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ИРО ФГБОУ ВО «Башкирский государственный медицинский университет» Минздрава РФ, Уфа, Россия

О ВРАЧЕБНОЙ ДЕЯТЕЛЬНОСТИ АНТОНА ПАВЛОВИЧА ЧЕХОВА. К 165-ЛЕТИЮ СО ДНЯ РОЖДЕНИЯ

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On the Medical Activities of Anton Pavlovich Chekhov. On the 165th Anniversary of His Birth

Резюме

Антон Павлович Чехов приобрел всемирную славу как писатель, вместе с тем по образованию он был врачом и немалую часть жизни посвятил медицине. В университете его учителями были выдающиеся ученые — терапевт Григорий Антонович Захарьин, хирург Николай Васильевич Склифосовский, гигиенист Федор Федорович Эрисман. К медицинской практике Чехов приступил, будучи студентом 2-го курса, на базе Чикинской земской больницы в подмосковном городе Воскресенске, там же получил место уездного врача после окончания университета. Позднее занимался частной практикой в Москве. По отзывам коллег Антон Павлович Чехов был превосходным диагностом и талантливым психотерапевтом. Отличался исключительной доброжелательностью, терпением и деликатностью по отношению к пациентам. В 1890 г. совершил поездку на Сахалин, где впервые осуществил перепись населения, изучил условия жизни ссыльных, собрал сведения о заболеваниях и причинах смерти. По результатам исследования написал фундаментальный труд «Остров Сахалин». В 1890-е гг. приобрел усадьбу в Мелихово, в 70 км от Москвы, где выполнял обязанности земского врача, боролся с холерой, построил четыре школы, пожарный пункт, почтовую станцию, колокольню и дорогу до станции, организовал общественную библиотеку. В своих литературных произведениях Чехов создал целую галерею реалистичных портретов врачей. Благодаря врачебному опыту и знаниям, он профессионально точно отобразил клинические портреты пациентов с различными заболеваниями, такими как туберкулез, сыпной и брюшной тиф, депрессивное расстройство, мания преследования и др. В 1897 г. у Чехова случилось сильное легочное кровотечение, был диагностирован туберкулез. С 1899 г., по совету врачей, Антон Павлович переехал в Ялту, где по-прежнему помогал всем, кто к нему обращался за врачебной помощью. Организовал строительство туберкулезного санатория и лично внес крупную сумму, делал многочисленные пожертвования больным. В 1904 г. состояние Антона Павловича значительно ухудшилось, ему порекомендовали лечение в Германии, на курорте Баденвейлер, где 2-го июля 1904 г. Чехова не стало.

Ключевые слова: *врачебная деятельность А.П. Чехова, роль Чехова-врача*

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Abstract

Anton Pavlovich Chekhov gained worldwide fame as a writer, but he was also a doctor by education and dedicated a significant part of his life to medicine. At the university, his studied under outstanding scientists — therapist Grigory Antonovich Zakharyin, surgeon Nikolai Vasilyevich Sklifosovsky, hygienist Fyodor Fyodorovich Erisman. Chekhov began his medical practice as a second-year student at the Chikinskaya Zemstvo Hospital in the Moscow Region town of Voskresensk, where he secured a position as a district physician after graduating from the university. Later, he practiced privately in Moscow. According to colleagues, Anton Pavlovich Chekhov was an excellent diagnostician and a talented psychotherapist. He was distinguished by exceptional kindness, patience and tact in relation to patients. In 1890, he went to Sakhalin, where he was the first to conduct a population census, studied the living conditions of exiles, collected data on diseases and causes of death. Based on the results of his research, he wrote a fundamental work, Sakhalin Island. In the 1890s, he acquired an estate in Melikhovo, 70 km from Moscow, where he served as a zemstvo doctor, fought cholera, built four schools, a fire station, a post office, a bell tower and a road to the railway station, and organized a public library. In his literary works, Chekhov created a vast gallery of realistic portrayals of doctors. Thanks to his medical experience and knowledge, he professionally accurately depicted clinical portraits of patients with such various diseases as tuberculosis, typhus and typhoid fever, depressive disorder, persecution mania, etc. In 1897,

Chekhov suffered from severe pulmonary hemorrhage and was diagnosed with tuberculosis. From 1899, following medical advice, Anton Pavlovich moved to Yalta, where he continued to help everyone who turned to him for medical help. He initiated the construction of a tuberculosis sanatorium and personally contributed a large sum, made numerous charitable donations to the sick. In 1904, Anton Pavlovich's condition worsened significantly, he was recommended treatment in Germany, at the Badenweiler resort, where Chekhov died on July 2, 1904.

Key words: *medical activity of A.P. Chekhov, the role of Chekhov the doctor*

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No doubt, medical sciences have greatly impacted my literary work; they have widened by observations, enriched me with knowledge, the real value of which for me as a writer can be perceived only by a doctor…

Aphides eat grass, rust corrodes iron, and false pretences kill the soul.

A. P. Chekhov

Taganrog — Moscow (1860–1884)

Anton Pavlovich Chekhov is known all over the world as a great writer, but he dedicated a large part of his life to medicine. Chekhov was born in 1860 in Taganrog, in the family of a second-guild merchant. It is worth mentioning that both grandfathers of Anton Pavlovich (both paternal and maternal) were peasant serfs, who bought themselves and their families out, which was quite rare in the serf Russia[1]. Chekhov's father, Pavel Egorovich, was not a very successful businessman, but he played violin and sang; his mother, Evgenia Yakovlevna, cared for her husband and children and was very tender-hearted. Besides Anton, the family had four sons and a daughter. All children were well-educated and belonged to the intellectual society. Anton was a writer and doctor; Aleksander[2] and Mikhail — writers, Nikolay — artist, Ivan — teacher. Maria, the daughter, was a teacher in a gymnasium and did painting. Chekhov said that they had inherited their talents from their father, while the soul — from their mother.

Chekhov fell for literature when he was a young man and studied at the gymnasium; however, after graduation, he chose medicine. This is what his parents wanted: they hoped that this way their son would have a decent salary. The thing is that in 1876 Chekhov's father went into bankruptcy and fled with his family from the debtor's prison[3] to Moscow, where his eldest sons had already moved to: Aleksander was studying at the university and Nikolay was attending the art school. Only 16-year-old Anton remained in Taganrog; he was finishing his studied at the gymnasium, earning his living by tutoring, selling remaining property and sending money to Moscow, where the family were very poor for the first several years. Chekhov always made sure that his family is financially secure, he especially tried to make his mother's life easier; however, he earned money not as a doctor, but as a writer [1–3].

In 1879, Chekhov was a year 1 student of the Medical Department at the Imperial Moscow University (now I. M. Sechenov First Moscow State Medical University). Chekhov liked Moscow, the life was bubbling there.

Figure 1. *A.P. Chekhov among his family and friends (1890)*

[1] The 1803 Free Grain Farmer Ordinance stated that a peasant serf could become free by paying a buyout. Over the period from 1803 to 1861, 1.5 % of serfs (approx. 150,000) got free.
[2] Aleksander's son, Mikhail Chekhov, is an outstanding actor and theatre teacher.
[3] Debtor's prisons were abandoned in the Russian Empire in 1895.

The second half of the XIX century was the period of significant progressive transformations undertaken by Aleksander II. Liberation of the serfs, Zemstvo Reform, granting independence to universities, relaxation of censorship and other reforms were a stimulus for the scientific and cultural explosion. Russian scientists made fundamental discoveries: Dmitry Mendeleev — periodic law, Ilya Mechnikov — phagocytosis, Ivan Sechenov and Ivan Pavlov — laws of the brain function. A constellation of Russian writers — Lev Tolstoy, Nikolay Leskov, Mikhail Saltykov-Shchedrin, Fyodor Dostoevsky, Vladimir Korolenko and others — are known all over the world.

The Moscow Medical School was flourishing. At the university, Chekhov was taught by the outstanding scientists — internist Grigory Antonovich Zakharin, surgeon Nikolay Vasilyevich Sklifosovsky, hygienist Fyodor Fyodorovich Erisman.

The most recognised for Chekhov was Zakharin. He mentioned that his favourite writer was Tolstoy, while Zakharin was his favourite medical professional. Zakharin was considered to be the most outstanding Russian clinician of that time and an unbeaten diagnostician. He was the father of a therapeutic school, where the diagnosis was based on a thorough interview with the patient, unlike objectivists, who relied mostly on laboratory and instrumental test results. In treatment activities, Zakharin advocated an individual approach and emphasised, in addition to medications, the role of the doctor's personality for the patient. Even one hundred and fifty years later, these approaches in the medicine are fundamental, despite the development of hi-tech.

Chekhov followed Zakharin's principles and paid special attention to the patient's mental state. As remembered by his fellow men, Chekhov dreamt of teaching medical psychology to students. His was ahead of his epoch, because this discipline was included into curricula at higher medical educational institutions only in the second half of XX century.

Chekhov was a year 1 student, when his humorous story — A Letter to the Scientist Neighbour — was published for the first time. Some say that the story was written under the impression from the lectures on the Darwin's Theory of Evolution. After his successful debut, Chekhov was invited by other publishing houses. Journals paid five kopecks for one line, and Chekhov's remuneration was a source of income for the whole family. The family could not count on the eldest brothers, who led Bohemian life. Chekhov believed that literature was his temporary job and used pen names under his works.

His medical practice began when Chekhov was a year 2 student. A younger brother of Anton Pavlovich, Ivan, was hired as a teacher and received a big flat in Voskresensk (now Istra) 30 km from Moscow, and the family used to spend their summer there. There Chekhov met an outstanding therapeutist Pavel Arsenievich Arkhangelskiy, Chief Physician at Chikinskaya district hospital, and started helping during patient visits during summer. In 1884, when Chekhov graduated from the university, he started working there as a district doctor. Arkhangelskiy spoke of the young doctor in very warm terms, "He was very attentive, and it was obvious that he loved his job, he loved his patients. He always attentively listened to the patient; he never raised his voice despite tiredness, even if the patient talked about something unrelated to the illness…" [1, 2].

Doctor and writer (1885–1890)

Once certified as a doctor, Chekhov lost himself in his work; he had 30–40 patients every day, attended patients at home, participated in post-mortem examinations and court hearings; during holiday, he worked as the Chief Physician in Zvenigorod hospital. It is worth noting that district doctors earned far less than the staff at central clinics; in addition, Chekhov treated half of his patients free of charge.

Chekhov was thinking about a doctorate thesis work, and during one year he collected extensive information on the history of medicine in Russia. In his work, Chekhov presented medical evidence, that False Dmitry, who claimed to be a son of Ivan the Terrible, was a fake. The point is that Dmitry, the son of Ivan the Terrible, who died at the age of nine years old, had epilepsy, which does not disappear with the age, and False Dmitry did not suffer from epilepsy.

Chekhov intended to devote himself entirely to medicine and quit scribblings, as he called literature. But in 1886 he received a letter from Dmitry Grigorovich, a well-known writer of that time, who admired Chekhov's talent and persuaded him to use his real name under his works.

Motivated by a high opinion of the patriarch of literature, who predicted the worldwide fame to Dostoevsky, Chekhov continued his writing and returned to Moscow. The thesis was not finished, but the collected materials are a valuable source of information on the history of medicine.

In Moscow, Chekhov was a private doctor, he had a sign "Doctor Chekhov" on his door; and he spent his nights at a table. Chekhov jokingly mentioned that medicine was his wife and literature was his lover; when he's fed up with one of them, he went to the other, but he needed them both. "I treat, and I write", he said to himself. In summer, he worked at Chikinskaya hospital or substituted the Chief Physician in Zvenigorod. He wrote, "I had several hundred patients during the summer, but earned only one ruble" [1, 2].

Colleagues called Chekhov an outstanding diagnostician. His fellow men told lots of stories about Chekhov's diagnostic talent and his clear-sightedness. Chekhov was the first to diagnose an aortic aneurysm in Isaac Levitan, the disease which later killed the painter. He persuaded Vladimir Korolenko that his illness was not dangerous, and he would recover, and this is what happened. When 73-year-old Lev Tolstoy got ill, it was Chekhov who predicted favourable outcome, while other doctors did not believe in it. Konstantin Stanislavsky recollected that he had a visitor when Chekhov was at his house. The writer observed that man, and when he left, Chekhov asked questions about him. Stanislavsky asked about the reason for Chekhov being interested, and Chekhov answered that the man was a suicide. Indeed, several years later, he poisoned himself. It is interesting to note that when Chekhov met Sergey Rakhmaninov for the first time, he said that

he'd become famous. When Rakhmaninov asked how he knew, Chekhov answered that it's written all over his face.

A talented psychotherapist, he cured patients, whom other doctors could not help. Levitan, who was on the verge of suicide because of severe depression, thought that Chekhov was the only one who could save him, and he saved him. Maria Pavlovna, the writer's sister, recollected that Chekhov's patients told that they felt better even if they just sat by Anton Pavlovich. Apparently, his personal charm had a role to play: his smiling eyes, social ease, empathy, tact.

However, he also had tragical accidents, typical of the work as a doctor. Chekhov was right to write that only doctors had horrible days and hours. In 1887, he was called by his fellow painter, the mother and three sisters of whom had typhoid.

At that time, infectious diseases, including typhoid, were the main cause of death. In 1884, the causative agent of typhoid was identified; it caused severe fever with stupor, hence the name of the disease — typhoid ("typhos" in Greek, meaning fog). In the absence of antibiotics, which would appear only half a century later, a half of all typhoid patients died. Chekhov did all he could, but the painter's mother, and then one sister, died; and Chekhov witnessed the death of the sister. Deeply shaken by what had happened, Chekhov removed the "Doctor Chekhov" sign from his door...

By the end of 1880s, Chekhov was the well-known writer; in 1888, he was awarded the most prestigious literature award in Russia — Pushkin Award by the Academy of Science. The next year was tragic for Chekhov: his elder brother Nikolay died of tuberculosis.

Tuberculosis was one of the most common diseases in the XIX century; in urban areas, one in ten people died. In 1882, when Chekhov was a year 3 student, Robert Koch isolated a tuberculosis pathogen; however, the first TB drug, streptomycin, appeared only in 1943. In 1890, Koch proposed to treat TB patients with tuberculin[4], a mix of live and killed tubercular bacteria. It soon appeared that the drug was a cause of death. Chekhov was one of the first to report the danger of using tuberculin. Key therapeutic approaches in TB patients were high calorie diet, good rest and southern sun.

The death of 30-year-old Nikolay Chekhov came like a thunderbolt for his family. Anton Pavlovich also had several episodes of blood spitting, a typical symptom of tuberculosis, but he covered it up, did not get tested and treated; probably he realised that the condition was untreatable. When his brother died, Chekhov all of a sudden decided to move to Sakhalin, the place where convicts were expelled to. Throughout Siberia, at the world's end, a cold and restless island of convicts.

Sakhalin (1890–1891)

Chekhov set himself a task to see and describe the life of convicts on Sakhalin, whose fate did not bother anyone. No one had volunteered to go there to do research. Anton Pavlovich was again thinking about writing a scientific paper and was thoroughly preparing for it: he studied all available sources.

On Sakhalin, the Russian flag was hoisted in 1853, and several years later, after unsuccessful attempts to relocate free serfs here, the island become the place for convicts.[5] It is worth noting that starting from the mid-XVIII century and up to the early XX century, death sentence was quite rare in Russia; a punishment for criminal offences was banishment to Siberia; and the more grave the crime, the farther east the offender was relocated. Sakhalin was the farthest location.

Chekhov started his journey to Sakhalin in April 1890, alone, on his own money. He travelled 11,000 versts in 2.5 months, almost half of this journey was on horses, in giggling wagons. Drunk wagoners, sometimes lack of any food at guesthouses, except vodka, oceans of mud instead of roads, making the wagon trip on several occasions, and he had to spend the rest of his journey in wet clothes. The spring in that area was the coldest in 40 years.

On Sakhalin, Chekhov spent three months and three days. He was the first to count the population: 10 thousand people; he travelled around all convict settlements and completed each card by himself. He collected information about diseases and causes of death. When studying the healthcare system condition, he found out that there were no medications at all; doctors examined convicts mostly to determine how many lashes they can stand, while the medical assistant enjoyed when convicts were punished. As ever, Chekhov was interested in the mental state of the population, who were forced to relocate there. He concluded that despair and inhuman conditions made them inhumane; they became insensitive to other people's grief and pain, both of convicts and their guards.

The report of his journey is Sakhalin Island, a book, written by Chekhov during five years. This is a fundamental description of the history of the island, living conditions of convicts and their health, containing extensive actual and statistical data. After the book was finished, Chekhov said that medicine could not accuse him of betrayal, he contributed as much as he could. However, the Head of the Moscow University refused to accept the book as a thesis paper [4].

This story is not new. For example, such outstanding scientists as Nikolay Lobachevsky and Dmitry Mendeleev, were not accepted to the Russian Academy of Science. It can be assumed that the decision was influenced by the burning social relevance of the book, while after the assassination of Aleksander II in 1881, the country was hit by counter-reforms: universities were restricted in their freedoms, censorship became stricter again, etc.

The situation was aggravated by an official refutation announced by Sakhalin officials, who emphasised that the critical essays about Sakhalin written by Chekhov had nothing to do with the reality [5].

Nevertheless, Sakhalin Island made the society and government think about the life of convicts and take

[4] Later, tuberculin was isolated from boiled Mycobacterium tuberculosis and used for diagnostic purposes only.
[5] The decision to ban convict camps on Sakhalin was passed by the State Council in 1906.

Figure 2. *A.P. Chekhov at his desk (1891)*

partial measures to implement improvements proposed by Chekhov. Corporal punishment for women was banned; orphan homes got more money for running costs; medications were provided; and life-long relegation and convict service were banned. Chekhov sent two thousand children books to Sakhalin to establish a library. Together with Princess E. Naryshkina, who was in charge of patronage of convicts, he opened an orphanage for 120 minor criminals on Sakhalin.

In 1891, the Black Earth region and Middle Volga were starving because of bad harvest, and Anton Pavlovich started an active campaign to help the starving people; for the collection 'Relief Aid', he prepared a chapter from his future book about Sakhalin. Being impressed by severe Sakhalin conditions, for two years he could write only about Sakhalin; "saturated with Sakhalin", as he used to say. The trip to Sakhalin damaged the health of Anton Pavlovich: now he had arrhythmia.

After Sakhalin, the meaning of life became the centrepiece of his work. In his diary, he made a record: "To save his life, a Moslem digs a well. It would be great if every one of us left a school, a well or anything like this after them, so that the life goes on and does not pass without a trace" [2]. Apparently, purchase of a mansion near Moscow is associated with the implementation of this idea.

Melikhovo (1892–1898)

In 1892, Chekhov bought an abandoned mansion in Melikhovo, near Serpukhov, 70 km away from Moscow, he brought his parents and his sister there and got very active.

Anton Pavlovich started his acquaintance with Melikhovo serfs by asking them not to call him Master, because he was a doctor and would treat them. In a separate wing, they organised a medical station, and a flag was hoisted, so that villagers could see when doctor Chekhov was there. On such days, there was a queue of wagons and people, both adults and children. The only assistant to Chekhov was his sister Maria: she recorded patients, dispensed medications, applied bandages and other simple manipulations. All medical assistance, including medications, was free. Very soon, Chekhov gained the trust and love of the locals. Villagers used to say, "Our doctor is even better than in Moscow..." [2].

Anton Pavlovich advocated the interests of villagers in the country council, and it is only due to his involvement that the construction of the tanning enterprise on river Luytorka, where the locals were getting their water from, was banned. The abandoned mansion in Melikhovo soon became a garden; Chekhov planted one thousand of fruit trees, apple and cherry trees.

In summer 1892, the southern regions of Russia were battling an outbreak of cholera, and Chekhov felt compelled to step in as a district doctor in Melikhovo, refusing to be paid for it.

It is worth explaining that, similar to plague and Siberian plague, cholera is an extremely dangerous infection. The previous cholera epidemics in Russia in the 1850s killed over one million people. In 1883, the cholera bacterium was discovered, and it was established that the cause of infection was an ill person; the disease spreads with infected water and food. The high mortality rates of cholera were due to diarrhoea and severe dehydration: vomiting and diarrhoea caused the daily loss of up to 20 litres of fluid, so that the death could occur within days. Antibiotics and infusion therapy were essential, but in the XIX century both were absent; in other words, there was hardly any therapy, the most common treatment techniques of that time — blood-letting and emetics — made the patients' condition even worse.

Fighting epidemics was primarily the task of district doctors, whose job was tough; one doctor had up to 20–30 thousand people to attend to, who lived within 20 km.

The jurisdiction of district doctor Cheknov included 25 villages, four schools, and one monastery. Chekhov notified his publisher that he would be writing again only when there is no more threat of cholera epidemics, although it meant empty pockets for him. He procured disinfectants from manufacturers, went around the villages in his jurisdiction and controlled the sanitary condition there; he arranged for construction of barracks for ill people, visited patients, sometimes 4–5 times a day; in one year, he attended to approximately one thousand patients.

If in 1848 cholera epidemics in Serpukhov district killed over 4,000 people, this time there were only 14 cases of the disease, including 4 deaths. There were no cholera patients in the area serviced by Chekhov. In 1894, when the risk of epidemics passed, Chekhov retired as a district doctor and started writing again, but he still treated everyone who came to him for help: he always kept his stethoscope and tendon hammer on his table [1, 5–7].

His extensive medical experience and knowledge helped Chekhov professionally depict the clinical presentation of a disease in his works. For instance, The Black Monk, Gusev, and Late-Blooming Flowers describe tuberculosis. His story Typhus details the clinical manifestation of spotted fever, The Bishop — of typhoid fever, A Doctor's

Figure 3. *A.P. Chekhov (1893)*

Visit — of depressive disorder, and Ward No. 6 — of persecution complex. Chekhov's works are full of description of doctors and other medical staff and give a true idea of conditions in medical institutions.

Besides writing, Anton Pavlovich focused on social work. He was an active member of the anti-alcoholism committee in Russia, which was formed under the auspices of the Public Health Protection Association. In 1895, he was elected a district councillor and focused on the organisation of medial help and public education. The same year, Chekhov was approached by his colleagues, who mentioned lack of funds to publish The Annals of Surgery. At that time, Chekhov was building a school in Melikhovo and was unable to provide funds, but he did his best to save the medical journal, and he succeeded.

During his life in the rural area, Anton Pavlovich used his own money to build four schools, fire depot, post office, bell tower, and a road to the Lopasnya station (it was named the Chekhov station in 1965). He established a public library in Melikhovo. The same year, he sent two thousand books to his home city, Taganrog. Chekhov dreamt of building a hospital in Melikhovo, but he did not have time.

In 1897, during a meeting with his publisher, Chekhov had a severe pulmonary bleeding, which could not be stopped until morning, and he was admitted to the hospital. To stop the bleeding, ice was applied to his chest and was taken orally; the patient was recommended to rest as much as possible. To improve the blood values, high calorie diet and subcutaneous arsenic were used. Chest pain was treated with applications, rubs, iodine tincture, oral codeine, and morphine [1, 2, 8, 9].

After the therapy, Chekhov's condition improved significantly, and two weeks later he insisted on being discharged. One year later, in 1899, he followed the doctor's recommendations and relocated to Yalta.

'Exile' to Yalta (1899–1904)

Once in Yalta, Chekhov dived into the social life. He was elected a member of the board of trustees of Yalta gymnasium, a member of Yalta Red Cross Committee; he participated in the organisation of jubilee Pushkin festivities; organised collection of funds for starving children in the Samara Province.

In summer 1901, Anton Pavlovich was treated with kumiss in Bashkiria, near Ufa, at Andreevsky resort, which was one of the best resorts in the Ufa Province. The same year, he got married to an actress Olga Leonidovna Knipper; after the church wedding, they moved to Bashkiria. Kumiss-cure resort was 40 houses in a birch grove. Fresh air, wild strawberry openings, June warmth, the picturesque view of steppes, fishing on Dema, where occasionally trout could be fished out, attention and care of Doctor Varavka, calorie-rich food, and four kumiss bottles daily. There, Anton Pavlovich gained over five kilograms, for the first time in many years; however, he has never become a fan of kumiss. One month later, despite persuasion by the doctor, Chekhov started his journey to Yalta.

In remembrance of the writer, in 1904, Chekhov's Garden House was installed on Chekhov's Hill, a place across the resort, where Anton Pavlovich enjoyed watching the surrounding landscape for hours. In the 1920s, Andreevsky resort was renamed A. P. Chekhov Resort, and the house, where Anton Pavlovich lived, became a museum.

In Yalta, Chekhov created his famous plays. However, he did not quit medicine. He still helped everyone, who came to him for medical assistance. The local doctors invited Chekhov to take part in discussion of complicated cases. While living in Yalta, Chekhov wrote an appeal to help poor TB patients, which was published in numerous newspapers and journals, and a lot of donations were received. He organised construction of Yauzlar resort in Yalta (now it is A. P. Chekhov resort) for TB patients and contributed five thousand roubles. Chekhov was always asked for help, advice or money, and tried not to refuse. He arranged for placement of patients to clinics, paid for their treatment, donated money for patients.

In his letter to his editor and friend Aleksey Suvorin, Anton Pavlovich wrote, "The universe is fine. The only bad thing is us. We lack justice…" [11]. All his life, Chekhov was an advocate of justice. In 1902, his protest to the so-called academician incident had a public response. The point is that in 1902 Maksim Gorky was elected an honorary academician in literature[6], but the Academy of Science cancelled its decision as directed by the higher-level authorities. As a response to it, Chekhov, who was an honorary academician from 1900, quit his title.

[6] The title "Honorary Academician in Belles-lettres of the Russian Language and Literature of the Imperial Academy of Science" appeared in 1899; in 1900, Chekhov, Lev Tolstoy, Vladimir Korolenko and others were named honorary academicians.

In January 1902, the VIII Pirogov Conference of Doctors organised by Pirogov Society, the most established medical association in Russia, was held in Moscow. Anton Pavlovich was going to take part in the conference, but due to his poor health he could not leave Yalta [12, 13].

Despite the southern sun and sea being beneficial for his health, in Yalta Chekhov was separated from his usual company and creative atmosphere, from active social life; he missed bubbling Moscow, his house near Moscow, where he often hosted friends and acquaintances. In summer, Yalta was full of summer residents, and in winter it looked deserted; also, his wife was not beside him, she preferred theatres; the cold house was not suitable for life in winter. Chekhov called Yalta exile. His condition deteriorated. As a conclusion to his death wish addressed to his sister, Anton Pavlovich wrote, "Help those who are poor. Take care of our mother. Live in peace" [1, p. 741).

Badenweiler resort — Moscow (June–July 1904)

In spring 1904, Chekhov's condition deteriorated; he suffered from shortness of breath and cough, he had to take narcotics to kill pain. Somebody recommended bringing Chekhov to Badenweiler resort in Germany, and his wife followed the recommendation. A German doctor examined Chekhov upon arrival to Badenweiler and left speechless. He could not understand how the patient managed to travel in such poor condition; especially that Chekhov was a doctor and realised the situation. Chekhov understood the situation perfectly; before his departure, he said to one of his acquaintances, "This is where I will die" [1, p. 810]. Probably, he wanted to spare his grieving family and give them hope. One month later, on the 2 July 1904, Chekhov died… The coffin with the writer's body was transferred to Moscow, and on the 9 July he was buried in the Novo-Devitchi Convent cemetery (now it is the Novo-Dyevitchiye cemetery).

One day, talking to Ivan Bunin, Anton Pavlovich mentioned that he would be remembered, and his works would be read somewhere seven years after his death. As a matter of fact, Chekhov remains one of the most popular writers world-wide, even one hundred and fifty years later. As for his contribution to medicine, Chekhov was a wonderful doctor and managed to do a lot despite his short life. He helped a lot of people, selflessly battled cholera, travelled to Sakhalin and created a scientific work about the life on the island, engaged in charity and executive activities, created a portrait gallery of doctors and clinical portraits of patients. Chekhov's works are considered one of the most useful sources of psychotherapy, and the role of doctor Chekhov is immeasurable.

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ТЕРАПИЯ ГЕМОРРАГИЧЕСКОЙ ЛИХОРАДКИ С ПОЧЕЧНЫМ СИНДРОМОМ: ПАТОФИЗИОЛОГИЧЕСКОЕ ОБОСНОВАНИЕ И ПРАКТИЧЕСКОЕ ПРИМЕНЕНИЕ

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Treatment of Hemorrhagic Fever with Renal Syndrome: Pathophysiologic Rationale and Practical Application

Резюме

Современная терапия геморрагической лихорадки с почечным синдромом (ГЛПС) преимущественно основывается на мнении экспертов и данных небольших обсервационных исследований, результаты которых не всегда воспроизводятся в клинической практике. В связи с отсутствием эффективных противовирусных средств лечения ГЛПС продолжается поиск оптимальной патогенетической терапии. Клиническое течение ГЛПС характеризуется последовательным развитием периодов лихорадки, гипотензии, олигурии, полиурии и реконвалесценции. Для каждого из периодов свойственны определенные патофизиологические механизмы, знание которых необходимо для правильной организации лечения больных ГЛПС. В данной работе рассмотрены патогенетическое обоснование и опыт практического применения используемых при ГЛПС методов лечения, таких как противовоспалительная терапия, коррекция водно-электролитных, гемодинамических и гемокоагуляционных нарушений, экстракорпоральная детоксикация и симптоматическая терапия.

Ключевые слова: *геморрагическая лихорадка с почечным синдромом, хантавирусы, патогенез, терапия*

Конфликт интересов

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

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Abstract

Current treatment of hemorrhagic fever with renal syndrome (HFRS) is primarily based on expert opinion and data from small observational studies, the results of which are not always confirmed in clinical practice. Due to the lack of effective antiviral agents for the treatment of HFRS, the search for optimal supportive therapy continues. The clinical course of HFRS is characterized by the sequential development of phases of fever, hypotension, oliguria, polyuria and convalescence; each of these phases is characterized by certain pathophysiological mechanisms, knowledge of which is necessary for the correct management of patients with HFRS. This narrative review provides the pathophysilogic rationale and practical experience of using treatment methods for HFRS, such as anti-inflammatory therapy, correction of fluid, electrolyte, hemodynamic and hemocoagulation disorders, as well as, renal replacement therapy and symptomatic therapy.

Key words: *hemorrhagic fever with renal syndrome, hantavirus, pathogenesis, treatment*

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Abbreviations: AKI — acute kidney injury, ARDS — acute respiratory distress syndrome, CVP — central venous pressure, DIC — disseminated intravascular coagulation, ECMO — extracorporeal membrane oxygenation, HFRS — hemorragic fever with renal syndrome, HPS — hantavirus cardiopulmonary syndrome, MAP — mean arterial pressure, RCT — randomised clinical trial, RRT — renal replacement therapy, SBP — systolic blood pressure

Introduction

Hemorrhagic fever with renal syndrome (HFRS), widespread in Eurasia, along with hantavirus pulmonary syndrome (HPS), endemic to North and South America, is a clinical manifestation of human hantavirus infections and is characterized by severe progression with frequent life-threatening complications.

Annually, an average of approximately 23,500 cases of HFRS are reported, with one-third occurring in the Russian Federation. The case fatality rate, which varies depending on the pathogen strain, endemic region, and detection rate of mild disease forms, ranges from 0.1% in Puumala-virus infections in Northwestern Europe to 14% in Dobrava/Belgrade-virus infections in Southwestern Russia [1, 2].

HFRS is an acute, self-limiting viral disease that typically resolves with complete recovery in mild cases without therapeutic intervention. However, in severe disease progression — observed in 20-25% of hospitalized patients — lack of treatment, delayed initiation, inadequate therapy, or overtreatment may result in adverse clinical outcomes.

The potential for specific prophylaxis of HFRS caused by hantaviruses circulating in Russia remains limited. Culture-derived inactivated bivalent and polyvalent HFRS vaccines, developed by researchers at the M.P.Chumakov Federal Scientific Center for Research and Development of Immunobiological Preparations under the direction of E.A.Tkachenko, have successfully completed preclinical studies and are currently in preparation for clinical trials [3].

Current management of HFRS is based on expert opinion and data from small observational studies, the results of which are not always reproducible in clinical practice. To date, only four randomized clinical trials have been published: two evaluating ribavirin for HFRS [4,5], one assessing ribavirin for HPS [6], and one investigating glucocorticoids for HPS [7]. Treatment often employs syndromic management approaches developed for bacterial sepsis that fail to account for HFRS-specific pathogenesis. Some pharmacologic agents traditionally used in HFRS, such as nonsteroidal anti-inflammatory drugs, may pose safety concerns [8]. Given these limitations, a critical review of therapeutic approaches to HFRS is warranted, incorporating emerging pathophysiological insights and available clinical observations.

Pathophysiological rationale for the treatment of HFRS

HFRS has been divided into six stages (incubation, febrile, hypotensive, oliguric, diuretic, and convalescent). Each stage exhibiting distinct pathophysiological mechanisms and corresponding therapeutic opportunities. This periodicity is most pronounced in severe cases, though during the acute phase, key clinical and pathogenetic features of HFRS stages may overlap (Figure 1).

Incubation period. Following exposure to a sufficient infectious dose of viral particles that enter through the respiratory and/or digestive tract mucosa, hantaviruses first interact with antigen-presenting cells before contacting microvascular endothelial cells whose surface receptors serve as viral targets [9,10]. Viral entry into endothelial cells and subsequent replication with release of new virions occurs without significant cytopathic effects [9,10]. While hantaviruses may be detected within or on other cell types (dendritic cells, macrophages, epithelial cells, etc.), this likely reflects their phagocytic and adhesive functions rather than active viral replication. The prevailing hypothesis suggests preferential infection of venous microvascular endothelium — renal in HFRS and pulmonary in HPS.

The incubation period typically lasts 1-2 weeks. Reported extensions to 6 weeks may represent post-exposure infections from contaminated fomites after leaving endemic areas. Both the number of infected endothelial cells and viremia levels likely peak at the end of the incubation period, declining with the onset of neutralizing antibody production and subsequent inflammatory responses [9,10].

The ability to diagnose HFRS during the incubation period by detecting viremia in individuals at risk of infection has provided the rationale for exploring post-exposure passive immunization and antiviral chemoprophylaxis [11, 12]. However, the likelihood of implementing these therapeutic approaches in clinical practice appears remote.

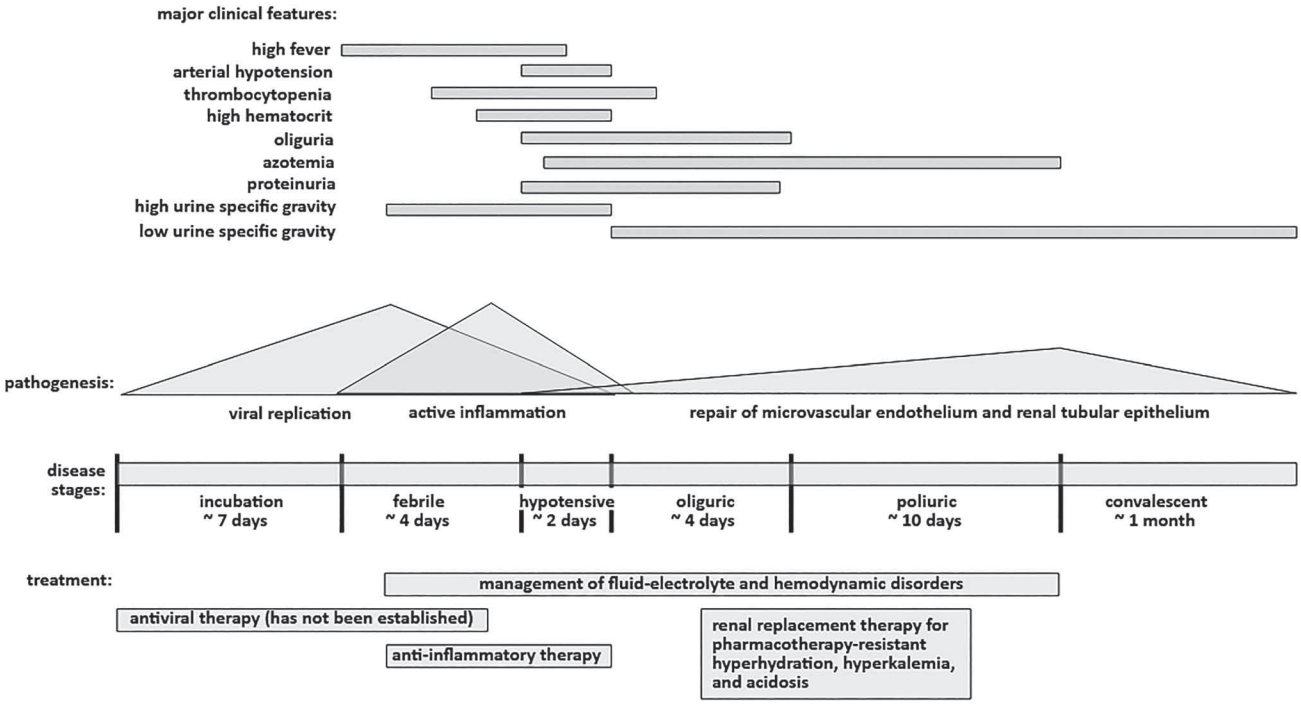

Figure 1. *Proposed framework for clinical timeline, pathogenesis and management of HFRS*

Febrile stage. The acute onset of high fever marks the initiation of an inflammatory response aimed at suppressing viral replication. Antibody binding to viral particles on the surface of infected endothelium serves as a signal for the activation of cytotoxic immune effector cells (polymorphonuclear leukocytes, monocytes/macrophages, and cytotoxic T-lymphocytes) [13, 14]. By attacking infected endothelial cells, these effector cells generate proinflammatory cytokines and cytotoxic mediators (including phagocyte-derived hydrolases and atomic oxygen) [15, 16]. Inflammatory activity peaks at the end of the febrile period and remains elevated during the next hypotensive stage [17].

Endothelial damage in the microcirculatory vessels, corresponding to the degree of inflammatory activity, manifests as increased vascular permeability with plasma extravasation and interstitial edema (so-called "capillary leak"), along with vasodilation and thrombus formation predominantly observed in the venous segment of the microvasculature [18, 19].

Clinical manifestations of inflammatory microcirculatory disturbances may become apparent during the latter half of the febrile period, presenting as: erythema and puffy edema of the facial, cervical, and shoulder skin regions, conjunctival edema and injection, decreased visual acuity (resulting from edema of ocular structures), nausea, vomiting, and diarrhea (secondary to gastrointestinal microcirculatory dysfunction), lumbar and abdominal pain (due to renal edema), headache (indicating developing cerebral edema), non-productive cough (suggesting incipient pulmonary interstitial edema).

The main therapeutic approaches during the febrile period should include antiviral and anti-inflammatory medications, along with maintenance of normal fluid balance.

Hypotensive stage. The hypotensive phase, a hallmark of severe HFRS, represents the most critical stage of the disease. This phase is driven by generalized endothelial dysfunction secondary to a hyperergic inflammatory response, which precipitates hypovolemia (due to plasma extravasation from increased vascular permeability and dehydration caused by persistent high-grade fever) and venodilation with subsequent blood pooling in the venous compartment. These pathophysiological changes may culminate in shock. Notably, in a subset of HFRS patients with predominant pulmonary capillary and venular endothelial involvement, shock may be preceded by acute respiratory distress syndrome (ARDS). Both shock and ARDS constitute the most severe, life-threatening complications of HFRS and serve as the primary contributors to disease-related mortality [18].

Extensive damage to the microvascular endothelial lining, accompanied by concurrent thrombosis and fibrinolysis, can lead to disseminated intravascular coagulation (DIC) when the balance between these processes is disrupted. DIC may manifest with either thrombotic or hemorrhagic complications. In the most severe cases of HFRS, thrombotic-hemorrhagic pituitary involvement may occur. In less severe disease, microcirculatory disturbances during the hypotensive phase are predominantly localized to the kidneys, initially presenting as

prerenal (ischemic) acute kidney injury (AKI). However, prolonged renal ischemia rapidly progresses to intrinsic renal AKI due to acute tubular necrosis.

The intense inflammatory response mediates viral clearance, as evidenced by multiple studies demonstrating rapid reduction in viral load coinciding with the hypotensive phase [5,20-22]. This decline in antigenic load is subsequently followed by marked attenuation of inflammatory activity. By the onset of the oliguric phase, this is clinically manifested by resolution of high-grade fever and disappearance of microvascular inflammatory signs.

Pathophysiologically-guided management during the hypotensive phase should include: continued anti-inflammatory and antiviral therapy, maintenance of normovolemia, vasopressor support when indicated, and respiratory support as clinically warranted.

The precarious balance between concurrent thrombosis and fibrinolysis [19,23] renders the following interventions particularly hazardous: anticoagulants, anti-platelet agents, fibrinolytic inhibitors, blood products and coagulation factors. For the same reason, extracorporeal detoxification methods should be avoided during active inflammation, as they may precipitate decompensation of existing DIC [24,25]. The toxemia in HFRS is mediated by short-lived inflammatory mediators (cytokines) and ischemic byproducts (lactate). Consequently, effective detoxification can be achieved through anti-inflammatory therapy and restoration of tissue perfusion.

Oliguric stage. The oliguric phase of HFRS represents the clinical manifestation of acute tubular necrosis, which develops secondary to renal hypoperfusion during the febrile and hypotensive phases due to inflammatory microcirculatory disturbances. Renal ischemia leading to tubular epithelial necrosis results from both systemic hypovolemia (due to capillary leak syndrome and dehydration) and renal-specific microcirculatory dysfunction (characterized by venular thrombosis, increased vascular permeability, and interstitial edema that collectively impair hemodynamics and urinary flow).

While some studies have characterized HFRS-associated renal pathology as interstitial or tubulointerstitial nephritis based on biopsy findings from convalescent patients [26,27], we contend this classification may not fully capture the disease's pathophysiological complexity. During the oliguric phase of HFRS, renal histopathology does not meet diagnostic criteria for interstitial/tubulointerstitial nephritis. Rather, the findings are consistent with acute tubular necrosis secondary to inflammatory microcirculatory disturbances [18,28].

During the oliguric phase, following resolution of active inflammation, vascular endothelial repair commences. The disease transitions to the polyuric phase as vascular permeability normalizes and microthrombosis ceases within the renal microvasculature. The oliguric phase in HFRS is typically short-lived. However, prolonged oliguria may occur in patients who experienced sustained shock during the acute phase. Prolongation of the oliguric phase may also result from either renal microvascular re-thrombosis (triggered by extracorporeal therapies or transfusion of coagulation factors/platelets), or fluid imbalance, particularly iatrogenic hyperhydration that impairs resolution of renal interstitial edema.

Volume overload represents a critical iatrogenic complication during the oliguric phase, potentially leading to hydrostatic pulmonary edema, cerebral edema and spontaneous renal rupture as a result of severe renal parenchymal edema. These life-threatening complications arise from combined effects of increased intravascular hydrostatic pressure and compromised tissue integrity due to inflammatory-mediated vascular leakage.

Optimal fluid management constitutes the cornerstone of oliguric phase treatment and is typically sufficient when properly implemented. This requires strict monitoring of intake/output balances and precise volume titration to maintain euvolemia. With meticulous management, most patients (including those with anuria) avoid renal replacement therapy (RRT) which remains high-risk until endothelial integrity is restored and hemostatic stability is achieved.

Poliuric stage. The polyuric phase of HFRS reflects gradual recovery of glomerular filtration alongside slower restoration of tubular reabsorptive capacity [26, 27]. At the onset of the polyuric phase, the glomerular filtration rate may be as low as a few milliliters per minute, with excreted urine essentially representing plasma ultrafiltrate that has bypassed tubular reabsorption. Consequently, this phase can be marked by progressive azotemia, hyperkalemia, and acidosis. In rare cases of HFRS, uremic encephalopathy or pericarditis may develop. A hallmark feature of this stage is arterial hypertension (potentially escalating to hypertensive crisis with encephalopathy and seizure syndrome), resulting from prior renal ischemia and persistent endothelial dysfunction. Additionally, due to preceding microcirculatory disturbances in the gastrointestinal system, patients frequently exhibit gastric and intestinal paresis.

Management during the polyuric phase should focus on maintaining fluid and electrolyte balance. When pharmacological management fails to correct hyperhydration, hyperkalemia, or acidosis, RRT may be required. In HFRS patients, azotemia — even with serum creatinine levels elevated 10-fold or higher — typically resolves without uremic toxicity or long-term sequelae.

Convalescent stage. The convalescent stage, commencing with the resolution of polyuria, typically lasts one to several months, during which nearly all HFRS patients achieve complete recovery. The asthenia and laboratory evidence of renal dysfunction observed during convalescence generally require no pharmacological intervention.

Patient Management

A presumptive diagnosis of HFRS should be considered in patients presenting with otherwise unexplained high-grade fever and a history of exposure to endemic areas during the incubation period. The clinical diagnosis is established based on recognition of the characteristic disease course with pathognomonic symptoms appearing in each disease phase. Definitive diagnosis requires serological confirmation through detection of anti-hantavirus IgM antibodies and demonstration of rising anti-hantavirus IgG titers during the course of illness. The diagnostic workup for HFRS must include exclusion of clinically similar conditions requiring specific diagnostic evaluation and treatment, such as systemic bacterial infections, tropical malaria and systemic vasculitides.

Patients with HFRS typically require hospitalization between days 3-4 of illness. Admission to a facility equipped with RRT capabilities is strongly recommended. In severe cases, appropriate stabilization measures must be implemented prior to transfer to prevent clinical deterioration during transportation. Given the risk of rapid clinical deterioration (including shock, ARDS, overt DIC, and AKI with pulmonary or cerebral edema), patients with severe HFRS require intensive care unit admission under the supervision of clinicians experienced in managing this disease [29].

Patients may be discharged for outpatient follow-up during the polyuric phase when the following conditions are met: subjective well-being is satisfactory, and there is a consistent trend toward normalization of renal function parameters.

Antiviral therapy

No targeted antiviral therapy for hantavirus infections has been established to date [1]. The clinical utility of ribavirin, proposed nearly 40 years ago for HFRS treatment based on in vitro activity, remains uncertain. While one randomized controlled trial (RCT) demonstrated therapeutic benefit [4], subsequent RCT failed to replicate these findings [5]. Moreover, a separate RCT conducted in HPS showed no clinical effect [6]. In current HFRS treatment guidelines, ribavirin — when considered at all — is categorized as an optional rather than essential therapeutic agent [30].

Preclinical studies utilizing cell cultures and animal models have identified several compounds capable of inhibiting hantavirus replication [31, 32]. However, none of these agents have progressed to clinical application for human treatment.

The potential utility of antiviral therapy in HFRS is constrained by the brief window of active viral replication. Viral loads typically declines following symptom onset, and by the time of hospitalization, viral replication may have already been terminated by the adaptive immune response.

The hyperergic immune response characteristic of HFRS raises significant concerns regarding the potential efficacy of passive immunization strategies — whether through donor immunoglobulins or antiviral monoclonal antibodies. Low antibody titers observed in patients during early disease stages likely reflect active immunoglobulin binding to virion surfaces rather than impaired antibody production.

The therapeutic use of interferons or interferon inducers in HFRS may pose significant safety risks due to their potential to exacerbate inflammatory responses.

Anti-inflammatory therapy

Glucocorticoids currently represent the treatment of choice for HFRS-associated inflammation [30]. The primary therapeutic effect of these agents involves suppression of polymorphonuclear leukocyte and monocyte/macrophage activity. This results in decreased synthesis and secretion of inflammatory mediators responsible for increased vascular permeability ("capillary leak"), pathological vasodilation, endothelial structural integrity disruption, and microcirculatory thrombosis secondary to endothelial damage.

Glucocorticoid therapy in HFRS was first proposed seventy years ago [33], yet specific indications, optimal dosing regimens, and treatment duration remain poorly defined to date.

According to the Chinese Medical Association's consensus guidelines [30] — which reflect the most extensive clinical experience with HFRS management — glucocorticoids are recommended for febrile-phase patients with marked exudative manifestations (facial/conjunctival hyperemia/edema, serous cavity effusions, hemoconcentration, proteinuria, etc.), and hypotensive-phase patients developing shock. Chinese clinical guidelines recommend short-course intravenous glucocorticoid therapy (typically 3-5 days, not exceeding 7 days) using one of the following protocols: hydrocortisone (100 mg once or twice daily), or dexamethasone (5-10 mg once or twice daily), or methylprednisolone (20-40 mg once or twice daily).

In our clinical view, indications for glucocorticoid therapy in HFRS align with those for intravenous fluid resuscitation during both febrile and hypotensive phases. Critically, the initial glucocorticoid dose should be administered prior to fluid infusion to mitigate vascular permeability. Glucocorticoid dosing and administration frequency should be individualized, guided by anti-inflammatory response criteria including resolution of high-grade fever and prevention of febrile recurrence. Notably, anti-inflammatory therapy becomes unnecessary upon transition to the oliguric phase, necessitating immediate glucocorticoid withdrawal.

The lack of mortality benefit with glucocorticoid therapy, demonstrated in an RCT of 60 HPS patients

(30 treated with methylprednisolone versus 30 receiving placebo) [7], has often been interpreted as conclusive evidence against their efficacy in hantavirus infections. This analysis importantly overlooks that the investigated methylprednisolone pulse therapy (16 mg/kg/day for 3 days) was initiated during the cardiopulmonary phase of HPS — that is, after establishment of the hyperergic inflammatory response. Furthermore, the study authors themselves note the insufficient statistical power of this RCT to adequately assess between-group mortality differences (8 fatalities in the methylprednisolone group versus 12 in the placebo group).

Other therapeutic options for anti-inflammatory management in HFRS remain constrained. Notably, administration of non-steroidal anti-inflammatory drugs — which impair compensatory mechanisms maintaining renal blood flow — results in exacerbated renal injury in HFRS patients [8,30]. Several studies have investigated targeted modulation of specific inflammatory mediators in HFRS management. Initial case reports described successful use of icatibant (a selective bradykinin B2 receptor antagonist) in two patients with severe HFRS [34,35]. However, subsequent observations failed to confirm consistent therapeutic efficacy of this high-cost agent. Further clinical trials are required to establish evidence-based recommendations for its incorporation into routine practice [36]. The use of long-acting anti-inflammatory medications (e.g., anti-cytokine monoclonal antibodies) or agents with delayed onset of action (e.g., JAK inhibitors, aminoquinoline derivatives) appears clinically unwarranted in HFRS given the transient nature of inflammatory activation in this condition.

Management of Fluid-Electrolyte, Hemodynamic, and Hemostatic Disorders

Maintaining normal fluid balance is an essential component of HFRS therapy. Measures to normalize fluid status should be implemented in two stages: replenishing the water deficit within the first 3–6 hours of therapy initiation, followed by maintaining the equilibrium of fluid intake and excretion [30].

Hospitalization of HFRS patients is typically preceded by 2–4 days of high fever, with daily fluid loss amounting to approximately 1% of the patient's body weight. Oral fluid rehydration is often impeded by the lack of pronounced thirst (due to the iso- or hypotonic dehydration typical in early-stage HFRS) and frequent concomitant nausea and vomiting. Compounding this, dehydration coincides with hypovolemia resulting from capillary leak syndrome and vasodilation. Notably, the external signs of these processes (e.g., facial edema and flushing) may mask the underlying fluid deficit, creating a false impression of euvolemia.

Intravenous fluid therapy should be initiated with isotonic polyionic crystalloids or 0.9% sodium chloride. The initial infusion volume and rate must be tailored to the estimated fluid deficit and adjusted according to hemodynamic status. Close clinical monitoring is essential during the initial resuscitation phase.

In patients without arterial hypotension, the initial infusion rate during the first 1-2 hours of therapy should be approximately 500 mL/hour (or ~8 mL/kg/hour), followed by isotonic crystalloid administration at 250 mL/hour for the subsequent 2-4 hours. A total initial fluid volume of 1500-2000 mL is typically sufficient, provided there is marked clinical improvement in the patient's condition and the ability to resume oral intake.

In patients with systolic blood pressure (SBP) below 90 mm Hg or mean arterial pressure (MAP) below 65 mm Hg, intravenous fluid therapy should be initiated in the prehospital setting (concurrently with glucocorticoid administration). During the first hour of treatment, a minimum of 1000 mL (approximately 15 mL/kg) should be infused. If target hemodynamic parameters are achieved (SBP >90 mm Hg and MAP >65 mm Hg), the infusion rate should be reduced to 500 mL/hour for the next 2 hours, followed by 250 mL/hour for 4 hours, and may be discontinued after 6 hours of sustained blood pressure stabilization. The total initial fluid volume typically amounts to approximately 3 liters.

For persistent hypotension during the first hour of therapy, the infusion rate should be increased. If no clinical improvement is observed after administration of approximately 30 mL/kg of isotonic crystalloids, vasopressors and albumin solution should be initiated. Notably, in HFRS patients, dehydration rarely exceeds 5% of total body weight. Fluid replacement should therefore not exceed 50 mL/kg, after which ongoing fluid therapy must be strictly matched to measured fluid losses.

A frequent management error in HFRS is the continued administration of large-volume fluids to correct central venous pressure (CVP). Importantly, the observed CVP reduction results primarily from inflammatory vasodilation in the venous microcirculation rather than significant hypovolemia.

The infusion rate should be reduced upon clinical signs of incipient inflammatory pulmonary edema (unproductive cough, dyspnea). If ARDS develops, standard management (including lung-protective ventilation and dexamethasone) should be initiated while continuing slow fluid replacement over 12-18 hours to address the estimated minimal fluid deficit.

In cases of progressive ARDS with refractory hypoxemia, venoarterial extracorporeal membrane oxygenation (ECMO) should be considered [1]. While venovenous ECMO is the recommended modality for sepsis-associated ARDS [37], this approach may be contraindicated in HFRS-related ARDS due to the disease-specific propensity for pulmonary microvascular thrombosis.

In HFRS patients with ARDS who receive inappropriate fluid therapy (excessive volume and/or rate), continuous RRT may be required to eliminate fluid overload [38,39]. When considering RRT during the hypotensive phase of HFRS — particularly in the context of persistent inflammatory activity and unstable hemostasis — a careful risk-benefit assessment is essential.

Current HFRS treatment guidelines recommend vasopressor therapy only when fluid resuscitation fails (defined as persistent hypotension in adults after infusion of 3000 mL over 2-3 hours) or if hypotension recurs after initially successful fluid administration [30].

The dose of vasopressors — preferably norepinephrine — should target a MAP of 65-75 mm Hg. Higher doses may exacerbate microcirculatory dysfunction. In HFRS, assessing vasopressor efficacy based on urine output restoration is misguided, as oliguria is only partially attributable to hypotension. Similarly, initiating vasopressors concurrently with fluid resuscitation — a strategy sometimes advocated in bacterial sepsis [37] — is inappropriate in HFRS. Sepsis-induced hypotension (typically observed in surgical or nosocomial infections) is primarily distributive in nature and, unlike in HFRS, frequently occurs in patients without significant hypovolemia.

If vasopressor therapy proves ineffective, clinicians should assess for potential pituitary hemorrhage with acute adrenal insufficiency (requiring hydrocortisone replacement) [40] and consider venoarterial ECMO for hemodynamic support [1].

After initial volume status correction, the majority of patients require only sustained anti-inflammatory treatment and careful fluid balance management. Failure to maintain proper fluid balance (with daily fluid intake exceeding losses by >750 mL) is particularly hazardous during the oliguric phase, potentially precipitating hydrostatic pulmonary and/or cerebral edema. Fluid overload results in dilutional hyponatremia, which may prompt inappropriate sodium-containing fluid administration, thereby exacerbating iatrogenic volume overload.

In HFRS patients with clinical signs of volume overload during the oliguric phase, loop diuretics may be considered. According to guidelines from the Chinese Medical Association, furosemide is the diuretic of choice, initiated at 20-40 mg IV, with dose escalation (if no response occurs within 2-4 hours) to 100-200 mg administered 2-4 times daily, up to a maximum daily dose of 800 mg [30]. For refractory cases with pulmonary or cerebral edema, RRT should be initiated. Importantly, oligo(an)uria without hypervolemia should not be considered an indication for diuretic therapy.

After volume overload, hyperkalemia unresponsive to medical management represents the second most frequent indication for RRT in HFRS, with onset typically occurring during the polyuric stage. Pharmacological intervention for "asymptomatic" hyperkalemia is warranted when serum potassium levels exceed 6.5 mmol/L, whereas neuromuscular or electrocardiographic manifestations necessitate treatment at levels above 5.5 mmol/L. Management of hyperkalemia in HFRS patients typically involves infusion of an insulin-glucose solution. In cases with ECG abnormalities, intravenous calcium chloride or gluconate administration is additionally required. For refractory cases, adjunctive therapies may include furosemide, potassium-binding cation-exchange resins (e.g., Kalimate), or beta-2 adrenergic agonists (e.g., salbutamol). In hyperkalemia complicated by metabolic acidosis, intravenous sodium bicarbonate (50-100 mmol as a 4% solution, 50-100 mL infusion) should be administered.

In patients with HFRS, metabolic acidosis primarily develops due to lactate accumulation resulting from inflammatory microcirculatory disturbances. Acidosis correction is typically achieved through tissue perfusion restoration with anti-inflammatory and infusion therapy. Attempts to correct lactic acidosis through RRT during active inflammation (febrile phase, hypotensive phase, or early oliguric stage) may lead to further microcirculatory thrombosis and prove both ineffective and potentially hazardous. In rare cases of HFRS with prolonged oliguria, acidosis may progress due to impaired renal excretory function. When pharmacological management fails, this may necessitate RRT.

Uremic intoxication requiring RRT is an exceptionally rare manifestation of AKI in HFRS. Typically, diagnoses of uremic encephalopathy and/or pericarditis in HFRS patients are misattributed to either hypervolemia-related complications (cerebral edema, serous cavity transudation) or hypertensive encephalopathy.

In HFRS patients, anuria and azotemia are typically reversible. In the absence of progressive hypervolemia, hyperkalemia, or acidosis, these findings alone should not be considered absolute indications for RRT.

Arterial hypertension (with potential progression to hypertensive encephalopathy and seizure activity) is a hallmark feature of the polyuric phase in HFRS. In most cases, a short-term course of combination therapy with an angiotensin-converting enzyme inhibitor and calcium channel blocker proves sufficiently effective. Hypertensive crisis requires emergent vasodilator therapy (sodium nitroprusside or nitroglycerin) or alpha-adrenergic blockade (urapidil), with mandatory continuous medical supervision during administration.

Sinus bradycardia, which may occur during any phase of HFRS, typically follows a benign course. However, cardiac monitoring is essential, with preparedness to administer atropine or initiate temporary pacing in cases of hemodynamic instability [41].

Correction of hemostatic abnormalities in HFRS is indicated only in cases of active bleeding. Over 97% of HFRS cases in Russia are caused by Puumala virus infection [42], which typically presents without overt

clinical signs of hemorrhagic syndrome. In Puumala virus infections, overt DIC manifestations (thrombotic or hemorrhagic events) typically occur following interventions that disrupt the thrombo-fibrinolytic balance, such as platelet/plasma transfusions (for laboratory parameter correction), antifibrinolytic administration, or RRT [18].

Notably, thrombocytopenia in HFRS (often considered an indication for platelet transfusion) likely reflects not a true platelet deficiency, but rather reversible aggregation and sequestration in the microvasculature. This is supported by the rapid, substantial platelet count increase during the oliguric phase: following resolution of active inflammation, levels typically rise from 20-40×10^3/μL to 200-400×10^3/μL or higher within 2-3 days.

In our view, prophylactic anticoagulation in HFRS should also be considered potentially harmful. The characteristic microvascular thrombotic activation in this disease reflects inflammatory mechanisms (so-called 'immunothrombosis') [19]. We posit that appropriately administered glucocorticoid therapy — targeting the underlying inflammation — should suffice for thromboprophylaxis in HFRS.

Adjunctive Symptomatic Management

For pain management — typically resulting from combined inflammatory and hydrostatic renal edema — opioid analgesics may be warranted in select cases after excluding emergent conditions (renal rupture, renal vessel thrombosis, urinary obstruction, mesenteric thrombosis, pancreatitis, or acute coronary syndrome).

Gastrointestinal dysfunction in HFRS, resulting from inflammatory microcirculatory disturbances, may cause elevated intra-abdominal pressure. This can exacerbate renal impairment and compromise respiratory function. In severe cases, nasogastric/intestinal decompression is required, while milder presentations may be managed with cleansing enemas.

Vasopressor therapy may exacerbate gastrointestinal hypoperfusion, potentially leading to erosive-hemorrhagic mucosal injury [43, 44]. Therefore, when vasopressors are required in HFRS patients, concomitant acid-suppressive therapy (e.g., proton pump inhibitors) should be initiated.

Nausea, vomiting, and hiccups — frequent and distressing symptoms in HFRS — may arise from either gastropathy or metabolic disturbances. For persistent cases, central dopamine and serotonin receptor antagonists (e.g., metoclopramide, domperidone, ondansetron) can be employed as antiemetic therapy.

Other pharmacologic agents frequently recommended in HFRS management include vitamins, angio- and cardiocytoprotective drugs, and antiplatelet agents, though their clinical utility remains unestablished.

Conclusion

The infectious and pathological processes in HFRS are self-limiting, and well-structured supportive care is generally sufficient to ensure patient recovery. The distinct pathophysiological features of HFRS that differentiate it from bacterial sepsis must be considered when managing syndrome-based complications such as shock, ARDS, DIC, and AKI. The lack of consensus in HFRS management guidelines reflects both limited high-quality evidence and inconsistent research methodologies in existing studies. Multicenter clinical trials could help establish optimal therapeutic approaches for this disease.

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НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ У ПАЦИЕНТОВ С НОРМАЛЬНОЙ МАССОЙ ТЕЛА: ЭПИДЕМИОЛОГИЯ, АКТУАЛЬНЫЕ ВОПРОСЫ СКРИНИНГА И ДИАГНОСТИКИ, ПОДХОДЫ К ТЕРАПИИ

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Nonalcoholic Fatty Liver Disease in Patients with Normal Body Weight: Epidemiology, Current Issues of Screening and Diagnosis, Approaches to Therapy

Резюме

Неалкогольная жировая болезнь печени (НАЖБП) в настоящий момент времени представляет собой серьезную медико-социальную проблему для общественных систем здравоохранения в связи с ее широким распространением, потенциальным риском развития цирроза печени (ЦП) и гепатоцеллюлярной карциномы (ГЦК). Кроме того, наличие НАЖБП в соматическом континууме пациента сопряжено с достоверно большей частотой развития сердечно-сосудистых событий и сахарного диабета типа 2 (СД2). Наиболее часто НАЖБП регистрируется у пациентов с избыточной массой тела. Отдельного внимания исследователей и клиницистов заслуживают пациенты с НАЖБП, имеющие нормальную массу тела. Несмотря на, казалось бы, относительно благоприятный профиль «метаболического здоровья» риск прогрессирования НАЖБП в ЦП и ГЦК, а также сопряженность с сердечно-сосудистыми событиями в обсуждаемой группе пациентов ничуть не меньше, чем в группе пациентов с НАЖБП и высоким индексом массы тела (ИМТ). Отсутствие ранних симптомов и нарушений со стороны некоторых показателей, характеризующих «метаболическое здоровье» у пациентов с НАЖБП и нормальной массой тела, способствует поздней и несвоевременной диагностике заболевания печени и, как следствие, его прогрессированию и формированию тяжелых сосудистых и метаболических нарушений в последующем. В представленном обзоре авторы предлагают некоторые эпидемиологические данные о распространенности НАЖБП у пациентов с нормальной массой тела, вариантах клинического течения НАЖБП у обсуждаемой группы пациентов и предлагают сделать особый акцент на очевидную необходимость значительно более широкого вовлечения пациентов с нормальной массой тела в клинические и научные исследования, посвященные детальному изучению патогенеза, вопросов организации медицинской помощи и лечения НАЖБП.

Ключевые слова: *неалкогольная жировая болезнь печени, инсулинорезистентность, индекс массы тела, сахарный диабет 2, цирроз печени*

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Abstract
Nonalcoholic fatty liver disease (NAFLD) is currently a serious medical and social problem for public health systems due to its high prevalence, potential development of liver cirrhosis (LC) and hepatocellular carcinoma (HCC). In addition, the presence of NAFLD in the patient's somatic continuum is associated with a significantly higher incidence of cardiovascular events and type 2 diabetes mellitus (T2DM). The most frequent NAFLD is registered in patients with excessive body weight. Patients with normal body weight deserve special attention of researchers and clinicians. Despite the seemingly relatively favorable profile of "metabolic health", the risk of progression of NAFLD to CKD and HCC, as well as conjugation with cardiovascular events in this group of patients is no less than in the group of patients with NAFLD and high body mass index (BMI). The absence of early symptoms and abnormalities of some indicators characterizing "metabolic health" in patients with NAFLD and normal body weight contributes to late and untimely diagnosis of liver disease and, as a consequence, its progression and the formation of severe vascular and metabolic disorders in the future. In the presented review the authors offer some epidemiological data on the prevalence of NAFLD in patients with normal body weight, variants of the clinical course of NAFLD in the discussed group of patients and propose to make a special emphasis on the obvious need for a much wider involvement of patients with normal body weight in clinical and scientific studies devoted to a detailed study of the pathogenesis, issues of organization of medical care and treatment of NAFLD

Key words: *non-alcoholic fatty liver disease, insulin resistance, body mass index, diabetes mellitus, liver cirrhosis*

Conflict of interests
Co-author of the article Nikitin I.G. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article has passed the peer-review procedure adopted by the journal. Nikitin I.G. did not participate in the decision to publish this article.
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NAFLD — non-alcoholic fatty liver disease, BMI — body mass index, DM2 — type 2 diabetes mellitus, PEMT —phosphatidylethanolamine N-methyl transferase, HOMA-IR — Homeostasis Model Assessment of Insulin Resistance

NAFLD is a chronic, progressive disease, the cause of which is fat accumulation in hepatic cells and subsequent pericellular inflammation, triggering universal fibrogenesis processes facilitating HC and HCC [1-3]. Of note, NAFLD is a diagnosis by exclusion: while searching for the final diagnostic concept, it is necessary to rule out a number of monogenetic causes — viral, autoimmune, other metabolic liver disorders, which morphologically manifest as steatosis; some drug-induced injuries to the liver, excessive drinking. Since the first description of NAFLD in the late 1990s [1–3], this clinical-morphological hepatic disorder has taken the lead in terms of the incidence and the number of associated HC and transplantation cases in the corresponding statistical reports in Europe and the USA [3]. Moreover, numerous epidemiological experimental development models of some chronic non-infectious disease clearly show that NAFLD morbidity will rise [4, 5]; it means a significant increase in the detection rate of DM2 and cardiovascular conditions as well as associated chronic cardiac failure (CCF).

1. Overweight is currently seen as the main cause and trigger of NAFLD, which is confirmed by the data from large-scale population studies: the incidence of NAFLD grows in parallel with an increase in BMI [1, 4]. At the same time, clinicians can clearly identify two special categories among their patients: first — overweight individuals with *normal* fat content in their hepatic tissue; second — individuals with normal BMI, no insulin resistance and DM2 and with *clinical-morphological signs* of NAFLD. Data from previous epidemiological studies (Dionysos study in Europe) show that the incidence of NAFLD among individuals with normal BMI can be 16–18% [1, 4, 6]. Asian epidemiological studies

among subjects with chronic non-infectious diseases reported NAFLD in 20–22% of population with normal weight; in the analysed cohort, the most common factors of metabolic disorders were hyperuricemia, high pro-inflammatory cytokine levels, age over 50 years old, male sex [3, 7, 8]. The data summarised until now allowed a number of researchers to introduce a new definitive term into clinical practice — "NAFLD in slim individuals/NAFLD in patients with normal body weight" (initially, this phenotype was described as NAFLD in individuals with BMI of < 30 kg/m^2; however, since the body weight is not a diagnostic criterion of NAFLD, the term "NAFLD in slim individuals/NAFLD in patients with normal body weight" was proposed [1, 4]. In this regard, it is advisable to remind obesity classification depending on BMI:

- Deficient body weight: BMI of 18.5 kg/m^2 or less.
- Normal body weight: BMI varies from 18.5 to 25 kg/m^2.
- Pre-obesity: BMI of 25 to 30 kg/m^2.
- Stage 1 obesity: BMI of 30 to 35 kg/m^2.
- Stage 2 obesity: BMI of 36 to 40 kg/m^2.
- Stage 3 obesity: BMI of over 40 kg/m^2, and obesity is usually associated with a pathology.

Despite the fact that NAFLD in individuals with normal body weight is not a rare phenotype of this disease, pathophysiologic mechanisms of its development are still far from being clear. It is obvious that not all people with normal body weight and NAFLD have metabolic disorders, which would made them susceptible to hepatic dysfunction. Therefore, a thorough study of the causes and detailed explanation of the pathophysiologic mechanisms of NAFLD in patients with normal body weight become an important task for future researches and clinical practice. The evaluation of environmental factors, occupational characteristics, genetic status, lifestyle becomes the benchmark in the thorough study of this population. Assuming various causes and possible mechanisms of NAFLD in patients with normal body weight, the disease is likely to develop similar to patients with a higher BMI. This fact can evidence that excessive fat tissue in a patient is not a mandatory condition for non-alcoholic steatohepatitis (NASH), progressive fibrosis, HC and HCC. Moreover, some clinical and pathomorphological studies show both higher severity of liver involvement and higher mortality rates among patients with normal body weight or even lean patients with NAFLD vs. patients with excessive BMI [9].

Given relatively few symptoms of NAFLD and the absence of marked changes in laboratory results and almost normal anthropometric measurements, it is quite challenging for a clinician to suspect a hepatic disorder in individuals with normal body weight.

NAFLD epidemiology in patients with normal body weight

Traditionally, the incidence of NAFLD in the population was nearly always evaluated with the use of a single criterion — BMI, with the normal value being below 25 kg/m^2. This BMI value us used mostly in European or North American epidemiological population-based studies, whereas in numerous similar studies conducted in Asia or Pacific, the normal BMI value is below 23 kg/m^2 [4]. Anyway, when these values are used separately for various populations with normal BMI, the incidence of NAFLD varies greatly and makes 5–34% (**Figure 1**).

A number of factors significantly impacted this marked difference in the NAFLD incidence rates in patients with normal body weight: study design; diagnostic methods used for NAFLD patients; study location; sample uniformity and size; and groups selected for a comparative analysis. Some studies used very thorough and objective methods for NAFLD diagnosis; e.g., fine-needle aspiration of the liver, which used to be the golden diagnostic standard for this disease. In other patients, other methods were used: magnetic resonance imaging with the use of specific applications for processing and interpretation of the data; computer tomography; controlled signal attenuation parameter; traditional ultrasonic examination of the abdominal cavity; and in a number of cases, the diagnosis was based mostly on laboratory result interpretation (transaminase, bilirubin, protein synthesis ability of the liver). As shown in **Figure 1**, the highest NAFLD incidence rates were recorded in India (mostly in males), in people, who look healthy and do not smoke and have sedentary lifestyle. Overall, ethnic population-based studies showed that in Asian males, the insulin resistance rates are almost 3.5 times higher than in African American and Caucasian males. Besides, fat content in the liver of Asian males is almost two times higher than in other ethnic populations [4, 10]. Thus, it can be assumed that this population (males of the Indo-Asian origin) is the most susceptible to NAFLD. One published meta-analysis, which comprises data from 84 studies with the total number of subjects exceeding ten million people, demonstrated that among patients with NAFLD, about 20% of the total number of analysed subjects had normal body weight or were lean (95% CI; 15.9–23.0) [11]. An analysis of the general population in 23 studies, comprising over 113,000 patients irrespective of the presence or absence of NAFLD, demonstrated that just 5.1% of subjects (95% CI; 3.7–7.0) had NAFLD with a normal BMI. At the same time, in 19 studies with over 45,000 of subjects with a normal BMI value, included in the analysis, 11% (95% CI; 7.8–14.1) had NAFLD. It is quire obvious that the data are significantly non-homogenous; however, in Europe in

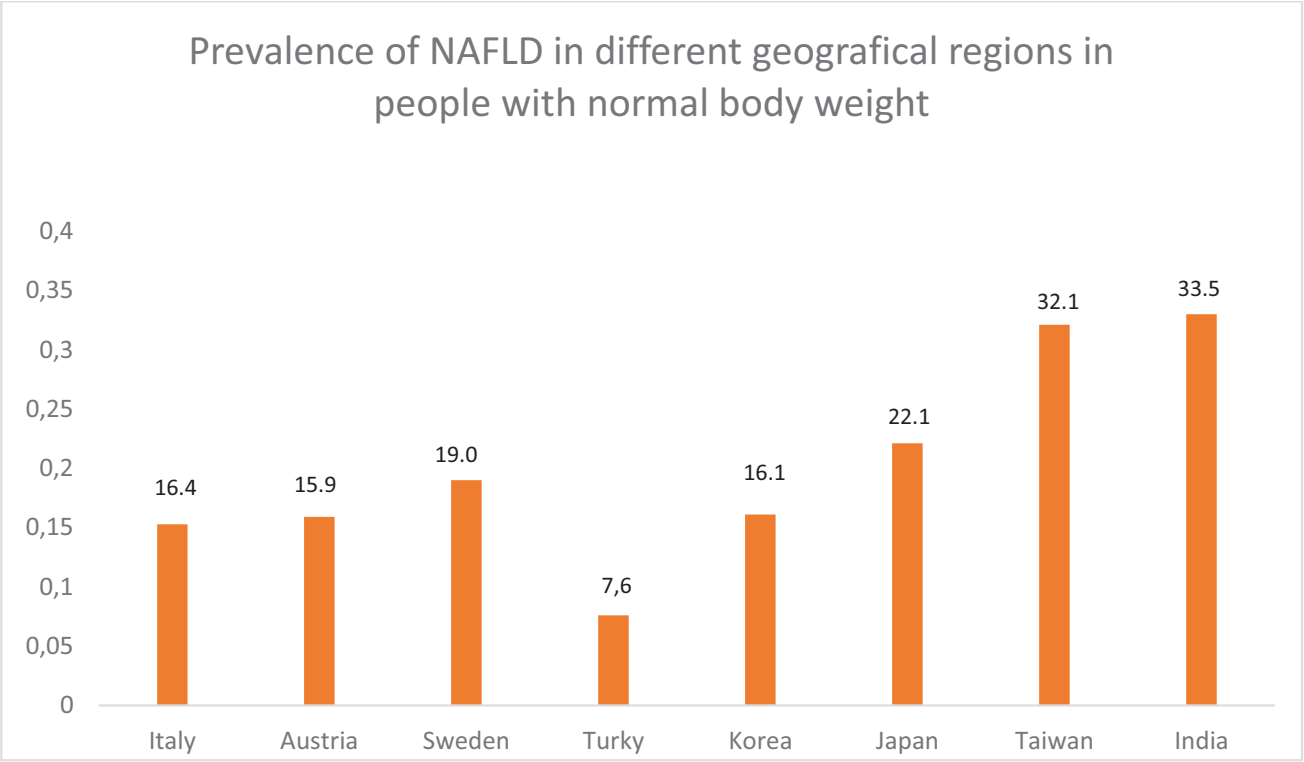

Figure 1.
Prevalence of NAFLD in different geographical regions in people with normal body weight [1, 4]

general, the incidence of NAFLD in individuals with the normal body weight was higher than in other locations. Interesting data were reported in the Global NAFLD/NASH Registry from 18 countries, which demonstrated that approximately 8% of all patients had normal BMI, fewer individual diagnostic signs of metabolic syndrome and a lower rate of hepatic cirrhosis (the sign was evaluated at the first visit to the doctor, taking into account the assumed disease duration) [4, 12].

Current epidemiological data demonstrate growing incidence of NAFLD not only among obese patients, but also in individuals with the normal body weight. Recent studies showed that over the past 15 years, NAFLD morbidity almost doubled: from 5.6% in 2000 to 12.6% in 2023, respectively [11, 12]. Individual population-based studies demonstrate different NAFLD rates in various geographic regions and ethnic groups with overweight, but not obesity (BMI < 30 kg/m^2 for Europeans and < 25 kg/m^2 for Asians). A Hong Kong study in 911 subjects, who met the analysis inclusion criteria and were selected from census databases, showed that the incidence of NAFLD in this population was 19.4%, in Japan — 15.2%, in Belgium — 2.8% [11, 13]. In this regard, the question "How reliable is the use of BMI as a screening benchmark in patients with suspected NAFLD?" remains highly disputable.

Clinical features and laboratory attributes of NAFLD in patients with the normal body weight; outcomes and mortality rates

The results of recent published studies show a tendency that non-obese patients with diagnosed NAFLD have better metabolic health background (**Table 1**).

For instance, fasting plasma triglyceride and glucose levels, high density lipoprotein, adiponectin, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), and waist circumference in the mentioned population are very often intermediary. The sex and age distribution demonstrates that younger men are the most numerous cohort of patients with NAFLD and normal body weight vs. overweight patients, where women prevail. Besides, according to the results of a multifactor analysis of the aggregate data from the National Health and Nutrition Examination Survey (NHANES III) in the USA, DM2 and arterial hypertension are more common for overweight individuals with NAFLD; in terms of ethnicity, this group included mostly Latin Americans [11, 13]. Nevertheless, a lot of researchers point to the similarity of pathogenetic links of NAFLD development in patients with normal body weight and obese individuals, and emphasise a similarly higher risk of metabolic disorders in both groups vs. general population.

Table 1. Clinical characteristics and mortality associated with NAFLD in non-obese patients

The author of the study	Average age of patients	Region	BMI	The patient's metabolic profile	Mortality rate
Akyuz [8]	41.2+11.8	Turky	23.6+1.3	The predominance of young men, normal blood pressure, higher hemoglobin levels, lower prevalence of metabolic syndrome, less pronounced liver fibrosis	Mortality is similar in patients with NAFLD and obesity
Kim [7]	51.6+9.7	Korea	23.4+1.3	The obvious prevalence of men, higher levels of fasting plasma glucose, insulin, HOMA-IR, uric acid; no differences in metabolic parameters compared with overweight patients	Higher risk of mortality from cardiovascular events and overall mortality compared to patients with normal body weight without NAFLD
Cruz [9]	42.4+8.4	USA	23.1+1.7	The predominance of males, mostly of non-Caucasian origin, a lower prevalence of T2DM, lower levels of cytolysis enzymes and HOMA-IR, a lower degree of steatosis with a morphologically greater severity of inflammation	Higher overall mortality compared to patients without NAFLD
Feldmann [10]	56.7+12.9	Austria	23.6+1.8	Waist circumference, levels of liver enzymes — AST, ALT, GGTP, levels of the main parameters of the atherogenic fraction of the lipidogram, fasting plasma glucose, HOMA-IR had intermediate values between those in healthy people and in patients with NAFLD and obesity	Higher overall mortality compared to patients without NAFLD
Francanzani [5]	45.7+12.9	Italy	23.0+1.2	Less pronounced arterial hypertension and thinner intima media in the carotid arteries	No long-term mortality study has been conducted
Hagstrom [12]	51.4+13.4	Sveden	23.1+2.7	Older age, lower levels of transaminases, and lower representation of NASH as a form of NAFLD at the monitoring initiation stage,	Similar overall mortality with patients with NAFLD without obesity, higher mortality from cardiovascular events
Lee [13]	43.4+6.6	China	20,2+ 1.4	Predominance of males, lower expression of transaminases, intermediate values of fasting plasma glucose and HOMA-IR	No long-term mortality study has been conducted

Fascinating and sometimes very ambiguous are the published data on outcomes and mortality rates in patients with normal body weight and lean patients with NAFLD. For example, studies in the Swedish cohort of patients with NAFLD and normal body weight, despite a relatively favourable prognosis at the beginning of the observation period (during the first three years of the follow-up, there was a lower incidence of an active parenchymal process — steatohepatitis and marked fibrosis), later demonstrated a significantly higher risk of hepatic disorders vs. patients with a higher or even high BMI, including adjustment for age and fibrosis stage by the start of the observation [4, 11]. The obtained data supported significantly higher rates of NAFLD progression in patients with the normal body weight and lean patients. Another cohort-based study conducted among lean patients with NAFLD in Italy, UK, Australia, and Spain, where the total number of subjects was 1,339, with the follow-up period of eight years, showed potential development of diabetes, acute cardiovascular diseases, HCC and other intrahepatic cancer in 8.9% of cases [11, 13]. Even of more interest are the data from the National Health and Nutrition Examination Survey III (NHANES III) registry, with the average dynamic follow-up and periodic examination of patients during 18 years. It has been shown that, for instance, the weighted unadjusted all-cause mortality was higher in patients with NAFLD vs. lean subjects without NAFLD (40.9% vs. 17.9%; $p < 0.001$). The adjusted risk factor of all-cause mortality (HR) in non-obese patients with NAFLD was 2.44 (95% CI; 1.77–3.37) and remained statistically significant even after adjustment for comorbidity, metabolic factors, sex and age, and other demographic parameters. A separate adjustment for demographic variables demonstrated that the cardiovascular mortality was significantly higher in lean patients with NAFLD (15.1% vs. 3.7%; $p < 0.001$). Thus, the cardiovascular mortality in this population grew by 240%! The most common causes of death in patients with the normal body weight and NAFLD were malignancies (25.7%), cardiovascular diseases (21.6%) and infections (13.5%). Another recent study [13], which is of utmost interest, demonstrated that the aggregate all-cause mortality in lean patients

with NAFLD was significantly higher (76.3%) than in patients with NAFLD and normal BMI (51.7%), patients with NAFLD and higher BMI (27.2%) and patients without NAFLD (20.7%) over the ten-year follow-up period. A separate adjustment, which showed the development of cardiovascular conditions in this study, demonstrated in the long-term follow-up the following: 16.9% in lean patients with NAFLD, 5.6% in patients with NAFLD and normal BMI, 8.8% in patients with NAFLD and high BMI; $p < 0.001$.

Of interest are the studies, which show significantly lower serum phosphatidylcholine and lysophospatidylcholine levels and higher glutamate concentrations in patients with NAFLD with normal body weight and lean patients vs. a similar population without NAFLD. Glucose tolerance impairment in patients with NAFLD and normal body weight was similar to that in obese patients with NAFLD; DM2 rates were almost the same (approx. 30%). This proves the idea that fat accumulation in the liver can play a vital role in the development of insulin resistance and DM2 even without obesity [14, 15].

Based on the mentioned studies, the following conclusion can be made: despite less body fat, less marked dyslipidemia, lower transaminase levels, the risk of cardiovascular disease, progressive hepatic conditions, malignancies and all-cause mortality associated with NAFLD in patients with the normal body weight and lean patients is the same or higher than in individuals with a higher BMI. The causes of such an increased risk are still unclear; this phenomenon can be associated with specific NAFLD pathogenesis in non-obese patients.

Hypothesised causes of NAFLD in patients with the normal body weight

Numerous recent clinical and epidemiological studies show a number of important factors facilitating development of NAFLD in patients without excessive body weight. These key factors include environmental factors (diet and eating behaviour), genetic factors, endocrine dysfunction. No doubt, these factors interact and impact the possibility of NAFLD development, often if there is more visceral fat, irrespective of BMI. It allows making an assumption about a "common metabolic pathway" underlying NAFLD, irrespective of the body build.

Environmental factors: diet and eating behaviour

Excessive consumption of saturated fats and animal protein, sucrose and highly refined carbohydrates is the main component in the development of NAFLD [1, 4]. Regular consumption, e.g. of sugar-containing beverages, is closely associated with the development of NAFLD in children and adults. It has been shown that individuals with NAFLD consume three times as many sugared beverages as individuals without NAFLD [16–19]. Fructose is a simple sugar, which, together with glucose, forms sucrose, i.e. table sugar. Experiments and clinical practice have demonstrated that regular fructose consumption significantly boosts steatogenesis de novo in the liver, causing mitochondrial disorientation, marked endoplastic reticulum stress, and reduces fatty acid oxidation, leading to significant shifts in biocoenosis of gut microflora, the most active component of a number of metabolic processes in the body. Such shifts facilitate the development of parenchymatous hepatic inflammation and create conditions for insulin resistance [17]. Regular consumption of fructose and NAFLD development are the subject of numerous studies [4, 16]. For example, correlation between regular fructose consumption and a more advanced stage of fibrosis in patients with NAFLD and higher rates of its active form (steatohepatitis) has been demonstrated; this correlation is clearly observed in children [17].

Until now, the main dietary recommendations for patients with NAFLD were related mostly to individuals with a high body weight. When comparing, for instance, diets with restricted consumption of facts and carbohydrates in obese patients with NAFLD, only restricted consumption of carbohydrates allowed to significantly reduce fat deposits in the liver, together with a reduction in insulin resistance, abdominal obesity and total fat weight [20, 21]. Eight to ten weeks of restricted consumption of highly refined carbohydrates (fructose, glucose) in young men with NAFLD significantly reduced fat deposits in the liver and body weight values and completely normalised liver transaminase, gamma glutamine transpeptidase and total cholesterol. At the same time, liver fat reduction did not depend on changes in the body weight or obesity [22]. Isocaloric sugar replacement with starch for ten days (!) resulted in decrease in visceral fat, total fat in the liver, reduction in insulin resistance and steatogenesis de novo in obese children, who previously reported high daily consumption of sugar (over 50 g daily) [22]. Favourable impact of the diet with low fructose content, low glycaemic load and glycaemic index on the metabolism parameters was observed in children with NASH, who previously consumed significantly more fructose vs. children in general population [17]. Taking into account the mentioned data, the European Association for the Study of the Liver (EASL) recommends that people living with NAFLD follow the Mediterranean diet and exclude fructose and ultra-processed food from their diet [2, 4]. For patients with NAFLD and

the normal body weight, some components of the diet become extremely important. For example, choline deficit in volunteer males caused a significant increase in transaminase levels and fat accumulation in the liver tissue [20]. Other studies in NASH Clinical Research Network [20, 21] demonstrated that choline deficit in the diet of postmenopausal women for a month and a half resulted in significant shift in the liver function tests and was associated with marked hepatic inflammation. Adequate daily choline consumption is 550 mg for men and 425 mg for women; however, the majority of people often fail to consume the required amount of choline [15]. Since choline is a compound found mostly in animal-derived products, the chance of NAFLD in vegans and vegetarians is significantly higher [14, 15, 20, 21].

Choline biosynthesis is actively facilitated by phosphatidylethanolamine N-methyl transferase (PEMT), which catalyses phosphatidylcholine synthesis. Phosphatidylcholine is an integral component of the lipoprotein secretion system, particularly that of low density lipoprotein (LDL), in the liver [15]. Studies show that in individuals with NASH, PEMT expression was lower than in patients with simple steatosis; also, PEMT expression correlated with the platelet levels in the course of fibrosis progression in patients with NASH. It is interesting to note that numerous studies demonstrated a remarkable pattern: lower PEMT expression in lean patients and individuals with normal BMI [23, 24]; in animal models, it has been reported that PEMT -/- mice were protected against obesity, despite fat rich diet. PEMT gene is regulated by oestrogen, that is why choline deficit can be most obvious during menopause, manifesting as body weight gain, a higher risk of insulin resistance and development of NAFLD. To sum up the analysed results, we can conclude that choline deficit, caused by low PEMT expression or insufficient consumption with food, can be associated with potential development of NAFLD and is a condition for condition progression, especially in individuals with normal body weight.

Extremely important environmental factors impacting NAFLD development are smoking and alcohol consumption. Strictly speaking, the diagnostic criteria for NAFLD suggest absence of any significant alcohol consumption; however, currently, significant alcohol consumption has a very broad interpretation. For example, in the USA, the acceptable weekly alcohol consumption for men and women is 294 g and 196 g, respectively; in Europe, these values are lower: 210 g and 140 g, respectively. Values for the Asians are even lower: 140 g for men and 70 g for women [24, 25]. Currently, numerous epidemiological studies evaluate the impact of alcohol consumption on the course of NAFLD. For instance, a detailed examination of the French cohort with NAFLD demonstrated significantly higher mortality rates in patients, who consumed 7 units of alcohol a day (i.e., 56 g of absolute ethanol), while consumption of less than one unit per week was associated with higher survival rates [26, 27]. The impact of alcohol on liver diseases is especially obvious in obese individuals: with BMI > 30 kg/m^2, the liver toxicity of alcohol doubles and significantly increased the chance of HCC [27, 28].

Smoking is another significant factor in NAFLD progression. Large-scale Asian studies demonstrated that fibrosis progression rates in smokers with NAFLD were almost two times higher than in non-smokers in the same cohort [29].

Genetic factors

There is no doubt that obesity is the most significant independent risk factor of NAFLD, even with adjustments to sex, arterial hypertension, age, and metabolic health markers (homocysteine, lipid profile, transaminase, uric acid, fasting plasma glucose levels). It is obvious that there is a specific cohort of patients, who do not develop NAFLD even with obesity and chronic excessive calorie consumption. At the same time, it is well-known that there is J-shape correlation between NAFLD and BMI. It is worth noting that the risk of liver disorders is also significantly higher in individuals with BMI below 19 kg/m^2 [1, 5, 6, 9]. All this evidences the presence of a genetic component in the development of NAFLD — candidate genes, the activity of which can be associated both with NAFLD development and a protective role in its prevention.

The studies of gene *PNLPA3* polymorphisms in the development and progression of NAFLD are well-known [23, 30, 31]. For example, the single nucleotide polymorphism, associated with I148M (rs738409) replacement in gene *PNPLA3,* is the key genetic risk factor of NAFLD, while identification of this polymorphism is an advisable component of examination of patients with NAFLD in numerous clinical guidelines in the European Union and USA [23]. Close association between NAFLD development and progression and polymorphisms of genes *MBOAT7* (membrane of domain O-acyltransferase 7) and *TM6SF2* (antigen 2 of transporter 6 transmembrane family) has been identified. It is worth noting that all these studies were conducted only in obese or overweight individuals, whereas in patients with NAFLD with the normal body weight or lean patients, the study of genetic polymorphism of a number of candidate genes is described in very disorganised and sporadic publications [1, 4, 23]. Therefore, of note is a study of Japanese researchers [4], who evaluated the incidence of NAFLD in various communities of obese and overweight patients and patients

with the normal body weight. The authors conclude that genotype PNLPA3 rs738409 (GG, homozygotic variant) doubles the risk of NAFLD in patients with the normal body weight vs. obese and overweight patients, who did not have mutation in this gene. At the same time, using the BMI-based classification, there were no differences in the incidence of genetic variants of genes *MBOAT7* and *TM6SF2* in the mentioned groups of patients. One European study [4] in 187 Austrian citizens showed a higher incidence of the risk allele (rs738409) of gene *PNLPA3* in individuals with NAFLD and the normal body weight vs. obese and overweight patients: patients with the normal body weight had the risk allele in 4% of cases, whereas other patients had this allele only in 0.3% of cases. Similar rare studies in patients with the normal body weight and NAFLD, conducted in various geographic locations (Europe, South and Southeast Asia, Japan), demonstrated the same pattern: the incidence of the risk allele rs738409 of gene *PNLPA3* was significantly higher in patients with the normal body weight and lean patients with NAFLD vs. obese and overweight individuals [4, 23].

The risk allele AA of variant V175M (rs7946) in gene *PEMT*, causing the loss of its activity, was reported 1.7 times more often in the group of patients with NAFLD vs. controls [23]. Other genetic polymorphisms of *PEMT* (rs4646343, rs3761088, rs12325817) were associated with intensive triglyceride accumulation in hepatic cells because of restricted choline diet [4, 23]; allele variants rs 4646365 and 1531100 were associated with higher rates of NAFLD diagnosis in menopausal women. Detailed exome sequencing in pooled results from two patients with NAFLD and six healthy individuals showed that only allele variant rs7946 in gene *PEMT* and rs2290532 in the gene associated with oxysterole (*OSBPL10*) were closely related to NAFLD [23], whereas another study [32], where the close association between allele rs7946 of *PEMT* gene and the risk of NAFLD was shown, did not observe any association between variants of gene *OSBPL10* with NAFLD.

Another group of very diverse genetic disorders is lipodystrophies. This group is characterised by a common phenotype: adipose tissue deficit without obvious nutritional deficiency and active metabolism [33, 34]. A typical pattern of these conditions is NAFLD, the pathogenetic mechanisms of which are based on the inability of the body to accumulate lipids in the form of fats. For these conditions, typical pathogenic variants of genetic mutations have been identified, which are often family-related: genes encoding hormone sensitive lipase (*LIPE*), perilipin 1 (*PLIN1*), peroxisome proliferator-activated receptor gamma (*PPARG*), lamin A/C (*LMNA1*), v-akt murine thymoma viral oncogene homolog (*AKT2*), and cell death-inducing DFFA-like effector (*CIDEC*) [4, 33]. Hepatic steatosis in such patients is observed almost in 100% of cases, thus assuming that NAFLD in lean individuals can be a specific type of ectopic fat accumulation, the mechanisms of which are similar to lipodystrophy. Later, the definition was given to the concept of polygene risk, related to insulin resistance and marked reduction in fat mass in the lower limbs, which are the integral signs of lipodystrophy. Later researches showed that the polygene index of the risk of lipodystrophy is closely associated with NAFLD, severe fibrosis and reduction in fat mass in the lower limbs [34].

Endocrine and other factors of NAFLD development in patients with the normal body weight

Endocrine disbalance is another factor of NAFLD. It is well known that the risk of NAFLD is significantly higher in postmenopausal women [4, 35]. This fact can be explained by the loss of oestrogen protection together with increasing body weight, dyslipidaemia and impaired glucose tolerance. Another known hormonal factor of NAFLD and NASH is hyperandrogenism, irrespective of resistance and obesity. An increased circulating testosterone level was associated with a higher degree of steatosis, higher levels of proinflammatory cytokines and fibrosis stage in middle-aged women [35]. A completely separate form of liver damage is NAFLD in patients with hypothyroidism. Hormone replacement therapy has obvious favourable effect on steatosis regression, reduction of fibrosis, and biochemistry normalisation [36]. Currently, there are no proper studies of the characteristics of the endocrine profile in patients with NAFLD and normal body weight.

When thinking about possible pathophysiological components of NAFLD development in individuals with the normal body weight, it is essential to mention the studies, which demonstrated synergetic effects of fats and fructose on oestrogen deficit development, which causes damage to hepatic cell functions [35]; similar correlation was found between choline deficit and oestrogen levels, which can be associated with a higher risk of NAFLD in the population under discussion. For instance, the average hepatic fibrosis score in postmenopausal women with NAFLD was significantly higher vs. premenopausal women with NAFLD, despite almost the same level of choline consumption with food. Besides, it should be remembered that oestrogens are a potent *PEMT* expression regulator: reduced oestrogen production is associated with lower *PEMT* expression, which is one of the most important pathophysiological mechanisms of NAFLD development in postmenopausal women caused by chronic choline deficit [4, 15, 16, 20].

Key considerations of NAFLD screening and therapy in patients with the normal body weight

Currently, there are no generally recognised and accepted recommendations for patients with NAFLD and normal body weight, despite high incidence of NAFLD and unfavourable outcomes in the population in question; none of the professional medical communities currently recommends screening among patients with NAFLD and normal body weight. For example, the practical guidelines of the American Association for the Study of Liver Diseases (AASLD) do not recommend regular NAFLD screening even in high risk groups (DM2, obesity) due to the lack of scientific evidence, which could prove the efficiency of various diagnostic approaches, therapy regimens and, as a result, economic justification and adequate advantages of the screening. There are various, sometimes completely opposite, opinions in this regard. Some specialists still recommend examination of patients with an obvious risk of hepatic disorders: individuals with DM2 or metabolic syndrome (MS); patients over 50 years of age. It is possible to use relatively simple laboratory and imaging devices, forecasting algorithms (complete blood count, blood biochemistry, abdominal ultrasound examination, various scales) to form an idea of the degree of fibrosis and to forecast the rates of its progression [37, 38]. However, to the contrary, the European and Asian guidelines propose screening among patients at the highest risk of NAFLD, including patients with DM2 and obesity [38]. At the same time, numerous local clinical guidelines and recommendations admit the presence of NAFLD in individuals with the normal body weight and lean patients, especially in those who show the signs of metabolic syndrome or belong to the Asian population. It is obvious that the development of consensus guidelines for the screening, therapy, forecast, and evaluation of long-term risks is essential for the optimal management of ***all*** patients with NAFLD.

Currently, there are no direct indication of the screening and therapy of NAFLD in patients with the normal body weight in many guidelines. A lot of important and fundamental questions arise: e.g., Is the visceral fat, and not the total body fat content, a more significant factor of NAFLD in patients with the normal body weight vs. obese patients? If the answer is "yes", then are there currently more efficient alternatives to the use of BMI as an obesity marker for the NAFLD screening? There are a number of published studies promoting the idea that waist circumference is a more accurate indicator of adipose tissue distribution in the body, meaning that this is a better method for identification of a cohort with a significantly higher risk of cardiovascular diseases [1-3, 38, 39]. However, the widespread introduction of this simple and inexpensive diagnostic approach as a standard measure of obesity, especially in primary case settings, requires complete transformation of the diagnostic process. Waist circumference measurement will be an important component of obesity diagnosis, especially in patients with normal BMI. The fundamental question can sound as follows: "Is NAFLD in individuals with the normal body weight a separate clinical entity, which requires specific diagnostic and therapeutic approaches, or is it a subtype of the classic obesity-related NAFLD, responding to weight management, management of hyperlipidemia, arterial hypertension and insulin resistance?". Even in patients with the normal body weight with clinical and morphological signs of NAFLD, many metabolic health parameters are significantly altered: there are differences in triglyceride levels, waist circumference, log HOMA-IR, age, waist circumference vs. patients with the normal body weight, who does not suffer from NAFLD [38]. This fact allows drawing a conclusion that NAFLD in individuals with the normal body weight is a form of liver damage similar to that in obese patients [3]. At the same time, individuals with the normal body weight and NAFLD have a higher risk of hypertriglyceridemia, insulin resistance, central obesity and hyperuricemia vs. obese patients [3, 39].

We believe that this is essential to emphasise the attitude of the cohort under discussion to the diet and exercises. Numerous studies demonstrated that in overweight and obese patients with NAFLD, loss of 5% of the baseline weight is associated with clinical and laboratory stabilisation of NAFLD in 75% of cases [40]. It was found out later that a similar pattern can be observed in patients with NAFLD and normal body weight: after the loss of some weight (no more than 5% of the baseline value) and exercises, 57% of patients with the normal body weight showed repression of clinical and laboratory signs of NASH [22]. It is believed that the results can evidence that weight management and controlled exercises are useful and universal therapeutic approaches in the management of ***all*** patients with NAFLD.

Recently, drug management of NAFLD has been changing rapidly, and new approaches have been appearing; at the same time, it is essential to understand whether medicinal products developed for drug management of classical obesity-related NAFLD, are equally efficient for NAFLD patients with the normal body weight, which requires large-scale clinical trials. Such clinical trials should be conducted without delay, and potential efficacy of some drugs should be evaluated, e.g., of sodium-glucose linked transporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP1) agonists, obeticholic acid, pioglitazone and saroglitazar, a fixed combination of antagonists of glucose-dependent insulinotropic peptide/glucagon-like peptide 1.

Despite a lot of common pathophysiological components of NAFLD in individuals with various body weight, it is necessary to clearly define the key aetiological and pathophysiological factors, environmental factors, genetic characteristics in order to shape an individualised approach to the selection of the therapy and management of NAFLD patients with the normal body weight. The role of various diet factors and a specific nutrition composition have hardly been studied and compared to other significant risk factors of NAFLD in patients with the normal body weight. Numerous studies consistently prove the correlation between hepatic dysfunction and choline deficit, which is known to have a specific phenotype of diet-mediated obesity resistance. But are there any other nutrient factors, which might facilitate NAFLD development; and if there are any such factors, then how do they interact with functional genetic variants, as it can be observed, e.g., between choline and PEMT? Also, it is highly possible that there are other, yet unknown, environmental factors, for instance, biological or herbal supplements, promoting NAFLD development in individuals with the normal body weight.

Recent attempts to use cluster analysis turned out to be very interesting; it allows identifying five various diabetes subtypes, each of which is very specific in terms of patient characteristics and the risk of complications [39, 41]. It is obvious that the use of this classification model for patients with non-homogenous disease brings about more targeted therapy and management approaches as compared to a universal principle, which is currently applied. It is quite possible that a similar cluster analysis could be used also to characterise NAFLD progression: from the group of patients with relatively benign disease progression to patients with severe and progressive condition, which allows developing various therapeutic strategies for the patient management. Besides, studies in the group of NAFLD patients with the normal body weight should continue in order to evaluate the incidence of this form of disease in various geographical locations and ethnicities and to thoroughly analyse eating habits. An objective idea of the long-term sequelae of NAFLD in individuals with the normal body weight, characteristics of this disease variant, its progression rates and progression-promoting factors is the essential condition for the development of an adequate therapeutic strategy in the patient population in questions.

Other environmental factors such as intestinal dysbiosis, malnutrition, long-term drug therapy, parenteral feeding are the subject of a separate discussion and analysis of other, very versatile mechanisms of NAFLD development, including patients with the normal body weight [42, 43].

Therefore, NAFLD in patients with the normal body weight is a frequent clinical condition. The phenotype of these patients does not demonstrate (at least externally) any signs of metabolic illness as compared, e.g., to patients with NAFLD and obesity. It can be assumed that NAFLD developing in patients with the normal body weight and in lean patients is a clinical situation promoted by a composition of several conditions: diet, geographical location and ethnicity, genetic factors, age, and eating habits. At the same time, like with many things in life, a patient with the normal body weight is not the primary target of an attending physician trying to diagnose NAFLD and the rate of disease progression. Diet, choline consumption, alcohol consumption, menstrual function, age, ethnicity and geographical location, as well as hormone status evaluation are the subject of a separate examination in NAFLD patient with the normal body weight. In order to lower the NAFLD incidence in the population under discussion, a thorough development of screening for such patients, which is not tied to BMI values, is required. This patient cohort needs further thorough study; a therapeutic strategy should be actively developed, and patients should take more active part in clinical trials to evaluate the value and significance of diagnostic approaches and planned therapy.

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Стародубова А.В.: существенный вклад в разработку концепции или планировании научной работы, либо получение, анализ или интерпретацию работы

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МУКОВИСЦИДОЗ: НОВЫЕ ТЕНДЕНЦИИ В МЕТОДАХ ТЕРАПИИ

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Cystic Fibrosis: New Trends in Therapy Methods

Резюме

Несмотря на увеличение продолжительности и заметное улучшение качества жизни больных, на сегодняшний день муковисцидоз остается одним из тяжелых пульмонологических заболеваний, ведущим к инвалидизации. В связи с актуальностью проблемы терапии данного заболевания, ежегодно стартуют разработки новых препаратов для лечения муковисцидоза.

Данный обзор описывает новейшие достижения в лечении муковисцидоза, также представлены промежуточные результаты ведущихся клинических исследований. В процессе подготовки обзора были использованы различные базы научных данных: Scopus, Web of Science, EMBASE.

Описаны результаты исследований новых препаратов, предназначенных для противовоспалительной терапии данного заболевания — ацебилустата, препарата LAU-7b, JBT-101.

Рассмотрены результаты исследования альгината олигосахарида, снижающего вязкость мокроты у больных муковисцидозом. Эффект препарата был продемонстрирован на примере усиления действия антибиотика азтреонама, эффективного против Burkholderia cepacia complex — группы патогенных микроорганизмов, часто поражающих дыхательную систему больных муковисцидозом.

Описаны исследования различных препаратов генной терапии муковисцидоза — вещества ABO401, препарата SP-101, представлены результаты клинических исследований аденоассоциированного вектора 4D-710, липосомных наночастиц, в том числе препаратов MRT5005, RCT2100, таргетной терапии корректора галикафтора, комбинаций ивакафтор+лумакафтор, тезакафтор+ивакафтор, ивакафтор+тезакафтор +элексакафтор и ванзакафтор+тезакафтор+деутивакафтор.

Особенное внимание в обзоре было уделено доставке трансгена при помощи векторов, описаны преимущества и недостатки данного метода. Описаны основные современные методы геномного редактирования, их возможности, преимущества и недостатки.

Показана роль таргетной терапии как фактора, способного значительно уменьшать тяжесть течения заболевания. Препараты таргетной терапии способны частично восстанавливать функцию аномального белка у больных муковисцидозом, а значит снижать степень проявления симптомов и значительно повышать качество жизни пациента. Описана необходимость дальнейшей разработки данного направления.

Ключевые слова: *муковисцидоз, обзор, таргетная терапия, противовоспалительная терапия, генная терапия, геномное редактирование, вирусный вектор, патогенетическая терапия*

Конфликт интересов

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

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Abstract

This review provides information on recent advancements in the treatment of cystic fibrosis and presents interim results from ongoing clinical trials. Various scientific databases, including Scopus, Web of Science, and EMBASE, were utilized during the preparation of this review.

The results of studies on new drugs such as acebilustat, LAU-7b, JBT-101 designed for anti-inflammatory therapy of this disease are also presented.

The review describes various approaches to cystic fibrosis therapy — substance ABO401, SP-101. It includes clinical trial results for the adeno-associated vector 4D-710, liposomal nanoparticles, including the drugs MRT5005, RCT2100, the corrector galicaftor, as well as the drugs lumacaftor+ivacaftor, tezacaftor+ivacaftor, tezacaftor+ivacaftor+elexacaftor и tezacaftor+vanzacaftor+deutivacaftor.

Special attention is given to transgene delivery using vectors with a detailed discussion of the advantages and disadvantages of this method. The main modern genome editing techniques, their capabilities, advantages and disadvantages are also described.

The results of the study on the oligosaccharide structures, which reduces sputum viscosity in patients with cystic fibrosis, are presented. This reduction in viscosity enhances the effectiveness of the antibiotic aztreonam, which is active against the Burkholderia cepacia complex — a group of pathogens, which is often responsible for inflammation in cystic fibrosis patients.

The role of targeted therapy as a factor capable of significantly reducing disease severity was highlighted. Targeted therapy drugs can partially restore the function of the abnormal protein in cystic fibrosis patients, thereby reducing symptom severity and significantly improving the patient's quality of life. The necessity of further development in this field was emphasized.

Key words: *cystic fibrosis, review, targeted therapy, genetic therapy, gene editing, genetic vector*

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DNA — deoxyribonucleic acid, CFTR — cystic fibrosis transmembrane conductance regulator

Introduction

One of the most common genetic diseases globally is cystic fibrosis; its manifestations deteriorate the quality of patients' lives, forcing them to fight for preservation of their usual functions. The therapy of cystic fibrosis is currently one of the burning topics in healthcare. The importance of this problem for the healthcare system is that, despite early diagnosis of cystic fibrosis, this disease is associated with short patient life and results in early disablement. This article discusses the key areas of therapy development for the treatment of cystic fibrosis and presents results of recent studies in this area. This literature review analyses articles from Scopus, PubMed, Free Medical Journals, eJournals for the past five years.

Cystic fibrosis is a systemic, genetically determined disease

Cystic fibrosis is a genetically determined, autosomal-recessive disease, which is characterised by the involvement of all exocrine glands [1]. An initial defect in the cystic fibrosis transmembrane conductance regulator (CFTR) causes dysfunction of a number of organs and systems, including pathologies of the respiratory system, intestine and reproductive system. This is a systemic disorder, requiring a specific therapeutic approach [2]. On the average, one child in every 4,500–6,000 newborns has cystic fibrosis, and the mean life expectancy in patients with cystic fibrosis varies from 28 to 47.7 years old [3].

This disease is monogenetic: the gene of cystic fibrosis is located on the long arm of the 7th chromosome (the most common mutation in this gene is F508del) and encodes CFTR protein. This protein participates in the active transport of chlorine ions. Currently, mutations in the gene of CFTR protein are divided into seven groups; however, gene therapy can be used for correction of several of them. A mutation results in CFTR protein dysfunction, causing changes in ion transport processes: the number of chlorine ions and water molecules excreted via CFTR protein drops. In turn, it results in changes in the composition and viscosity of exocrine gland secretory product. Thus, one of the most important pathogenetic links in cystic fibrosis development is impaired transportation of a thick secretory product: its movement slows down [4]. A comprehensive therapy of cystic fibrosis should include genetic, pathogenetic (target) and symptomatic therapy.

Genetic therapy of this condition is a subject to wide discussions. Recent studies bring hope that in the future this therapy will contribute to the treatment of cystic fibrosis; however, currently the backbone is targeted therapy [5].

Anti-inflammatory therapy

As of today, anti-inflammatory therapy is one of the most important components in the therapy of cystic fibrosis. This is due to the severity of the intoxication syndrome, which significantly affects the quality of patients' life.

Acebilustat is a synthetic low-molecular leukotriene A4 hydrolase inhibitor; it inhibits leukotriene B4 production, which participates in the pathogenesis of cystic fibrosis as a result of attracting neutrophils to the inflammation site. A randomised, double-blind study of acebilustat demonstrated that, although the drug did not impact the forced expiratory volume over the first second, it delayed and reduced pulmonary exacerbation in subjects [6].

LAU-7b is a synthetic fenretinide analogue of retinol, which targets cell membrane lipids by affecting protein transport and inflammation. LAU-7b can trigger immune-mediated neutrophilic reaction, which blocks bacterial elimination from the site and slows down inflammation. A randomised, double-blind phase II study of LAU-7b demonstrated favourable effect on respiratory function preservation in subjects [7].

JBT-101 is mentioned as an anti-inflammatory drug, which is a type II non-immunosupressive cannabis-receptor agonist, stimulating inflammation elimination due to an increase in the production of special mediators and reduction in inflammatory molecule concentration. The drug demonstrated positive results in the study of its effects in cystic fibrosis patients: inflammation subsided, and patients noted reduction in disease-related pain [8].

One of the most significant factors affecting the quality of life and life expectancy of cystic fibrosis patients is efficient management of bacterial lung damage. One of the most common pathogens observed in cystic fibrosis patients is closely related gram-negative bacteria Burkholderia cepacia [9].

In a randomised, double-blind study, Fischer R., et al. (Journal of Cystic Fibrosis, 2022) evaluated alginate oligosaccharide, which makes mucous in cystic fibrosis patients less viscous. It proved to be efficient in enhancement of the action of aztreonam: the study analysed the reduction rate of microbial load of Burkholderia cepacia complex after the use of a combination of alginate oligosaccharide and aztreonam vs. aztreonam and placebo. The effect was demonstrated with the combined use of alginate oligosaccharide solution for inhalation and aztreonam. Six out of twelve quality criteria in study subjects showed relative improvement after the use of alginate oligosaccharide vs. placebo [10].

Gene therapy

Since the *CFTR* gene was discovered, over 2,000 genetic variants of the gene have been identified. This finding brought hope for possible correction of this erroneous variant and insertion of a normal copy of the gene. However, CFTR sensibility to modulators is far from 100%. Approximately 10% of cystic fibrosis patients have mutations, where CFTR protein either is not synthesised at all or is synthesised in insufficient amounts, making patients insensitive to CFTR modifiers. Also, there are reports on individual intolerance of these products, which is observed in 10–20% of cystic fibrosis patients [11].

One gene therapy involves transgene delivery by adenovirus-associated vectors. Studies of this therapy report absence of any favourable or side effects. Later, studies in this field aimed to boost tropism of adenovirus-associated vectors; find unknown vector serotypes; search for new promotors; enhance expression levels of a required protein; and find it in the lungs. Also, an important component of studies was attempts to lower the immunological potency of these vectors [12].

Studies in this area are conducted by several large companies. Abeona Therapeutics has completed preclinical trials of ABO401. This product is a capsid of an adenovirus-associated vector, serotype 204, and contains a functional copy of human *mini-CFTR gene*. Its potential benefits include high specificity as regards the lung epithelium and possible transduction of bronchial cells and nasal epithelial cells [13].

Spirovant Sciences is developing SP-101. It uses an adenovirus-associated vector capsid with high tropism towards lung epithelium cells. In 2020, the US Food and Drug Administration (FDA) assigned this product the status of an orphan medicinal product [12].

4D Molecular Therapeutics is conducting phase 1/2 clinical trials of 4D-710. The results of lung biopsy material of subjects sampled on week 4–8 after therapy initiation show absence of any signs of pulmonary inflammation, as well as approx. 400% increase in CFTR protein expression vs. materials sampled from healthy subjects. Also, there were no reports of safety concerns of the product [14].

Another gene therapy is transgene delivery by lentivirus vectors. The benefits of these vectors include relatively long duration of expression and possible preservation of the required transgene in cells even if they divide. It is achieved due to low immunological potency, possible integration of various populations in cells, and their integration in their genome. Drawbacks of these genes are potential potentiation of insertion mutagenesis and higher risks of neoplastic aberration of cells. Currently, trials in this area are in the pre-clinical phase [12].

A separate group of gene therapies of cystic fibrosis includes non-virus transgene delivery using liposomes and polymer nanoparticles. The benefits of using liposomes to deliver transgene are simplicity of scaling and high informational capacity, making them safe and efficient, as demonstrated by clinical trials [15].

When comparing liposome nanoparticles for the packing and delivery of chemically modified messenger RNA of CFTR protein to ivacaftor, both these products demonstrate comparable efficiency, evidencing the possibility of using the former in the therapy of cystic fibrosis [16].

Currently, an inhalation product, which could deliver intact messenger RNA of CFTR protein to the lung tissue, has been actively developed. The first clinical study of the inhalation delivery by liposome nanoparticles in cystic fibrosis patients was conducted using MRT5005. The study show that the forced expiratory volume per 1 second remained stable, with no improvements for the patients; however, the product demonstrated safety and relatively good tolerability [17]. Despite completed phase 1 and 2 clinical trials of MRT5005, there is no official information on the transition to phase 3, or project completion.

ReCode Therapeutics has been conducting phase 1b clinical trials to evaluate the safety of RCT2100, an inhalation gene therapy using liposome nanoparticles [18].

In pre-clinical studies, CFTR messenger RNA delivered by a liposome nanoparticle, selectively targeting the organs, restored CFTR protein function in the lung cells, sampled from cystic fibrosis patients. These results demonstrate potential efficacy of the product in cystic fibrosis patients, who do not respond to the existing target therapy [19].

Results of studies of the use of polymers have been published. One study demonstrated the possibility to improve the quantity of liposome nanoparticles penetrating mucous layers due to particle covering with polyethylene glycol at the molecular level. This approach allowed boosting the efficacy of nucleic acid administered to murine lung cells in vivo [12].

Of note, one of the crucial tasks of the gene therapy is improving the method of gene structure delivery to epithelial cells because of mucous present on the epithelial surface, mucociliary clearance, and deeper location of the epithelial stem cells. Due to the constant cellular turnover, this therapy faces the need for repeated gene structure delivery, and it is associated with a higher risk of spontaneous cell mutagenesis. Also, there is a risk of immune response to the vector protein. In addition, currently, there is no comprehensive information regarding the types of cells, which should be the primary target of the therapy in order to ensure the highest treatment efficacy; and there are no reports on the possible action of the product on several target cells at a time [20–22].

Genome editing

This method allows correcting a gene mutation and, basically, saving the individual from their disease, i.e. cystic fibrosis in this case. Several techniques can be used for genome editing.

CRISPR/Cas9: this method is based on generation of a breakage defect in deoxyribonucleic acid (DNA) using CRISPR-associated endonucleases (proteins Cas), which are specifically programmed. The accuracy of this method is a result of the action of a specific directing ribonucleic acid, which is complementary to the target chain of the DNA section. The method is highly efficient, since a specific target gene can be selected, and several aberrant genes can be edited at once. Gene correction with the CRISPR/Cas9 system is possible using only one protein; and ribonucleic acid, which directs the gene editing process, can be purchased or synthesised in the laboratory over a short period of time, making this technique not only an accurate, but also an inexpensive method. The drawback of the method is the large size of protein Cas9, which cannot fit in the adenovirus-associated vector [23].

ZFN — zinc finger nucleases. These are protein domains, the composition of which includes zinc and the structure of which resembles a finger. Each domain can form a unique link only with its specific three-nucleotide DNA section. The benefit of the method is its low immunological potency and small protein size; however, drawbacks are superior: the method can cause numerous damages to the integrity of DNA strands, which are initially not a target of a specific ZFN complex. Also, the costs of reproducing a specific ZFN type in laboratory settings are high, and this process is technologically challenging [24].

TALEN is a technology based on the operation of domain structures, which are complementary not to the three-, but one-nucleotide sequence. This method is associated with fewer cytotoxic effects, but it is sensitive to DNA methylation and is less efficient [25].

Base editing is a method of genome editing based on transformation of a specific letter in the DNA text. Base editors can edit only specific types of single base change (C→T, G→A, A→G, T→C), but cannot correct other specific mutations (e.g., C→A or G→T). At the same time, unlike CRISPR/Cas9, no double-stranded breakages are created. The efficacy of this method is high, since there are no random insertions and deletions because DNK remains intact. Still, this system is too large to be delivered by adenovirus-associated vectors, and it is quite challenging to edit a DNA sequence, where several A or C residues are close to one another [26].

Prime editing is a genome editing, using a modified enzyme Cas9, which cuts a non-complementary DNA chain and builds a new chain with the help of reverse transcriptase and specific pgRNA (prime editing guide RNA). The method is quite efficient as it can correct various types of mutations (insertions, deletions, single base changes); however, the system is still too big for adenovirus-associated vectors and bears a risk of adverse effects for a non-target DNA sequence, as well as mutagenesis for the target sequence [27].

At the moment, the outlooks of wide application of this genome editing method are quite vague, because the number of successfully corrected mutations is low. However, genome editing using the prime editing method in cystic fibrosis patients is promising for the future genetic engineering studies.

Target therapy

There are molecules, which can partially restore the function of abnormal CFTR protein, making its structure close to normal. A therapeutic approach depends on the class of mutation.

At the moment, the most current therapy is the use of CFTR modifiers, i.e. products, which directly restore protein functions. These products include potentiators, correctors, amplifiers, stabilisers [28].

Potentiators target class III mutations, where regulatory CFTR domains function incorrectly, causing production of a normal amount of non-functional CFTR protein on the cell membrane; and class IV mutations, where chloride transport via the ion channel decreases due to its very fast closure. Potentiators, including ivacaftor (VX-770) and genistin, affect the mutated CFRT protein located in the apical cell membrane, triggering the ion channel and promoting its opening.

Lumacaftor (VX-809), curcumin, 4-phenylbutyrate/genistin, sildenafil analogue (KM11060), tezacaftor (VX-661) are correctors. They target class II mutations, since correctors create conditions, where mutant CFTR protein moves to the apical membrane, where the protein takes the correct configuration [28].

At the moment, patients with class I mutations are treated with products, which stimulate stop codon reading in messenger RNA, ensuring continued translation of CFTR protein. They include, for instance, ataluren, a product used for the treatment of Duchenne muscular dystrophy. Currently, there is not enough evidence to determine the efficacy of ataluren in the therapy of cystic fibrosis patients with class I mutations. An earlier study reported favourable results of the use of ataluren in a post hoc analysis in subgroups of subjects, who were not treated with inhalation aminoglycosides for a long time; however, these results were not reproduced in a later study, suggesting that the earlier results could have been random [29].

Two other groups of products — amplifiers and stabilisers — are currently studied and are not used in clinical settings. Amplifiers reconstruct protein translation during ribosome movement along the messenger RNA; this is how PTI-428 works. Stabilisers prolong the period, during which CFTR remains in membrane plasma.

First generation CFTR modifiers should be discussed separately. The first potentiator, which was used in clinical settings, is ivacaftor (VX-770). Ivacaftor is used mostly for patients with mutation G551D. This pathological mutation causes delayed CFTR channel opening. Therefore, its efficacy in patients with the most common CFTR mutation — F508del — increases if it is used in a combination with a corrector (lumacaftor or tezacaftor) [30, 31].

These conclusions underlie the development of a new product — lumacaftor+ivacaftor, a second CFTR modifier, which has dual action on the pathogenetic target. This product is the first CFTR modifier registered in the Russian Federation in December 2020. Lumacaftor+ivacaftor combination is associated with the following side effects: high blood pressure, worsening of short-term respiratory symptoms [32, 33]. However, despite the correlation with the identified side effects, the product is very efficient regarding the bronchopulmonary system and the rate of exacerbations. This combination is safe, and the majority of side effects are not side reactions, but complications of the disease, and resolve within two weeks with therapy. Also, if the starter dose is reduced for the first two weeks of the therapy, the rate and severity of side effects can be corrected [34].

The third first generation CFTR modifier (tezacaftor+ivacaftor) is used in children over six years of age, who have heterozygous mutation F508del or homozygotic mutation F508del/F508del; this combination has demonstrated better results and safety in clinical settings vs. lumacaftor+ivacaftor [35].

Galicaftor (ABBV-2222, previously known as GLPG2222) is a new corrector developed by AbbVie. The use of this product in a study resulted in significantly reduced chloride levels in sweat. While the product was well tolerated, it did not demonstrate any clinically significant increase in forced vital capacity values in cystic fibrosis patients. At the same time, high doses of galicaftor, used as a monotherapy in heterozygous patients with mutation F508del, as well as galicaftor+ivacaftor, used in homozygotic patients with mutation F508del, demonstrated a higher percent of estimated forced expiratory volume over the first second and reduced sweat chloride levels [36, 37].

Let's discuss second generation CFTR modifiers. Iva caftor+tezacaftor+elexacaftor is the first second generation modifier for the therapy of patients over six years of age. This product, developed by Vertex Pharmaceuticals and combining triple therapy, which can be used in children with cystic fibrosis, has proven safety. A one-year follow-up of children treated with this product showed positive dynamics in functional capacities and functional resistance [38].

Ivacaftor+tezacaftor+elexacaftor, combining a CFTR corrector and CFTR potentiator, demonstrates high efficacy among target therapy products for the therapy of cystic fibrosis. This combination makes it possible to boost CFTR functions on the cell surface, resulting in higher CFTR activity, i.e. the genetic defect is corrected, if the patient has a respective mutation in their genome. Study results show weight and height gain, better body mass index, and normal sweat test results in cystic fibrosis patients (in 28.5% of subjects). Also, there are reports on significantly improved pulmonary functions: higher forced vital capacity and forced expiratory volume over the first second [39].

It is known that the product is efficient not only for its primary objectives, it has favourable effects on

chronic rhinosinusitis progression in cystic fibrosis patients: nasal polyps disappear, and paranasal sinus pneumatisation significantly improves [40].

Vertex Pharmaceuticals is currently developing a product with a novel triple combination as a next generation successor of ivacaftor+tezacaftor+elexacaftor. The product contains tezacaftor, one of the three modifiers, used in ivacaftor+tezacaftor+elexacaftor, together with two novel modifiers — vanzacaftor (VX-121) and deutivacaftor (VX-561). Deutivacaftor is an ivacaftor analogue, where one of tert-butyl groups was substituted with a deuterated group. This modified version of ivacaftor demonstrated comparable pharmacological activity in pilot studies. Also, deutivacaftor is more stable in the body, so it could be taken once daily. That is why tezacaftor+vanzacaftor+deutivacaftor was initially developed to improve compliance of patients with cystic fibrosis therapy, because, unlike ivacaftor+tezacaftor+elexacaftor, it would be taken once instead of twice daily [36].

In 2025, Vertex reported results of three phase 3 clinical trials, where itezacaftor+vanzacaftor+deutivacaftor was studied vs. ivacaftor+tezacaftor+elexacaftor in cystic fibrosis patients with responsive mutations: SKYLINE 102 and SKYLINE 103 studies, evaluating over 1,000 adults and young people over 12 years of age [41].

At the same time, a third study, RIDGELINE 105, was conducted, where vanzacaftor+tezacaftor+deutivacaftor was tested in children between 6 and 11 years of age. Results demonstrated that patients had stable respiratory function both with ivacaftor+tezacaftor+elexacaftor and the novel therapy; however, the novel therapy turned out to be more efficient in reduction of sweat chloride ion levels, indirectly proving higher CFTR protein levels [42].

Conclusion

Cystic fibrosis is a genetic condition, where exocrine glands and body systems function incorrectly. The main cause of the disease is *CFTR* gene mutation, resulting in dysfunction of the protein responsible for chloride ion and water transport. As a consequence, secret viscosity increases, and its transport slows down. The main therapy as of today is target therapy.

Anti-inflammatory therapy is essential for the management of cystic fibrosis. Acebilustat allowed delaying and mitigating pulmonary exacerbations in patients, despite no effect for the forced expiratory volume over the first second. LAU-7b preserved pulmonary function in subjects in a randomised, double-blind study. JBT-101 demonstrated inflammation reduction, and patients reported improvement in their pain syndrome. Unlike the mentioned products, alginate oligosaccharide demonstrated efficiency due to reduced mucous viscosity.

Gene therapy of cystic fibrosis is very promising. Adenovirus and adenovirus-associated vectors are being actively studied in order to reduce their immunological potency and boost CFTR protein expression. Adenovirus-associated products ABO401 and SP-101 have promising benefits of high specificity in relation to epithelial cells, while 4D-710 significantly increases CFTR protein production. The benefits of lentivirus vectors are long-term gene expression, but there is also a risk of oncogenic cell transformation. Non-viral methods of transgene delivery using liposomes demonstrated their efficacy and safety. Unlike MRT5005, RCT2100 restored CFTR protein function in pulmonary cells of patients. Currently, studies are ongoing to evaluate promising delivery methods using polymer nanoparticles, and possible solutions to the objectives of the gene therapy are studied.

Genome editing methods make it possible to target *CFTR* gene mutations. CRISPR/Cas9 is the most precise technique; however, it requires modifications because of the protein Cas9 size. ZFN and TALEN are less efficient and more expensive methods. Base editing and prime editing allow editing DNA without two-strand breakages, but they have limitations due to the system size and side effects. Genome editing cannot be used in clinical settings, but is being actively studied.

Target therapy is the main therapy for cystic fibrosis; its objective is partial restoration of CFTR protein function. At the moment, the most common therapy is the use of CFTR modifiers. These are potentiators, correctors, amplifiers, and stabilisers. Potentiators (ivacaftor) facilitate ion channel opening and are usually used in a combination with other classes of modulators. Correctors assist CFTR protein in reaching the apical cell membrane and are used in combinations with other products Two other groups of products (amplifiers and stabilisers) are being studied.

Despite good tolerability of galicaftor, it did not demonstrate any efficacy in improving the forced vital capacity. Nevertheless, a combination of galicaftor and ivacaftor in homozygotics carriers of mutation 508del resulted in a higher percent of estimated forced expiratory volume over the first second and reduced sweat chloride levels.

Lumacaftor+ivacaftor, a combined CFTR modifier, demonstrated efficacy and is the first CFTR modifier registered in the Russian Federation. Associated side effects are merely a complication of the underlying disease and are corrected with the starter dose reduction. Tezacaftor+ivacaftor, another first generation CFTR modifier, demonstrated even better results and safety. Ivacaftor+tezacaftor+elexacaftor demonstrates high efficacy among target therapy products in patients with cystic fibrosis. The product boosts patients' functions and improves their quality of life. Ivacaftor+tezacaftor+elexacaftor has favourable effects for the associated otorhinolaryngologic pathology. Modified tezacaf

tor+vanzacaftor+deutivacaftor combination gives high hopes. This product has been studied, and results show reduced sweat chloride levels, indirectly pointing out to higher CFTR protein levels. Also, the product is more efficient as compared to ivacaftor+tezacaftor+elexacaft or; it is associated with better compliance as it is taken only once daily.

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ОСОБЕННОСТИ СОСТОЯНИЯ СИСТЕМЫ КОЛЛАГЕНОЛИЗА И ФАКТОРЫ РИСКА ЕЕ ИЗМЕНЕНИЙ У ПАЦИЕНТОВ ПРИ ДЛИТЕЛЬНОМ ПОСТКОВИДНОМ СИНДРОМЕ

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Features of the State of the Collagenolysis System and risk factors of Its Changes in Patients with Long-Term Post-COVID Syndrome

Резюме

Цель: оценить состояние системы коллагенолиза у пациентов при длительном постковидном синдроме, определить особенности и факторы риска ее изменений. **Материалы и методы исследования.** В исследование было включено 178 пациентов (мужчин — 59, женщин — 119; возраст 57,15±12,4 лет) после перенесенной новой коронавирусной инфекции (НКВИ) 12 и более недель назад. В зависимости от наличия или отсутствия симптомов длительного постковидного синдрома пациенты, перенесшие НКВИ 12 и более недель назад, были разделены на 2 группы: первую группу составили 88 пациентов с симптомами «Long-covid»; вторую группу — 90 обследуемых без каких-либо симптомов «Long-covid». **Результаты.** Средний период после перенесенной НКВИ составил 8,5[3,6;12,4] месяцев. У всех пациентов, перенесших НКВИ, тканевый ингибитор матриксных металлопротеиназ 1 типа (TIMP1) был выше референсного значения (135 пг/мл). У пациентов первой группы TIMP1 был ниже, чем во второй группе: 315,5 [145,0;410,0] пг/мл против 513,5 [415,0; 865,0] пг/мл (p <0,001). Следовательно, при длительном постковидном синдроме развивается коллагенолитический паттерн на фоне увеличения риска формирования фиброза. **Заключение.** У пациентов, перенесших НКВИ, с длительным постковидным синдромом состояние системы коллагенолиза характеризуется развитием коллагенолитического паттерна на фоне преобладающих процессов коллагенообразования в сравнении с бессимптомными пациентами, перенесшими НКВИ 12 недель назад и более, который может быть рассмотрен как патогенетический механизм формирования «Long Covid».

Ключевые слова: *система коллагенолиза, длительный постковидный синдром*

Конфликт интересов

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

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Авторы заявляют об отсутствии финансирования при проведении исследования

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До начала исследования было получено одобрение Этического комитета на его проведение, а также на формы информированного согласия больного, которые до включения в исследование были подписаны всеми больными.

Протокол исследования был одобрен локальным этическим комитетом «Пермского краевого клинического госпиталя для ветеранов войн» (№ 137 от 21.04.2020)

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Abstract

Objective: to assess the state of the collagenolysis system in patients with long-term post-COVID syndrome, to determine the features and risk factors of its changes. **Materials and methods.** The study included 178 patients who had had a new coronavirus infection (NCVI) 12 weeks or more ago, depending on the presence or absence of symptoms of long-term post-COVID syndrome, patients who had NCVI 12 or more weeks ago were divided into 2 groups: the first group consisted of 88 patients with Long-covid symptoms; the second group consisted of 90 subjects without any symptoms of Long-covid. **Results.** The median period after NCVI was 8.5 [3.6; 12.4] months. In all patients who underwent NCVI, tissue inhibitor of matrix metalloproteinase type 1 (TIMP1) was higher than the reference value (135 pg/ml). In the patients of the first group, TIMP1 was lower than in the second group: 315.5 [145.0; 620.0] pg/mL vs. 513.5 [220.0; 865.0] pg/mL ($p<0.001$). Therefore, in long-term post-COVID syndrome, a collagenolytic pattern develops against the background of an increased risk of fibrosis. **Conclusion.** In patients who have undergone NCVI with a long-term post-COVID syndrome, the state of the collagenolysis system is characterized by the development of a collagenolytic pattern against the background of the prevailing processes of collagen formation in comparison with asymptomatic patients who had NCVI 12 weeks ago or more, which can be considered as a pathogenetic mechanism for the formation of "Long Covid".

Key words: *collagenolysis system, long-term post-COVID syndrome*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

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TIMP1 — tissue inhibitor of matrix metalloprotease, type 1, ILAV — indexed left atrium volume, LVMMI — left ventricle myocardium mass index, LVMM — left ventricle myocardium mass, NCVI — novel coronavirus infection, MMP — matrix metalloproteinase, PCR test — polymerase chain reaction, GFR — glomerular filtration rate, CKD — chronic kidney disease, LV EF — left ventricle ejection fraction, LV — left ventricle, echoCG — echocardiography, AUC — Area Under Curve, ROC — Receiver Operating Characteristic, cSPAP — calculated value of systolic pulmonary arterial pressure, WC — waist circumference, OR — odds ratio, RR — relative risk, PWVcf — carotid-femoral pulse wave velocity, CAVI — cardio-ankle vascular index, TNF-α — tumour necrosis factor alpha

Introduction

The long-lasting post-COVID syndrome is a real challenge to the healthcare system [1]. According to various estimates, two (2) to 86% of patients suffer from the long-lasting post-COVID syndrome [2, 3]. There are more and more evidences of new risk factors and pathogenic mechanisms of the so-called long COVID.

The main pathophysiological hypotheses to explain persistent post-COVID-19 symptoms are direct viral toxicity, endothelial damage, dysregulated immune response, hyperinflammation, hypercoagulation and poor adaptation of angiotensin converting enzyme [4].

One of the most speculative areas pertaining to the pathological pathways of development of long-lasting post-COVID syndrome, is the state of the collagen disorganisation system and its changes, determined on the basis of the ratio between matrix metalloproteinases (MMPs) and their inhibitors. There are two contrary hypotheses: some researchers present evidences of profibrotic process progression, while others mention collagen disorganisation activation and an increase in MMPs [5, 6].

In this study, we attempted to demonstrate the collagen disorganisation status of post-NCVI patients, who have long-lasting post-COVID syndrome, and asymptomatic patients, using the concentration of an integrated index, i.e., tissue inhibitor of matrix metalloprotease, type 1.

Objective of the study is to evaluate the collagen disorganisation status of patients with post-COVID syndrome; to identify the features and risk factors of its changes.

Materials and Methods

Before commencement, the study was approved by the Ethics Committee, and all informed consent forms were signed by all patients.

An observational, cross-sectional clinical study was conducted for a period from 2021 to 2024 in outpatient settings. Out of 802 patients, who needed medical attention, 178 patients were enrolled in the study (59 males, 119 females; age: 57.15 ± 12.40 years old); they had NCVI at least 12 weeks before enrolment, met the inclusion criteria and did not have any of the non-inclusion criteria.

Inclusion criteria: outpatient patients aged 18+ years old, who had NCVI confirmed with polymerase chain reaction test (PCR test) and smear test for SARS-CoV-2.

Non-inclusion criteria were any acute infections; pneumonia; exacerbation of chronic bronchopulmonary diseases; myocardial infarction or unstable angina, pulmonary embolism, acute decompensated cardiac insufficiency within three months before the enrolment; congenital and acquired cardiac defects; severe renal conditions; chronic kidney disease (CKD), stage 4–5; haematologic and rheumatologic diseases; history of malignancies and active tumours; acute inflammation; cognitive disorders and mental conditions; refusal to sign the informed consent form.

Depending on the presence or absence of the symptoms of long-lasting post-COVID syndrome, patients, who had NCVI at least 12 weeks ago, were divided into two groups: the first group were 88 patients with the long COVID symptoms (30 males, 58 females; age: 56.39 ± 12.8 years old); the second group comprised 90 subjects without any long COVID symptoms (29 males, 61 females; age: 55.69 ± 10.97 years old).

The long-lasting post-COVID syndrome (long COVID) was verified in accordance with the recommendations of the World Health Organisation [7].

In addition to the routine clinical, laboratory and instrumental examinations, all patients underwent iron exchange assessment.

All patients underwent echocardiography (echoCG) using Vivid S5 device (General Electric, USA), and the following parameters were measured: Simpson's left ventricle ejection fraction (LV EF); the ratio of E mean (the highest velocity of early LV filling) to e' mean (early diastolic velocity of fibrous ring) based on tissue Doppler sonography; LV myocardial mass index (LVMMI) for individuals with the normal body weight (LVMM/body surface area) and obese individuals (LVMM/height^{2,7}); indexed left atrium volume (ILAV); calculated value of systolic pulmonary arterial pressure (cSPAP); tricuspid annular plane systolic excursion (TAPSE); right atrium arterial interference (RAAI) as TAPSE to cSPAP ratio.

All patients underwent 3D sphygmoplethysmography using VaSeraVS-1000 device (Fucuda Denshi, Japan), and the following parameters were measured: mean cardio-ankle vascular index (CAVI1); pulse wave velocity (PWV) in the carotid-femoral segment (PWVcf) (right and left); PWV in the shoulder-ankle segment (right and left) (R-PWV and L-PWV); B-PWV in the brachial artery (B-PWV); PWV in the aorta (PWVa); C-PWV in the carotid (C-PWV); augmentation index (R-AI).

In order to evaluate the calculated renal filtration function, blood creatinine and cystatin C levels were measured; glomerular filtration rate (CKD-EPIcre and CKD-EPIcys using an online calculator) and morning urine albumin/protein to creatinine ratio were calculated [8]. Serum cystatin C concentration was determined by ELISA using Expert Plus Microplate reader (Biochrom Ltd., UK) and Vector-Best reagent kit (Novosibirsk, Russia).

The inflammatory process was evaluated by measuring tumour necrosis factor alpha (TNF-α) and interleukin-1β by ELISA using Vector-Best reagent kit (Novosibirsk, Russia) and Lazurite reader (Dynex Technologies Inc., USA).

The collagen disorganisation status was assessed by measuring the concentration of the integrated index, i.e., tissue inhibitor of matrix metalloprotease, type 1 (TIMP1), by ELISA using SEA 552Hu kit from Cloud-Clone Corp. (USA/China) and Stat Fax 2100 photometer (Awareness Technology, USA).

STATISTICA 10.0 (v.10.0.1011) was used for statistical processing of results. For the quantitative attributes, the arithmetic mean value (M) ± standard deviation (SD) or the median value with the lower and upper quartile (Me [LQ; UQ]) were calculated, depending on their degree of normality of distribution. The type of distribution was analysed using Shapiro-Wilk and Kolmogorov-Smirnov tests. For the qualitative attributes, the absolute frequency and percentage (%) were calculated. For the comparison of data in both groups depending on their distribution, both parametric and non-parametric statistical methods were used: for quantitative attributes — Student t-test or Mann-Whitney test; for qualitative attributes — χ^2 test. The significance level of the zero statistic hypothesis was $p < 0.05$. In order to analyse the relationship between the quantitative attributes outside the normal distribution, Spearman's rank correlation was used; for qualitative

Table 1. *Characteristics of patients included in the study (n=178)*

Indicator		Significance
Sex (total included in the study, n — 178), n (%)	men	56/31,5
	female	122/68,5
Age (total included in the study, n — 178), ages, MS±D	men	55 [45,75;62,25]
	female	60 [48,0;66,75]
Sex (with the symptoms of «Long-covid», n — 88), n (%)	men	30/34,1
	female	58/65,9
Age (with the symptoms of «Long-covid», n — 88), ages, Me[LQ; UQ]	men	57 [46,25;65,5]
	female	60 [47,25;67,75]
Sex (without the symptoms of «Long-covid», n — 90), n (%)	men	26/32,2
	female	64/67,8
Age (without the symptoms of «Long-covid», n — 90), ages, Me[LQ; UQ]	men	54 [45,5;61,0]
	female	59 [48,0;66,0]
Comorbid pathologies:	GD + BA, abs./%	24/13,5
	GD + BA + type 2 DM, abs./%	9/5,1
	GD + BA + COPD, abs./%	8/4,5
Obesity:	I degree, abs./%	54/30,3
	II degree, abs./%	26/14,6
	III degree, abs./%	10/5,6
Smoking:	quantity, abs./%	40/22,5
	seniority, ages, Me[LQ; UQ]	12 [7;22,5]
Have been immunized against COVID-19, abs./%		22/12,4
	Therapies received by patients	
Beta-adrenoblockers, abs./%		61/34,3
Thiazides / thiazide-like/loop diuretics, abs./%		28/15,7
iACE, abs./%		26/14,6
ARBs, abs./%		52/29,2

Note. GD — hypertensive disease, BA — bronchial asthma, type 2 DM — type 2 diabetes mellitus, COPD — chronic obstructive pulmonary disease, iACE — angiotensin-converting enzyme inhibitors, ARBs — angiotensin receptor blockers

attributes, the mutual contingency coefficient developed by A. A. Chuprov was used [9]. The significance level of the zero statistic hypotheses in the evaluation of relationships was $p < 0.05$. In order to select a TIMP-1 value as a parameter representing the collagen disorganisation status, to identify the risk factors of its changes in patients with long post-COVID syndrome, the cutoff point was identified using the ROC curve for all values, with the calculation of the area under curve (AUC) of > 0.5 at $p < 0.05$ and operational characteristics of sensitivity and specificity. To determine odds ratios (OR), relative risk (RR) and 95% CI for OR and RR, 2×2 contingency tables were made; χ^2 value was calculated with determination of the achieved significance level with Yates' correction for continuity.

Results and Discussion

The mean period after the past NCVI was 8.5 [3.6;12.4] months. Evaluation of the integrated index TIMP1 demonstrated compromised collagen disorganisation status in all post-NCVI patients, manifesting mostly as its transformation towards collagen production with respective TIMP1 levels above the reference threshold (135 pg/mL). However, in group 1 patients with long-lasting post-COVID syndrome, TIMP1 exceeded the reference values, still it was lower than in group 2, i.e., asymptomatic patients: 315.5 [145.0;410.0] pg/mL vs. 513.5 [415.0; 865.0] pg/mL ($p < 0.001$). The data show that patients with long-lasting COVID-syndrome develop a collagenolytic pattern caused by an increased risk of fibrosis.

In order to further analyse fibrotic processes in patients with long post-COVID syndrome, a decision was made to find a cut-off point for all TIMP1 values by plotting a ROC curve and to perform classification depending on the presence of long-lasting post-COVID syndrome (Fig. 1).

For TIMP1 values in all post-NCVI patients, the obtained cut-off point was between ≤ 410 pg/mL and > 135 pg/mL, with sensitivity of 78.3% and specificity of 73.7% (AUC=0.786, p=0.001). In group 1, 57 (64.8%) patients had TIPM1 value between ≤ 410 pg/mL and > 135 pg/mL, in group 2 — 18 (20.0%) patients (p < 0.001). Thus, if TIPM1 is between ≤ 410 pg/mL and > 135 pg/mL, OR of long-lasting post-COVID syndrome increases 7.4 times (OR=7.355, 95% CI=3.555;15.382), RR — 3.2 times (RR=3.234, 95% CI=2.093;5.154).

In order to identify the risk factors of collagenolytic pattern development due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome, group 1 patients were divided into two subgroups: subgroup 1 included 57 patients with 135 < TIMP1 ≤ 410 pg/mL, subgroup 2 comprised 31 patients with TIMP1 > 410 pg/mL.

The clinical and anamnestic characteristic of patient subgroups with long-lasting post-COVID syndrome is presented in Table 2.

The correlation analysis did not reveal any correlation between waist circumference (WC) and body mass index (BMI) with TIMP1 concentrations.

The course of NCVI and long-lasting post-COVID syndrome in subgroups of patients is presented in Table 3.

The correlation analysis demonstrated medium inverse correlation for long COVID in any variants: weakness (r=–0.315, p=0.031), feeling generally unwell (r=–0.315, p=0.022), fatigue, impaired attention concentration and memory (r=–0.315, p=0.045), shortness of breath (r=–0.344, p=0.021), lower quality of life (r=–0.364, p=0.001), with TIMP1 concentrations (r=–0.298, p=0.005); and strong direct correlation between NCVI vaccination and TIMP1 concentration (r=0.538, p=0.038).

OR and RR values for long COVID were calculated for the following variants: presence of weakness, feeling generally unwell, fatigue, shortness of breath, lower quality of life with the development of the collagenolytic pattern due to prevailing fibrotic processes. It is reported that OR was 5.3 (OR=5.334, 95% CI=1.726; 17.216, p=0.035), RR — 2.9 (RR=2.901, (95% CI=1.379; 7.168 p=0.015). OR for long COVID in the variant of impaired attention concentration and memory is 6.3 (OR=6.314, 95% CI=1.562; 29.600, p=0.023), RR — 4.2 (RR=4.170, 95% CI=1.378; 16.960 p=0.025).

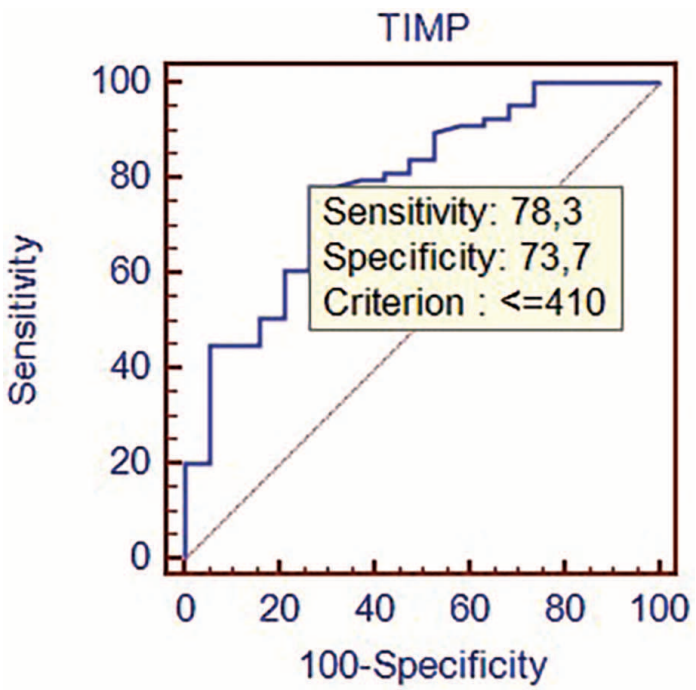

Figure 1. *ROC curve for 135< tissue inhibitor of matrix metalloproteinase type 1(TIMP1) ≤410 pg/mL in new coronavirus infection patients as an integral index reflecting the state of the collagenolysis system*

Table 2. *General clinical characteristics by subgroups of patients with long-term post-COVID syndrome (n=88)*

Indicator	First subgroup (135<TIMP1 ≤ 410 пг/мл, *n* = 57)	Second subgroup (TIMP1> 410 пг/мл, *n* = 31)	*P*
Sex, abs, m/w, abs. /%	17 (29,8)/ 40 (70,2)	13 (41,9)/ 18 (58,1)	0,566/ 0,729
Age, years Me[LQ; UQ]	57,11±12,92	55,10±12,56	0,485
Smoking, abs. /%	9/15,8	8/25,8	0,516
Body circumference, sm Me[LQ; UQ]	88 [70,0;105,0]	67 [67,0;95,0]	0,034
BMI > 30 kg/m^2, абс. /%	6/10,5	11/35,5	0,045
BMI, kg/m^2	27,2±6,10	29,02±5,21	0,123
AH, abs. /%	26/45,6	8/25,8	0,305
Angina pectoris, abs. /%	8/14,0	1/3,2	0,219
ACS history, abs. /%	5/8,8	0/0,0	0,497
PCI/CB history, abs. /%	3/5,3	0/0,0	0,494
Stable CHF, abs. /%	7/12,3	1/3,2	0,307
FP, abs. /%	5/8,8	1/3,2	0,587
VRD, abs. /%	11/19,3	6/19,4	0,997
Stroke/TIA, abs. /%	2/3,5	0/0,0	0,729
type 2 DM, abs. /%	6/10,5	0/0,0	0,184
BA, abs. /%	9/15,8	0/0,0	0,075
COPD, abs. /%	2/3,5	0/0,0	0,776
iACE/ARA/ARNI, abs. /%	22/38,6	12/38,7	0,838
Aldosterone antagonists, abs. /%	3/5,3	0/0,0	0,494
Beta-adrenoblockers, abs. /%	17/29,8	5/16,1	0,388
Thiazides / thiazide-like/loop diuretics, abs. /%	8/14,0	2/6,5	0,540
AC, abs. /%	11/19,3	7/22,6	0,931
Statins, abs. /%	11/19,3	5/16,1	0,938
Antiagregants/anticoagulants, abs. /%	12/21,1	3/9,7	0,291
Sugar-reducing medications, abs. /%	6/10,5	0/0,0	0,154
Inhalation HCs, abs. /%	6/10,5	0/0,0	0,154

Abbreviations: TIMP — Tissue Inhibitor of Matrix Metalloproteinases, BMI — body mass index, AH — arterial hypertension, ACS — acute coronary syndrome, PCI — percutaneous coronary intervention, CB — coronary bypass, CHF — chronic heart failure, FP — atrial fibrillation, VRD — ventricular rhythm disturbances, TIA — transient ischemic attack, DM — diabetes, BA — bronchial asthma, COPD — chronic obstructive pulmonary disease, iACE — angiotensin-converting enzyme inhibitors, ARA — angiotensin receptor antagonists, ARNI — angiotensin II receptor antagonists and neprilysin inhibitors, AC — calcium antagonists, HCs — glucocorticoids

Table 3. *Variants of the course of Covid-19 and long-term post-COVID syndrome by subgroups of patients (n = 88)*

Indicator	First subgroup (135<TIMP1 ≤ 410 пг/мл, *n* = 57)	Second subgroup (TIMP1> 410 пг/мл, *n* = 31)	*P*
Covid-19 without hospitalization, abs. /%	33/57,9	12/38,7	0,422
Covid-19 + pneumonia, abs. /%	32/56,1	5/16,1	0,776
Covid-19 + pneumonia + hospitalization, abs. /%	24/42,1	19/61,3	0,424
Covid-19 + pneumonia+PIT, abs. /%	6/10,5	0/0,0	0,184
Covid-19 + other hospital complications, abs. /%	1/1,7	0/0,0	0,749
Vaccination from Covid-19, abs. /%	**6/10,5**	**19/61,3**	**<0,001**
«Long Covid» (weakness), abs. /%	**32/56,1**	**6/19,4**	**0,047**
«Long Covid» (general malaise), abs. /%	**32/56,1**	**6/19,4**	**0,047**
«Long Covid» (fatigue), abs. /%	**32/56,1**	**6/19,4**	**0,047**
«Long Covid» (impaired concentration and memory), abs. /%	**23/40,4**	**3/9,7**	**0,038**
«Long Covid» (dyspnea), abs. /% abs	**32/56,1**	**6/19,4**	**0,003**
«Long Covid» (reduced quality of life), абс. /%	**32/56,1**	**6/19,4**	**0,047**
Pulmonary fibrosis by CT, % Me[LQ; UQ]	41,0 [10,0;64,0]	19,0 [10,0,0;30,0]	0,076

Abbreviations: TIMP — тканевый ингибитор матриксных металлопротеиназ (Tissue Inhibitor of Matrix Metalloproteinases), Covid-19 — new coronavirus infection, PIT — intensive care room, CT- computed tomography

NCVI vaccination reduces OR of development of the collagenolytic pattern due to prevailing fibrotic processes in post-NCVI patients, thus, of long-lasting post-COVID syndrome, by 92.5% (OR=0.075, 95% CI=0.021; 0.254 p=0.013), RR — by 82.8% (RR=0.172, 95% CI=0.070; 0.391, p=0.005).

An analysis of laboratory parameters demonstrated that subgroup 1 patients have lower platelet concentrations (p=0.040) within the normal range, a higher lymphocyte count (p=0.029) and higher D-dimer levels (p=0.048). There were no statistically significant correlations with TIMP1 levels for all parameters (complete blood count: WBC; ESR; blood biochemistry: CRP, fasting plasma glucose, HbA1c, total cholesterol, LDL, HDL, TG, uric acid, potassium, sodium, urea, NT-proBNP) between subgroups.

In echoCG, statistically significant differences between subgroups were obtained only for TAPSE; however, there was no correlation between this parameter and TIMP1 levels.

The renal filtration function in subgroups was evaluated. Cystatin C levels were significantly higher in subgroup 1 vs. subgroup 2 (0.84 [0.71;0.99] vs. 0.72 [0.58;0.89], p=0.025). There were no differences in eGFR based on CKD-EPI creatinine (group 1 77.0 [66.3;85.9], group 2 85.0 [72.3;92.8], p=0.533), and eGFR based on CKD-EPI (cystatin C) (group 1 71.0[56.5;88.75], group 2 78.0[67.0;88.0], p=0.329).

The correlation analysis made it possible to identify medium direct correlation between TIMP1 levels and cystatin C concentrations in blood (r=0.297, p=0.025). ROC curve plotting for all cystatin C concentrations allowed obtaining a cut-off point of ≥ 0.736 mg/L, which makes it possible to treat this parameter as a risk factor of collagenolytic pattern due to prevailing fibrotic processes in patients with long post-COVID syndrome, with sensitivity of 52.6% and specificity of 71.0% (AUC=0.633, p=0.034) (Fig. 2).

Cystatin C values of ≥0.74 mg/L increase OR of collagenolytic pattern due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome by 3.2 times (OR=3.245, 95% CI=2.317; 7.343, p=0.019), RR — by 2.0 times (RR=2.045, 95% CI=1.501; 13.412, p=0.03).

An analysis of 3D sphygmoplethysmography results demonstrated higher PWVcf (p=0.044) and CAVI1 index (p=0.037) in subgroup 1 (13.40[10.35;15.7]) vs. subgroup 2 (12.3[10.23;13.7]).

A correlation analysis demonstrated medium reverse correlation between TIMP1 levels and PWVcf (r=–0.355, p=0.027). ROC curve plotting for all PWVcf values allowed obtaining a cut-off point of ≥ 11.6 m/s,

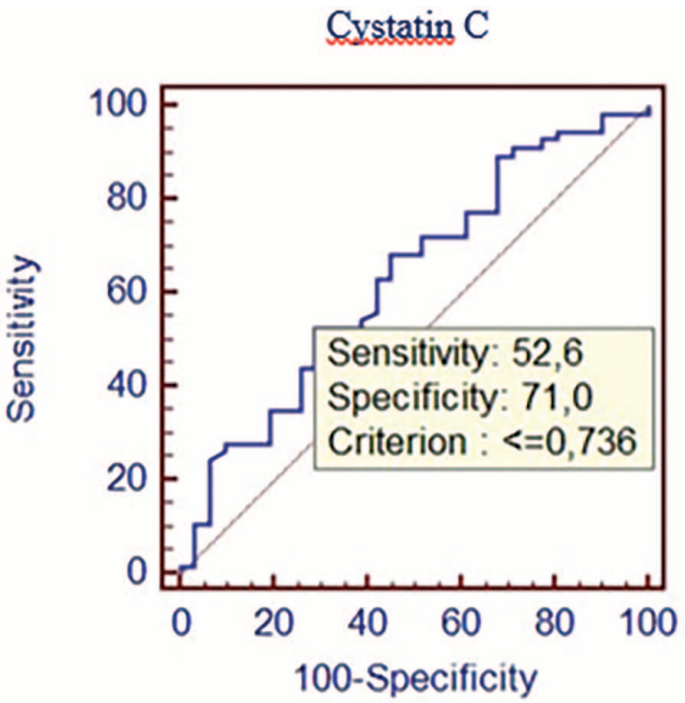

Figure 2. *ROC curve for cystatin C>0.736 mg/l in patients with long-term post-COVID syndrome as a risk factor of the development of a collagenolytic pattern against the background of predominant fibrosis processes*

which makes it possible to treat this parameter as a risk factor of collagenolytic pattern due to prevailing fibrotic processes in patients with long post-COVID syndrome, with sensitivity of 46.9% and specificity of 85.2% (AUC=0.640, p=0.027) (Fig. 3).

Also, there is medium reverse correlation between CAVI1 and TIMP1 levels (r=–0.360, p=0.03). ROC curve plotting for all CAVI1 values allowed obtaining a cut-off point of ≥ 7.1, which makes it possible to treat this parameter as a risk factor of collagenolytic pattern due to prevailing fibrotic processes in patients with long post-COVID syndrome, with sensitivity of 34.7% and specificity of 92.6% (AUC=0.667, p=0.009) (Fig. 3).

PWVcf value of ≥ 11.6 m/s increases OR of collagenolytic pattern due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome by 3.5 times (OR=3.543, 95% CI=2.589; 11.203, p=0.04), RR — by 2.4 times (RR=2.411, 95% CI=1.827; 9.673, p=0.001). CAVI value of ≥7.1 increases OR of collagenolytic pattern due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome by 3.0 times (OR=3.002, 95% CI=2.267; 8.406, p=0.02), RR — by 2.1 times (RR=2.146, 95% CI=1.622; 10.157, p=0.04).

Ferrokinetics, apoptosis and inflammation biomarkers were analysed in patients with long-lasting post-COVID syndrome (see Table 4).

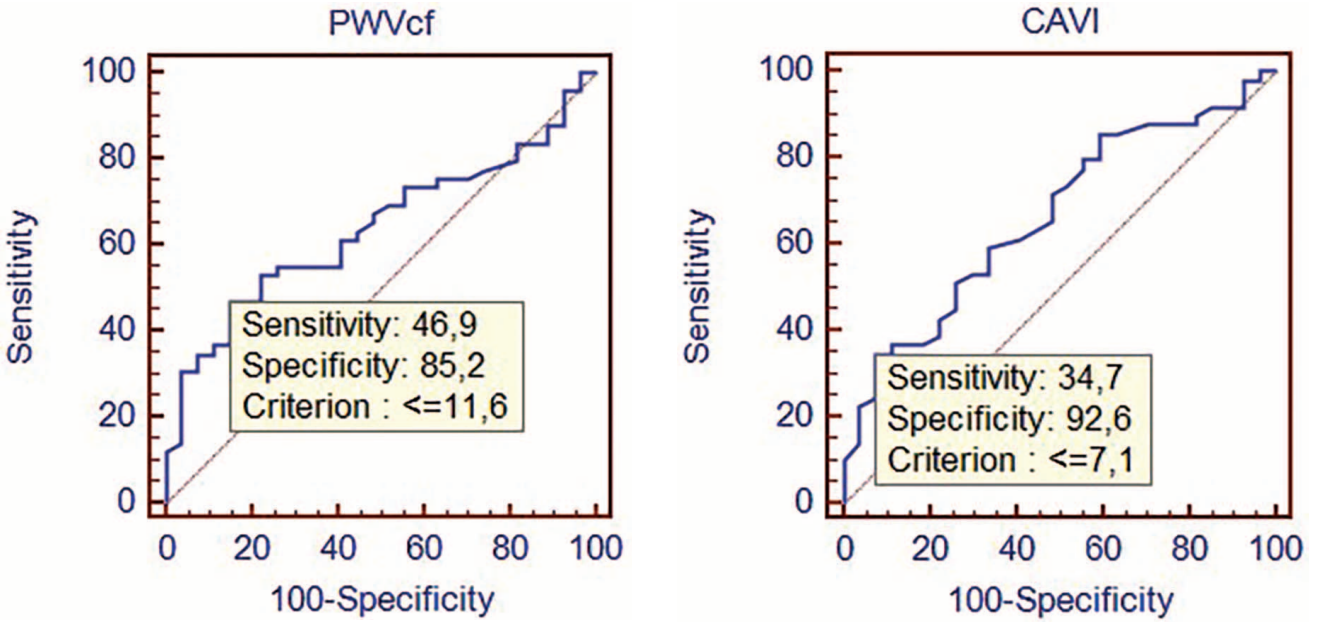

Figure 3. *ROC curves for pulse wave velosity (PWVcf) ≥11.6 m/s and cardio-ankle vascular index (CAVI1) ≥7.1 in patients with long-term post-COVID syndrome as risk factors of the development of a collagenolytic pattern against the background of predominant fibrosis processes*

Table 4. *Ferrokinetics and biomarker indicators for groups of patients with long-term post-COVID syndrome (n=88)*

Indicator Me[LQ; UQ]	First subgroup (135<TIMP1 ≤ 410 пг/мл, *n* = 57)	Second subgroup (TIMP1> 410 пг/мл, *n* = 31)	*P*
Serum iron, μmol/L	19,0[13,8;20,1]	19,0[13,42;24,47]	0,884
OJSS, μmol/L	**58,0[47,47;71,97]**	**52,0[44,72;58,57]**	**0,033**
Ferritin, ng/mL	**416,0[66,0;675,0]**	**240,0[75,0;347,0]**	**0,005**
CNTJ, %	**30,8[19,2;56,1]**	**36,8[21,4;59,6]**	**<0,001**
Transferrin, mg/mL	3,04[2,06;4,26]	3,08[1,99;3,30]	0,726
Alpha-FNO, pg/mL	**4,9 [0,00;6,35]**	**0,16 [0,00;1,00]**	**0,002**
Interleukin-6, **pg/mL**	2,04[1,18;3,83]	2,00[0,76;4,06]	0,826

Abbreviations: TIMP1 — Tissue Inhibitor of Matrix Metalloproteinases 1, OJSS — total iron-binding capacity of serum, CNTJ — iron saturation factor of transferrin, Alpha-FNO — tumor necrosis factor alpha

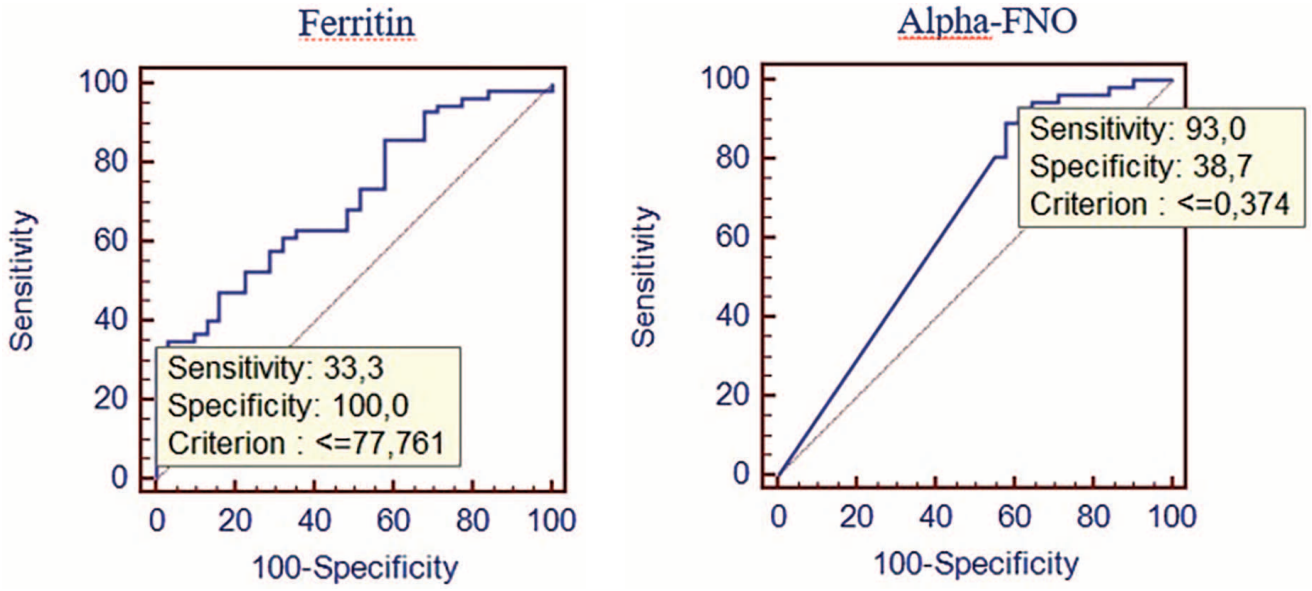

Figure 4. *ROC curves for ferritin >77.76 ng/ml and tumor necrosis factor alpha (alpha -FNO) >0.374 pg/ml in patients with prolonged post-COVID syndrome as risk factors of collagenolytic pattern development against the background of predominant fibrosis processes*

A correlation analysis demonstrated medium reverse correlation between TIMP1 level and ferritin concentration (r=–0.280, p=0.01). ROC curve plotting for all ferritin values allowed obtaining a cut-off point of > 77.76 ng/mL, which makes it possible to treat this parameter as a risk factor of collagenolytic pattern due to prevailing fibrotic processes in patients with long post-COVID syndrome, with sensitivity of 33.3% and specificity of 99.0% (AUC=0.707, p=0.002) (Fig. 4).

Also, there is medium reverse correlation between TNF-α and TIMP1 levels (r=–0.325, p=0.008). ROC curve plotting for all TNF-α values allowed obtaining a cut-off point of ≥ 0.374 ng/mL, which makes it possible to treat this parameter as a risk factor of collagenolytic pattern due to prevailing fibrotic processes in patients with long post-COVID syndrome, with sensitivity of 93.0% and specificity of 38.7% (AUC=0.652, p=0.005) (Fig. 4).

Ferritin value of ≥ 77.76 ng/mL increases OR of collagenolytic pattern due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome by 1.9 times (OR=1.904, 95% CI=1.438; 8.659, p=0.015), RR — by 1.5 times (RR=1.504, 95% CI=1.256; 7.238, p=0.023). TNF-α value of > 0.374 pg/mL increases OR of collagenolytic pattern due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome by 3.5 times (OR=3.518, 95% CI=1.922; 5.361, p=0.038), RR — by 2.3 times (RR=2.344, 95% CI=1.482; 11.006, p=0.02).

Our data on the development of the collagenolytic pattern due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome correlate with results of a study conducted by Zingaropoli M.A., et al. (2023), reporting that, three months after discharge, patients with COVID19-pneumonia experience reduction in plasma TIMP-1 levels ($p < 0.0001$), while plasma MMP-9 concentration rises (p=0.0088) [6]. Moreover, the authors found positive correlation between plasma TIMP-1 levels and chest CT results (ρ=0.2302, p=0.0160), emphasising its potential use as a fibrotic load biomarker. The authors conclude that increased MMP-9 levels and decreased plasma TIMP-1 concentration show ongoing inflammation and fibrosis three months after NCVI.

An evidence of ongoing inflammation in this study in patients with long COVID and specific collagen disorganisation status was determination of TNF-α values. After reporting long COVID in 67.8% of 333 patients eight months after NCVI, Schultheiß C. et al. (2022) identified a number of inflammatory markers and concluded that long COVID is associated not with autoantibodies, but with increased plasma IL-1β, IL-6 and TNF-α values [10]. The authors assume induction by COVID-19 of these cytokines in pro-inflammatory macrophages of lungs, which creates self-sustained reverse correlation.

Another study reported data, which do not correlate with our results on the presence of a collagenolytic pattern due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome [11]. Significantly lower MMP-10 and TIMP-1 values were found in both groups of patients with knee osteoarthritis nine months after COVID-19 vs. healthy subjects. It is assumed that reduced, and not increased MMP values are associated with pathogenetic immunosuppressive therapy of arthritis.

In our study, cystatin C is a risk factor of collagen disorganisation system transformation, which demonstrates persistent inflammation in long-lasting post-COVID syndrome. These data correlate with results of the study by Medori M.C. et al. (2023), where patients with long COVID had their serum profiled using mass spectrometry [12]. A multivatiate ROC analysis identified a biomarker panel of 11 proteins, including cystatin C. The authors conclude that the identified biomarkers are associated with inflammatory processes, confirming literature evidences that patients with long COVID develop an inflammation, which damages many tissues, including glomerules, on subclinical level. It is advisable to make clarifications, given that the use of cystatin C as a biomarker to calculate GFR is limited by chronic inflammation (according to Russian guidelines and KDIGO 2024 recommendations).

In this study, risk factors of collagenolytic pattern development due to prevailing fibrotic processes, associated with ongoing inflammatory processes, in patients with long-lasting post-COVID syndrome were arterial stiffness parameters: PVWcf and CAVI1. It is a well known fact that vascular physiology remains impaired for at least 12 months after onset of SARS-CoV-2, even in healthy adults [13, 14]. One recent observational study confirmed evidences of positive linear correlation between C-reactive protein levels and increased arterial stiffness [15].

The results show that long COVID-19 is associated with a number of persistent haematological changes, including altered RBC, anaemia, lymphopenia and increased levels of inflammation markers, such as ferritin, D-dimer and IL-6 [16, 17]. These changes can help understand the pathophysiology of long COVID-19 and associated symptoms better [18]. In this study, increased ferritin levels recorded in patients with long COVID-19 are associated with reduced TIMP1 within higher concentration range, representing more severe inflammation processes, and can have a role in persistence and progression of long COVID-19.

Thus, it has been established that risk factors of collagenolytic pattern development due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome were higher concentrations of cystatin C, PWVcf, CAVI, ferritin and TNF-α.

Conclusions

In post-NCVI patients with long-lasting post-COVID syndrome, collagen disorganisation status is characterised by the development of collagenolytic pattern due to prevailing fibrotic processes vs. asymptomatic patients, who had NCVI at least 12 weeks ago, which can be seen as a pathogenetic mechanism of long COVID development. In the presence of such a transformation in the collagen disorganisation system in post-NCVI patients, OR of long-lasting post-COVID syndrome increases 7.4-fold, RR — 3.2-fold in any variants of the course of the disease. Risk factors of the development of collagenolytic pattern due to prevailing fibrotic processes in patients with long-lasting post-COVID syndrome were an increase on cyststin C levels to > 0.736 mg/L, PWVcf to $\geq$11.6 m/sc, CAVI to $\geq$7.1, ferritin to > 77.76 ng/mL and TNF-α to > 0.374.

Вклад авторов:

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Козиолова Н.А.: концептуализация, анализ, редактирование рукописи, общее руководство;

Чернявина А.И.: методология, валидация, исследование, создание черновика;

Author Contribution:

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

Masalkina O.V.: Conducting research, preparing, creating and presenting the manuscript, particularly writing the initial draft.

Polyanskaya E.A.: checking the overall reproducibility of the results critical review and editing.

Koziolova N.A.: conceptualization, formal Analysis, writing—review and editing, supervision;

Chernyavina A.I.: methodology, validation, investigation, writing—original draft

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ИЗМЕНЕНИЕ СОСТАВА НЕНАСЫЩЕННЫХ ЖИРНЫХ КИСЛОТ ПЛАЗМЫ КРОВИ У МУЖЧИН, ПРОЖИВАЮЩИХ В СЕЛЬСКИХ РАЙОНАХ НОВОСИБИРСКОЙ ОБЛАСТИ, В ЗАВИСИМОСТИ ОТ УПОТРЕБЛЕНИЯ АЛКОГОЛЯ

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Changes In the Composition of Unsaturated Fatty Acids in The Blood Plasma In Men Living in Rural Areas of the Novosibirsk Region, Depending on Alcohol Consumption

Резюме

Цель исследования — изучить различия в содержании ненасыщенных жирных кислот (ННЖК) в плазме крови у мужчин, проживающих в сельских районах Новосибирской области, в зависимости от их алкогольного статуса. **Материалы и методы**: в рамках одномоментного эпидемиологического исследования по Новосибирской области были обследованы жители сельских районов (мужчины) в возрасте 60,04±10,55 (от 35 до 74 лет). Алкогольный статус участников определяли с помощью анкетирования. Количество разных алкогольных напитков было пересчитано в дозы чистого алкоголя. Все участники исследования были разделены на три группы по употреблению доз алкоголя в неделю: 1 группа — малое потребление алкоголя (МП); 2 группа — умеренное потребление алкоголя (УП); 3 группа — высокое потребление алкоголя (ВП). Методом высокоэффективной жидкостной хроматографии в плазме крови определяли уровни омега-3, -6 и -9 ННЖК. **Результаты**. Установлено, что в группе мужчин с ВП алкоголя более высокие уровни альфа-линоленовой омега-3 (p=0,041) и дигомо-гамма-линоленовой (p=0,002), докозатетраеновой (p=0,017), докозапентаеновой (p=0,023) омега-6 ННЖК в крови, по сравнению с группой мужчин с МП алкоголя. **Выводы**. Получены статистически значимые различия концентраций в крови альфа-линоленовой, дигомо-гамма-линоленовой, докозатетраеновой, докозапентаеновой ненасыщенных жирных кислот у мужчин 35-74 лет, проживающих в сельских районах Новосибирской области, в зависимости от употребления алкоголя.

Ключевые слова: *жирные кислоты, кровь, алкоголь, факторы риска*

Конфликт интересов

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

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Abstract

The aim of the study was to investigate differences in the content of unsaturated fatty acids (UFA) in blood plasma in men living of rural areas of the Novosibirsk region, depending on their alcohol status. **Materials and methods:** as part of a single-stage epidemiological study in the Novosibirsk region, rural residents (men) aged 60.04±10.55 (from 35 to 74 years) were examined. The alcohol status of the participants was determined by means of a questionnaire. The number of different alcoholic beverages was recalculated in doses of pure alcohol. All study participants were divided into three groups based on alcohol consumption per week: group 1 — low alcohol consumption (LC); group 2 — moderate alcohol consumption (MC); group 3 — high alcohol consumption (HC). The levels of omega-3, -6, and -9 UFA in blood plasma were determined by high-performance liquid chromatography. **Results**: It was found that the group of men with HC had higher concentrations of omega-3 alpha-linolenic acid (p=0,041) and omega-6 digomo-gamma-linolenic (p=0,002), docosatetraenoic (p=0,017), docosapentaenoic (p=0,023) UFA in blood, compared with group of men with LC. **Conclusions**: In the study, we found statistically significant differences in blood concentrations of alpha-linolenic acid, digomo-gamma-linolenic acid, docosathetraenoic acid, and docosapentaenoic acid unsaturated fatty acids were obtained in men aged 35-74 years living in rural areas of the Novosibirsk region, depending on alcohol consumption.

Key words: *fatty acids, blood, alcohol, risk factors*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The work was carried out within the framework of the budget topic under State Assignment No. FWNR-2024-0004

Conformity with the principles of ethics

The study was approved by the local ethics committee of the Research Institute of Therapeutic Microbiology and Microbiology — branch of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences (protocol No. 69, dated September 29, 2020). Each participant signed an informed consent

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IHD — ischaemic heart disease, MI — myocardial infarction, CCF — chronic cardiac failure, CVD — cardiovascular diseases, TC — total cholesterol, LDL cholesterol — low-density lipoprotein cholesterol, HDL cholesterol — high-density lipoprotein cholesterol, TG — triglycerides, NAFLD — non-alcoholic fatty liver disease, FA — fatty acids, UFA — unsaturated fatty acids, ALA — α-linolenic fatty acid, EPA — eicosapentaenoic fatty acid, DHA — docosahexaenoic fatty acid, LA — linoleic fatty acid, GLA — gamma-linolenic fatty acid, DHGLA — dihomo-gamma-linolenic fatty acid, AA — arachidonic fatty acid, DTA — docosatetraenoic fatty acid, DPA — docosapentaenoic fatty acid, GEX — hexadecenoic fatty acid, OL — oleinic fatty acid, MID — mead fatty acid, SEL — selacholeic fatty acid

Introduction

Globally, three million people (5.3% of all deaths) die of alcohol abuse annually. The share of men is 7.7%, while women account for 2.6% of all alcohol-related deaths. Among people aged 20 to 39 years old, alcohol-related mortality is approximately 13.5% [1].

Alcohol abuse and problem drinking are associated with a higher risk of cardiovascular diseases (CVD). However, the dose/reaction correlation between the amount of alcohol consumed and the risk of ischaemic heart disease (IHD) varies a lot between those regularly consuming alcohol and those drinking alcohol from time to time [2]. An increase in the average daily ethanol consumption positively correlates with the risk of arterial hypertension, hypercholesterolemia, including higher levels of low-density lipoprotein cholesterol (LDL cholesterol), smoking, physical inactivity [3]. However, studies of the correlation between alcohol consumption and the risk of CVD show contradicting results [4, 5]. A combination of various effects leads to U-shape or J-shape dose-dependent correlation between alcohol and IHD [2, 6, 7]. The Northern European and Northern American population consume beers and spirits, usually on weekends, while episodic consumption of spirits is typical for the Eastern European population [8].

The study of fatty acids (FA), including unsaturated fatty acids (UFA), is gaining more attention, with the emphasis on the amount and type of consumed acids. However, FAs possess various physiological functions even within one class [9]. The association between omega-3 UFA and alcohol consumption [10] has been actively discussed. A number of studies established that the prognostic value in CVD belongs to lower concentrations of blood omega-3 (eicosapentanoic,

docosahexaenic) and increased levels of omega-6 (linolic, gamma-linolenic, dihomo-gamma-linolenic, arachidonic, docosatetraenoic, docosapentaenoic) UFAs. A study of the omega-3/omega-6 UFA ratio showed higher blood concentrations of omega-6 UFA in decompensated chronic cardiac insufficiency. However, after fluid retention was managed, this ratio changed, and omega-3 UFA levels rose [11]. LURIC study demonstrated direct associations between docosatetraenoic and docosatetraenoic omega-6 UFA concentrations and inflammation markers (C-reactive protein, interleukin-6, fibrinogen and VCAM-1), as well as association with a higher risk of CVDs [9].

Alcohol abuse is an established risk factor of CVD [1-3]. As compared to non-drinkers, alcohol abuse is associated with a high risk of hypercholesterolemia (OR 1.76; CI: 1.12–2.75), hypertriglyceridemia (OR 2.69; CI: 1.52–4.77), overweight (OR 1.68; CI: 1.04–2.71), smoking (OR 2.24; CI: 1.48–3.41). An increase in the average daily dose of ethanol is related to the risk of arterial hypertension (OR 1.04; CI: 1.11–2.75) [3].

The objective of this study was to evaluate the differences in plasma omega-3, omega-6 and omega-9 UFA concentrations in male subjects living in rural area of the Novosibirsk Region, depending on their drinking status.

Materials and Methods

Subjects were examined during the cross-sectional, epidemiological study titled Epidemiology of Cardiovascular Diseases and Their Risk Factors in the Novosibirsk Region, in 2022–2023. Within the scope of this study, physicians at the Scientific Research Institute of the Therapy and Preventive Medicine, a branch of the Federal State Budgetary Scientific Institution Federal Research Centre, Cytology and Genetics Institute of the Siberian Section of the Russian Academy of Science examined 300 male subjects living in rural area of the Novosibirsk Region, aged 60.04±10.55 (35 to 74 years of age). Key inclusion criteria: correctly completed questionnaire, including data on alcohol consumption. Exclusion criteria for all subjects: incomplete questionnaire or missing data on alcohol consumption in the questionnaire. The study was approved by the Local Ethics Committee at the Scientific Research Institute of the Therapy and Preventive Medicine, a branch of the Federal State Budgetary Scientific Institution Federal Research Centre, Cytology and Genetics Institute of the Siberian Section of the Russian Academy of Science (Minutes No. 69 dated September 29, 2020). Each subject signed the informed consent form.

According to the WHO data, a standard alcohol unit is an amount of an alcoholic beverage, containing ethyl alcohol, the amount of which equals to 10 g of absolute alcohol (12.7 mL). One unit is: for beer (5%) — 250 mL, red strong wine (18%) — 70 mL, dry wine/champagne (13%) — 100 mL, vodka (40%) — 30 mL [1].

All subjects underwent an analysis of their alcohol consumption status: amount of alcohol consumed (daily/weekly/monthly/yearly alcohol consumption; amount of alcohol consumed at a time); type of alcoholic beverages (beer, dry wine/champagne, strong wine, homemade strong tinctures, vodka, cognac, and other spirits). Alcohol consumption at a time (a short period of time, e.g., one evening) was evaluated: strong spirits ≥ 200 mL, strong wine ≥ 500 mL, dry wine ≥ 700 mL, beer ≥ 2 litres. The study questionnaire was adopted from the ESSE-RF project questionnaire [12].

In order to analyse alcohol data, all data from the questionnaire were converted to absolute alcohol units (various alcoholic beverages) for each subject. Units were added together, and all subjects were divided into three groups, depending on weekly alcohol consumption (Table 1). Group 1 (mild alcohol consumption (MC)): < 8 units for men; group 2 (moderate alcohol consumption (ModC)): ≥ 8 units to < 16 units for men; group 3 (high alcohol consumption (HC)): ≥ 16 units for men [1, 13]. The groups were comparable in terms of their clinical-biochemical attributes.

All subjects underwent plasma UFA spectrum examination. Blood was drawn from the ulnar vein following 12 hours of fasting. Laboratory tests included measurement of plasma levels of the following FAs: α-linolenic (C 18:3, omega-3, ALA), eicosapentanoic (C 20:5, omega-3, EPA), docosahexaenic (C 22:6, omega-3, DHA), linolic(C 18:2, omega-6, LA), gamma-linolenic (C 18:3, omega-6, GLA), dihomo-gamma-linolenic (C 20:3, omega-6, DHGLA), arachidonic (C 20:4, omega-6, AA), docosatetraenoic (C 22:4, omega-6, DTA), docosapentaenoic (C 22:5, omega-6, DPA), hexadecenoic (C 16:1, omega-9, GEX), oleinic (C 18:1, omega-9, OL), mead (C 20:3, omega-9, MID), selacholeic (C 24:1, omega-9, SEL) using high-performance liquid chromatography. Serum lipid profile (total cholesterol (TC), high-density lipoprotein cholesterol (HDL cholesterol), triglycerides (TG)) was measured using Konelab Prime 30i analyser (Thermo Fisher Scientific, Finland) and DiaSys kit (Germany). Friedewald formula was used to calculate LDL cholesterol levels.

For statistical processing of the results, SPSS (version 23.0) (Statistical Package for the Social Sciences, USA) was used. The normality of parameter distribution was assessed using Kolmogorov-Smirnov test. The data are presented as a median value or percentiles [25%; 75%]. The Kruskal-Wallis non-parametric test was used to compare several groups, while independent groups were compared with the help of the Mann-Whitney test. Differences in quality attributes were identified using Pearson's test (χ^2). Presence of the correlation between FA and alcohol units was determined using correlation analysis (Spearman's rank correlation (r)). Differences were statistically significant at $p < 0.05$.

Results

The questionnaire completed by the subjects allowed obtaining information on the eating habits, chronic disease status (Table 1). There were no statistically significant differences in dietary preferences, such as consumption of fish, meat, seafood, butter and vegetable oil, vegetables, fruit, dairy products among subjects. In terms of serum lipid profile, groups differed in TC and HDL cholesterol levels (Table 1).

We established statistically significant differences between high alcohol consumption and mild alcohol consumption groups in α-linolenic, dihomo-gamma-linolenic, docosatetraenoic and docosapentaenoic FA (Table 2).

A correlation analysis was performed in order to identify possible correlations between FAs and alcohol units. The following correlations were found: gamma-linolenic FA (r=0.293; p=0.006), docosapentaenoic FA (r=0.308; p=0.004) and beer consumption. Also, there is moderate correlation between arachidonic FA (r=0.401; p=0.034) and wine consumption, as well as weak correlation between dihomo-gamma-linolenic FA (r=0.206; p=0.016) and vodka consumption.

Table1. *Clinical and biochemical characteristics of the study participants, Me [25%; 75%]*

Parameters	Group 1 (MC) n=260	Group 2 (ModC) n=25	Group 3 (HC) n=15	P*
Age, years	63,0 [55,0; 68,0]	56,0 [45,0; 62,0]	50,0 [42,0; 65,0]	0,001
BMI, kg/m^2	29,3 [26,2; 33,6]	29,4 [22,4; 33,8]	27,7 [22,7; 35,9]	0,692
SAD, mmHg	146,5 [135,5; 164,5]	151,5 [134,0; 166,25]	148,0 [135,0; 165,0]	0,867
DAD, mmHg	94,0 [86,5; 102,5]	100,0 [89,25; 113,5]	90,0 [85,0; 101,0]	0,108
Total cholesterol, mmol/l	5,0 [4,3; 5,8]	5,7 [5,4; 6,2]	5,5 [4,5; 5,7]	0,022
Triglycerides, mmol/l	1,5 [1,1; 2,1]	1,4 [1,0; 1,8]	1,4 [0,8; 2,1]	0,348
HDL-C, mmol/l	1,2 [1,0; 1,5]	1,4 [1,1; 1,8]	1,2 [0,9; 1,7]	0,029
LDL-C, mmol/l	3,0 [2,3; 3,7]	3,5 [3,0; 4,0]	2,9 [2,7; 3,4]	0,124
Liver diseases (including NAFLD), n (%)	13 (5%)	3 (12%)	1 (7%)	0,666
Stomach ulcer or duodenal ulcer, n (%)	30 (11%)	3 (12%)	2 (13%)	0,737
Cardiovascular diseases (including coronary heart disease, MI, CHF), n (%)	99 (38%)	4 (16%)	3 (20%)	0,035

Note: BMI — body mass index, NAFLD — a non–alcoholic fatty liver disease, SAD — systolic blood pressure, DAD — diastolic blood pressure, HDL-C — high-density lipoprotein cholesterol, LDL-C — low-density lipoprotein cholesterol, n % — number of respondents in the group (%of the total number of respondents in the group).
* — Kruskal-Wallis criterion for comparing three groups, Pearson criterion for comparing qualitative characteristics

Table 2. *Concentration of plasma fatty acids in groups depending on the status of alcohol consumption, Me [25%; 75%]*

FA, nmol/ml	Group 1 (MC) n=260	Group 2 (ModC) n=25	Group 3 (HC) n=15	p
ALA	105,5 [80,0; 127,0]	96,0 [74,5; 127,0]	116,0 [103,0; 139,0]	**0,041**
EPA	55,0 [37,0; 71,0]	50,0 [33,5; 66,0]	63,0 [58,0; 79,0]	0,136
DHA	178,0 [131,7; 222,5]	159,0 [108,0; 206,5]	196,0 [155,0; 265,0]	0,090
LA	3488,5 [3217,5; 3745,7]	3517,0 [3309,5; 3733,0]	3374,0 [3052,0; 3759,0]	0,224
GLA	85,0 [64,0; 102,0]	97,0 [58,5; 111,5]	89,0 [74,0; 114,0]	0,261
DHGLA	199,5 [132,7; 269,0]	200,0 [120,0; 307,0]	282,0 [253,0; 324,0]	**0,002**
AA	1229,5 [1044,5; 1334,0]	1154,0 [922,0; 1310,5]	1279,47 [1233,0; 1342,0]	0,110
DTA	31,0 [26,0; 34,2]	29,0 [22,0; 36,5]	33,0 [31,0; 37,0]	**0,017**
DPA	34,0 [27,0; 44,0]	35,0 [25,5; 43,0]	42,0 [33,0; 50,0]	**0,023**
GEX	70,0 [60,0; 80,0]	68,0 [62,0; 78,0]	78,0 [61,0; 84,0]	0,431
OL	1993,5 [1544,2; 2462,0]	1677,0 [1237,5; 2457,0]	2130,0 [1761,0; 2676,0]	0,243
MID	24,0 [20,0; 28,0]	23,0 [18,5; 27,5]	23,0 [21,0; 29,0]	0,741
SEL	87,0 [74,0; 104,2]	91,0 [80,5; 108,0]	101,0 [80,0; 115,0]	0,157

Примечание: p — сравнение между 1 и 3 группами
Note: p — is a comparison between groups 1 and 3

Discussion

Some studies evaluate the association between omega-3 FA and alcohol [3, 13, 14]. In the body, α-linolenic FA is a biochemical basis for long-chain omega-3 UFA. The levels of long-chain polyunsaturated omega-3 UFAs, including eicosapentanoic and docosahexaenic acids, are associated with susceptibility to alcohol in vertebrate and invertebrate models [15, 16]. Long-chain polyunsaturated FAs inhibit development of acute functional alcohol tolerance, i.e., omega-3 UFA, particularly eicosapentanoic acid, is essential for the normal response to alcohol [15, 16]. In humans, acute ethanol tolerance is closely associated with susceptibility to alcohol abuse. It has been established that three weeks of supplements containing eicosapentanoic and docosahexaenic UFAs significantly reduced the stress level and cortisone concentrations in alcohol-dependent individuals abstaining from alcohol [17]. Impact of FAs on the response to ethanol can be a result of genetic factors. There is considerable genetic contribution to alcohol response variability in humans [15, 18]. Understanding genetic factors is essential for establishing susceptibility to alcohol and development of an efficient therapy [15].

In this study, we found statistically significant increase in blood concentrations of α-linolenic omega-3 UFA in the group of high alcohol consumption vs. mild alcohol consumption group. The concentration of the long-chain eicosapentanoic and docosahexaenic omega-3 UFAs was also higher in this group, however not statistically significant.

Dihomo-gamma-linolenic UFA is a product of elongation of omega-6 gamma-linolenic acid using delta-6-desaturase, which is a product of linoleic acid desaturation (18:2, omega-6) [19]. Alcohol is known to inhibit delta-6 and delta-5-desaturases, which participate in conversion of omega-6 UFA. Alcohol directly affects cell membrane composition, increasing the level of omega-6 polyunsaturated FA in membranes, thus boosting their flowability and damage to the cells. This pathological effect can be partially mitigated by changing the omega-6/omega-3 FA ratio by adding omega-3 UFA [19].Also, in the CHS study (a study of the cardiovascular health), dihomo-gamma-linolenic UFA is proposed as a potential biomarker in the development of unfavourable events, such as stroke [20].

We established an increase in blood concentrations of dihomo-gamma-linolenic FA by 29% in the high alcohol consumption group. Gamma-linolenic and arachidonic FA concentrations tended to rise in the high alcohol consumption group; however, the increase was not statistically significant. Concentrations of docosatetraenoic and docosapentaenoic omega-6 UFAs, products of arachidonic FA metabolism, varied considerably in mild and high alcohol consumption groups, p=0.017 and p=0.023, respectively. This study design does not allow making assumptions as to the mechanisms of these changes.

Study Limitation

The study enrolled a small sample size; subjects were divided into groups unevenly; and there was no control group (non-drinkers). Also, the questionnaire did not take into account omega-3 FA supplements. The study was cross-sectional, so no follow-up is used.

Conclusion

This study demonstrated that alcohol consumption changes UFA spectrum. It has been shown that in male subjects aged 35–74 years old, living in rural areas of the Novosibirsk Region, from the high alcohol consumption group, the concentrations of α-linolenic omega-3 UFA and dihomo-gamma-linolenic, docosatetraenoic, docosapentaenoic omega-6 UFA were higher than in the mild alcohol consumption group. Therefore, identification of any changes in the unsaturated fatty acid profile can be used as an additional prognostic biomarker, allowing to assess the risk of CVD and their complications in male subjects consuming high amounts of alcohol.

Вклад авторов:

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Шрамко В.С.: сбор, анализ и интерпретация данных; разработка концепции и дизайна исследования

Стахнёва Е.М.: анализ и интерпретация данных, написание и подготовка рукописи к публикации

Каштанова Е.В.: анализ и интерпретация данных; проверка критически важного интеллектуального содержания и утверждение рукописи для публикации

Щербакова Л.В.: анализ и интерпретация данных, статистическая обработка результатов

Полонская Я.В.: анализ и интерпретация данных

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Author Contribution:

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

Shramko V.S.: data collection, analysis and interpretation; development of the research concept and design

Stakhneva E.M.: data analysis and interpretation, writing and preparation of a manuscript for publication

Kashtanova E.V.: data analysis and interpretation; verification of critical intellectual content and approval of the manuscript for publication

Shcherbakova L.V.: data analysis and interpretation, statistical processing of results

Polonskaya Ya.V.: data analysis and interpretation

Ragino Yu.I.: data analysis and interpretation, approval of the manuscript for publication

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ЦЕРЕБРАЛЬНАЯ МАСКА СИНДРОМА ТАКОЦУБО

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Cerebral Mask of Takotsubo Syndrome

Резюме

Синдром такоцубо (СТ) — это остро развивающаяся и обычно обратимая дисфункция миокарда преимущественно левого желудочка, клинически и электрокардиографически напоминающая острый коронарный синдром. Среди причин развития данной патологии указывают тяжелые психоэмоциональные потрясения и физические состояния, в числе которых тяжелые заболевания головного мозга. Самыми частыми симптомами заболевания в острый период являются боль за грудиной и одышка, реже — сердцебиение, синкопальные состояния. Тяжелое течение СТ может осложняться кардиогенным шоком, отеком легких, острым нарушением мозгового кровообращения, остановкой сердца. Представленное клиническое наблюдение демонстрирует необычное течение СТ, при котором тяжесть состояния пациента определялась поражением центральной нервной системы.

Мужчина 68 лет госпитализирован в тяжелом состоянии в реанимационное отделение: после тяжелого психоэмоционального напряжения обнаружен дома без сознания. При осмотре констатированы сопор, правосторонний парез взора, опущение правого угла рта, тяжелый неврологический дефицит по шкале NIHSS. При компьютерной томографии головного мозга неотчетливо определялся ишемический очаг в бассейне левой средней мозговой артерии. На электрокардиограмме зафиксирован двухфазный и отрицательный зубец Т в AVL, V3-V6. При эхокардиографии выявлено снижение фракции выброса левого желудочка до 32 %, выраженные нарушения локальной сократимости, в том числе циркулярные. Отмечено повышение маркеров некроза миокарда. Выставлен диагноз сочетанного ишемического повреждения головного мозга и сердца, начато лечение. На следующий день значимая положительная динамика — пациент в сознании, неврологический дефицит отсутствует. При магнитно-резонансной томографии головного мозга данных за ишемический инсульт не получено. На электрокардиограмме в динамике отсутствуют отрицательные и двухфазные зубцы Т, по данным эхокардиографии — нормализация фракции выброса левого желудочка, отсутствие зон гипокинезии.

Связь начала заболевания с тяжелым эмоциональным напряжением, несоответствие зон нарушения локальной сократимости бассейну одной коронарной артерии с циркулярным поражением левого желудочка, отсутствие морфологического субстрата, объясняющего столь выраженный неврологический дефицит в остром периоде, быстрое полное восстановление кардиологической и неврологической дисфункции позволили сделать вывод о первичной форме СТ. Катехоламиновый выброс вызвал острую дисфункцию левого желудочка, которая осложнилась гипоперфузией мозга с прогрессирующим его отеком.

Таким образом, СТ в остром периоде может имитировать не только типичную, ангинальную форму инфаркта миокарда, но и церебральную.

Ключевые слова: *Синдром такоцубо, ишемический инсульт, инфаркт миокарда*

Конфликт интересов

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

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Abstract

Takotsubo Syndrome (TS) is an acutely developing and typically reversible myocardial dysfunction, predominantly affecting the left ventricle, which clinically and electrocardiographically resembles acute coronary syndrome. Among the etiological factors of this pathology, severe emotional stress and physical conditions, including severe brain diseases, are noted. The most common symptoms in the acute phase include chest pain and dyspnea, while palpitations and syncope occur less frequently. Severe cases of TS may be complicated by cardiogenic shock, pulmonary edema, acute cerebrovascular accident, cardiac arrest. The presented clinical case demonstrates an atypical course of TS, in which the severity of the patient's condition was determined by central nervous system involvement

A 68-year-old man was admitted in critical condition to the intensive care unit: after experiencing severe emotional stress, he was found unconscious at home. Upon examination, the patient was in a state of sopor with right-sided gaze paresis, right-sided mouth corner drooping, and severe neurological deficit, as assessed by NIHSS.

Computed tomography of the brain revealed a poorly defined ischemic lesion in the vascular territory of the left middle cerebral artery. Electrocardiography showed biphasic and negative T waves in AVL, V3-V6. Echocardiography revealed a reduction in left ventricular ejection fraction to 32 % and the regional walls motion abnormality including circular hypokinesis. Elevated levels of myocardial necrosis markers were observed. A diagnosis of combined ischemic brain and myocardial injury was established, and treatment was initiated. The following day, significant positive dynamics were observed—the patient regained consciousness, had no neurological deficit. Magnetic resonance imaging of the brain did not reveal evidence of stroke. There are no negative and biphasic T waves on the electrocardiogram, echocardiography demonstrated normalization of left ventricular ejection fraction and the absence of hypokinetic zones.

The correlation between disease onset and severe emotional stress, the discrepancy between the regional walls motion abnormality and the vascular territory of a single coronary artery with circular involvement of the left ventricle, the absence of a morphological substrate explaining the pronounced neurological deficit in the acute phase, and the quick, complete recovery of cardiac and neurological function led to the conclusion of a primary form of TS. A catecholamine surge induced acute left ventricular dysfunction, which was further complicated by cerebral hypoperfusion with progressive brain edema.

So, in the acute phase TS may mimic not only the typical anginal form of myocardial infarction but also a cerebral event.

Key words: *Takotsubo Syndrome, acute ischemic stroke, myocardial infarction*

Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Cerebral mask of Takotsubo Syndrome» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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TC — Takotsubo cardiomyopathy, ACS — acute coronary syndrome, ACVA — acute cerebrovascular accident, ECG — electrocardiography, echoCG — echocardiography, MRI — magnetic resonance imaging

Takotsubo cardiomyopathy (TC) is an acute and usually reversible myocardial dysfunction, mostly in the left ventricle, which is associated with circular reduction in myocardial contractility, seen clinically and on ECG as acute coronary syndrome (ACS) [1]. In Japanese, takotsubo means an octopus trap, a ceramic pot with a round basis and narrow neck. This is the form of the left ventricle at the end of the systole due to transient ball-shaped widening of apical segments and midsegments.

N. Sato et al. were the first to describe TC in 1990. Publications emphasised the correlation between this syndrome and negative psychoemotional factors. For this reason, TC is called the broken heart syndrome, stress-induced cardiomyopathy. However, results of later studies demonstrate that physical factors are more often the cause of TC than emotional [1]. Physical triggers include GI bleeding, surgery, severe brain conditions (acute cerebrovascular accidents, subarachnoid haemorrhage, cerebrocranial accidents), thyrotoxicosis, pheochromocytoma, severe pain (pneumothorax, renal or biliary colic), abstinence symptom (alcohol, opiates), β2-adrenoceptor agonist overdose, etc. Since the physical factors, which can trigger acute ballooning of myocardium sections, are numerous, it was suggested to identify all variants of TC, caused by physical factors, as secondary TC, whereas the classical disease progression under the influence of psychoemotional stress is called primary TC [2]. It is assumed that the main pathogenetic causes are direct cardiotoxic action of catecholamines, myocardial stupor (hybernation), coronary artery spasm, oxidative stress, vegetative imbalance, inflammatory and metabolic conditions of the myocardium [1, 2].

The accurate incidence of TC is currently unknown. According to the 2018 global consensus, the incidence of the syndrome is 1–3% of all patients hospitalised with suspected acute myocardial infarction with elevated ST,

and in women the rate of TC can reach 5–6%. Patients are mostly postmenopausal women; however, recently the disease is reported in men of 50–75 years of age [3].

Clinical presentation of acute TC is often similar to ACS, with or without elevated ST. The most common symptoms of this disease during the acute phase are retrosternal pain (up to 75% of cases) and shortness of breath (up to 52% of cases). Palpitations (up to 12%) and syncope (up to 9%) are less common. The main clinical manifestations of TC caused by physical triggers are the symptoms of the underlying physical illness. Severe TC can be complicated by cardiovascular shock, pulmonary oedema, acute cerebrovascular accident (ACVA), cardiac arrest [3].

The presented clinical case demonstrates atypical TC progression, where the main clinical manifestations and patient's condition severity depended on the rate of central nervous system involvement.

Male, 68 years old, was admitted to the A&E of Saratov Regional Clinical Hospital at 3.00 pm on April 15, 2024. Upon admission, he did not have any complaints due to his severe condition. Past medical history was presented by his relatives. The patient was the head of a farm business, where a large fire occurred recently, the roof collapsed and people died. He lived alone, called his relatives at around 8.00 am, and did not complain of anything. At 11.00 am he was found at home unconscious. The past history shows that he did not have any bad habits and known cardiovascular diseases; he had no family history of cardiovascular pathologies. The patient underwent regular medical examinations and led an active life.

Upon admission, his condition was serious. His consciousness was close to semi-consciousness; Glasgo Coma Score: 10 points. When painful stimulus and loud call were used, the patient opened his eyes for a short time; he did not follow instructions. The skin was of normal colour. Overweight (body mass index: 27.7 kg/m^2). Cardiac sounds were muffled, rhythmic. The pulse was of equal volume and exertion, 96 beats per minute. Blood pressure: 130/80 mm Hg. Vesicular respiration, without rale, 19/min. Right gaze palsy. The face is asymmetrical: the right angle of mouth is lower than the normal level. Sensorimotor aphasia. 24 points on the NIHSS, which corresponded to severe neurologic impairment.

Brain computer tomography: projection of the left parietal region with an unclear area of lower density, 13×11×12 mm, 26 HU, which was interpreted as a sign of possible ischaemic stroke in the left medial cerebral artery system (Figure 1). The quantification scale of early ischaemic changes in brain substance based on ASPECTS CT results: 9 points, i.e. a small ischaemic site. Duplex scanning of brachiocephalic arteries showed hemodynamically insignificant stenosis (10–15%) in the bifurcation of the left common carotid artery.

Electrocardiography (ECG) showed sinus tachycardia with heart rate of 100 beats per minute, signs of blocked anterior branch of the left bundle of atrioventricular bundle, two-phase and negative T wave in the septal-apical-side area of the left ventricle (Figure 2). Echocardiography (eco-CG) showed a drop in ejection fraction to 32% (Simpson). Insignificantly widened left atrium cavity (index left atrial volume: 36 mL/m^2), grade2 mitral, tricuspid regurgitation; marked hypokinesia of lower, lower lateral segments at the apical, middle, basal levels; lower septal, anterior septal segments at the middle and basal levels of the left ventricle; grade 1 pulmonary hypertension (systolic pressure in the pulmonary artery: 43 mm Hg).

Laboratory test results showed leucocytosis, hyperglycaemia, dyslipidemia, minor hyperazotemia, high myocardial necrosis markers, high natriuretic peptides. The most important laboratory parameters upon hospital admission and their changes are presented in Table 1.

A preliminary diagnosis was determined. Primary diseases: 1. Brain infarction (unknown origin) in the left medial cerebral artery system, dated April 15, 2024. Sensorimotor aphasia. Central right facial palsy. Right gaze palsy. 2. Ischaemic heart disease. Acute non-Q septal-apical-lateral myocardial infarction without elevated ST, dated April 15, 2024. Atherosclerosis of aorta and carotid arteries without hemodynamically significant stenosis. Relative mitral valve insufficiency, grade 2; tricuspid valve insufficient, grade 2. Grade 1 pulmonary hypertension. Overweight (body mass index: 27.7 kg/m^2). Dyslipidemia. Complications**:** Brain swelling. IIA circulation failure with reduced ejection fraction (32%).

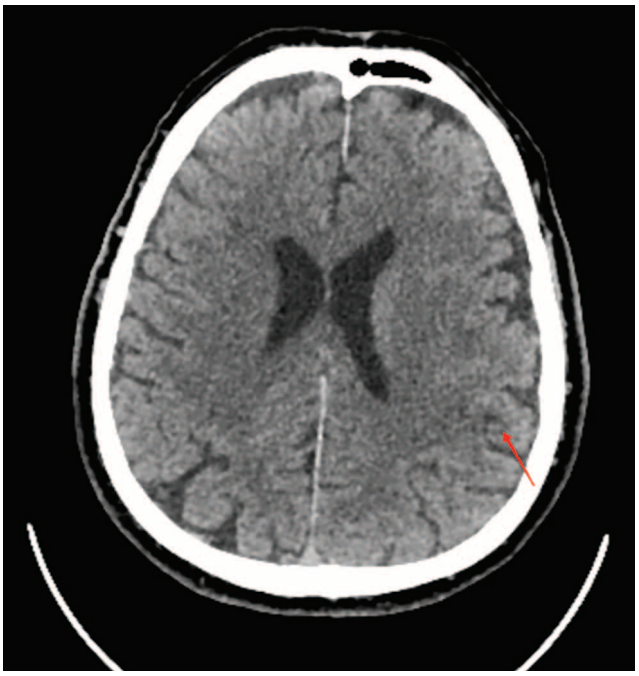

Figure 1. *Computer tomography of the brain, first day of illness*

Note. A zone of low-density measuring 13×11×12 mm with density characteristics of 26 HU is extremely indistinctly defined on the left parietal lobe

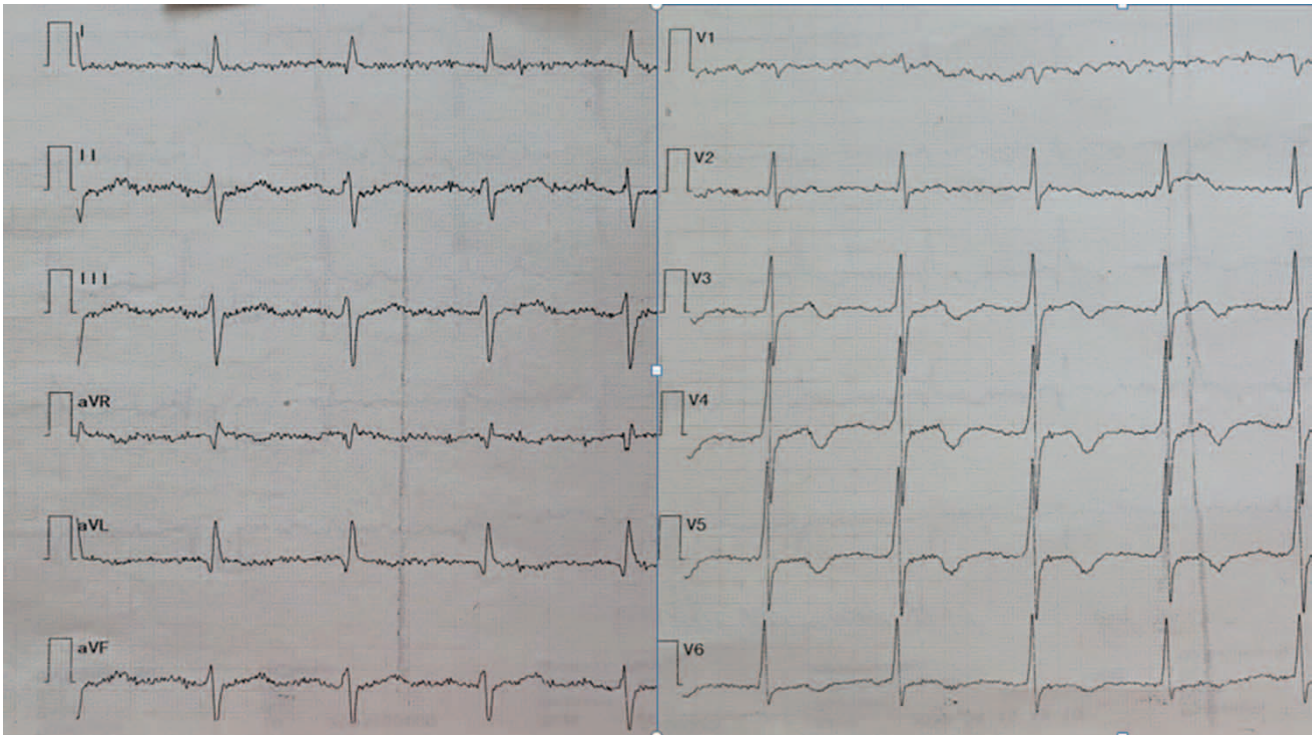

Figure 2. *ECG of the patient upon admission, first day of illness*
Note. Sinus tachycardia. Incomplete right bundle brunch block, biphasic and negative T wave in AVL, V3-V6

Table 1. *Laboratory tests of the patient upon admission to hospital and during dynamic observation*

Test, units of measurement	Upon admission to hospital	On the 6th-7th day of hospitalization	Reference values
Leukocytes, 10^9/l	11,2	4,6	4-9
Glucose, mmol/l	10,5	5,1	<6,1
Total cholesterol, mmol/l	5,6	4,3	-
LDLs, mmol/l	3,9	2,4	-
Creatinine, mmol/l	130	103	56-115
GFR (CKD-EPI) / ml/min/1,73 м^2,	48	64	>60
Troponin-I hs, ng/ml	1,7	0,4	<0,5
CPK tot, Ed/l	517	251	<200
CPK-MB, Ed/l	69,5	24	<25
NT-proBNP, пг/мл / pg/ml	824	561	<125

Note. LDLs — low-density lipoproteins, GFR (CKD-EPI) — glomerular filtration rate calculated by the CKD-EPI, Troponin-I hs — Troponin-I, high sensitivity, CPK tot — Creatine Phosphokinase total, CPK-MB — Creatine Phosphokinase MB, NT-proBNP — N-terminal prohormone of brain natriuretic peptide
Reference values for total cholesterol and LDLs are not given because target values for these parameters are calculated individually.

According to the studies, acute myocardial infarction increases the risk of ACVA and vice versa. In 2010, Omar et al. suggested a concept of acute cardiocerebral infarction. Despite its low incidence (1–6% of cases), this combination worsens prognosis for patients and limits the therapy of each individual condition [4]. Clinically, there are three forms of this pathology, depending on the timing of the damage [5]. Type one: simultaneous myocardial and cerebral infarction. This is possible in embolism from the left heart in atrial fibrillation; in crossed embolism from the central circulatory system because of the open foramen ovale; and in aortic dissection, if the affected area includes both coronary and carotid arteries. Type two: primary heart involvement. In acute myocardial infarction, strokes are usually cardioembolic due to the development of such complications as atrial fibrillation and ventricular cavity thrombosis. Also, acute reduction in myocardial contractility in some myocardial infarction patients causes brain hypoperfusion, progressive brain swelling, and neurological symptoms. Type three: primary brain involvement. Cardiac changes during acute craniocerebral accident are associated with vegetative nervous system dysfunction and increased catecholamine

production, which can cause TC and decompensation of existing ischaemic heart disease. Therefore, the examination and follow-up in this patient were performed to clarify the origin of the ischaemic myocardial and cerebral damage.

The patient was treated with cerebral protectants (ethylmethylhydroxypyridine succinate, Cerebrolysin), antiedemics (magnesium sulphate), double disaggregation (acetylsalicylic acid, clopidogrel), lipid-lowering (atorvastatin), cardiotropic drugs (metoprolol succinate, enalapril), and gastroprotectors (esomeprazole). Anticoagulants were prescribed for preventive purposes because of early severe stroke (enoxaparin). Given that the patient was in semiconscious state, he was put on artificial lung ventilation in order to ensure clear airways and prevent secondary hypoxic damage to the brain. No thrombolytic therapy for the stroke was performed because the patient was admitted to the hospital more than 4.5 hours after disease onset. It was decided not to perform coronary angiography and possible percutaenous coronarography intervention due to suspected large brain damage and serious condition of the patient.

The therapy resulted in significant improvement of the patient's condition and neurological status. The next day after admission, the patient is conscious, lucid, knows who he is, knows the place and time, is reasonable, answers questions asked, fully follows instructions, does not have any complaints. NIHSS score is 0 points, no neurological deficit. In order to assess the nature and extent of the brain damage, brain magnetic resonance imaging (MRI) was performed 24 hours after the previous imaging (T1, T2W and diffusion). There were no areas of high magnetic resonance signal in the brain and cerebellum matter, i.e. there were no signs of ACVA (Figure 3).

ECG results (April 17, 2024): no tachycardia; no signs of impaired repolarization in the form of negative and two-phase T waves (Figure 4).

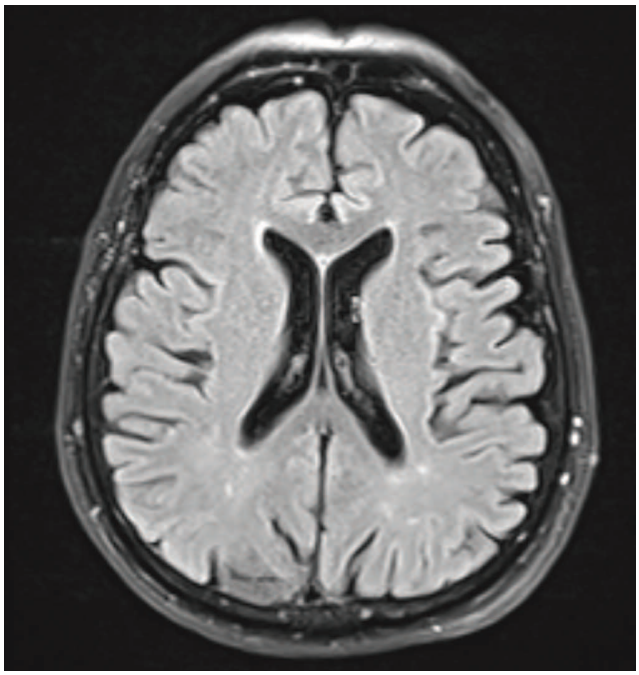

Figure 3. *Magnetic resonance imaging of the brain, second day of illness. Stroke not detected.*

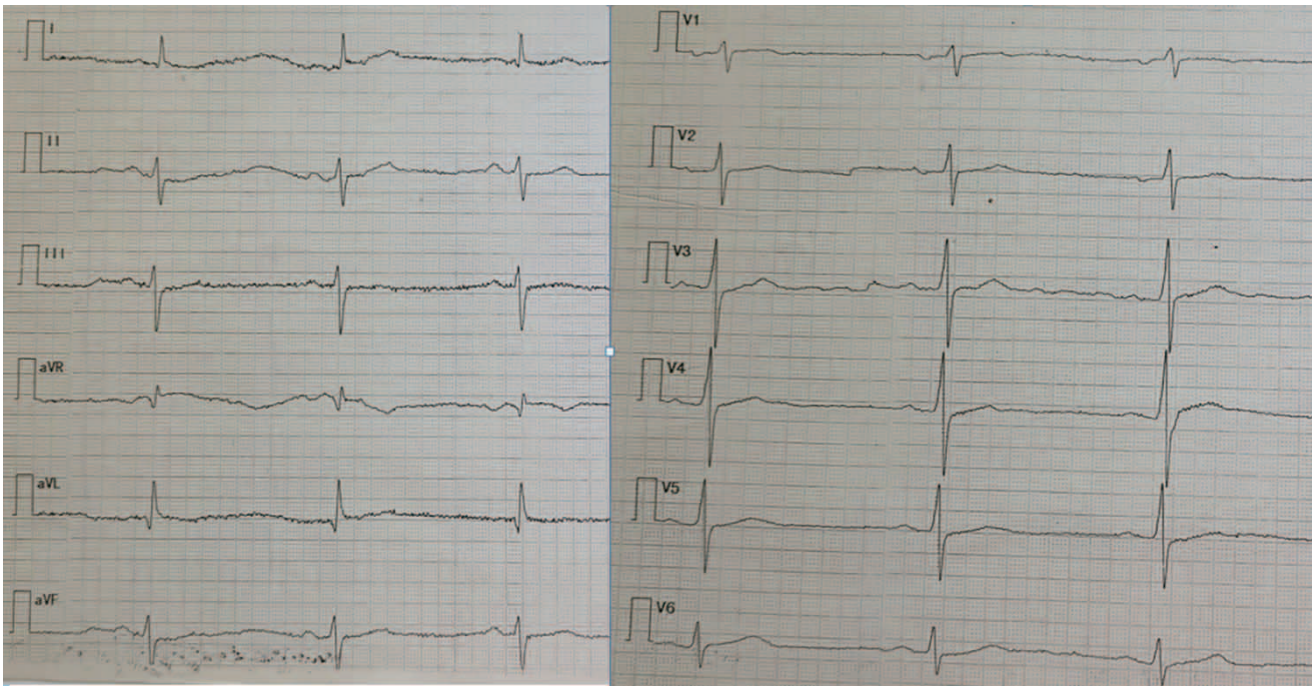

Figure 4. *ECG of the patient, third days of illness. Tachycardia has been stopped, there are no repolarization disorders*

ECG results (April 17, 2024) show significant favourable changes: ejection fraction normalised (61%, Simpson) and no signs of impaired local contractility. Laboratory test results showed normal WBC count, normal levels of creatinine, serum glucose, and markers of myocardial necrosis (Table 1). Glicated haemoglobin value was 5.2%, and it was concluded that hyperglycaemia observed upon admission was a stress reaction and not a sign of long-lasting carbohydrate metabolism impairment. Holter ECG monitoring results (April 17, 2024): sinus rhythm with an average rate of 60 beats per minute, individual auricular extrasystoles; no QT elongation, ST excursions, irregular repolarization processes.

Complete correction of neurological deficit within 24 hours without any MRI changes allowed to rule out stroke and diagnose transient ischaemic attack. Fast normalisation of ECG manifestations and echoCG parameters, absence of the typical clinical signs caused some doubts about the diagnosis of acute ischaemic myocardial damage. Given the correlation of disease onset with emotional stress, mismatch between areas of impaired local contractility and one coronary artery with circular damage to the left ventricle, significantly higher levels of N-terminal pro brain natriuretic peptide with insignificant increase in troponin concentrations, higher laboratory parameters, which indirectly point out to hypercatecholaminemia, TC was suggested.

The international diagnostic criteria for TC (InterTAK Diagnostic Criteria) were proposed in 2018 [3]. The patient had the following criteria of this pathology: transient signs of left ventricle dysfunction, regional abnormality of left ventricle wall movement beyond the blood flow in one coronary artery, prior emotional trigger, changes seen on ECG (including inverted T wave), moderately elevated cardiospecific markers, higher levels of natriuretic peptide. There was no solid clinical evidence of infectious myocarditis; heart MRI was not performed due to technical reasons. Once his condition stabilised, the patient was offered coronary angiography, but he refused. Of note, according to this document [3], even obstructive lesion of the coronary system did not rule out TC. The international diagnostic criteria emphasise that acute neurological disorders can trigger Takotsubo cardiomyopathy.

This clinical situation brought up a question: What occurred first? Did acute neurological accident trigger Takotsubo cardiomyopathy, or vice versa? Clear correlation of disease onset with psychoemotional stress, absence of morphologic substrate (extensive ischaemic stoke, head injury), which could explain marked neurological deficit during the acute phase, fast and complete restoration of the cardiological and neurological function allowed concluding the presence of the primary form of Takotsubo cardiomyopathy. Acute left ventricle dysfunction in this patient was likely to be complicated by cerebral hypoperfusion and progressive brain swelling, which caused these marked neurological symptoms. The same pathogenetic mechanism underlies cerebral clinical form of acute myocardial infarction. The main difference is that in ischaemic necrosis of the myocardium, the damage is persistent, while in this patient the left ventricle function recovered quickly, and neurological deficit completely disappeared.

The patient's therapy was adjusted: disaggregants, blood thinners, cerebral and GI protectants were cancelled. The recommended therapy in outpatient settings: lipid-lowering drugs (rosuvastatin 20 mg + ezetemibe 10 mg), low doses of angiotensin-converting enzyme inhibitors (perindopril 2.5 mg daily). Beta-blockers were not prescribed since the patient was susceptible to bradycardia. Two and six months after discharge from the hospital, the patient's state of health was satisfactory; he had good exercise tolerance; no complaints, kept active lifestyle without bad habits, and followed recommendations. With the therapy, blood pressure is normotensive (110–120/70–79 mm Hg); low-density lipoproteins two months later: 1.36 mmol/L, which is a target value for patients with a very high cardiovascular risk.

Therefore, during the acute phase, Takotsubo cardiomyopathy can look similar not only to the typical, anginal form of myocardial infarction, but also to the cerebral form. Fast recovery of the left ventricle function in this patient resulted in complete disappearance of neurological deficit and favourable outcome, despite severe clinical manifestations during the acute phase. Physicians should be made aware of this pathology; it will allow avoiding overdiagnosing acute ischaemic heart disease and excessive drug load.

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Тяпкина М.А.: сбор, анализ, интерпретация данных, разработка общей концепции и дизайна статьи, написание рукописи, проверка критически важного интеллектуального содержания, принятие окончательного решения о готовности рукописи к публикации, согласие быть ответственным за все аспекты работы.

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СИНДРОМ ГИЙЕНА-БАРРЕ У ПАЦИЕНТА С ИНФЕКЦИОННЫМ ЭНДОКАРДИТОМ: КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ И ОБЗОР ЛИТЕРАТУРЫ

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Guillain-Barre Syndrome in A Patient with Infectious Endocarditis: Clinical Observation and Literature Review

Резюме

Синдром Гийена-Барре (СГБ) — это тяжелое аутоиммунное заболевание периферической нервной системы, представляющее собой наиболее частую причину развития острого вялого тетрапареза, которое может приводить при отсутствии адекватной терапии к жизнеугрожающей дыхательной недостаточности. Взаимосвязь СГБ и инфекционного эндокардита изучена недостаточно.

У пациента 54 лет через 2 недели после перенесенной острой респираторной вирусной инфекции в течение 2 дней наросли онемение и слабость в нижних конечностях, госпитализирован с подозрением на ишемический инсульт. При компьютерной томографии (КТ) головного мозга — данных за острую очаговую патологию не получено, выявлены левосторонний гайморит и этмоидит. В анализе ликвора — белок — 0,8 г/л (норма — до 0,2 г/л), цитоз в пределах нормы. Прозериновая проба отрицательная. Клинико-инструментальная картина расценена как СГБ. При эхокардиографическом исследовании выявлены вегетации на створках митрального клапана (МК), отрыв хорд его передней створки — «молотящая створка», митральная регургитация 3 степени. Несмотря на проводимую антибактериальную, иммуномодулирующую и др. терапию, отмечалось сохранение неврологической симптоматики, развитие тромбоэмболии легочной артерии, внутрибольничной двусторонней полисегментарной пневмонии, сепсиса с летальным исходом. При аутопсии подтвержден инфекционный эндокардит с отрывом хорд МК, обильным ростом Pseudomonas aeruginosa, скудным ростом Klebsiella pneumoniae и Acinetobacter baumannii, тромбоз правого предсердия. Патологических изменений в ткани головного мозга не обнаружено.

Таким образом, синдром Гийена-Барре в редких случаях может сочетаться с инфекционным эндокардитом и оказывать негативное влияние на течение и прогноз заболевания.

Ключевые слова: *синдром Гийена-Барре, инфекционный эндокардит, демиелинизация, нейропатия*

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

Соответствие принципам этики
Информированное согласие пациента не требуется в силу невозможности его получения в виду смерти пациента.

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Abstract
Guillain-Barré Syndrome is a severe autoimmune disease of the peripheral nervous system, representing the most common cause of acute flaccid tetraparesis, which can lead to life-threatening respiratory failure in the absence of adequate therapy. The relationship between GBS and infective endocarditis is not well studied.

A 54-year-old patient experienced increasing numbness and weakness in the lower extremities two weeks after an acute respiratory viral infection, and was hospitalized with suspected ischemic stroke. Brain computed tomography revealed no data for acute focal pathology but showed left-sided sinusitis and ethmoiditis. Cerebrospinal fluid analysis showed protein at 0.8 g/L (normal up to 0.2 g/L), with cytosis within normal limits. The neostigmine test was negative. The clinical and instrumental picture was assessed as Guillain-Barré Syndrome. Echocardiography revealed vegetations on the mitral valve (MV) leaflets, rupture of the anterior leaflet chordae ("flail leaflet" of the MV), and grade 3 mitral regurgitation. Despite ongoing therapy, including antibacterial and immunomodulatory treatment, the patient continued to exhibit neurological symptoms, developed pulmonary artery thromboembolism, nosocomial bilateral polysegmental pneumonia, and sepsis, leading to a fatal outcome. Autopsy confirmed infective endocarditis with rupture of the MV chordae, abundant growth of Pseudomonas aeruginosa, scant growth of Klebsiella pneumoniae and Acinetobacter baumannii, and right atrial thrombosis. No pathological changes were found in the brain substance.

Thus, Guillain-Barré Syndrome in rare cases can be associated with infective endocarditis and negatively impact the course and prognosis of the disease.

Key words: *Guillain-Barré syndrome, infective endocarditis, demyelination, neuropathy*

Conflict of interests
The authors declare no conflict of interests

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Conformity with the principles of ethics
Informed consent of the patient is not required due to the impossibility of obtaining it due to the death of the patient

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BP — blood pressure, ALT — alanine aminotransferase, AST — aspartate aminotransferase, IV immunoglobulin — intravenous immunoglobulin, ALV — artificial lung ventilation, CT — computer tomography, MV — mitral valve, GBS — Guillain — Barre syndrome, US — ultrasound examination

Introduction

Guillain-Barre syndrome (GBS) is a severe autoimmune disease of the peripheral neural system, the most common cause of acute flaccid quadriparesis, which, if left untreated, can result in life-threatening respiratory distress [1].

GBS is the most common form of acute polyneuropathy. Annually, the global incidence of this disease varies from 0.6 to 2.4 per 100,000 people. GBS is diagnosed more often in men than in women; the incidence grows with the age [2].

There are the following clinical forms of GBS (Figure 1) [2]:

1) Classical sensorimotor (30–85%);
2) Isolated motor (10–70%);
3) Paraparetic (5–10%);
4) Oesophageal-cervicobrachial (< 5%);
5) Facial diplegia with paresthesia (< 5%);
6) Isolated sensor (< 1%);
7) Miller Fisher syndrome (5–25%);
8) Bickerstaff's brainstem encephalitis (< 5%).

Aetiology and Pathogenesis

The aetiology of GBS is still unclear; however, its development is assumed to be related to a past infection, primarily to Campylobacter jejuni, zika virus, flu, and SARS-CoV-2 virus (after 2020) [3, 4].

Patients with GBS caused by an infectious disease produce anti-gangliosides antibodies by molecular mimicry. Bacterial cross-reactive antigen identified by macrophages and T cells induces B cells for the development of anti-gangliosides response. These antibodies bind both to nerve fibre gangliosides and microbial antigens. Activated endoneural macrophages release cytokines and free radicals, penetrate compact myelin, periaxonal

space and sometimes block nervous conductivity or cause axonal degeneration. Activated T cells release pro-inflammatory cytokines, fix complement, damage Schwann cells, and cause myelin dissolution.

In acute inflammatory demyelinating polyradiculoneuropathy, immune damage occurs mostly in the myelin sheath and associated components of Schwann cells, whereas in acute motor axonal neuropathy, the key target is neural axon membranes (axilemma).

The clinical signs of GBS are caused by interruption of ascending and descending neuroanatomic pathways in the transverse plane of the spinal cord. Despite the proven relationship between GBS and infectious agents, in a number of cases the disease is identified as idiopathic [5].

Clinical presentation of Guillain-Barre syndrome

Patients with the classical sensomotor form of GBS have distal paresthesia or loss of sensation with weakness, which starts from lower limbs and progresses to the upper limbs and cranial nerves. A typical sign is weakening or diminishment of tendon reflexes in the majority of patients during the first days of the disease. Vegetative nervous system impairments are a common sign and can include unstable blood pressure, arrhythmias, pupil dysfunction, and gut or urinary bladder dysfunction. Often patients report pain syndrome, which can be muscular, radicular or neuropathic. The disease can have acute or subacute onset; patients can become disabled within two weeks. However, if the peak clinical signs appear within the first 24 hours or four weeks after disease onset, GBS is unlikely. GBS is characterised by monophasic clinical progression, however, some patients can have recurrences [6].

Atypical clinical presentation

GBS can have atypical clinical presentation. In the majority of cases, weakness and sensor signs are bilateral; however, they can be asymmetrical, mostly proximal or distal, they can start from lower, upper limbs or simultaneously in all limbs. Weakness can be preceded by severe diffuse pain or isolated dysfunction of cranial nerves. Children under six years of age often have non-specific or atypical clinical manifestations, such as pain without clean localisation, irritability, meningism or unsteady gait. Inability to identify these signs as early onset of GBS can result in delayed diagnosis. In some patients with atypical GBS, especially with isolated motor form, electromyographic examination can show normal or even enhanced reflexes over the entire period of disease duration [7].

Specific Forms of Guillain-Barre Syndrome Depending on the Symptoms

Some patients demonstrate a clear and persistent clinical variant of GBS, which does not progress to the classical pattern of loss of sensation and weakness. These variants include: weakness without sensor signs (isolated motor variant); weakness restricted to the cerebral nerves (bilateral facial nerve palsy with paresthesia), upper limbs (oesophageal-cervicobrachial form) or

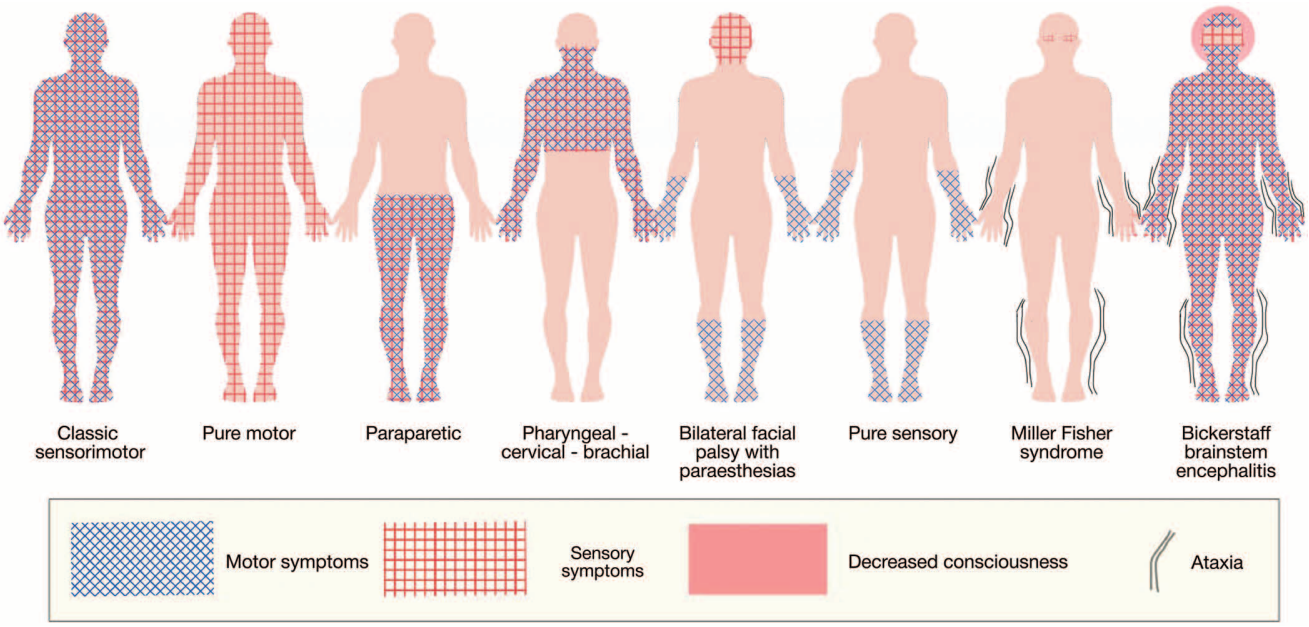

Fig.1. *Clinical forms of Guillain-Barré syndrome [2]*

lower limbs (paraparetic variant); and Miller Fisher syndrome, which in its full manifestation includes ophthalmoplegia, areflexia and ataxia [8]. GBS variants are rarely straightforward, they partially coincide with the classical syndrome or demonstrate characteristics typical for other forms. In addition to the mentioned variants, GBS often includes Bickerstaff's brainstem encephalitis and isolated sensor variant, since they have common clinical or pathophysiological signs. However, inclusion of these clinical variants is a subject of discussions, because they do not meet the diagnostic criteria for GBS [9].

Diagnostics of Guillain-Barre Syndrome

In the absence of adequately sensitive and specific biomarkers of the disease, the diagnosis of GBS is based on the clinical manifestation and test results and is confirmed with additional data, such as cerebrospinal fluid examination and electromyographic study. The two most commonly used sets of diagnostic criteria of GBS developed by the National Institute of Neurological Disorders and Stroke in 1978 (revised in 1990) andBrighton Collaboration in 2011 [10] are still relevant today.

Cerebrospinal fluid examinations are used mostly to rule out other causes of weakness, other than GBS, and should be performed during initial patient examination. A classical sign of GBS is a combination of higher protein levels and normal cell count in cerebrospinal fluid (known as albuminocytologic dissociation). However, protein levels can remain within the normal range in 30% to 50% of patients during the first week after disease onset and in 10% to 30% of patient during the second week. Marked pleocytosis (> 50 cells/μL) is not typical of GBS and is possible, e.g., in leptomeningeal malignancies, infectious or inflammatory conditions of the spinal cord or nerve roots. Moderate pleocytosis (10–50 cells/μL) is likely to be observed in GBS patients, but clinicians should consider alternative diagnoses, e.g., infectious causes of polyradiculitis [11].

Diagnostic Criteria of Guillain-Barre Syndrome [2, 12]

Criteria essential for the diagnosis:

1. Progressive bilateral weakness in the upper and lower limbs (initially only lower limbs can be affected).
2. Reduced or absent tendon reflexes in affected limbs (at a certain time point during disease progression).

Symptoms confirming the diagnosis:

- Progressive phase lasts for a period of up to four weeks (usually less than two weeks).
- Relatively symmetrical symptoms and signs.
- Relatively mild sensor symptoms and signs (absent in isolated motor variant).
- Cranial nerve involvement, especially facial nerve palsy.
- Vegetative dysfunction.
- Muscle or root pain in the back or limbs.
- Increased protein levels in cerebrospinal fluid. Normal protein levels do not rule out the diagnosis.
- Electromyographic signs of motor or sensorimotor neuropathy. Normal electrophysiological characteristics at early stages of the disease do not rule out the diagnosis.

Symptoms placing the diagnosis in question:

- Increased levels of mononuclear cells or polymorphonuclear cells in spinal fluid (> 50×10^6/L).
- Marked, persistent asymmetric weakness.
- Gut or urinary bladder dysfunction at early stages of the disease, or persistent dysfunction over the disease duration.
- Severe respiratory dysfunction with limited limb weakness at the onset of the disease.
- Sensor symptoms with limited weakness during the course of the disease.
- Fever at the onset of the disease.
- Significantly increased sensitivity, pointing to a spinal cord trauma.
- Hyperreflexia or clonic seizures.
- Extension plantar reflexes.
- Abdominal pain.
- Slow progression with limited weakness, no damage to breathing muscles.
- Continuous progression for over four weeks after symptom manifestation.
- Alteration of consciousness (except for Bickerstaff's brainstem encephalitis).

Therapy of Guillain-Barre Syndrome

The therapy should be initiated if a patient is unable to walk ten metres. Evidence of therapy efficacy in ambulatory patients is limited; however, treatment should be considered, especially if patients experience rapidly progressive weakness or other serious symptoms, such as vegetative dysfunction, bulbar or respiratory distress. Clinical trials demonstrated efficacy of intravenous (IV) immunoglobulin, if started within two weeks after the onset of weakness, and of plasma separation, if started within four weeks. No evidence of the efficacy outside these windows has been reported [13].

IV immunoglobulin (0.4 g/kg of body weight daily for five days) and plasma separation (200–250 mL of plasma/kg of body weight, five sessions) are equally efficient

in the management of GBS. IV immunoglobulin and plasma separation have similar risks of side effects. Since IV immunoglobulin is more accessible and easy to use than plasma separation, it is used more often. It is worth noting that plasma separation followed by IV immunoglobulin did not demonstrate superior efficacy vs. both methods used separately. In clinical settings, where resources are limited, small-scale plasma separation can be a cost-effective and relatively safe alternative to traditional plasma separation; however, this approach cannot be recommended for wide use until its efficacy is proven in future studies [14].

Besides IV immunoglobulin and plasma separation, other therapies did not demonstrate any efficacy in the management of GBS. Eight randomised, controlled clinical trials did not identify any significant benefits of using corticosteroids in GBS patients, and oral corticosteroids even had unfavourable impact on the prognosis [14].

In the presence of clinical signs of an infection, antibacterial or antiviral therapy can be initiated in patients with GBS [15].

The relationship between GBS and infective endocarditis has not been sufficiently studied.

Case Study

A 54-year-old patient suddenly developed weakness and numbness in his lower limbs, more marked on the left side. Two days later, he fell on the stairs because of increasing weakness in his lower limbs. The patient was hospitalised with suspected ischaemic stroke in the bed of the right medial cerebral artery. His past medical history shows that he did not control his BP; two weeks before the incident, he had acute respiratory virus infection, his body temperature rose to 37.3 °C, but he did not call for medical assistance. The patient denies chronic conditions, nicotine and drug addiction.

Upon admission, he was in serious condition. The skin was unremarkable, with bruises all over his lower and upper limbs, sustained at various times. Auscultation findings: harsh breathing, large bubbling rales over the whole surface of the lungs. Respiratory rate: 25 respirations per minute. BP: 170/105 mm Hg. Auscultation findings: muffled heart tones, systolic murmurs at the apex, irradiating to the left axillary region. Heart rate: 78 beats per minute. No signs of congestion in the central circulatory system. Neurological status upon admission: lucid, Glasgow coma scale: 15 points. Meningeal signs are not observed. Fields of vision are normal; no gaze palsy; pupils are round; OD=OS; photoreactions are preserved. Horizontal end-position nystagmus when looking to the left; asymmetric nasolabial folds because of the left part of the face (preclinical sings); the tongue is on the midline; swallowing, voice set and articulation are preserved. Motor functions: quadriparesis up to four points; Barre test on the upper and lower limbs show more quick lowering movement of the left limbs. Weaker tendon reflexes, D=S. No pathological foot reactions. Sensitivity is normal. Coordination tests: the patient misses targets because of weakness in his limbs.

Brain CT: no signs of acute cerebrovascular accident; left-sided acute maxillary sinusitis and ethmoiditis were diagnosed.

During the 12 hours spent in the inpatient clinic, the patient's neurological status changed negatively: quadriparesis reached three points in the upper limbs and two points in the lower limbs. Mild dysphagia and dysarthria appeared. The patient was consulted by a neurologist once again. To rule out ischaemic stroke in the vertebrobasilar system, *brain CT* was performed; no focal pathology was observed. *CT angiography* of brachiocephalic arteries, intracranial section of brachiocephalic arteries, and the circle of Willis did not show any hemodynamically significant stenosis and acute pathologies.

A *clinical analysis of spinal fluid* showed an increase in protein concentrations to 0.8 g/L (normal range: 0.22–0.33 g/L). Electroneuromyography was not performed due to technical difficulties. Taking into account past medical history, clinical presentation, no CT signs of ischaemia, no CT angiography signs of occlusion, GBS or generalised myasthenia were suspected. To rule out myasthenia, a proserine test was performed, which came back negative.

Echocardiography showed signs of mucoid degeneration and detached anterior mitral leaflet chords — flail leaflet. Hypoechogenic and isoechoic overlaps along the leaflet edge, most likely vegetations, were observed. Stage 3 mitral insufficiency. *Transesophageal echocardiography* confirmed infectious endocarditis, once vegetation on the anterior leaflet of MV were found (Figure 2). Also, a blood clot was found in the right atrial cavity, which was attached to the wall (Figure 3).

A comprehensive examination was undertaken: *ultrasound examination (US) of brachiocephalic arteries and radial arteries* with rotating tests*; ultrasound examination of lower limb veins; ultrasound examination of kidneys, adrenals, retroperitoneal space; no pathologies were identified. Abdominal ultrasound:* signs of chronic calculous cholecystitis, moderate diffuse changes in the liver.

One major and one minor Modified Duke Criteria (2015) were used to make a diagnosis for the patient:

Primary disease: Subacute primary infectious endocarditis of the anterior leaflet of the intact mitral valve.

Concurrent disease: Guillain-Barre syndrome.

Background disease: Mucoid degeneration of mitral leaflets.

Primary disease complications: Detached anterior mitral leaflet chords. Stage 3 mitral insufficiency. Chronic cardiac insufficiency with preserved ejection fraction, stage IIA, NYHA functional class II.

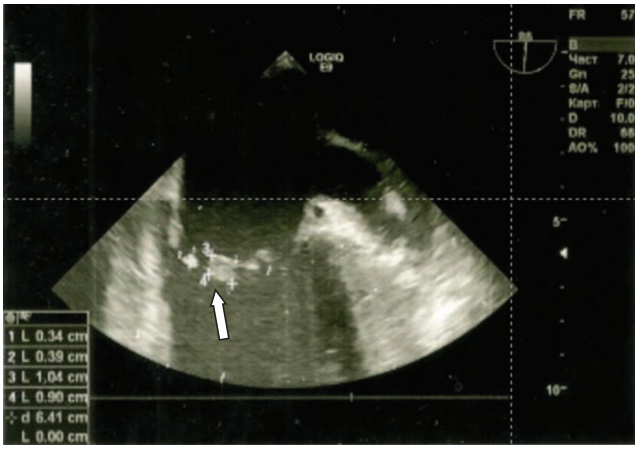

***Fig.** 2. Transesophageal echocardiography. Two vegetations on the anterior leaflet of the mitral valve are 0.34*0.39 cm and 1.04*0.9 cm in diameter (indicated by an arrow)*

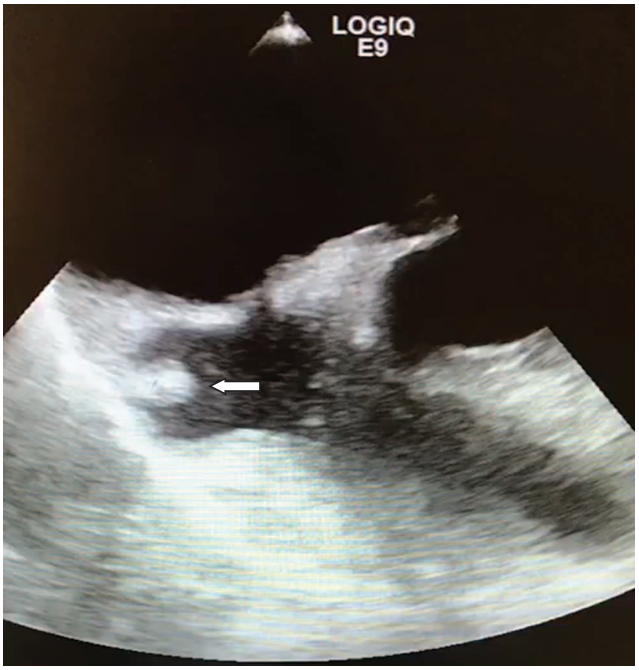

***Fig.** 3. Transesophageal echocardiography. Thrombus in the cavity of the right atrium (indicated by an arrow), fixed to the wall*

Comorbidities: Stage II hypertensive disease, uncontrolled. Target BP values: 120–130/70–79 mm Hg. A very high risk of cardiovascular complications. Right atrium thrombosis. Gallstone disease: chronic calculous cholecystitis, remission. Acute maxillary sinusitis (left side). Acute ethmoiditis.

Multiple *blood culture for sterility:* no flora growth was observed. Laboratory test results are presented in Table 1.

Antibacterial therapy was initiated (meropenem trihydrate 1 g IV three times daily; linezolid 600 mg IV two times daily). Several thromboconcentrate transfusions were performed because of persistent low platelet count. Once low platelet count was corrected, anticoagulant therapy was initiated. Because of aggravated respiratory insufficiency, the patient was connected to ventilatory support. On day 3, tracheostomy was performed.

On day 3 after hospital admission, quadriparesis was one point; no tendon reflexes were observed. Immunomodulating therapy was initiated (human plasma proteins with immunoglobulin G content of no less than 98%, 400 mg/kg/day), and the neurological status improved: muscle strength in the upper and lower limbs rose from one to three points in proximal sections and from one to two points in distal sections. The patient was transferred to unassisted breathing with oxygen insufflation of 5 L/min.

***Table 1.** Results of laboratory research methods.*

Indicators \ Day of hospitalization	Reference values	1	3	7	10	12	14
Hemoglobin, g/l	130-160	134	119	112	87	91	90
Тромбоциты, x10⁹/l	150-400	6	82	226	275	438	454
Platelets, x10⁹/l	4-9	9,2	10,1	17,6	11,67	21,79	25,7
Band neutrophils, %	1-6	-	-	7	-	4	8
Segmented neutrophils, %	47-72	80,9	81,2	78	-	91	85
Creatinine, mmol/l	70-120	75,5	73	90,1	83,6	109,3	284,8
Urea, mmol/l	2,5-8,3	6,2	5,55	13,4	16,69	20,54	49,93
Total protein, g/l	65-85	61,1	68	72,6	63,5	62,7	60,4
Albumin, g/l	35-52	39,7	33,7	31,1	27,5	27,6	25,7
Alanine aminotransferase (ALT), U/l	10-41	19,7	25,4	38,5	362	341	1060,8
Aspartate aminotransferase (AST), U/l	11-41	37,9	27,9	27,2	292	178	1699,6
Alkaline phosphatase, U/l	30-120	82,8	86,7	72,4	88,1	108,8	124,8
Potassium, mmol/l	3,5-5,1	3,89	4,6	3,8	3,9	4,2	7,7
Procalcitonin, ng/ml	< 0,05	-	0,1	0,47	-	6,3	30,15

Despite the therapy, on day 12 after hospital admission, the patient's condition deteriorated: body temperature rose to 38.0 °C, respiratory distress worsened, the patient was again connected to a lung ventilator.

Inoculation of intratracheal tube discharge showed the presence of Pseudomonas aeruginosa (10^5 CFU/mL), Acinetobacter baumannii (10^7 CFU/mL).

Chest CT revealed signs of bilateral multisegmental pneumonia; *when IV bolus contrast medium was used* — signs of thromboembolism of the left lower lobe artery.

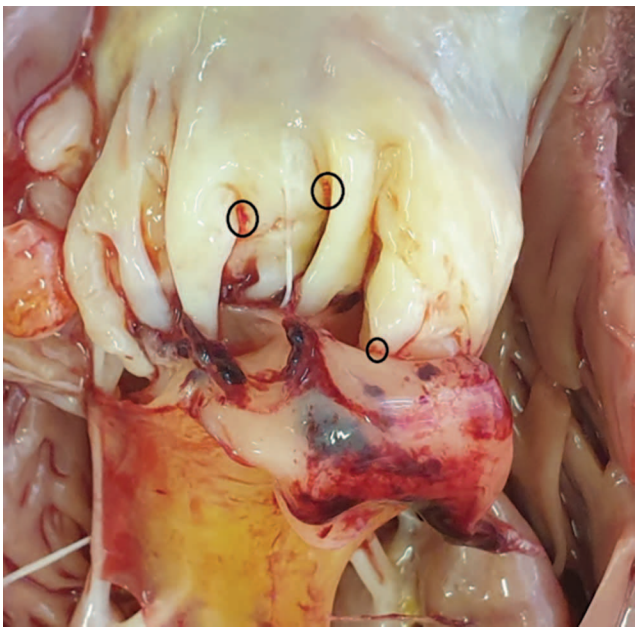

***Fig.** 4. Vegetations (marked with a circle) on the endocardium of the mitral valve*

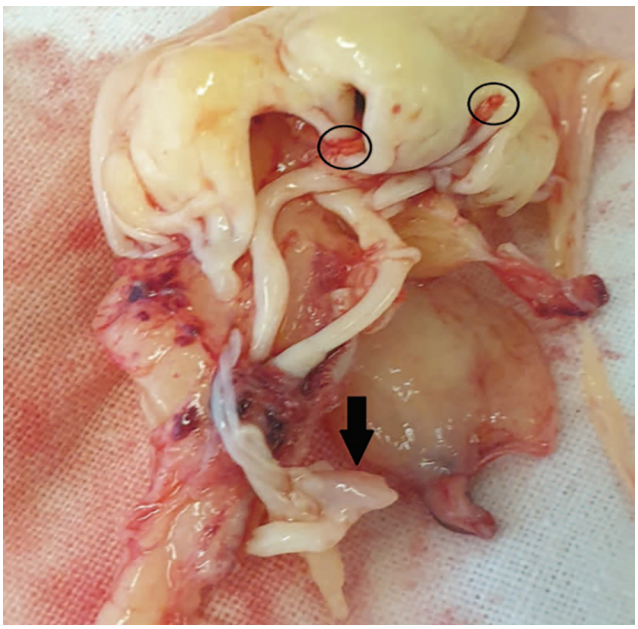

***Fig.** 5. Vegetations (marked with a circle) on the endocardium of the mitral valve. Mitral valve leaflet rupture (arrow)*

Antibacterial therapy was adjusted: meropenem trihydrate was cancelled; polymyxin B 100 mg IV two times daily was initiated; linezolid 600 mg IV two times daily.

Despite the therapy, the patient's condition kept deteriorating: on day 13 after hospital admission, multiple organ failure progressed (acute kidney injury, hyperkalemia) due to sepsis, cytolytic syndrome; ECG results showed atrial fibrillation paroxysm with tendency to hypotonia, which required inotropic support initiation.

On day 14, the monitor showed asystole. Resuscitation was unsuccessful. Natural death was recorded.

Postmortem examination results confirmed infectious endocarditis (pink vegetations on MV endocardium (Figures 4, 6), detached MV chords (Figure 5), excessive growth of Pseudomonas aeruginosa, poor growth of Klebsiella pneumoniae and Acinetobacter baumannii); blood clot was found in the right atrial cavity. No pathological changes were found in the brain substance.

Final postmortem diagnosis:

Primary diagnosis: Infectious endocarditis of the mitral valve (microbiological examination of the heart valve No. 46518: excessive growth of Pseudomonas aeruginosa, poor growth of Klebsiella pneumoniae and Acinetobacter baumannii).

Primary diagnosis complications: Sepsis: bone marrow hyperplasis, enlarged spleen (190 g), bilateral multisegmental pneumonia (microbiological examination of the heart valve No. 46518: excessive growth of Pseudomonas aeruginosa, poor growth of Klebsiella pneumoniae and Acinetobacter baumannii). Critical illness polyneuropathy. Detached mitral leaflets. Blood clot in the right atrial appendage. Thromboembolism of segmental branches of the left pulmonary artery. Pulmonary oedema. Brain swelling.

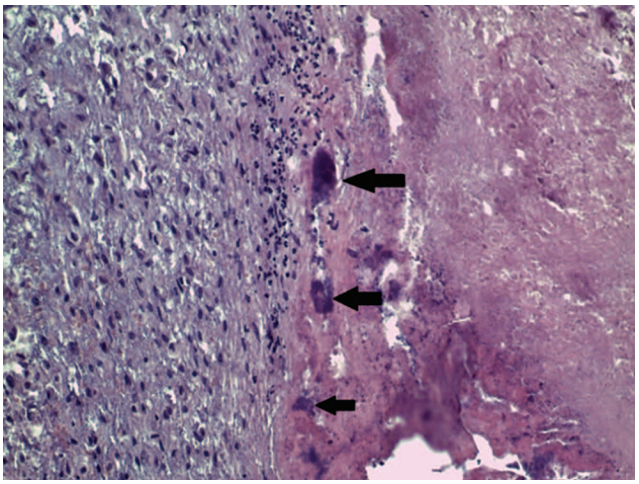

***Fig.** 6. Acute endocarditis with bacterial colonies (indicated by arrows). Staining with hematoxylin and eosin, magnification x200*

Secondary diagnosis: Arterial hypertension (heart weight: 360 g, left ventricle myocardial thickness: 1.6 cm, artery-arteriolar nephrosclerosis). Atherosclerosis of aorta (stage 4, grade 3), atherosclerosis of arteries in the base of brain (stage 1, grade 1), atherosclerosis of coronary arteries (stage 3, grade 3, 25% stenosis). Nodular prostatic hyperplasia.

Clinical Case Discussion

Often GBS develops one to three weeks after a past infectious disease caused by cytomegalovirus, influenza viruses, *zika* virus, etc., or a bacterial infection, such as *Campylobacter jejuni* and *Mycoplasma pneumoniae* [12]. Since 2020, the provoking infection list includes *SARS-CoV-2* [4]. In 2023, an overview was published on the development of GBS in patients after varicella-zoster virus infection [16]. There are individual reports on GBS in patients with acute infectious endocarditis of the intact [17] or prothetic [18] valves.

According to the patient, two weeks prior to hospitalisation, he had acute respiratory virus infection, when his body temperature rose to 37.3 °C, which was complicated by acute left-sided maxillary sinusitis and ethmoiditis (seen on brain CT upon admission).

In classical GBS, symptoms progress within two to four weeks, starting from the feet and progressing to hip muscles, hands, shoulder girdle, body and, in severe cases, throat muscles [2, 6]. In this patient, the symptoms developed much faster: for the first time, he experienced weakness in his lower limbs two days prior to hospitalisation; neurologist diagnosed motor dysfunction, more on the left side, weak reflexes on both sides; 12 hours later, mild dysphagia and dysarthria developed. Bowel and bladder functions were intact.

The severity of patient's condition was promoted by infectious endocarditis, diagnosed with the help of transthoracic echocardiography and confirmed with the help of transesophageal echocardiography. It is quite difficult to identify the time when the vegetation formed, because the patient denied body temperature hikes above 38 °C, Lukin spots or Janeway lesions or other signs of the disease before hospitalisation.

Infectious endocarditis can trigger various systemic complications. Septic embolism of vital organs, including brain, can develop approximately in 25% of cases. The risk of embolic complications is higher in staphylococcal infectious endocarditis, when vegetations are located on MV and/or if vegetation size exceeds 10 mm [17]. In this patient, vegetations were found on the anterior leaflet of the mitral valve, and they were larger than 10 mm. However, tests and examinations performed upon admission (brain CT and CT angiography of the intracranial section of brachiocephalic arteries) ruled out vascular embolism in the brain. Progressive weakness in the limbs, weak and then absent tendon reflexes, development of dysphagia and dysarthria, absence of CT signs of ischaemia, negative proserine test, analysis of the clinical analysis of spinal fluid (albuminocytologic dissociation), allowed diagnosing GBS and initiating successful immunomodulating therapy. In this case, the primary disease is more likely to be infectious endocarditis, which developed after a past acute respiratory virus infection with maxillary sinusitis and ethmoiditis; GBS is a concurrent disease. However, given the complex aetiopathogenesis mechanisms, GBS cannot be ruled out as one of the complex immune complications of acute/subacute infectious endocarditis.

In the majority of patients (approximately 75% of all cases), GBS is relatively asymptomatic, and its symptoms regress even without therapy. This patient benefited from immunomodulating therapy for the management of GBS. However, despite the antibacterial therapy, the patient developed sepsis with multiple organ failure and died.

Conclusion

Therefore, this is a clinical case study of a patient with infectious endocarditis of the mitral valve after a recent acute respiratory virus infection, complicated with left-sided maxillary sinusitis and ethmoiditis and Guillain-Barre syndrome. Clinical pathogenetic correlations and management of patients with the two severe conditions require further studies.

Вклад авторов:

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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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