorganism was established: 1) the microorganism should be found in all cases of this disease; 2) all manifestations of this disease should be explained by the number and distribution of microorganisms; 3) the causative agent of each infection should be found in the form of a morphologically well-defined microorganism. Koch proved that every wound disease had a specific pathogen. It was another victory. Robert Koch's name rose among medical professionals, thanks to the achieved results.

In 1880, Koch got an invitation to the Imperial Department of Health in Berlin. Robert Koch moved to Berlin with his family. Emmy's expectations finally started to come true: a big city, society, the opportunity for her daughter to attend an aristocratic school. However, the psychological dissonance between spouses increased over the years, and the marriage ended in an amicable divorce in 1893.

In Berlin, Robert Koch got absolutely new working conditions: a laboratory, equipment, experimental

animals. Koch worked with his assistants: military medics Georg Gaffky and Friedrich Loeffler. Research was conducted at the Higher Veterinary School. First of all, the task was to find a way to make pure bacteria cultures. The problem was solved: a solid growth medium based on gelatin was developed.

It was here, in this laboratory, that Koch worked on the identification of the causative agents of tuberculosis — the discovery that brought him fame and honor. Tuberculosis was previously considered a spontaneous disease promoted by poor housing and living conditions and lack of food. There was also an opinion that tuberculosis was a hereditary disease. After several years of studying tuberculosis at the Valde-Grâce hospital in Paris, physician and researcher Jean-Antoine Villemin concluded that the disease was contagious but did not find its causative agent. Research results remained unconfirmed.

Pathologist Julius Cohnheim always found tubercles from decayed tissues and pus in the organs affected by tuberculosis, but the pathogen was also not found. At the Charité hospital (where student Koch tried to practice under the watchful eye of Virchow), Robert Koch, government adviser to the Imperial Department of Health, received research material – sputum and blood of tuberculosis patients. At this time, his assistants were working on other issues: Gaffky was looking for the causative agent of typhoid fever, Loeffler — that of diphtheria. Work in the laboratory did not stop for a moment, but Koch could not find the causative agent of tuberculosis. Despite the failures, he continued his experiments.

Another TB patient, male, 36, was admitted to Charité hospital. The patient died very quickly. Koch took a sample of his lung tissue for research but again — got no results. The researcher did not give up: he put the lung tissue preparation in a bath filled with a newly invented solution of methylene blue with potassium hydroxide. A day later, Koch saw, under the microscope, a uniformly colored blue field, and nothing on the preparation. This could be anything: a happy coincidence, fair luck, or insight. We only know the fact: Koch added Vesuvin, a red-brown dye for leather, to the preparation. Destroyed lung tissue cells were stained matt brown. Bright blue tiny bacilli moved on this background. Here it was – the «invisible» microbe. Thus, tubercle bacillus was found in preparation No. 271.

But then there were several inconsistencies. Laboratory animals, rabbits and guinea pigs were not infected by the injection of «bacilli» In addition, «bacilli» do not replicate in an artificial environment (it was later established that tuberculosis bacilli replicate only in living organisms). Then another victory followed. Koch was able to grow a culture on warm serum and could prove that one could be infected with tuberculosis by inhalation of bacilli. His experiment, called Noah's Ark, confirmed that brilliantly: all animals placed in a closed box became ill after inhalation of contaminated air entering through a pipe.

Koch prepared the work «On the Etymology of Tuberculosis», but the Berlin Society of Scientific Medicine, led by Virchow, rejected it. Koch turned to the Society of Physiologists. On March 24, 1882, Robert Koch presented a report at the Physiological Institute. Virchow, who was in attendance, applauded.

Later, Koch also found a way of disinfecting tuberculosis bacteria: steam and mercuric chloride. Despite the fact that no treatment options were proposed for tuberculosis, the report on the etymology of this disease played a huge role. Until that moment, tuberculosis had appeared as a mysterious, suddenly occurring disease. Now the pathways of transmission of this pathogen were established.

Koch went further in his research. And again, circumstance set the direction of his work: in 1883, there was a cholera break out in Egypt, England and France. Pasteur (69, partially paralyzed, working on a rabies vaccine) sent physicians Roux and Thuillier to Egypt. Koch travelled there with Gaffky and Fischer (at that time, Loeffler had found diphtheria bacillus and stayed to continue this study). But in Alexandria, where the expedition arrived, the cholera outbreak had subsided. So, there were fewer preparations for research. The physicians did not give up. The death of twenty-six-year-old Thuillier from cholera came as a great shock. Probably, this fact made the researchers decide to continue their work by any means. Robert Koch and his assistants moved to India, where cholera was almost a regular disease.

Having sufficient research material, Koch proved that cholera was spread through contaminated water, food, and from person to person. At that time, India had problems with supply of clean water, so the disease was widespread.

In July 1884, at the Berlin conference, Koch presented a brilliant report about cholera. The next task was to find a way to treat tuberculosis since its infectious origin had been proven and transmission routes had been found.

In August 1890, at the Tenth International Medical Congress in Berlin, Koch announced that he had

found a drug for treating tuberculosis. He called this drug «tuberculin».

This report drew a huge response not only among medical professionals but also among the public. The number of people wishing to get tuberculin was fantastic: individuals with tuberculosis, relatives of patients, and physicians looking for a panacea for their patients. Tuberculin was widely used. Robert Koch seemed at the peak of his career, and insidious tuberculosis had been defeated forever.

But then reports of deaths after tuberculin injections started emerging. This drug did not help treat tuberculosis but improved the condition of patients with lupus. Subsequently, tuberculin was used in the diagnosis of tuberculosis, and present-day phthisiology of the 21st century is impossible without this drug discovered by the great scientist. But at that time the disappointment was comparable to the euphoria at the first reports of the wonderful properties of tuberculin. One can only guess why such a perfectionist like Koch made such a mistake. But there was still a lot of work to do. He had to admit the error and continue research, both on tuberculosis and in other areas.

Koch's ideas were still relevant to scientists and physicians even in the second half of the 20th century; tuberculin therapy was continued to be studied and used by phthisiologists E. Z. Mirzoyan in 1965 and V. A. Krylov in 1995.

If the life of the physician that was filled with painstaking work could be reduced to a list of achievements, then Robert Koch's record of accomplishments would look as follows: discovery of Bacillus anthracis and spore formation mechanism, development of anthrax vaccine; work on the etiology of wound infections, formulation of Henle – Koch postulates; development of a method for growing bacterial cultures on solid media; introduction of aniline dyes in laboratory practice; discovery of tubercule bacillus, establishment of transmission routes of tuberculosis and the infectious nature of this disease; finding Vibrio cholerae and evidence of cholera transmission routes; development and presentation of tuberculin, which is still used to this day for the diagnosis of tuberculosis; implementation of practical use of microphotography; development of a device for sterilizing growth media that cannot withstand temperatures above 100 °C (Koch apparatus); implementation of Abbe condensers; developing a pure culture of tetanus pathogen (together with Kitasato Shibasaburō); development of a vaccine against cattle plague; finding in the blood of patients with recurrent typhoid spirochetes causing this disease; identification of the mechanism of transmission of sleeping sickness.

Robert Koch is one of the founders of microbiology. His greatest discoveries are invaluable. The new methods used by Koch in his laboratory work allowed his assistants – Emil Adolf von Behring, Friedrich Loeffler, Richard Pfeiffer, Kitasato Shibasaburō, August Paul von Wasserman — to conduct their own successful research and medical practice. The highest recognition of Robert Koch as a scientist was the Nobel Prize awarded to him in 1905 for his work on the study of tuberculosis – the discovery of tuberculosis «bacillus» (Koch), mycobacteria culture on growth media and obtaining a pure culture, confirmation of the infectious nature of this disease by infection of animals and the development of tuberculosis in them.

Author Contribution:

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

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M.V. Veselova: search for literature, writing and editing the article

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DOI: 10.20514/2226-6704-2020-10-6-414-421

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ФАКТОР НЕКРОЗА ОПУХОЛИ-АЛЬФА И ВОЗРАСТ-АССОЦИИРОВАННАЯ ПАТОЛОГИЯ

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Tumor Necrosis Factor-Alpha and Age-Related Pathologies

Резюме

В обзоре отражены современные представления о понятии «*inflammaging*» и роли субклинического воспаления при различной возраст-ассоциированной патологии. Особое внимание уделено фактору некроза опухоли-α — ключевому цитокину, принимающему важное участие как в патогенезе хронических воспалительных заболеваний, так и в процессах старения. Повышенное содержание фактора некроза опухоли-α приводит к возникновению и прогрессированию различных заболеваний, к усугублению старческой астении, к инвалидизации и смертности лиц пожилого и старческого возраста. Фактор некроза опухоли-α оказывает влияние на различные факторы риска сердечно-сосудистой патологии, способствует возникновению и прогрессированию атеросклероза и связанных с ним заболеваний. Этот цитокин может усугублять также различные метаболические нарушения, в первую очередь, инсулинорезистентность и сахарный диабет. Фактор некроза опухоли-α — ключевой цитокин, стимулирующий костную резорбцию (с возникновением остеопороза) и саркопению. Имеющиеся в настоящее время данные подтверждают важную роль фактора некроза опухоли-α при различных возраст-ассоциированных заболеваниях.

Ключевые слова: *воспаление, цитокины, фактор некроза опухоли-α (ФНО-α), атеросклероз, старение, старческий возраст, долгожители*

Конфликт интересов

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Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 26.05.2020 г.

Принята к публикации 08.07.2020 г.

Для цитирования: Тополянская С.В. ФАКТОР НЕКРОЗА ОПУХОЛИ-АЛЬФА И ВОЗРАСТ-АССОЦИИРОВАННАЯ ПАТОЛОГИЯ. Архивъ внутренней медицины. 2020; 10(6): 414-421. DOI: 10.20514/2226-6704-2020-10-6-414-421

Abstract

Modern concepts about the «inflammaging» and the role of subclinical inflammation in various age-associated pathology are described in the review. Particular attention is paid to the tumor necrosis factor-α, a key cytokine that

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plays an important role in the pathogenesis of chronic inflammatory diseases as well as in aging. The increased levels of tumor necrosis factor-α leads to the onset and progression of various diseases, to severity of frailty, to disability and mortality of elderly persons. Tumor necrosis factor-α affects different risk factors for cardiovascular diseases, contributes to the onset and progression of atherosclerosis and related pathology. This cytokine can also aggravate various metabolic disorders, mainly — insulin resistance and diabetes mellitus. Tumor necrosis factor-α is a key cytokine that stimulates bone resorption (up to osteoporosis) and sarcopenia (up to cachexia). Currently available data confirm the important role of tumor necrosis factor-α in various age-associated disorders.

Key words: *inflammation, cytokines, tumor necrosis factor-α (TNF-α), atherosclerosis, aging, old age, long-livers*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 26.05.2020
Accepted for publication on 08.07.2020

For citation: Topolyanskaya S.V. Tumor Necrosis Factor-Alpha and Age-Related Pathologies. The Russian Archives of Internal Medicine. 2020; 10(6): 414-421. DOI: 10.20514/2226-6704-2020-10-6-414-421

Chronic subclinical inflammation is increasingly considered as one of the key phenomena in the aging process and is termed *inflammaging* [1]. This kind of inflammation has five basic characteristics: it is minor, asymptomatic, controllable, chronic and systemic. In contrast to the typical response to a particular pathogenic agent, inflammation does not disappear with aging; it persists, resulting in various pathological changes [2].

Along with *inflammaging*, some authors propose the concept of *anti-inflammaging*, which means that long-livers seem capable of coping with chronic subclinical inflammation through an anti-inflammatory response [3, 4]. If inflammaging is considered the key to understanding aging processes and age-related diseases, then anti-inflammaging can obviously be considered one of the secrets of longevity.

It is noteworthy that despite the increased level of pro-inflammatory cytokines (including tumor necrosis factor-α), long-livers often maintain good health and do not develop any serious age-related diseases. From this perspective, subclinical inflammation in long-livers can be considered as a consequence of a favorable compensatory response aimed at reducing chronic antigenic load. However, an excessive inflammatory response can be harmful. Therefore, the rate of reaching the threshold pro-inflammatory state and personal ability to adapt to various stressful effects seem to be crucial for the development of age-associated diseases [5].

Both clinical and experimental studies show that pro-inflammatory cytokines (primarily, tumor necrosis factor-α and interleukin-6) play an important role in the onset and progression of age-associated subclinical inflammation. The increased level of these cytokines in the blood serum of elderly and senile patients is associated with increased morbidity, disability and mortality. [6, 7]. With aging, the expression of tumor necrosis factor-α (TNF-α) and interleukin-6 increases, and the imbalance between pro-inflammatory and anti-inflammatory cytokines results in subclinical inflammation, accelerates the aging process and contributes to different age-related diseases. Pro-inflammatory cytokines cause cell aging by stimulating the overproduction of reactive oxygen species, while damage to deoxyribonucleic acid (DNA), in turn, activates pro-inflammatory cytokines, blocks cell cycle and contributes to cell aging [2].

A common pro-inflammatory cytokine such as TNF-α, described in 1975 as a circulating antitumor cytokine, plays an important role in immune response in elderly people. TNF-α was previously thought to be produced mainly by activated macrophages and lymphocytes, but later, its expression was revealed in endothelial and epithelial cells, in smooth muscle cells of blood vessels and cardiomyocytes [8, 9].

It was later discovered that TNF-α is a key cytokine and an essential component of the immune system that stimulates the expression of genes required for controlling inflammation and tissue damage. The TNF-α family is considered as a group of cytokines that have critical functions in different immune responses, in the inflammation process, differentiation, and

control of proliferation of different cells and their apoptosis [10,11]. TNF-α is regarded as the main pro-inflammatory mediator responsible for the activation of the immune system during infectious processes. Bacterial agents and many other stimuli induce the synthesis of TNF-α, which (along with other pro-inflammatory mediators) recruits and activates neutrophils, macrophages and lymphocytes in tissue damage or infection sites [10].

The level of TNF-α increases with age and is associated with different age-related diseases. It was found that tumor necrosis factor-α increases in elderly people and even in long-livers [6, 7, 12]. An increased TNF-α level is accompanied by an increased risk of cardiovascular diseases [12]. According to several authors, TNF-α plays a role in the pathogenesis of atherosclerosis and Alzheimer's disease [12].

Increased blood TNF-alpha in elderly people is considered as a factor that enables to predict a fatal outcome regardless of the associated pathology [6, 13]. The relationship between TNF-α and mortality, regardless of dementia or cardiovascular diseases, suggests that TNF-α has an effect apart from cardiovascular disease [6]. Another study also demonstrated that higher levels of TNF-α are associated with increased mortality among elderly people [14]. Also, the relationship between high TNF-α concentration in plasma and mortality in long-livers suggests that this cytokine has specific biological effects and can be considered as a marker of senile asthenia in people at a very advanced age [13].

Analysis of TNF-α genetic polymorphisms in long-livers, octogenarians and younger people showed no differences in the distribution of TNF-α genotypes in the –308 position in these age groups. However, *GA* genotype (*TNF-α-308AG*) was associated with a lower frequency of dementia in long-livers. Few long-livers (carriers of *AA* genotype) had a higher risk of mortality and usually had an increased TNF-α level in blood plasma [15]. Other authors noted longer life expectancy in women with *TNF-α-308AG* genotype in comparison with women with *GG* genotype [16]. Genetic studies also revealed that the A allele of the *TNF-α-308* gene (*TNF-α-308A*) is associated with the risk of coronary heart disease [17].

Multifunctional pro-inflammatory cytokine TNF-α has an effect on several risk factors for cardiovascular diseases, in particular, insulin resistance, dyslipidemia, endothelial dysfunction and endothelial activation of cell adhesion molecules [18]. The high level of TNF-α in long-livers is associated with a low ankle-brachial index, which can be a sign of peripheral atherosclerosis. Other effects of TNF-α can also contribute to the development and progression of atherosclerosis and to the high risk of thromboembolic complications. This pertains to the stimulation of TNF-α synthesis of other pro-inflammatory mediators, for example, interleukin-6, C-reactive protein, fibrinogen, as well as white blood cells [8]. At the same time, TNF-α induces smooth muscle cell proliferation and increases the adhesion of leukocytes to endothelial cells, inducing the expression of cell adhesion molecules (E-selectin, ICAM-1 (CD54) and VCAM-1 (CD106)), as well as the expression of various endothelial cells cytokines, including interleukin-6 [8].

It was shown that already at the early stage of atherosclerosis, TNF-α stimulates endothelial dysfunction, increases the permeability of the endothelium, and promotes the migration of leukocytes into the vascular wall. Increased vascular permeability contributes, in turn, to the formation of atherosclerotic plaques. At later stages, this pro-inflammatory cytokine increases apoptosis of smooth muscle cells of blood vessels and macrophages (which contributes to the rupture of atherosclerotic plaques), induces the synthesis of matrix metalloproteinases and procoagulant activity, reducing the transcription of anticoagulant genes, thrombomodulin and protein C [19].

TNF-α contributes to dyslipidemia by increasing triglycerides, total cholesterol, as well as low-density lipoprotein cholesterol and lowering the concentration of high-density lipoproteins. TNF-α takes part in lipid metabolism, reducing the activity of 7-hydroxylase and lipoprotein lipase and stimulating the production of triglycerides in the liver [18].

Results of clinical and experimental studies indicate the important role of TNF-α in atherogenesis and the onset of vascular dysfunction with underlying arterial hypertension and pathological myocardial remodeling [9, 20]. Over the past 20 years, the idea that not only dyslipidemia but also inflammation is actively involved in atherosclerotic process and the development of cardiovascular diseases, including coronary heart disease (CHD), became firmly entrenched in cardiology [21, 22]. Both chronic coronary heart disease and acute myocardial infarction are inflammatory processes where pro-inflammatory cytokines such as TNF-α and acute-phase proteins, for example, C-reactive protein, play an important role [22, 23].

TNF-α is considered as a key pro-inflammatory cytokine, which is involved in atherogenesis and

contributes to mild systemic inflammation in the cardiovascular system. The effects of TNF-α on the cardiovascular system include not only its contribution to vascular dysfunction but also its effect on cardiomyocytes [9]. Direct evidence of TNF-α-stimulated vascular dysfunction was shown in a study conducted on healthy volunteers: intra-arterial injection of this cytokine in high doses led to acute local vascular inflammation in 30 minutes. Abnormal endothelium-dependent vasodilation and persistent increase in the release of plasminogen activator from endothelial cells were simultaneously registered [24]. Injection of a lower dose of TNF-α in healthy volunteers was accompanied by increased basal vascular resistance, that was blocked by pretreatment with a non-selective cyclooxygenase inhibitor [25]. It can be assumed that the registered effects of TNF-α were mediated not only by decreased bioavailability of nitric oxide but also by increased cyclooxygenase-dependent production of vasoconstrictors [26].

TNF-α concentration in the heart of healthy people is low and has no effect on its contractile function. However, the injection of exogenous TNF-α inhibits the contractile activity of cardiomyocytes. This pro-inflammatory cytokine can also reduce the absorption of calcium ions by sarcoplasmic reticulum and the sensitivity of myofilaments to calcium. In addition to reducing the contractility of cardiomyocytes, TNF-α can induce their hypertrophy [9].

Coronary artery occlusion in myocardial infarction causes a rapid increase in the level of pro-inflammatory cytokines, including TNF-α. Although an early increase in TNF-α after myocardial infarction helps to stabilize the function of the left ventricle, prolonged stimulation of TNF-α triggers its dysfunction in the later phases after acute coronary syndrome. Chronic exposure to high TNF-α concentrations results in dysfunction of the left ventricle and increased activity of matrix metalloproteinases, that contribute to the degradation of the matrix and, ultimately, to increased apoptosis of cardiomyocytes [27].

A number of studies demonstrated that high levels of TNF-α in serum can persist for many months after myocardial infarction [22, 28]. According to the observations of some authors, long-term maintenance of high TNF-α level becomes a risk factor for repeated cardiovascular events. Pro-inflammatory cytokines (including TNF-α) are produced predominantly in the peri-infarction zone. Therefore, a persistent increase in the level of cytokines after myocardial infarction may be the result of increased cardiac muscle infiltration by inflammatory cells. The expression of TNF-α after myocardial infarction can persist over time in intact cardiomyocytes, which suggests the possible long-term role of this cytokine in the remodeling of the myocardium and blood vessels [28].

In general, the effect of TNF-α on cardiomyocytes has many aspects and depends on the effect on a particular type of receptor and the cytokine form (membrane-associated or soluble). When acting type 1 receptors, TNF-α causes inhibition of myocardial contractility. This dysfunction can arise due to the stimulation of oxidative stress during the formation of reactive oxygen species and increased production of nitric oxide synthase (accompanied by the production of nitric oxide and peroxynitrite), activation of phospholipase A2, arachidonic acid and sphingomyelinase [9, 29]. TNF-α may have independent negative inotropic effects and inhibit the expression of contractile proteins (in particular, heavy chains of α-myosin and cardiac α-actin). Also, TNF-α can cross-interact with the β-adrenergic receptor system and inhibit the contractility of cardiomyocytes by altering signals to these receptors [29].

Besides reducing contractility, TNF-α enhances the transcription of genes that contribute to myocardial hypertrophy in heart failure. However, this pro-inflammatory cytokine stimulates apoptosis of cardiomyocytes, cardiac fibrosis, pathological myocardial remodeling, which contributes to the progression of heart failure [30, 31]. TNF-α activates the renin-angiotensin-aldosterone system (RAAS) in the heart, which leads to increased remodeling of the left ventricle, increased collagen level and apoptosis of cardiomyocytes [32].

Increased TNF-α level in patients with chronic heart failure (CHF) was demonstrated in a number of studies that confirmed the role of this pro-inflammatory cytokine in CHF pathogenesis, especially with an intact ejection fraction [29, 33]. The expression of TNF-α by cardiomyocytes leads to the inhibition of their contractile activity. At the same time, TNF-α can interact with β-adrenergic receptors, thereby exacerbating the negative inotropic effect [9, 29, 34–38].

TNF-α, along with other pro-inflammatory cytokines, plays a role in the pathogenesis of atrial fibrillation. A number of recent studies demonstrated that the risk of atrial fibrillation with increased TNF-α increases markedly [39]. There is no clear specific

pathogenetic relationship between pro-inflammatory cytokines (including TNF-α) and atrial fibrillation yet. However, several concepts link chronic inflammation with the development and progression of structural and electrophysiological atrial remodeling [39–40].

Both clinical and experimental studies have established that TNF-α can have a negative effect on the remodeling of the left ventricle and other heart chambers by inducing metalloproteinases and activating proteolytic processes [41]. At the same time, a reliable direct correlation was found between TNF-α level in serum and the diameter of the left atrium [42].

With a persistent but slightly increased TNF-α level, many mechanisms that contribute to vasoconstriction, and, therefore, arterial hypertension, are triggered [9]. Serum TNF-α is conclusively and independently associated with blood pressure in healthy individuals. In a study by Bautista L. E. et al. (2005), the average plasma TNF-α level was four times higher in patients with arterial hypertension [43]. There is a complex cross-regulation between RAAS and TNF-α signaling under physiological conditions. TNF-α inhibits renin expression in adrenal gland cells and juxtaglomerular kidney cells [9]. At the same time, there is a TNF-α-related decrease in the production of angiotensinogen in the cells of renal proximal tubules [44].

The TNF-α-triggered induction of such a powerful vasoconstrictor as endothelin causes a significant vasoconstrictor effect [45]. The endothelin B2 receptor, which mediates such vasoconstriction, is not expressed by smooth muscle cells under normal conditions. However, its amount increases with different cardiovascular diseases (for example, diseases of peripheral arteries, pulmonary hypertension, coronary heart disease and ischemic stroke). Such changes suggest the possible involvement of TNF-α in the development of abovementioned pathological processes [9]. Also, TNF-α induces the production of thromboxane A2 by endothelial and smooth muscle vascular cells and also reduces insulin-mediated vasodilation [9, 25].

According to some authors, TNF-α is one of the key cytokines that trigger and enhance inflammatory response after a stroke. Several studies showed that TNF-α-positive cells can be found in the brain of patients with severe ischemic stroke from the third day after the acute cerebrovascular event (stroke); these cells persist for up to 15 months after the vascular event. Serum concentration of TNF-α increases within 6 hours after stroke and remains high for 10 days [46].

Increased TNF-α level contributes to different metabolic disorders. The study by Swaroop J. J. et al. (2012) revealed, in patients with type 2 diabetes mellitus, a significant relationship between the TNF-α level and the functioning of pancreatic β-cells, insulin resistance index and insulin level [47]. Many authors believe that TNF-α is one of the key cytokines involved in the onset of insulin resistance and type 2 diabetes mellitus. High level of TNF-α induces insulin resistance in adipocytes and peripheral tissues, thus disrupting the transmission of insulin signals through serine phosphorylation [48]. TNF-α also interferes with the endothelial pathways of insulin signaling and exacerbates insulin resistance [49–50].

At the same time, a direct relationship was established between the level of pro-inflammatory cytokines, including TNF-α, and the concentration of blood creatinine, as well as the severity of chronic kidney disease [51]. It was shown that high levels of TNF-α and other pro-inflammatory mediators contribute to a more rapid decrease in glomerular filtration rate and progression of chronic kidney disease, even taking into account the influence of other factors [51]. In the kidneys, pro-inflammatory cytokines induce the expression of reactive oxygen radicals, lipids, and adhesion molecules, and stimulate pathological matrix accumulation and procoagulant activity of endothelial cells [51–53].

Also, TNF-α is a key factor that stimulates pathological bone resorption in cases of different inflammatory diseases. This pro-inflammatory cytokine can directly stimulate the synthesis of osteoclast precursors, and can indirectly enhance osteoclastogenesis by increasing RANKL expression (an essential mediator of osteoclastogenesis, cytokine of tumor necrosis factor family) on osteoclastic precursors. In addition, it was found that TNF-α was able to inhibit bone formation by suppressing osteoblast differentiation [54].

TNF-α (known as cachectin) causes increased basal energy expenditure, anorexia, and muscle loss in vivo. A definite relationship was found between TNF-α level and wasting (up to cachexia) in the cases of chronic inflammatory diseases, including infection with the human immunodeficiency virus, rheumatoid arthritis and oncological diseases [55]. High blood levels of TNF-α are coupled with lower muscle mass and strength in elderly patients [13].

According to some authors, increased TNF-α concentration is associated with senile asthenia, a significant decrease in muscle strength, the risk of cerebrovascular and cardiovascular diseases, as well as a more rapid decrease in cognitive abilities in elderly patients [56].

The effect of TNF-α and other pro-inflammatory cytokines on sarcopenia can be explained by several factors. For many years, it was believed that the induction of the breakdown of muscle proteins is the main pathway underlying the relationship between inflammation and sarcopenia. Later, additional mechanisms of the effect of pro-inflammatory cytokines (primarily, TNF-α) on muscles were found, including the stimulation of mitochondrial dysfunction and oxidative stress. In turn, the effect of TNF-α on mitochondrial dysfunction can be mediated by nitric oxide, which plays a significant role in mitochondrial functioning. It is known that TNF-α is a strong inducer of the synthesis of nitric oxide and so contributes to apoptosis stimulation and increased production of reactive oxygen species [57].

At the same time, several experimental and clinical studies demonstrated that TNF-α was able to inhibit the production of erythropoietin and activate hepcidin, which can cause anemia of chronic inflammation. It was established that this cytokine is involved in a complex mechanism that regulates erythropoietin synthesis in response to a hypoxic stimulus, and reduces the sensitivity of erythroid cells to the effects of erythropoietin. Stimulation of the synthesis of reactive oxygen species by TNF-α also makes a certain contribution to the suppression of erythropoietin production. At the same time, the inhibitory effect of TNF-α on the formation and differentiation of erythroid stem cells was revealed [58].

A recent experimental study demonstrated that TNF-α also plays a role in the regulation of megakaryocytic lineage. This pro-inflammatory cytokine stimulated platelet hyperreactivity and thrombosis in a mouse model of aging. Neutralization of TNF-α and its receptors, in contrast, decreased platelet hyperreactivity. Based on the data obtained, the authors of this work suggested that *inflammaging* contributes to platelet hyperreactivity and increases the risk of thrombosis during aging [59].

A clinical study involving 424 senile individuals observed over eight years revealed a gradual increase in plasma TNF-α concentration associated with cognitive dysfunction. According to the results of magnetic resonance imaging, an increased level of TNF-α was associated with decreased volume of brain gray matter and increased hyperintensity of white matter. This paper also shows an inverse correlation between TNF-α concentration and cognitive impairments, which were assessed using the Mini-Mental State Examination scale (MMSE) [60]. These results suggest that TNF-α level in the blood will be one of the potential biomarkers of age-related changes in the brain.

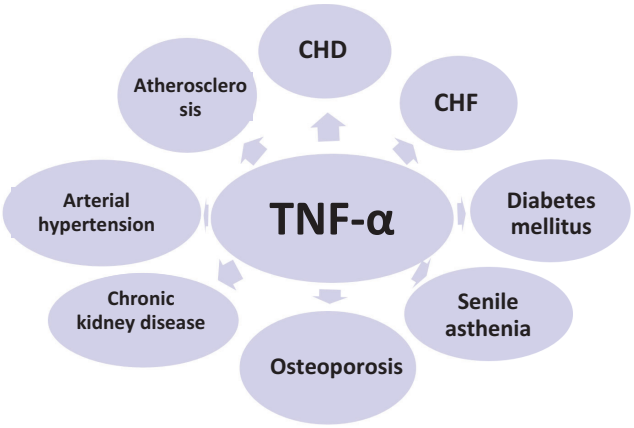

Figure 1. *TNF-α and age-related diseases*

Note: TNF-α — tumor necrosis factor-alfa, CAD — coronary artery disease, CHF — chronic heart failure

Clinical and experimental studies indicate the important role of TNF-α in immune response in elderly people and the increased level of cytokine with aging. This pro-inflammatory cytokine is associated with different age-related diseases and, most probably, with increased mortality. TNF-α can have an effect on several risk factors for cardiovascular diseases and contribute to the development and progression of atherosclerosis. Further studies are required to study the role of tumor necrosis factor-α in subclinical inflammation and the development of different pathological conditions in senile individuals and long-livers.

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DOI: 10.20514/2226-6704-2020-10-6-422-429

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КОЖНЫЕ ПРОЯВЛЕНИЯ ПРИ КОРОНАВИРУСНОЙ БОЛЕЗНИ 2019 ГОДА (COVID-19)

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The Dermatological Manifestations in the Coronavirus Infection COVID-19

Резюме

В статье обсуждается разнообразие кожных проявлений у пациентов с новой коронавирусной инфекцией COVID-19, характеристики которых аналогичны возникающим при обычных вирусных инфекциях, а частота встречаемости определятся сопутствующей патологии и особенностей медикаментозного лечения. Выделяют несколько групп кожных проявлений в зависимости от причины и механизма развития: ангииты кожи; папуло-сквамозные сыпи и розовый лишай; кореподобная сыпь и инфекционные эритемы; папуло-везикулезные высыпания; токсидермии; уртикарные высыпания и артифициальные поражения. Многообразие клинической картины кожных проявлений коронавирусной инфекции требует глубокого анализа для правильной интерпретации и дифференциальной диагностики поражений кожного покрова при COVID-19 с другими инфекционными экзантемами и дерматозами.

Ключевые слова: *коронавирусная инфекция, COVID-19, кожные проявления, экзантема*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 08.10.2020 г.
Принята к публикации 25.11.2020 г.

Для цитирования: Дворников А.С., Силин А.А., Гайдина Т.А. и др. КОЖНЫЕ ПРОЯВЛЕНИЯ ПРИ КОРОНАВИРУСНОЙ БОЛЕЗНИ 2019 ГОДА (COVID-19). Архивъ внутренней медицины. 2020; 10(6): 422-429. DOI: 10.20514/2226-6704-2020-10-6-422-429

Abstract

The variety of dermatological manifestations in patients with the novel coronavirus infection COVID-19, the incidence of which depends on concomitant pathology and the characteristics of drug treatment, and their characteristics are similar to those that occur with conventional viral infections is discussed. At the present time it is proposed to distinguish several groups depending on the cause and mechanism of development: angiitis of the skin; papulo-squamous rash and pink lichen; measles rash and infectious erythema; papulo-vesicular rash; toxidermia; urticarial eruptions and artifical

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lesions. The variety of the clinical picture of the skin manifestations of coronavirus infection requires in-depth analysis in order to interpret correctly the skin lesions and other infectious exanthema and dermatoses in patients with COVID-19.

Key words: *coronavirus infection, COVID-19, dermatological manifestations, rash*

Conflict of interests

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

Sources of funding

The authors declare no funding for this study

Article received on 08.10.2020

Accepted for publication on 25.11.2020

For citation: Dvornikov A.S., Silin A.A., Gaydina T.A. et al. The Dermatological Manifestations in the Coronavirus Infection COVID-19. The Russian Archives of Internal Medicine. 2020; 10(6): 422-429. DOI: 10.20514/2226-6704-2020-10-6-422-429

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) spread quickly in most countries of the world and led to a pandemic [1].

A probable (clinically confirmed) case of COVID-19 includes clinical manifestations of acute respiratory infection, including the following: elevated body temperature of more than 37.5 °C and one or more symptoms (cough, shortness of breath, feeling of stuffiness in chest, sore throat, signs of nasal congestion or rhinitis, impairment or loss of smell, taste (dysgeusia), conjunctivitis, general weakness and myalgia, headache) in the presence of at least one of the following epidemiological signs: 1) return from a foreign trip 14 days before the onset of symptoms; 2) close contact over the past 14 days with a person who was monitored for COVID-19 and fell ill subsequently; 3) close contact over the past 14 days with a person with laboratory-confirmed COVID-19; 4) professional contact with persons who have suspected or confirmed COVID-19 [2].

Coronavirus is transmitted via respiratory droplets upon contact with infected people, during coughing, sneezing and talking, as well as by droplets on the surface, for example, on bedding or bathroom equipment [3].

There are now ample scientific papers describing skin manifestations associated with COVID-19. Algorithms for diagnosing dermatological symptoms have been proposed [4–6].

The variety of the clinical presentation of skin manifestations of coronavirus disease requires thorough analysis for the correct interpretation and differential diagnosis of skin lesions in cases of COVID-19 and other infectious exanthems and dermatoses. Timely identification of skin manifestations in patients with symptoms of acute respiratory diseases can make diagnostic search significantly easier [7].

Dermatological Symptoms of COVID-19

Dermatological symptoms in patients with COVID-19 are very diverse; their incidence depends on age, comorbidities and drug treatment of patients.

Recalcati S. (2020) observed skin manifestations in 18 (20.4%) of 88 hospitalized patients in northern Italy. He focuses on the fact that 60 (40.5%) out of 148 patients with a positive COVID-19 test who had already taken medications in the previous 15 days were excluded from the study beforehand [8]. Eight (44%) out of 18 patients developed exanthema with the onset of the first clinical symptoms of COVID-19, the rest – after discharge from hospital. Skin manifestations included mainly erythematous rash (14 patients); in three patients, it was in the form of generalized urticaria and vesicles similar to the signs of chickenpox. Overall, skin manifestations were most often located on the torso and were accompanied by slight itching; they disappeared within several days and had no correlation with disease severity. The authors suggested that the abovementioned symptoms were similar to those that develop in cases of conventional viral infections.

Marzona A.V. et al. (2020) described a rash similar to chickenpox rash in 12 (54.6%) of 22 patients with COVID-19. All seven patients who underwent skin biopsy showed histological results that corresponded to viral infection [9].

Other Italian authors suggested that exanthema similar to chickenpox was a rare but specific skin manifestation associated with PCR-confirmed coronavirus disease. The authors described a rash that appeared three days after the onset of specific clinical symptoms of COVID-19; it was spread across the torso, of small size, with no itching, and disappeared without scarring after eight days [10].

One also described petechial and reticular rash in patients with COVID-19: almost asymptomatic, accidentally found elements on the mucosa of cheeks, gums, in the vestibule of the oral cavity, on the mucosa of lips. Rash in the form of spots of opal-like color and small, slightly elevated papules with striae on their surface (*Wickham striae*). Rash similar to livedo, in the form of a tree branch or a fern leaf on hyperemic mucosa [7, 9, 11].

Acro-ischemia: cyanosis of fingers and toes, skin blisters and dry gangrene were described in a number of patients from the Chinese city of Wuhan with severe COVID-19 [12].

Some authors reported the development of symptoms resembling frostbite in connection with coronavirus disease ("COVID toes") [13].

Preliminary results of a systematic meta-analysis based on publications from PubMed/MEDLINE and medRxiv databases using the keywords «COVID-19», «2019-nCoV» and «coronavirus» published during the period from December 31, 2019 to May 03, 2020 revealed the following: 46 articles with a total of 998 patients from nine countries met the inclusion criteria declared in these works (confirmed novel coronavirus disease (COVID-19), skin symptoms appeared several days after the first symptoms of COVID-19). A smaller part of these articles (9) contained information on skin manifestations of COVID-19 in more than five patients in the sample. The most common skin findings were frostbite-like lesions (n = 402, 40.2%), maculopapular lesions (n = 227, 22.7%), urticaria (n = 89, 8.9%), vesicular elements (n = 64, 6.4%), livedoid and necrotic lesions (n = 28, 2.8%), and other undescribed skin elements and lesions (n = 192, 19.8%). Pain and burning were reported in at least 85 (8.5%) cases, and itching – in 256 (25.6%) patients. The prevalence of skin manifestations of COVID-19 ranged from 0.19 to 20.45% [14].

Skin manifestations of coronavirus disease are shown in Fig. 1 [15].

Like other countries, Russia has accumulated data on the prevalence and features of skin signs of COVID-19. These signs have been divided into

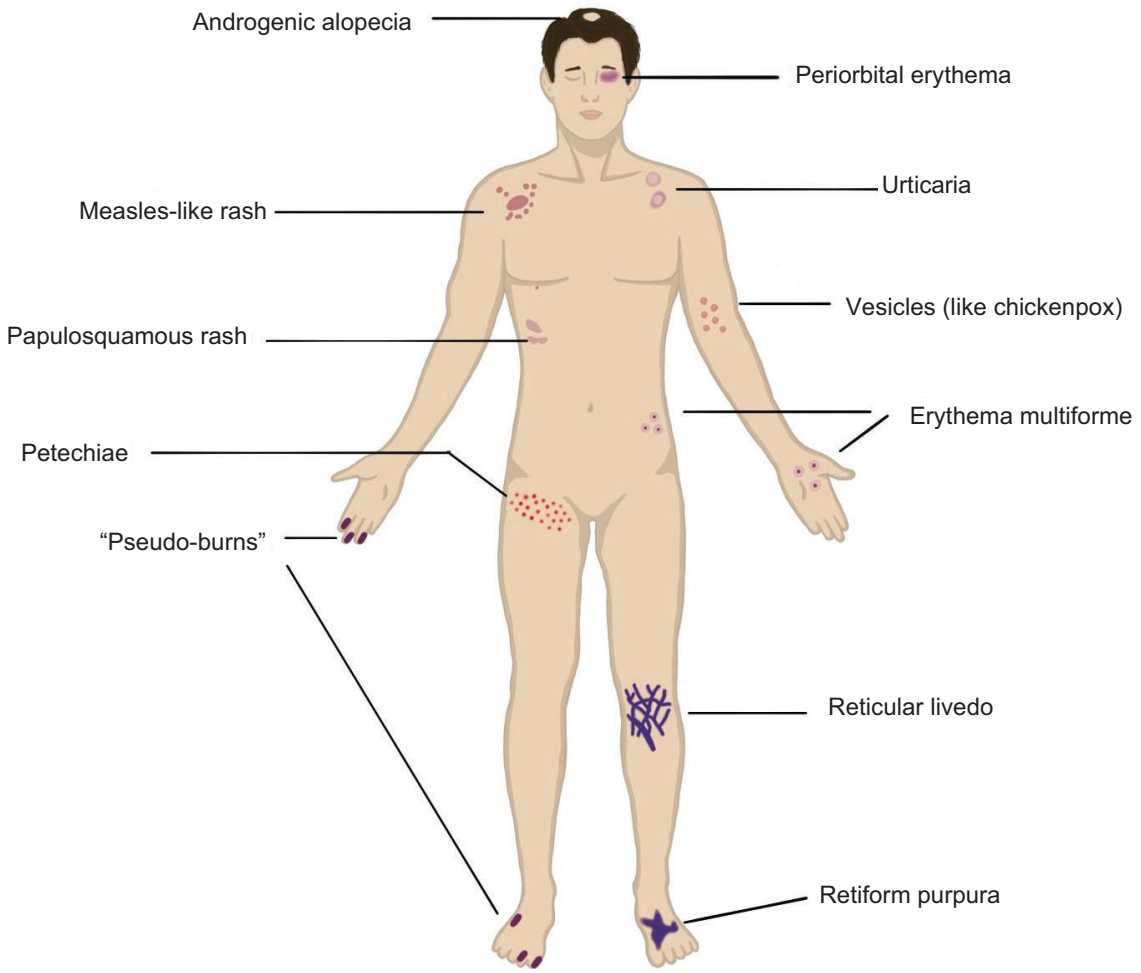

Figure 1. *Skin signs of coronavirus disease (COVID-19)*

several groups depending on their cause and mechanism of development [2]:
- skin angiites;
- papulosquamous rash and pityriasis rosea;
- measles-like rash and infectious erythems;
- papulovesicular rash;
- urticarial rash and artificial lesions;
- toxidermias.

Skin Angiites

Skin angiites, in most cases, are of infectious and allergic origin; they usually manifest in the form of acute erythema nodosum in connection with acute respiratory viral infection (ARVI). In cases of coronavirus disease, small skin vessels are also involved in the pathological process due to the deposition of circulating immune complexes in the form of deposits with viral antigens. Endothelial dysfunction, especially in older people and individuals with atherosclerotic diseases of the cardiovascular system, can aggravate the deposition process since smooth muscle cells of the middle lining of the vascular wall can produce interleukin-6, a key cytokine for the development of inflammation and cytokine storm syndrome [16]. Also, hypoxia accompanying severe disease can contribute to the development of distal angiitis – rash on distal phalanges, distal parts of the body (ears, nose, fingers), i.e., the so-called acral rash or acro-dermatitis. Such localization of rash is typically characterized by a benign course and rapid reverse development (within 2-3 weeks).
Infection-associated thrombotic and ischemic skin lesions may be caused by a direct vascular invasion of an infectious agent, vascular occlusion, or disseminated intravascular coagulation.
Casas Galvan C. et al. (2020) identified asymmetric distal erythema and swelling with vesicles or pustules that were described as of ***«pseudo-frostbite»*** type in 71 (19%) of 375 patients with COVID-19 [17].
Mazzotta F., Troccoli T. (2020) described purple erythematous lesions on the toes of a 13-year-old boy with COVID-19 that disappeared within a short period of time. The authors suggested that such skin lesions can be caused by acro-ischemia due to endothelial damage and microthrombosis caused by a viral invasion [18].
Kolivras A. et al. (2020) presented their own observation of "pseudo-frostbite" caused by COVID-19 in a patient with psoriasis [19]. These skin manifestations (purpura, reticular livedo and thrombotic and ischemic lesions) confirm the hypothesis about hypercoagulation significantly contributing to the high mortality rate in patients with COVID-19.

Papulosquamous Rash, Maculopapular Rash and Pityriasis Rosea

Dursun R. and Temiz S.A. (2020) describe an increase in the number of cases of papulosquamous rash or annular erythema during the COVID-19 pandemic; this was represented by papules and small plaques located on the shoulders, upper chest and back, less often – on the face, scalp. The rash tends to be confluent and is characterized by the absence of a "herald patch". The rash usually disappears without scars, with foci of hypopigmentation with telangiectasias or, in some cases, superficial cicatricial atrophy [20]. The authors do not exclude the contribution of the reactivation of Human Herpes Virus 6 (HHV-6) and focus on two diseases with etiopathogenesis influenced by HHV-6: Kawasaki disease and pityriasis rosea.
Many infectious diseases (infectious mononucleosis, measles, scarlet fever, herpes, hepatitis B and C, infections caused by Zika, Ebola and HIV) can be accompanied by maculopapular rash [21]. Casas Galvan C. et al. (2020) reported that maculopapular rash was observed in 18 (47%) of 375 patients diagnosed with COVID-19. Several patients showed signs of perivascular inflammation, while some had rash similar to pityriasis rosea. The authors reported that in several cases, there were infiltrating papular lesions resembling erythema multiforme [17]. Recalcati S. et al. (2020) found maculopapular rash in 14 (77.8%) of 18 patients with COVID-19, while Hedou M. et al. (2020) reported a similar rash in two patients [8, 22]. Jones V.G. et al. (2020) reported a case of Kawasaki disease in a six-month-old female patient with a positive COVID-19 test. Clinical presentation with fever, conjunctivitis, enlarged papilla of the tongue, dry and cracked lips, polymorphic maculopapular rash and swelling of limbs met the criteria for Kawasaki disease [23].

Measles-like rash and infectious erythems are similar to rash in cases of measles and other infections, which indicates common pathogenetic mechanisms of viral exanthems. A causative agent with tropism for skin and lymphatic tissue epithelium appears on the skin epithelium and in lymph nodes, and viremia usually results in exanthema [24].

Papulovesicular Rash

Skin rash can be a manifestation of bacterial (staphylococcal skin infections, gonococcal bacteremia) and viral infections (enterovirus infections, herpes simplex, herpes zoster, chickenpox, HIV, parvovirus B19). In this case, vesiculobullous and papulovesicular rash can be observed; it can be local or generalized. Extensive skin lesions characterize papulovesicular rash in patients in subfebrile condition with excessive sweating lasting many days in connection with COVID-19. Herpes simplex and herpes zoster are usually manifested by limited lesions; chickenpox usually causes a more generalized papulovesicular rash [21].

Casas Galvan C. et al. (2020) described small monomorphic vesicles located on the torso in 34 (9%) of 375 patients with COVID-19 included in the study. The authors reported that the vesicular rash did not resemble polymorphic vesicles typical of varicella [17]. On the other hand, Hedou M. et al. (2020) described the manifestations of oral herpes in an intubated patient, and Tammaro A. et al. (2020) reported herpes-related vesicular lesions localized on the torso in three patients [22, 25].

Urticarial Rash

Urticarial rash may be a premonitory symptom of COVID-19 or may appear with the first symptoms of the disease. Besides, urticaria develops with drug intolerance and can be considered a variant of toxidermia. Acral blisters in cases of COVID-19 are considered a specific symptom.

In one of the largest studies of skin manifestations of COVID-19, Casas Galvan C. et al. (2020) reported that in 71 (19%) of 375 patients, urticaria was observed, mainly on the torso; in several patients, rash was localized on the palms [17]. Recalcati S. et al. (2020) demonstrated that skin lesions were observed in 18 (20.4%) of 88 patients with COVID-19, and urticaria was found in three of them. Skin rash was localized mainly on the torso, while urticaria severity was not associated with disease severity [8]. Hedou M. et al. (2020) observed urticaria in 2 (1.9%) of 103 patients with COVID-19. One of these patients developed rash at the prodromal stage of infection [22].

Henry D. et al. (2020) found urticaria in a 27-year-old female patient with a positive COVID-19 test and with no fever; she had rash localized on the face and limbs [11]. In contrast, van Damme C. et al. (2020) reported two patients with urticarial rash spread all over the torso, with fever; these manifestations were actually the first symptoms of COVID-19 [26].

Therefore, it is obvious that urticaria can be a fairly common skin manifestation of viral infection. In this regard, during the pandemic, patients with urticaria should be carefully examined for COVID-19.

Other Causes of Dermatological Symptoms During the COVID-19 Pandemic

Lifestyle changes, including extended contact with personal protective equipment and excessive adherence to personal hygiene rules, can also cause skin lesions, for example, skin injury due to the pressure of protective equipment on the skin. It may result in contact dermatitis or urticaria [27–29]. Exacerbations of existing skin diseases such as seborrheic dermatitis, atopic dermatitis and acne are often observed.

Artificial lesions (trophic changes in facial tissues) are due to patients lying in a prone position for prolonged periods in order to improve lung ventilation. Medical workers often have skin lesions of the nose, hands, cheeks and forehead. Frequent use of hand hygiene products is associated with a higher incidence of hand dermatitis. Increased risk of Goldman-Fox syndrome is reported – «green nails» infected with pseudomonas in medical professionals with the possibility of transmitting pseudomonads to the patients [29].

Antimalarial drugs, in particular, chloroquine and hydroxychloroquine, can aggravate the severity of the manifestations of previously diagnosed psoriasis, or cause other skin reactions (onychodystrophy, discoloration of hair and skin, photosensitivity, dermatitis) [30].

Treatment of patients with COVID-19 and a history of autoimmune and chronic inflammatory diseases (especially patients with psoriasis, atopic dermatitis, connective tissue diseases and purulent hydradenitis) taking biological agents or immunosuppressants is a challenge [31].

The European Dermatology Working Group published its recommendations to continue treatment with immunomodulators for patients with COVID-19, including immunosuppressive therapy, since the exacerbation of underlying diseases in such patients can adversely affect the state of their immune system [32]. The authors of these recommendations believe that several conventional systemic immunomodulatory drugs, such as cyclosporine, can affect antiviral

immunity mechanisms. However, they warn that it is not yet known how SARS-CoV-2 affects the course of atopic dermatitis, especially in patients receiving treatment with immunomodulating agents.
The possibility of concomitant infections in the ICU should also be considered, in particular, secondary *Candida auris* [33]. Like SARS-CoV-2, *Candida auris* can be viable on surfaces made of plastic, stainless steel, copper and cardboard [34].

Toxidermias

Every year, many people worldwide develop undesirable skin reactions in response to drug treatment. Drug toxidermias are not only the most common undesirable skin reactions; they are hard to diagnose, especially at the early stages.
Toxidermia is an acute inflammatory disease of the skin and/or mucosae caused by the hematogenous spread of an allergen that enters the body by oral, inhalational, intravenous, subcutaneous, intramuscular or intravaginal routes [35].
The development and active implementation of new drugs, uncontrolled self-medication of patients, repeated courses of the same drugs – all currently observed in connection with the COVID-19 pandemic – contribute to increased drug toxidermias. Differential diagnosis of skin manifestations in cases of coronavirus disease with toxidermias in senile patients requires a thorough analysis [36]. In this regard, physicians should focus their attention on considering the possible development of undesirable skin reactions in different clinical manifestations at any time after taking a drug, or in the case of simultaneous prescription of several drugs. A physician prescribing drug treatment should consider risk factors for the development of undesirable skin reactions, including elderly age, multiple comorbidity and polypharmacy – to assess the benefit/risk ratio of previously taken and currently prescribed drugs.

Mixed Infections in Patients with COVID-19 and Exanthems

Bibliographic search by keywords «mixed infection», «Covid-19», «exanthema» in the PubMed database returned information about one clinical observation made by researchers from France and the UK [37].
A clinical case of a female patient, 18, with confirmed Dengue fever (positive laboratory result for NS1 virus antigen) and COVID-19 (PCR – gene E, RdRP gene, N gene positive) was presented. Along with intoxication, respiratory symptoms and cervical lymphadenopathy, there was a roseola-like maculopapular exanthema on the patient's torso, limbs and face that quickly developed into scarlatiniform rash. There were no areas of healthy skin, but there was a rash described as «white islands in a sea of red». No lesions of the mucosa, hands or feet were found. Itching stopped by day 10 from disease onset; there were no scratches.
Clinical symptoms of Dengue fever and COVID-19 have much in common, which makes them difficult to diagnose. The abovementioned patient had a prolonged fever, facial hyperemia, skin erythema, generalized acne, myalgia, arthralgia, retroorbital pain, photophobia, scarlatiniform exanthema and headache. Some of these symptoms are similar to those of COVID-19. Thrombocytopenia and increased liver enzymes were reported both for Dengue fever and COVID-19. Immune-mediated damage or direct cytotoxicity due to active virus replication in hepatocytes may be associated with liver damage in both Dengue fever and COVID-19. Clinical presentation may be caused by hypoxic hepatitis due to anoxia or drug-induced damage of the liver (for example, paracetamol, antiviral drugs, etc.) [38].
As for skin rash, the authors lean towards the theory that it developed due to Dengue fever since rash described as «white islands in a sea of red» is typical for this disease.
Analysis of available literature sources on the study of the relationship of exanthemas and increased immunoglobulin E level in blood serum in patients with COVID-19 revealed nothing. Only one study by C. Lucas et al. (2020), where the immune status of 113 patients with a moderate and severe course COVID-19 was analyzed, demonstrated that severe COVID-19 was accompanied by increased levels of interleukins 5, 13, immunoglobulin E and eosinophils. No information on exanthems in these patients was provided [39].
In cases of COVID-19, not only the respiratory but also the gastrointestinal tract is involved in the pathological process – and it can also be the «site of entry» for infection [40]. High expression of angiotensin-converting enzyme 2 receptors in COVID-19 was observed not only in type II alveolocytes but also in endothelial cells of arteries and veins, smooth muscles of the arterial wall, immune cells, glandular epithelial cells of the stomach, duodenum and rectum. This may cause gastrointestinal symptoms [41].

These data indicate the multifactorial nature of COVID-19, including the specific features of innate immune response and the state of hypercoagulation, damage to lung tissue, nervous and cardiovascular system, gastrointestinal tract, and syndrome of monocytes/ macrophages activation culminating in increased secretion of cytokines, leading to the exacerbation of the disease course and mortality. These general symptoms may cause skin lesions that have a polymorphic manifestation and require further study.

Conclusion

Analysis of the currently available literature revealed a limited number of studies on the association of various skin lesions with both COVID-19 and viral infections in general. However, timely detection and accurate diagnosis of skin manifestations in cases of COVID-19 can play a key role in the early diagnosis and treatment of this disease.

The American Academy of Dermatology, one of the largest dermatological organizations in the world, recently launched the much-needed COVID-19 patient registry to track skin manifestations. Careful documentation and reliable reporting of skin lesions associated with COVID-19 are necessary to improve our understanding of the epidemiology and mechanisms of manifestation of this disease. Timely diagnosis of skin manifestations, comorbidities and improvement of treatment methods will increase the level of high-quality medical care.

Author Contribution:

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

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DOI: 10.20514/2226-6704-2020-10-6-430-457

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АМИЛОИДОЗ СЕРДЦА: ВЗГЛЯД ТЕРАПЕВТА И КАРДИОЛОГА

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Cardiac Amyloidosis: Internist and Cardiologist Insight

Резюме

Амилоидоз сердца (амилоидная кардиомиопатия) — поражение сердца, обусловленное внеклеточным отложением амилоида. В ряде случаев может быть локальное поражение структур сердца, например, предсердий, чаще поражение сердца является частью системной (генерализованной) патологии. В зависимости от белка-предшественника амилоида выделяют 36 типов амилоидоза, среди которых — наследственные и приобретенные формы. Амилоидоз сердца необходимо диагностировать как при выявлении амилоидной инфильтрации при эндомиокардиальной биопсии, так и при утолщении стенки левого желудочка >12 мм в отсутствии артериальной гипертензии или других причин для развития гипертрофии левого желудочка при выявлении амилоида внесердечной локализации. Сердце чаще всего поражается при AL-, ATTR-, AA-, AANF-типах амилоидоза. Скрининговое обследование на амилоидоз необходимо при хронической сердечной недостаточности неясной этиологии (особенно с сохраненной фракцией выброса левого желудочка), рефрактерной к терапии, в сочетании с протеинурией и хронической болезнью почек 4-5 стадии; идиопатической фибрилляции предсердий и нарушениях проводимости, утолщении стенки левого желудочка неясной этиологии, наличии низкого вольтажа зубцов при электрокардиографии, необъяснимой артериальной гипотензии и легочной гипертензии. Скрининг на амилоидоз должен включать как неинвазивные методы, в т.ч. электрофорез и иммунофиксацию белков крови и мочи, исследование на свободные легкие цепи иммуноглобулинов лямбда и каппа, ^{99}Tc-DPD-сцинтиграфию, генетическое тестирование (при подозрении на наследственные варианты

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амилоидоза), так и морфологическое исследование биоптатов различной локализации с окраской Конго красным и поляризационной микроскопией.

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

Конфликт интересов

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

Источники финансирования

Работа выполнена в рамках государственного задания ФГАОУ ВО РНИМУ им. Н.И.Пирогова МЗ РФ (№ госрегистрации НИР АААА-А18-118040390145-2)

Благодарности

Авторы выражают благодарность главному врачу ГКБ им. В.М.Буянова ДЗМ Саликову А.В. за административную поддержку работы

Статья получена 01.10.2020 г.

Принята к публикации 10.11.2020 г.

Для цитирования: Резник Е.В., Нгуен Т.Л., Степанова Е.А. и др. АМИЛОИДОЗ СЕРДЦА: ВЗГЛЯД ТЕРАПЕВТА И КАРДИОЛОГА. Архивъ внутренней медицины. 2020; 10(6): 430-457. DOI: 10.20514/2226-6704-2020-10-6-430-457

Abstract

Cardiac amyloidosis (amyloid cardiomyopathy) is a disease damage to the heart caused by extracellular amyloid deposition. In some cases, there may be local damage to the structures of the heart, for example, the atria; more often, heart damage is part of a systemic (generalized) pathology. Depending on the amyloid precursor protein, 36 types of amyloidosis are described, among which hereditary and acquired forms are distinguished. Cardiac amyloidosis is diagnosed 1) in the case of the amyloid infiltration in the myocardial bioptates or 2) in the case of non-cardiac amyloid deposition and the left ventricular wall thickening >12 mm without arterial hypertension and other reasons. The heart is most often affected in AL-, ATTR-, AA-, AANF-types of amyloidosis. Cardiac amyloidosis should be considered in patients with a heart failure with an unclear etiology, especially with preserved left ventricular ejection fraction, refractory to treatment, with proteinuria and CKD 4-5, in patients with idiopathic atrial fibrillation and conduction disturbances, in patients with left ventricular wall thickening of unclear etiology, low ECG voltage, unexplained arterial hypotension and pulmonary hypertension. Screening for cardiac amyloidosis should include non-invasive methods such as electrophoresis and immunofixation of blood and urine proteins, the free light lambda and kappa chains of immunoglobulins, 99Tc-DPD scintigraphy, genetic testing (if hereditary variants of amyloidosis are suspected), as well as a histological examination of biopsy samples stained with Congo red and polarizing microscopy.

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

Conflict of interests

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

Sources of funding

The work was carried out within the framework of the state assignment of Russian National Research Medical University n.a. N.I. Pirogov, Ministry of Health of the Russian Federation (R&D state registration number AAAA-A18-118040390145-2)

Acknowledgments

The authors express their gratitude to the chief physician of the City Clinical Hospital. V.M. Buyanova of the Moscow City Health Department Salikov A.V. for administrative support of the work

Article received on 01.10.2020

Accepted for publication on 10.11.2020

For citation: Reznik E.V., Nguyen T.L., Stepanova E.A. et al. Cardiac Amyloidosis: Internist and Cardiologist Insight. The Russian Archives of Internal Medicine. 2020; 10(6): 430-457. DOI: 10.20514/2226-6704-2020-10-6-430-457

ACEI — angiotensin-converting enzyme inhibitor, AH — arterial hypertension, CHF — chronic heart failure, CHFpEV — chronic heart failure with preserved ejection fraction, CMP — cardiomyopathy, ECG — electrocardiogram, EchoCG — echocardiography, EV — ejection fraction, ICD — implantable cardioverter defibrillator, LV — left ventricle, MRI — magnetic resonance imaging, NSAID — non-steroidal anti-inflammatory drug, NT-proBNP — N-terminal prohormone of cerebral natriuretic factor, PET — positron emission tomography, RNA — ribonucleic acid, TTP — transthyretin

Introduction

Amyloidosis is a group of diseases characterized by extracellular deposits of a specific glycoprotein (amyloid) [1]. Amyloid infiltration of tissues and organs can result in their enlargement, damage/death of their cells and impaired functioning [2, 3]. The clinical picture can be quite different; it depends on organs damaged by amyloid deposits and on the type of their functional impairment. Although amyloidosis is quite common in clinical practice, unfortunately, this disease is remained unaddressed by Russian science societies, scientific journals and medical specialists who, despite their vast experience and expertise, not diagnose amyloidosis, especially cardiac amyloidosis. This review touches on the issues of modern-day classification, clinical picture, diagnosis and management of patients with cardiac amyloidosis.

Classification of amyloidosis

Based on different amyloid precursor proteins, there are currently 36 types of amyloidosis (Table 1) [4]. For clinical purposes, we can identify local and systemic (generalized) types of amyloidosis: local types are characterized by one organ involved, and systemic types — by several organs and systems [5].

Table 1. *Classification of amyloidosis [4]*

Type	Precursor protein/place of its synthesis in systemic forms	Systemic (S) and/or localized (L)	Acquired (A) or hereditary (H)	Target organs
AL	Λ and κ-immunoglobulin light chain/ Bone marrow	S, L	A, H	All organs, usually except CNS, macroglossia and periorbital purpura are almost pathognomonic
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	Serum amyloid A (SAA-protein) / liver	S	A	All organs except CNS
ATTP	Transthyretin, wild type/liver	S	A	Heart mainly in males, Lung, Ligaments, Tenosynovium
	Transthyretin, variants/liver	S	H	PNS, ANS, heart, eye, leptomen
$A\beta_2M$	b2-Microglobulin, wild type	S	A	Hemodyalisis associated: Musculoskeletal System
	b2-Microglobulin, variant	S	H	Hemodyalisis associated: ANS
AGel	Gelsolin, variants	S	H	PNS, cornea
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, variants	S	A	Kidney
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney

Table 1. *[The end].*

Type	Precursor protein/place of its synthesis in systemic forms	Systemic (S) and|or localized (L)	Acquired (A) or hereditary (H)	Target organs
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte Chemotactic Factor-2	S	A	Kidney
AFib	Fibrinogen a, variants	S	H	Kidney
ACys	Cystatin C, variants	S	H	PNS, skin
ABri	ABriPP, variants	S	H	CNS
Adan	ADanPP, variants	L	H	CNS
Aβ	Ab protein precursor, wild type	L	A	CNS
	Ab protein precursor, variant	L	H	CNS
AαSyn	α-Synuclein	L	A	CNS
Atau	Tau	L	A	CNS
APrP	Prion protein, wild type	L	A	CJD, fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, fatal insomnia, PNS
Acal	(Pro)calcitonin	L	A	C-cell thyroid tumors
AIAPP	Islet amyloid polypeptide	L	A	Islets of Langerhans, Insulinomas
AANF	Atrial natriuretic factor / atria	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC	Lung surfactant protein	L	A	Lung
AGal7	Galectin 7	L	A	Skin
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin	L	A	Senile aortic media
Aker	Kerato-epithelin	L	A	Cornea
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblastassociated protein	L	A	Odontogenic tumors
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfurvitide	L	A	Iatrogenic
ACatK	Cathepsin K	L	A	Tumor associated

Determination of cardiac amyloidosis

Diagnosis of cardiac amyloidosis (amyloid cardiomyopathy) can be established if endomyocardial biopsy reveals amyloid infiltration or if there are extracardiac sites of amyloid and a thickened left ventricular (LV) wall > 12 mm with no arterial hypertension (AH) or any other conditions that can cause LV hypertrophy [6]. Heart damage occurs in connection with systemic AL, ATTR, AA, Aβ2m, AApoAI amyloidosis and local atrial AANF amyloidosis (Table 2) [1]. The most common types of amyloidosis associated with heart damage are AL (70–80% of cardiac amyloidosis), ATTR (15–25%), and AA amyloidosis (2–7%) [5, 6].

Table 2. *Main types of amyloidosis with cardiac involvement [2, 7]*

Type	Age, years	Gender	Laboratory data	Treatment
AL	>50	M≥F	Increase of free lambda or kappa chains in serum with an abnormal ratio (norm 0.26-1.65). M-gradient in serum and / or urine. Decreased normal immunoglobulins. Proteinuria.	Chemotherapy Stem cell transplantation in selected patients
Дикий ATTR	60-80	M:F > 250: 1	No	1.Suppression of TTP synthesis (liver transplantation; TTP gene «switches») 2.Stabilization of TTP (tafamidis, diflunisal, green tea, AG10) 3. Cleavage of amyloid fibrils (doxycycline with taurursodeoxycholic acid, monoclonal antibodies)
Наслед-ственный ATTR	Depends of mutation: V122I in afroamericans — 60-65 years; 20-30 years in Portugale, Shweden, Greese, Kipr; >40 years in Great Britain	50-72% M	No	
AA	20-30 years after the onset of the chronic inflammatory disease	M=F	Increased ESR, C-reactive protein, SAA protein in the blood. Proteinuria.	Treatment of the underlying disease Cytostatics Monoclonal antibodies Dimethyl sulfoxide Eprodisate Heparin Statins Fibrillex
AANF	Oderly	>F	No	
Aβ2M	Hemodyalisis patients and severe predyalisis CRF		Increase in the level of β2-microglobulin in the blood, antibodies to it	

Note: F — women, M — men, ESR — erythrocyte sedimentation rate, CKD — chronic kidney disease

Epidemiology

Until recently, amyloidosis was considered a rare disease; this diagnosis was often established during autopsy. According to the National Amyloidosis Center, the prevalence of amyloidosis in the UK is 0.8/100,000 population [8]. Among Medicare (National Health Insurance Program) patients in the United States who were hospitalized for chronic heart failure (CHF) in 2000–2012, there was a significant increase in the prevalence (from 8 to 17 per 100,000 people per year) and the incidence (from 18 to 55 per 100,000 people per year) of cardiac amyloidosis; the most pronounced growth was observed after 2006 [9].

Unfortunately, there are no statistics on amyloidosis on the website of the Federal State Statistics Service (www.gks.ru). At the V. M. Buyanov State Clinical Hospital of the Department of Health of Moscow, the detection frequency of amyloidosis was low for the period from 2008 to 2017; in 2018–2019 it amounted to 30–53 per 100,000 people per year [10].

AL amyloidosis

AL amyloidosis develops as a result of extracellular deposition of fibrils formed by monoclonal immunoglobulin light chains (gamma globulins; most often lambda, less often kappa) secreted by a pathological clone of plasma cells or B lymphocytes [2, 11]. AL amyloidosis belongs to the group of monoclonal gammopathies [6, 12]. Monoclonal gammopathies are often found in people aged

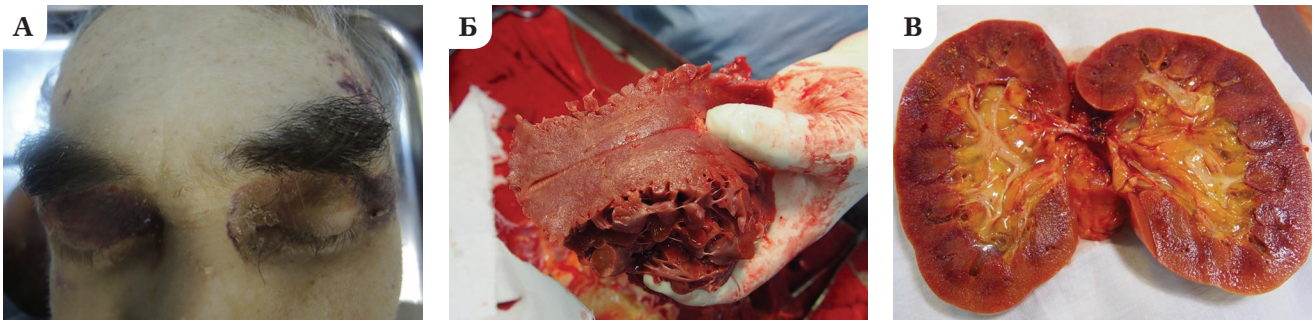

Figure 1: A. *Periorbital hemorrhages of the different ages («panda eyes», «raccoon eyes»).* ***B*** *and* ***C****. Damage of the heart and the kidney in the patient with amyloidosis, macropreparations. Large volume of amyloid deposits leads to the tissue compaction usually. The affected organ acquires a yellowish tint, «waxy» or «greasy» appearance (photos from the archive Dr Stepanova E.A.).*

over 50, which is the reason for screening this age group for gammopathies. However, monoclonal gammopathy does not always indicate AL amyloidosis: it can be found in 40% of patients with ATTR amyloidosis [2, 13–15].

The formation of an abnormal clone of plasma or B cells in the bone marrow is called plasma cell or B cell dyscrasia [5]. All patients with plasma cell dyscrasia and lymphoproliferative diseases are at risk of AL amyloidosis [5]. They also should be tested for AL amyloidosis. The formation of an abnormal cell clone outside the bone marrow can result in local amyloidosis (amyloidosis of the trachea, bronchi, larynx, bladder, etc.) [5, 16].

Cardiac amyloidosis is found in 33–60% of patients with AL amyloidosis [6]. Heart failure associated with AL amyloidosis develops relatively early — in 22% of patients as early as the onset of disease [5]. Heart damage in AL amyloidosis almost always occurs in connection with damage to other organs, most often, kidneys, blood vessels, the peripheral nervous system, liver, gastrointestinal tract, soft tissues [2]. Isolated cardiac involvement occurs in less than 5% of cases [6]. Eleven percent of patients with AL amyloidosis have orthostatic hypotension at diagnosis [5].

Despite a smaller increase in LV mass, the prognosis for AL amyloidosis with cardiac damage is worse than for ATTR amyloidosis. On average, cardiac AL amyloidosis with clinical signs of chronic heart failure (CHF) without treatment results in a fatal outcome within six months after the onset of symptoms [17]. Heart damage is the main predictor of a poor prognosis; the management strategy should be chosen depending on the severity of this damage [6] (Figure 1).

ATTR amyloidosis

Transthyretin amyloidosis (ATTR) is caused by the deposits of an abnormal transthyretin protein [15]. Transthyretin (TTR) is a carrier protein of thyroxine (T4) and complex retinol-binding protein/vitamin A; it is a tetramer and consists of four identical subunits. About 95% of transthyretin is synthesized in the liver, less than 5% — in the vascular plexus of the brain and retinal pigment epithelium. Less than 1% of transthyretin carries thyroxine in human serum; most of the circulating transthyretin is unconjugated [18, 19].

ATTR amyloidosis can be divided into family type (mutant, hereditary, with autosomal dominant type of inheritance with incomplete penetrance; it is caused by mutation in the gene encoding transthyretin synthesis) and senile type (not caused by mutations; in the English literature sources, it is called “wild type,” or “Alzheimer’s heart disease”) with no mutations in the transthyretin gene. In both cases, transthyretin tetramers decompose to amyloidogenic monomers [5].

“Wild type” ATTR amyloidosis is more common in men aged over 65. Its prevalence in people aged over 75 is 1–3%, in people aged over 80 — 20–30% [6], in patients with CHF — 11–13.3% [20], with degenerative aortic stenosis — 16%, and with carpal tunnel syndrome — 7–8% (Table 3) [15, 21].

The most important sign is cardiac involvement with a developing pattern of restrictive or hypertrophic cardiomyopathy (CMP) and heart failure (HF), rhythm and conduction disorders [6]. Carpal tunnel syndrome is a frequent comorbidity [6].

Table 3. *Prevalence of ATTR amyloidosis [20, 22-26]*

Patient group	Frequency of proven ATR amyloidosis	Type of the ATTR-amyloidosis
Afroamericans	3,4%	Hereditary Val122Ile
Population of Northwest Ireland	1%	Hereditary Thr60Ala
CHFpEF with LV wall thickness ≥12 mm	13,3%	Wild ATTR-amyloidosis
CHFrEF with LV wall thickness ≥12 mm	11%	Wild ATTR-amyloidosis
CHF (RF, Almazov's centre)	4,6%	Hereditary ATTR-amyloidosis
Hypertrophic cardiomyopathy	5%, у лиц старше 55 лет — у 7,6%/ 5%, older 55 years — 7,6%	Hereditary ATTR-amyloidosis
Aortic stenosis in patients with the transcatheter aortic valve implantation	16%	NA
Aortic stenosis in persons > 65 years in patients with the aortic valve replacement	6%	NA
Conduction disturbances requiring the installation of a pacemaker	2%	Wild ATTR-amyloidosis
Patients with carpal tunnel syndrome	7-8%	Both types
Older 75 years old	1-3%	Almost all with wild ATTR-amyloidosis
Older 80 years old	20-30%	Wild ATTR-amyloidosis

Note: CHFpEF — chronic heart failure with preserved left ventricular ejection fraction, CHFrEF — chronic heart failure with low left ventricular ejection fraction

Hereditary ATTR amyloidosis is less common: 7–9% of all cases of amyloidosis [6]; 40,000–50,000 diagnosed patients in the world [15]. Recent studies revealed ~~it~~ hereditary ATTR amyloidosis in 5% of patients with hypertrophic cardiomyopathy [22]. Hereditary ATTR amyloidosis developed due to gene mutations and replacement of amino acids in the transthyretin molecule. At present, there are more than 120 different mutations in the transthyretin gene; 110 of them are amyloidogenic [26]. Mutations lead to the dissociation of the transthyretin tetramer into monomers (destabilization), prone to improper folding and aggregation with the formation of toxic amyloidogenic intermediate products [18, 19, 27]. Most patients are heterozygotes. Therefore, they have not only mutant but also normal non-mutant transthyretin.

The phenotype of hereditary ATTR amyloidosis can be predominantly neurological, or predominantly cardiological, or mixed. The most common mutation, *Val122Ile* (found in 3–10% of African Americans), is characterized by predominant cardiac symptoms. The most frequent sign of *Val30Met* mutation is amyloid polyneuropathy. However, its late onset may be manifested by cardiomyopathy. The *Thr60Ala* mutation (found in 1% of the population in Northwest Ireland) is characterized by a mixed cardiac and neurological phenotype combined with gastrointestinal damage [28–33].

Screening for ATTR amyloidosis should be performed in elderly patients with definite clinical signs of CHF, especially with chronic heart failure with preserved LV ejection fraction (CHFpEF) (with no history of arterial hypertension (AH)), hypertrophic, restrictive cardiomyopathy, degenerative aortic stenosis and thickness of the interventricular septum (T_{IVS}) ≥ 12 mm in patients with CHF, hypertrophic, restrictive cardiomyopathy, degenerative aortic stenosis and LV wall thickness ≥ 12 mm for no clear reason for left ventricular hypertrophy (LVH) (Table 4).

Life expectancy for patients with «wild type» ATTR amyloidosis after diagnosis/manifestation of heart failure (HF) is 2–6 years [15]. The prognosis for patients with hereditary ATTR amyloidosis depends on the mutation and is determined by cardiac involvement.

AA amyloidosis

AA amyloidosis (reactive, secondary amyloidosis) develops in connection with chronic inflammatory diseases that are usually difficult to manage [5, 6].

Table 4. *Diagnostic keys (indications for screening) ATTR amyloidosis [14]*

Anamnesis/physical examination	Imaging	Clinico-instrumental data
➢ Right ventricular heart failure of unclear etiology ➢ CHFpEF, especially in men ➢ Intolerance to ACE inhibitors or beta-blockers ➢ Carpal tunnel syndrome (bilateral) ➢ Spinal stenosis ➢ Ruptured biceps tendon ➢ Unexplained peripheral neuropathy (loss of heat / cold sensitivity, postural hypotension, unstable stool) ➢ Unexplained atrial rhythm and conduction disturbances, incl. requiring pacemaker installation	➢ Accumulation of PYP, DPD or HMDP isotopes in the myocardium during scintigraphy ➢ Signs of symmetric LV (and RV) hypertrophy in the absence of aortic stenosis or long-term hypertension ➢ Infiltrative phenotype (biventricular hypertrophy, pericardial effusion, thickened leaflets, atrial septum) ➢ Diffuse subendocardial or transmural late accumulation of gadolinium or increased extracellular volume on MRI ➢ Apical sparing on longitudinal strain imaging ➢ Decreased contractility ➢ Restrictive type of diastolic dysfunction ➢ Reducing the ECG voltage ➢ Pseudoinfarction pattern in the absence of violations of local contractility during echocardiography	➢ HF with unexplained thickening of the LV wall without dilatation ➢ Concentric thickening of the LV wall, possibly with a mismatch between QRS voltage and LV wall thickness ➢ Decreased longitudinal LV function despite normal LVEF ➢ Aortic stenosis with RV wall thickening, especially with low pressure gradient

Note: LV — left ventricle, RV — right ventricle, HF — heart failure, EF — ejection fraction, CHFpEF — chronic heart failure with preserved left ventricular ejection fraction, DPD- ^{99m}technetium-3,3-diphosphono- 1,2-propanodicarboxylic acid; HMDP — hydroxymethylene diphosphonate; PYP- technetium pyrophosphate

AA amyloid is formed from the SAA serum precursor (serum amyloid A), which is an acute-phase protein produced by the liver in response to inflammation [1, 4, 5]. Since SAA is actively produced by the synovial membrane of joints, an additional risk factor for amyloidosis is the manifestation of an inflammatory disease with joint syndrome [1, 4, 5].

Any chronic inflammatory disease can be considered a risk factor for AA amyloidosis. Screening for AA amyloidosis should be carried out in cases of chronic seropositive and seronegative polyarthritis (rheumatoid arthritis, ankylosing spondylitis, juvenile chronic arthritis, psoriatic arthropathy, Reiter's syndrome, etc.), chronic inflammatory bowel diseases (Crohn's disease, ulcerative colitis), chronic suppurative diseases (bronchiectasis, osteomyelitis, etc.), tuberculosis, solid malignant tumors, autoinflammatory diseases (Table 5) [5].

Adequate management of the underlying disease should be performed to prevent AA amyloidosis [5, 34]. Assessing the risk of the development and progression of AA amyloidosis requires monitoring SAA,

Table 5. *Autoinflammatory diseases [60, 61]*

Polygenic	Monogenic		
	Pathology	Inheritance type	A gene with a mutation
Osteoarthritis Gout Pseudogout Sarcoidosis Erythema nodosum Accumulation diseases Atherosclerosis, etc.	Periodic illness (familial Mediterranean fever)	AR	*MEFV*
	Hyperimmunoglobulinemia D with periodic febrile syndrome	AR	*MVK*
	Tumor necrosis factor α receptor-associated periodic syndrome (TRAPS)	AD	*TNFRSF1A*
	Familial cold urticarial	AD	*NLRP3 (или CIAS1)*
	Macle-Wells syndrome (familial nephropathy with urticaria and deafness)	AD	
	Neonatal Onset Multisystemic Inflammatory Disease — NOMID, hronic Infantile Neurological Cutaneous and Articular syndrome — CINCA	AD	

Note: AR — autosomal recessive, AD — autosomal dominant, MEFV — Mediterranean fever, MVK — mevalonate kinase, TNFRSF1A — tumor necrosis factor receptor superfamily 1A, NLRP3 — Nod-like receptor family NALP, the main component of NLRP3-inflammasome, recognizes molecular fragments associated with damage (DAMP; uric acid crystals, mitochondrial DNA, S100 proteins, etc.) or pathogens (PAMP; lipopolysaccharides, peptidoglycans, bacterial nucleic acids) and initiating the process of inflammation

C-reactive protein, ferritin, calgranulin (S100A12 serum marker of neutrophilic activity) levels [5].
AA amyloidosis most often causes kidney damage with the development of nephrotic syndrome and/or renal failure. Heart is rarely involved (in 2–3% of patients) [6].

AANF amyloidosis

AANF is a local amyloidosis with atrial damage. It is more common in elderly women (aged over 80) but can also occur in younger patients with valve abnormalities or atrial fibrillation [35, 36]. Atrial natriuretic peptide (ANP) is the precursor protein. It is most commonly found during autopsy. It is extremely rarely found during lifetime due to the risk of atrial perforation with endomyocardial biopsy [6].

Clinical picture of amyloidosis

Most patients with amyloidosis have multiple organ damage (Figure 1, Table 6).

Table 6. *Possible manifestations of amyloidosis [6, 45]*

Clinical picture	Involvement of the cardiovascular system	Features
	Left, right ventricular, or biventricular heart failure	Shortness of breath, choking Weakness, fatigue Heartbeat Swelling of the neck veins Pathological III tone Edema Hepatomegaly Hydrothorax Hydropericardium Ascites
	Presyncope / syncope, orthostatic hypotension	Caused by low cardiac output, rhythm and conduction disturbances, amyloidosis of the nerve plexuses of blood vessels
	Angina pectoris syndrome, myocardial infarction	Caused by amyloid infiltration of coronary vessels
	Signs of tricuspid and mitral valve insufficiency	Caused by amyloid infiltration of valves and subvalvular structures
	Rhythm disturbances	In 50% of patients Most often atrial fibrillation Supraventricular tachycardia Less commonly, ventricular tachycardia Premature Ventricular Excitation Syndrome
	Conduction disorders	Atrioventricular block Sinoatrial block His bundle branch block
	Sudden cardiac death	Due to arrhythmias, electromechanical dissociation
	Damage to the nervous system	**It is detected in 17% of patients with AL-amyloidosis, in many patients with hereditary amyloidosis**
	Progressive symmetric distal sensorimotor polyneuropathy	It is caused by degeneration of the myelin sheath of nerves, as well as compression of the nerve trunks by amyloid deposits and ischemia as a result of amyloid deposits in the walls of blood vessels. First, pain and temperature are disturbed, then vibration and positional sensitivity, later motor disturbances join. Early symptoms are paresthesias, painful dysesthesias (numbness). The lower limbs are involved more often than the upper ones, the ability to move is impaired

Table 6. *[Continuation].*

Erectile dysfunction, impotence	Caused by dysfunction of the autonomic nervous system
Urinary retention, bladder dysfunction	May be complicated by recurrent urinary infection
Sweating disorders	Caused by dysfunction of the autonomic nervous system
Tunnel Syndrome	In 20% of all patients, early sign; pain and paresthesia in fingers I-III of the hand with gradual atrophy of the thenar muscles
Gastrointestinal manifestations	**Observed in 70% of patients with amyloidosis**
Dysphagia	Caused by amyloid infiltration of the esophagus
Nausea, vomiting	
Early satiety	
Ulceration, gastrointestinal perforation, bleeding	Amyloid infiltration of the esophagus may manifest as dysphagia stomach and intestines
Chronic diarrhea, malabsorption	Caused by infiltration of the intestinal wall with amyloid, dysfunction of the autonomic nervous system
Severe constipation	
Alternating constipation and diarrhea	
Prepiloric obstruction of the stomach, mechanical intestinal obstruction	
Unintentional weight loss	Due to malabsorption, autonomic dysfunction
Macroglossia	Pathognomonin for AL-amyloidosis, observed in 15% of patients, is due to pronounced infiltration of the tongue with amyloid. Often visible are imprints of teeth on the lateral surfaces of the tongue, abnormal phonation, difficulty in swallowing, speaking, breathing
Hepatomegaly, cholestasis; rarely intrahepatic portal hypertension, severe jaundice, hepatic failure, hepatic coma	In AA and AL amyloidosis, liver damage is observed in almost 100% of cases
Spleen involvement	
Splenomegaly	Macroscopically, the spleen may appear as «sago» (amyloid deposits in lymphoid follicles) or «sebaceous» (diffuse amyloid deposits).
Hyposplenism	May lead to thrombocytosis, thrombosis
Spontaneous rupture of the spleen	Seldom
Nephropathy	**In AA amyloidosis, the kidneys are affected in 100%, in AL — in 80-90% of patients**
Albuminuria, proteinuria, nephrotic syndrome	In nephrotic syndrome, antithrombin III deficiency is common, with an increased risk of thrombosis
Azotemia, renal failure	
Increased kidney size	It persists even with the development of end-stage renal failure
Chronic kidney disease	
Acute kidney injury	

Table 6. [Continuation].

	Respiratory system damage	More common in AL amyloidosis
	Hoarseness or change in tone of voice	Caused by the deposition of amyloid in the vocal cords
	Cough, shortness of breath	Обусловлены отложением амилоида в альвеолярных перегородках/ Caused by the deposition of amyloid in the alveolar septa
	Recurrent pleural effusion	It is caused by amyloidosis of the pleura, does not depend on the effectiveness of the treatment of edematous syndrome, often contains an admixture of blood
	Loss of the musculoskeletal system	**It rarely occurs, in 5-10% of patients with AL-amyloidosis, it is associated with amyloid deposition in bones, articular cartilage, synovia, ligaments and muscles**
	Carpal tunnel syndrome, manifested by intense pain and paresthesias in fingers I-III of the hand with atrophy of the thenar muscles	It is caused by compression of the median nerve by amyloid, which is deposited in the wrist ligaments. Detected in 20% of patients with AL-amyloidosis
	Pseudohypertrophy (hypertrophied muscle relief with a decrease in muscle strength) or muscle atrophy, difficulty in movement, pain syndrome	
	Lumbar spinal stenosis	
	Ruptured biceps head	
	Skin lesions	**Observed in almost 40% of patients with AL-amyloidosis**
	Periorbital purpura («raccoon eyes», «panda eyes»)	Occur at the slightest stress (cough, straining), the result of vascular fragility
	Papules, plaques, nodules, vesicular eruptions, induration of the skin, similar to scleroderma, pigmentation disorders (from pronounced intensification to total albinism), alopecia, trophic disorders, perspiration disorders	
	Other clinical manifestations	
	Clouding of the vitreous humor leading to gradual loss of vision; obstruction of the lacrimal canal leading to chronic open-angle glaucoma, keratitis, abnormal blood vessels in the eye	With AL and ATTR types
	Cachexia	Due to lesions of the gastrointestinal tract, autonomic dysfunction with trophic disorders
	The defeat of the thyroid gland with the development of the clinical picture of hypothyroidism	Described in AL amyloidosis
	The defeat of the adrenal glands with the development of their failure	More often with AA amyloidosis
	Lymphadenopathy	

Table 6. *[The end].*

	Sjogren's syndrome	
	Hemorrhagic syndrome, bleeding	Caused by the deposition of amyloid in the vascular wall, sometimes in combination with a deficiency of coagulation factors (X, less often V or IX)
ECG	Reducing the voltage of the ECG teeth Pseudo-infarction pattern	
ECHO	Thickening of the LV wall (> 12 mm) in patients without hypertension and a history of aortic stenosis, sometimes with thickening of the RV wall	Nonspecific trait
	Grainy or glowing myocardium	In 26% of patients
	Preserved LVEF	Decreased LVEF in the late stages of the disease
	Normal or reduced volume of the LV cavity	
	Diastolic dysfunction, restrictive type of transmitral flow on Doppler	
	Dilation of the left atrium	As the disease progresses, dilatation of both atria
	Thickening of the interatrial septum, atrioventricular valves	
	A small amount of fluid in the pericardial cavity	
	LVEF to global longitudinal strain ratio >4	
CMI	Diffuse transmural or subendocardial late gadolinium enhancement (LGE) in LV, RV	
	Enhanced myocardial uptake on T1-weighted images	
	Increased extracellular volume fraction (usually> 0.4)	
	Failure to suppress myocardial signal during PSIR (phase-sensitive inversion recovery)	
Scintigraphy	Increased accumulation of the isotope in the heart	
Laboratory data	Disproportionately high NT-proBNP values, chronic mild troponin elevation with normal ECG	
	Monoclonal gammopathy	AL amyloidosis
Genetic testing	Mutations in hereditary ATTR and other types amyloidosis	Differential diagnosis of familial and hereditary ATTR amyloidosis
Biopsy	The gold standard of diagnostics, allows for histological verification and typing of amyloid	

Cardiac amyloidosis

Clinical picture

The clinical picture of cardiac amyloidosis is nonspecific. First, patients have complaints of weakness, fatigue, decreased exercise tolerance, palpitations, dyspnea during exercise; later — at rest, a suffocating feeling at night [15]. Later stages are characterized by frequent development of right ventricular HF (edema of lower limbs, hepatomegaly, ascites, hydrothorax, hydropericardium, anasarca). A specific feature of HF is its resistance to management.

Amyloidosis should be suspected in patients with a history of AH, whose BP normalizes with time and with intolerance to angiotensin converting enzyme inhibitors (ACEI), angiotensin II or beta-blockers receptor antagonists due to hypotension. Orthostatic hypotension often develops due to decreased cardiac output and dysfunction of the autonomic nervous system (amyloidosis of vascular plexuses). In severe cases, orthostatic hypotension is accompanied by syncopal conditions. Fainting, as well as palpitations, can also be caused by cardiac arrhythmias and conduction disorders: atrial fibrillation, supraventricular, rarely ventricular tachycardia, pre-excitation syndrome, sinoatrial or atrioventricular blocks, sick sinus syndrome [6].

Obstruction of the intramural branches of coronary arteries is often found; it leads to ischemia, right up to myocardial infarction [37]. Increased risk of thrombosis and antithrombin III deficiency in connection with nephrotic syndrome may contribute to it [6].

The most common causes of death associated with cardiac amyloidosis are refractory CHF, rhythm and conduction disorders, electromechanical dissociation [6].

Electrocardiography

Electrocardiogram (ECG) reveals low *QRS* voltage (< 0.5 mV in limb leads and/or < 1.0 mV in precordial leads, Figure 2) in 46–66% of patients with amyloidosis [6].

Typical echocardiography (EchoCG) demonstrates a combination of low ECG voltage and thickened heart walls. The signs of LV hypertrophy on ECG should not be a reason for excluding cardiac amyloidosis [15]. In some patients, the following can be observed: QS complex in at least two chest leads («pseudo-infarct pattern») [5], T wave inversion or ST depression in lateral chest leads, often with no local contractility disorders on EchoCG.

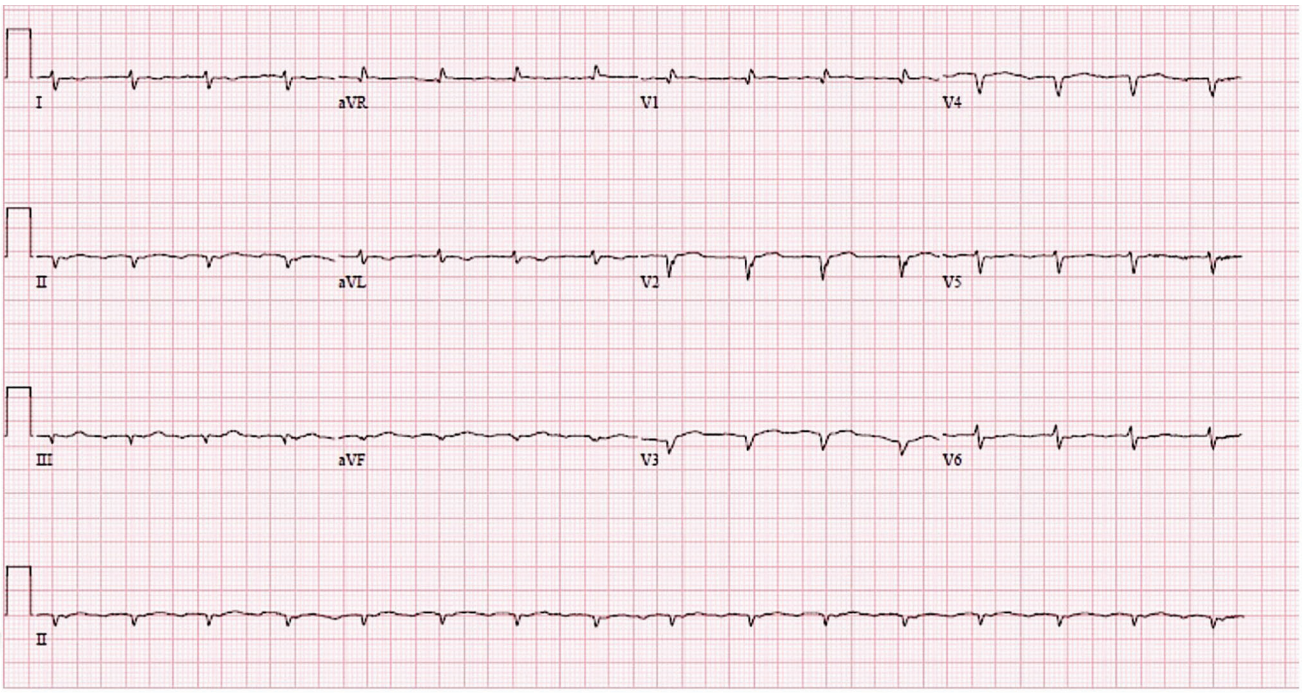

Figure 2. *ECG of a patient with cardiac amyloidosis (photos from the archive of authors)*

Holter ECG monitoring

Holter ECG monitoring can help to identify episodes of rhythm and conduction disorders and low heart rate variability, which indicates dysfunction of the autonomic nervous system [6].

Echocardiography

Imaging examinations of patients with cardiac amyloidosis demonstrate a picture of restrictive or hypertrophic cardiomyopathy (CMP) [5].

EchoCG-signs of amyloid CMP include symmetrical thickening of LV walls (> 12 mm) with no reason for hypertrophy, normal size and diastolic volume of LV, increased systolic size. The term «myocardial hypertrophy» is incorrect in this case [6]. LV wall thickness > 15 mm is rarely observed in cases of AH. Therefore, if there is a thickening of heart walls of unknown etiology, LV wall thickness > 15 mm, even with AH, discrepancies between wall thickness and QRS voltage on ECG, cardiac amyloidosis should be suspected [2].

Thickened interatrial septum, diffuse or local LV hypokinesis are also typical for amyloidosis (Figure 3) [38].

LV ejection fraction (EF) is often within normal but may decrease as the disease progresses. Myocardial

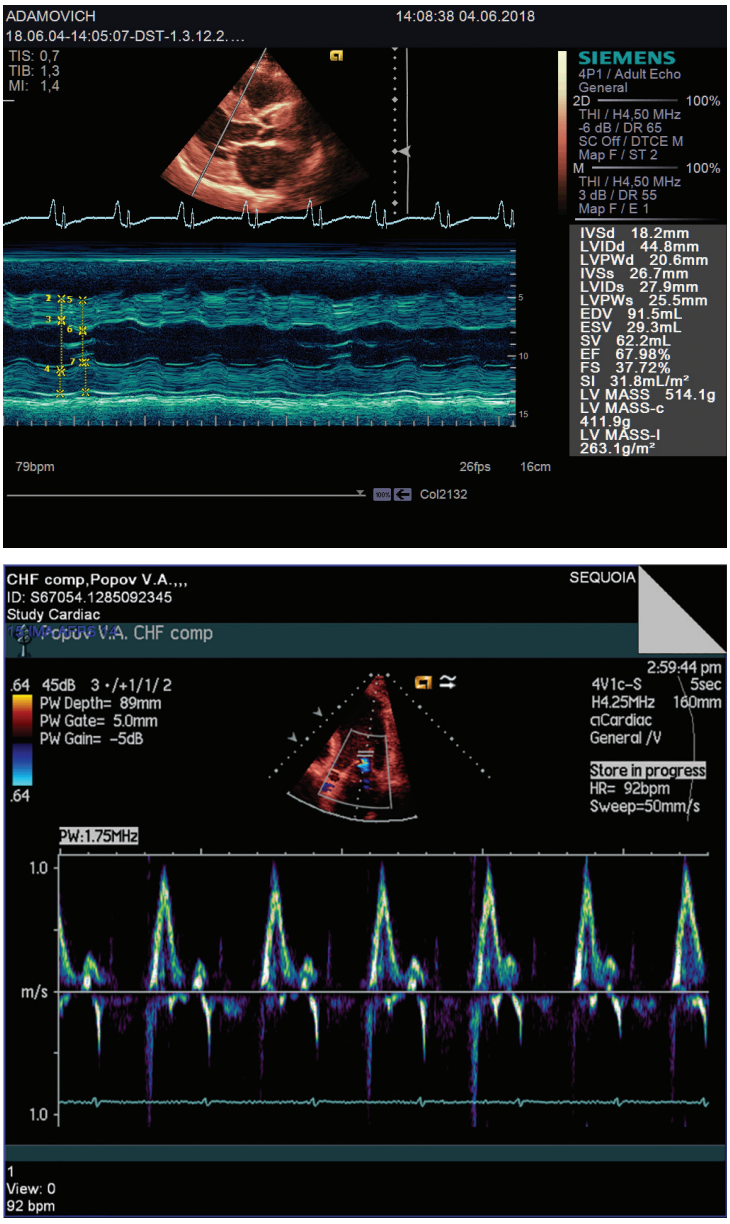

Figure 3. *Transthoracic echocardiography of a patient with cardiac amyloidosis. In the upper part, there is a thickening of the walls of the left ventricle, B-mode, apical four-chambered position. In the lower part, restrictive type of diastolic dysfunction, transmitral flow, pulse wave Doppler (photos from the archive Dr Reznik E.V.)*

granularity or fluorescence occurs in 26% of patients due to the higher echogenicity of amyloid deposits in comparison with normal myocardium [5, 38].

Disorders of longitudinal contractility, especially of LV basal segments, are typical for amyloidosis. Impaired LV diastolic function from mild relaxation impairment to severe restriction, and atrial dilatation are also typical [6].

Amyloidosis is also characterized by a thickening of the RV free wall and its dysfunction, as well as a thickening of valve cusps with blood regurgitation. Mitral and tricuspid insufficiency develops more often. Pericardial effusion is observed in 50% of patients; in some cases, cardiac tamponade may develop [6].

Specific ECG and EchoCG parameters have low sensitivity and specificity in cases of cardiac amyloidosis. EchoCG can not help to establish a definite diagnosis of amyloid CMP [6].

Cardiac MRI

Cardiac magnetic resonance imaging (MRI) in patients with amyloidosis reveals a symmetrically thickened LV wall, most often without obstruction of the outflow tract, sometimes — a thickened right ventricle (RV), atrial dilatation. Contrasting in delayed phase typically shows diffuse damage of all segments of ventricles and sometimes also of atria (Figure 4).

Deposits are most often of subendocardial or transmural type. In such cases, LV systolic function remains within normal [39, 40]. The new myocardial T1-mapping method allows a more precise assessement of myocardial damage caused by amyloidosis, and calculating the volume of the amyloid deposit in intercellular space, which is a marker of disease severity ("amyloid burden") and correlates with the survival rate [41]. Despite its high accuracy, MRI cannot be used as the only method for establishing cardiac amyloidosis diagnosis [15].

Scintigraphy and positron emission tomography

In cases of ATTR amyloidosis, there is active uptake of several isotopes in the heart. However, there is no or minimal uptake thereof in cases of AL amyloidosis [2]. This allows diagnosing ATTR-CMP at the early stages (Table 7).

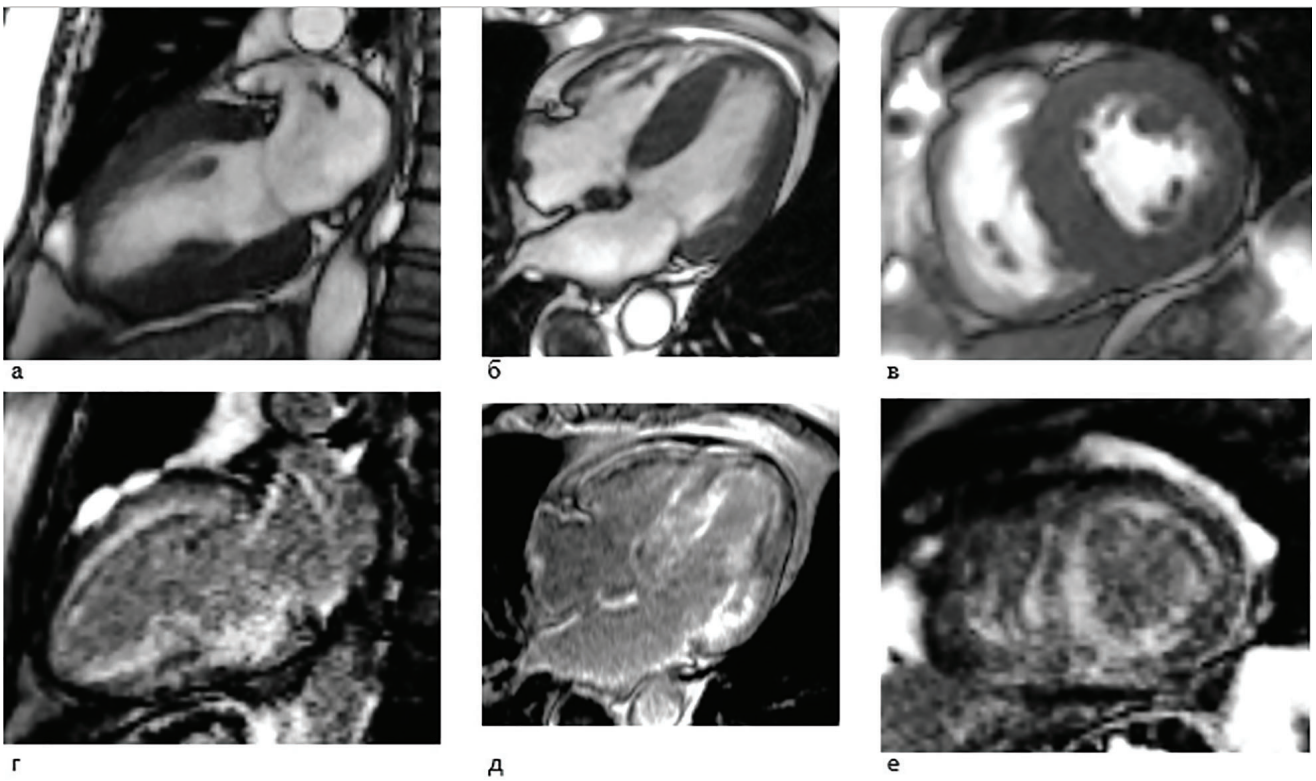

Figure 4. *MRI of a patient with cardiac amyloidosis (photos from the archive Dr Ustyuzhanin D.V.)*

Table 7. *Radioisotopes for Imaging TTR-Amyloid in the Heart*

Radiotracer	Imaging Modality	Mechanism of Uptake	Amyloid Subtype Uptake	Imaging Capability	Considerations
Bone avid tracers primarily used in the United States					
^{99m}Tc-PYP	Planar/SPECT	Bone tracer	ATTR-CM	Diagnostic; possibly early detection	Some uptake in patients with AL amyloidosis, less than ATTR amyloidosis
Bone avid tracers primarily used outside the United States					
^{99m}Tc-DPD ^{99m}Tc-HMDP	Planar/SPECT	Bone tracer	ATTR-CM	Diagnostic; possibly early detection	Some uptake in patients with AL amyloidosis, less than ATTR amyloidosis
Amyloid-binding radiotracers					
^{11}C-PIB	PET	Amyloid deposits	ATTR-CM, AL amyloidosis	Possibly quantitation of amyloid burden, disease monitoring	Short half-life, expensive isotope relative to SPECT tracers
^{18}F-флорбетапир	PET	Amyloid deposits	ATTR-CM, AL amyloidosis	Possibly early detection, quantitation, and disease monitoring	Expensive isotope relative to SPECT tracers
^{18}F-флорбетабен	PET	Amyloid deposits	ATTR-CM, AL amyloidosis	Possibly early detection, quantitation, and disease monitoring	Expensive isotope relative to SPECT tracers
^{18}F-NaF	PET	Bone tracer	Equivocal ATTR-CM	Possibly early detection, quantitation, and disease monitoring	No uptake in patients with AL amyloidosis, equivocal uptake in patients with ATTR-CM

Note: The tracers ^{99m}Tc-MDP and ^{99m}Tc-aprotinin are not recommended. ^{11}C-PIB indicates Pittsburgh compound B; ^{18}F-NaF, sodium fluoride; ^{99m}Tc-DPD, ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP, hydroxymethylene diphosphonate; ^{99m}Tc-PYP, technetium pyrophosphate; 123I, iodine-123; AL, amyloid light chain; ATTR-CM, transthyretin amyloidosis with predominant cardiomyopathy (either wild-type or hereditary); PET, positron emission tomography; and SPECT, single-photon emission computed tomography

Positron emission tomography (PET) allows differentiating amyloidosis from cardiac pathology of another etiology [15].

Biomarkers

Patients with amyloidosis should be tested for the levels of troponin T/I and N-terminal prohormone of cerebral natriuretic factor (NT-proBNP) [6]. NT-proBNP of over 1,800 ng/l and troponin T over 0.025 ng/ml are nonspecific, but the most informative parameters that indicate the severity of cardiac amyloidosis [5]. The presence of amyloid CMP can be almost excluded if NT-proBNP level is < 332 ng/l. When troponin and NT-proBNP levels are high for no specific reason, cardiac amyloidosis should be excluded [15]. A decrease in the NT-proBNP level is a cardiological criterion for the response to treatment and remission (Table 8) [6].

The diagnostic value of a new biomarker, circulating retinol-binding protein 4, was recently demonstrated [15].

Diagnosis of cardiac amyloidosis

The gold standard for amyloidosis diagnosis is a histological examination with Congo red staining and polarized microscopy (Figure 5). In cases of systemic forms of amyloidosis, subcutaneous fatty tissue and endoscopic biopsy samples from the gastrointestinal tract are taken for screening. If screening biopsy gives a negative or equivocal result, the material is taken from a clinically affected organ. The sensitivity of myocardial biopsy is about 100%, rectal submucosa — 75–85%, salivary glands — 58%, abdominal subcutaneous fatty tissue — 75% (79–100% in cases of AL amyloidosis, in samples > 700 mm^2 — 100%).

Table 8. *Stages of cardiac amyloidosis [14, 44, 62]*

Biomarker		Threshold (*)
Troponin	Troponin T	<0,035 мкг/л (0,05 нг/мл)/ <0,035 mcg/l (0,05 ng/ml)
	Troponin I	<0,1 мкг/л/ <0,1mcg/l
	hs-Troponin T	<77 нг/л/ <77 ng/l
Brain natriuretic peptide	NT-ProBNP	<332 нг/л (3000 пг/мл)/ <332 ng/l (3000 pg/ml)
	BNP	<100 нг/л/ <100 ng/l
Stage	**Definition**	**Median survival, months (% over 4 years*)**
I	Troponin T, Troponin I, NT-proBNP < than threshold	26,4 (57%)
II	or Troponin T > than threshold, or Troponin I > than threshold, or NT-proBNP > than threshold	10,5 (42%)
III	Troponin T > than threshold, or Troponin I > than threshold, AND NT-proBNP > than threshold	3,5 (18%)

Note: * NT-proBNP — N-terminal of the prohormone brain natriuretic peptide; hs — high sensitive

The incidence of severe complications (including perforation of the right ventricle, cardiac tamponade) during endomyocardial biopsy is 1%. Therefore it should not be performed if amyloid is found in biopsy samples of another location [5].

If the presence of amyloid deposits in tissue is confirmed, amyloid typing with a panel of antisera is required. The most effective typing method is an immunohistochemical study based on the reaction of antibodies with a precursor protein [5]. A more reliable but less accessible method is mass spectrometry, which allows identifying a specific protein [6].

Diagnosis of cardiac AL amyloidosis

If AL amyloidosis is suspected, screening for monoclonal gammopathies and B cell or plasma cell dyscrasia should be performed (Figure 6). Monoclonal gammopathy can be found by electrophoresis and immunofixation of proteins from serum and daily urine. The most sensitive and cheap method for detecting monoclonal gammopathy is a quantitative Freelite method using immunoglobulin free lambda and kappa light chains [5]. If a monoclonal gammopathy is found, then a trephine biopsy should be performed to confirm the presence of plasma cell B cell dyscrasia. Twenty percent of patients with AL amyloidosis at the time of diagnosis have multiple myeloma as comorbidity, which is associated with a lower survival rate: 1 year for 39% and 81% in the case of presence and absence, respectively. Multiple myeloma in patients with AL amyloidosis can be excluded using the PET method. Clonality and malignancy of the pathological cell clone should be defined using cytogenetic tests and immunophenotyping; FISH test (fluorescence in-situ hybridization) should also be performed. The most common cytogenetic abnormality in cases of AL amyloidosis is translocation t(11;14), which is found in approximately 40–60% of patients. Trisomy, deletion 17p, or abnormal t(11;14) are associated with an unfavorable prognosis [42].

Figure 5. A. *Massive deposits of amyloid in the liver, macropreparation.* ***B.*** *«Sebaceous spleen», macro preparation.* ***B–I*** *Microscopic picture of amyloidosis. Amyloid deposits are characterized by the ability to birefringence and dichrosis with the glow of apple-green and yellowish-green colors when studying preparations stained with Congo red in polarized light. Micropreparations with liver tissue, Congo red staining, × 20:* ***B*** *– polarized light, crossed polaroids,* ***G*** *– bright field. Micropreparations with heart tissue:* ***D.*** *Clusters of amorphous eosinophilic masses in the interstitium, stained with hematoxylin eosin, × 20.* ***E.*** *Congophilic deposits in the interstitium, stained with Congo red, × 20.* ***F, I.*** *Characteristic apple-green glow of amyloid deposits when examined in polarized light, different crossing angle of polaroids, × 20 (photos from the archive Dr Stepanova E.A.)*

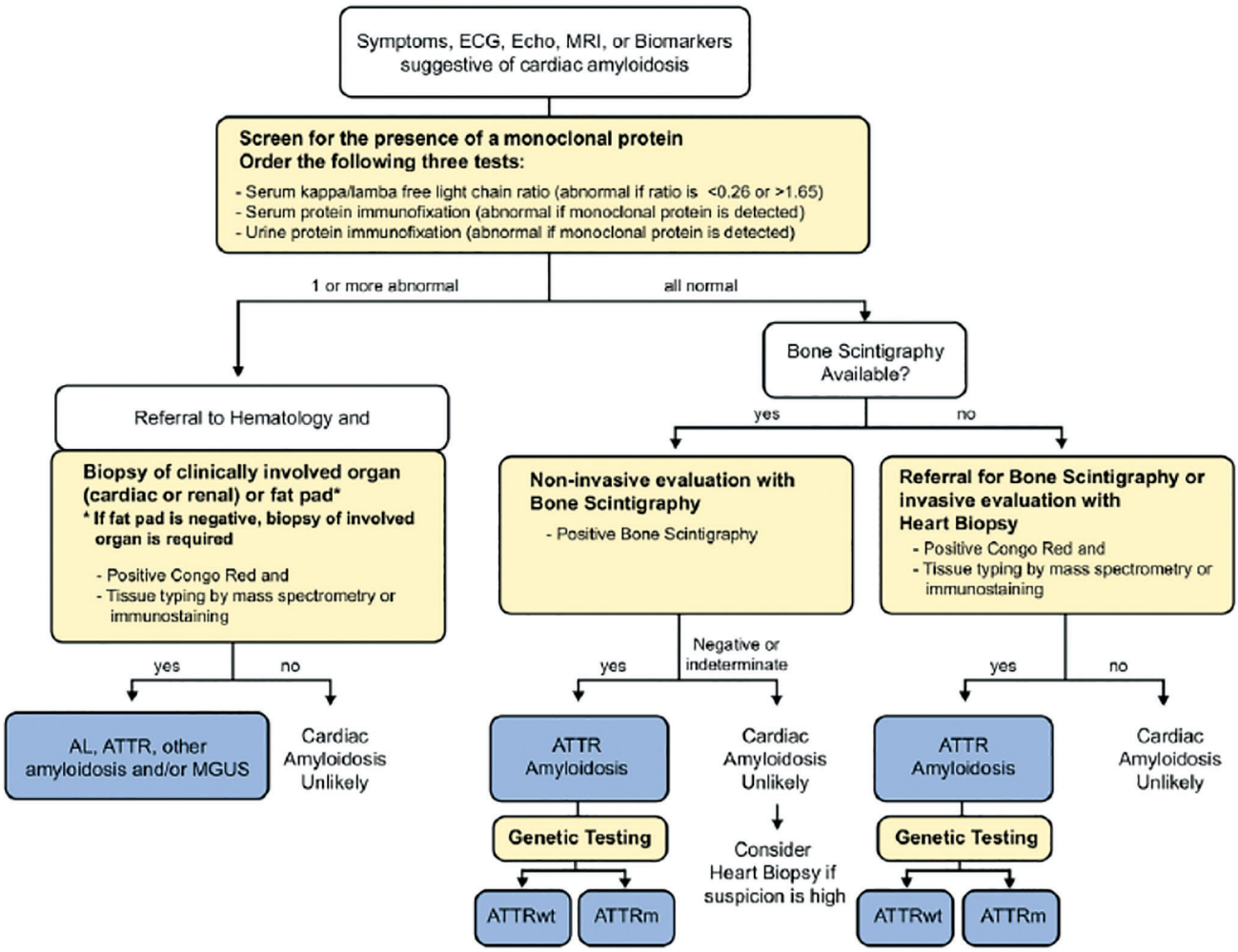

Figure 6. *Algorithm for the diagnosis of cardiac amyloidosis [15]*

ECG — electrocardiogram; Echocardiography — echocardiography; MRI — magnetic resonance imaging; EMB — endomyocardial biopsy; SCF — subcutaneous fatty tissue; MGUS, monoclonal gammopathy of undetermined significance; ATTR-AC — ATTR-cardiac amyloidosis, AC — cardiac amyloidosis

Diagnosis of ATTR amyloidosis

Diagnosis of ATTR amyloidosis can be established used scintigraphy, single-photon emission tomography with different isotopes that allow non-invasive diagnosing with very high specificity (> 99%) and sufficient sensitivity (86%) and avoiding endomyocardial biopsy [43–45]. A visual three-point scale was proposed for assessing the results of scintigraphy based on isotope accumulation in the myocardium: 0 — no isotope accumulation in the myocardium, from 1 to 3 (grade) — increasing accumulation. It was demonstrated that moderate absorption of 99mTc-DPD (grade 1) can also be observed in cases of AA and AApoA1 amyloidosis; in cases of diagnosed AL amyloidosis, a slight isotope accumulation (grade 1 and in 10% of cases — grade 2) is often recorded. Diagnosis of ATTR amyloidosis can be established in a non-invasive way using DPD scintigraphy if there is moderate or significant isotope accumulation (grade 2–3) and no plasma cell dyscrasia and immunoglobulin free light chains. Scintigraphical changes appear earlier than changes on EchoCG and can be considered as an early sign of ATTR CMP (Figure 7) [43–45].

Subcutaneous tissue biopsy for ATTR amyloidosis is associated with a minimum risk of complications, although its sensitivity amounts to 45% for ATTR amyloidosis of the mutant type and 15% for the wild type. In the case of negative biopsy of non-affected organs (subcutaneous tissue, bone marrow) and persisting suspicion of cardiac ATTR amyloidosis, endomyocardial biopsy is indicated [15].

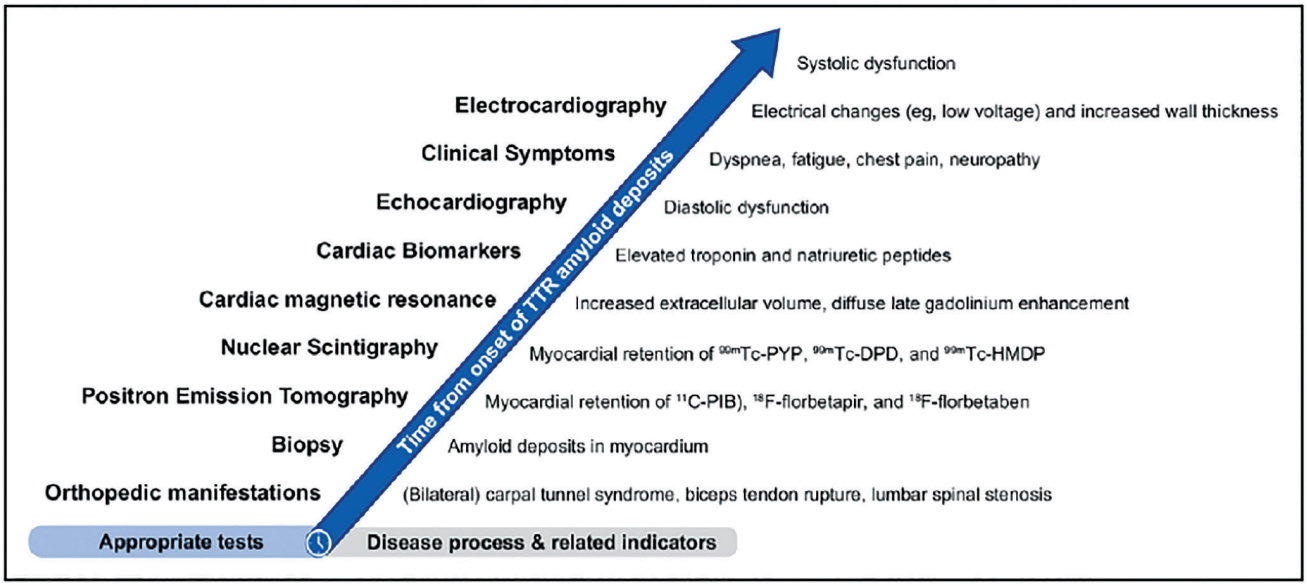

Figure 7. *Progression of ATTR-amyloid cardiomyopathy [14]*

ECG — electrocardiogram; PNP — polyneuropathy, CHF — chronic heart failure; ^{11}C-PIB — indicates Pittsburgh compound B; ^{99m}Tc-DPD — ^{99m}technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP — hydroxymethylene diphosphonate; ^{99m}Tc-PYP — technetium pyrophosphate

If signs of ATTR amyloidosis are found during scintigraphy or in biopsy results, genetic tests should be performed [15]. The genetic test alone is enough to diagnose ATTR amyloidosis in patients with typical clinical symptoms and family history. Precise identification of the mutation helps to assess the prognosis and effectiveness of treatment [43, 46].

Cardiac ATTR amyloidosis is often not diagnosed or is misdiagnosed as hypertrophic or restrictive CMP, or CHFpEF with unknown etiology. Heart Failure Bridge Clinic (USA) has developed and implemented criteria for screening for cardiac amyloidosis in cases of CHFpEF and the algorithm for its diagnosis. The following are the criteria for screening for amyloidosis:

1. Age 50+ years;
2. Thickness of interventricular septum (T_{IVS}) ≥ 12 mm;
3. Body mass index (BMI) ≤ 30 kg/m^2;
4. Low QRS voltage on ECG;
5. Central or peripheral neuropathy, carpal tunnel syndrome.

If a patient has ≥ 2 of these criteria, a diagnostic procedure should be performed in order to exclude/confirm cardiac amyloidosis (Figure 8). This algorithm helped diagnose cardiac amyloidosis in 15% of patients with CHFpEF [47].

Management of amyloidosis

According to the modern view, management of amyloidosis of any type can be pathogenetic (anti-amyloid, aimed at reducing the production or elimination of precursor proteins) and syndrome-based [5].

Pathogenetic management of ATTR amyloidosis

Tremendous success was achieved in recent years in the management of ATTR amyloidosis. The following are the main management aspects:

1. Suppression of transthyretin synthesis (liver transplantation; transthyretin gene switches).
2. Stabilization of transthyretin (tafamidis, diflunisal, green tea, AG10 TTR-stabilizer).
3. Cleavage of amyloid fibrils (doxycycline/ taurodeoxycholic acid (TUDCA), monoclonal antibodies) [48].

Liver transplantation

For many years, the only effective way to slow the progression of hereditary ATTR amyloidosis was liver transplantation, which led to the synthesis of less amyloidogenic wild transthyretin instead of

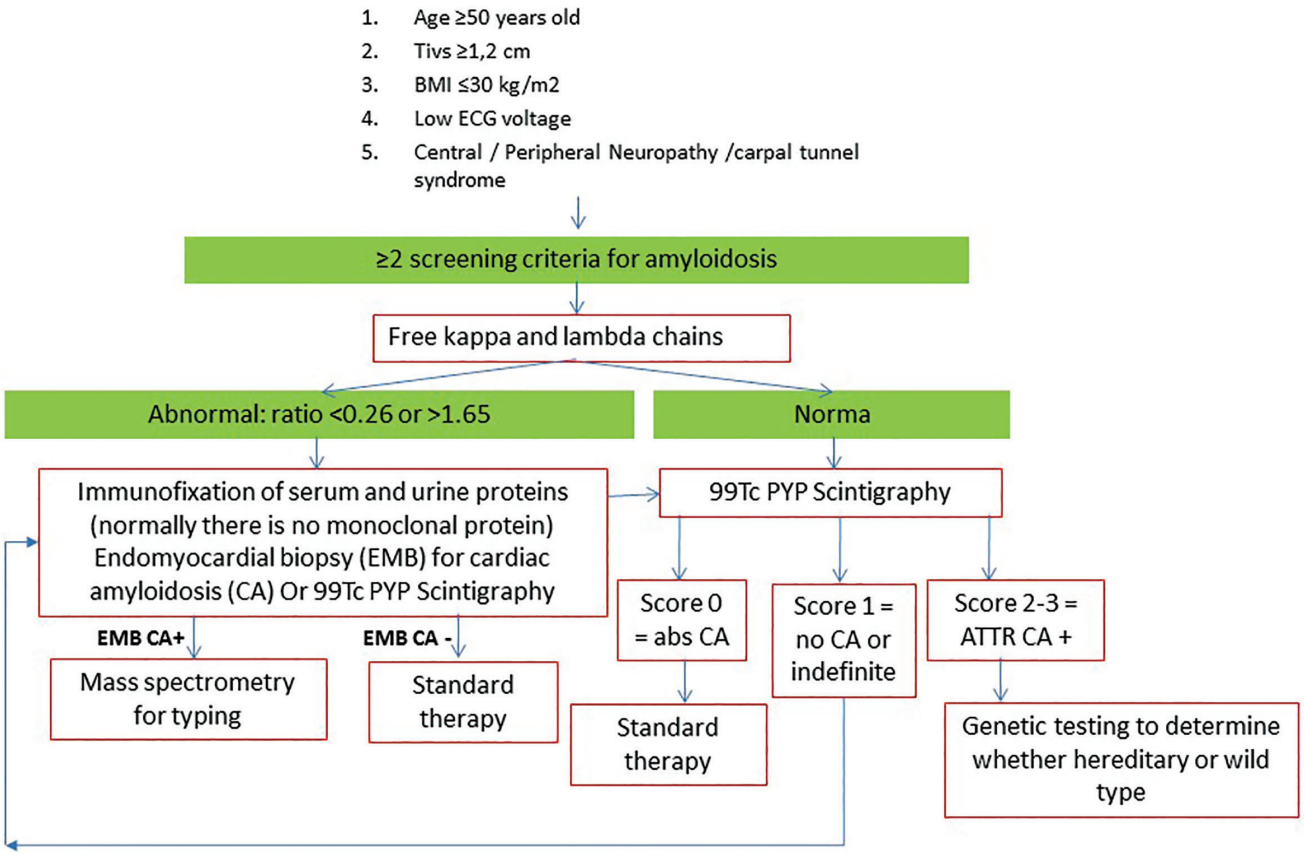

Figure 8. *Algorithm for the diagnosis of cardiac amyloidosis in CHFpEF [43].*

CHFpEF — chronic heart failure with preserved ejection fraction; EMB AS — endomyocardial biopsy for cardiac amyloidosis; ^{99m}Tc-PYP — ^{99m}technetium pyrophosphate

the mutant one. Ten-year survival after liver transplantation reaches 70%. However, progressive deposition of amyloid in the nervous system and the heart due to wild transthyretin continues [6]. Heart transplantation in cases of wild type ATTR amyloidosis is very rarely accompanied by repeated amyloid deposition. However, it is rarely performed due to the elderly age of patients [42].

Transthyretin stabilizers

Transthyretin stabilizers (tafamidis and diflunisal) prevent the dissociation of the transthyretin tetramer, preventing amyloid deposition in tissues.

Tafamidis

Tafamidis is a benzoxazole derivative that stabilizes the transthyretin tetramer by slowing down monomer formation, incorrect folding and amyloidogenesis. Long-term efficacy and safety of tafamidis in slowing disease progression and improving the survival rate of patients with ATTR polyneuropathy, hereditary transthyretin-amyloid cardiomyopathy, and also CMP in connection with wild type ATTR amyloidosis was confirmed [49, 50]. Tafamidis should be considered in patients with clinically evident CHF due to ATTR amyloidosis (both hereditary and wild) in order to improve exercise tolerance and the quality of life and reduce the frequency of hospitalizations for cardiovascular reasons and cardiovascular mortality rate [21].

Diflunisal

Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) with the ability to stabilize transthyretin. Slower progress of neuropathy during two years of treatment with diflunisal compared with the placebo, as well as improved quality of life was demonstrated. Side effects of diflunisal are the same as those of other NSAIDs [49].

ATTR gene switches (Transthyretin protein knockdown (reduction) agents (gene silencing))

Inotersen and patisiran reduce the synthesis of both wild and mutant transthyretin by 75–81% through the destruction of transthyretin mRNA (inotersen — by nuclear RNaseH1 (ribonuclease H1), patirisan — by cytoplasmic RNA-induced silencing complex). This slows or stops disease progression and results in new neurological signs. Inotersen can cause thrombocytopenia, bleeding, glomerulonephritis, and decreased kidney and liver function. The safety profile of patisiran is more favorable [49]. It may be the agent of choice in patients with atrial fibrillation (AF) taking anticoagulants [48].

Further lines of research for the management of ATTR amyloidosis

In future, it will be wise to reduce the cost of treatment with tafamidis, to continue studies of diflunisal, to study the combination of taursodeoxycholic acid (TUDCA) with doxycycline, which affects the destruction of amyloid masses, to study new selective stabilizers of transthyretin (epigallocatechin-3-gallate (EGCG), catechin from green tea), AG-10, CHF5074 (a NSAID derivative that does not block cyclooxygenase and has no corresponding side effects), to study monoclonal antibodies against incorrectly folded transthyretin (PRX004), the second generation of gene silencers transthyretin (AKCEA-TTR-LRx, vutrisiran — ALNTTRsc02) [21], and combinations of stabilizers and switches of the transthyretin gene [49].

Pathogenetic management of AL amyloidosis

The synthesis of immunoglobulin light chains is stopped using [5, 51] various chemotherapeutic agents (alkylating agents, steroids, proteasome inhibitor — bortezomib) and/or immunomodulating drugs combined with autologous stem cell transplantation. Treatment regimens are similar to those used for multiple myeloma but usually include the use of dexamethasone [13, 51]. Melphalan in combination with prednisolone or dexamethasone in large doses also yields a good result but can also cause acute leukemia or myelodysplasia. After remission in 20% of patients (who have no severe comorbidities), high-dose chemotherapy is conducted, followed by the injection of autologous blood stem cells. Subsequent administration of growth factors can increase CHF and hypotension. Injection of stem cells may be associated with ventricular arrhythmias due to the toxic effects of cryoprotectant dimethyl sulfoxide [51]. New agents, ixazomib and carfilzomib, have several advantages over bortezomib, but their evidence base is currently limited. [13].

Doxycycline has also demonstrated an antiamyloid effect *in vivo* and *in vitro*. Its addition to standard treatment for cardiac AL-amyloidosis reduced short-term mortality. An international phase III study is currently underway, where the efficacy of bortezomib with doxycycline is compared to that of the standard treatment scheme (NCT03474458) [48].

Phase III study of RNA-interference drug (resuviran) showed increased mortality in patients with amyloid CMP (ENDEAVOR; NCT02319005). Therefore, this study was stopped [48].

Young patients with isolated heart damage can be treated with orthotopic heart transplantation (1-yr survival is 50–89.5%, 5-yr survival is 20–65%) combined with high-dose chemotherapy (1-yr survival reaches 75%) [51]. Indications include good hematological remission with persisting severe HF. Contraindications are the following: diarrhea (weight loss, malabsorption), autonomic nervous system involved, impaired nutritional status, damage to the gastrointestinal tract, kidneys, respiratory tract [48].

Recommended treatment strategy for AL CMP includes 3 stages [48]:

1) Induction of chemotherapy: in most cases includes schemes with bortezomib that are aimed at minimizing or stopping the production of immunoglobin light chains.
2) Cardiac transplantation usually after 6 months to ensure cardiovascular stability during high-dose chemotherapy.
3) High-dose chemotherapy with melphalan, followed by autologous stem cell transplantation 6 months after stage 2.

New drugs for management of AL amyloidosis

Daratumumab is a monoclonal antibody against CD38 (differentiation cluster 38). After treatment with this agent, 129 patients with refractory AL amyloidosis showed a good hematological response without significant toxic effects [42]. Venetoclax, a BCL-2 (B-cell lymphoma 2 protein) inhibitor, was recently used for the management of multiple myeloma, especially in cases of mutation t(11; 14), which also occurs in connection with AL amyloidosis [42].

Pathogenetic management of AA amyloidosis

Pathogenetic management of AA amyloidosis includes management of the underlying disease in accordance with clinical recommendations and also management for amyloid deposits. Cytostatics used in patients with AA amyloidosis can help achieve clinical improvement; in some patients, they prevent or slow down renal failure and improve the prognosis.

Management for amyloid deposits

Tocilizumab, a monoclonal antibody against interleukin-6, demonstrated its efficacy in reducing the level of circulating SAA protein and controlling the progression of amyloidosis in cases of several joint diseases. This effect does not depend on the underlying disease [34].

Dimethyl sulfoxide is a derivative of the intracellular low-density lipoprotein molecule that causes amyloid resorption [34]. It should be used in high doses (at least 10 g/day), which is hardly possible due to its extremely unpleasant odor [5].

Eprodisate is a low molecular weight molecule, similar to heparan sulfate. Competitively binding with glycosaminoglycans, it inhibits the polymerization of amyloid fibrils and prevents the stabilization of amyloid deposits [52].

Heparin can slow the progression of AA amyloidosis by disrupting the stabilizing bonds between glycosaminoglycans and SAA in deposits; its action is similar to that of eprodisate [53]. Statins can also have a positive effect by inhibiting the isoprenoid pathway through specific blocking of farnesyl transferase [54].

Fibrillex is a new agent that contributes to amyloid resorption and destruction. It can be prescribed as an addition to the management of the underlying disease or treatment with colchicine [5].

New therapeutic targets

R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (CPHPC) is a small molecule that can bind to two subunits of serum amyloid P component (SAP) thereby reducing its concentration in serum. Thirty-one patients with amyloidosis demonstrated its positive effect on kidney function without significant side effects [55].

Dezamizumab, an antibody against SAP, is safe and reduces the amount of amyloid in the liver, although it showed no effect on amyloid deposits in the heart and kidneys [42].

Monoclonal antibodies against amyloid (11-1F4) that opsonize fibrils and facilitate their removal demonstrated a positive cardiac response in 8 of 12 treated patients [56].

The possibility of inhibition of SAA protein transcription with antisense oligonucleotides was shown using mouse models; it reduced the level of SAA in blood by 50% and significantly reduced amyloid deposits [56]. Clodronic acid, also used in mouse models, demonstrated the capacity for the prevention and management of amyloidosis [57].

Syndrome-based management

Syndrome-based management of amyloidosis is aimed at reducing the severity of symptoms and signs of HF, correction of rhythm and conduction disorders, correction of hypertension and hypotension, etc. (Table 9).

Management of CHF

Management of CHF in cases of amyloidosis is based on a low-salt diet, loop diuretics (preferably with high bioavailability, i.e., torasemide and bumetanide) and mineral corticoid receptor antagonists. In cases of severe CHF and/or nephrotic syndrome, large doses of diuretics are

Table 9. *Syndromic therapy of cardiac amyloidosis [63]*

Clinical situation	Medicine	Note
Fluid retention, edema syndrome, orthopnea	A loop diuretic, often in combination with a mineralocorticoid receptor antagonist	Careful dose titration, prevention of hypovolemia
Supraventricular arrhythmias (atrial fibrillation / flutter)	β-blocker	Indicated only in cases of tachycardia, in most cases should be avoided due to heart rate-mediated maintenance of cardiac output
	Amiodarone	Generally, well tolerated. Able to maintain sinus rhythm
	Verapamil, diltiazem	Contraindicated, because toxic effect develops rapidly due to binding to amyloid fibrils
	Digoxin	Contraindicated due to the possibility of rapid development of glycosidic intoxication due to binding to amyloid fibrils
	Anticoagulant therapy	Should be administered even with sinus rhythm or low CHA2DS2VASC score due to high risk of atrial thrombosis
Prolongation of the QT interval		It is necessary with extreme caution to prescribe drugs that prolong the QT interval with careful monitoring of its duration, incl. antipsychotics (haloperidol, quetiapine, olanzapine), tricyclic antidepressants (amitriptyline, nortriptyline, citalopram), antiemetics (metoclopramide, ondansetron), antibiotics (ciprofloxacin, azoles)

often required to maintain euvolemia. However, this can lead to the underfilling of the decreased and rigid LV with a decrease in cardiac output and the development of hypotension, dizziness, fainting, and prerenal acute kidney damage. In this regard, it is extremely important to evaluate the balance between fluid taken and lost and to titrate the dose of diuretics carefully [6].

There is no separate evidence base for using ACE inhibitors, angiotensin II receptor antagonists, and neprilysin inhibitors (ARNI) in patients with cardiac amyloidosis. These drugs can be poorly tolerated due to hypotension (probably due to concomitant dysfunction of the autonomic nervous system). Therefore, they should be prescribed in patients with CHF and amyloidosis with great caution, and their dose should be carefully titrated.

Patients with amyloidosis usually do not tolerate beta-blockers, especially in high doses and those with alpha-blocking effect, because they reduce heart rate and, consequently, cardiac output and blood pressure. In later stages, compression stockings and midodrine may be beneficial.

Non-dihydropyridine calcium channel antagonists (verapamil, diltiazem) are contraindicated in patients with amyloidosis due to their accumulation in amyloid deposits, leading to heart block.

Mechanical support of blood circulation in patients with cardiac amyloidosis is technically possible but is a low class (IIB) recommendation. Two-year survival of patients with cardiac amyloidosis treated with mechanical support of blood circulation is lower than in those without amyloidosis; however, in some patients, it may become a way to move towards heart transplantation [5].

Management of arrhythmias

Cardiac glycosides are contraindicated in patients with amyloidosis due to the possible accumulation in amyloid of a toxic dose with the development of paradoxical reactions [5].

Among antiarrhythmic agents used for restoring sinus rhythm, only amiodarone is relatively safe in cases of paroxysmal AF and amyloidosis. Rhythm control strategy in these patients may be of lesser importance than in the general population since atrial work aimed at filling ventricles is minimal or absent.

Ablation and/or implantation of cardioverter defibrillator (ICD) is indicated in some patients due to the high risk of fatal tachyarrhythmias. Data on the results of catheter ablation in cases of cardiac amyloidosis are limited. Long-term results are probably worse than in patients without amyloidosis. If life expectancy is less than one year, ICD is not recommended for the primary prevention of sudden death. Sudden death in cases of amyloid cardiomyopathy is often associated with electromechanical dissociation, which is also an argument against inserting ICD in these patients. ICD should be considered in every individual case for secondary prevention in patients with frequent unstable or persistent ventricular tachycardia.

Patients with severe cardiac amyloidosis have an increased risk of developing intracardiac thrombi. Left atrial thrombosis was found in 33% of patients with ATTR CMP by means of transesophageal echocardiography; most of these patients took anticoagulants [5]. Due to the high risk of thrombosis in patients with cardiac amyloidosis, anticoagulant treatment should be prescribed (warfarin or oral anticoagulants that are not vitamin K antagonists). They are indicated not only for the management of intracardiac thrombosis, AF (regardless of CHA2DS2-VASc scale points), atrial arrhythmias but also when there is sinus rhythm with echocardiographic signs of mechanical left atrial dysfunction [5]. AL amyloidosis is often accompanied with coagulation factor X deficiency and hemorrhages. Therefore, anticoagulants should be prescribed with caution [5, 59, 60].

Management of conduction disorders

Heart blocks, sick sinus syndrome, chronotropic incompetence are often found in cases of cardiac amyloidosis and require implantation of a permanent pacemaker. Permanent right ventricular apical pacing can cause interventricular dyssynchrony and further decrease in stroke volume and cardiac output. In this regard, biventricular stimulation is preferred. With the development of CHF, the lower limit of stimulation frequency can be increased to maintain cardiac output.

Management of orthostatic hypotension

Mineralocorticoids or glucocorticoids for continuous administration are recommended for orthostatic hypotension, but this therapy increases the risk of HF decompensation [5].

Conclusion

Understanding pathogenesis has led to successful diagnosis and management of all forms of amyloidosis, including cardiac amyloidosis. Clinical alertness of cardiologists regarding the possibility of cardiac amyloidosis is extremely important for its timely diagnosis. Screening for amyloidosis should be performed in patients with CHF of unknown etiology, idiopathic AF, low ECG voltage, especially in combination with left ventricular myocardium thickness of 12 mm or more, proteinuria, chronic kidney disease stage 4–5, arterial hypotension and pulmonary hypertension. Early diagnosis allows achieving the best treatment results. Therefore, the disease that was previously considered incurable may soon become treatable or, at least, a slowly progressing condition.

Author Contribution:

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

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

T.L. Nguyen (ORCID ID: https://orcid.org/0000-0002-8856-4542): writing the text of the manuscript; review of publications on the topic of the article

E.A. Stepanova (ORCID ID: https://orcid.org/0000-0001-7760-5858): scientific consultation, editing the manuscript, corrections in the process of writing the manuscript, providing morphological illustrative material, comments on it

D.V. Ustyuzhanin (ORCID ID: https://orcid.org/0000-0002-0402-3977): scientific consultation, editing the manuscript, corrections in the process of writing the manuscript, providing illustrative material for magnetic resonance imaging, comments on it

I.G. Nikitin (ORCID ID: https://orcid.org/0000-0003-1699-0881): scientific consultation, manuscript editing, general supervision of the research team

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DOI: 10.20514/2226-6704-2020-10-6-458-467

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МОДЕЛЬ ПРОГНОЗИРОВАНИЯ ГИПЕРТРОФИИ МИОКАРДА ЛЕВОГО ЖЕЛУДОЧКА У ПАЦИЕНТОВ С ОБСТРУКТИВНЫМ АПНОЭ СНА

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Model for Prediction of Left Ventricular Myocardial Hypertrophy in Patients with Obstructive Sleep Apnea

Резюме

Обструктивное апноэ сна (ОАС) диагностируется у 25% взрослых лиц и сопровождается высокими фатальными рисками кардиоваскулярных осложнений. Гипертрофия миокарда левого желудочка (ГЛЖ) признается одним из маркеров таких рисков. В настоящем исследовании нами предпринята попытка создания математической модели прогнозирования ГЛЖ среди пациентов с ОАС с различной степенью тяжести заболевания. **Материалы и методы.** В проспективное когортное исследование включены 368 пациентов (358 муж. возраст 46,0 [42,0; 49,0] лет) с диагностированным ОАС, артериальной гипертензией, ожирением I-II степени (классификация ВОЗ, 1997). Характер и тяжесть апноэ сна верифицировалась в ходе ночной компьютерной сомнографии (КСГ) на аппаратном комплексе WatchPAT-200 (ItamarMedical, Израиль) с оригинальным программным обеспечением zzzPAT™SW ver. 5.1.77.7 (ItamarMedical, Израиль) путём регистрации основных респираторных полиграфических характеристик в период 23:00 — 7:30. Эхокардиография, допплерография сердца и сосудов выполнялась в одно- и двухмерном режимах в стандартных эхокардиографических позициях с помощью ультразвукового сканера Xario-200 (Toshiba, Япония) с использованием датчика частотой 3,5 МГц. Гемодинамические показатели систолической функции левого желудочка (фракция выброса (ФВ), конечный систолический объём (КСО), ко-

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нечный диастолический объём (КДО)) определялись при количественной оценке двухмерных эхокардиограмм модифицированным методом Simpson. Оценку систолической функции правого желудочка (ПЖ) проводили в «М»-режиме путём измерения систолической экскурсии фиброзного кольца трикуспидального клапана (TAPSE). **Результаты.** Наилучшими предикторами прогнозирования ГЛЖ при различной степени тяжести ОАС следует считать ESS и TSat90% (AUC = 0,975; SD = 0,00741; ДИ 95% [0,953; 0,988]), позволяющих предложить прогностическую модель с чувствительностью в 93,7% и специфичностью в 93,8%, после проведения анкетного скрининга и компьютерного сомнографического исследования. **Выводы.** Предлагаемая модель клинического прогнозирования ГЛЖ среди пациентов с ОАС различной степени тяжести основывается на тщательно спланированном анализе анкетных и инструментальных данных, хорошо применима в условиях реальных диагностических процедур широким кругом врачей терапевтической практики.

Ключевые слова: *обструктивное апноэ сна, гипертрофия левого желудочка, эхокардиография, клиническая модель предсказания, WatchPAT-200, компьютерная сомнография, КСГ, амбулаторная практика*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 30.10.2020 г.
Принята к публикации 19.11.2020 г.

Для цитирования: Горбунова М.В., Бабак С.Л., Боровицкий В.С. и др. МОДЕЛЬ ПРОГНОЗИРОВАНИЯ ГИПЕРТРОФИИ МИОКАРДА ЛЕВОГО ЖЕЛУДОЧКА У ПАЦИЕНТОВ С ОБСТРУКТИВНЫМ АПНОЭ СНА. Архивъ внутренней медицины. 2020; 10(6): 458-467. DOI: 10.20514/2226-6704-2020-10-6-458-467

Abstract

Obstructive sleep apnea (OSA) is diagnosed in 25% of adults and associated with high fatal risks of cardiovascular complications. Left ventricular hypertrophy (LVH) is recognized as one of the markers of such risks. In this study, we attempted to create a mathematical model for predicting LVH among OAS patients with various levels of disease severity. **Materials and methods.** In a prospective cohort study, we included 368 patients (358 male; age 46.0 [42.0; 49.0] yr.) with diagnosed OSA, arterial hypertension, grade I-II obesity (WHO classification 1997). The severity of sleep apnea was verified during nighttime computed somnography (CSG) on WatchPAT-200 hardware (ItamarMedical, Israel) with original software zzzPAT™SW ver. 5.1.77.7 (ItamarMedical, Israel) by registering the main respiratory polygraphic characteristics from 11.00 PM to 7:30 AM. Verification of LVH was performed in one- and two-dimensional modes in standard echocardiographic positions using Xario-200 ultrasound scanner (Toshiba, Japan) with 3.5 MHz transducer. Hemodynamic parameters of left ventricular (LV) systolic function (EF %, ESV, EDV) were determined by quantitative assessment of two-dimensional echocardiograms using the modified Simpson method. Evaluation of the systolic function of the right ventricle (RV) was performed in the «M»-mode by measuring the systolic excursion of the fibrous ring of the tricuspid valve (TAPSE). **Results.** ESS and TSat90% (AUC = 0.975; SD = 0.00741; CI 95% [0.953; 0.988]) should be considered the best predictors for predicting LVH in various degrees of OSA severity, allowing us to offer a predictive model with a sensitivity of 93.7% and specificity of 93.8%, after conducting a questionnaire screening and computer somnographic study. **Conclusions.** Our proposed model of clinical prediction of LVH among patients with various degrees of OAS is based on a carefully planned analysis of questionnaire and instrumental data, and is well applicable in real diagnostic procedures by a wide range of therapeutic practitioners.

Key words: *obstructive sleep apnea, left ventricular hypertrophy, echocardiography, clinical prediction model, WatchPAT-200, computed somnography, outpatient practice*

Conflict of interests

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

Sources of funding

The authors declare no funding for this study

Article received on 30.10.2020
Accepted for publication on 19.11.2020

For citation: Gorbunova M.V., Babak S.L., Borovitsky V.S. et al. Model for Prediction of Left Ventricular Myocardial Hypertrophy in Patients with Obstructive Sleep Apnea. The Russian Archives of Internal Medicine. 2020; 10(6): 458-467. DOI: 10.20514/2226-6704-2020-10-6-458-467

AHI — apnea-hypopnea index, BMI — body mass index, BP — blood pressure, BSA — body surface area, cMRI — cardiac magnetic resonance imaging, CPAP — continuous positive airway pressure therapy, CVC — cardiovascular complications, DT — deceleration time, ECHO CG — cardiac echocardiography, EDV — end diastolic volume, EFT — epicardial fat thickness, ESV — end systolic volume, GCP — good clinical practice, HbA1c — glycated hemoglobin, HDL — high density lipoproteins, IVRT — isovolumic relaxation time, LA — left atrium, LAVI — left atrial volume index, LDL — low density lipoproteins, LV — left ventricle, LVDD — left ventricular diastolic dysfunction, LVEF — left ventricular ejection fraction, LVH — left ventricular hypertrophy, LVMMI — left ventricular myocardial mass index, NPS — night polysomnography, OSA — obstructive sleep apnea, PASP — pulmonary artery systolic pressure, RAVI — right atrial volume index, REM — rapid eye movement sleep (paradoxical sleep), STOP-BANG — questionnaire for the markers of obstructive sleep apnea, TAPSE — tricuspid annular plane systolic excursion, URT — upper respiratory tract, VE/VA — ratio of early to late ventricular filling velocity, WM — waist measurement

Introduction

Obstructive sleep apnea (OSA) is a heterogeneous parasomniac disease with repeated collapses of the upper respiratory tract (URT) during sleep; it can be found in approximately 25% of the adult population and is the leading cause of excessive sleepiness, deterioration of quality of life and labor productivity, and increased risk of traffic accidents [1]. Moreover, OSA is directly associated with an increased risk of fatal and nonfatal cardiovascular complications (CVC) [2, 3]. The typical manifestation of severe sleep apnea is left ventricular myocardial hypertrophy (LVH) — increased left ventricular myocardial mass, with its structural remodeling as a result of overload with excessive volume/pressure. LVH in patients with OSA should be considered as a risk factor for coronary heart disease, chronic heart failure, cardiac rhythm disorders, myocardial infarction and stroke [4]. Twelve-lead electrocardiography (12-lead ECG), echocardiography (ECHO-CG), and cardiac magnetic resonance imaging (cMRI) are considered the best methods for detecting LVH. Currently, cMRI is regarded as the "universal standard" for studying cardiac structure [5]. However, there is an ongoing intensive search for medical models for predicting LVH in patients of different therapeutic groups intended to be clearer to practitioners. Our study aimed to identify LVH predictors regardless of systolic blood pressure (SBP) and body mass index (BMI) that will allow proposing a model of LVH probability in patients with OSA of different severity.

Materials and methods

Study design. This cohort observational study included 368 patients (358 males (97.3%), age 46.0 [42.0; 49.0] years) with confirmed obstructive sleep apnea, arterial hypertension, obesity grade I–II according to the WHO classification (1997) who signed an informed consent form. It was a single-center prospective parallel group study with visits on the 3rd, 6th and 12th months in order to assess the metabolic effects of long-term CPAP therapy. The inclusion criteria were: 1) complaints of night snoring and/or respiratory failure at night and scoring more than 3 points on the STOP-BANG scale [6]; 2) obesity BMI > 30 kg/m^2 and/ or abdominal obesity (WM > 94 cm in men, WM > 80 cm in women), and any two of the following metabolic signs:

- fasting plasma glucose level > 5.6 mmol/l and/or HbA1c > 5.7%;
- SBP > 140 mm Hg or DBP > 90 mm Hg or taking antihypertensive drugs during the last 12 months;
- dyslipidemia with increased plasma triglycerides > 1.7 mmol/l; high LDL level > 3.0 mmol/l or low HDL level < 1 mmol/l for men and < 1.2 mmol/l for women, or treatment for dyslipidemia.

Individuals with clinically significant comorbidities and the following conditions were excluded from the study: pregnancy and lactation; type 1 and 2 diabetes mellitus; syndromic forms of obesity; severe somatic comorbidity (thyroid function abnormality, renal and hepatic failure, decompensated heart failure, severe hemodynamic cardiac rhythm disorders, previous myocardial infarction and stroke three months before screening, systemic inflammatory disease, cancer); use of systemic glucocorticosteroids three months before screening; medical history of mental illness and/or that detected during clinical examination; drug and alcohol dependence; patients with pronounced airway obstruction (FEV_1 < 50%), restrictive diseases (VC < 80%), daytime arterial blood saturation SpO_2 < 90% (FiO_2 = 21%).

All patients received optimal antihypertensive and hypolipidemic therapy, followed recommendations on lifestyle changes, dietary intervention and developed physical activity programs. Baseline parameters of patients are shown in Table 1.

This study was carried out at the Department of Phthisiology and Pulmonology of the Faculty of Medicine of the A. I. Evdokimov Moscow State University of Medicine and Dentistry (A. I. Evdokimov MSUMD of the Russian Ministry of Health) at the Central Union Hospital of the Russian Federation (Moscow); it met good clinical practice (GCP) standards and the principles of the Helsinki Declaration and was approved by the Interacademic Ethics Committee of A. I. Evdokimov MSUMD.

Table 1. *Baseline patients' parameters*

Parameter	Patients (n=368)
Age, years	46,0 [42,0; 49,0]
Gender, (male/female, n, %)	358 (97,3)/10 (2,7)
BMI, kg/m²	33,3 [31,7; 35,3]
Neck circumference, cm	44,0 [43,0; 45,0]
Waist circumference, cm	112 [106; 117]
Visceral Adiposity Index, (VAI)	3,11 [2,67; 3,62]
Systolic blood pressure (SBP), mm Hg	145,5 [136; 150]
Diastolic blood pressure (DBP), mm Hg	93,0 [88; 97]
Current smokers (n, (%))	38 (10,3)
Former smokers (n, (%))	210 (57,1)
Never smoked (n, (%))	120 (32,6)
Epworth sleepiness scale (ESS), score	12,0 [9,0; 13,0]
Apnoea-hypopnea index (AHI) (events/h)	28,9 [14,8; 54,0]
Oxygen desaturation index (ODI), (events/h)	18,75 [8,57; 45,28]
Percentage of time with oxygen saturation < 90%, (TSat90), %	18,75 [8,57; 45,28]
Total cholesterol, mmol/L	5,13 [4,83; 5,76]
HDL, mmol/L	0,95 [0,89; 1,02]
LDL, mmol/L	3,52 [3,04; 3,97]
Triglycerides, mmol/L	2,11 [1,98; 2,34]
Apolipoprotein B, g/L	1,31 [1,19; 1,43]
Leptin, ng/ml	25,53 [18,58; 31,05]
Uric acid, μmol/L	440,5 [420,0; 4679,0]
HOMA-IR	4,31 [3,43; 5,37]
Creatinine, μmol/L	84,0 [80,0; 89,0]
Glomerular filtration rate (GFR), ml/min/1.73m2	94,5 [88,0; 101,0]

Echocardiography and Doppler ultrasound of heart and blood vessels were performed in M- and 2D modes in standard echocardiographic views using the Xario 200 ultrasound scanner (Toshiba, Japan) with a 3.5 MHz sensor. Hemodynamic parameters of the LV systolic function (ejection fraction (EF), end-systolic volume (ESV), end-diastolic volume (EDV)) were defined by quantitative assessment of 2D echocardiograms using a modified Simpson method. Left ventricular myocardial mass index (LVMMI) was calculated as the ratio of LV myocardial mass calculated by the ASE formula to body surface area (BSA). LVMMI of more than 115 g/m² in men and 95 g/m² in women was considered as LVH [7]. To determine the geometry (type) of LV (normal, concentric remodeling, concentric and eccentric hypertrophy), relative thickness index (RTI) was calculated according to the formula (2xPWTd)/EDD, where PWTd is posterior wall thickness at the end of diastole and EDD is the end-diastolic diameter [8]. The volume of the left atrium (LA) was determined by the biplane formula area/length indexed to body surface area (BSA). The right atrium volume index (RAVI) was calculated by the formula: RAVI = (0.85 × S2/L)/BSA, where S is the area of LA; L is the length of LA; BSA is body surface area [9]. The LV diastolic function was investigated using pulsed-wave Doppler and color Doppler flow mapping [10]. Assessment of the systolic function of the right ventricle (RV) was performed in M-mode by measuring tricuspid annular plane systolic excursion (TAPSE). Epicardial fat thickness (EFT) was determined perpendicularly to the right ventricular free wall in B mode from the parasternal position, along the left ventricular long axis, at end systole, on the line which most perpendicular to the aortic ring [12].

Night somnography (NSG). To detect obstructive sleep apnea, we performed night somnography using a computer-based somnography (CSG) method based on the technology for determining apnea episodes and their consequences by varying changes in peripheral arterial tone (PAT technology) in accordance with unified rules and recommendations of AASM (American Academy of Sleep Medicine) [13, 14]. OSA was found using a WatchPAT-200 portable device for CSG (ItamarMedical,

Caesarea, Israel) with original zzzPAT™SW software ver. 5.1.77.7 (ItamarMedical, Caesarea, Israel) by measuring the main respiratory polygraphic parameters during the period between 11:00 p.m. and 7:30 a.m. Sleep apnea-hypopnea index (AHI) from 5/h to 15/h corresponded to mild OSA, from 15/h to 30/h — to moderate OSA, more than 30/h — to severe OSA. Assessment of nocturnal desaturation ODI, mean and minimum nocturnal saturation (SpO_2), heart rate (HR), and sleep stages was performed in accordance with international recommendations [15, 16].

Statistical analysis. Statistical analysis was performed with the Medcalc statistical software package® ver. 19.2 (MedCalc Software, Belgium; https://www.medcalc.org) and StatPlus:mac® ver. 7 (AnalystSoft Inc.; www.analystsoft.com/ru/). Quantitative data were checked for normal distribution using the Kolmogorov-Smirnov test (with Lilliefors correction) and D'Agostino-Pearson test. Nonparametric data were presented as median (Me), upper and lower quartile (LQ-UQ) as Me [25%; 75%]. To develop a rule that allows estimating the probability of an event, we used simple logistic regression (with the determination of the predictors of the greatest weight) and multiple logistic regression (to build a predictive model). The quality of the obtained model was evaluated by its sensitivity, specificity, and the area under the ROC curve. Model quality assessment was performed according to the value of the expert logistic regression scale in accordance with the criteria set by Hosmer DW (2000), Julkowska MM (2019) [17, 18].

Table 2. *Clinical characteristics OSA patients*

Characteristics	Group A (n=102)	Group B (n=98)	Group C (n=168)
Age, years	44,0 [40,3; 50,0]	47,0 [42,0; 50,0]	46,0 [43,0; 48,0]
Gender, (male/female)	100/2	94/4	164/4
BMI, kg/m^2	32,1 [30,7; 34,1]	33,6 [32,4; 34,8] *	34,1 [32,3; 35,7] ##
Neck circumference, cm	43,0 [42,0; 44,0]	44,0 [43,0; 45,0] *	45,0 [44,0; 46,0] ##
Waist circumference, cm	106 [104; 113]	112 [108; 117] **	114 [109; 118] ##
Visceral Adiposity Index, (VAI)	2,61 [2,22;3,10]	3,13 [2,84;3,49] *	3,48 [2,87;4,08] ##
Epworth Sleepiness Scale (points)	9,0 [8,0; 12,0]	12,0 [9,0; 13,0] **	12,0 [9,0; 14,0] ##

Note: Quantitative data are presented as Me [25%; 75%].
Description: *p <0.05 between group A-B; * * p <0.0001 between group A-B
#p <0.05 between group A-C; ##p <0.0001 between group A-C

Table 3. *Basic polygraphic parameters OSA patients*

Parameter	Group A (n=102)	Group B (n=98)	Group C (n=168)
Apnea–hypopnea index (AHI), h^{-1}	12,7 [9,9; 14,2]	25,7 [21,4; 28,3] **	55,0 [40,9; 68,4] ##
Desaturation index, (ODI), h^{-1}	5,5 [2,5; 8,7]	17,6 [10,8; 20,3] **	47,1 [23,9; 59,1] ##
TSat90, %	1,7 [0,2; 6,9]	12,0 [1,68; 17,0] **	28,5 [13,7; 39,0] ##
SpO_2 mean, %	94,0 [92,0; 94,8]	93,0 [90,0; 93,5] **	91,0 [89,0; 92,0] ##
SpO_2min, %	83,0 [79,0; 88,0]	78,0 [70,0; 82,0] *	72,0 [66,8; 78,3] ##
Night HR min, min^{-1}	45,5 [41,0; 50,8]	43,0 [40,0; 46,0] *	45,0 [40,0; 48,0] #
Night HR max, min^{-1}	100,0 [94,3; 103,0]	99,0 [91,0; 105,0]	102,0 [99,0; 109,0] #
Sleep stages			
REM, %	21,4 [19,1; 25,5]	19,4 [15,3; 25,5]	14,7 [12,9; 19,6] ##
Light sleep, %	59,6 [53,8; 63,1]	66,6 [56,2; 73,8] *	78,9 [71,6; 82,2] ##
Deep sleep, %	19,8 [16,6; 23,1]	13,4 [10,1; 18,5] **	6,5 [4,9; 11,0] ##

Note: Quantitative data are presented as Me [25%; 75%].
Description: *p <0.05 between group A-B; * * p <0.0001 between group A-B
#p <0.05 between group A-C; ##p <0.0001 between group A-C
Definition of abbreviations: TSat90 % — night time spent with oxygen saturation below 90%; SpO2 mean — mean night saturation; SpO2min — minimum night saturation; Night HR min — minimum night heart rate; Night HR max — maximum night heart rate; REM — rapid eye movement sleep

Results

Analysis of Cardiovascular Signs of Obstructive Sleep Apnea

All patients were divided into the following groups depending on OSA severity. Group A, with mild sleep apnea, included 102 patients (100 males; 44.0 [40.3; 50.0] years); group B with moderate course — 98 patients (94 males; 47.0 [42.0; 50.0] years); group C with severe course — 168 patients (164 males; 46.0 [42.0; 48.0] years). Table 2 presents the clinical features of these groups. The severity of excessive sleepiness correlated with OSA severity in all groups. This parameter varied widely. For example, in group A, it was mild/moderate (53.9% / 33.3%), in group B — moderate/significant (38.8% / 13.3%), in group C — moderate/significant (53.6% / 20.2%), indicating a high baseline heterogeneity of patients. The main polygraphic parameters in all groups were characterized by frequent episodes of desaturation with the events of nocturnal hypoxemia, tachy-/bradycardia, and reduced deep sleep. Nocturnal polygraphic parameters are presented in Table 3.

LV systolic function was not impaired in all groups. High intergroup difference was found in the assessment of ESV, LVEF, LV myocardial mass index (LVMI), left and right atrial volume indices, several parameters of the right ventricle, epicardial fat thickness (Table 4).

Table 4 Parameters of the left and right parts of the heart (ECHO-KG)

Parameter	Group A (n=102)	Group B (n=98)	Group C (n=168)
Left atrium (LA) size, cm	3,9 [3,7; 4,2]	4,2 [3,9; 4,5] *	4,3 [4,0; 4,6] ##
LAVI, ml/m²	27,0 [25,0; 31,0]	31,0 [28,0; 33,0] **	31,5 [29,0; 34,0] ##
EDV, ml	125,0 [120,0; 133,0]	130,0 [120,0; 138,0]	135,0 [126,0; 152,0] ##
ESV, мл	42,5 [37,0; 48,8]	47,0 [38,0; 51,0]	51,0 [45,0; 60,0] ##
EF, %	66,0 [62,3; 69,0]	63,0 [61,0; 67,8] *	60,0 [58,0; 64,0] ##
LVMI, g/m²	114,0 [103,0; 120,0]	118,0 [111,0; 129,0] **	125,0 [116,0; 132,0] ##
The normal geometry of the left ventricule, n, %	57 (55,9)	30 (30,6)	24 (14,3)
Left ventricular concentric remodeling, n, %	1 (0,9)	2 (2,0)	4 (2,4)
Concentric LVH, n, %	27 (26,5)	53 (54,1)	123 (73,2)
Eccentric LVH, n, %	17 (16,7)	13 (13,3)	17 (10,1)
RAVI, ml/m²	24,0 [19,0; 30,8]	31,0 [24,0; 35,0] **	34,0 [29,0; 37,0] ##
Right ventricular wall thickness, cm	0,44 [0,39; 0,49]	0,50 [0,46; 0,55] **	0,53 [0,49; 0,55] ##
Right ventricle long-axis diameter, cm	3,30 [2,80; 3,50]	3,40 [3,00; 3,80] *	3,70 [3,20; 4,00] ##
EF, mm	5,50 [4,50; 6,00]	6,50 [5,50; 7,00] **	7,50 [6,38; 8,00] ##
TAPSE, мм	23,0 [21,0; 25,0]	22,0 [21,0; 24,0] *	21,0 [19,8; 24,0] ##
PASP, mmHg	30,0 [27,0; 34,8]	35,0 [30,0; 38,0] **	36,0 [32,0; 42,0] ##
VE/VA, м/с	1,15 [1,00; 1,18]	1,07 [0,91; 1,12] *	1,04 [0,92; 1,13] #
IVRT, мс	95,0 [90,0; 99,8]	99,0 [92,5; 109,0] *	102,0 [96,8; 116,0] ##
DT, мс	190,0 [173,0; 202,0]	209,0 [197,0; 223,0] **	214,0 [201,0; 230,0] ##
LVDD, n (%)	15 (14,7%)	26 (26,5%)	67 (39,8%)
LVDD: type I, n (%)	15 (14,7%)	24 (24,5%)	59 (35,0%) ##
LVDD: type II, n (%)	0 (0%)	2 (2,0%)	8 (4,8%)
LVDD: type III, n (%)	0 (0%)	0 (0%)	0 (0%)

Note: Quantitative data are presented as Me [25%; 75%].
Description: *p <0.05 between group A-B; ** p< 0.0001 between group A-B
#p <0.05 between group A-C; ##p <0.0001 between group A-C
Definition of abbreviations: LA — left atrium; LAVI — left atrial volume index; EDV — end-diastolic volume; ESV — end-systolic volume; EF — ejection fraction; LVMI — left ventricular mass index; LVH — left ventricular hypertrophy; RAVI — right atrial volume index; EF — epicardial fat thickness; TAPSE — systolic excursion of the fibrous ring of the tricuspid valve; PASP — pulmonary artery systolic pressure; VE/VA — ratio of the early (E) to late (A) ventricular filling velocities; IVRT — isovolumic relaxation time; DT — deceleration time; LVDD — left ventricular diastolic dysfunction

Among patients with severe OSA (group C), individuals with the diastolic dysfunction (DD) of the left ventricle (LV) prevailed — unlike in groups A and B. At the same time, initial manifestations of DD in the form of impaired LV relaxation were found in all groups, indicating the redistribution of transmitral flow toward the atrial component. DD progression led to changes in blood flow only in 2% of patients (n = 2) in group B and 4.8% of patients (n = 8) in group C, which was associated with increased LA pressure. LVH was found in 43.2% of patients (n = 44) in group A, 67.4% of patients (n = 66) in group B, and 83.3% of patients (n = 140) in group C. Analysis of LV remodeling types revealed an increase in LV concentric hypertrophy cases depending on OSA severity.

Development of a Model of LVH Probability in Patients with OSA

To establish the predictors/signs that have the best influence on event probability prediction, we performed preliminary statistical analysis. When developing a model of logistic regression, the method of step-by-step elimination of signs was used. The method was performed for all patients aged 46.0 [42; 49] years, with BMI of 33.3 [31.7; 35.3] kg/m².

Table 5. *Mathematical model: time on saturation less than 90%, Epworth sleepiness scale*

Logarithmic likelihood — 2 null model	**453,915**
Logarithmic likelihood — 2 complete model	135,875
Chi-square	318,040
df (degrees of freedom)	2
Level of significance	**P <0,0001**
Cox & Snell R Square	0,5786
Nagelkerke R2	0,8164

We formulated 74 logistic regression equations (based on the number of possible predictors) that assess the possibility of LVH in patients with OSA in order to find a diagnostic rule. Then, two predictors with the highest weight (out of 74 signs) were identified. The following parameters had the greatest prognostic weight: TSat90% — time for saturation less than 90%; ESS — Epworth Sleepiness Scale (points). The results are shown in Table 5.

The likelihood value was a negative double value of the logarithm of the similarity function (–2LL) that was highly significant during the test (after adding influence variables, –2LL was 135.875, which was 318.040 less than the baseline value). This virtually meant that a combination of predictors significantly improves the model. Cox/Shell R^2 ratios and Nagelkerke R^2 obtained from the ratio of likelihood functions demonstrated a high predictive value of this model of 81.64%. Moreover, $\chi 2$ predictors with a level of 318.040 at 2 degrees of freedom ($p < 0.0001$) convincingly demonstrated a high correlation of predictors with the probability of LVH detection in a patient with OSA of different severity. A summary for each variable of this predictive model is shown in Table 6.

According to the model developed, when the threshold value for ESS increases, the probability of LVH increases by 2.79 times (with a fixed value of another predictor), allowing to establish LVH in 93.75% of OSA cases reliably (AUC = 0.975; SD = 0.00741; CI 95% [0.953; 0.988]). The area under the ROC curve (AUC) with a level of 0.975 indicates the excellent quality of the model, its high sensitivity and specificity (Fig. 1).

We set «the cut-off levels» for ESS at 10 points and for TSat90% at 5.2%. This means that each predictor above these levels is already sufficient to predict LVH (ESS has sensitivity of 89.4%; specificity of 92.9%; TSat90% has sensitivity of 93.7%; specificity of 87.6%), and their combination allows not to take into account the «cut-off level» (it works for any value of the parameter) with sensitivity of 93.7% and specificity of 93.8% (Fig. 2). Therefore, there are

Table 6. *MODEL: coefficients and standard errors*

Variable	*Ratio*	*SE*	*P*	*OR*	*CI 95%*
TSat90%	0,21717	0,043	<0,0001	1,24	[1,14; 1,35]
ESS	1,02658	0,156	<0,0001	2,79	[2,06; 3,79]
Constant	-11,48453	1,563	<0,0001	-	-

Note: Definition of abbreviations: SE — standard error; P — significance level; OR — odds ratio; CI — confidence interval; TSat90% — night time spent with oxygen saturation below 90%; ESS — Epworth Sleepiness Scale (points)

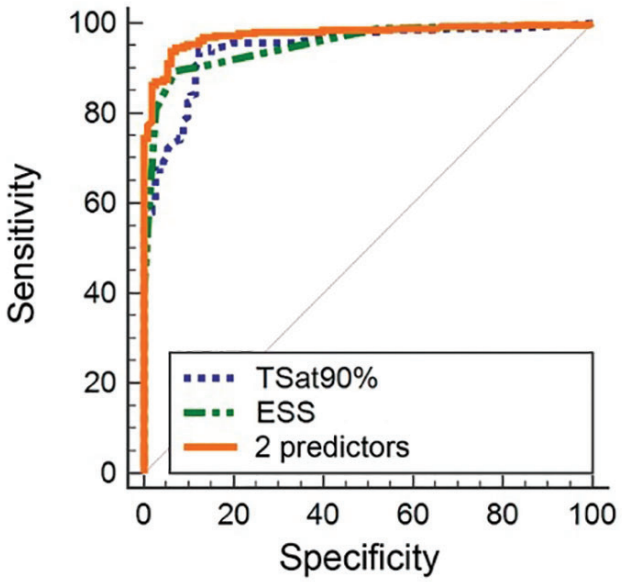

Figure 1. *Graphical representation of the sensitivity and specificity of a model using 2 predictors. Definition of abbreviations: TSat90% – night time spent with oxygen saturation below 90%; ESS – Epworth Sleepiness Scale (points); Orange line – predictive probability of 2 predictors*

objective prerequisites for developing a model for predicting LVH using ESS (patient questionnaire) and TSat90% (computer somnography) in patients with OSA of any severity.

During this work, we created a model for predicting LVH described by the following equation:

$$\mathbf{Z = (-11{,}48453) + 1{,}02658 \times (E) + +0{,}21717 \times (T)}$$

where «Z» is the sum of the numerical values of signs; «E» is the number of points according to the Epworth Sleepiness Scale, «T» is the time for saturation less than 90% (% of total sleep time).

The sum (Z) is equal to the numerical value of signs multiplied by the discriminant coefficient of the sign (1.02658 for the number of points on the ESS Sleepiness Scale and 0.21717 for TSat90%) and summed with a constant (–11.48453). Given the logistic function of the following type: $f(z) = \frac{1}{1+e^z}$, where e = 2.71828947 (base of natural logarithm), we can calculate the probability of LVH using "the probability formula" [15]:

$$p = \frac{e^z \times 100}{1 + e^z} = \frac{e^{(-11{,}48453)+1{,}02658\times(E)+0{,}21717\times(T)} \times 100}{1 + e^{(-11{,}48453)+1{,}02658\times(E)+0{,}21717\times(T)}}$$

Probability ρ > 50% shows a high risk of LVH in a patient with OSA.

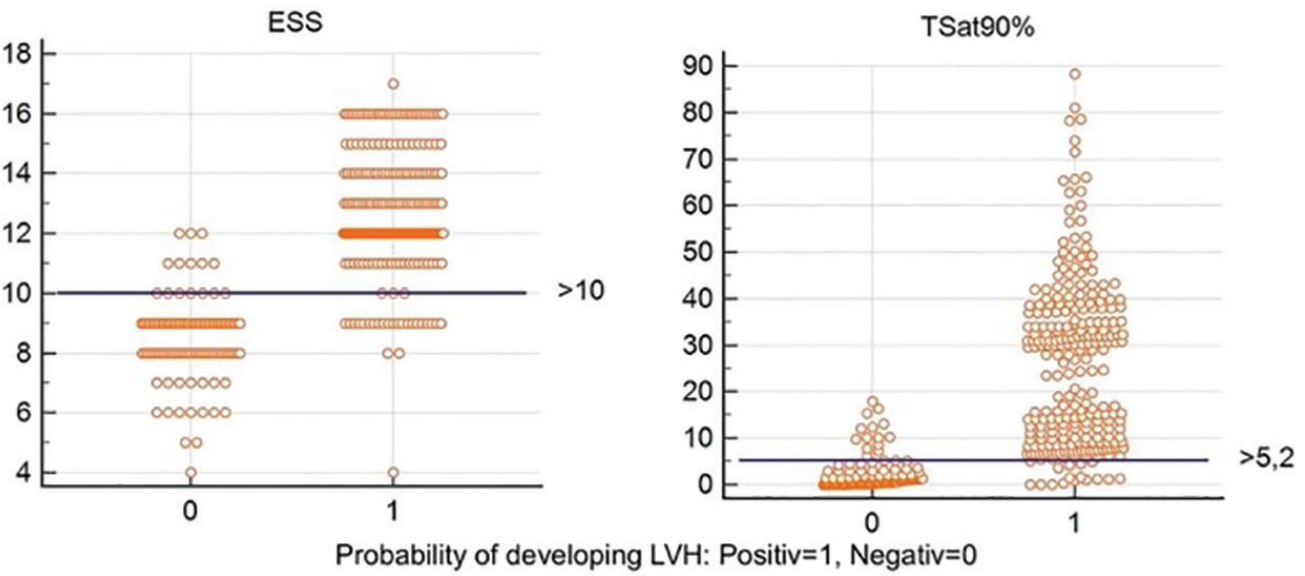

Figure 2. *Graphical representation of the «feature cut-off threshold» for 2 predictors. Definition of abbreviations: TSat90% – night time spent with oxygen saturation below 90%; ESS – Epworth Sleepiness Scale (points); LVH – left ventricular hypertrophy*

Clinical Examples of LVH Probability Calculation

Let us consider the data of a patient with OSA, male, 42, who has 16 points on the ESS Sleepiness Scale (during the survey) and TSat90% = 8.83% (according to the results of computer somnography).

$$Z = (-11{,}48453) + 1{,}02658 \times 16 + \\ + 0{,}21717 \times 8{,}83 = 6{,}86$$

$$p = \frac{e^z \times 100}{1+e^z} = \frac{2{,}71828947^{(6{,}86)} \times 100}{1+2{,}71828947^{(6{,}86)}} = \\ = \frac{953.38545294278 \times 100}{1+953.38545294278} = \frac{95338.545294278}{954.38545294278} = \\ = 99.9\ (\%)$$

The risk of LVH probability in this patient with OSA is 99.9% (> 50%) — **HIGH.**

Another patient with OSA, male, 49, with 5 ESS points (during the survey) and TSat90% = 1.05% (according to the results of computer somnography).

$$Z = (-11{,}48453) + 1{,}02658 \times 5 + \\ + 0{,}21717 \times 1{,}05 = -6{,}12$$

$$p = \frac{e^z \times 100}{1+e^z} = \frac{2{,}71828947^{(-6{,}12)} \times 100}{1+2{,}71828947^{(-6{,}12)}} = \\ = \frac{0.0021984 \times 100}{1+0.0021984} = \frac{0.21984}{1.0021984} = 0.22\ (\%)$$

The risk of LVH probability in this patient with OSA is 0.22% (< 50%) — **LOW.**

Results and Discussion

When a patient with OSA develops a persistent "vicious loop" of systemic inflammation, chronic damage to vital organs and systems develops. Results of a series of studies revealed that the heart and blood vessels are the most exposed organs. The relationship between OSA and cardiovascular conditions such as resistant arterial hypertension (RAH), atrial fibrillation (AF), and chronic heart failure (CHF) was confirmed in large prospective clinical studies [2, 3]. In our opinion, left ventricular myocardial hypertrophy (LVH), increased left ventricular myocardial mass and its structural remodeling as a result of overload by volume/pressure in patients with OSA, can be considered as the best marker of such cardiovascular risks. Despite the high accuracy and diagnostic value of cardiac magnetic resonance imaging (cMRI) as a universal standard for LVH diagnosis, its low accessibility and high cost in real clinical practice make urgent the search for alternative approaches, including medical prediction models. Our proposed model is based on a carefully planned analysis of clinical and instrumental data that can be performed in an outpatient and inpatient setting. Moreover, the predictors we defined, i.e. TSat90% — time for saturation less than 90% (CSG parameter) and ESS — sleepiness according to the Epworth scale (questionnaire parameter), not only have high sensitivity and specificity of LVH prognosis in patients with OSA of different severity, but also allow the practitioner to change the diagnostic and treatment strategy towards early prescription and extending of combination therapy of obstructive sleep apnea.

Author Contribution:

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

M.V. Gorbunova (ORCID: https://orcid.org/0000-0002-2039-0072): contribution to the development of the concept and design, the author's role in the collection, analysis and interpretation of data, the author's consent to be responsible for all aspects of the work

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

V. S. Borovitsky (ORCHID): the role of the author in conducting medical statistical analysis, responsibility for building a mathematical model and regression equations

Zh. K. Naumenko (Scopus Author ID: 687383, ORCID: https://orcid.org/0000-0002-4804-6142): the role of the author in conducting all types of ultrasound examination of patients and interpreting the data obtained

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

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DOI: 10.20514/2226-6704-2020-10-6-468-474

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КОМПЛЕКСНАЯ ОЦЕНКА ФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ТОНКОЙ КИШКИ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ

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Assessment of the Functional Status of the Small Intestine in Patients with Non-Alcoholic Fatty Liver Disease

Резюме

Цель работы. Комплексное исследование функционального состояния тонкой кишки и изучение сопряженности его нарушений с развитием неалкогольной жировой болезни печени. **Материалы и методы.** Обследовано 86 больных неалкогольной жировой болезнью печени на стадии стеатоза и стеатогепатита по результатам ультразвукового исследования печени на аппарате «SONIX OP» (Канада) и теста FibroMax компании BioPredictiv (Париж, Франция). Пациентам проводилось исследование глюкозы сыворотки крови на анализаторе «Huma Star 600» (Германия) и инсулина методом иммуноферментного анализа. Рассчитывался показатель инсулинорезистентности HOMA-IR. Для определения нарушений полостного пищеварения в тонкой кишке проводили нагрузочный тест с растворимым крахмалом, мембранного пищеварения — с сахарозой, всасывания — с глюкозой. Избыточный бактериальный рост определяли с использованием водородного дыхательного теста на анализаторе ЛактофаН2 компании АМА (Санкт-Петербург). Для оценки толстокишечной микрофлоры проводили посев кала на дисбиоз. **Результаты.** По клиническим данным, у пациентов с неалкогольной жировой болезнью печени поражение тонкой кишки протекает в стертой форме, однако при исследовании ее функционального состояния выявляется существенное снижение полостного и мембранного пищеварения, усиление всасывания. У обследованных больных констатировано повышение инсулина сыворотки крови по сравнению с контрольной группой (16,64±0,78 мкМЕ/мл против 10,46±0,56 мкМЕ/мл, p <0,0001). Индекс HOMA-IR также был увеличен у пациентов по сравнению с контрольной группой (2,84±0,11 против 2,05±0,07, p <0,0001). Избыточный бактериальный рост был диагностирован у 62 (72%) больных, при этом при стеатозе печени — у 33 (55%), при стеатогепатите 1 степени активности — у 11 (61,1%), при стеатогепатите 2 степени — у 6 (66,7%), при стеатогепатите 3 степени — у 2 (100%) пациентов. По результатам посева кала дисбиоз был выявлен у 56 (65,1%) пациентов. При проведении корреляционного анализа выявлены отрицательные связи между степенью избыточного бактериального роста и полостным пищеварением, между степенью избыточного бактериального роста и мембранным пищеварением, положительная связь — между степенью избыточного бактериального роста и всасыванием. **Заключение.** Неалкогольная жировая болезнь печени сопровождает-

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ся нарушениями пищеварительной и резорбтивной функций тонкой кишки, развитием дисбиоза. Эти нарушения нередко носят субклинический характер и могут быть выявлены и оценены после специальных исследований.

Ключевые слова: *неалкогольная жировая болезнь печени, мальабсорбция, избыточный бактериальный рост*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 07.09.2020 г.

Принята к публикации 10.11.2020 г.

Для цитирования: Вахрушев Я.М., Лукашевич А.П. КОМПЛЕКСНАЯ ОЦЕНКА ФУНКЦИОНАЛЬНОГО СОСТОЯНИЯ ТОНКОЙ КИШКИ У ПАЦИЕНТОВ С НЕАЛКОГОЛЬНОЙ ЖИРОВОЙ БОЛЕЗНЬЮ ПЕЧЕНИ. Архивъ внутренней медицины. 2020; 10(6):468-474. DOI: 10.20514/2226-6704-2020-10-6-468-474

Abstract

The aim. A comprehensive study of the functional state of the small intestine and the study of the relationship of its disorders with the development of non-alcoholic fatty liver disease. **Materials and methods.** 86 patients with non-alcoholic fatty liver disease at the stage of steatosis and steatohepatitis were examined according to the results of ultrasound examination of the liver using the SONIX OP apparatus (Canada) and the FibroMax test of BioPredictiv company (Paris, France). Patients underwent a blood glucose test using an Huma Star 600 analyzer (Germany) and insulin using an enzyme-linked immunosorbent assay. The HOMA-IR insulin resistance index was calculated. In order to determine abnormal digestive disorders in the small intestine, a stress test was performed with soluble starch, membrane digestion with sucrose, absorption with glucose. IDBs were evaluated using a hydrogen breath test on a LactofN2 apparatus from the AMA firm (St. Petersburg). To assess colonic microflora, stool was sown for dysbiosis. **Results.** According to clinical data, in patients with non-alcoholic fatty liver disease, damage to the small intestine occurs in a non-manifest form. However, in the study of the functional state of the small intestine in patients, a significant decrease in cavity and membrane digestion, increased absorption are detected. In patients with non-alcoholic fatty liver disease, an increase in blood insulin was observed compared with the control group (16,64±0,78 μIU/ml versus 10,46±0,56 μI/ml, p=0,000002). The HOMA-IR insulin resistance index was also increased in patients compared with the control group (2,84±0,11 versus 2,05±0,07, p=0,00003). Excessive bacterial growth was diagnosed in 62 (72%) of patients with non-alcoholic fatty liver disease, while with liver steatosis — in 33 (55%), with steatohepatitis 1 degree of activity — in 11 (61,1%), with steatohepatitis 2 degrees — in 6 (66,7%), with steatohepatitis 3 degrees — in 2 (100%) of patients. According to the results of stool stool, dysbiosis was detected in 56 (65,1%) of patients with non-alcoholic fatty liver disease. A correlation analysis revealed negative relationships between the severity of excessive bacterial growth and digestive digestion, between the severity of excessive bacterial growth and membrane digestion, and a positive relationship between the severity of excessive bacterial growth and absorption. **Conclusion.** Non-alcoholic fatty liver disease is accompanied by disorders of the digestive and resorptive functions of the small intestine, and the development of dysbiosis. These disorders are often subclinical in nature and can be identified and evaluated after special studies.

Key words: *non-alcoholic fatty liver disease, malabsorption, excessive bacterial growth*

Conflict of interests

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

Sources of funding

The authors declare no funding for this study

Article received on 07.09.2020

Accepted for publication on 10.11.2020

For citation: Vakhrushev Ya.M., Lukashevich A.P. Assessment of the Functional State of the Gut in Patients with Non-Alcoholic Fatty Liver Disease. The Russian Archives of Internal Medicine. 2020; 10(6): 468-474. DOI: 10.20514/2226-6704-2020-10-6-468-474

ALT — alanine aminotransferase, AST — aspartate aminotransferase, EBG — excessive bacterial growth, NAFLD — non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease [1–5]. NAFLD includes fatty degeneration, fatty degeneration with inflammation and hepatocyte damage — non-alcoholic steatohepatitis and fibrosis with possible progression to liver cirrhosis [6]. Despite the active study of various factors contributing to NAFLD, many aspects of its pathogenesis are still not fully clear.

Information on the possible significance of intestinal dysbiosis in the development of NAFLD has emerged in recent times [3, 7, 8]. At the same time, there are no comprehensive studies on intestinal microbiota, although intestinopathy may be a risk factor for metabolic liver disorders. Solving the problem from this point of view would allow studying the functional relationships of the liver and intestines with NAFLD.

The **objective of our work** is a comprehensive study of the functional status of the small intestine and the study of the relationship between its disorders and NAFLD.

Materials and methods

The analysis included 86 patients with NAFLD; 60 of them with hepatic steatosis (69.8%), and 26 with steatohepatitis (30.2%). As for disease activity, steatohepatitis of grade I was found in 18 (69.2%) patients, grade II — in 6 (23.1%) patients, and grade III — in 2 (7.7%) patients, respectively. The mean age of the patients was 46.3 ± 7.5 years. Sixty-four women (74.4%) and 22 (25.6%) men were examined. The mean age of female patients was 49.1 ± 5.6 years, and of the male patients — 41.2 ± 6.3 years.

Inclusion criteria: age 18–60 years, NAFLD at the stage of steatosis and steatohepatitis according to the results of liver ultrasound using the SONIX OP device (Canada). Ultrasonic signs of NAFLD included an enlarged liver, increased liver echogenicity compared to the echogenicity of kidneys, relatively reduced density of the liver compared with that of the spleen (liver spleen index less than 1), decreased sound conductivity, and difficult visualization of the branches of hepatic and portal veins. Steatohepatitis activity was determined by biochemical blood tests for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) using the Huma Star 600 apparatus (Germany). Assessment of the extent of liver fibrosis was carried out by sonoelastography using the AIXPLORER analyzer (France) and FibroTest and FibroMax tests manufactured by BioPredictiv (Paris, France).

Exclusion criteria: liver injury of another etiology (alcoholic, drug, viral, autoimmune), inflammatory bowel diseases, pregnancy and lactation, cancer, mental disorders.

Patients took a serum glucose test using the Huma Star 600 blood analyzer (Germany). Insulin level in blood serum was determined by enzyme immunoassay using monoclonal antibodies from DRG Insulin ELISA standard set of reagents. In order to determine the compensable degree of increased insulin level, the HOMA-IR insulin resistance index was calculated using the following formula: [fasting insulin (IU/ml) × fasting glucose (mmol/l)]/22.5.

In addition to clinical data, results of the study of the stages of the digestive process and the state of intestinal microflora were used to assess the functional status of the small intestine. In order to determine abnormalities of cavitary digestion, membrane digestion and absorption in the small intestine, stress tests were performed with polysaccharide (soluble starch), disaccharide (sucrose) and monosaccharide (glucose), respectively. All stress tests were performed the same way: first, fasting glucose level in capillary blood was determined, then patients took per os 50 g of soluble starch, sucrose or glucose dissolved in 200 ml of water, then the glycemia level was re-evaluated after 30, 60 and 120 minutes using the EKSAN-G device with MG-1 glucose oxidase membrane.

Excessive bacterial growth (EBG) was defined using a hydrogen breath test performed on the Lactofan2 device manufactured by AMA (St. Petersburg). First, the fasting concentration of hydrogen in expired air was measured. Then, patients took per os 20 g of lactulose dissolved in 200 ml of water. Hydrogen concentration was measured every 20 minutes for 2 hours. The test result was considered positive with an increase in hydrogen gradient of more than 10 ppm during the 1st hour of the study [9]. The severity of EBG was evaluated depending on hydrogen concentration: grade 1 — increase from 10 to 50 ppm, grade 2 — from 50 to 100 ppm, grade 3 — more than 100 ppm [10].

The state of colonic microflora was evaluated by the concentration of E. coli, Streptococci, Enterococci, Bifidobacteria, Lactobacilli, Staphylococcus aureus, yeast-like fungi, Proteus, Klebsiella, Clostridia, Pseudomonas aeruginosa and other opportunistic microorganisms in 1 g of feces [11]. The severity of dysbiosis was evaluated according to the classification developed by I. B. Kuvaeva and K. S. Ladodo (1991) [12].

Data obtained during this study were compared with the parameters of the control group that included 30 healthy individuals aged 18 to 60 years.

Patients were enrolled in the study after signing a Patient Informed Consent form per the order No. 390n of the Ministry of Health and Social Development of the Russian Federation of April 23, 2012 (registered by the Ministry of Justice of the Russian Federation on May 5, 2012, under No. 24082), in compliance with ethical principles.

Data analysis was performed using StatSoft Statistica 10.0.1011. Normality of distribution was checked with Kolmogorov — Smirnov and Shapiro — Wilk tests; equality of variances was checked with Levene's test. Most samples were close to normal distribution. Therefore, statistical methods for parametric distributions were used. A correlation analysis method with the calculation of Pearson's linear correlation coefficient *(r)* was used to perform dependency analysis. Statistical significance of differences (p) in quantitative values between independent groups was carried out using Student's t-test for independent samples. T-test for dependent samples was used for dependent groups. The data are presented as M ± SD, where M is the mean value, and SD is the standard deviation. Differences between the groups were considered statistically significant with a probability of the valid null hypothesis of no differences between the groups (p) < 0.05.

Results

Patients complained of discomfort and pain in the right hypochondrium — 22 (25.6%), in the paraumbilical area — 24 (27.9%), and in the large intestine area — 14 (16.3%). The following dyspeptic symptoms were mentioned: bitter taste in the mouth — in 11 (12.8%) patients, nausea — in 14 (16.3%) patients, epigastric burning — in 10 (11.6%) patients, flatulence — in 32 (37.2%) patients, constipation — in 20 (23.3%) patients, diarrhea — in 15 (17.4%) patients, a combination of constipation and diarrhea — in 7 (8.1%) patients. According to physical examination, a coated tongue was found in 67 (77.9%) patients, tender abdomen in the right hypochondrium — in 18 (20.9%) patients, in the paraumbilical area — in 28 (32.6%) patients, and in the large intestine area — in 12 (14.0%) patients. An enlarged liver was observed in 26 (30.2%) patients. Thus, NAFLD is accompanied by clinical signs of liver and intestinal damage.

The study of the functional status of the small intestine revealed no significant differences depending on the stage of NAFLD. However, changes were found at all 3 stages of the digestive process (Table 1).

The test with soluble starch showed a significantly reduced increase in glycemia level in patients with NAFLD compared to the control group, indicating the inhibition of cavitary hydrolysis in the small intestine. The test with sucrose also revealed a reduced increase in glycemia level in patients with NAFLD compared to the control group, indicating the insufficiency of membrane hydrolysis in the small intestine. The increase in glycemia level during the test with glucose in patients with NAFLD was significantly higher compared to the control group, indicating increased absorption in the small intestine. Glycemia in patients with NAFLD did not decrease to baseline after 120 minutes from the beginning of the study.

The test for serum insulin level in patients with NAFLD showed basal insulin of 16.64 ± 0.78 μIU/ml vs 10.46 ± 0.56 μIU/ml in the control group (p < 0.0001). To analyze the obtained data, the HOMA-IR insulin resistance index was calculated, and its increase was observed in patients with NAFLD compared to the control group (2.84 ± 0.11 vs 2.05 ± 0.07, p < 0.0001).

A coprology test showed steatorrhea in 50 (58.1%) patients with NAFLD, creatorrhea in 22 (25.6%) patients, amylorrhea in 34 (39.5%) patients.

EBG was diagnosed in 62 (72%) patients with NAFLD (there was an increase in hydrogen content in expired air of more than 10 ppm compared with the baseline before the 60th minute of the study). Considering cases of liver steatosis, EBG was found in 33 (55%) patients, in cases of steatohepatitis of activity grade 1 — in 11 (61.1%) patients, in cases of steatohepatitis of activity grade 2 — in 6 (66.7%) patients, in cases of steatohepatitis of activity grade 3 — in 2 (100%) patients.

Overall, the increase in hydrogen concentration in expired air in patients with NAFLD by the 60th minute of the study was 64.3 ± 7.8 ppm vs 24.4 ± 6.5 ppm in the control group (p < 0.0001). EBG analysis in terms of severity demonstrated grade 1 in 40 (64.5%) patients, grade 2 in 19 (30.7%) patients, and grade 3 in 3 (4.8%) patients. At the same time, there was no reliable relationship between the stage of NAFLD and the severity of EBG.

During the EBG test, two peaks of hydrogen concentration — small intestinal and large intestinal — were observed in 24 (38.7%) patients with NAFLD, i.e., there was EBG along with retained ileocecal valve function (Fig. 1). Thirty-eight (61.3%) patients demonstrated a continuous increase in hydrogen concentration, i.e., EBG with ileocecal insufficiency (Fig. 2).

Correlation analysis with Pearson's linear correlation coefficients revealed negative associations

Table 1. *The state of the hydrolysis-resorption process in the small intestine in patients with non-alcoholic fatty liver disease (mmol/l)*

Loading tests	Test period	Patients with steatosis (n=60) M±SD	Patients with steatohepatitis (n=26) M±SD	Group of control (n=30) M±SD
With starch	On an empty stomach	5,67±0,1** p^2 <0,0001	5,54±0,12** p^2 <0,0001	4,6±0,49
	In 30 minutes after load	5,98±0,2* ** p^1=0,002 p^2 <0,0001	5,74±0,21* ** p^1=0,003 p^2 <0,0001	6,95±0,18* p^1 <0,0001
	In 60 minutes after load	5,77±0,2* p^1=0,04	4,79±0,35* p^1 <0,0001	5,87±0,38* p^1 <0,0001
	In 120 minutes after load	4,93±0,25* p^1 <0,0001	4,79±0,38* p^1=0,0015	4,34±0,36* p^1=0,0008
With sucrose	On an empty stomach	5,93±0,11** p^2 < 0,0001	5,68±0,12** p^2 <0,0001	4,69±0,44
	In 30 minutes after load	7,02±0,88* p^1=0,005	6,93±0,67* p^1=0,002	6,89±0,18* p^1 <0,0001
	In 60 minutes after load	6,72±0,25* ** p^1 <0,0001 p^2 <0,0001	6,2±0,78	5,07±0,41
	In 120 minutes after load	4,97±0,16* ** p^1 <0,0001 p^2=0,0004	5,27±0,47** p^2=0,002	4,33±0,37
With glucose	On an empty stomach	5,41±0,1** p^2 <0,0001	5,67±0,1** p^2 <0,0001	4,71±0,2
	In 30 minutes after load	8,8±0,2* ** p^1 <0,0001 p^2 <0,0001	8,94±0,15* ** p^1 <0,0001 p^2 <0,0001	7,0±0,17* p^1 <0,0001
	In 60 minutes after load	7,9±0,33* ** p^1 <0,0001 p^2 <0,0001	6,56±0,47* p^1=0,002	5,91±0,17* p^1 <0,0001
	In 120 minutes after load	6,18±0,19* ** p^1 <0,0001 p^2 <0,0001	6,34±0,22* ** p^1=0,0004 p^2 <0,0001	4,5±0,32

Note: * — reliable changes compared to baseline (p^1 <0,05); ** — reliable changes compared to group of control (p^2 <0,05); n — number of observations

between the severity of EBG and cavitary digestion in the small intestine (r = –0.68, p < 0.05) and between the severity of EBG and membrane digestion (r = –0.53, p < 0.05). A positive association was found between the severity of EBG and absorption (r = 0.44, p > 0.05).

Results of stool culture revealed dysbiosis in 56 (65.1%) patients with NAFLD. At the same time, a decrease in the amount of obligate microflora was observed — bifidobacteria less than 10^9 CFU/g in 22 (39.3%) patients and lactobacilli less than 10^7 CFU/g in 20 (35.7%) patients. Lactose-negative and hemolytic Escherichia coli were obtained in diagnostically significant titer — in 15 (26.8%) and 12 (21.4%) with a decreased proportion of viable E. coli — in 18 (32.1%) patients, respectively. These or other pathogenic bacteria — staphylococci, yeast, clostridia and veillonella — were found in many patients.

Dysbiosis of grade 1 was diagnosed in 20 (35.7%) patients, grade 2 — in 25 (44.6%) patients, grade 3 — in 11 (19.6%) patients with NAFLD. At the same time, there was a positive association between the severity of dysbiosis and the stage of NAFLD (r = 0.54, p > 0.05). When conducting a correlation analysis between the severity of dysbiosis and the HOMA-IR index, a positive association was found (r = 0.72, p < 0.05), i.e., there is a direct relationship between the degree of intestinal microflora disturbance and the severity of insulin resistance.

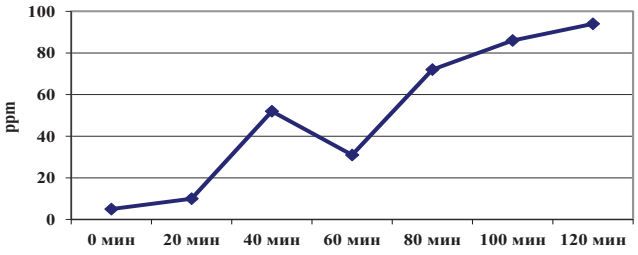

Figure 1. *Excessive bacterial growth with preserved function of the ileocecal valve*

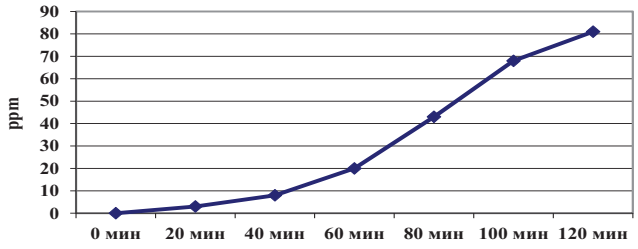

Figure 2. *Excessive bacterial growth with impaired function of the ileocecal valve*

Discussion

Patients with NAFLD are characterized by increased glucose resorption in the intestine in connection with decreased abdominal and parietal digestion. An increase in glucose absorption can be explained by increased blood insulin level and existing insulin resistance. Increased permeability of the intestinal epithelium in NAFLD may also occur due to a decreased level of ZO-1, one of the tight junction proteins of the intestinal epithelium [7]. Our data are confirmed by literature sources; according to the latter, contamination of the small intestine by pathogenic and opportunistic microorganisms leads to decreased digestive and membrane digestion, impaired enterohepatic circulation with the formation of toxic metabolites, which causes increased permeability of intestinal wall for toxins, and decreased barrier functions of liver and intestine [3].

During our study, EBG was found in most patients, and its severity correlated with the increasing severity of NAFLD. Similar data were obtained by other researchers, who found that EBG is more common in patients with steatohepatitis than in the average population and varies from 50% to 77.8% [7, 10, 13]. The reasons behind EBG in NAFLD are unknown. There is an ongoing discussion over evidence of decreased gastrointestinal motility in patients with NAFLD. The rate of orocecal transit in patients with NAFLD was slow in 22% of cases. That may be one of the conditions causing the development and progression of EBG in the small intestine [14]. Dysfunction of the ileocecal valve is critical for the development and progression of EBG since, in this situation, fecal microflora retrogradely colonizes the small intestine [2].

According to our studies, pathogenic microflora prevails in the structure of microbiota in cases of EBG. Earlier, A. A. Kozhevnikov et al. (2017) found that 16S rRNA sequencing in children with hepatic steatosis revealed an increased level of Escherichia coli compared to the control group [15]. According to E. Yu. Plotnikova (2017), patients with steatohepatitis and obesity showed an increase in the Bacteroidetes level and a decrease in the Firmicutes level at the level of phyla compared to healthy individuals. The Firmicutes level is reduced in patients with steatohepatitis and obesity mainly due to two families: Lachnospiraceae and Ruminococcaceae, with the largest decrease in Blautia and Faecalibacterium genera. An increased level of Proteobacteria is associated with an increase in the Enterobacteriaceae level (especially Escherichia) [8]. Qualitative and quantitative disorders in the composition of microbiota are considered an inducer of TNFα-stimulated inflammatory response in the liver [3, 7, 8]. Several mechanisms through which EBG contributes to the progression of NAFLD are proposed: excessive amount of bacterial endotoxins in the blood (lipopolysaccharide, peptidoglycans, lipoteichoic acid, bacterial flagellin, non-methyl fragments of bacterial DNA), increased permeability of the intestinal wall, and increased production of endogenous ethanol [13]. The close functional relationship between the state of the liver and intestinal microflora is also evidenced by the research conducted by A. A. Kozhevnikov et al. (2017), when probiotics containing Lactobacillus were used in children with NAFLD, resulting in a decreased ALT level in 80% of cases [15].

Conclusion

NAFLD is often and expectedly accompanied by the dysfunction of the small intestine, in particular, abnormal digestion and absorption, as well as dysbiosis. These disorders are often subclinical and can be found and assessed only after specific tests. The study of enteric functions broadens our understanding of the pathogenesis of NAFLD and suggests the need for not only NAFLD management but also the correction of enteric functions and restoration of microbiocenosis.

Author Contribution:

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

Ya.M. Vakhrushev (ORCID ID: https://orcid.org/0000-0001-9424-6316): development of the concept and design of the study; checking critical intellectual content; final approval of the manuscript for publication

A.P. Lukashevich (ORCID ID: https://orcid.org/0000-0003-4634-2658): collection, analysis and interpretation of data; justification and writing of the manuscript

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DOI: 10.20514/2226-6704-2020-10-6-475-482

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ДИАГНОСТИКА СТРЕПТОКОККОВОЙ ИНФЕКЦИИ ВРАЧАМИ ОТДЕЛЕНИЯ НЕОТЛОЖНОЙ МЕДИЦИНСКОЙ ПОМОЩИ: ПЕРВЫЙ ОПЫТ ПРИМЕНЕНИЯ «СТРЕПТАТЕСТА»

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Diagnostics of Streptococcal Infection by Emergency Department Doctors: First Experience of Application of the «Streptatest»

Резюме

Эффективность лечения острого тонзиллита напрямую зависит от этиологической диагностики и соблюдения принципов рациональной этиотропной антибактериальной терапии. В настоящее время в качестве единственного показания к назначению системной антибактериальной терапии рассматривается стрептококковый генез воспаления. Представлены результаты клинико-статистического анализа вызовов к пациентам с острым тонзиллитом и проведением экспресс-диагностики стрептококковой инфекции с использованием «Стрептатеста». За период с 30.07.2018г по 30.11.2018г врачами бригад отделения неотложной медицинской помощи взрослому и детскому населению проведена экспресс-диагностика β-гемолитического стрептококка группы А у 252 пациентов с острым тонзиллитом с жалобой на «боль в горле», возраст которых варьировал от 3 до 44 лет. Данная экспресс-диагностическая система «Стрептатест», основанная на методе иммунохроматографического анализа, позволила в ранние сроки выявить у 117 (46,4%) пациентов β-гемолитический стрептококк группы А и своевременно назначить этиотропную антибактериальную терапию. Вторая группа составила 135 (53,6%) пациентов с полученным отрицательным результатом экспресс-теста «Стрептатест». В группе с положительным результатом проведения экспресс-теста основную часть составили дети дошкольного и школьного возраста — 92 (78,6%) пациента. У 114 (97,5%) пациентов с выявленным β-гемолитическим стрептококком группы А клинические симптомы по шкале Центора в модификации МакАйзека оценены от 3 до 5 баллов. Ранняя этиологическая верифи-

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кация острого тонзиллита позволила соблюдать стратегию предупреждения распространения антимикробной резистентности и снижения устойчивости микроорганизмов к антибактериальным препаратам.

Ключевые слова: *скорая и неотложная медицинская помощь, β-гемолитический стрептококк группы А, «Стрептатест»*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 28.07.2020 г.
Принята к публикации 28.10.2020 г.

Для цитирования: Плавунов Н.Ф., Кадышев В.А., Ким С.С. и др. ДИАГНОСТИКА СТРЕПТОКОККОВОЙ ИНФЕКЦИИ ВРАЧАМИ ОТДЕЛЕНИЯ НЕОТЛОЖНОЙ МЕДИЦИНСКОЙ ПОМОЩИ: ПЕРВЫЙ ОПЫТ ПРИМЕНЕНИЯ «СТРЕПТАТЕСТА». Архивъ внутренней медицины. 2020; 10(6): 475-482. DOI: 10.20514/2226-6704-2020-10-6-475-482

Abstract

The effectiveness of the treatment of acute tonsillitis directly depends on the etiological diagnosis and adherence to the principles of rational etiotropic antibiotic therapy. Currently, streptococcal genesis of inflammation is considered as the only indication for the appointment of systemic antibiotic therapy. The article presents the results of clinical and statistical analysis of calls to patients with acute tonsillitis and express diagnostics of streptococcal infection using «Streptatest». For the period from 30.07.2018 until 30.11.2018 Doctors of the emergency department teams for adults and children performed express diagnostics of group A β-hemolytic streptococcus in 252 patients with acute tonsillitis complaining of «sore throat», whose age ranged from 3 to 44 years. This rapid diagnostic system «Streptatest», based on the method of immunochromatographic analysis, made it possible to identify as early as possible in 117 (46.4%) patients β-hemolytic streptococcus group A and promptly prescribe etiotropic antibiotic therapy to them. The second group consisted of 135 (53.6%) patients with a negative result of the «Streptatest» rapid test. In the group with a positive result of the express test, the main part was made up of children of preschool and school age — 92 (78.6%) patients. In 114 (97.5%) patients with diagnosed group A β-hemolytic streptococcus, clinical symptoms according to the McIsaac modified Centor scale were rated from 3 to 5 points. Early etiological verification of acute tonsillitis made it possible to follow the strategy of preventing the spread of antimicrobial resistance and reducing the resistance of microorganisms to antibacterial drugs.

Key words: *ambulance and emergency medical care, group A β-hemolytic streptococcus, «Streptatest»*

Conflict of interests

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

Sources of funding

The authors declare no funding for this study

Article received on 28.07.2020
Accepted for publication on 28.10.2020

For citation: Plavunov N.F., Kadyshev V.A., Kim S.S. et al. Diagnostics of Streptococcal Infection by Emergency Department Doctors: First Experience of Application of the «Streptatest». The Russian Archives of Internal Medicine. 2020; 10(6): 475-482. DOI: 10.20514/2226-6704-2020-10-6-475-482

AT — acute tonsillitis, EDAC — emergency departments for adults and children, GABHS — group A beta-hemolytic streptococcus

Introduction

Acute respiratory infections with damage to the upper respiratory tract play a leading role in the structure of seasonal incidence in both children and adults [1]. The most common pathogens of acute tonsillitis (AT) are respiratory viruses (adenoviruses, Epstein – Barr virus, enteroviruses), but others can also cause inflammation of the pharyngeal lymphatic ring and AT. Among bacterial pathogens that

cause respiratory pathologies, group A beta-hemolytic streptococcus (GABHS) is of primary importance; it is the causative agent of AT in 20–40% of cases in children and in 10–20% of cases in adults [1–3]. The probability of AT with streptococcal etiology is minimal in people younger than 3 years and older than 45 [4, 5].

The problem of AT is still relevant both from the professional and the general medical point of view due to the high incidence rate and unjustifiably high frequency of uncontrolled antibacterial treatment.

Most research is devoted to the study of the course of severe AT and emerging complications. However, mild and moderate forms of AT require a more differentiated approach to treatment and competent prescription of antibiotic therapy. Under these conditions, the etiological diagnosis of AT remains a serious issue and is rarely performed in an outpatient setting [6].

It is important to differentiate diseases caused by GABHS from other infections, including viral ones, in order to prescribe early and adequate antibiotic treatment. The conventional bacteriological test for the AT pathogens (the most reliable method) is difficult to perform due to specific cultivation conditions of streptococcus and the duration from 24 to 48 hours in a hospital laboratory. Rapid diagnosis of streptococcal infection using the Streptatest express diagnostic system can be performed within 5 minutes; it can be used during the examination of patients with AT by physicians of mobile emergency teams without additional equipment required [7].

The Streptatest express diagnostic system is a second-generation test based on immunochromatographic assay to determine a specific antigen of group A streptococcus using one oropharyngeal swab. The average specificity and sensitivity of this innovative test system is 95% and 97%, respectively [3]. The use of Streptatest by physicians of mobile emergency teams at the prehospital phase allows early detection of patients with GABHS, timely prescription of appropriate etiotropic antibacterial therapy, prevention of post-streptococcal complications, and ensures a favorable prognosis [8].

Over the last few years, clinical and paraclinical scales were proposed for scoring the probability of streptococcal infection. The most common one is McIsaac Modification of Centor Score (Score) [5]. Despite its widespread use, there is evidence of the low specificity of this method [8].

The **objective of the study** was to define the feasibility of using the Streptatest rapid diagnostic system to determine group A beta-hemolytic streptococcus *in vitro* in the context of emergency medical care by physicians of mobile emergency teams for adults and children of the State Budgetary Institution "A. S. Puchkov Emergency Medicine Station" of the Department of Health of Moscow (SBU "Puchkov EMS" of DHM).

Study objectives

1. To identify the prevalence of GABHS in patients with acute tonsillitis who called the emergency medical service for medical attention.
2. To determine the diagnostic accuracy of the McIsaac Modified Centor Score in the diagnosis of acute tonsillitis by the mobile teams of the Emergency Departments for Adults and Children (EDAC) in patients with a positive Streptatest rapid test result.
3. To perform the follow-up of patients with a positive Streptatest rapid test result.

Materials and methods

An open-label prospective observational study with a follow-up period of four months for the diagnosis of GABHS in patients with acute tonsillitis was conducted at SBU «Puchkov EMS» of DHM from July 30 to November 30, 2018. The 357 patients who called for medical attention (213 male and 144 female patients, mean age 29.16 ± 1.34 years) with a complaint of "sore throat" and an established diagnosis of «acute tonsillitis» received full medical care in accordance with "Standards for the Provision of Emergency Medical Care to Adults and Children by Emergency Care Teams" [9].

Rapid diagnosis of the etiology of acute tonsillitis was performed using Streptatest in 252 patients who met the following inclusion criteria: age between 3 and 44 years, no antibiotic therapy a week before the examination and at the time of visit, total assessment of clinical symptoms of AT according to McIsaac Modification of Centor Score of two or more points.

The study had the following exclusion criteria: patient younger than 3 years and older than 44; assessment of clinical symptoms of AT according to the McIsaac Modification of Centor Score of one point or less; antibacterial therapy at the time

of examination or within a week before using the Streptatest rapid test.

All patients signed written informed consent forms to undergo AT diagnosis using the Streptatest rapid test with the results recorded on an EDAC call card (recording form No. 110/u) and in the clinical and diagnostic evaluation record of individual examination of a patient diagnosed with acute tonsillitis using the McIsaac Modification of Centor Score and Streptatest express diagnostic system (see chart).

Before the beginning of this study, physicians were trained how to use Streptatest, interpret its results and the rules for filling out the medical record «Clinical and diagnostic evaluation of individual examination of a patient diagnosed with acute tonsillitis using the Score». The Score includes the following clinical symptoms of AT, each scoring 1 point: body temperature over 38 °C; no cough; enlargement and tenderness of submandibular lymph nodes; swelling of tonsils and the presence of exudate; age 3–14 years.

During the study, the patients' state was monitored; for this purpose, the information obtained from district city local clinics was analyzed. One day after being diagnosed with AT, patients were provided with case follow-up by a physician of a local city clinic. Analysis of information about the diagnosis established by the physician at the clinic, prescribed treatment and the presence of complications was carried out.

Antibacterial therapy was prescribed to all patients with a positive Streptatest result and also to patients with a negative rapid test result, with Score points higher than 3, and taking into account clinical symptoms indicating disease severity.

The study used the Streptatest express diagnostic system for *in vitro* determination of group A beta-hemolytic streptococcus (BIOSYNEX SA, France (Code according to All-Russian Classifier of Products by Type of Economic Activity-2 (OKP) 21.20.23.110).

The procedure for the Streptatest rapid test was as follows. First, an extraction reagent was prepared *in vitro*. Four drops of extracting reagent A were placed in an extraction tube, and four drops of extracting reagent B were added and then gently shaken to mix both solutions. The patient's tongue was held with a spatula and a sample was taken from palatine tonsils and pharynx with a special swab. The swab was put into a prepared extraction tube and swirled in the solution for one minute. The swab was then squeezed against the wall inside the tube and disposed of. A test strip was lowered into the tube to the extracting solution, and the result was analyzed after five minutes. There are two areas on test strip: test area and control area. The results were

date: _____ time: _____ Department No. _____ Team No.: _____ Call card No.

Table 1

Parameter	Score	If present, mark with "V"
Body temperature > 38 °C	1	
No cough	1	
Increased and tender cervical lymph nodes	1	
Swelling of tonsils and presence of plaques	1	
Age 3–14 years	1	
Age 15–44 years	0	
Age 45+ years	-1	
Total score		

Table 2

Centor McIsaac Score	Recommended therapy
1 point	No antibiotic required
2 points	Antibiotic at the discretion of physician
3–5 points	Antibiotic required

For differential diagnosis of viral and streptococcal tonsillopharyngitis according to the clinical picture, the Centor McIsaac Score is used.
Positive parameters in Table 1 should be marked with "V." Total score should be indicated in the "Total score" line.
Table 2 provides reference information on the interpretation of the Centor McIsaac Score.
Table 3 indicates the need for AB therapy depending on the Centor McIsaac Score.

Table 3

	Yes	No
In accordance with Centor McIsaac Score, antibiotic therapy required		

POSITIVE

Two colored lines in control and test areas. Even a pale line should be considered as a positive result.

NEGATIVE

One purple line in control area

If there are no lines, the test was performed incorrectly. The procedure should be repeated.

Table 4

Parameter	Positive	Negative
Streptatest rapid test		

* Mark with "V"

Table 5

	Yes	No
In accordance with rapid test result, antibiotic therapy required		

For differential diagnosis of viral and streptococcal tonsillopharyngitis, the Streptatest express diagnostic system is used.
In Table 4, positive (two lines) or negative (one line) test result should be marked with "V."
Table 5 indicates the need for AB therapy in accordance with the rapid test result.

Scheme. *Card of clinical and diagnostic assessment of individual observation of a patient diagnosed with acute tonsillitis (tonsillitis) using the Centor McIsaac scale and the «Streptatest» express diagnostic system*

interpreted based on the appearance of a purple line in the control area, indicating that the test was performed correctly. The absence of a line in the test area corresponded to a negative result, and one line — to a positive result, indicating the presence of GABHS [7].

Statistical processing of the results was carried out using mathematical statistics methods, Statistica 10.0 (StatSoft Inc. USA). Qualitative values were presented in absolute numbers (n) and percent (%) and compared by Pearson's χ^2 test. The following parameters were calculated from the data set: arithmetic mean of variation series (M) and its error (m), standard deviation (δ). White and Wilcoxon – Mann – Whitney nonparametric criteria were used; the significance of differences in data obtained was evaluated by Pearson's χ^2 test, $p < 0.05$ was considered as the significance level.

Results

Express diagnosis of streptococcal infection using Streptatest was performed in patients who met the inclusion criteria. During the study, EDAC physicians established the diagnosis of AT in 252 patients with various diseases of the upper respiratory tract, with complaints of "sore throat"; mean age was 13.1 ± 1.28 years (3 to 44 years). The ratio of male to female patients was 1.13:1, respectively.

Results of the rapid test allowed dividing patients into two groups. Group 1 included patients with AT and detected GABHS — 117 (46.4%) individuals; group 2 included patients with AT and a negative Streptatest rapid test result — 135 (53.6%) individuals.

According to the data shown in Table 1, a positive Streptatest result was most often observed in patients aged 3 to 29 years (113; 96.7%), mean age was 17.14 ± 0.62 years. Among the patients of group 2 (135 patients), children aged under 18 prevailed — 110 (81.5%) patients, mean age was 7.31 ± 0.72 years.

Group 1 included 67 (57.3%) male and 50 (42.7%) female patients. There were 68 male patients (50.4%) and 67 female patients (49.6%) in group 2. Patients of both groups were distributed by gender with no significant statistical difference ($p > 0.05$).

As shown in Table 2, patients of group 1 were diagnosed with streptococcal tonsillitis on average on the 3rd day of disease. The clinical picture of AT in most patients (102; 87.2%) included sore throat combined with febrile temperature with average duration of fever of 4.57 ± 0.32 days. The reaction of regional peripheral lymph nodes (submandibular, anterior and posterior cervical) was additionally evaluated. Enlarged lymph nodes were observed in 87 (74.4%) patients. Clinical symptoms in 114 (97.5%) patients with GABHS scored 3 to 5 points on the Score. All patients in this group were prescribed etiotropic antibacterial therapy according to the National Clinical Recommendations of the Ministry of Health of the Russian Federation «Acute tonsillopharyngitis» (2016) and Clinical Recommendations of the Ministry of Health of the Russian Federation «Acute tonsillitis in children» (2016) [8, 10].

Patients of group 2 were diagnosed with AT on average on the 4th day of disease. Febrile temperature was recorded in most patients (118; 88.1%), with average duration of 5.2 days. Clinical symptoms with 3 to 5 points according to the Score were observed in 129 (95.5%) patients. Antibiotic therapy was recommended in 79 (58.5%) patients. Systemic antibiotic therapy in cases of a negative Streptatest result is due to disease severity, long-term febrile fever, age-related features of patients, and present comorbidities [10].

Table 1. *Distribution of patients diagnosed with Acute tonsillitis by age*

The result is a rapid test	Age of patients						In total
	3-7 years	8-11 years	12-15 years	16-18 years	19-29 years	30-44 years	
Positive rapid test result (first group, **n=117**) absolute %	27 (23,1)	17 (14,5)	21 (18,0)	27 (23,1)	21 (18,0)	4 (3,3)	117 (46,4)
Negative rapid test result (second group, **n=135**) abs %	57 (42,2)	23 (17,1)	17 (12,6)	13 (9,6)	17 (12,6)	8 (5,9)	135 (53,6)
In total, **n=252** abs %	84 (33,3)	40 (15,9)	38 (15,1)	40 (15,9)	38 (15,1)	12 (4,7)	252 (100)

Table 2. *Criteria for the evaluation of the application of the rapid test «Streptatest»*

Group of patients	Age, years M±m	The time of diagnosis, days M±m	Febrile temperature		Score of the Centre scale of McIsaac		Antibacterial therapy	
			Frequency absolute %	Duration, days M±m	2 points absolute %	3-5 points absolute %	Recommended by a doctor absolute %	Not recommended by a doctor absolute %
Group 1 (n=117) positive result «Streptatest»	11,60±0,98	2,53±0,49	102 (87,2)	4,57±0,32	3 (2,5)	114 (97,5)	117 (100)	0
Group 2 (n=135) Negative result «Streptatest»	6,14±1,09	3,50± 0,32	119 (88,1)	5,22±0,54	6 (4,5)	129 (95,5)	79 (58,5)	56 (41,1)
Significance of differences	p =0,04	p =0,02	p =0,01	p =0,05	p =0,03	p =0,01	p =0,01	p =0,01

The clinical picture of AT in patients of both groups included plaques on the anterior surface of tonsils. Cough was observed in 3 (2.6%) patients of group 1 and in 9 (6.7%) patients of group 2.

There were 243 (96.4%) patients from both groups (group 1 — 114, group 2 — 129) with clinical symptoms that scored 3 to 5 points on the Score, who needed antibacterial therapy according to the study design. Results of rapid GABHS diagnosis revealed that 129 patients (53.1%) of group 2 required no antibiotic therapy.

Among 117 patients of group 1, 91 (77.8%) patients were examined by physicians of local city clinics; diagnosis of AT was confirmed in 79 patients (86.8%) and was not confirmed in 12 (13.2%) patients. In 64 (81%) patients, a starting antibacterial drug recommended by the EDAC physician (amoxicillin or amoxicillin clavulanate for 10 days) was administered. The average duration of administration of amoxicillin/ amoxicillin clavulanate recommended by EDAC physicians and continued in an outpatient setting in 49 (76.6%) patients was 8.3 ± 2.7 days. For the other 15 (23.4%) patients, outpatient physicians replaced the starting antibacterial therapy with macrolide drugs. No complications of AT were observed.

Follow-up history of 26 (22.2%) patients (adults — 19, children — 7) with streptococcal tonsillitis could not be traced due to the refusal of patients (or patients' parents) to be examined by a physician at the local city clinic.

Discussion

The study on collection and processing of data concerning the use of the Streptatest medical test in 252 patients with AT revealed a positive result in 117 (46.4%) patients. Most of this group were children — 92 (78.6%): of preschool age — 27 (23%) children (mean age 6.14 ± 0.34) and of school age — 65 (55.6%) (mean age 16.31 ± 0.78). The group of patients with a negative Streptatest result had 57 (42.2%) children of preschool age (mean age 4.18 ± 0.92 years) and 53 (39.2%) children of school age (mean age 10, 17 ± 0.13 years) (Table 3). The data obtained are consistent with the recommendations of the Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis (2012), which justifies the rapid test for children and adolescents but not for adults due to the relatively lower prevalence of GABHS-tonsillopharyngitis in older age [11].

Clinical symptoms corresponding to 4–5 points according to the most common McIsaac Score indicate the probability of AT with GABHS etiology of more than 50%. However, implementation of a number of clinical and paraclinical scales (Walsh, 1975; Breese, 1977; Centor, 1981; McIsaac, 1998) in clinical practice in many countries allowed to reduce the use of antibacterial drugs but did not solve the problem of identifying patients with streptococcal tonsillitis [4]. These data were confirmed in

Table 3. *Comparative distribution of patients diagnosed with Acute tonsillitis by age*

Group of patients	Age of patients		
	3-7 years absolute (%)	**7-18 years absolute (%)**	**19-44 years absolute (%)**
Group 1 (n=117) positive result «Streptatest»	27(23%)	65(55,6%)	25(21,4%)
Group 2 (n=135) Negative result «Streptatest»	57(42,2%)	53 (39,2%)	25 (18,5%)
Significance of differences	ρ =0,003	ρ =0,014	ρ =0,68

our study. In the group of patients with a negative Streptatest result (135 patients), patients with clinical symptoms scoring 3 to 5 points on the McIsaac Score were found in 95.5% (129 patients). The high frequency of clinical symptoms of AT using the Score in both groups clearly demonstrates the shortcomings of detecting AT with streptococcal etiology only in accordance with this Score.

Acute tonsillitis is one of the main reasons for prescribing antibiotic therapy at the prehospital stage. Most acute inflammatory diseases of the oropharynx are of viral etiology. Despite this, general practitioners in 95% of cases [4] prescribe antibiotic therapy. This is due to the difficulty in differential diagnosis between streptococcal tonsillitis and viral disease.

Experience of using rapid tests for GABHS in patients with AT in European countries (France, Finland) and the USA has reduced the frequency of unjustified prescription of antibiotics (in France by 41%) without an increase in complications [11]. In our study, there were 243 (96.4%) patients from both groups (group 1 (n = 117) — 114 (97.5%) patients, group 2 (n = 135) — 129 (95.5%) patients) with clinical symptoms scoring 3 to 5 points according to the Score, who needed antibacterial therapy according to the study design. Results of rapid diagnosis for GABHS showed that 129 (53.1%) patients of group 2 required no antibiotic therapy.

Using the Streptatest rapid test allowed the physicians of the Emergency Department for Adults and Children of SBU «Puchkov EMS» of DHM) to expand diagnostic capabilities and recommend the appropriate etiotropic antibacterial therapy on time.

Conclusions

1. *In vitro* determination of group A β-hemolytic streptococcus using the Streptatest express diagnostic system allowed physicians of EDAC mobile teams to verify presence of GABHS in patients diagnosed with «acute tonsillitis» during initial treatment in 117 (46.4%) patients.
2. The group of patients with a positive Streptatest rapid test result mainly included children of preschool and school age.
3. Simplicity, rapid result, high sensitivity and specificity, and the fact that the test requires no special conditions enabled effective use of the Streptatest express diagnostic system by the physicians of EDAC mobile teams for differential diagnosis of streptococcal etiology of acute tonsillitis and recommend etiotropic antibacterial therapy on time.

Author Contribution:

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

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