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HYPERTENSIVE CRISIS IN MODERN GUIDELINES: HOW TO AVOID MISTAKES IN DIAGNOSIS AND TREATMENT. BASED ON THE MATERIALS OF THE RUSSIAN NATIONAL «HUMAN AND MEDICINE» CONGRESS AND THE III CARDIOLOGY SUMMIT

Abstract

The prevalence of hypertension is about 40 % according to Russian and world statistics. Approximately 1–2 % of patients with hypertension have high blood pressure throughout their lives, which requires urgent or emergency care. Hypertensive crisis is an acute condition caused by a sudden increase in blood pressure to individually high values, accompanied by clinical symptoms and requiring a controlled reduction to prevent target organ damage. According to the severity of clinical symptoms, hypertensive crisis is divided into uncomplicated and complicated. Typical signs of hypertensive crisis include malignant hypertension, severe hypertension associated with other clinical conditions, a sudden increase in blood pressure due to pheochromocytoma associated with organ damage, severe hypertension during pregnancy or preeclampsia. Hypertensive crisis is associated with various acute conditions, most often stroke (ischemic and hemorrhagic), acute cardiogenic pulmonary edema, acute heart failure, acute coronary syndrome, acute kidney injury, acute aortic dissection and eclampsia. The main goals of the treatment of hypertensive crisis are relief of the crisis, post-crisis stabilization, and prevention of repeated hypertensive crises. In patients with an uncomplicated hypertensive crisis, a decrease in mean blood pressure by 10 % during the first hour and by another 15 % during the next 2–3 hours is recommended. Therapy of complicated hypertensive crisis consists in the mandatory use of intravenous drugs with a predictable and controlled effect. The prognosis in patients with a hypertensive crisis, especially complicated one, is not favorable due to the high risk of short-term and long-term mortality. Patients who have undergone a hypertensive crisis require long-term follow-up.

Key words: *hypertension, hypertensive crisis, stroke, acute coronary syndrome, aortic dissection, pulmonary edema, hypertensive encephalopathy, target organ*

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BP — blood pressure, DIC-syndrome — disseminated intravascular coagulation syndrome, CAD — coronary artery disease

From April 8 to 11, 2019, the XXVI Russian National «Human and Medicine» Congress and the III Cardiology Summit were held in Moscow. Hypertension has become one of the key topics of the Congress and the Summit. The physicians paid great attention to the problem of diagnosis and therapy of urgent and emergency conditions caused by hypertension.

Relevance

According to the World Health Organization, there are 1.13 billion patients with hypertension in the world [1]. Russian epidemiological studies indicate that the prevalence of hypertension is an average of 40 % [2]. Approximately 1–2 % of these patients have high blood pressure (BP) throughout their lives, which requires urgent or emergency care. It should be noted that of all calls to the ambulance service, 15–25 % were related to high blood pressure.

Hypertensive crisis — this is a condition caused by a sudden increase in blood pressure to individually high values, accompanied by clinical symptoms and requiring a controlled decrease in blood pressure to prevent damage to target organs.

Typical manifestations of hypertensive crisis include malignant hypertension, severe hypertension associated with other clinical conditions, sudden increase in blood pressure due to pheochromocytoma associated with organ damage, severe hypertension during pregnancy or preeclampsia.

Hypertensive crisis is of great importance in elderly patients, especially since in many of them severe uncontrolled hypertension is asymptomatic. The study, which included 1,546 elderly patients (mean age 69 years) who were hospitalized for a hypertensive crisis, showed that 56 % of patients experienced nonspecific symptoms such as dizziness, palpitations, and headache. While symptoms indicative of target organ damage, chest pain and focal neurological symptoms were observed only in 28 % and 16 % of patients, respectively [3].

Risk factors and causes of hypertensive crisis

During sessions at the "Human and Medicine" Congress and the Third Cardiology Summit, factors that provoke a hypertensive crisis and methods for their correction were discussed. The triggers of hypertensive crisis include: non-adherence to antihypertensive therapy regimen, ineffective antihypertensive therapy, psychoemotional stress, excessive intake of salt and liquid, intake of psychoactive substances, alcohol abuse, history of preeclampsia. One study showed that factors potentially associated with the development of hypertensive crisis are female gender, high obesity, hypertension or coronary artery disease (CAD), the presence of somatoform disorders, a large number of antihypertensive drugs, poor adherence to therapy. At the same time, the lack of adherence to antihypertensive therapy was the most significant risk factor and was associated with an increase in the risk of hypertensive crisis by 6 times [4]. In another recent study, it was demonstrated that old age, CAD, congestive heart failure and chronic renal failure are associated with hypertensive crisis [5].

In most guidelines, the clinical classification of hypertensive crisis based on the severity of clinical symptoms and the presence of complications is preferred. Based on this classification, uncomplicated and complicated hypertensive crises are identified.

Uncomplicated hypertensive crisis is characterized by a significant increase in blood pressure with relatively intact target organs. Uncomplicated hypertensive crisis is of 2 types:

without sympathoadrenal activity and with sympathoadrenal activity (tachycardia, hyperthermia, etc.).

Complicated hypertensive crisis is accompanied by acute or progressive damage to target organs (brain, heart, kidneys, liver) and is a threat to the patient's life, which requires controlled intensive antihypertensive therapy. Hypertensive crisis accompanies various acute conditions. With cerebral infarction the frequency is 24.5 %, with hypertensive encephalopathy — 16.3 %, with intracerebral hemorrhage or subarachnoid hemorrhage — 4.5 %. Acute pulmonary edema is accompanied by a hypertensive crisis in 22.5 % of cases, acute heart failure — in 14.3 % of cases, and acute coronary syndrome — in 12 % of cases. Acute kidney injury in <10 % of cases is accompanied by hypertensive crisis. It must be remembered that an increase in hepatic enzymes, in most cases due to HELLP-syndrome (hemolysis, thrombocytopenia, liver damage, usually occurs in the III trimester of pregnancy), can also be accompanied by hypertensive crisis in 0.1–0.8 % of cases. In addition, hypertensive crisis can accompany retinal hemorrhage in 0.01–0.02 % of cases. Among the vascular causes of hypertensive crisis, eclampsia (4.5 %) and acute aortic dissection (2 %) are identified [6].

At the "Human and Medicine" Congress, the topic of malignant hypertension was discussed in detail, given the poor prognosis of patients and high mortality. In these patients, severe hypertension (usually of the 3rd degree) associated with changes in the fundus (hemorrhage and/or optic papilla edema), microangiopathies and syndrome of disseminated intravascular coagulation (DIC), as well as encephalopathy (in about 15 % of cases), acute heart failure and sudden deterioration of renal function is generally revealed. The basis of this condition is fibrinoid necrosis of the small arteries of the kidneys, retina and brain. The term "malignant" reflects an extremely unfavorable prognosis of this condition if untreated [7].

It is noteworthy that in many patients in emergency departments with pain or other conditions, there may be an acute increase in blood pressure, which independently returns to normal values when the pain decreases and will not require special measures to reduce it.

Examination of patients with hypertensive crisis

A training course was set up for practitioners at the "Human and Medicine" Congress where approaches to the diagnosis of emergency conditions caused by hypertension were discussed.

During the history taking and direct examination of a patient with an abnormal increase in blood pressure, the presence of symptoms and signs of target organ damage should be assessed. In particular, it is necessary to carefully review headache, dizziness, shortness of breath, chest pain, vomiting and changes in vision.

In patients with hypertensive crisis, it is important to assess the duration and severity of previous hypertension, as well as ongoing drug therapy, including the use of OTC drugs such as sympathomimetics, and drug abuse (in particular cocaine).

During the direct examination of the patient, it is important to correctly measure blood pressure using a cuff of the appropriate size. In addition, the presence of signs of heart failure should be assessed in patients: elevated pressure in the jugular veins, wheezing in the lungs, gallop rhythm, peripheral edema. In case of hypertensive crisis, detailed neurological examination with cerebellar tests, as well as fundus examination, is mandatory.

Patient complaints may be specific to target organ damage. Chest pain may indicate the presence of ischemia or myocardial infarction, back pain may be evidence for aortic dissection, dyspnea may indicate pulmonary edema or congestive heart failure. The presence of neurological symptoms, including convulsions, visual impairment and impaired consciousness may indicate the presence of hypertensive encephalopathy. It should be taken into account that in patients with hypertensive encephalopathy somnolence, lethargy, tonic-clonic convulsions and cortical blindness can precede loss of consciousness. However, focal neurological symptoms rarely occur

and stroke should be excluded when said symptoms occur.

The European guidelines for the treatment of patients with hypertension provide examinations that must be performed in patients with emergency conditions due to hypertension [8]. Standard examinations include: 12-lead electrocardiography, fundoscopy, tests for hemoglobin, platelets, fibrinogen, creatinine, glomerular filtration rate, electrolytes, lactate dehydrogenase, haptoglobin, urine albumin/creatinine ratio, urinary sediment microscopy (erythrocytes, leukocytes, casts) as well as pregnancy test in women of reproductive age. In addition to these studies, some tests are performed according to indications. Troponin, MB-fraction of creatine phosphokinase and the N-terminal pro-brain natriuretic peptide (NT-proBNP) are determined in cases of suspected myocardial damage, for example, with chest pain or acute heart failure); chest X-ray with volume overload; echocardiography with suspected aortic dissection, heart failure, ischemia; computed angiography of the chest and/or abdominal cavity with suspected aortic dissection; computed tomography or magnetic resonance imaging of the brain with suspected damage; ultrasound examination of the kidneys in cases of suspected kidney damage or renal artery stenosis; urine drug screen in cases of suspected use of amphetamine or cocaine.

The choice of optimal therapy for hypertensive crisis

The main objectives of hypertensive crisis therapy are: relief of crisis, post-crisis stabilization and prevention of repeated hypertensive crises.

The rate of decrease in blood pressure in hypertensive crisis is a debatable issue. The ideal rate of decrease in blood pressure in uncomplicated hypertensive crisis has not been precisely determined. In clinical guidelines, a decrease in mean BP by 10 % during the first hour and by another 15 % during the next 2–3 hours is recommended. It should be remembered that a more rapid decrease in blood pressure can lead to ischemia of organs. A gradual decrease in the level of blood pressure is recommended to be carried out with tablet antihypertensive drugs sublingually. In the absence of an effect from the tablet form and/or the presence of nausea and vomiting, parenteral drugs may be administered.

Therapy of complicated hypertensive crisis has become an important topic of discussion at the "Human and Medicine" Congress. Treatment of complicated hypertensive crisis consists in the mandatory use of intravenous drugs with a predictable and controlled effect. In complicated hypertensive crisis, BP reduction should be carried out as follows: in the first hour, mean BP decreases by 25 % (target level of diastolic BP ≥ 100 mm Hg), during 2 to 6 hours — to the target systolic BP of 160 mm Hg and/or diastolic BP of 100–110 mm Hg, during 6 to 24 hours — blood pressure should be maintained at the level achieved in the first 2–6 hours, during 24 to 48 hours — maintenance of blood pressure figures according to the latest clinical recommendations.

It is important to remember that BP reduction according to this principle is performed in all patients except for acute aortic dissection, acute ischemic or hemorrhagic stroke, eclampsia/preeclampsia, acute coronary syndrome, acute cardiogenic pulmonary edema. Urapidil, nitroglycerin, nitroprusside, esmolol, metoprolol and some other drugs are currently used for intensive antihypertensive therapy.

The choice of drug depends on the clinical manifestation. In patients with acute coronary syndrome, an immediate decrease in systolic blood pressure to <140 mm Hg is necessary. The first-line drug is nitroglycerin (dose of 5–200 mg/min with increase by 5 mg/min every 5 min), urapidil is its alternative (12.5–25 mg by bolus, 5–40 mg/h as continuous infusion). In the case of acute cardiogenic pulmonary edema, systolic blood pressure should be immediately reduced to <140 mm Hg. The drug of first choice is nitroglycerin with furosemide, and the alternative drug is urapidil. In patients with acute aortic dissection, an immediate rapid decrease in systolic blood pressure to <120 mm Hg within 5–8 minutes and a decrease in heart rate to <60 beats/min have been shown to be effective. The drugs of first choice are esmolol (0.5–1 mg/kg

by bolus; 50–300 mg/kg/min — continuous infusion) and nitroprusside (0.3–10 mg/kg/min with increase by 0.5 mg/kg/min every 5 min until the target BP is achieved), or nitroglycerin, or nicardipine (5–15 mg/h via continuous infusion, initial dose of 5 mg/h with increase every 15–30 min by 2.5 mg until target BP is achieved, then it should be reduced to 3 mg/h); their alternative is metoprolol (15 mg i. v., usually 5 mg i. v. with repeat dosing at 5-minute intervals) or labetalol (0.25–0.5 mg/kg; 2-4 mg/min until target BP is achieved, then 5–20 mg/h). However, in patients with cerebral stroke, the reduction of blood pressure should be extremely careful. The initial decrease in blood pressure should be no more than 10–15 % of the initial value under continuous monitoring of the patient's neurological status. In patients with unspecified stroke, antihypertensive therapy in the acute period is carried out only in the case of systolic blood pressure above 200 mm Hg. In patients with diagnosed subarachnoid hemorrhage of nontraumatic origin, antihypertensive therapy is carried out only with systolic blood pressure above 170 mm Hg. In patients with baseline systolic BP ≥220 mm Hg, BP is reduced to <180 mm Hg. In the case of malignant hypertension accompanied by acute kidney injury or without it, blood pressure should be reduced within a few hours, and mean BP should be reduced by 20–25 %. The drugs of first choice are labetalol and nicardipine, and nitroprusside and urapidil are alternative drugs. In patients with diagnosed hypertensive encephalopathy, an immediate decrease in mean BP by 20–25 % with labetalol or nicardipine is recommended (nitroprusside is an alternative drug). In patients with eclampsia and severe preeclampsia/HELLP syndrome, systolic blood pressure should be immediately reduced to <160 mm Hg and diastolic blood pressure — to <105 mm Hg. For this purpose, labetalol or nicardipine and magnesium sulfate are recommended. When prescribing drug therapy, in addition to efficacy, possible contraindications and adverse events should be taken into account. For example, esmolol is contraindicated in atrioventricular blockade of the 2nd or 3rd degree, systolic heart failure, asthma and bradycardia, and nitroprusside should be used with caution in renal and hepatic insufficiency [7].

The prognosis of patients after hypertensive crisis

Mortality among patients with hypertension, and in particular, hypertensive crisis, decreased significantly after the widespread introduction of antihypertensive drugs into clinical practice. The results of the studies indicate that the survival rate in patients with malignant hypertension increased from 37 % in the 1960s to 91 % in the 2000s. However, the long-term prognosis of patients who experienced a hypertensive crisis remains not very favorable. The results of a retrospective study with 670 adults with hypertensive crisis demonstrate that the increase in short-term mortality is due to neurovascular causes, and long-term mortality for 12 months — due to cardiovascular causes. The mean survival period in patients in whom the hypertensive crisis was due to a neurovascular cause was 14 days, in patients with a cardiovascular cause of hypertensive crisis — 50 days [8]. According to an extensive multicenter study, which included patients with hypertensive crisis who received intravenous therapy, nosocomial mortality was 6.9 %, followed by a 90-day mortality rate of 4.6 %. More than half of these patients (59 %) had new development or worsening of organ failure, most often kidney injury, acute heart failure, ischemia or myocardial infarction and encephalopathy [9]. According to another analysis in the European registry, 30-day mortality in patients with hypertensive crisis requiring parenteral therapy was 4 %, and the overall risk of damage to vital organs was 19 % [10].

In clinical guidelines, it is recommended, after discharge from the hospital once BP reaches a safe stable level during oral therapy, to perform follow-up with a monthly medical visit until the optimal target BP level is reached, and long-term follow-up by specialists subsequently.

Conclusion

Diagnosis and therapy of emergency conditions caused by hypertension became the subject of scientific discussion at the National "Human and Medicine" Congress and the III Cardiology Summit. Hypertensive crisis is a life-threatening condition that requires a controlled decrease in blood

pressure to prevent damage to target organs, usually with the help of intravenous therapy.

At the "Human and Medicine" Congress and the III Cardiology Summit, clinical algorithms for managing patients at the level of primary health care were tested. Today, algorithms for dyspepsia, non-alcoholic fatty liver disease, hypertension, hypercholesterolemia, stable coronary artery disease, tobacco dependence, type 2 diabetes mellitus, acute and recurrent cystitis, acute otitis media, acute and recurrent tonsillopharyngitis, acute bronchitis, acute and chronic rhinosinusitis and vaccination are approved and available for use in clinical practice.

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DOCTOR F. P. HAASS AND THE POLICE HOSPITAL AS THE FIRST EMERGENCY HOSPITAL IN MOSCOW

Abstract

A brief description and the work field of the doctor and humanist F. P. Haass (Friedrich Joseph Haass), who came to Moscow as a family doctor and gave all his knowledge and medical art to his new homeland, is provided. His path is shown from a family practice to the organization of Moscow healthcare, the chief doctor and hospital builder, the organizer of prison medicine, the great philanthropist and humanist who cared for the poor and destitute. His sequence in the implementation of the idea of the need to organize the provision of ambulance and emergency medical care for the poor who were injured in the streets, frostbite, with fever, bitten by animals, etc, is shown. The work area of the Police Hospital, the characteristics of doctors — the main followers and successors of the work of F. P. Haass, a combination of their medical and scientific activities, contribution to medical science are presented. The history of the creation of the first Pasteur station in Russia to provide emergency care for bites of rabid animals is reflected. The role and merits of S. V. Puchkov in preserving the humanistic traditions of Dr. F. P. Haass in the Aleksandrovskaya (Police) Hospital, his achievements in preserving and perpetuating the memory of F. P. Haass, the opening of the monument to F. P. Haass at Maly Kazenny Lane, a large public activity of S. V. Puchkov in Moscow are shown. The importance of family traditions in the upbringing of dedicated medical service, which were followed by S. V. Puchkov's eldest son, A. S. Puchkov, is presented. Graduate of the Moscow University, A. S. Puchkov ("doctor with honors") continued the work of F. P. Haass and his father, proved to be a brilliant organizer and became the creator of the modern emergency care in Moscow that F. P. Haass had dreamed about.

Key words: *doctor and humanist F. P. Haass, Police Hospital, Pasteur station, S. V. Puchkov, A. S. Puchkov, the history of the emergency care organization*

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Introduction

The name of doctor F. P. Haass (Friedrich Joseph Haass), a great humanitarian and a philanthropist, is widely known in Russia. The German doctor, who was very young when he came to Russia at Count Repnin's invitation as a family doctor, devoted all his knowledge and medical art to his new homeland. He mastered the Russian language to the level of proficiency, and his motto was 'Hurry up for the good deeds'. From the very beginning of his work in Russia, the young competent doctor, who had a vast and successful private practice, worked a lot for the common good, cared about the downtrodden and the poor, helped the elderly and the orphans in the poorhouses, almshouses and shelters. As early as 1807 (when he was 27 years old) his achievements were rewarded with an appointment to the position of the Chief Doctor at the Pavlovskaya Hospital by the order of the Empress Maria Fedorovna. He was involved in the War of 1812 as a military surgeon. He took part in the battles of Smolensk and Borodino, went to Paris, visited his motherland and returned to Moscow [1]. In 1825, the military governor-general of Moscow, Count D. V. Golitsyn, invited him to help stop the typhoid epidemic which was rife in the Prison Castle (of Butyrskaya prison). With his friend, professor A. I. Paul, Haass was actively involved in the fight against the epidemic — he set up a temporary hospital in the Pokrov army barracks, where sick prisoners were quarantined. Their work stopped further outbreak of the epidemic in the Prison Castle [2]. That same year, in 1825, Haass was appointed Chief Doctor of Moscow (State Physician). He brought order and cleaned up all of the hospital institutions, pharmacy warehouses, and made stealing impossible, which provoked conflicts with civil servants, and led to his subsequent resignation. Doctor Haass petitioned for the "introduction of a special doctor in Moscow, who would monitor and organize care of the suddenly sick in need of immediate help". He provided substantiated reasons, citing Hamburg as an example, where the majority of 1,794 people who needed help were saved. Moscow authorities reacted negative to this request, considering this measure "excessive" and "useless", as each police unit in Moscow had "a doctor authorized on establishment" [1].

In 1826, F. P. Haass was invited to help fight the epidemical eye illness (presumably trachoma) which had struck the cantonist department of the Pokrov army barracks, and he achieved great success in performing this task. Soon after, following the spread of infectious eye diseases in Moscow, Count D. V. Golitsyn asked Haass to join a special committee, under his chairmanship, for the establishment of an eye hospital in Moscow. The work of the committee, members of which also included his colleague's professor Paul and doctor Brosse, was successful, and in six months the hospital opened in a temporary and later in a permanent building. Haass was a member of its Council. He remained there right until his death, sharing his experience and knowledge, and collecting contributions for the hospital. The Moscow Eye Hospital is one of the oldest eye clinics in the world; it was headed by P. F. Brosse for more than 30 years [2].

F. P. Haass made an invaluable contribution to the protection of the rights of the most deprived people in Russia — prisoners and convicts. The big cities, most notably Moscow and Saint Petersburg, started creating prison stewardship committees. In 1828, at the instigation of the military governor-general of Moscow, Count D. V. Golitsyn, Haass was appointed Chief Prison Doctor of Moscow. The stewardship committees had to restore order in the complex prison establishments, make the life of the miserable prisoners and deportees easier, and to monitor their food provision and medical service. Doctor Haass relentlessly performed these activities until his death, and it was the main reason why the progressive community saw him as a humanitarian and a Christian, the main reason why common people called him holy Doctor Haass [1].

The establishment and work area of the Police Hospital as the first emergency hospital in Moscow

Despite his multiple public duties, Haass did not forget about his intentions to create a hospital for the suddenly sick. The numerous achievements of Dr. Haass include the establishment of the first Russian hospital for "emergency cases and free aid to people found unconscious in the streets and

homeless sick people" in 1844 with the support of the military governor-general of Moscow, Count D. V. Golitsyn. The establishment and reconstruction of the hospital in the building of the former Orthopedics Institute at Maly Kazenny Lane was funded by Dr. Haass and other contributors. Initially, it housed 150 sick prisoners from the Staro-Yekaterininskaya Hospital, and on May 2, 1945, the hospital started operating as the "hospital for the homeless" [2]. The police sent to the hospital sick people who were not accepted by other hospitals due to the lack of places or for other reasons. Later on, the number of patients increased to at least 240 people — they were taken from everywhere because "Haass did not reject anyone, by common belief"; patient care was more attentive and easier to access. It was widely known as the Haass Hospital, and it bears this name to this day. During Haass' time there were about 30,000 patients from the very bottom of the society: poor people run over by coaches, people with frostbite, starving people, homeless youth. Haass made personal rounds to all the patients. There was an outpatient department where first aid was provided. The hospital gave all the possible support to the deprived: it organized journeys back home for the poor peasants from the other cities, sent the elderly and feeble to poorhouses, found new families for the homeless youth [1, 2]. The Haass hospital had attending physicians and physician assistants. The physicians of the Police Hospital were Haass' allies in the constant fight against serious illnesses affecting Moscow residents: typhus fever, smallpox, relapsing fever, etc. There were also patients who required the assistance of psychiatrists.

After the death of F. P. Haass, the Police Hospital doctors maintained and observed the traditions established under the guidance of this great humanitarian. The professional and personal qualities of these worthy followers of Haass are reflected in the publications of N. N. Blokhina [3]. The direct successor for the position of the Police Hospital Chief Doctor was Khristofor Fedorovich Pal. One of the first Police Hospital doctors, psychiatrist V. F. Sobakinsky, continued his medical career here. Traditions of dedication to the professional duty and sense of charity helped the scientific development of the doctors of the Police Hospital,

Figure 1. *Monument to F. P. Haass in the court of the Police Hospital (sculptor N. A. Andreev, 1909)*

supported their efforts for the maximum utilization of medical science achievements. The Police Hospital was the place for active and relentless work of the physicians who developed science and wholeheartedly pursued a common target — to help the afflicted against all odds. Almost all the physicians who worked in the hospital had post-doctoral degrees in medicine.

Ivan Ivanovich Neyding (1839–1904) joined the Police Hospital as a physician in 1860 after graduating from the Faculty of Medicine of the Moscow University as "the first doctor with honors". In 1866, he received his post-doctoral degree in medicine for his thesis titled 'On Artery Atheroma', and he was appointed an assistant professor of the Forensic Medicine Department of Moscow University. Later he became an anatomist at the Anatomic Pathology Department. In 1878, he became an associate professor of forensic medicine and, in 1879, he became a professor of forensic medicine. Attending physician S. S. Kaminsky dedicated his academic paper 'On the Doctrine of the Gestation Course Affected by Typhus and Relapsing Fever' "to my fellow attending physicians of the Moscow Police Hospital". The Police Hospital doctors kept the spirit of mutual respect and trust, traditions of devotion and unselfishness. The gold standard of professional and ethical conduct was brilliantly demonstrated by Doctor N. P. Fiveysky. S. V. Puchkov wrote about him: "N. P. Fiveysky was a true unmercenary in the medical profession. He had

vast practice and lived a modest life of a single person, so he could have gained an immense fortune. However, it was not his cause. He left just some tangible property, which he had actually distributed two months before his death and an insignificant amount of money" [2, 3].

Sergey Vasilyevich Puchkov (1856–1926) graduated from the Faculty of Medicine of the Moscow University in 1881 and became an attending physician of the Police (from 1883 the Aleksandrovskaya) Hospital. He worked there for 36 years, up to 1918, as the Chief Doctor from 1906 [3]. The Police Hospital had always been a hospital with the most serious-case patients. Charters of many other city hospitals did not allow to receive the "feverish" patients — patients with fever (basically infectious cases), patients with serious psychiatric pathologies, and patients with rabid animal bites. It is no coincidence that Police Hospital physicians S. V. Puchkov and A. A. Gvozdev initiated rabies prevention. Pasteur station — the first one in Moscow — was created with donations collected also at the initiative of these doctors. It was officially opened on July 17, 1886 in the hospital at Maly Kazenny Lane. The first vaccination was performed on July 25 on five peasants (aged from 13 to 40) from Rzhev, Kaluga and Kasimov who had been delivered in a very bad condition. Thousands of people with animal bites came to the hospital hoping to be treated. Upon arrival they were immediately examined and vaccinated against rabies. It turned out that even 40–60 days after the bite the vaccine had a positive effect on many patients. Physicians and medical students eager to learn the new methods of rabies treatment could directly ask for help from the attending physicians. Therefore, Pasteur found in the Russian doctors strict advocates of his methods [4, 5].

S. V. Puchkov put much effort to preserve and perpetuate the memory of the great doctor and humanitarian F. P. Haass after a period of neglect. The widely-known biographical essay of A. F. Koni about F. P. Haass was largely based on the materials collected by Puchkov. In 1910, Sergey Vasilyevich added Koni's essay in his book 'On the Portrait of Dr. Haass' [2]. Sergey Vasilyevich also initiated collection of donations to erect a monument to the kind doctor which was opened in the hospital court in autumn of 1909. The sculptor, N. A. Andreev, declined to take a fee for this work. S. V. Puchkov, who was also a member of the Moscow City Duma, made a proposal to tidy up the grave of Haass at the Vvedenskoye cemetery. During all the pre-revolutionary years he tried to organize annual children holidays under the banner "At the Kind Grandpa Haass'" next to the monument engraved with the motto 'Hurry up for the good deeds'. This holiday tradition has now been revived by the Children and Teenagers Welfare and Hygiene Scientific Institute which is located in the former Police Hospital building. The Memorial Museum Room of Dr. F. P. Haass was also opened.

During his multi-year work in the City Committee for Public Health, S. V. Puchkov presented a report on the construction of new hospitals, namely the 3rd City Hospital in Sokolniki for infectious patients, the Alekseevskaya Hospital — Morozov main children's hospital (together with the Chief Doctor of the hospital N. N. Alekseev),

Figure 2. *Dynasty of Puchkov doctors. S. V. Puchkov with his son Alexander*

the Soldatenkovskaya Hospital (together with its first Chief Doctor F. A. Getye). During World War I, Puchkov was elected vice chairman of the Committee for the establishment of the Red Cross' main warehouse in Moscow. The 1st distribution hospital with 900 beds for the wounded warriors evacuated to Moscow was built at this warehouse. The principal task for Sergey Vasilyevich Puchkov during these years was to create the Bratskoye cemetery. This cemetery, which opened in February 1915, became the main subject matter of a small book that he wrote and published the same year. [5]. Years filled with everyday work in the hospital, in the City Duma, in various public organizations passed, and Alexander Sergeevich Puchkov (1887–1952), the son and the successor, grew up beside him [3].

Puchkov Junior, like his father, not only became a doctor but also continued the family tradition to hurry up for the good deeds. In 1906, he graduated from the 4th Moscow Secondary School, and in 1911 he graduated from the Faculty of Medicine of the Moscow University as a "doctor with honors".

He worked as an expert in the city hospitals. In 1914, he was called up for military service and was assigned to the Red Cross. During those years, as a young doctor, A. S. Puchkov proved himself as a brilliant organizer, as recalled by a member of the Academy of Sciences, N. N. Burdenko, who worked with him at the Red Cross. From 1918 to 1921, he served in the Red Army and was the head of the military hospital trains. Starting from 1921, he worked at the Moscow City Health Department. In 1922, he was the head of the central station for the transportation of patients. In 1923, he became the head of the first-aid station of the Sheremetyevskaya Hospital in Moscow. Alexander Sergeevich always held dear and espoused the ideals of his father. For instance, this can be illustrated by the surviving letter of Puchkov Jr. to A. F. Koni. "I told you," he wrote on May 8, 1923, "that your books had always been a kind of a moral lighthouse for me which elucidated many dark issues of the everyday life..." Further, he wrote: "I am occupied with the administrative issues (first aid) all day long, and there is absolutely no time to stay with my own company

Figure 3. *Alexander Sergeevich Puchkov, 1887–1952*

and this is so hard". In another letter that was sent three years later, on December 24, 1925, he informed Koni: "I am coming to Saint Petersburg in January to visit the first-aid station and I look forward to seeing you... I handle only the first-aid station now but, to my astonishment, I am not less but even busier than before..." A. S. Puchkov was directly involved in the organization of seven first-aid stations in Moscow, and in the organization and equipment of specialized automobile transport. During the Great Patriotic War, he personally supervised the work of the first-aid mobile medical teams in the affected districts of the city. In 1946, A. S. Puchkov defended his doctoral thesis titled 'Organization of the First-Aid Station in Moscow'. In 1947, Medgiz Publishing House published A. S. Puchkov's monograph titled "Organization of the Emergency Medical Care in Moscow" [6,7,8]. The multi-year fruitful work brought A. S. Puchkov two Orders of Lenin, one Order of the Red Banner of Labour. His awards included medals 'For the

Defense of Moscow' and 'For Valorous Labour in the Great Patriotic War'. On November 6, 1944, Puchkov was given the honorary title of Honored Doctor of the Russian Soviet Federative Socialist Republic [6, 7].

Conclusion

Doctor F. P. Haass, having become the Chief Doctor of Moscow in 1825, substantiated the need to organize 'immediate' medical aid to the suddenly sick, and implemented his intention in the Police Hospital at Maly Kazenny Lane. His work was continued by the staff of the Aleksandrovskaya (former Police) Hospital, including Doctor S. V. Puchkov. Having grown up inside the Aleksandrovskaya (former Police) Hospital and absorbed the ideas of devotion and assistance to people, A. S. Puchkov created this service almost anew [9, 10]. For 30 years (1922–1952) he was the head of the Moscow city first-aid station, and he created the service that F. P. Haass had dreamed about. Following the Government Decree of the City of Moscow No. 421 dated May 16, 1995, the Moscow City First-Aid Station was named after Alexander Sergeevich Puchkov.

Author Contribution:

V. R. Kuchma, N. F. Plavunov — concept and design of the research

E. I. Shubochkina, V. A. Kadyshev — material collection and processing, writing

V. R. Kuchma — editing

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HEMORRHAGIC FEVER WITH RENAL SYNDROME: THE CHALLENGE OF OUR TIME

Abstract

We analyzed more than 30 original articles and reviews to evaluate the current state of the issues of epidemiology, treatment, and prevention of hemorrhagic fever with renal syndrome in the world. A literature search was conducted using the Cochrane Library, PubMed, eLIBRARY databases and official WHO, UR Rospotrebnadzor, Rospotrebnadzor of the Russian Federation, and Center for Disease Control and Prevention data.

Hemorrhagic fever with renal syndrome (HFRS) is an acute infectious disease characterized by fever, hemodynamic disorders, hemorrhagic syndrome and kidney damage in the form of acute interstitial nephritis with the development of acute kidney injury. It is caused by RNA-containing viruses of the Hantaan genus, belongs to the group of zoonotic infections, and is transmitted through the air.

The Udmurt Republic is one of the regions of the Volga Federal District endemic for HFRS. Annually, from 300 to 2,000 people get sick in the territory of the republic. HFRS affects the most able-bodied part of the population, mainly men aged 20–50. Mortality reaches 20% in certain years of observation. The doctor's lack of caution regarding HFRS (the initial period of the disease has similar symptoms with acute respiratory diseases) leads to late hospitalization of the patient, often with serious complications that are fatal.

The main diagnostic search is carried out by the general practice service of the outpatient clinic. The materials of the article can help to correctly establish a preliminary diagnosis, taking into account clinical and epidemiological data, as well as to prescribe the necessary amount of laboratory and instrumental tests to clarify the diagnosis.

Key words: *hemorrhagic fever with renal syndrome, current clinical course, gene polymorphism, pathogenesis, etiotropic treatment for HFRS, vaccination*

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HFRS — hemorrhagic fever with renal syndrome, UR — Udmurt Republic

Hemorrhagic fever with renal syndrome (HFRS) is an acute viral, natural focal disease characterized by systemic lesion of small vessels, hemorrhagic syndrome, hemodynamic disorders and kidney damage in the form of acute interstitial nephritis with the development of acute renal injury.

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Background

For the first time, V. A. Targanskaya described the clinical signs of HFRS in humans in the scientific literature in 1935, during outbreaks in the Far East. World interest in this disease arose only during the war in Korea (1951–1954), when about 2.5 thousand troops from the UN expeditionary force stationed in the demilitarized zone of the Korean Peninsula fell ill. In 1976, H. W. Lee, P. W. Lee and K. Johnson isolated, using indirect immunofluorescence analysis, specific HFRS virus antigen in lung tissue samples from field mice (Apodemus agrarius coreae) [23] captured in an endemic zone near the Hantaan River in South Korea.

Etiology

In various countries, a number of causative agents belonging to the genus Hantavirus, which are pathogenic for humans, have been isolated and registered: Puumala, Dobrava-Belgrade, Seoul and Amur viruses [9].

The virus belongs to the Bunyaviridae family and to the independent genus Hantaan. More than 25 serologically and genetically distinct hantaviruses are known.

Epidemiology

The incidence of hantavirus infection ranges from 150,000 to 200,000 cases per year worldwide. The highest incidence rates are recorded in China — up to 50 thousand cases, in Russia — about 6 thousand cases per year, and in Korea — 1–2 thousand cases per year [1]. Isolated cases have been reported in Germany, Great Britain, France, Belgium, Pakistan, and Iran [2, 11]. Natural foci of infection in Eurasia are constantly expanding; cases of HFRS in the Balkans, Malaysia, and Japan have been confirmed [15]. In the European part of Russia, 98% of cases of HFRS are recorded, in the Far East — 2% of cases. Natural foci of HFRS in Russia are the Middle Urals, Cis-Urals, Ulyanovsk, Samara, Orenburg regions, and Khabarovsk Territory [3].

In the Volga Federal District, 85.5% of all cases of HFRS in the Russian Federation are registered. The Udmurt Republic (UR) is in the first place among the subjects of the Russian Federation in the incidence of HFRS and is one of the largest natural foci. HFRS affects the most able-bodied part of the population, mainly men aged 20–50. The peak incidence is in the age group of 20–29 years. Mortality reaches 20%.

The natural susceptibility to infection is high, depending on the nature of employment and the extent of contact with the natural focus. An analysis of the causes and conditions of infecting within UR indicates that in 42% of cases, infection occurred in everyday life, in 32% of cases when working in a garden, and in 16% of cases when visiting a forest. The proportion of industrial infection was 5.1%. Employments of the risk group are: chauffeurs, geologists, oil workers, builders, road workers, and machine operators.

One of the promising areas is the molecular genetic analysis of gene polymorphism in patients with HFRS [17]. Molecular genetic methods make it possible to study the heterogeneity of hantavirus populations in nature, characterize the epidemic significance of strains, and determine the quantitative load of the virus.

Hantavirus infection is a natural focal zoonosis, and the mouse-like rodents are the reservoir and source of infection for humans. A portal of entry is the mucous membrane of the respiratory tract, less often the skin and the mucous membrane of the digestive system. Infection is transmitted predominantly through air (90% of cases) (with aspiration of the virus from dried rodent feces), rarely by contact (through damaged skin and mucous membranes), and by the alimentary route (ingestion of contaminated products). Human-to-human transmission of the virus is not possible.

An increase in the incidence is observed from May to December (the infection has summer-autumn seasonal prevalence), which is associated with an increase in the number of rodents by the end of summer. The peak falls on August.

According to the State report "On the State of the Sanitary-Epidemiological Well-Being of the Population of the Moscow Region in 2018" for the last 5 years (2014–2018), 106 people fell ill with HFRS (in 2018 — 11 people).

Pathogenesis and Clinic

The first researchers of HFRS, A. I. Churilov (1941), A. I. Kazbintsev (1944), A. A. Smorodintsev (1944), and V. G. Chudakov (1957), were also the first to suggest vasotropic properties of the HFRS virus.

To date, there is no doubt the pathogenesis of clinical forms of hantavirus infection is immune-mediated [1, 3, 4]. A key role passes to the immune response of a macroorganism: an increase in the level of vasomodulators, antiplatelet agents, impaired adhesive activity of the endothelium, a

change in anticoagulation potential, structural damage to the endothelium with low activity of repair processes, the development of a "cytokine storm", an increase in vascular permeability, the development of plasmorrhea (massive capillary leak), hemoconcentration and tissue hyperhydration, followed by the development of disseminated intravascular coagulation syndrome and multiple organ failure [10].

There is also a genetically determined predisposition to severe HFRS associated with gene polymorphism. One of the most accessible approaches used in molecular genetic studies of multifactorial diseases, including infectious etiology, is to study the associations of the disease with polymorphic gene loci, the protein products of which are involved in the pathogenesis of the disease. Most studies in this direction are devoted to single nucleotide polymorphism as the most common form of individual genetic variability [12].

The generalized nature of the infection involving various organs and systems in the pathological process determines the polymorphism of symptoms regardless of the causative agent (hantavirus serotype).

In the clinical pattern of the disease, 6 mains clinical pathogenetic syndromes are distinguished:

1) General symptoms of infection.
2) Hemodynamic disorders (central and microcirculatory), hypovolemia and hemodynamic stress.
3) Acute kidney injury.
4) Disseminated intravascular coagulation.
5) Abdominal (dyspeptic) syndrome.
6) Respiratory syndrome.

Standard course consists of several periods: incubation (from 7 to 45 days); febrile (from 3 to 10 days); oliguric (4–12 days); diuretic, and convalescence (from 3 weeks to 3–12 months):

1) Incubation (from 7 to 45 days).
2) Febrile phase (from 3 to 10 days). Most patients fell ill acutely. Chills, headache, pain in muscles and joints, dry mouth, thirst, sometimes slight cough, and pronounced fatigue appear. In a small proportion of patients, the appearance of pronounced signs of the disease is preceded by a prodromal phase: general malaise, fatigue, and loss of appetite. In most patients, fever reaches high numbers (up to 38–40 °C) on the first day of the disease. The duration and height of the fever are related to the severity of the disease. During the oliguric phase, the temperature decreases; sometimes it can persist at subfebrile numbers.

An intense headache combined with fever and vomiting requires differential diagnosis with meningitis.

An objective examination reveals severe hyperemia of the skin of the face, neck, upper body, associated with autonomic disorders at the level of the centers of the cervical and thoracic spinal cord. Most noticeable signs are scleral and conjunctival injection, hyperemia of the mucous membrane of the oropharynx, and the appearance of the spotted enanthema of the upper palate. Perhaps the development of hemorrhagic syndrome in the form of petechial rash on the inner surfaces of both shoulders, lateral surfaces of the trunk and on the chest (whiplash symptom), ecchymosis at the injection site, and short nosebleeds. Symptoms of endothelial damage (cuff, pinch and tourniquet signs) are determined.

Blood pressure is normal or with a tendency to hypotension, relative bradycardia is characteristic [18].

Some patients note a feeling of heaviness in the lower back. At the end of the initial phase, there is a decrease in urine output and urinary frequency.

During this phase, an increase in serum creatinine, urea, a decrease in urine specific gravity and the appearance of single fresh red blood cells and proteinuria are observed. In most patients, complete blood count is characterized by moderate leukopenia and, less commonly, mild leukocytosis and stab shift to the left, signs of hemoconcentration (RBC and hemoglobin increase) associated with plasmorrhea and hypovolemia. The pathognomonic symptom of HFRS in the early phase is thrombocytopenia, due to the damaging effect of the virus, the development of immunopathological reactions, an increase in the adhesive properties of platelets, the formation of cell aggregates with microcirculation delay in the vessels, and a violation of the rheological properties of the blood.

3) Oliguric phase (from 4 to 12 days). Body temperature drops to normal, sometimes rising again to subfebrile: the "double-humped" curve. General symptoms reach a maximum, signs of hemodynamic disorder, kidney injury, and hemorrhagic rash intensify. The most constant sign of a transition to the oliguric phase is the appearance of

lower back pain of varying intensity: from unpleasant sensations of heaviness to sharp and painful, nausea, vomiting, not associated with the ingestion of food or medicine. Many patients have abdominal epigastric or mesogastric pain. The disease can be accompanied by both the appearance of loose stool and constipation in case of intestinal paresis. In HFRS, the blood content of toxins of intestinal origin also increases (indican, ammonia, phenol, paracresol, etc.).

The entry of intestinal toxins into the systemic circulation increases with functional bowel obstruction, which develops due to wall edema and electrolyte imbalance. Intestinal paresis is accompanied by an increase in intra-abdominal pressure, which disrupts the blood circulation in the abdominal and retroperitoneal organs (kidney) and lungs.

In the oliguric phase, the liver is enlarged and painful on palpation. Nausea, vomiting and abdominal pain predict a severe course of renal failure. Frequent vomiting, hiccup, abdominal pain, phenomena of mild signs of peritoneal irritation that are not associated with the infection, absence of stool, bloating and dry, coated tongue give the impression of an acute surgical pathology.

Asthenia and adynamia increase. The face is hyperemic; with increasing renal failure, blush gives way to pallor and, mainly in severe cases of the disease, hemorrhagic signs intensify: subconjunctival hemorrhage, ecchymosis, nosebleeds and macrohematuria, hematomas at the injection sites, less often intestinal bleeding, hematemesis, and hemoptysis. Diagnosis is characterized by visual impairment (decreased visual acuity, "flying flies", cloudy vision) associated with retinal microcirculation disorder [18, 29].

At the beginning of the oliguric phase, blood pressure is within normal limits, and in severe cases hypotension develops [34].

A detailed pattern of acute kidney injury is characterized by progressive oligoanuria and uremic intoxication, water-electrolyte imbalance, and increasing metabolic acidosis.

Blood picture reveals thrombocytopenia. An increase in the level of residual nitrogen, urea, creatinine, as well as hyperkalemia, hypermagnesemia, hyponatremia, and signs of metabolic acidosis are characteristic. In the urinalysis, massive proteinuria (up to 33–66 g/l) is noted, the intensity of which changes during the day ("protein shot"), hematuria, urinary casts, epithelial cells (the so-called Dunaevsky cells). From the second half of the oliguric phase, low urine specific gravity develops.

Significant changes occur in the state of the coagulation system. Usually, hypercoagulation persists, but in severe cases, hypocoagulation develops. It is associated with the consumption of plasma coagulation factors due to the formation of microthrombi in small vessels.

4) Diuretic phase (from 13 to 21 days). Vomiting ceases, pain in the lower back and abdomen gradually disappear, sleep and appetite normalize, the daily urine output increases (up to 3–10 l), nocturia is characteristic. The duration of polyuria and isohypostenuria depending on the severity of the clinical course can range from several days to several weeks. However, the improvement development does not always run parallel to the increase in urine output. Sometimes in the early days of diuretic phase, azotemia still increases, dehydration, hyponatremia and hypokalemia may develop, hypocoagulation persists; therefore, this phase is often called the "uncertain prognosis" stage [18, 29].

Laboratory shifts consist in a certain decrease in red blood cells, hemoglobin, and an increase in platelets. Serum urea and creatinine levels gradually decrease, hypokalemia often develops. Changes in urine (Zimnitsky test) are characterized by an extremely low specific gravity, not exceeding 1,001–1,005. A small amount of protein, moderate hematuria and urine casts, sometimes leukocyturia, a small amount of epithelium cells are determined in urine sediment.

5) Convalescent phase (from 3 weeks to 3–12 months). General condition improves significantly, daily urine output restores, urea and creatinine levels normalize. In convalescents, asthenic syndrome is detected: general weakness, fatigue, decreased efficiency, and emotional lability. There is also a vegetovascular syndrome in the form of hypotension, muffled heart sounds, shortness of breath at little physical exertion, tremor of the fingers, increased sweating, and insomnia. During this phase, there may be heaviness in the lower back, sign of concussion and nocturia, isohypostenuria persists for a long time (up to 1 year or more). Secondary bacterial infection may be associated with the development of pyelonephritis, which is most often observed in patients with acute kidney injury [18].

Despite the obvious similarity of the leading symptom complex, HFRS clinical and course features associated with different hantavirus serotypes were noted. HFRS caused by the Puumala virus is characterized by a clear alternation of clinical phases and typical symptoms with recovery in most cases. At the same time, a high frequency of respiratory syndrome in the initial period of infection with subsequent progression of acute kidney injury was noted. Often there is a liver lesion manifested by hepatomegaly, jaundice and cytolysis [4, 7, 11].

HFRS caused by the Hantaan virus has been described in detail by Korean, Chinese, and Russian clinicians; it has not changed much at present [10, 13]. It is characterized by a typical cyclic course, the severity of acute kidney injury and hemorrhagic syndrome. In the Far East of Russia, severe forms of Hantaan infection account for up to 30–40% of observations in the Khabarovsk, Primorsky Territories, and the Amur Region, which makes this pathogen more virulent than Puumala virus [13].

Severe forms of HFRS associated with different hantaviruses demonstrate the entire symptom complex of multiple organ failure in the form of various combinations of hemodynamic disorders and dysfunction of the kidneys, liver, heart, lungs, and nervous system.

Typical complications of HFRS, such as pulmonary edema, rupture of a kidney capsule, intestinal and uterine bleeding, disseminated intravascular coagulation and acute kidney injury, are the causes of death.

Complications

Acute kidney injury (AKI) is a severe clinical syndrome of the acute phase of HFRS [4]. In patients with HFRS, isolated cases of chronic kidney disease (CKD) have been described, including those requiring renal replacement therapy [7, 22, 34]. However, authors from the Far East region, where the most severe cases of HFRS are observed within Russia, did not describe outcomes in chronic kidney disease [20].

The development of DIC accompanies all cases of TSS in HFRS.

As a complication of HFRS (with indicating in the diagnosis), DIC is considered for life-threatening thromboembolic (rarely: pulmonary embolism, ischemic stroke, etc.) or hemorrhagic (gastrointestinal bleeding, hemorrhagic stroke, hemothorax, etc.) manifestations [34].

Clinical signs of lung damage in hemorrhagic fever with renal syndrome (HFRS), according to several authors, are recorded in 6–18% of patients and are observed mainly in severe cases of the disease [24]. Pulmonary edema with progressive respiratory failure is one of the causes of fatal outcomes in HFRS and is a constant finding in pathological examination. At the same time, data on the features of the pulmonary pathology development in this disease remain scarce and are given only in reports regarding the clinical description of respiratory disorders in seriously ill patients.

A number of authors [21] noted a significant prevalence of lung tissue lesions in HFRS and demonstrated the pathogenetic heterogeneity of these lesions. On the one hand, there is a pulmonary pathology of the initial period in the form of respiratory distress syndrome, which is based on an increase in the permeability of the endothelium of the pulmonary vessels under the influence of the vasotropic activity of the causative agent, and on the other hand, there is nephrogenic pulmonary edema, which occurs at the peak of acute kidney injury and is a complication of HFRS.

According to published data, pulmonary damage in patients with HFRS is observed with all serotypes, however, with a different frequency. Moreover, the fact that there is no single term for the designation of pulmonary pathology in HFRS by various researchers draws attention. Pathogenetically, single clinical and radiological changes are interpreted as "respiratory syndrome" [6], "pulmonary-renal syndrome" [10], and "hantavirus pulmonary syndrome on Puumala infection" [9].

Laboratory diagnosis of the disease consists of determining antibodies to hantavirus, indicating a specific antigen and hantavirus RNA.

Disease Outcomes

Among the outcomes of acute kidney injury, the most frequent is recovery. According to the UR Rospotrebnadzor data, fatal outcome is observed in 1–3% of cases [3].

Outpatient Follow-Up

After discharge from the hospital, patients need follow-up for timely identification and treatment of the consequences of the disease. Patients are discharged after clinical and laboratory recovery, but not earlier than 14 days from the onset of the disease. Patients are discharged with open sick leave, which is extended for a period of 10 days. The duration of the release from work is determined by the severity of the disease.

Outpatient follow-up lasts from 1 to 3 months. Subsequently, check-ups should be carried out once every three months during the first year and 2 times during the second year after discharge. The first check-up is carried out in 1 month after discharge with urine, urea, creatinine and blood pressure examination, then — in 3, 6, 9, and 12 months. Subsequently, the follow-up includes: nephrologist consultation, blood pressure monitoring, fundus examination, urinalysis, and Zimnitsky test.

In the absence of complaints and internal organ changes, after this period, patients with a history of HFRS are deregistered. During the convalescent phase, the patient is advised to avoid heavy manual labor, shaking during transferring, hypothermia and overheating, visiting sauna, playing sports for 3–6–12 months, depending on the severity of the disease.

Treatment

HFRS treatment includes detoxification, antioxidant therapy, azotemia and protein catabolism management, correction of water-electrolyte imbalance and acid-base state, management of DIC, prevention and treatment of complications (cerebral edema, pulmonary edema, uremia, hemorrhage in pituitary gland and other organs, bacterial complications). The question of pathogenetic treatment and the use of drugs is debatable: ribavirin, icatibant, favipiravir, anti-hantavirus monoclonal antibodies. A number of authors noted the insufficient effectiveness of ribavirin intravenous administration in HFRS [38.59]. Drugs are being developed based on avb3 (heterodimer of transmembrane cell receptors interacting with the extracellular matrix and transmitting extracellular signals), VEGFR2 (Vascular Endothelial Growth Factor Receptor 2) and SFK (Src family kinases) inhibitors.

Prevention

A promising issue is the prevention of the disease. In anti-epizootic work, nonspecific and specific prevention is distinguished.

Nonspecific prevention includes the destruction of rodents in foci, the use of respirators when working with dusty rooms, the storage of products in warehouses protected from rodents and other constantly acting and universally implemented measures of veterinary-sanitary and organizational economics nature aimed at the prevention of infectious diseases.

Measures for the prevention of infectious diseases in the territory of the Russian Federation are regulated by the sanitary and epidemiological rules (SP 3.1.7.2614-10) of 2010: "Prevention of Hemorrhagic Fever with Renal Syndrome". The nature of specific preventive measures is determined by the characteristics of the infectious disease, the epizootic situation of the economy and the surrounding territory (region).

The most effective and reliable method of preventing HFRS is vaccination in contaminant areas. Hantavirus vaccines are currently being used in South Korea, China and Japan. Vaccines are prepared on the basis of the hantavirus serotype Hantaan, common in the Far East. RAMS Institute of Poliomyelitis and Viral Encephalitis named after M. P. Chumakov developed the first vaccine against hemorrhagic fever with renal syndrome (HFRS), "CombiHFPS-Wak", which is a bivalent, whole-virion, inactivated, concentrated, adsorbed vaccine. "CombiHFPS-Wak" contains antigens of two serotypes of the hantaviruses Puumala and Dobrava. There are currently no vaccines approved in Russia. Thus, HFRS is currently characterized by a high incidence rate with the formation of moderate and severe forms and frequent development of complications.

The effectiveness of vaccination has been confirmed over the past 20 years in China, South and North Korea. However, HFRS vaccines produced in these countries based on the Hantaan and Seoul viruses do not have a protective effect against the Puumala virus. The introduction of a cultural, bivalent, inactivated, adsorbed HFRS vaccine "CombiHFRS-Wak", which has passed preclinical tests for compliance with the requirements for immunobiological medicinal products for human use, would reduce the incidence of HFRS.

Conclusion

Hemorrhagic fever with renal syndrome is a widespread zoonotic infection, the relevance of which is determined by the increase in the incidence rate in the world with the expansion of the natural foci, a frequent severe course of the disease, and a high mortality rate among the able-bodied population. Timely diagnostic and treatment of the population is of great importance in the prevention of severe course, complications and adverse outcomes of HFRS. The main diagnostic search is carried out by the therapeutic service of the outpatient clinic.

To ensure a favorable outcome of the disease, it is necessary to correctly establish a preliminary diagnosis, taking into account clinical and epidemiological data, and also to prescribe the necessary amount of laboratory and instrumental tests to clarify the diagnosis. Conducting anti-epidemic measures, the introduction of a cultural, bivalent, inactivated, adsorbed vaccine against HFRS can help reduce the incidence.

Contribution of Authors

Bagautdinova L.I. — concept and design development
Borodina J.I. — interpretation and critical analysis of the results, formulation of conclusions
Monakhov K.M. — collection and analysis of primary clinical data
Tsarenko O.E. — manuscript writing

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PRO-INFLAMMATORY CYTOKINES IN PATIENTS WITH CHRONIC KIDNEY DISEASE: INTERLEUKIN-6 IN FOCUS

Abstract

Objective of the study. To assess the clinical and pathogenetic significance of serum interleukin-6 (IL-6) in patients with chronic kidney disease. **Materials and methods.** A cross-sectional study enrolled 288 patients with chronic kidney disease (CKD) aged 16 to 86 years, average age (54.5 ± 14.5) years. The study enrolled 146 (50.7%) women and 142 (49.3%) men. Depending on the value of estimated glomerular filtration rate (eGFR), all the examined patients were divided into two groups: 1st (n = 154) — persons with eGFR > 60 ml/min; 2nd (n = 134) — patients with eGFR < 60 ml/min, i.e. renal failure. CKD was identified when there was evidence of damaged and/or reduced renal function. Glomerular filtration rate was calculated using the Hoek equation based on measurement of serum cystatin C, and severity of CKD was based on eGFR values. All patients had concentration of creatinine, cystatin C and IL-6 in their blood serum studied. **Results.** In the 2nd group of patients with eGFR below 60 ml/min, average age [(57.9 ± 14.5) years vs. (51.6 ± 13.9) years; p < 0.05], systolic blood pressure [(142 ± 24) mm Hg vs. (133 ± 22) mm Hg; p < 0.05], cystatin C [1.815 (1.430–3.070) mg/l vs. 0.980 (0.900–1.100) mg/l; p < 0.05)] and IL-6 [2.761 (1.400–6.495) pg/ml vs. 1.754 (0.849–3.226) pg/ml; p < 0.05)] levels in blood serum were significantly higher compared with the 1st group. An inverse correlation was found between serum IL-6 and eGFR level (r = –0.144; p = 0.018). **Conclusion.** In patients with chronic kidney disease with an eGFR level below 60 ml/min, an increase in systolic blood pressure and serum IL-6 concentration was observed. In chronic kidney disease, an increase in the content of IL-6 was accompanied by a decrease in glomerular filtration rate and an increase in diastolic blood pressure.

Key words: *chronic kidney disease, glomerular filtration rate, interleukin-6, inflammation, progression, cardiovascular complications*

Conflict of interests

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IL — interleukin, BMI — body mass index, rGFR — estimated glomerular filtration rate, diabetes mellitus — diabetes mellitus, GFR — glomerular filtration rate, TNF-α — tumor necrosis factor-alpha, CKD — chronic kidney disease, CGN — chronic glomerulonephritis,

Introduction

The problem of early diagnosis, prevention and treatment of chronic kidney disease (CKD) in the clinical course of adult diseases remains relevant for modern-day medicine. Timely assessment of the severity of CKD and associated cardiovascular and cerebral complications is of great practical importance for primary and secondary prevention [1]. All researchers recognize the multifactorial nature of the origin and progression of CKD [2, 3]. The widespread prevalence of diseases accompanied by CKD and cardiovascular events necessitates further study of this problem [4]. A number of studies established that in the occurrence and progression of CKD, a change in the interleukin (IL)-6 level in serum [5, 6] and kidney tissue [7, 8] is of importance. IL-6 is absent in a healthy kidney, and its plasma level ranges from 1 to 2 pg/ml [8]. According to some researchers, IL-6 is produced by activated monocytes/macrophages, fibroblasts, endothelial cells, as well as mesangial and epithelial cells of the renal tubules [9, 10]. According to current data, IL-6 is one of the most important mediators of the acute inflammation phase [11–13]. In acute inflammatory diseases, IL-6 secretion is maximally stimulated, and its plasma level can reach values of 1,000 pg/ml. In muscles and adipose tissue, IL-6 stimulates the mobilization of energy, which leads to an increase in body temperature, and in the liver, it is the main stimulator of the synthesis of acute phase proteins. In addition, this cytokine stimulates the proliferation and differentiation of B- and T-cells, as well as leukocytopoiesis. On the cell surface, IL-6 binds to a heterodimeric receptor complex, which is referred to as the type I cytokine receptor and consists of two transmembrane proteins: IL-6 receptor and gp130 (CD130). This receptor binds several other interleukins, which belong to the IL-6 superfamily based on this feature. The role of pro-inflammatory cytokines in the development of cardiovascular complications is being actively studied. However, the relationship between serum IL-6 and CKD markers remains poorly understood.

Study objective

To evaluate the clinical and pathogenetic significance of serum IL-6 in patients with chronic kidney disease.

Materials and methods

We examined 288 patients with chronic kidney disease (CKD) aged 16 to 86 years, the average age was (54.5 ± 14.5) years. The study involved 146 (50.7%) women, average age (54.5 ± 14.6) years, and 142 (49.3%) men, average age (54.6 ± 14.4) years ($p > 0.05$). Depending on the estimated glomerular filtration rate (eGFR), patients were divided into two groups: the 1st (n = 154) — individuals with eGFR > 60 ml/min (88 women / 66 men) and the 2nd (n = 134) — patients with eGFR < 60 ml/min, i.e. with kidney disease (58 women / 76 men).

According to the international guidelines, CKD was diagnosed according to signs of damage and/or decreased renal function [14]. To assess the severity of CKD, eGFR was used; its value was calculated using the Hoek equation proposed in 2003: GFR = 80.35 / Cystatin C — 4.32 [15]. The inclusion criterion was the presence of CKD signs. The study did not enroll patients on corticosteroid and immunosuppressive therapy, with thyroid disease, fever and CKD stage 5D. In all patients, height (cm) and body weight (kg) were measured, body mass index (BMI) was determined by the Kettle method: BMI, kg/m^2 = weight, kg / height, m^2. Systolic and diastolic blood pressure (SBP and DBP, mm Hg), heart rate (HR, beats/min) were measured by

conventional methods. Serum concentrations of cystatin C (mg/l) and creatinine (μmol/l) were analyzed in all patients. The serum IL-6 level (pg/ml) was determined using the Vector-Best JSC (Novosibirsk, Russia) reagent kit via enzyme-linked immunosorbent assay. Study results were registered on the ChroMate Microplate Reader (USA, 2015). According to the kit manufacturer's instructions, a concentration of 10 pg/ml was taken as the upper limit of the standard.

Statistical analysis was carried out using the Statistica 10.0 software package (Statsoft, USA), which enables to perform parametric and nonparametric analysis. The results are presented as arithmetic mean (M) and standard deviation (SD) for characters with a normal distribution, and interquartile range (25th quartile; 75th quartile) in case of a nonparametric distribution of the characteristic. Intergroup comparisons were carried out using the nonparametric Mann — Whitney test, and in the presence of signs with a normal distribution, the Student t-test. The linear relationship between the variables was measured using the Pearson correlation test. The null hypothesis of the absence of differences and relationships was rejected at $p < 0.05$.

Results

In the patients examined, the cause of CKD was: overweight and obesity — 206 (71.5%), symptomatic hypertension — 48 (16.65%), essential hypertension — 88 (30.5%), type 2 diabetes mellitus (DM 2) — 62 (21.5%), chronic obstructive pulmonary disease — 38 (13.1%), chronic pyelonephritis — 23 (7.9%), chronic glomerulonephritis (CGN) — 42 (14.5%), stable forms of coronary heart disease — 66 (22.9%) and gout — 2 (0.6%).

The number of patients with primary kidney disease in the analyzed subgroups did not significantly differ. The proportion of patients with chronic pyelonephritis was 13 (56.5%) in the 1st and 10 (43.5%) in the 2nd group. CGN was present in 18 (42.8%) patients in the 1st and 24 (57.2%) in the 2nd group ($p > 0.05$). More than half of the examined patients [154 (53.4%)] had CKD stage 1 and 2. At the same time, the proportion of patients with severe nitrogen excretory dysfunction was insignificant (Table 1) and amounted to 46 (15.9%). There were significantly more patients with CKD stage 3A than with stage 3B, 20.5% and 10.1% respectively ($p < 0.05$); 7.2% of the examined patients had end-stage renal disease (Table 1).

The average age of the examined patients in the 2nd group was significantly higher ($p < 0.05$). The gender composition of the examined groups was not similar (in the 1st group, the proportion of females was higher compared to the 2nd group). BMI, diastolic blood pressure and heart rate in the study groups were equivalent (Table 2). SBP was significantly higher in patients of the 2nd group compared with the 1st group ((142 ± 24) mm Hg versus (133 ± 22) mm Hg; $p < 0.05$). According to the distribution criteria, in patients of the 2nd group, serum cystatin C and creatinine were significantly higher ($p < 0.05$), and eGFR was significantly lower ($p < 0.05$). The median and interquartile serum IL-6 values were significantly higher in patients with eGFR < 60 ml/min, i.e. in the 2nd group [2.761 (1.400–6.495) pg/ml versus 1.754 (0.849–3.226) pg/ml; $p < 0.05$] than in the 1st group.

The conducted correlation analysis revealed the presence of a reliable negative relationship between serum IL-6 and eGFR value ($r = -0.144$; $p = 0.018$).

Table 1. *The population of examined patients with CKD*

Stages of chronic kidney disease, NKF KDOQI, 2002	n (%)
Stage 1, kidney damage with normal or elevated GFR	46 (16.0%)
Stage 2, kidney damage with a mild GFR decrease	108 (37.5%)
Stage 3A, moderate GFR decrease	59 (20.5%)
Stage 3B, significant GFR decrease	29 (10.1%)
Stage 4, severe GFR decrease	25 (8.7%)
Stage 5, end-stage renal disease	21 (7.2%)

Notes. CKD — chronic kidney disease; NKF KDOQI — National Kidney Foundation Kidney Disease Outcomes Quality Initiative; GFR — glomerular filtration rate; n — the number of patients

Table 2. *Clinical and laboratory parameters of examined subgroups*

Parameters	1st group (n = 154)	2nd group (n = 134)
Age in years	(51.6 ± 13.9)	(57.9 ± 14.5) *
Gender, female — male	60.3% — 46.5%	39.7% — 53.5%
Systolic blood pressure, mm Hg	(133 ± 22)	(142 ± 24)*
Diastolic blood pressure, mm Hg	(86 ± 14)	(87 ± 15)
Heart rate, beat/min	(79 ± 14)	(80 ± 15)
Body mass index, kg/m^2	(28.3 ± 5.2)	(31.0 ± 3.6)
Interleukin-6, pg/ml	1.754 (0.849–3.226)	2.761 (1.400–6.495) *
Plasma creatinine, μmol/l	69.3 (57.6–83.0)	115.9 (88.4–307.0) *
Serum Cystatin C, mg/l	0.980 (0.900–1.100)	1.815 (1.430–3.070) *
Estimated GFR, ml/min	77.6 (68.7–84.9)	39.9 (21.8–51.8) *

Notes. BP — blood pressure; GFR — glomerular filtration rate; n — the number of patients; * p < 0.05

Table 3. *Correlation between IL-6 value and clinical and laboratory parameters*

Parameters	Interleukin-6, pg/ml	
	R =	P =
Systolic blood pressure, mm Hg	0.063	0.303
Diastolic blood pressure, mm Hg	0.119	0.050
Body mass index, kg/m^2	0.011	0.850
Plasma creatinine, μmol/l	0.023	0.710
Serum Cystatin C, mg/l	0.038	0.533
Estimated GFR, ml/min	0.144	0.018

Notes. IL — interleukin; GFR — glomerular filtration rate; R — correlation; P — reliability

In addition, there was a tendency for a close relationship between serum IL-6 and diastolic blood pressure (r = 0.119; p = 0.050).

Discussion

The practical significance of identifying groups of patients with CKD and pro-inflammatory cytokinemia is the need to assess not only cardiovascular, but also renal complications [12, 13]. The damaging effects of pro-inflammatory cytokines on the kidney were first described by R. J. Shalhoub et al. in 1974 [16]. After 20 years, C. Luttricken et al. (1994) described the molecular mechanism of IL-6 action [17]. It was shown that with a change in the structure of the glomeruli, interstitium, and perivascular zone, cytokine receptors can be expressed, thereby triggering inflammation and further progression of pathological changes [18]. In particular, the expression of IL-6 receptors on mesangial cells indicates the activation of the immune process in the tissue, i.e. that mesangial cells began to ingest IL-6, while losing their ability to ingest immune complexes [7]. The role of IL-6 in proliferative and inflammatory processes in the kidney tissue is well demonstrated in the work of I. A. Rakityanskaya et al. (1998) [7]. Numerous cross-sectional studies have also shown that IL-6 secretion moderately increases in chronic mild inflammatory process, which is typical of CKD [11–13]. This fact is clearly reflected in our study, where (Table 2) in patients with renal failure, a statistically significant IL-6 increase was noted. We also managed to demonstrate, although not a strong, but reliable relationship between eGFR value and serum IL-6 (Table 3). Earlier, we showed a close relationship between another pro-inflammatory cytokine (TNF-α, tumor necrosis factor-alpha) and eGFR [19].

IL-6 is a glycoprotein consisting of 184 amino acids, which acts through the formation of a receptor complex on cell membranes. The receptor

complex consists of two parts: specific IL-6 receptor and non-specific CD130 transmembrane receptor [20, 21]. The latter is responsible for conducting the signal into the cell and consists of two identical subunits that form the bed for the IL-6 receptor. There are two types of specific IL-6 receptor: bound to the cell membrane (IL-6R) and soluble, freely circulating in the blood (IL-6Rs). Both receptors are activated when IL-6 is attached. It is believed that the sensitivity of these two types of receptors is quite high (0.5–2.0 nM) and almost the same [22, 23]. It was established that IL-6 increase is observed in obesity and type 2 diabetes mellitus [24]. Considering this, the proportion of patients that were overweight and had type 2 diabetes mellitus in our study was quite large. Previously, an IL-6 increase was shown to be associated with proliferation of vascular smooth muscle cells and increased production of platelet-derived growth factor [25, 26]. This probably explains the participation of pro-inflammatory cytokines in the occurrence of cardiovascular complications in CKD. We were not able to identify a correlation between IL-6 level and SBP (Table 3), although in the 2nd group, the values of the pro-inflammatory cytokine and SBP were significantly higher (Table 2). At the same time, there was a tendency for a close relationship between IL-6 level and DBP (Table 3).

The resulting interference between serum IL-6 and hemodynamic parameters is partly explained by the concept according to which IL-6 induces vasoconstriction and increases the activity of the sympathetic nervous system. In our previous work, we found that an increase in the concentration of proinflammatory cytokines (TNF-α) is associated with an increase in vascular stiffness [19]. Thus, we would like to note that the pathogenetic mechanisms of CKD progression involving proinflammatory cytokines, in particular IL-6, are extremely complex, diverse, and require further study.

Conclusions

1. In patients with CKD with an eGFR level below 60 ml/min, IL-6 increase is recorded.
2. In CKD, serum IL-6 level is closely related to the glomerular filtration rate and diastolic blood pressure.

Contribution of Authors

I. T. Murkamilov — writing of the text
Zh. A. Murkamilova, N. A. Redzhapova, Z. R. Rayimzhanov — collection and processing of data
K. A. Aitbaev, V. V. Fomin, I. S. Sabirov, F. A. Yusupov — editing

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HEART RATE VARIABILITY IN PATIENTS WITH CHRONIC RHEUMATIC HEART DISEASE

Abstract

Objective. Evaluation of heart rate variability in patients with rheumatic heart disease. **Material and methods.** The study enrolled 230 patients, of whom 156 patients with mitral stenosis (CRHD), 36 patients with mitral valve regurgitation, and 38 patients with acquired aortic stenosis were selected. CHF functional class was determined using a 6-minute walk test according to the standard method; there were no patients with FC IV. HRV values were obtained using the Kardiotekhnika-04-3R (M) cardiorespiratory monitor with an estimation of time domain and frequency domain. **Results.** The CRHD patients had lower HRV indicators in the time (SDNN — 126.38 ms, SDANN — 112.07 ms, RMSSD — 32.79 ms) and frequency domain (VLF — 2,098.59 ms^2; LF — 865.39 ms^2, HF — 323.48 ms^2) compared with patients with mitral valve regurgitation and aortic stenosis. Evaluation of HRV within patients with CRHD, depending on the presence or absence of combined mitral-aortic stenosis, did not show differences in the general and sympathetic tone of the ANS. In patients with combined mitral-aortic stenosis, only a decrease in parasympathetic tone was revealed: RMSSD — 31.18 ms, HF — 286.36 ms^2. Stratification of patients according to FC CHF showed an increase in parasympathetic tone: RMSSD was 26.67 ms for FC I and 43.69 ms for FC III; HF was 254.67 ms^2 for FC I and 541.23 ms^2 for FC III. The sympathetic and general tone of the ANS was minimal in patients with FC II CHF. A study of the change of indicators over 5 years did not demonstrate a significant increase in the time domain, and the main indicators of the frequency domain decreased significantly: VLF from (1,882.73 ± 119.48) to (1,603.54 ± 99.22) ms^2; HF from (334.34 ± 33.13) to (252.87 ± 17.84) ms^2, LF from (819.48 ± 94.41) to (647.01 ± 42.50) ms^2. A decrease in the frequency domain was also observed when comparing the HRV results of survived and deceased patients. **Conclusions.** The patients with CRHD had lower values of the ANS tone in comparison with patients with other acquired heart valve disease. The smallest values of the general tone of the ANS and SNS were observed in those studied with CRHD with FC II CHF, and the activity of the PNS was maximum at FC III. After 5 years of follow-up, only the frequency indices of HRV were significantly reduced.

Key word: *rheumatic heart disease, heart rate variability, chronic heart failure*

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AS — aortic stenosis, ANS — autonomic nervous system, HRV — heart rate variability, MVR — mitral valve regurgitation, PNS — parasympathetic nervous system, SNS — sympathetic nervous system, FC — functional class, CRHD — chronic rheumatic heart disease, CHF — chronic heart failure, HF — high-frequency component of the spectrum, LF — low-frequency component of the spectrum, pNN50 — percentage of NN50 of the total number of successive NN interval differences, RMSSD — root mean square of successive NN intervals, SDNN — standard deviation of NN intervals for

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the considered period, SDNNidx — average standard deviations for all 5-minute sections, VLF — very-low-frequency component of the spectrum.

Heart rate variability (HRV) assessment in various conditions has been of interest for many years. In cardiology, this is because low HRV values are associated with the risk of sudden cardiac death and the number of ventricular arrhythmias [1]. Rhythms with low variability are observed in case of impairment of the autonomic regulation of the heart function and damage to the automatic cells of the main pacemaker [2]. An increase in the activity of the sympathetic nervous system (SNS) with a change in baroreflex effects on the heart function is considered one of main mechanisms of hypertension development, which leads to left ventricular hypertrophy and progression of renal failure [3]. However, the data evaluating HRV are often contradictory [4].

The outcome of cardiovascular disease is chronic heart failure (CHF) accompanied by an increase in SNS activity and a decrease in the parasympathetic nervous system (PNS) tone. Initially, increased activity of the SNS is a compensatory mechanism that serves to maintain cardiac output. However, as the systolic function of the left ventricle decreases, increased activity of the SNS leads to the progression of CHF. In CHF, there is a decrease in baroreflex and an increase in cardiac afferent and chemoreceptor reflexes [5]. Developing decompensation of CHF is accompanied by a decrease in HRV, and effective treatment leads to an improvement in HRV to the values of compensated patients [6]. Although HRV cannot be attributed to standard cardiovascular risk factors [7], the tool that allows to evaluate the activity of the autonomic nervous system (ANS) should not be disregarded [8].

In recent times, HRV analysis has been carried out using the time domain, the frequency domain (spectral analysis), geometric and nonlinear analysis [9]. Mostly, time domain analysis of HRV is used, which is based on the analysis of changes in successive RR (NN) intervals with an estimate of the duration and the difference in the duration of adjacent NN intervals. The integral indicator, which reflects the entire period of HRV observation, depending on SNS and PNS activity, is the standard deviation from the average duration of all sinus intervals. Spectral methods of HRV assessment allow to analyze the frequency components of rhythm oscillations quantitatively [10]. The respiratory component of the spectrum shows the activity of the PNS, and the activity of the vasomotor center and SNS underlies the vasomotor component of the spectrum.

Literature that describes HRV is more often devoted to patients with hypertension and coronary heart disease, which are the main causes of CHF. There are few works related to the follow-up monitoring of patients with chronic rheumatic heart disease (CRHD) [11] and the assessment of HRV impairment in heart failure associated with acquired heart disease.

The objective was to evaluate HRV in patients with heart failure associated with CRHD.

Materials and Methods

The study enrolled 230 patients. All of the patients signed informed consent and underwent examination at the regional cardiology clinic. One hundred and fifty-six patients with Echo signs of mitral stenosis were selected in the CRHD group (determined by the area of the mitral valve orifice and the average pressure gradient on the mitral valve). CRHD was diagnosed taking into account the data of outpatient and discharge records, medical history, and history of acute rheumatic fever. Patients with congenital heart disease, connective tissue disease and possible non-rheumatic causes of mitral stenosis were excluded from the study. The average age was (55.35 ± 0.69) years; 132 women (84.6%) and 24 men (15.4%). The two comparison groups included patients without a history of acute rheumatic fever: with mitral valve regurgitation (MVR), determined via Doppler echocardiography according to the regurgitation flow (average age (52.13 ± 9.67) years; 28 women (77.8%) and 8 men (22.2%)) and with acquired aortic stenosis (AS) determined according to the pressure gradient across the valve (average age (55.54 ± 9.05) years; 15 women (39.5%) and 23 men (60.5%)).

NYHA functional class (FC) of CHF was determined using a 6-minute walk test according to the

standard method [12]; patients with FC IV were not enrolled because they had atrial fibrillation.

HRV values were obtained using Kardiotekhnika-04-3R (M) cardiorespiratory monitor, Inkart. The time and frequency domains were also evaluated; the recording time was reduced to 24 hours. The time domain was estimated using the following indicators: standard deviation of NN intervals for the considered period (SDNN, ms); standard deviation of the average NN intervals for all 5-minute sections (SDANN, ms); average standard deviations for all 5-minute sections (SDNNidx, ms). The difference in the duration of the NN intervals was assessed by the percentage of NN50 of the total number of successive pairs of NN intervals (pNN50, %); the root mean square of successive NN intervals (RMSSD, ms) [13]. The frequency domain was evaluated by: low-frequency band with power from 0.04 to 0.15 Hz (LF); very-low-frequency band with power below 0.04 Hz (VLF); high-frequency band with power from 0.15 to 0.40 Hz (HF). HRV re-assessment was carried out after 5 years of follow-up.

Statistical data were processed using IBM SPSS Statistics 23.0. Verification of distribution normality for quantitative indicators was carried out using the Kolmogorov — Smirnov test. In the normal distribution, M (mean), m (standard error), CI (95% confidence interval for the mean), and p (achieved significance level) were calculated. The differences were considered statistically significant at $p < 0.05$. Quantitative indicators in the groups were compared using Student's t-test; ANOVA was used for multiple comparison.

Results

Comparison of HRV assessment results in the groups with various valve disease (Table 1) shows an increase in the general tone of the ANS (SDNN — 140.10 ms), the activity of the central regulatory mechanisms (VLF — 2,830.47 ms^2) and sympathetic tone in both the time domain (SDANN — 123.10 ms) and the frequency domain (LF — 1,374.93 ms^2) in the group of mitral valve regurgitation. The lowest general tone of both ANS and SNS was observed in patients with CRHD, and those with AS had intermediate values of HRV. The PNS tone assessed via time indicators did not significantly differ, although it was highest in the groups with MVR (RMSSD — 35.00 ms) and AS (RMSSD — 35.70 ms). In the frequency domain of the PNS assessment, the situation was similar to the general tone of the ANS and SNS: HF was highest in the group with MVR — 436.17 ms^2, and lowest in the CRHD group — 323.48 ms^2.

Table 1. *Heart rate variability in rheumatic heart disease, mitral valve regurgitation and aortic stenosis groups*

HRV indicators	CRHD M (CI 95%)	MVR M (CI 95%)	AS M (CI 95%)	p
SDNN (ms)	126.38 (121.84; 130.92)	140.10 (134.75; 145.45)	131.81 (125.18; 138.44)	0.001
pNN50 (%)	7.62 (6.81; 8.43)	7.90 (6.37; 9.43)	7.86 (6.63; 9.10)	0.888
RMSSD (ms)	32.79 (30.81; 34.77)	35.00 (31.83; 38.17)	35.70 (32.54; 38.87)	0.522
SDNNidx (ms)	46.60 (44.77; 48.42)	54.30 (51.69; 56.91)	50.65 (48.01; 53.29)	0.001
SDANN (ms)	112.07 (107.68; 116.46)	123.10 (117.93; 128.27)	116.89 (110.35; 123.43)	0.002
VLF (ms^2)	2,098.59 (1,847.04; 2,350.15)	2,830.47 (2,437.10; 3,223.83)	2,331.16 (2,059.70; 2,602.63)	0.001
LF (ms^2)	865.39 (743.98; 986.80)	1,374.93 (1,152.97; 1,596.90)	1,010.57 (881.78; 1,139.35)	0.001
HF (ms^2)	323.48 (283.83; 363.12)	436.17 (328.51; 543.83)	356.65 (304.17; 409.12)	0.021

Note. AS is aortic stenosis, HRV is heart rate variability, CI is confidence interval, MVR is mitral valve regurgitation, CRHD is chronic rheumatic heart disease.

Table 2. *The effect of combined mitral-aortic stenosis on heart rate variability in rheumatic heart disease*

HRV indicators	CRHD without AS M (CI 95%), n = 114	CRHD with AS M (CI 95%), n = 42	p
SDNN (ms)	127.83 (122.45; 133.20)	120.75 (113.28; 128.22)	0.301
pNN50 (%)	7.28 (6.39; 8.17)	8.94 (6.96; 10.91)	0.186
RMSSD (ms)	31.18 (29.33; 33.03)	39.06 (32.67; 45.46)	0.028
SDNNidx (ms)	47.17 (45.14 ; 49.20)	44.38 (40.15; 48.60)	0.238
SDANN (ms)	113.45 (108.25; 118.65)	106.69 (99.41; 113.96)	0.469
VLF (ms^2)	2,159.86 (1,862.84; 2,456.87)	1,860.25 (1,429.58; 2,290.92)	0.227
LF (ms^2)	799.33 (695.77; 902.89)	1,122.38 (682.02; 1,562.73)	0.926
HF (ms^2)	286.36 (252.83; 319.89)	467.88 (326.86; 608.89)	0.027

Note. AS is aortic stenosis, HRV is heart rate variability, CI is confidence interval, CRHD is chronic rheumatic heart disease.

Table 3. *Heart rate variability change in survivors with rheumatic heart disease, 5-year follow-up*

HRV indicators	Initial M ± m, n = 135	After 5-year follow-up M ± m, n = 135	p
SDNN (ms)	122.91 ± 3.44	119.41 ± 3.25	0.170
pNN50 (%)	7.55 ± 0.58	6.42 ± 0.57	0.078
RMSSD (ms)	33.29 ± 1.69	30.91 ± 1.14	0.145
SDNNidx (ms)	46.55 ± 1.28	43.73 ± 1.19	0.002
SDANN (ms)	108.24 ± 3.25	106.00 ± 3.09	0.376
VLF (ms^2)	1,882.73 ± 119.48	1,603.54 ± 99.22	0.015
LF (ms^2)	819.48 ± 94.41	647.01 ± 42.50	0.072
HF (ms^2)	334.34 ± 33.13	252.87 ± 17.84	0.011

Note. HRV is heart rate variability.

Since HRV values differed in patients with CRHD and AS, we decided to divide the patients with mitral stenosis into two groups: with combined mitral-aortic stenosis (CRHD with AS) and without combined mitral-aortic stenosis (CRHD without AS), and to compare HRV values in these groups (Table 2). It turned out that only PNS indicators significantly differed, and their values were higher in the group of CRHD with AS: in the time and frequency domains: RMSSD — 39.06 ms, HF — 467.88 ms^2. Differences in general tone and SNS between groups were not obtained. A linear regression analysis showed the dependence of the area of the mitral valve orifice on HRV indicators: HF ($p = 0.003$), SDANN ($p = 0.037$), VLF ($p = 0.018$), LF ($p = 0.302$), RMSSD ($p = 0.001$), SDNN ($p = 0.022$).

Five years later, in patients who maintained sinus rhythm, there was a decrease in the indicators of the time domain analysis (Table 3): SDNN by 3.5 ms, RMSSD by 2.38 ms, SDANN by 2.24 ms, and pNN50 by 1.13%. These changes, however, were not significant, except for a decrease in SDNNidx by 2.82 ms. The values of the spectral analysis indicators reduced significantly: VLF by 279.73 ms^2 and by HF by 81.47 ms^2; a decrease in LF by 172.47 ms^2 was insignificant.

It is important that HRV indicators differed depending on CHF FC, determined by the 6-minute walk test (Table 4). RMSSD and pNN50%, which reflect PNS activity, increased from FC I to FC III. Similarly, the frequency domain index (HF) almost doubled in FC III, in comparison with FC I and FC II CHF. In the time domain, SDANN, which reflects SNS activity, was minimal in the group with FC II CHF, although there was no significant difference between the groups. However, according to the frequency domain in the group with FC II, LF, which also reflects SNS activity, was minimal. Similarly to the SNS tone, the general tone varied: SDNN and VLF, reflecting the function of central regulation mechanisms, which were minimal in FC II CHF.

Over a five-year follow-up period, 10 patients died (out of 156) and the initial HRV values in the group

Table 4. *Heart rate variability depending on function class of chronic heart failure*

HRV indicators	FC I M (CI 95%), n = 21	FC II M (CI 95%), n = 90	FC III M (CI 95%), n = 45	p
SDNN (ms)	138.83 (121.73; 155.93)	122.07 (112.98; 131.15)	139.00 (128.13; 149.87)	0.032
pNN50 (%)	6.17 (2.79; 9.54)	5.53 (4.40; 6.67)	10.54 (8.51; 12.57)	0.001
RMSSD (ms)	26.67 (20.74; 32.59)	29.06 (26.43; 31.69)	43.69 (36.68; 50.71)	0.001
SDNNidx (ms)	53.51 (44.11; 62.89)	42.79 (39.77; 45.81)	54.69 (49.66; 59.73)	0.001
SDANN (ms)	119.67 (104.58; 134.75)	109.66 (100.73; 118.59)	119.54 (109.04; 130.04)	0.192
VLF (ms^2)	2,743.67 (1,647.82; 3,839.52)	2,219.58 (1,609.45; 2,829.71)	2,678.00 (2,112.18; 3,243.82)	0.001
LF (ms^2)	1,074.50 (634.76; 1,514.24)	777.96 (579.47; 976.46)	1,463.31 (944.10; 1,982.52)	0.001
HF (ms^2)	254.67 (168.44; 340.89)	219.66 (184.75; 254.57)	541.23 (369.85; 712.61)	0.001

Note. HRV is heart rate variability, CI is confidence interval, FC is function class.

Table 5. *Heart rate variability in survived and deceased subjects*

HRV indicators	Survived M (CI 95%), n = 146	Deceased M (CI 95%), n = 10	p
SDNN (ms)	125.86 (121.62; 130.10)	134.00 (96.73; 171.27)	0.345
pNN50 (%)	7.74 (6.90; 8.59)	5.80 (2.76; 8.84)	0.153
RMSSD (ms)	33.20 (31.13; 35.27)	26.80 (20.25; 33.35)	0.107
SDNNidx (ms)	46.98 (45.17; 48.79)	41.00 (29.69; 52.31)	0.004
SDANN (ms)	111.31 (107.21; 115.41)	123.20 (87.15; 159.25)	0.613
VLF (ms^2)	2,108.81 (1,852.38; 2,365.23)	1,949.00 (663.51; 3,234.49)	0.003
LF (ms^2)	894.67 (766.23; 1,023.10)	436.40 (234.20; 638.60)	0.001
HF (ms^2)	333.45 (291.62; 375.28)	177.40 (97.55; 257.25)	0.014

Note. HRV is heart rate variability, CI is confidence interval.

of the deceased and those who survived were compared. Comparison of time domain HRV values in patients with CRHD (Table 5) showed a decrease in PNS (pNN50, RMSSD) and an increase in general ANS tone (SDNN) and SNS tone (SDANN), but the differences between the groups were insignificant. Only a decrease in SDNNidx was significant. However, all frequency domain indicators (VLF, LF, HF) in deceased patients were significantly reduced.

Discussion

A comparison of patients with CRHD, AS and MVR in terms of time domain indicators shows a lower general ANS tone and SNS tone in the CRHD group. Frequency domain indicators showed a similar pattern: the lowest values of SNS and PNS tone and VLF were observed in the CRHD group. The highest HRV values were observed in the group with MVR, and intermediate — in the group with AS. Since valve regurgitation, as a rule, is asymptomatic for a long time, and decompensation occurs late, it is clear why HRV values reflecting the exertion of regulatory systems were the best in the group with MVR. In the literature, the decrease in the variability values in AS is described in patients with asymptomatic AS and even a connection between the reduced indicators and mortality is indicated [14]. But does the combination of MS and AS have an additional effect on HRV? It turned out that HRV values did not differ in both time

and frequency domains (neither the ANS general tone, nor the SNS tone) in the CRHD group with or without mitral-aortic stenosis. Only the effect of combined mitral-aortic stenosis on the PNS tone with a decrease in time and frequency domains was revealed. Probably, in the case of two-valve stenosis, PNS is activated as a compensatory reaction to hemodynamic cardiac changes. Linear regression analysis showed a relationship between the main indicators of the time and frequency domains of HRV and the area of the mitral valve orifice.

After 5 years, in patients with CRHD, HRV values decreased in both time and frequency domains, but the decrease was not significant in the time domain. This is probably due to the slow progression of CHF and a gradual change in neurohumoral activation, or perhaps no significant changes of the ANS general tone and the SNS tone should be expected in CRHD. Since in CHF the compensatory activation of SNS is associated with impairment of the cardiac pumping function and a decrease of the ejection fraction [10], which are usually absent in CRHD. In the frequency domain, HRV in the group of CRHD decreased significantly: VLF reflecting the action of central ergotropic and humoral-metabolic regulation mechanisms [2], and HF reflecting the activity of the parasympathetic cardioinhibitory center of the medulla oblongata. Apparently, the decrease in these HRV indicators is associated not only with the gradual progression of CHF [13], but also with the possible depletion of the ANS regulatory mechanisms against the background of mitral stenosis with a decrease in the PNS tone. Clarification of emerging issues may require a longer follow-up period for patients with CRHD.

It is believed that there is a significant relationship between the severity of heart failure and HRV: in patients with CHF FC I–II, there is a moderate decrease in total HRV associated with inhibition of PNS and increased activity of the SNS [2]. In CHF FC III–IV, a significant decrease in total HRV already exists against the background of the autonomic denervation of the heart. The latter leads to a significant decrease in all indicators of HRV and normalization of the vagosympathetic balance [10]. However, this is true primarily for patients with heart failure associated with coronary heart disease, cardiomyopathies, and hypertension. In patients with CRHD, an assessment of the frequency and spectral indicators of HRV showed a significant increase in the PNS tone in the group of CHF FC III. The minimum values of the indicators of total HRV, sympathetic and parasympathetic tone were observed in patients with CHF FC II, which distinguishes patients with CRHD from patients with CHF associated with coronary heart disease and hypertension.

In deceased patients, in terms of the time domain, there was an increase in the general and sympathetic tone of the ANS with a decrease in the tone of the PNS, but the indicators did not reach statistical significance. In patients with coronary heart disease and post-infarction cardiosclerosis, SDNN and SDANN usually decrease [1, 2]. The results are probably associated with a small group of deceased patients, and data collection for a longer follow-up period and in the larger group will show the direction of movement of time domain HRV values. A different situation was observed in patients with CRHD in frequency domain terms. And the slow Mayer second-order waves (VLF) associated with blood plasma renin, angiotensin and aldosterone; and slow Traube — Goering first-order waves (LF); and the values of the high-frequency (respiratory) range (HF^2) in the deceased group were significantly lower than in patients who survived. Thus, we can assume a decrease in the activity of the humoral-metabolic regulation mechanisms of both the superior sympathetic thoracic ganglion and the cardioinhibitory center of the medulla oblongata with a decrease in vagus nerve activity in deceased patients with CRHD. The described HRV changes are probably associated with changes in the geometry and structure of the cardiac chambers, since patients did not have data for acute rheumatic fever at the time of HRV assessment.

Conclusion

Therefore, a decrease in the general ANS tone was observed in CRHD patients in comparison with patients with MVR and AS. The minimal values of the general tone of the ANS and SNS were registered in patients with CHF FC II, while PNS activity increased to the maximum in CHF FC III. After five-year follow-up, a decrease in both time and frequency domain indicators of HRV was noted, but significant changes were obtained only for VLF

and HF. The situation was similar in the deceased patients with lower values of the frequency domain indicators in comparison with the patients who survived.

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HEMOSTASIS PARAMETERS IN PATIENTS AFTER CORONARY ARTERY BYPASS SURGERY FOR STABLE ANGINA

Abstract

The objective of research is to assess the significance of hemostatic profile in the postoperative period after coronary artery bypass surgery for predicting the one-year functioning of the grafts.

Materials and methods. 46 men, who had coronary artery bypass surgery (CABS) for stable angina, were examined. 23 of them had 2 type diabetes mellitus (DM2), 23 of them did not have diabetes mellitus. All patients underwent fibrinogen, soluble fibrin monomer complex, D-dimer, induced platelet aggregation and lupus anticoagulant blood tests on the 14th day after surgery. The patients had coronary and bypass graft angiography for the assessment of graft patency a year after surgery.

Results. During the postoperative period, there were no statistically significant differences between patients with DM2 and patients without DM2 in the results of the above hemostatic profile tests (p value for the Mann-Whitney test is >0.05). Lupus anticoagulant was detected in 9 patients with DM2 and in 12 patients without DM2 (p value for Fisher's exact test is 0.554). 10 patients with DM2 and 6 patients without DM2 had graft occlusions a year after surgery; the differences for this sign were not statistically significant (p value for Fisher's exact test is 0.18). Fibrinogen, soluble fibrin-monomer complex, D-dimer, and induced platelet aggregation tests did not demonstrate prognostic significance in relation to graft occlusions in both groups of patients (p for χ^2 in the logistic regression model is >0.05). The factors associated with higher risk of graft occlusion in patients with DM2 were high ratio between screening and confirmatory test for the detection of lupus anticoagulant (odds ratio 2.27; 95% -confidence interval 1.119–1.238; p <0.05).

Conclusion. After coronary bypass surgery, the one-year risk of graft thrombosis is higher in patients with DM2 and high positive LA activity

Key words: *coronary artery bypass surgery, diabetes mellitus, lupus anticoagulant, hemostasis parameters, prognosis*

Conflict of interests

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

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ADP — adenosine diphosphate, Ab — antibodies, LA — lupus anticoagulant, CAD — coronary artery disease, MI — myocardial infarction, CABS — coronary artery bypass surgery, SFMC — soluble fibrin monomer complexes, T2DM — type 2 diabetes mellitus, LA1 — lupus anticoagulant screening test (dilute Russell's viper venom time), LA2 — lupus anticoagulant confirmatory test (phospholipid-enriched dilute Russell's viper venom time), LA ratio — the ratio between the lupus anticoagulant screening and confirmatory tests (LA1/LA2).

Introduction

The need for cardiac surgery among the population in our country grows year by year due to the increase in the number of patients with coronary artery disease (CAD) [1]. Without diminishing the successes of modern interventional cardiology, it should be noted that coronary artery bypass surgery (CABS) is the preferred method of revascularization in multivessel hemodynamically significant coronary artery disease.

Among the most important issues in coronary surgery is post-CABS relapse of myocardial ischemia (angina relapse, myocardial infarction (MI)), due to which there is a need for coronary reinterventions [2]. Morphological background for these outcomes is generally based on the insufficiency of grafts due to their thrombosis, intimal hyperplasia, atherosclerosis progression [3]. In this case, patients with T2DM have a worse post-CABS prognosis as compared to people without carbohydrate metabolism disorders [4].

Identification of coronary graft occlusion predictors would make it possible to form risk groups among patients who have undergone CABS, and work out an effective strategy of secondary prevention for said patients.

According to the available literary data, the post-CABS activation of the hemostatic system affects the possibility of adverse clinical outcomes. In particular, higher D-dimer levels one month following CABS are associated with angina relapse [5]. In their study, B. Yanagawa et al. confirmed the significance of fibrinogen as a biochemical predictor of coronary graft occlusion in the long post-operative term [6].

The understudied issue is the impact of antiphospholipid antibodies (Ab) on the prognosis in patients with CAD in cases when there are no grounds for making a diagnosis of antiphospholipid syndrome (asymptomatic carriage or transient occurrence of Ab to cardiolipin, Ab to β2-glycoprotein-1, or Ab with lupus anticoagulant (LA) properties). The question of the predictive value of LA identification for patients who have undergone CABS remains open.

The **objective** of our study was to assess the existence of the relationship between the hemostatic system parameters in the post-CABS period and the development of coronary graft occlusions within one post-operative year.

Materials and Methods

The prospective cohort study was conducted in 2016–2018. The study design was approved by the local ethics committee. Voluntary informed consents were obtained from all the patients participating in the study.

The study included 46 males who had undergone coronary bypass surgery for grade III–IV stable angina according to the Canadian classification. The surgery was indicated for two- and three-vessel coronary artery disease with 50% and over stenosis [7]. Among 46 patients, 23 had T2DM, and 23 did not have diabetes. Clinical profiles of the patients are presented in Table 1.

Patients with T2DM and patients without T2DM were not significantly different in age, body mass index, smoking status, and cardiovascular comorbidity. However, the patients with T2DM had much greater waist circumference.

The inclusion criteria: male, CABS undergone under cardiopulmonary bypass for grade III–IV stable angina.

The exclusion criteria: MI experienced less than 12 weeks before the surgery, perioperative MI,

Table 1. *Clinical characteristics of patients*

Clinical sign	Patients with DM2 (n = 23)	Patients without DM2 (n = 23)	ρ for Mann—Whitney test, ρ(U)/ρ for Fisher test, ρ(F)
Age, years. Me (P25; P75)	59 (53; 74)	58 (51; 65)	ρ(U) = 0.221
Body mass index, kg/m^2 Me (P25; P75)	28.8 (25.3; 33.3)	26.8 (25.8; 30.7)	ρ(U) = 0.175
Waist circumference, cm Me (P25; P75)	103 (95; 112)	89 (80; 95)	**ρ(U) = 0.000**
One myocardial infarction, (%±S$_ρ$) Second myocardial infarction, (%±S$_ρ$)	14 (61 ± 10%) 3 (13 ± 7%)	19 (83 ± 8%) 2 (8.7 ± 6%)	ρ(F) = 0.189 ρ(F) = 1.000
Arterial hypertension, (%±S$_ρ$)	19 (83 ± 8%)	20 (86.9 ± 8%)	ρ(F) = 0.189
III functional class of angina pectoris, (%±S$_ρ$) IV functional class of angina pectoris, (%±S$_ρ$)	19 (83 ± 7.8%) 4 (17.4 ± 8%)	20 (86.9 ± 7.8%) 3 (13 ± 7%)	ρ(F) = 189 ρ(F) = 1.000
Smoking status, (%±S$_ρ$)	13 (56.5 ± 10%)	16 (69.6 ± 10%)	ρ(F) = 0.542
Hemodynamically significant atherosclerosis of the internal carotid arteries, (%±S$_ρ$)	5 (21.7 ± 9%)	6 (26.1 ± 9%)	ρ(F)=1.000
Hemodynamically insignificant atherosclerosis of the internal carotid arteries, (%±S$_ρ$)	14 (60.9 ± 11%)	9 (39 ± 10%)	ρ(F) = 0.238

Note: AH — arterial hypertension, BMI — body mass index, Me (P25; P75) — median, upper and lower quartiles, ICA — internal carotid arteries, abs. — absolute number, S$_ρ$ — standard error of the proportion, G — grade, DM2 — type 2 diabetes mellitus. P-values in bold indicate that there are statistically significant differences among the groups

diseases and conditions requiring prescription of oral anticoagulants, suppurative-septic complications that occurred due to the undergone CABS.

All the patients underwent CABS under cardiopulmonary bypass. A conduit and its application technique were selected by an operating surgeon on a case-by-case basis, depending on the clinical situation. Table 2 provides information of what conduits and in what combinations they were used in both groups of patients.

On Day 10–14 following the operation, blood sampling was conducted in all patients for the assaying of fibrinogen, soluble fibrin monomer complexes (SFMC), D-dimers, lupus anticoagulant (LA) and induced platelet aggregation. As antiplatelet therapy, all the patients received only acetylsalicylic acid at a dose of 100 mg. Low molecular heparins were discontinued on Day 4 following the operation.

Fibrinogen was assayed by the Sysmex 560 automatic coagulometer using Siemens reagents. D-dimer level was measured by NycoCard diagnostic kits manufactured by Nicomed using NycoCard Reader II reflectometer. To detect SFMC, reagents manufactured by Tekhnologiya-standart were used. LA was assayed by the Sysmex ca-560 automatic coagulometer using Siemens reagents LA1 Screening Reagent and LA2 Confirmation Reagent. The screening test (LAC Screen) contains diluted Russell's viper venom and is intended for the screening assay of lupus anticoagulant. The confirmatory test (LAC Confirm) contains phospholipid-enriched diluted Russell's viper venom and is intended for the LA confirmation. Following the testing, the ratio between the screening and confirmatory tests (LA ratio) was calculated. With the LA ratio of 1.2–1.5, the LA content was considered as low, with the LA ratio within 1.5–2 — as moderate. If the LA ratio exceeded 2, the LA content was considered as high.

Platelet aggregation was assayed by the Chronolog model 490 optical c using inductors (ADP, Epinephrine) manufactured by Chrono-log. The induced aggregation parameters were determined by the light transmission curve. Epinephrine (5 μg/ml) and ADP (5 μg/ml) were used as aggregation inductors.

Table 2. *The main strategies for coronary artery bypass surgery and the types of grafts used*

Grafts used	Patients with DM2 (n = 23)	Patients without DM2 (n=23).	ρ for the Fisher test, ρ(F).
LITA + SV (% ± $S_ρ$)	14 (60.9 ± 10.9%)	12 (52.2 ± 10.4%)	ρ(F) = 0.766
LITA + RA + SV (% ± $S_ρ$)	0	3 (13 ± 7%)	ρ(F) = 1.000
LITA + RA (% ± $S_ρ$)	0	1 (4.3 ± 4.3%)	ρ(F) = 1.000
RA + SV (% ± $S_ρ$)	1 (4.3 ± 4.3%)	1 (4.3 ± 4.3%)	ρ(F) = 1.000
Only SV, (% ± $S_ρ$)	8 (34.8 ± 9.9%)	5 (21.7 ± 8.6%)	ρ(F) = 0.513
Sequential venous grafts, (% ± $S_ρ$)	12 (52.2 ± 10.4%)	8 (34.8 ± 9.9%)	ρ(F) = 0.373
Two grafts, (% ± $S_ρ$)	19 (83 ± 7.8%)	15 (65.2 ± 9.9%)	ρ(F) = 0.314
Three grafts, (% ± $S_ρ$)	4 (17.4 ± 7.9%)	7 (30.4 ± 9.6%)	ρ(F) = 0.314
The total number of grafts, (% ± $S_ρ$)	50	51	ρ(F) = 1.000

Note: CV — calf vein; abs.– absolute number, $S_ρ$ — standard error of the ρroportion. DM2 — type 2 diabetes mellitus; LITA — left internal thoracic artery; RA — radial artery; SV -saphenous vein

Within one year following the surgery, the patients were in real-life clinical practice settings: they were followed up by a cardiac rehabilitation professional, cardiovascular surgeon, as well as general practitioner in their home area. All the patients received acetylsalicylic acid at a dose of 100 mg/day, as well as beta-blockers and statins at individually adjusted doses. Nineteen patients with T2DM and 19 patients without diabetes received ACE inhibitors. Angiotensin receptor blockers were prescribed to two patients with T2DM and three patients without T2DM. The patients who received Clopidogrel for the experienced MI before the surgery continued its administration up to 12 months after the MI (10 patients with T2DM and 9 patients without diabetes). Seventeen patients with T2DM received oral antidiabetic drugs as a monotherapy or combination therapy, 4 patients received therapy with insulin, and 2 patients controlled the glycemia through a low carbohydrate diet.

One year after the surgery, coronary graft angiography was performed in all of the patients to assess the graft patency.

Statistical methods. The type of distribution of continuous quantitative data was assessed by calculating the Shapiro—Wilk test. To compare two groups by quantitative measures, the Mann—Whitney U-test was applied. The two-tailed Fisher's test was used to compare the groups by qualitative binary features. Four subgroups were compared by quantitative features using the Kruskal—Wallis test. The potential occlusion of coronary grafts was predicted by the logistic regression analysis. The critical value of the significance level is ρ <0.05.

Results

Diabetes mellitus is a disease that contributes to the activation of hemostasis, therefore, first of all, the diabetic and non-diabetic patients were compared on all tested hemostatic parameters. The results are presented in Table 3.

No significant differences in the mentioned hemostatic parameters were revealed between the groups. The borderline difference was observed in the ADP-induced platelet aggregation: this aggregation was somewhat higher in the patients with T2DM.

Lupus anticoagulant was detected in 9 patients with T2DM and 12 patients without DM (ρ-value for the Fisher's test is 0.554). Among the tested diabetic patients, LA was detected in small amounts in 8 patients, and in a moderate quantity in 1 patient. In the non-diabetic patients, the small quantity of LA was reported in 9 cases, and the moderate one — in 3 cases. There were no cases of significant quantities of LA.

Table 4 presents values of the screening and confirmatory tests for lupus anticoagulant, as well as their ratios in both groups of patients.

Table 3. *Comparison of hemostasis in the postoperative period in patients with and without type 2 diabetes mellitus*

The studied parameter of hemostasis	Reference Values	Patients with DM2 (n=23) , Me (P25; P75)	Patients without DM2 (n=23). Me (P25; P75)	p for the Mann—Whitney test
Fibrinogen, g/l	2–4	4.65 (3.7; 5.5)	3.9 (3.6; 5.3)	0.398
Soluble fibrin monomer complexes, mg/100 ml	3.5–15	19 (12; 26)	24 (14; 26)	0.899
D-dimer, mg/ml	≤0,3	0,5 (0.3; 1.3)	0,5 (0.4; 0.9)	0.499
Epinephrine-induced platelet aggregation, 5 μg/ml, %	78–88 *	40 (29; 56)	46 (31; 52)	0.955
ADP-induced platelet aggregation, 5 μg/ml, %	69–88 *	62 (51; 72)	58 (31; 62)	0.054

Note: * — reference values are provided for persons who do not receive antiplatelet therapy
Me — median, P25; P75 — upper and lower quartiles. ADP — adenosine diphosphate; DM2 — type 2 diabetes mellitus

Table 4. *The significance of screening and confirmatory tests for the determination of lupus anticoagulant and LA ratio in patients with and without diabetes mellitus*

Parameter	Patients with DM2 (n=23), Me (P25; P75)	Patients without DM2 (n=23). Me (P25; P75)	p for the Mann—Whitney test
LA1 screening, Dilute Russell's viper venom time, s	61 (56.3; 66.1)	60 (55.9; 72.2)	0.811
LA2 confirmative, phospholipid-rich dilute Russell viper venom time, s	44.8 (40.1; 47.0)	42,3 (39.5; 47)	0.238
LA ratio	1.27 (1.19; 1.35)	1.31 (1.16;1.46)	0.451

Note: Me — median, P25; P75 — upper and lower quartiles. DM2 — type 2 diabetes mellitus

Relapse of angina during a year following the surgery occurred in 9 patients with T2DM and 14 patients without DM. There were no significant differences in the pain syndrome relapse incidence (p-value for the Fisher's test is 0.119). Based on the coronary graft angiography results, graft occlusions were found in 16 of 46 patients. Ten coronary graft occlusions occurred in the diabetic patients and 6 — in the non-diabetic patients. No occlusions of 2 or more grafts in the same patient were found during the study. Twenty percent of grafts (10 of 50) failed in the patients with T2DM, and 12% of grafts (6 of 51) — in the non-diabetic patients. No significant differences were revealed between the groups by the number of failed grafts (p-value for the Fisher's test is 0.288). Among the patients with T2DM, the pain syndrome relapse in 5 cases was due to the graft occlusion, in 4 cases — was not due to that reason, and asymptomatic graft occlusion was found in 5 patients. That is, pain syndrome relapse in patients with T2DM was not associated with the graft occlusion (p-value for the Fisher's test is 0.417). In the non-diabetic patients, all 6 cases of graft occlusions were associated with pain syndrome relapse, 8 cases of angina relapse were not related to graft occlusions, and no asymptomatic occlusions were found. That is, pain syndrome relapse in patients without T2DM is statistically related to graft occlusions (p-value for the Fisher's test is 0.048).

Coronary artery stenosis cases were revealed de novo in 6 patients with T2DM and 7 patients without DM (p-value for the Fisher's test). However, angina relapse with the normal bypass patency was due to exclusively this phenomenon only in one patient with T2DM and one non-diabetic patient. In other cases, there was a combination of graft occlusion and atherosclerosis progression (3 cases in each group, respectively), or asymptomatic atherosclerosis progression (2 and 3 cases, respectively).

A fair question is the impact of medication therapy on the post-operative prognosis. Of particular

interest is the influence of Clopidogrel on the post-CABS prognosis. Among the patients with T2DM, coronary graft occlusions were found in 5 patients who received Clopidogrel and in 5 patients who did not receive Clopidogrel (p-value for the Fisher's test is 0.675). In the non-diabetic patients, these values were 2 and 7, respectively (p-value for the Fisher's test is 1.000). That is, the administration of Clopidogrel did not affect the probability of graft occlusions. The patients who continued to take Clopidogrel following CABS received it for different periods of time (1 to 9 months) up to 1 year after the experienced MI. In the group of patients with T2DM, the median coarse of the drug administration in the patients with graft occlusions was 1 month; (P_{25} = 1 month; P_{75} = 5 months); and in the patients without graft occlusions — 6 months; (P_{25} = 5 months; P_{75} = 6 months). Nevertheless, no association between the course of Clopidogrel administration and the probability of graft occlusions was revealed in the patients with T2DM (p-value for the Mann—Whitney test is 0.605). A similar situation is observed in the non-diabetic patients: the median course of the drug administration in the patients with graft occlusions was 6 month; (P_{25} = 2 months; P_{75} = 7 months); and in the patients without graft occlusions — 5 months; (P_{25} = 5 months; P_{75} = 10 months) (p-value for the Mann—Whitney test is 0.858).

According to the data obtained, prescription of ACE inhibitors, angiotensin receptor blockers, as well as peculiarities of hypoglycemic therapy, did not affect the probability of coronary graft occlusions (p-value for the Fisher's test is ≥0.05).

In order to find out whether values of the hemostatic system parameters in the post-CABS period are associated with the probability of coronary graft occlusions, hemostatic parameters in the patients with graft occlusions were compared to those in the patients with properly functioning grafts, taking into account the existence of diabetes mellitus. The results are presented in Table 5.

As can be seen, no statistically significant differences in the hemostatic system parameters during the post-surgery period were reveled between the

Table 5. *Patients with and without graft occlusions according to the hemostasis parameters level in the postoperative period, considering presence or absence of diabetes mellitus: Comparison*

Parameter	Patients with DM2 without graft occlusion (n = 13), Me (P25; P75)	Patients with DM2 with graft occlusion (n = 10), Me (P25; P75)	Patients without DM2, without graft occlusion (n = 17). Me (P25; P75)	Patients without DM2 with graft occlusion (n = 6), Me (P25; P75)	Kruskal—Wallis test, p
Fibrinogen, g/l	4.25 (3.65; 4.95)	5.45 (4.5; 6)	4 (3.7; 5.3)	3.8 (3.1; 5.1)	3.697 p = 0.296
Soluble fibrin monomer complexes, mg/100 ml	17 (12; 26)	21 (18; 26)	24 (17; 26)	12 (4; 21)	6.222 p = 0.101
D-dimer, mg/ml	0.5 (0.3; 0.8)	0.7 (0.4; 1.4)	0.5 (0.4; 0.9)	0.4 (0.2; 0.5)	4.181 p = 0.243
LA ratio	1.195 (1.16; 1.129)	1.345 (1.25; 1.39)	1.36 (1.18; 1.48)	1.23 (1.15; 1.27)	7.002 p = 0.072
ADP-Induced platelet aggregation, 5 μg/ml, %	62 (57; 72)	63 (40; 71)	58 (33; 61)	59.5 (29; 65)	4.085 p = 0.254
Epinephrine-induced platelet aggregation, 5 μg/ml, %	43 (29; 61)	32 (30; 55)	48 (31; 53)	39.5 (33; 47)	0.738 p = 0.864

Note: Me — median, P25; P75 — upper and lower quartiles. DM2 — type 2 diabetes mellitus

patients with coronary graft occlusions and the patients without occlusions. However, the borderline differences were observed for LA ratios.

Lupus anticoagulant was previously found in 6 of 10 diabetic patients with graft occlusions; and only in 1 of 6 non-diabetic patients with graft occlusions (p-values for the Fisher's test are 0.102 and 0.069, respectively). That is, the fact of detecting the lupus anticoagulant following CABS was not associated with graft occlusions in the long term.

To give a final answer to the question of the impact of hemostatic parameters on the probability of graft occlusions, logistic regression analysis was performed.

There were 10 blocked grafts among the patients with T2DM (n = 23). Based on the logistic regression analysis, the only hemostatic parameter affecting the probability of coronary graft occlusions was LA ratio. The logistic regression equation in this case was as follows: $Y = B_0 + B_1 * LA_{ratio}$. χ^2 for the model as a whole — 6.676; p = 0.009; $B_0 = -15.827$; B = 12.279; prognostic χ^2 — 4.542; odds ratio = 2.27; 95% CI — 1.119–1.238; p = 0.033. Having calculated Y, the graft occlusion probability for any specific patient can be calculated by the formula $P = e^Y / (1 + e^Y)$, where e — base of the natural logarithm that approximately equals to 2.72. Y in this case is a natural logarithm of the odds ratio for a graft occlusion.

Example calculations. 1) LA ratio = 1.17 in patient A with type 2 diabetes mellitus on Day 14 following CABS.

$$Y = -15.827 + 12.279 * 1.17 = -1.461$$

The graft occlusion probability is calculated by the formula $P = e^Y / (1 + e^Y)$; $P = 2.72^{-1.461} / 1 + 2.72^{-1.461} = 0.188$; i.e., according to the logistic regression equation, the graft occlusion probability in the patient with these baseline data will be 18.8%.

2) LA ratio = 1.39 in patient B with type 2 diabetes mellitus on Day 14 following the CABS.

$$Y = -15.827 + 12.279 * 1.39 = 1.241$$

$P = 2.72^{1.241} / 1 + 2.72^{1.241} = 0.775$; i.e., according to the logistic regression equation, the graft occlusion probability in the patient with these baseline data will be 77.5%.

In the non-diabetic patients, the logistic regression analysis did not show any association between the hemostatic parameters and the prospective graft occlusion probability (p-value for χ^2 in the logistic regression model is >0.05).

Discussion

No statistically significant differences in blood content of the tested hemostatic parameters were revealed between the patients with and without T2DM in the post-CABS period. According to literary data, the patients with T2DM were expected to have more pronounced activation of both coagulative and vascular-platelet hemostasis [8]. The absence of significant differences in hemostasis status between the patients with T2DM and non-diabetic patients is likely due to that traumatic intervention under cardiopulmonary bypass is a strong activator of blood coagulation. At the same time, the patients with T2DM showed a tendency to higher ADP-induced platelet aggregation, which was fully consistent with hemostatic features described for patients with T2DM [9].

According to the data obtained, the content of fibrinogen, SFMC, D-dimer, as well as the induced platelet aggregation, was not related to graft occlusions within a post-operative year. This is partly confirmed by literary data: hypercoagulable state in the CABS perioperative period increases the probability of thrombotic events, but the impact of activated hemostasis on the coronary graft patency has not yet been proven. Based on the results of Study BARI 2D, high levels of fibrinogen and D-dimer following revascularization in patients with T2DM were associated with the risk of MI, stroke and total mortality within 5 years after the intervention [10]. The study conducted by M. Zacho et al. confirms the existence of a statistical relationship between the hypercoagulable state (based on thromboelastography findings) and the development of post-CABS thrombotic events. At the same time, the hypercoagulable state was not associated with

impaired coronary graft patency in the first postoperative months [11].

Based on the findings of this study, the patients with T2DM, unlike non-diabetic patients, showed no association between the pain syndrome relapse and the impaired coronary graft patency, the graft occlusions were asymptomatic in 5 of 10 cases. The most probable cause of this feature is silent myocardial ischemia as a manifestation of autonomic neuropathy (cardiovascular form). Among patients with CAD and T2DM, silent ischemia occurs at a frequency of up to 50%, and is an adverse prognostic factor [12]. Therefore, instrumental methods for diagnosis of myocardial ischemia (loading tests, 24-hour ECG monitoring) should be an integral part of the follow-up of patients with T2DM following CABS.

For the first time, the prospective study has demonstrated the negative impact of antibodies with LA potency on the prognosis of coronary graft operation in patients with T2DM. K. E. Morton et al. earlier established the association between the carriage of anti-cardiolipin antibodies and the high probability of coronary graft occlusions [13]. Following CABS, LA is found in a large number of patients (46 ± 7%). The identification of LA in the tested patients can include the following clinical situations:

1. Antiphospholipid syndrome — if LA remains in blood for more than 12 weeks, and there is a history of confirmed thrombosis (in particular, MI). Secondary thromboprophylaxis and hematologist follow-up are certainly indicated for such patients [14].
2. Asymptomatic LA carriage — if LA remains in the blood of patients without a history of thrombosis for more than 12 weeks [14].
3. Transient LA occurrence — occurs when LA is not found in blood in 12 weeks after the first identification. The occurrence of antibodies with LA potency can be a manifestation of systemic inflammation in response to major surgery under cardiopulmonary bypass [15].

The relevant objective is further study of the clinical significance of anti-phospholipid antibodies for the development of cardiovascular morbidity associated with atherosclerosis and atherothrombosis.

Conclusions

1. No significant differences in the blood content of fibrinogen, SFMC, D-dimer were revealed between diabetic and non-diabetic patients during the post-CABS period. The groups also had no differences in the induced platelet aggregation and the LA identification rate.

2. Coronary graft occlusions in the patients without T2DM manifested as angina relapse in all cases for a year following the surgery, but were not observed in the patients with T2DM.

3. Within one year following CABS, the patients with T2DM and high LA ratio are at an increased risk of coronary graft occlusions.

Contribution of Authors

Lisyutenko N.S. — collection and analysis of primary clinical data, manuscript writing
Morova N.A. — development of the concept and design, formulation of conclusions, interpretation and critical analysis of the results
Tsekhanovich V.N. — collection and analysis of primary clinical data, interpretation and critical analysis of results
All authors read the manuscript, approved its final version, and consented to publication

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INFECTIOUS ENDOCARDITIS COURSE AFTER ASCENDING AORTA REPLACEMENT WITH A VALVED CONDUIT

Abstract

Objective. To demonstrate the peculiarities of infectious endocarditis course in patients after ascending aorta replacement using a valved conduit based on the personal observations. **Material and methods.** Six cases of delayed infectious endocarditis after ascending aorta replacement using a valved conduit are presented. **Results.** The pathological process was represented by aortic root abscess, paraprosthetic phlegmon, fistula penetrated into the conduit wall and cardiac chambers. There was no vegetation on the prosthesis therefore the diagnosis was complicated. Period from fever onset to final diagnosis lasted from 1 week to 2.5 months. The first pathologic changes in all cases were detected using transesophageal echocardiography, but this method was not informative in the early stages of the disease. **Conclusion**. Infectious endocarditis in patients after ascending aorta replacement using a valved conduit has its own peculiarities. The most frequently, the process leads to the development of aortic root abscess. Diagnosis of infectious endocarditis in such cases is difficult. Infectious endocarditis should be suspected in patients — carriers of valved conduit with unexplained fever and treatment should be started in accordance with the diagnosis. In this case, structural changes visualization to confirm the disease is not necessary.

Key words: *infective endocarditis, aorta replacement, valved conduit, aortic root abscess.*

Conflict of Interests

The authors declare no conflict of interests

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IE — infectious endocarditis, TTE — transthoracic echocardiography, TEE — transesophageal echocardiography

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Introduction

In true and dissecting ascending aortic aneurysms, a complex reconstructive intervention is indicated: simultaneous ascending aorta and valve replacement using a valved conduit. A conduit is a vascular prosthesis with a pre-sewn mechanical or biological valve. Coronary arteries are cut off during the intervention and then implanted into the sewn vascular prosthesis. According to the literature data, from 1982 to 2002, the incidence of thoracic aortic aneurysms increased twofold [1]. In this regard, an increase in the number of patients requiring surgical treatment for ascending aortic aneurysms can be expected.

Like other carriers of artificial valves, patients who undergo such an operation are at risk for infectious endocarditis (IE). The incidence of IE is not showing a downward trend. The development of IE in patients with a history of ascending aorta replacement with a valved conduit has its own characteristics. Abscesses of the aortic root with tissue destruction, fistulas, mediastinitis with fistulas on the anterior chest wall, and vegetations on the inner wall of the conduit are described [2, 3]. Repeated replacement represents a significant risk, and the use of cryopreserved allografts is the method of choice for repeated surgery [2, 4]. The diagnosis of para-prosthetic changes is often complicated. Knowing the characteristics of the IE course in this group of patients can shorten the path to diagnosis and initiation of adequate treatment and in some cases will allow to avoid repeated intervention.

We observed 6 patients — carriers of valved conduit, who developed delayed IE after ascending aorta replacement. Diagnostic difficulties were observed in each case.

Case report

Case 1

A 53 year-old male patient Ye. In 2009, the Bentall — de Bono procedure of supracoronary replacement of the ascending aorta and the arch was performed for dissecting aortic aneurysm [5]. The patient has hypertension, gout. In May 2014, the patient was admitted to the Department of Pulmonology with fever up to 40 °C. Pneumonia was not confirmed, but on antibiotic therapy, the body temperature returned to normal, and he was discharged. Two weeks later, body temperature rose to 38 °C and progressive fatigue increased. On treatment, body temperature returned to normal. The patient was discharged, but at home he again suffered febrile fever, hypotension, and tachycardia. Hospitalized. The condition was regarded as serious. There were no rales in the lungs, cardiac murmurs. Complete blood count: hemoglobin — 99 g/l, WBC — 5.6×10^9, RBC — 3.09×10^{12}. ESR 33 mm/h. e 4%, n 4% b 1% s 56%, l 29%, m 5%. Urinalysis: protein 1 g/l, epithelium 4–5–6, white blood cells 8–10, red blood cells 2–3 per HPF. Ionic blood composition: urea 5.2 μmol/l, creatinine 142 μmol/l. GFR 48 ml/min. CRP 19.16 mg/l. ECG: left axis deviation, significant myocardial metabolic abnormalities. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were repeatedly performed due to suspected prosthetic valve endocarditis: there were no additional formations on the prosthesis, its function was not impaired, and the ejection fraction was normal. CT of the chest: emphysema, bronchiectasis. CT of the brain: focal lesions in the left hemisphere of the brain and cerebellum. Ultrasound examination: hepatosplenomegaly, hypoplasia of the left kidney. For a long time, the diagnosis remained unclear. Diagnostic search included screening for tuberculosis, syphilis, HIV infection, opportunistic infections, cancer, systemic inflammatory diseases. There was an attempt to explain the fever with bronchiectasis or another disorder. The diagnosis of IE was rejected due to the absence of changes on the prosthesis. In July (almost two months after the onset of fever), blood culture revealed S. aureus. On August 15 (almost three months after the onset of fever), TEE revealed abnormalities: the free edge of the lower wall of the prosthesis and its excessive mobility were visualized, blood flow appeared between the wall of the prosthesis and the aortic wall. The lower wall of the vascular prosthesis was thickened due to additional overlays. There were no additional formations on the valve flaps.

Clinical diagnosis: delayed prosthetic valve infectious endocarditis, acute, with damage to

the aorto-vascular anastomosis, S. aureus bacteriologically. Partial separation of the conduit. Brain embolism.

Condition after supracoronary replacement of the ascending aorta and the arch with the vascular prosthesis ATS medical 29 of July 2, 2009, for De Bakey type 1 dissecting aortic aneurysm with compression of the left renal artery.

Vancomycin was prescribed. From the next day, body temperature returned to normal and did not rise in the future. Vancomycin treatment continued for 28 days. Complete blood count and CRP level returned to normal. Due to moderate dysfunction of the prosthesis, it was decided to abstain from repeated replacement. The patient was discharged in satisfactory condition; echocardiography and cardiac surgeon's follow-up were recommended.

Case 2

A 19-year-old female patient K. The patient had congenital heart disease (bicuspid aortic valve, aortic valve stenosis, ascending aortic aneurysm, coarctation of the aorta, hypoplasia of the ostium of the right coronary artery, patent ductus arteriosus and abnormality of brachiocephalic arteries). In 2014, the Bentall — de Bono procedure of ascending aorta replacement with a valved conduit with reimplantation of the ostia of coronary arteries, aortic isthmus plasty, and ligation of patent ductus arteriosus was performed. Deterioration occurred on July 10, 2016, after a long stay on the beach and eating mushrooms and fat sour cream: dizziness, nausea, headache, and vomiting appeared. The patient and the doctor at the place of residence associated this deterioration with overheating and dietary errors. On July 13, weakness in the limbs, double vision, blurred speech and lethargy appeared. The patient was admitted to the Department of Neurology (ICU). Objectively: right-sided hemiparesis, oculomotor disorders. Brain MRI: multiple foci of ischemia. Echocardiography: no prosthesis dysfunction and additional formations were detected. Fever persisted from the moment of admission. The patient received levofloxacin. After blood culture was obtained (S. aureus), vancomycin was prescribed with improvement in the form of body temperature normalization. On August 26, abnormalities were revealed via TEE. Along the perimeter of the aortic fibrous ring, an anechogenic fluid space of up to 1.9 cm in height was visualized — an abscess cavity. Doppler ultrasound revealed blood flow in the cavity of the abscess. A defect in the connection of the conduit with the fibrous ring, the blood flow through it into the abscess cavity, and shunt from the abscess cavity to the right atrium were visualized. Along the walls of the conduit in the ascending section, a hypoechoic space was located. Conclusion. Signs of an abscess of the aortic fibrous ring with a partial detachment of the aortic conduit and drainage into the paraaortic tissue and into the cavity of the right atrium.

Clinical diagnosis: delayed prosthetic valve infectious endocarditis, acute, with damage to the prosthesis of the aortic valve and aorta, tricuspid valve, S. aureus bacteriologically. Abscess of the area of the fibrous ring of the aortic valve with drainage into the paraaortic tissues and into the cavity of the right atrium, partial detachment of the aortic conduit. False aneurysm of the ascending aorta. Complication. Brain embolism, secondary meningoencephalitis, intracerebral hemorrhage of the right frontal lobe. Right hemiparesis. Oculomotor disorders. Secondary post-congestive atrophy of the right optic nerve.

Condition after the Bentall — de Bono procedure of the ascending aorta and arch replacement with valved conduit Carbomedics 21mm-AR, No. S1014 478-B, with reimplantation of the coronary artery ostia, aortic isthmus plasty, and ligation of patent ductus arteriosus (September 24, 2014).

Operated on September 1, 2016. Paraprosthetic phlegmon with partial melting of the right coronary artery was detected. The cavity of the left ventricle is connected with a false aortic aneurysm; prosthetic detachment by 40% of the diameter of the circle, para-prosthesis to right atrium fistula. The Bentall — de Bono procedure for repeated replacement of the ascending aorta with a valved conduit MedInge ADM 21mm, No. 90972, with reimplantation of the ostium of the left coronary artery, suturing of the para-prosthesis to right atrium fistula, removal of vegetation from the

cavity of the right atrium and tissue treatment with an antiseptic solution was performed.

The postoperative period was complicated by pneumonia, septic shock, multiple organ failure, rhythm and conduction disorders. Despite long-term treatment, death occurred.

Pathological Diagnosis:
Principal diagnosis. I 33.0. Delayed prosthetic valve infectious endocarditis, acute, with damage to the prosthesis of the aortic valve and aorta, tricuspid valve. Focal productive myocarditis. Abscess of the fibrous ring of the aortic valve with drainage into the paraaortic fatty tissue, cavity of the right atrium, partial detachment of the aortic conduit, moderate tricuspid valve regurgitation. Complication of the underlying disease. Multifocal brain damage: secondary meningoencephalitis, intracerebral hemorrhage of the right frontal lobe.

Complications of the postoperative period. Right focal and confluent suppurative pneumonia (Kl. Pneumonia 10^8, Ps. Aeruginosa 10^8 were isolated bacteriologically from lung tissue). Severe dystrophic changes in the liver, kidneys, myocardium. Focal necronephrosis.

Condition after surgical replacement of the ascending aorta and the arch with a valved conduit for congenital heart disease, aortic aneurysm. Concomitant disease. Abnormality of brachiocephalic vessels: aneurysm of the proximal subclavian artery. Megacolon.

Case 3

A 55-year-old male patient P. On July 1, 2014, the Bentall — de Bono procedure for replacement of the ascending aorta with a valved conduit with reimplantation of the coronary artery ostium for true aortic aneurysm and bicuspid aortic valve, removal of blood clots from bifurcation. Aggravation on August 17, 2016: rise in body temperature to 39 °C with chills. Antibacterial treatment was initiated. Echocardiography (September 7): moderate hypertrophy of left ventricle walls, the function of the prosthesis is not impaired, additional formations are not visualized. Blood culture (September 7): S. aureus, sensitive to cephalosporins, carbapenems, was isolated. TEE (September 9): in the area of the fibrous ring along the perimeter of the conduit, heterogeneous echogenicity with the presence of anechogenic inclusions is visualized, Doppler ultrasound revealed moderate blood flow. Conclusion. Signs of an abscess of the area of attachment of the conduit to the fibrous ring. ECG: first-degree AV block, complete right bundle branch block. TEE (October 10): an increase in the abscess cavity, partial detachment of the prosthesis from the fibrous ring in the area of aortic-mitral contact with drainage of blood into para-aortic tissues, according to Doppler US, the abscess is completely stained with color.

Clinical diagnosis: delayed prosthetic valve infectious endocarditis, acute, with damage to the prosthesis of the aortic valve and aorta, S. aureus bacteriologically. Abscess of the area of attachment of the conduit to the fibrous ring. Partial detachment of the prosthesis from the fibrous ring in the area of aortic-mitral contact with drainage of blood into para-aortic tissues. Condition after the Bentall — de Bono procedure for replacement of ascending aorta with valved conduit Carbomedics 27 mm-AR, No. S10384178-B, with reimplantation of the coronary artery ostium (July 1, 2014) for ascending aortic aneurysm and bicuspid aortic valve. First-degree AV block, complete right bundle branch block.

Antibacterial therapy was carried out for 8 weeks. During therapy, body temperature returned to normal and did not rise anymore, blood and urine tests were normal, signs of prosthetic dysfunction did not progress, peripheral blood circulation was not affected. It was decided not to perform the surgery.

This case demonstrates the low ability of TTE in the early diagnosis of aortic root abscesses in carriers of conduits and the need for TEE performance with the first suspicion of an infection in this area.

Case 4

A 30-year-old patient P. History of ascending aorta replacement with a valved conduit for ascending

aortic aneurysm (visceral manifestation of psoriatic arthritis) and dissecting aortic aneurysm in 2013. Deterioration on September 23, 2018, when nausea, vomiting, diarrhea, mental disorders, psychomotor agitation appeared. Acute poisoning, intestinal infection was assumed. He was admitted to the central district hospital, from where he was transferred to the regional hospital. The condition was serious. Heart rate was 125 beats per minute. BP was 100/60 mm Hg. No rales during auscultation. TTE revealed no dysfunction of the prosthesis, additional formations. Complete blood count: hemoglobin 180 g/l, red blood cells 5.91×10^{12}, white blood cells 15.7×10^{9} e 5% n 22% s 59% l 9% m 5%. ESR 1 mm/h. Urinalysis: protein 1.32 g/l, white blood cells — high, red blood cells — high, hyaline casts 4–5–6, bacteria — high. Biochemical analysis: total protein 56 g/l, urea 14.3 mmol/l, creatinine 238 mmol/l, AST 308 U/l, ALT U/l, creatine kinase 7,283 U/l. Contrast-enhanced CT of the brain with densitometry: in the right hemisphere in the parietal lobe there is a zone of low density of irregular shape with clear contours measuring 26.5 × 27 × 38 mm, in the central part there is an area of increased density 16 × 22 × 9 mm, in the occipital lobe there is a section of reduced density measuring 13 × 28 × 27 mm, in the left hemisphere in the occipital lobe there is a zone of reduced density measuring 32 × 28 × 21 mm; in this zone vessels and a section of increased density measuring 16 × 10 × 7 mm were traced. During contrasting in areas of hemorrhagic impregnation, the accumulation of contrast was determined. Brain abnormalities are regarded as multiple cardioembolic infarctions of both hemispheres with secondary parenchymal hemorrhagic impregnation and the formation of intracerebral hemorrhages. Blood culture: S. aureus. TEE (October 4): along the perimeter of the fibrous ring, semicircular heterogeneous echogenicity with anechoic inclusions up to 8 mm in width is determined (aortic root abscess). Color Doppler imaging determines blood flow in the zone of conduit detachment from the fibrous ring, drainage of the abscess into the right chambers, regurgitation in the area of valve leaflet closure to the level of the left ventricle outflow tract (Figures 1, 2).

Clinical diagnosis: delayed prosthetic valve infectious endocarditis, acute, with damage to the aortic root, valved conduit, tricuspid valve, S. aureus bacteriologically. Abscess of the aortic root, drainage of the abscess into the right chambers. Conduit detachment. Tricuspid valve regurgitation. Bilateral polysegmental destructive pneumonia. Pleuritis. Cardioembolic infarctions of both hemispheres of the brain. Multiple infarctions of the spleen and both kidneys. Nephritis.

Condition after the Bentall — de Bono procedure for replacement of ascending aorta with valved conduit Carbomedics No. 25/28 SN S 1086553-B,

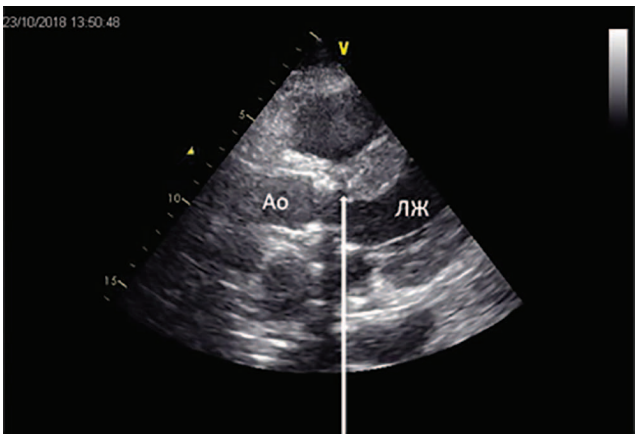

Figure 1. *Transesophageal echocardiography of patient P. LV – left ventricle. Ao – aorta. The arrow shows the zone of conduit detachment from the fibrous ring of the aorta*

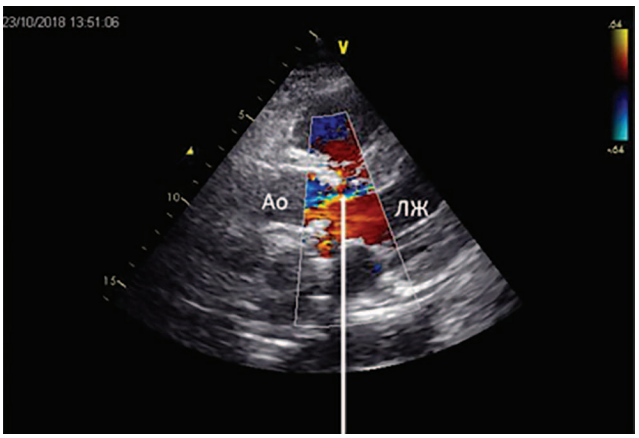

Figure 2. *Transesophageal Doppler echocardiography of patient P. LV – left ventricle. Ao – aorta. Color Doppler imaging determines blood flow in the zone of conduit detachment from the fibrous ring (arrow).*

with reimplantation of the coronary artery ostia (July 11, 2013) for ascending aortic aneurysm. Complications: multiple brain embolism with secondary parenchymal hemorrhagic impregnation and the formation of intracerebral hemorrhages of small volume.

Surgery was performed. About 500 ml of serous exudate were detected in both pleural cavities. The fibrous ring of the aortic valve was represented by an abscess with suppurative discharge. Five U-shaped sutures hold the aortic valve prosthesis (Figure 3).

An abscess cavity and a valved conduit at a distance of 5 cm were removed. There were no blood clots, vegetations, or elements that interfere the movement of the prosthesis (Figure 4).

The prosthesis fully retained its functionality. The cavity of the left ventricle and the rest of the prosthesis were treated with a 1.5% solution of hydrogen peroxide and a solution of betadine. Repeated replacement of the aortic valve and the ascending aorta with a valved conduit MedInzh 23/26 mm SN 102282 was performed. Before the implantation, ostia of the right and left coronary arteries were interconnected by an 8-mm vascular prosthesis according to the Cabrol procedure. The distal section of the vascular prosthesis was sewn into the remaining prosthesis. A vascular prosthesis of 8 mm was implanted in a valved conduit. Cabrol

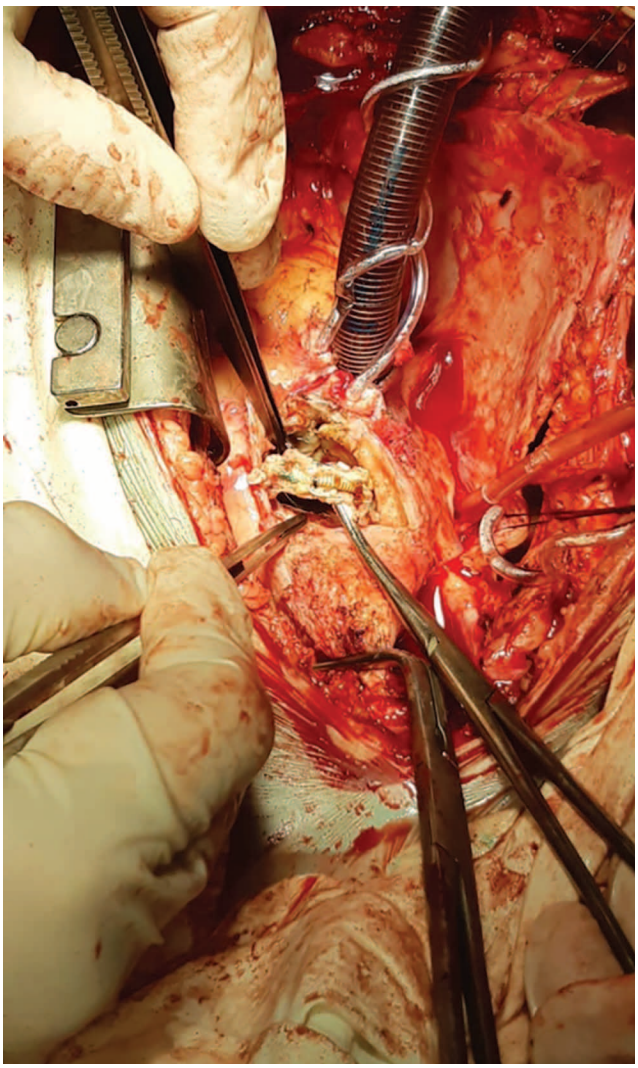

Figure 3. *Stage of operation – prosthesis removal. Prosthesis is impregnated with creamy pus. Freely removed. The area of fixation of the prosthesis is preserved only for 1/4 of the cuff circumference*

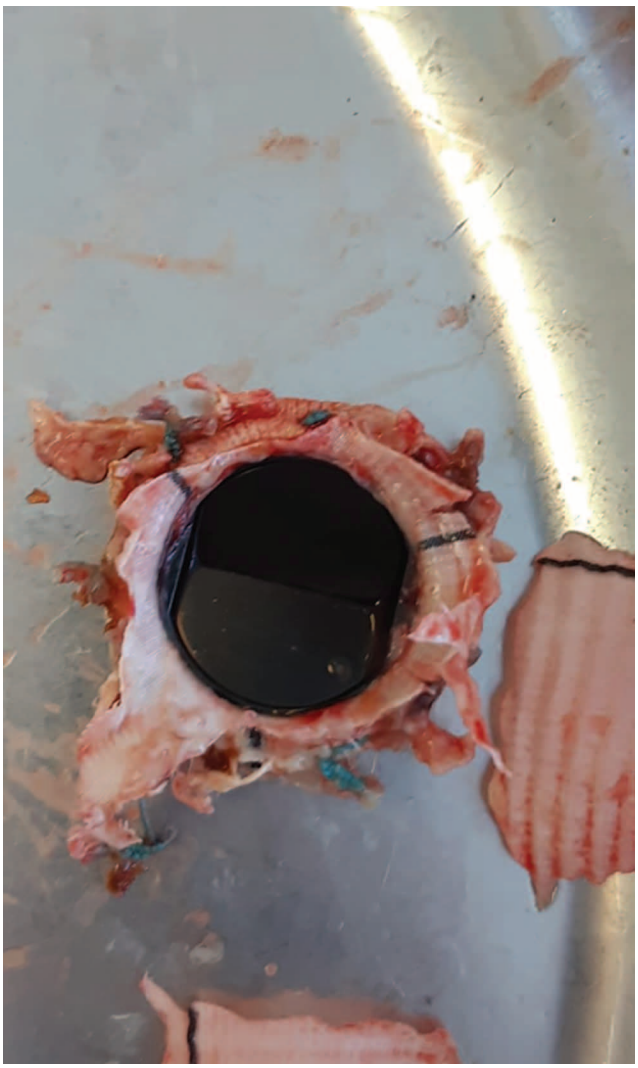

Figure 4. *Extracted prosthesis. There are no blood clots, vegetations or elements that interfere the movement of the prosthesis. The prosthesis fully retained its functionality*

shunt into the right atrium was performed using a patch of PTFE and 4.0 suture.

The postoperative period was complicated by mediastinitis, sepsis, septic shock, multiple organ failure. During treatment with reserve antibiotics, febrile fever persisted. It was decided to perform resternotomy for mediastinal drainage. When transferring the patient for transportation to the operating room, ventricular fibrillation occurred, three 270-J defibrillator discharges restored cardiac activity. The dose of inotropic support was increased, syndromic therapy, drainage of the pericardial cavity were performed. In connection with the progression of renal failure, prolonged renal replacement therapy with citrate anticoagulation was performed on the Prismaflex device. Repeatedly: rotation of antibiotic therapy, taking into account blood culture results. Hemodynamic disorders gradually increased, requiring an increase in doses of inotropic agents. On November 6, 2018, percutaneous tracheostomy was performed. The condition gradually worsened, resistant hypotension and saturation decrease were observed. Intensive treatment for a month and a half had no effect.

Pathological Diagnosis:
Principal diagnosis. I 33.0. Infectious endocarditis of the aortic valve prosthesis, the tricuspid valve, delayed, acute, S. aureus, Kl. pneumonia bacteriologically. Abscess of the aortic root, drainage of the abscess into the right chambers. Conduit detachment. Anterior suppurative mediastinitis. Fibrinous pericarditis. Bilateral focal and confluent suppurative pneumonia with abscessing in S9–S10 of the left lung (Klebsiella pneumoniae 10^7 was isolated from the lung). Multiple infarctions of the kidneys and spleen with organization. Anemia (Hb-75 g/l). Productive myocarditis. Glomerulitis.

Complications of the underlying disease. Multiple cardioembolic infarctions of both hemispheres of the brain with secondary parenchymal hemorrhagic impregnation and the formation of intracerebral hemorrhages of small volume. Severe dystrophic changes in the liver, kidneys, myocardium. Focal necronephrosis (serum urea — 25.8 mmol/l).

Condition after the Bentall — de Bono procedure for replacement of the ascending aorta with valved conduit Carbomedics No. 25/28 SN S 1086553-B, with reimplantation of the coronary artery ostia (July 11, 2013) for ascending aorta aneurysm.

Case 5

A 22-year-old patient B. Four years ago, he underwent ascending aorta replacement for aneurysm associated with congenital aortic defect. He became acutely ill on April 16, 2017, for no apparent reason, with body temperature rising to 38 °C with chills. He took antipyretics, without effect. On admission, the condition was serious. Hemorrhagic rash on the skin. BP was 100/70 mm Hg. Heart rate was 94 beats per minute. Breathing was vesicular, no rales. Rhythmic tones. No murmurs. Complete blood count: hemoglobin 141 g/l, white blood cells 10.1×10^9/l, red blood cells 4.3×10^{12}/l, platelets 81×10^9/l, ESR 20 mm/h, n 10% s 76% l 12% m 2%. Urinalysis: protein 0.66 g/l, leukocytes 1–3, red blood cells 6–8 per HPF. TTE revealed no vegetations, no prosthesis dysfunction. TEE (April 21, after 5 days from the onset of the fever): no abnormalities were detected. Based on the following signs: a foreign body in the heart, fever with high temperature, immune disorders (hemorrhagic rash, proteinuria, hematuria), and taking into account personal experience, despite the absence of Echo abnormalities, infectious endocarditis was diagnosed. Vancomycin therapy was initiated. There was no effect from antibiotic therapy. Further, blood culture revealed S. aureus, sensitive to benzylpenicillin and cephalosporins. The treatment was switched to benzylpenicillin. On benzylpenicillin, a clinical effect was noted — body temperature returned to normal, appetite appeared, skin rash disappeared, lab test results improved. TEE showed an increase in the volume of echo positive tissues in the aortic fibrous ring area; no other changes were noted. Antibacterial therapy was carried out for four weeks, after which the patient was discharged in satisfactory condition.

Clinical diagnosis: delayed prosthetic valve infectious endocarditis, acute, with damage to the aortic root, S. aureus bacteriologically. The Bentall procedure for replacement of the ascending aorta

with a valved conduit Carbomedics 25 mm, S\N S 1108497-B, with reimplantation of the coronary artery ostia for aneurysm of the ascending aorta and congenital aortic defect (November 12, 2013). Hemorrhagic vasculitis. Glomerulitis.

This case demonstrates the potential of timely drug treatment for managing the infection without surgical intervention.

Case 6

A 58-year-old patient A. In 2013, ascending aorta replacement with a valved conduit for aortic aneurysm was performed. On September 28, 2018, fever with body temperature of up to 38 °C and pain in the right lumbar region appeared. The patient was admitted to the hospital. On antibiotic therapy, episodes of fever with body temperature of up to 39.5 °C occurred. On October 7, 2018 TTE was performed: enlargement of both atria, hypertrophy of the left ventricle walls. No zones of hypokinesis were revealed; myocardial contractility was satisfactory. In the projection of the aortic valve and the ascending aorta, a valved conduit was visualized. Transaortic gradient was 14 mm Hg. There was no prosthesis dysfunction. Additional formations on the prosthesis were not located.

On October 16, changes were detected via TEE: on the half of the fibrous ring perimeter of the aortic valve, an abscess measuring 1.0 × 2.0 cm in height is visualized with heterogeneous contents and liquid inclusions. No blood flow in the abscess cavity was revealed. Antibacterial treatment was continued. On November 22, 2018, negative changes were revealed via TEE: aortic root abscess enlargement (Figure 5).

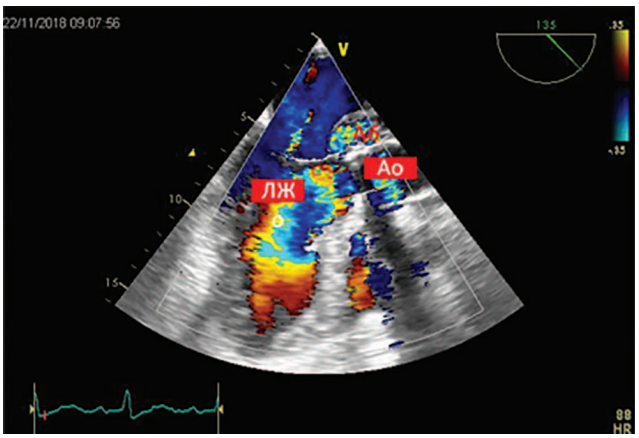

Figure 5. *Transesophageal Doppler echocardiography of patient A. LV – left ventricle. Ao – aorta. Ab – aortic root abscess. There is blood flow in the abscess cavity (stained with color)*

The abscess cavity is anechogenic, additional hyperechoic thin parietal structures (fibrin and vegetation overlays) are visualized in the cavity, height of the abscess cavity is 2.2 cm, spreads to 2/3 of the aortic valve fibrous ring and up to 5.0 cm along the ascending aorta. Intensive blood flow is recorded in the abscess cavity; there is minimal shunt to the left atrium. Doppler US revealed no significant aortic regurgitation, mitral regurgitation was negligible. Conclusion. Abscess of the aortic root with signs of incomplete detachment of the conduit and signs of drainage into the left atrium. S. epidermidis was isolated bacteriologically from the blood.

Clinical diagnosis: delayed prosthetic valve infectious endocarditis, acute, with damage to the aortic root, valved conduit, S. epidermidis bacteriologically. Abscess of the aortic root. Condition after the Bentall — de Bono procedure for replacement of the aortic valve and ascending aorta with valved conduit Carbomedics 25/58 No. S 1065975-B, with reimplantation of the coronary artery ostia (February 21, 2013).

Surgery was performed on November 29. Findings: valve detachment from the fibrous ring. The fibrous ring of the aortic valve is represented by an abscess with suppurative discharge. Seven U-shaped sutures hold the prosthesis. There is a cavity between the prosthesis and the fibrous ring. The Cabrol procedure for replacement of the aortic valve and the ascending aorta with a valved conduit with reimplantation of the coronary artery ostia and the Cabrol shunt were performed (surgery lasted 9 h 55 min). On December 11, 2018, a Vitatron E60DR pacemaker with ELBI 221C-53 / 211C-58 passive fixation electrodes was implanted.

The course of the postoperative period was complicated by multiple organ failure with the gradual relief of all symptoms on long-term treatment. Discharged in satisfactory condition.

Discussion

Statistical data on the incidence of IE after the ascending aorta replacement are scarce. Few reports available in the literature allow us to conclude that prosthetic valve IE in people after such intervention is relatively rare. Malashenkov A. I. et al. (2009), summarizing the long-term results of aorta replacement with a xenopericardial conduit containing a mechanical valve, noted the development of IE, which caused death, in three out of 121 patients [6]. In the group of 3,200 patients with proven IE, studied by Ramos A. et al. (2016), 27 patients were carriers of valved conduits [7]. According to Monsefi N. et al. (2014), IE occurred with a frequency of 0.3% within a period of up to 5 years after the surgery, and with a frequency of 3% after more than 5 years [8]. We did not encounter patients with IE after ascending aorta replacement until 2014, although such interventions have been performed for more than a quarter of a century in our center. Perhaps the appearance of these cases is associated with an increase in the volume of ascending aortic aneurysm surgery. However, the widespread increase in the number of interventions for ascending aortic aneurysms makes IE relevant. Of our patients, two fell ill with IE two years after the intervention, one in 4 years and three in 5 years.

Endocarditis in patients with a history of ascending aorta replacement has its own characteristics. There are reports of frequent damage to extravalve structures, which we also observed. Ramos A. et al. (2016) found paravalvular abscesses in 62.5% of IE cases in this group [7]. Colleagues from the A. N. Bakulev National Medical Research Center of Cardiovascular Surgery observed abscesses of the aortic root with tissue destruction and fistula formation, mediastinitis with fistulas on the anterior chest wall [2–4]. An infection normally does not extend to a vascular graft [7].

In our patients, the pathological process was manifested by the development of an abscess of the aortic root, paraprosthetic phlegmon, abscess burst in the right ventricle, left atrium, prosthesis detachment from the aortic ring. In one case, mediastinitis developed. In all the cases that we encountered, there were no vegetations on the valves and the prosthesis ring. The absence of vegetation, which is one of the "big" criteria of IE, determined diagnostic challenges. Severe paravalvular aneurysms can be visualized via TTE [9], but TEE is preferable for early diagnosis. In all cases, it was TEE that allowed us to visualize changes in the aortic root. Cardiac MRI can also be used to diagnose aortic root aneurysms [9].

Undoubtedly, personal experience and an idea of where the process is likely to occur, is of importance. The diagnosis of our first patient presented the biggest challenge. The time to the establishment of diagnosis was reduced from 2.5 months to 11 days as experience accumulated.

Conclusion

Fever may be the reason for the patient to visit the therapist, general practitioner, infectious disease specialist, or rheumatologist. For doctors of these specialties, awareness of the clinical signs of IE in patients with aortic conduit is as important as for a cardiologist and cardiac surgeon. Knowing the characteristics of IE in this group of patients will speed up diagnosis and improve treatment outcomes. Fever in carriers of a valved conduit should be a reason to immediately suspect IE. Considering such symptoms as the presence of a foreign body in the heart, high fever in the absence of obvious reasons, inflammatory changes in the blood, changes in the urine, the appearance of foci in the internal organs and brain that are suspicious facilitates the diagnosis. It is of great importance that, in carriers of aortic conduits, infection can lead to an abscess of the aortic root, which is difficult to visualize via TTE. In patients with a history of the ascending aorta replacement with a valved conduit, echocardiography is indicated at the slightest suspicion of IE. In patients without clear alternative reasons for fever, IE should be suspected and treatment should be performed even in the absence of convincing echocardiographic signs of IE. Changes in echocardiography may appear later, when drug treatment becomes ineffective and surgery becomes risky. Multiple repetition of blood culture is advisable. Early diagnosis increases the patient's chances for recovery. In our group, three out of six patients

received successful drug treatment and did not require surgical treatment.

Contribution of Authors

N. A. Morova — the contribution of the author to the development of the concept and design, the role of the author in collecting data, writing the manuscript, the role of the author in the final statement, consent to be responsible for all stages of the work.

V. N. Tsekhanovich — the role of the author in collecting data and verifying critical intellectual content, the role of the author in the final statement for publication.

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INFECTIOUS COMPLICATIONS AS PREDICTORS OF ADVERSE OUTCOME IN A PATIENT WITH SYSTEMIC LUPUS ERYTHEMATOSUS (CLINICAL CASE)

Abstract

Systemic lupus erythematosus is a systemic autoimmune disease. Over the past decades, great success has been achieved in its treatment. However, mortality in systemic lupus erythematosus is still high. An adverse outcome may occur because of kidney damage, damage of the nervous system, severe hematological disorders, etc. The factor of unfavorable prognosis is infectious complications.

The article presents a prospective clinical observation of a fatal case of severe course of systemic lupus erythematosus. The patient was treated in the rheumatology department of the State Regional Clinical Hospital in Saratov from 2007 to 2014.

The presence of high disease activity, multiple system disorders — polyarthritis, lupus nephritis, hepatitis, leukopenia, and recurrent necrotizing cutaneous vasculitis required the administration of high doses of immunosuppressive drugs.

The progressive course of the disease, resistance to hormonal therapy, the rapid development of infectious complications made the prognosis for the patient's life extremely unfavorable. Persistent autoimmune leukopenia was the background condition for the development of complications.

We used combined therapy — the oral administration of high doses of glucocorticoids together with intravenous injections (pulse therapy), broad-spectrum antibacterial drugs, intravenous immunoglobulin, drugs that improve tissue trophy and microcirculation. It was possible to decrease the disease activity, and also to restore the functional activity of the patient, to maintain low disease activity for 3 years, to prolong the life of a young patient by 8 years. The adverse combination of high activity of systemic lupus erythematosus with recurrent soft tissue infections caused difficulties for the therapy. Administration of adequate doses of cytostatic and biological agents were impossible due to leukopenia and secondary infection, which led to the death of the patient.

Key words: *systemic lupus erythematosus, severe course, necrotizing cutaneous vasculitis, leukopenia, treatment of systemic lupus erythematosus, infectious complications*

Conflict of Interests

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ANA — antinuclear antibodies, IVIG — intravenous immunoglobulin, GEB — genetically engineered biologics, GC — glucocorticoids, IC — infectious complications, MP — methylprednisolone, SLE — systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by a loss of tolerance to nuclear antigens, impaired activation of T- and B-lymphocytes with further polyclonal activation of B-lymphocytes that produce antibodies, and the formation of immune complexes that damage various organs and tissues [1]. Over the past decades, great success has been achieved in the treatment of SLE [2]. However, mortality in SLE remains high. According to the literature, the probability of fatalities in SLE is 2–5 times higher than in the general population. One of the factors of poor prognosis is the development of infectious complications (IC) [3].

According to the Rheumatology Department of the Regional Clinical Hospital data (Saratov), among eight patients who died in 2018 in the hospital, three were diagnosed with systemic lupus erythematosus. Two of three patients had a history of infection (one — history of cavernous tuberculosis, and one was diagnosed with sepsis associated with immunosuppression). At the same time, in none of these cases the infection was a direct cause of death. With the recurrent nature of the infection, the prognosis is aggravated.

Previously, we presented a case of combined severe SLE and skin infection [4]. We continued the patient's follow up.

We present the results of a prospective clinical observation of a patient M. Z., born in 1983, who was followed up in the Rheumatology Department of the SHCI "Regional Clinical Hospital" (RCH), Saratov, from 2007 to 2014.

Since February 2007, after acute respiratory infection (ARI), fever (37.7–38.1 °C), swelling of small joints of the hands, feet, redness and itching in the nasal bridge and cheeks after insolation appeared. In April 2007, she was admitted for examination and clarification of the diagnosis in the Rheumatology Department of the SHCI RCH in Saratov. No abnormalities in the cardiovascular, respiratory, digestive, nervous systems were detected. Past medical history was without findings. An objective examination revealed polyarthritis; laboratory tests revealed leukopenia (2.5×10^9/l), an increase in ESR to 43 mm/h, signs of nephritis (microhematuria, proteinuria — 1.2 g/l), glomerular filtration rate was normal (92 ml/min / 1.73 m^2 according to the MDRD formula), and anti-DNA antibodies were detected.

The diagnosis was: SLE, acute onset, moderate activity, nephritis, leukopenia, polyarthritis, photodermatitis. SLE SELENA-SLEDAI activity index amounted to 15 points. The changes of the main clinical and laboratory signs and treatment of the patient are presented in Figure 1.

The patient was treated with oral methylprednisolone (MP) 44 mg/day for a month with further dose reduction, hydroxychloroquine 200 mg/day, calcium supplements, gastroprotectors, antiplatelet agents, and angiotensin converting enzyme inhibitors (ACE inhibitors). In connection with nephritis, program pulse corticosteroid therapy (GC) of 500–1,000 mg was started in a regimen of once per month.

Over the next two years (June 2007 — May 2009), the disease progressed: cutaneous vasculitis, aphthous stomatitis, hepatitis (AST, ALT increase by 3.5–12.5 times), persistent leukopenia ($2.7–3.2 \times 10^9$/l), and moderate proteinuria (0.6–1.8 g/l) appeared. HIV and viral hepatitis were negative. With the SLE progression, SELENA-SLEDAI was 17–31 points.

Despite treatment correction in October 2007 (oral MP dose increase to 52 mg per day, program pulse MP therapy once every 3–4 weeks in combination with plasmapheresis, hepatoprotective agents), the effect was short-term and incomplete. The patient persisted with cutaneous vasculitis, hepatitis, nephritis, and leukopenia.

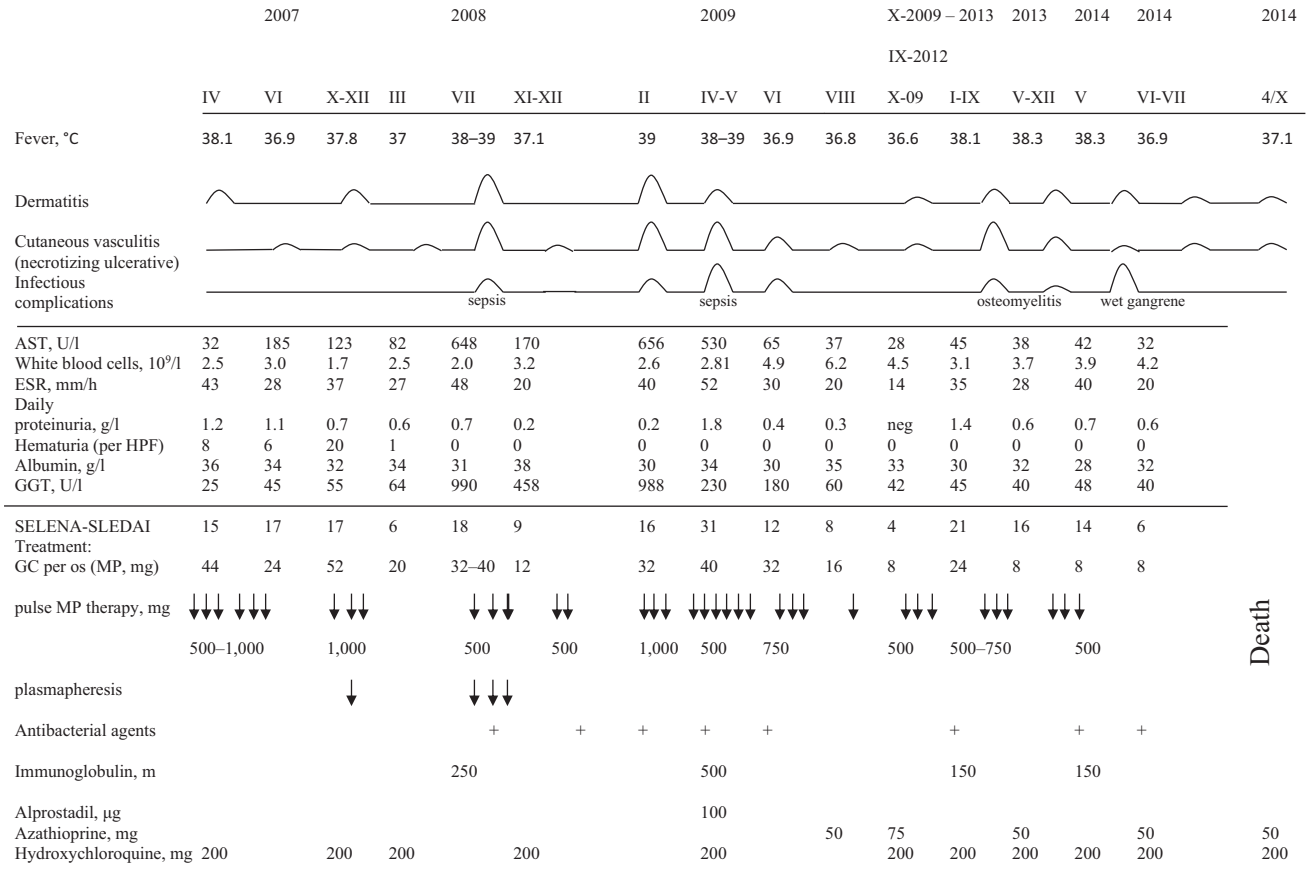

Figure 1. *Changes of the main clinical and laboratory signs and the treatment of patient M.*

Since July 2008, the course of SLE has been aggravated not only due to an increase in the activity of SLE, but also the addition of IC. Over the next 2–3 months, the formation of an abscess of the right buttock, left ankle joint, and suppurative bursitis of the right elbow joint were successively observed. Taking into account recurring suppurative IC, febrile fever with chills, stab shift up to 10%, the appearance of splenomegaly, sepsis was diagnosed in a patient with high SLE activity. Blood culture revealed Staphylococcus aureus. Antibacterial therapy was carried out with generation 3–4 cephalosporins and carbapenems, treatment with high doses of oral GC and pulse corticosteroid therapy continued, and intravenous immunoglobulin (IVIG) was administered, 250 ml in total. Short-term improvement occurred in November — December 2008 (Figure 1).

Despite the ongoing therapy, since February 2009, there has been a progression of aphthous stomatitis, dermatitis, and hepatitis (AST, ALT, GGT increase by 16.5, 6.3 and 20.0 times, respectively). There was a worsening of the signs of cutaneous vasculitis, palmar capillaritis onset, foci of ischemic tissue on the skin of the hands, feet, chest, elbow joints, knee joints with necrosis, spontaneous opening of the left buttock abscess, and persistent fever with body temperature of up to 39 °C with chills. Due to the lack of effect, pulse GC therapy was intensified (1,000 g of No. 1–3 every 3 weeks), high doses of oral MP were still used (32–40 mg per day), and high-dose treatment with 3–4 generation cephalosporins continued.

The patient's condition continued to deteriorate. In April — May 2009, during treatment in the Rheumatology Department of the SHCI RCH, the patient's condition was regarded as extremely serious, which was associated with SLE activity, recurring suppurative infection of the skin and soft tissues, and sepsis. All signs of SLE aggravated: ulcerative stomatitis, digital arteritis, lupus cheilitis, leukopenia and nephritis progressed, retinal vasculitis appeared, high titer of anti-DNA antibodies (175 U/ml) and antinuclear antibody were

detected. Based on the GFR (94 ml/min / 1.73 m^2) in the presence of kidney disease, stage 1 of chronic kidney disease (CKD) was diagnosed. Daily albuminuria was not evaluated.

Markers of antiphospholipid syndrome were negative, and coagulation test was within normal limits. The leading and most dreadful sign of SLE was necrotizing ulcerative vasculitis with areas of deep necrosis of the knee joint, elbow joint, the fingers of the hands, the skin of the feet and chest.

Subsequently, the patient developed dry necrosis of the distal phalanx of the second finger of the left hand. At this period, the diagnosis was as follows:

SLE, acute clinical course, severe activity (SELENA-SLEDAI — 31 points). Photodermatitis. Livedo reticularis. Palmar capillaritis. Generalized cutaneous vasculitis. Necrotizing ulcerative lesion of the skin and mucous membranes. Lupus cheilitis. Digital arteritis with the formation of dry necrosis of the distal phalanx of the second finger of the left hand. Nephritis (stage 1 CKD). Leukopenia, hepatitis, retinal vasculitis. Positive anti-DNA and antinuclear antibodies (ANA). History of polyarthritis.

Sepsis, acute clinical course. April, 2009: left thigh abscess incision and drainage (Figure 2). Infected wound of the right forearm, infiltration of the right buttock.

Complications: drug-induced Cushing's syndrome. Secondary hypertension.

On massive antibacterial therapy (generation 3–4 cephalosporins, carbapenems, fluoroquinolones, antifungal drugs), MP oral administration in a dose of 28–40 mg/day, MP pulse therapy 500–750 mg No. 6 with an interval of 14 days, additional administration of normal human immunoglobulin (500 ml) and 100 IU of anti-Staphylococcal immunoglobulin No. 1, and agents that improve trophy and microcirculation of tissues (IV infusion of pentoxifylline, actovegin, alprostadil), the patient's condition gradually began to improve. The patient's body temperature returned to normal, a decrease in the severity of cutaneous vasculitis, the disappearance of disorders of the retina, a decrease in hepatitis activity, an increase in the level of RBC and WBC were noted. After the formation of the demarcation line, exarticulation of the second finger of the left hand was performed.

As a result of the treatment, there was a sustained improvement in the patient's condition. A dose reduction of oral GC was initiated; taking into account hepatitis and nephritis, baseline therapy with cytostatic agents was prescribed: oral azathioprine 50 mg per day.

Over the next three years (from October 2009 to September 2012), on maintenance immunosuppressive treatment (MP 8 mg/day orally, azathioprine 50–75 mg/day, hydroxychloroquine 200 mg/day), SLE activity was minimal. Moderate dermatitis, a slight increase in the level of immunological markers, and moderate leukopenia were occasionally noted. Nephritis, hepatitis, cutaneous vasculitis and IC did not recur.

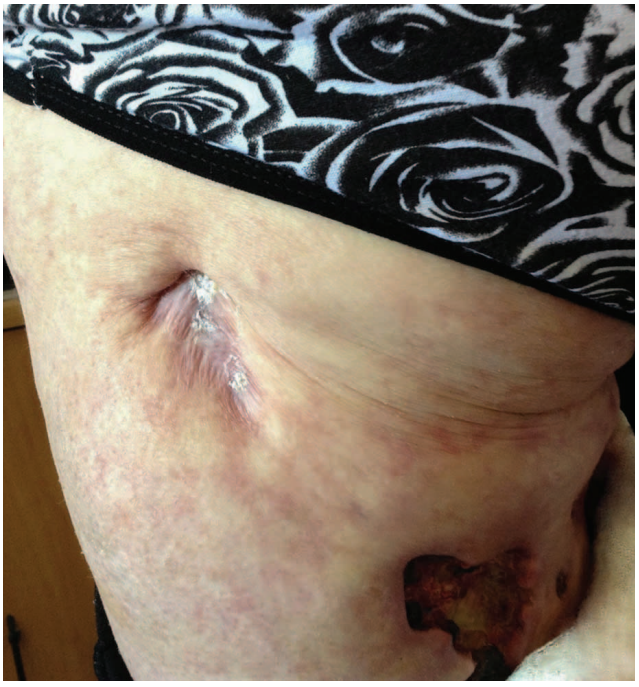

Figure 2. *In the region of the upper third of the left thigh, there is a deep soft tissue ulcer with foci of necrosis, suppurative exudate and partially with bloody crusts. In the area of the lower part of the left buttock, there is a rough scar after spontaneous opening of an abscess of soft tissues*

From January 2013, the patient showed an increase in SLE activity and recurrence of soft tissue infection associated with cutaneous vasculitis. The patient was repeatedly treated in the Rheumatology Department and periodically in the Septic Surgery Department of the SHCI RCH. SLE signs were the same: initially, cutaneous vasculitis, dermatitis, febrile fever, leukopenia, six months later — severe necrotizing ulcerative vasculitis with deep skin ulcers of the buttocks, thighs, mild nephritis (daily proteinuria 1.4 g/l), a significant increase in the level of anti-DNA antibodies.

In January 2013, the course of SLE was complicated by osteomyelitis of the middle and distal phalanges of the third finger of the right hand, which developed after the injury; in May 2014 — the development of wet gangrene of the right hand. Rheumatologists and surgeons carried out the treatment jointly. Oral MP doses were increased again to 24 mg/day, with a further decrease to 12 mg/day, and hydroxychloroquine was continued at a dose 200 mg/day. After the IC management, program therapy with MP 500.0–750.0 mg once every 1–2 months and treatment with small doses of azathioprine (50 mg/day) were performed. During the period of IC development, long-term (for 1.5 months) antibiotic therapy and IVIG was performed, and surgical treatment of wounds was carried out. Given IC, an adequate dose of cytotoxic drugs and GEBs could still not be prescribed. During this period, on treatment, SLE activity decreased slightly. SELENA-SLEDAI ranged from 6 to 11 points during the improvement. Relative stabilization of the patient's condition was noted in June — July 2014, after wet gangrene relief: cutaneous vasculitis, hepatitis did not recur, daily proteinuria, leukopenia did not increase. The patient took 15 mg/day MP orally, plaquenil 200 mg/day. The condition was regarded as satisfactory. The patient was discharged for outpatient treatment.

Subsequently, the patient went off the radar.

Later we managed to find out that in the fall of 2014, after contact with a sick child, the patient had a runny nose, dry cough, sore throat, muscle pain, fever (37.6–38.8 °C) with chills, general weakness, shortness of breath, and hemoptysis. She was hospitalized in her home area. On October 4, 2014, the patient died of progressive respiratory failure. According to the documents, the cause of death was pulmonary embolism. At the same time, taking into account recurrent infections and leukopenia, toxic shock syndrome cannot be ruled out, which caused acute deterioration of the patient's condition and death.

Discussion

The clinical pattern of SLE is very diverse, and the course is often unpredictable. In the presented clinical case, a severe clinical course was not expected considering the SLE onset without severe damage to internal organs and pronounced hematological signs and a good initial response to GC therapy.

A feature of the SLE course in the patient was the development of hepatitis with severe cytolysis syndrome, cholestasis, a moderate decrease in albumin levels, the presence of necrotizing ulcerative cutaneous vasculitis, and persistent leukopenia. Another feature of the clinical course was the development of severe recurrent IC of the skin and soft tissues, osteomyelitis, and wet gangrene of the right hand.

Despite recent advances in rheumatology, treatment of SLE still poses a challenge. High-dose cyclophosphamide therapy shown in cases of severe vasculitis, nephritis, was not possible with this combination of symptoms in the patient.

The standard treatment of severe SLE using high doses of oral GC and pulse therapy, cytostatic agents and IVIG is not always effective. Given the presence of severe hepatitis, cutaneous vasculitis, the ineffectiveness of treatment, it would be advisable to add GEB, anti-B-cell therapy (rituximab), to the treatment. Rituximab, recently used in SLE "off-label", is a promising tool for the treatment of patients, if standard therapy with GCs and cytostatic agents is ineffective [5]. However, recurrent severe IC was a contraindication to its use. It is known that IC aggravate the course of SLE, complicate the management of patients, while comprehensive immunosuppressive therapy and GEB worsen the prognosis [3].

In SLE, congenital and acquired abnormalities of the immune system increase the tendency to develop infectious diseases, including bacterial, viral and other infections [6].

ICs of soft tissues, which were repeatedly noted in the patient, are not characteristic of this disease. According to researchers, in SLE, pneumonia (36.8%), sepsis (18.1%), tuberculosis (13.5%), and urinary tract infections (12.9%) are most common [7].

According to monovariant analysis, significant causes of IC development are nephritis, SLE activity, the severity of leukopenia, high level of anti-DNA antibodies, low complement values, the use of GC in general and in a daily dose of more than 10 mg/day. According to multivariate analysis, statistically significant risk factors for the development of IC are the low complement values, the use of GC in a daily dose of more than 20 mg/day in combination with cyclophosphamide [8].

Apparently, long-term oral administration of GC in medium and high doses, as well as in the form of pulse therapy played a leading role in the development of IC in our patient. Cytotoxic drug use, in particular, azathioprine in adequate doses, was impossible due to recurrent infections, leukopenia and hepatitis. Severe ICs were a contraindication to GEB use.

For the treatment of the patient, the full range of available drugs was used both in high activity of SLE and in IC.

Prescribing treatment with GEB was not discussed due to the lack of clinical recommendations regarding their use in SLE at the time of the development of the disease, economic reasons when the patient's condition had stabilized, and contraindications associated with the recurrence of the infection.

Rheumatologists and surgeons observed the patient jointly, and because of this approach the patient lived for 8 years with such a persistent, treatment-resistant course of the disease. A fatal outcome in this patient could occur at any time, primarily related to a recurrence of IC against a background of a severe autoimmune disease and immunosuppression.

The development of new drugs for the treatment of SLE variants is necessary. The advent of genetically engineered biologics has taken a new step in the treatment of SLE [9]. GEB use for the treatment of severe forms of SLE with bone marrow, lung and kidney damage or in the presence of contraindications to cytostatic agents, and their timely prescription can reduce the time and the dose of hormones used, improve the prognosis of the disease.

Conclusions

Despite the achievements of modern rheumatology, in some cases, SLE remains a serious disease. Infectious complications make it hard to treat SLE, making it impossible to prescribe adequate immunosuppression therapy, including the use of GEB, and they remain one of the leading causes of death in patients with SLE.

Contribution of Authors

Nikitina N.M. — collection of information, literature review, paper design, article correction after reviewing
Alexandrova O.L. — collection of information, literature review, description of the clinical part of the article
Scriabin E.N. — collection of information
Magdeeva N.A. — collecting information, translating resumes into English, posting articles on the journal's website

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PRIMARY CEREBRAL LYMPHOMA. MENTAL DISORDERS AFTER BIOPSY (CASE REPORT)

Abstract

The article reviews the literature on the diagnosis and treatment of primary lymphomas of the central nervous system and describes a case of mental disorder before and after surgery in a patient with lymphoma of the third ventricle. Using an interdisciplinary approach, psychopathological dynamics is analyzed taking into account the structural and functional state of the brain, which allowed to clarify the possible causes of mental disorders and methods of treatment. Acute onset of confusion and headache was associated with disorders of the liquor outflow, due to the localization of the tumor. The reason for the disintegration of consciousness after surgery was brain hypoxia and the instability of connections between cerebral structures associated with it. The peculiarity of the consciousness recovery could be determined by premorbid personal traits.

Key words: *brain lymphoma; third brain ventricle; biopsy; disintegration of consciousness; mental disorders, psychopathology; psychopharmacotherapy*

Conflict of interests

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Lymphoma is a disease of lymphoid and myeloid tissue. Primary lymphoma of the central nervous system (PLCNS) is a rare form of non-Hodgkin lymphomas that occurs in the central nervous system and does not extend beyond it. The incidence of this pathology is 4–7 cases per 1,000,000 people [1–3]. PLCNS was first isolated as a nosological unit more than 80 years ago [4], then it was classified as sarcoma from reticular cells and microglioma. Improvement of diagnostic methods made it possible to finally confirm the lymphoid nature of PLCNS and contributed to an improvement in its detectability [5], which led to an increase in scientific and practical interest in this disease, including in special literature reviews [6, 7].

Localization of PLCNS is very diverse: single or multiple foci in the brain and spinal cord, eyeballs, in the structures of the anterior optic tract [8] and in

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cerebral meninges. Most often, cerebral lymphoma is supratentorial, in 15% of cases — infratentorial. In 60% of cases, the tumor is localized in the paraventricular zone (thalamus, basal ganglia, corpus callosum). Frontal lobes are involved in 20% of cases, temporal lobes — 18%, parietal — 15% and occipital — in 4% of cases [9].

At the initial detection, foci of various sizes are found, most often — clearly visible formations more than 2 cm in diameter. Visualization with contrast enhancement reveals a dense, homogeneous formation in immunocompetent patients and less formed, heterogeneous — in HIV-associated PLCNS. Peritumoral edema and a local mass effect are observed less frequently than with intracerebral neoplasms of a different etiology; in addition, calcifications or hemorrhages in the tumor are not typical for PLCNS [10].

It is believed that in the pathogenesis of lymphoma, both unfavorable external factors and a decrease in the effectiveness of the immune system play a role. Among the possible predisposing factors are the effects of radiation and vinyl chloride gas, tobacco, as well as the use of products containing carcinogens. Immunodeficiency conditions that contribute to the occurrence of lymphomas can be caused by HIV infection, Epstein—Barr virus, the effects of radiation therapy and organ transplantation.

People with intact immunity are more likely to suffer PLCNS after the age of 50 years. Symptomatically, the disease manifests itself fairly quickly. Apparently, in the early stages of its growth, any specific symptoms are absent. Primary symptoms occur when the local volume of the tumor tissue increases due to increased intracranial pressure, eye damage, compression of the surrounding brain tissue or conduction pathways. In general, pathological signs are determined by the volume and localization of intracranial lesions, however, there are some differences in the manifestations of this disease from intracranial tumors of a different genesis. So, in contrast to gliomas, meningiomas, and secondary tumor lesions of the central nervous system, structural epilepsy relatively rarely develops in PLCNS. At the same time, focal neurological symptoms, personality changes, headaches and drowsiness are observed in most cases [11]: focal neurological deficit is detected in 70% of cases of PLCNS, up to 43% of patients show behavioral or neuropsychiatric changes that, due to their nonspecificity, delay diagnosis; in 33% of cases there are signs of increased intracranial pressure (headache, nausea and vomiting), in 14% — epileptic seizures, in 4% — visual impairment.

Cerebral lymphoma often manifests with local symptoms. Cognitive and personality changes, as with other intracerebral tumors, can be observed at different locations (frontal lobes, corpus callosum, periventricular structures). Symptoms due to the mass effect (headache, nausea, vomiting) are less common than with gliomas and metastases.

Psychopathological symptoms are usually observed in combination with focal neurological deficit [12]. Some observations have shown a predominance of mental disorders in PLCNS. Melinz et al. (2002) described a patient with mania [13]. R. Fisher and C. Harper in 1983 [14] observed a case with PLCNS affecting the limbic system, which was manifested by depression and periodic vomiting. In recent work, Chinese colleagues showed that at the early stages, primary lymphoma can affect mood: the main and dominant symptom of the patient was depression, which was treated with drug therapy for a long time before the correct diagnosis was established [15].

Due to the relative rarity of primary cerebral lymphoma, a standard for managing patients with this pathology does not currently exist. To this day, the issue of the possibility and necessity of radiation therapy as a first-line treatment has been under discussion.

Patients with PLCNS sometimes require the administration of drugs to correct neurological disorders. However, caution is needed here: for example, the prophylactic use of antiepileptic drugs should be avoided, not only because of the lack of evidence of the efficacy of such prevention, but also because of the likelihood of increased toxic effects of chemotherapy.

Surgical methods are used mainly for diagnostic purposes through stereotactic biopsy. The radical removal of primary cerebral lymphoma does not increase life expectancy, but can lead to neurological disorders. When the tumor is localized in hard-to-reach places (brain stem), an open biopsy is more preferable. Surgical treatment is used for decompression with a rapid increase in the severity of the condition associated with impaired cerebrospinal fluid outflow and intracranial hypertension

[16]. As recently as 20 years ago, it was believed that the prognosis for primary lymphoma is unfavorable: life expectancy of patients ranged from two months to two years [17]. However, this pessimistic forecast is currently being revised [18].

The use of modern chemotherapy methods has significantly improved treatment outcomes. With the introduction of specific chemotherapy, there was a possibility of long-term complete remissions in more than 50% of cases [19].

The choice of chemotherapeutic drugs is determined by their activity and ability to penetrate the blood—brain barrier. Combined chemoradiotherapy provides higher patient survival [20].

The risk of relapse for patients receiving combination therapy is approximately 50%. Most relapses occur within the first 2 years from the end of the initial therapy, but later relapses are possible — within 5 years after completion of treatment. The risk of relapse is higher (more than 10%) in patients with systemic lymphoma, eye lymphoma and leptomeningitis [21]. The tumor recurs either at the site of the primary focus, or in other parts of the brain. Relapses worsen the prognosis, but with continued treatment, the chances of achieving a second remission are quite high. Some patients remain sensitive to therapy, despite numerous relapses. In patients with previous total head irradiation, there is a high risk of toxic damage to the nervous system. In elderly patients, the risk of developing a progressive neurological syndrome characterized by dementia, ataxia and dysuria is especially high. Typically, symptoms of a neurotoxic damage appear within the first year of treatment.

Despite the relatively large number of studies on the diagnosis and treatment of primary cerebral lymphoma, we have not been able to find any publications devoted to or describing mental disorders in this pathology or as a result of its treatment. It is generally recognized that the primary lymphatic tumor of the brain does not have specific psychopathological features, its symptoms are determined by localization. Without laying claim to participate in the diagnosis of the disease, the psychiatrist is faced with both the psychopathological manifestations of the disease and the consequences of the therapeutic effect. The relative rarity of the disease means every case when "something went wrong" is recorded.

Case Report

Female patient P., 53 years old, right-handed.

A trained doctor, she worked as the head of the laboratory.

She grew and developed in accordance with age; family history was without psychopathological disorders.

According to relatives, she aspired to be a leader and was responsible. At the same time, her husband noted that she "was tyrannical, with a bad temper, she took everything into her own hands, commanded everyone."

According to the discharge record presented, the disease first appeared in the form of strong and prolonged chills. She did not seek medical help. Five days later, dizziness appeared, followed by vomiting. Two days later, relatives noticed lethargy, impaired memory, disorientation in place and time. In the evening, she was admitted by the ambulance team in the intensive care unit of the local hospital. After 18 days, she was transferred to the intensive care unit of the N. N. Burdenko National Medical Research Center of Neurosurgery."

Via spiral computed tomography (SCT) of the brain before surgery (see Fig. 1A), a slight displacement of the middle structures of the brain to the right up to 2 mm was revealed. The lateral ventricles are asymmetric, D > S. The tumor tissue deforms the third ventricle. Convexital subarachnoid spaces of the cerebral hemispheres are not expanded. Basal cisterns are traceable.

An emergency biopsy of a tumor of the third ventricle, microsurgical third ventriculostomy was performed urgently. There were no complications with surgery. Access to the anterior horn of the right lateral ventricle was through interhemispheric access. An obvious presence of an insignificant amount of a tumor was found in the anterior part and in the area of the pituitary funnel; no signs of tumor tissue were observed in the lateral walls of the third ventricle. A small fragment of the tumor was sampled for biopsy. According to the results of an urgent biopsy — lymphoma.

On SCT scan of the brain after the surgery (see Fig. 1B), foci of pathological density in the substance of the brain were not detected. The lateral ventricles are moderately asymmetrically dilated in the projection of the bodies. The median structures

of the brain are not biased. Basal cisterns are traceable, not narrowed. Subarachnoid space is symmetrical, not expanded. Cerebellar sulci are underlined.

On the first day after the surgery the patient experienced steady motor anxiety, with a variety of unfocused movements secondary to depressed consciousness. The management of this condition was carried out without the administration of antipsychotics because of fears of a further decrease in the level of consciousness, but using soft fixation of the limbs to the bed, with inspection every two hours.

On the third day after the surgery, the patient's condition deteriorated sharply: a series of focal seizures occurred, the last one — with secondary generalization. After the first attack, anticonvulsant therapy was prescribed: Relanium 10 mg i.m., Convulex 1,000 mg by i.v. drop infusion, Keppra 2,000 mg i.v. After the third attack, depression of wakefulness level to stupor was noted, tracheal intubation was performed, the patient was placed on mechanical ventilation (MV). During the examination, myoclonic contractions of the facial muscles were observed. Due to MV, the patient did not respond to addressed speech.

In the next two days, the condition did not change: she lay in a given pose with her eyes closed, did not respond to addressed speech, a mimic reaction to pain stimuli appeared. Due to the absence of epileptic seizures and depression of consciousness, anticonvulsant therapy was canceled.

On the 5th day after the surgery the patient experienced an episode of ventricular fibrillation with ineffective blood circulation. Resuscitation (indirect cardiac massage, defibrillation, the introduction of antiarrhythmic drugs) led to the restoration of heart rhythm.

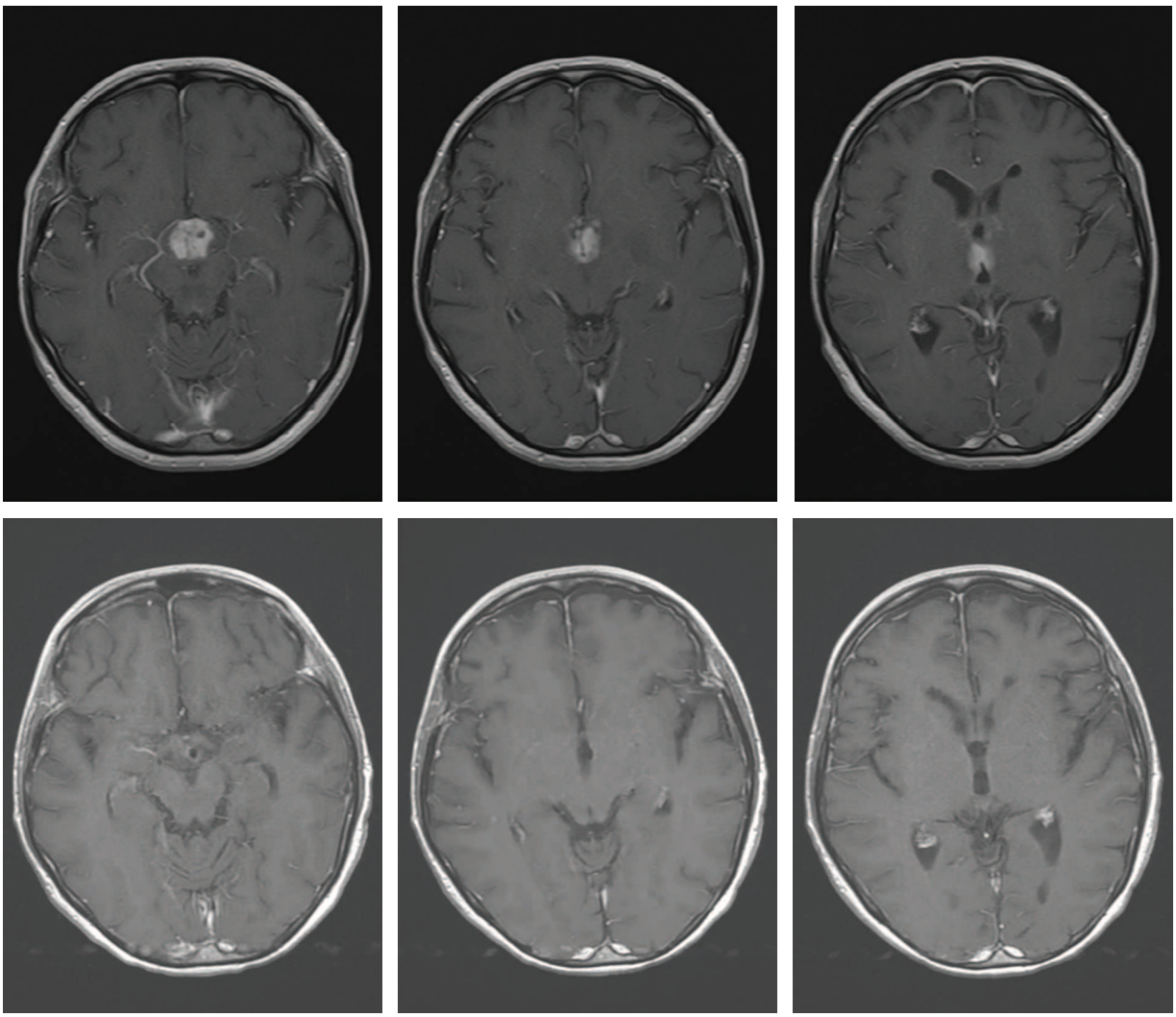

Figure 1. *SCT with contrast enhancement: A – before surgery. Hyperintense tumor in the projection of the third ventricle is visualized; B – after surgery*

Four days later, there was a short episode of atrial fibrillation with tachycardia, severe arterial hypotension up to 40/20.

All this time, the patient's level of activity remained the same (passive posture, periodic flexion in the elbow joints, lack of answers to questions, the presence of only intermittent half-opening of eyes in response to external stimuli).

A day later, pneumothorax was revealed in the patient, and therefore drainage was inserted.

The next day (on the 11th day after the surgery), eyes could spontaneously open.

On the 12th day, she responded, she brought her tongue out of the line of teeth when asked. Two weeks after the surgery, gaze fixation appeared.

Three days later, the recovery process was complicated by purulent tracheobronchitis, which required antibiotic therapy.

Despite the extremely rapid exhaustion associated with severe somatic complications, spontaneous recovery continued: 26 days after the surgery, the patient was awake during the day, watching what was happening, and spontaneous motor activity appeared. She still lay in a given position, but fixed her gaze on the addressed speech, carried out simple instructions, and the range of purposeful movements in the limbs widened. When using the cannula, it turned out that the speech function was preserved. This allowed us to identify fluctuations in the level of consciousness, manifested by episodes of psychomotor anxiety.

On the 31st day of hospitalization, taking into account the histological diagnosis, as well as the patient's condition, a chemotherapy course was started in monotherapy mode: Temozolomide 150 mg/m² — 250 mg orally daily from 1 to 5 days of the 28-day cycle. After the first week of therapy, taking into account the relative aggravation of the patient's condition, deterioration of hematological parameters (decrease in WBC count to 1.45 thousand per ml, neutrophils — to 0.43 thousand in ml, platelets — up to 22 thousand per ml), chemotherapy was interrupted.

The patient was transferred from the intensive care unit to the neurosurgical department 35 days after the surgery. On the same day, she was re-examined by a psychiatrist in connection with excitation: at the time of the examination she did not show complaints, contact was difficult due to the presence of a tracheostomy tube. During the examination, motor anxiety was noted, she tried to pull out the catheter, continued to do so, despite persuasion to stop.

A week later, on the 39th day after the surgery, the psychiatrist noted depleted facial expressions, indifferent facial expression. The patient was lying in bed, not trying to change her posture during the examination. Eye contact was maintained. By this time, steady contact with the patient was established, she turned out to be self-oriented, disoriented in time (she said that "it is now lunch", although the examination was carried out at 11.00 am), was not exactly oriented in the place ("in the Burdenko rehabilitation center"). She correctly listed the food eaten for breakfast. She could not explain the reason for being in the hospital. She stated that she wanted to "get out of this tale." She complained of weakness, expressed a desire to "remove the catheter." She answered questions, after a short pause, generally to the point. She followed simple and complex instructions. She assumed that her grandchildren and children were somewhere here: "They're walking somewhere." According to her husband, earlier relatives actually came to visit her one by one. She said, "The head doctor of the hospital specifically gives sedative medications in order to prevent meeting with relatives, so that there is no desire to communicate with them."

On the 42th after the surgery, according to her husband, she quickly forgot the current information. During the entire examination she was sitting in a chair. She was correctly oriented in time; however, she said she was in the "Semashko hospital." She complained that she had been under treatment for a long time, she was tired, her legs hurt from compression underwear, and she demanded to "let her out". She slept at night. She followed simple instructions. Aminophenylbutyric acid 500 mg/day, quetiapine 12.5 mg were prescribed upon excitation.

By the 46th day after the surgery, the patient was correctly oriented in her own situation and time, but was not always oriented in place. She complained about taking medication, stating that she did not need it, she said "they do it on purpose" in response to the question "why?" "I do not know, my relatives need it." She did not acknowledge that she was ill, she believed that it was invented despite the fact that she was repeatedly told about the disease and the course of treatment. Risperidone 0.5 mg x 2 times a day was prescribed.

An increase in the rehabilitation load (verticalization) led to the collapse of the patient (BP 80/50), after which she was in a state of drowsiness for several hours. After 2 hours, the condition stabilized, an episode of impaired consciousness was completely amnesized.

On the 49th day after the surgery, during examination she was lying in bed, practically without changing her posture, complained that "they inject drugs that are harmful, that are unnecessary," she asked for a break for one day, refused to eat curd, because "it is not crumbly". The daily dose of risperidone was increased to 2 mg.

On the 53rd day after the surgery, according to the daughter and the treating doctor, during the day the patient refused to take food, medicine, threw pills at the staff, relatives, and she could not be persuaded. On examination, she was lying in bed, turned to her interlocutor with a speech addressed to her. She engaged in the conversation calmly. She agreed to talk only in private with the doctor. She asked her relatives to leave the ward. She stated that she refuses pills and injections, as the drugs "harm her". She was not sure that she was being given the drugs that were actually prescribed. She demanded to show her the "doctor's prescription." She correctly named the current year, month, and day. She remembered the name of the hospital with a clue. It was difficult for her to say how many days she had been in the hospital. She was not sure if surgery had been performed. During the examination, her movements were calm. After lengthy persuasion, she agreed to take risperidone. She slept at night.

By the day of discharge (56 days after the surgery), there was a positive trend in the form of normalization of sleep, appetite, restoration of orientation in place and time. She was calm in the bed. She took drugs without persuasion, she did not express ideas of reference.

Follow-up data was obtained at a distance, according to the daughter.

After discharge from the institute, the patient underwent 6 courses of chemotherapy in an altered mode, taking into account the hematotoxicity of the initial regimen: 1) temozolomide 250 mg per day, from 1 to 4 days, and 2) rituximab — 375 mg/m^2 — once every 3 weeks intravenously by drop infusion (slowly). Rehabilitation treatment was carried out twice in a rehabilitation hospital.

After the first course of chemotherapy, motor deficiency significantly regressed: began to walk independently, go out to the street, fully maintain herself, it became possible to leave her at home alone. In the summer, on her own initiative, she worked in the garden near the house. Once, with the help of relatives, she went to work, where she spent several hours surrounded by employees, but she did not show signs of fatigue. In the first months in the evenings there were episodes of confusion, when she did not understand where she was, in the future said episodes stopped. Extreme passivity was noted in relation to measures for further recovery, as well as irritation in response to the offer of various available preoccupations. She spends a lot of time on the computer, makes meaningless purchases on the Internet. She is not interested in the life of loved ones, at the same time requires special attention. She says that she would like to go to work, although she formally understands that she is not able to do it.

Discussion

The observation described in this report is a complex case of the emergence and development of psychopathological symptoms in a patient with small lymphoma, localized in the projection of the third ventricle of the brain. Mental disorders in the form of impaired memory and disorientation debuted sharply, after chills, accompanied by cerebral symptoms (headache, vomiting, lethargy).

Apparently, the disturbances that appeared corresponded to the disintegration of consciousness in the form of increasing confusion. Against this background, minimal neurosurgical intervention was performed (open biopsy of the tumor, microsurgical third ventriculostomy). Despite the sparing nature of the surgery in the early postoperative period, impaired consciousness increased: disintegration gave way to depression. This occurred after a series of convulsive seizures that developed on the third day after the surgery, and then, on the 5th and 7th day, the condition worsened due to episodes of severe heart rhythm disturbance (atrial fibrillation) and pneumothorax diagnosed on the 10th day. Following these somatic disorders, despite emergency resuscitation interventions, an unconscious state lasted at least a week with further transition into depressed consciousness with limited contact.

Only after regression of somatic complications, signs of reintegration of consciousness appear, accompanied at first by episodes of unfocused excitement, and then by confabulations, protest reactions, ideas of reference, fear of poisoning, which regressed only after the prescription of risperidone.

The data of the correspondence follow-up study indicate that against the background of the resumption of chemotherapy with generally restored self-care and the cessation of episodes of confusion, there is a cognitive and emotional-personal decline with a predominant deficit of managerial functions in the form of difficulty in the formation and implementation of an activity program, insufficient criticism of her state and capabilities, blunted affect, impoverishment of interpersonal interactions and behaviors

The disorder of consciousness described in this report corresponds to the classical concept of psychopathology in tumors of the third ventricle [22]. Psychiatrists of the last century in some cases revealed phenomena such as lethargy, aspontaneity, depressed mood, sometimes confusion, disorientation, Korsakov-like syndrome and drowsiness, in others — euphoria, disinhibition, drowsiness, and sometimes motor anxiety. In some patients, a dynamic mosaic of pathological conditions was noted: drowsiness, apathy gave way to euphoria or labile delirious symptoms, impaired orientation and Korsakov-like conditions, fluctuating in intensity.

Of course, the cause of mental disorders in the preoperative period could be the blocked cerebrospinal fluid flow, and in the postoperative period — a violation of connection stability between structures responsible not only for monitoring vital functions, but also for consciousness. Heart rhythm disturbances and pneumothorax could lead to cerebral hypoxia, which seems to be a very likely cause of a significant slowdown in recovery of consciousness and mental activity in general.

It can also be assumed that some of the patient's personal characteristics, including her desire to control what is happening and people from her immediate environment (at home and at work), authoritativeness, and the complex establishment of trust were accentuated as a result of brain damage, transformed into paranoid suspicion, fear of losing control over events. The reduced, but not completely lost criticism of her own condition created the need for a person whom she could trust. Such a "confidant", if one follows the patient's logic and affiliation to medicine, could only be the doctor with whom she was more frank than with relatives, and only after a conversation with whom she agreed to receive psychotropic therapy.

The successful use of risperidone in this observation confirms the advisability of recommending the use of atypical antipsychotics in post-coma psychotic states, unlike typical ones that are safer for the process of reintegration of consciousness [23].

The effect of chemotherapy on the mental state in the above observation was ambiguous: if during the first attempt to conduct it, along with hematotoxicity, there was a slight increase in psychopathological symptoms, then, when it was planned, after discharge, on the contrary, the mental state improved, episodes of confused consciousness disappeared, self-service was restored.

Conclusions

1. Primary lymphoma of the brain is a relatively rare form of cerebral pathology, requiring special attention of doctors of various specialties, including psychiatrists.

2. Localization of primary lymphoma in the deep regions of the brain involves a quick change of severe psychopathological phenomena with a disturbance of consciousness, which, probably, are not subject to standard methods of symptomatic treatment, but require individual selection of psychopharmacotherapy and psychotherapeutic effects, aimed, in particular, at agreeing to comply with medical recommendations.

3. Against the background of chemotherapy in patients with primary cerebral lymphoma, both deterioration (probably due to intoxication) and improvement (following tumor regression) of mental state and social adaptation can occur.

Contribution of Authors

Ilyaev N.P., Maksakova O.A., Zaitsev O.S. — development of the study concept and design

Ilyaev N.P., Bykanov A.E., Troitsky A.P., Poddubsky A.A., Maryashev S.A. — data collection, and analysis of primary clinical data

Ilyaev N.P., Maksakova O.A., Zaitsev O.S. — manuscript writing

Zaitsev O.S., Pitskhelauri D.I., Kobyakov G.L., Troitsky A.A., Ilyaev N.P. — interpretation and critical analysis of the results, formulation of conclusions

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DIAGNOSIS OF GILBERT'S SYNDROME VIA PYROSEQUENCING IN CLINICAL PRACTICE

Abstract

Relevance. Gilbert's syndrome (GS) is a disease with an autosomal recessive type of inheritance caused by either impaired expression of the *UGT1A1* gene, which encodes the isoform of the uridine-5-diphosphate glucuronosyltransferase (UDP-GTA1), or structural modifications of UDP-GTA1. GS is characterized by unconjugated hyperbilirubinemia; drug metabolism disorders and the development of drug-drug interactions. For diagnosis of GS, molecular biological methods are used to determine single nucleotide polymorphisms (SNP). Data on the prevalence of SNP related to GS in Russia are scarce. **Study objective:** Detection of genetic variant (TA)5/6/7/8 (rs8175347) in the UGT1A1 gene (Gilbert's syndrome) by pyrosequencing in outpatient practice. **Material and methods:** 200 outpatients were examined. Of whom: men — 107 (53.5 %), women — 93 (46.5 %) aged 15 to 86 years; patients from 30 years and older formed the majority — 175 (87.5 %). Detection of the genetic variant (TA)5/6/7/8 (rs8175347) in the UGT1A1 gene (GS) was carried out by pyrosequencing using the PyroMark AmpliSens® Pyroscreen UGT1A1 genetic analysis system (manufactured by the Federal Budgetary Scientific Institution Central Research Institute of Epidemiology of Rospotrebnadzor, Russia). For comparison, sequencing according to F. Sanger was used. **Results:** Normal (TA)6/(TA)6 genotype was found in 71 (35.5 %) patients, (TA)6/(TA)7 genotype was found in 81 (40.5 %) (heterozygous status) and (TA)7/(TA)7 genotype — in 48 (24 %) (homozygous status). Rare (TA)5/(TA)6, (TA)5/(TA)7, (TA)6/(TA)8 and (TA)7/(TA)8 genotypes were not found. The results of the determination of (TA)6/(TA)7 genotypes in the homo- and heterogeneous status by pyrosequencing and Sanger sequencing were the same in all cases. In 30 out of 48 patients, GS was newly diagnosed, and in half of the cases these patients were persons of the older group. None of them showed an increase in bilirubin level. **Conclusion:** The incidence of GS in outpatients was 24 %. Pyrosequencing allows us to identify various variants of the (TA)5/6/7/8 polymorphism in the homo- and heterozygous status. AmpliSens® Pyroscreen UGT1A1 kit can be used in clinical practice to diagnose GS and to assess side effects of prescribed drugs.

Keywords: *Gilbert's syndrome, hyperbilirubinemia, uridine-5-diphosphate glucuronosyltransferase 1A1 (UDP-GTA1), pyrosequencing*

Conflict of interest

The authors declare no conflict of interests

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ULN — upper limit of normal, NB — unconjugated bilirubin, PCR — polymerase chain reaction, DM 2 — type 2 diabetes mellitus, GS — Gilbert's syndrome, UDP-GT — uridine-5-diphosphate glucuronosyltransferase

Introduction

Gilbert's syndrome (GS) is a bilirubin metabolism disorder with autosomal recessive inheritance, and it is the most common form of functional hyperbilirubinemia, characterized by an elevated level of unconjugated bilirubin (NB) in the absence of chronic liver disease of viral or other etiology, cholestasis, RH incompatibility, and hemolysis.

In 1901, French doctors A. N. Gilbert and P. Lereboullet described moderate persistent hyperbilirubinemia for the first time; the family nature of this disease was noted [1].

The prevalence of GS in the adult population in the world is variable: from 2–5 % [2, 3] to 40 % [4] — in the European population; up to 36 % — in the African population [5]. In children, the incidence of GS is almost 14 % [6]. In Russia, epidemiological studies on the prevalence of GS have not yet been conducted.

GS is much more common in males [2]. It is believed that the predominance of males is associated with the inhibitory effect of testosterone on the enzyme uridine-5-diphosphate glucuronosyltransferase (UDP-GT), which can lead to the formation of more bilirubin [7, 8].

The main physical symptom of pathology, known today as GS, is yellowness of the skin, sclera and mucous membranes. The most common complaints from patients are asthenic and dyspeptic symptoms. GS is normally manifested as a result of emotional overstrain, physical exertion, infectious diseases, starvation/low-calorie diet, taking certain medications [2, 6, 9]. On average, the content of NB is 3–4 times the upper limit of normal (ULN).

In the 2000s, the *UGT* gene was discovered with localization on the 2q37 chromosome, and the mechanism of its work is described. The main gene polymorphism (variant) *UGT1A1* which causes a decrease in the activity of the microsomal enzyme UDP-GT is now known [10].

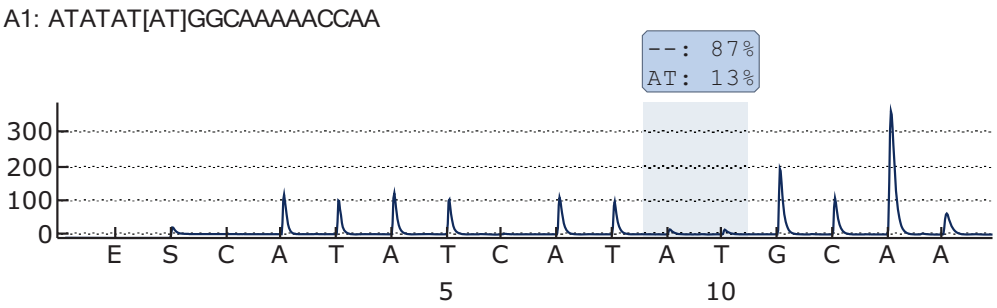
The biochemical and genetic basis of GS has already been established. Its development is due to impaired expression of the *UGT1A1* gene, which encodes the isoform of UDP-GTA1. In this case, a change in the number of *TA* dinucleotide repeats is detected in the promoter region of the gene (**polymorphic marker *rs8175347***). In most people, the promoter region includes six tandem repeats, i. e. sequence **A(TA)6TA(6)** — wild-type allele **1,* which is usually characterized by a normal level of NB. At mutations in the promoter region of the *UGT1A1* gene, insertion of an additional dinucleotide in the TA repeat region of *UGT1A1* occurs and their number increases to 7 repeats (allele **28*). In the population among alleles with altered expression, it is the most frequent; its presence leads to a decrease in the activity of UDP-GTA1. In addition, rarer variants of polymorphisms with 8 (allele **37*) and 5 (allele **36*) repeats associated with low and high levels of enzyme expression, respectively, are described [11]. More than 100 variants have already been described, which differ both in the coding sequence and in the promoter region [12].

The development of GS is also promoted by structural modifications of UDP-GTA1 itself. Its biochemical activity is aimed at converting unconjugated bilirubin into conjugated mono- and diglucuronide, as well as conjugation of small lipophilic molecules (steroids, hormones, neurotransmitters, drugs, carcinogens, and other xenobiotics) into hydrophilic forms for the purpose of their subsequent excretion [13]. Isoforms of UDP-GTA1 are found in various parts of the gastrointestinal tract [14].

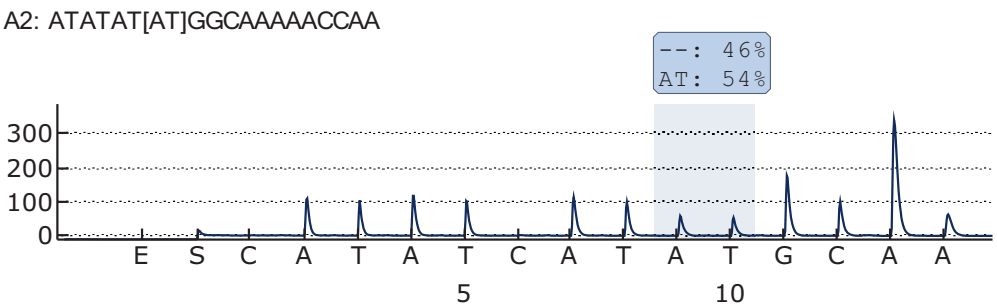
The autosomal recessive type of inheritance in GS provides an opportunity for a "healthy" gene to compensate for abnormalities of the second allelic gene. Heterozygous carriers are a smaller

part of the population, otherwise, with dominate inheritance, the abnormal gene would very quickly spread to the entire population. At the same time, a decrease in the activity of UDP-GTA1 in individuals with the presence of alleles of 7 and 8 (TA) repeats can lead to increased manifestations of GS, as well as to the development of adverse drug reactions and drug-drug interactions in cases when drugs metabolized by this enzyme are used.

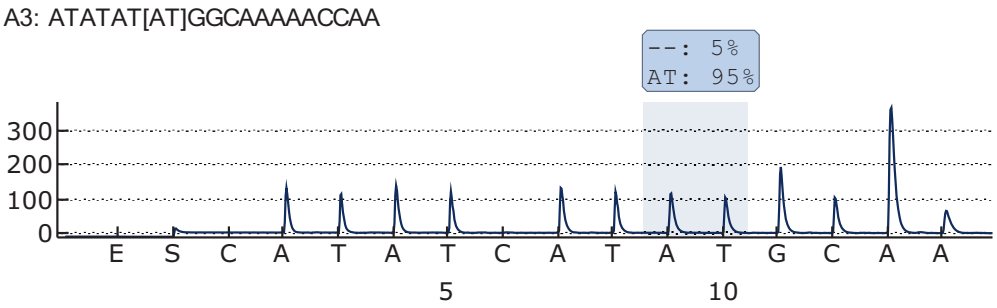
At present, the need for molecular biological methods to confirm GS is becoming increasingly important, which is associated not only with differential diagnosis, but also with the choice of the drug strategy. For the detection of single nucleotide polymorphisms, methods based on polymerase chain reaction (PCR) are used. Until recently, in laboratory practice, the most frequently used method was sequencing according to F. Sanger [13], which is quite complex and time-consuming. Today, the PyroMark genetic analysis system based on the pyrosequencing method [14], which is the detection of pyrophosphate released during DNA synthesis, seems to be much more convenient for the detection of single nucleotide polymorphisms.



a) Sample without mutation, 6/6 genotype.

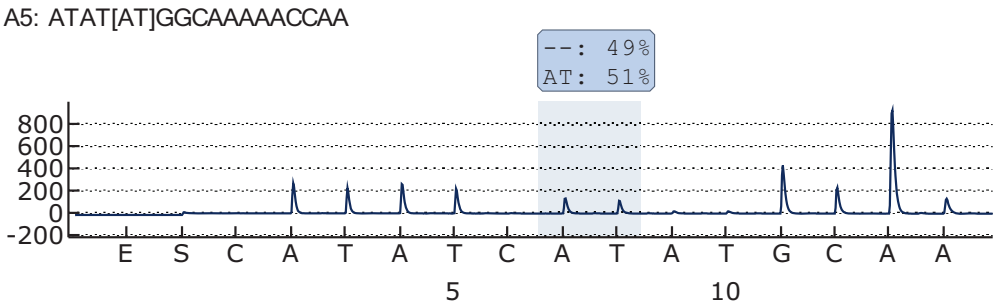


b) Sample with mutation (heterozygote), 6/7 genotype.

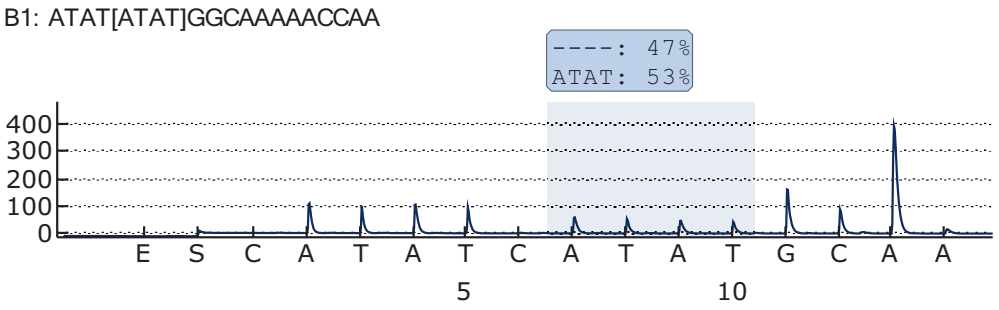


c) Sample with mutation (homozygote), 7/7 genotype.

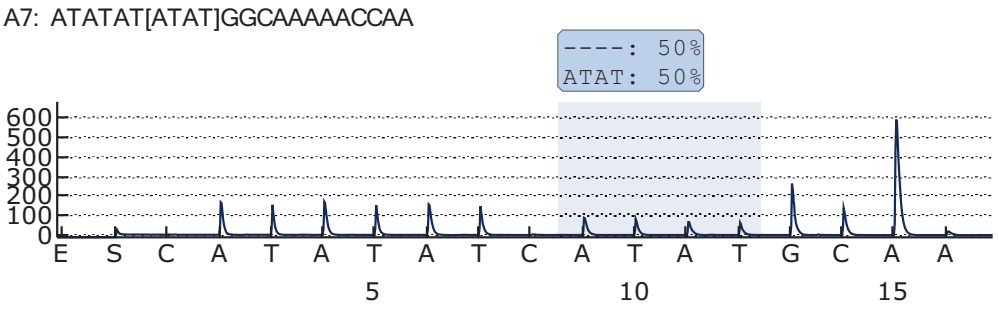
Figure 1. *Example of patterns of the UGT1A1 gene sequencing with detection of the most common genotypes*



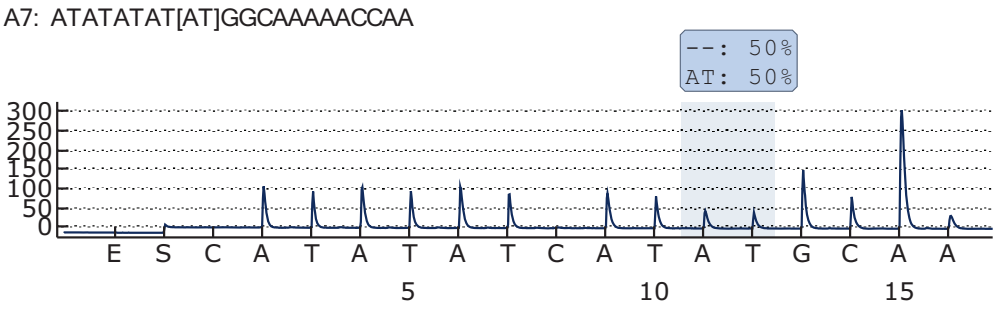
a) Sample with mutation (heterozygote), 5/6 genotype.



b) Sample with mutation (heterozygote), 5/7 genotype.



c) Sample with mutation (heterozygote), 6/8 genotype.



d) Sample with mutation (heterozygote), 7/8 genotype.

Figure 2. *Example of patterns of the UGT1A1 gene sequencing with detection of rare genotypes*

During pyrosequencing synthesis, a complementary DNA strand is constructed and the nucleotide sequence of the studied genetic locus, in particular the UGTA1 gene, is determined by the presence of detectable signals on the pyrosequencing pattern (Figures 1, 2). The use of the pyrosequencing method allows us to identify not only frequent polymorphisms (TA)6/7 in the homo- and heterozygous status, but also to identify rarer alleles (TA)5 and (TA)8 [15].

Based on the foregoing, **the objective of our study** was to detect genetic polymorphism (TA)5/6/7/8 (rs8175347) in the UGT1A1 gene (Gilbert's syndrome) by pyrosequencing in patients in outpatient practice.

This study is one of the stages of clinical trials of a medical device — Reagent kit for the detection of genetic polymorphism (TA)5/6/7/8 (rs8175347) in the UGT1A1 gene by pyrosequencing using the PyroMarkAmpliSens® Pyroscreen UGT1A1-screen genetic analysis system (Genetic Gilbert's syndrome profile), manufactured by the Federal Budgetary Scientific Institution Central Research Institute of Epidemiology of Rospotrebnadzor, Russia (Roszdravnadzor permit No. 1251/2015 dated December 22, 2015).

Material and methods

A single-center open-label cross-sectional clinical trial was conducted at Clinic No. 5 of Federal State Budgetary Healthcare Institution Clinical Hospital No. 85 of FMBA of Russia at the Center for Diagnosis and Treatment of Chronic Viral Hepatitis.

The group of examined patients consisted of 200 patients who came to the outpatient network in February-March 2016 for various reasons (acute and chronic infections, somatic pathology, examination, obtaining certificates, dental care, specialist consultations, vaccine prophylaxis, etc.).

Of that number: there were 107 males (53.5 %) and 93 females (46.5 %). The age of patients ranged from 15 to 86 years; patients from 30 years and older formed the majority — 175 (87.5 %). The group of people aged 15 to 29 years was small and included only 25 (12.5 %) people. All of the examined patients were employees of subordinate institutions of the FMBA of Russia or their relatives, and were observed on an outpatient basis in a medical institution for more than 3 years. In 18 cases, the diagnosis of GS was made earlier on the basis of detection of (TA)7 polymorphism by sequencing according to F. Sanger. A sample of patients was formed by random selection.

The detection of genetic (TA)5/6/7/8 (rs8175347) polymorphism in the UGT1A1 gene (Gilbert's syndrome) was carried out by pyrosequencing using the PyroMark AmpliSens Pyroscreen UGT1A1-screen genetic analysis system (manufactured by the Federal Budgetary Scientific Institution Central Research Institute of Epidemiology of Rospotrebnadzor, Russia; Certificate No. RZN 2016/4339).

In addition, in order to assess the clinical efficacy, safety and quality of the pyrosequencing-based reagent kit for the detection of genetic (TA)5/6/7/8 polymorphism, another molecular biological method of sequencing according to F. Sanger was used for comparison. This method is used in the diagnosis of GS in current laboratory practice and is the "gold standard" for the determination of genetic polymorphisms.

All individuals included in the study signed an informed consent to undergo genetic examination and for the publication of the results.

During the statistical analysis of primary data for quantitative variables, the main sample indicators were calculated. Frequencies of alleles and genotypes of the *rs8175347* marker in the *UGT1A1* gene were calculated as fractions of their total number in the sample.

Results and discussion

The UGT1A1 gene study performed using the pyrosequencing method allowed us to identify the normal (TA)6/(TA)6 genotype in 71 (35.5 %) patients, as well as (TA)6/(TA)7 polymorphism in 81 (40.5 %) (heterozygous status) and (TA)7/(TA) — in 48 (24 %) (homozygous status). Rare (TA)5/(TA)6, (TA)5/(TA)7, (TA)6/(TA)8 and (TA)7/(TA)8 genotypes were not found. It should be emphasized that the results on the detection of (TA)6/(TA)7 in the homo- and heterogeneous status obtained by pyrosequencing and sequencing (according to F. Sanger [13]), in all of the studied samples were comparable in 100 % of cases.

When six additional TA (thymine-adenine) repeats are inserted in the promoter region, the expression

of the gene and the functional activity of the UDP-GTA1 enzyme are reduced, and A(TA)7TAA polymorphism is formed. It must be remembered that only homozygous forms in the presence of seven or more TA repeats in both homologous chromosomes are relevant for the diagnosis of GS. A high frequency (40.5 %) of detection of a heterozygous status — (TA)6/(TA)7 to a greater extent may be of significance when a child is born to heterozygous parents. The development of GS can be at 25 % level in such cases.

The frequency (24 %) of the (TA)7 allele (Table 1) that we detected, which confirms the presence of GS, was significantly higher than expected, which requires further accumulation of information, and epidemiological studies to assess the prevalence of GS in Russia, since data on population genetic characteristics of *UGT1A1* of the inhabitants of our country are extremely few [2, 15–17].

In 18 of 48 patients, the diagnosis of GS was made earlier. Their (TA)7/(TA)7 genotype was also confirmed by pyrosequencing and sequencing. These were 13 men and 5 women, their age was determined in a wide range — from 15 to 57 years (of which 8 patients were under the age of 25 years). It is known that symptoms of GS usually occur during puberty and are very variable, depending on the specific effects of external factors (physical exertion, insolation, taking medications, etc.) [6]. At the same time, the time of initial diagnosis of GS in these patients varied significantly — from 3 years to 54 years.

A peculiarity of the clinical presentation was the absence of an increase in NB at the time of the study in the overwhelming majority of this group. Only in 3 cases there was an increase in the NB level (35 μmol/L, 60 μmol/L, 90 μmol/L, respectively).

Thus, the use of molecular biological methods made it possible to reveal genetic disease (GS) for the first time in 30 of 200 examined patients, in half of the cases mainly in people of the older group. None of them showed an increase in NB level.

A constant asymptomatic course is possible; in these cases the GS can be detected with incidentally detected abnormalities in blood chemistry. Timely diagnosis of Gilbert's syndrome makes it possible to distinguish it from other liver and blood diseases, to limit the intake of drugs with hepatotoxicity on time, to prevent liver crises, to modify the patient's lifestyle until discomfort caused by hyperbilirubinemia disappears completely.

In our opinion, the development of an algorithm for diagnosis of GS in the latent period is promising, which will subsequently allow to minimize the influence of adverse factors, avoid adverse drug reactions, and to improve the quality of life.

Recent studies have shown that the most common diseases in GS are hepatic, esophageal, stomach, duodenum and biliary tract disorders [18]. Apparently, this is due to embryogenetic generality, functional interrelations of the digestive organs, decreased detoxification ability of the liver, as well as a violation of the composition and rheological properties of bile, which is very typical for GS [19].

In our study, GS was diagnosed in 19/48 (39.6 %) examined patients with various diseases of the digestive system, and in 11/19 cases — with chronic viral hepatitis B and C (Table 2).

Patients with GS are at risk for the development of cholelithiasis [20–22]. In a recent molecular genetic study it was found that 70 % of individuals with cholelithiasis are homo- and heterozygotes for GS. In addition, there was a significant increase in the incidence of cholelithiasis in men with GS, which worsens the prognosis of the disease.

On the contrary, data were obtained on the presence of antioxidant properties of NB, which leads to a slowdown in the development of atherosclerosis, microangiopathy in individuals with GS, a decrease in the number of cardiovascular diseases and type 2

Table 1. *Distribution of patients (n = 48) with the (TA)7/(TA)7 genotype by sex and age*

Age, years / number of patients, n							
15–19	**20–29**	**30–39**	**40–49**	**50–59**	**60–69**	**70–79**	**80 and older**
6	6	7	7	7	11	3	1
Sex (m/f)							
5/1	6/0	3/4	6/1	2/5	4/7	2/1	0/1

Table 2. *Distribution of patients (n = 48) with the (TA)7/(TA)7 genotype*

Diagnosis	Number of patients, n
Gilbert's syndrome	18 (37.5 %)
Chronic hepatitis B	6 (12.5 %)
Chronic hepatitis C	5 (10.4 %)
Chronic pancreatitis	3 (6.25 %)
Non-alcoholic fatty liver disease	2 (4.2 %)
Gastroesophageal reflux disease	2 (4.2 %)
Chronic cholecystitis	2 (4.2 %)
Irritable bowel syndrome	1 (2.0 %)
Hypertension	3 (6.25 %)
Coronary artery disease	2 (4.2 %)
Other (acute herpes infection, tonsillitis, acute bronchitis, spinal osteochondrosis)	4 (8.3 %)

diabetes mellitus (DM 2), as well as in general mortality [23]. This phenomenon with an unclear mechanism was also reflected in the results of our work. Only 5 patients out of 48 with diagnosed GS had cardiovascular diseases. In addition, no homozygous (TA)7 polymorphism was diagnosed in any person of the general population with DM 2.

The use of molecular genetic analysis enables to build a strategy for diagnosis, treatment and prevention of the disease on a strictly individual basis [24]. To a certain extent, this also applies to patients with GS. Certainly, the control of risk factors and the exclusion of adverse effects inducing the development of this syndrome will help to maintain a good level of quality of life.

It is known that in patients with GS undesirable effects may be observed when taking a number of drugs due to impaired synthesis of enzymes involved in their metabolism. There is a whole group of drugs whose excretion requires glucuronidation (in particular, salicylates, corticosteroids, sulfonamides, etc.). They compete with bilirubin in the case of deficiency of UDP-GT, and cause or increase jaundice. The appearance of jaundice when testing a new drug is a "red flag" which indicates the feasibility of genetic examination of the patient for GS, since jaundice can be caused not by hepatotoxicity of the drug, but by the manifestation of GS [25, 26]. When an elevated serum NB level is recorded for long period of time, in clinical practice the method of pyrosequencing should be used, which allows to identify various variants of (TA)5/6/7/8 polymorphism (GS) in the homo- and heterozygous status, and to evaluate the efficacy of drugs and the risks of adverse reactions.

Author Contribution

Melnikova L.I. — development of the design of the clinical part of the study, the collection of materials.

Ilchenko L.Yu. — analysis of the data obtained, statistical data processing, writing text.

Dunaeva E.A. — performing pyrosequencing and sequencing in patients' blood samples, interpretation of the results.

Kozitsyna M.V. — project design development

Dribnokhodova O.P. — performing pyrosequencing and sequencing in patients' blood samples, interpretation of the results.

Mironov K.O. — research design, analysis of results, text editing.

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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