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СТРАТЕГИЯ ДЕПРЕСКРАЙБИНГА АНТИГИПЕРТЕНЗИВНЫХ ПРЕПАРАТОВ У ОЧЕНЬ ПОЖИЛЫХ И ОСЛАБЛЕННЫХ ПАЦИЕНТОВ: ОБЗОР СОВРЕМЕННЫХ ДАННЫХ

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Strategy for Depressing Antihypertensive Drugs in Very Elderly and Fragile Patients: A Review of Contemporary Data

Резюме

Антигипертензивные препараты снижают риск инсульта и сердечно-сосудистых заболеваний во всех возрастных группах. Однако, у пожилых и ослабленных пациентов антигипертензивное лечение связано с повышенным риском гипотонии, обморока, острого повреждения почек и гиперкалиемии, у таких пациентов риск нежелательных явлений может превышать пользу от антигипертензивного лечения, и для снижения этого риска предлагается отмена назначения препарата. Концепция депрескрайбинга антигипертензивных препаратов новая и многие практические аспекты требуют дальнейшего изучения в рандомизированных контролируемых исследованиях для определения долгосрочных эффектов, определяющих важные клинические результаты и качество жизни пожилых пациентов. Необходимо признать, что отмена антигипертензивных препаратов является областью с ограниченными доказательствами, с очень небольшим количеством клинических испытаний, оценивающих долгосрочные клинические эффекты. В данном обзоре рассмотрены обоснование и возможные препятствия к внедрению в клиническую практику контролируемой отмены антигипертензивных препаратов у лиц пожилого и старческого возраста. Приведены рекомендации по идентификации пациентов с высоким риском нежелательных явлений и алгоритму депрескрайбинга.

Ключевые слова: *артериальная гипертония, депрескрайбинг, пожилой и старческий возраст*

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Abstract

Article Title. Antihypertensive drugs reduce the risk of stroke and cardiovascular disease in all age groups. However, in elderly and frail patients, antihypertensive treatment is associated with an increased risk of hypotension, syncope, acute kidney injury and hyperkalemia; in these patients, the risk of AEs may outweigh the benefits of antihypertensive treatment, and drug withdrawal is proposed to reduce this risk. The concept of controlled withdrawal of antihypertensive drugs is new and many practical aspects require further study in randomized controlled trials to determine the long-

term effects on important clinical outcomes and quality of life in elderly patients. Given the limited evidence on long-term outcomes of controlled withdrawal of antihypertensive drugs, it must be recognized that withdrawal of antihypertensive drugs is an area of limited evidence, with very few clinical trials assessing long-term clinical effects. This review examines the rationale and potential barriers to the implementation of controlled withdrawal of antihypertensive drugs in the elderly. Recommendations for identifying patients at high risk of adverse events and a deprescribing algorithm are provided

Key words: *arterial hypertension, deprescribing, old and senile age*

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EH — essential hypertension, BP — blood pressure, DS — deprescribing, AE — adverse event, ABPM — ambulatory blood pressure monitoring

Introduction

The elderly patient population is the quickest growing globally; based on 2024 estimates, the number of adults aged 60–79 years will increase from 760 million in 2015 to 1,646 million in 2050, or from 10.4 % to 17.0 % of the global population [1]. It is predicted that the number of adults aged over 80 years will increase from 126.6 million in 2015 to 430.3 million in 2050, or from 1.7 % to 4.4 % of the global population [2]. Approximately 65 % adults aged 60–79 years and 80 % aged over 80 suffer from essential hypertension (EH), defined as blood pressure (BP) ≥140/≥90 mm Hg or administered EH pharmacotherapy; thus, it is predicted that the number of adults aged 60–79 years with EH will increase approximately from 494 million in 2015 to 1.07 billion in 2050, while that among adults aged ≥80 years will increase from 101 million in 2015 to 344 million in 2050. Thus, the number of elderly persons with EH in 2050 will exceed the total number of adults with EH aged 30–79 years globally in 2010 [2].

Hypotensive drugs decreases the risks of the stroke and cardiovascular diseases in all age groups [3]. The hypotensive treatment benefits in elderly, including intensive hypotensive therapy, have been confirmed in large-scale randomized trials (HYVET, SPRINT, STEP); however, it is important to note that subjects with severe senile asthenia were not enrolled into trials [4, 5, 6]. As a result, hypotensive drugs are used in elderly, with over half of those being over 80 years of age [2].

Randomized controlled trials have demonstrated that hypotensive treatment is associated with enhanced risks of hypotension, syncope, acute kidney injury, and hyperkalemia; in general, this risk is very low, affecting 5 to 16 per 10,000 patients treated per year [2]. However, in elderly and fragile patients this risk significantly increases during hypotensive treatment (to 131 per 10,000 patients per year) [4]. This results from altered pharmacokinetic and pharmacodynamic reactions in elderly, as well as polypharmacy that increases the risk of drug-drug interactions, including serious adverse events (AEs). In such patients the risk of AEs may exceed the benefits of hypotensive treatment, while the drug discontinuation is proposed to decrease this risk [5].

This review analyzes the justification and possible obstacles to the implementation of controlled hypotensive drug discontinuation among elderly and senile patients into clinical practice. Recommendations concerning the identification of patients with a high risk of adverse events and the deprescribing (DS) algorithm are provided.

Deprescribing Justification And Challenges

DS (drug discontinuation) presumes the systemic process of controlled discontinuation or reduction of drug administration under the physician's surveillance with the purpose of managing polypharmacy, decreasing drug-associated issues, and improving the patient treatment results [7]. A small, but growing amount of evidence analyzing the feasibility and safety of hypotensive drug discontinuation in elderly patients exists. Although short-term evidence confirm this, the long-term DS benefits and risks are indefinite.

The DS issue importance is underlined by the results of a secondary cross-sectional data analysis from 4 cohort studies among the nursing home dwellers in Australia, China, Japan, and Spain. In total 84.7 % non-fragile, 95.6 % fragile patients, and 90.6 % patients with severe senile asthenia were administered at least 1 drug corresponding to the STOPP criterion, with the most common being hypotensive drugs (from 53.0 % in China to 73.3 % in Australia). The use of hypotensive drugs was

more common among more fit patients, with the prevalence ratio (PR) of 1.15 (95 % CI 1.06–1.25) [8].

The majority of EH clinical guidelines are primarily aimed at the hypotensive treatment initiation and enhancement, with very few guidelines on the discontinuation of hypotensive drugs [9]. The discontinuation of drugs for the treatment of cardiovascular risk factors was included into several clinical guidelines on primary care in diabetes mellitus; however, it is hard to implement [10, 11]. New European EH guidelines consider for the first time the possibility of reducing hypotensive drugs in elderly fragile patients with BP <120 mm Hg or with severe orthostatic hypotension, although they do not propose specific discontinuation strategies due to the lack of data on the optimal process and possible results [9], so it is often difficult for physicians to implement DS into routine practice [12].

DS during EH treatment in elderly is justified based on several studies. The long-term 4-year randomized trial OPTiMISE (n=6,194) has demonstrated that the reduction of drug administration is possible in over half of patients aged over 80 years with SBP below 150 mm Hg without any evidence of harm concerning hospitalization or all-cause mortality. These results have demonstrated that the discontinuation of hypotensive drug may be a safe attempt to decrease polypharmacy in elderly patients with controlled BP [7]. A cohort study that enrolled nursing home dwellers aged over 65 years has demonstrated that DS (reduction of the total number of hypotensive drugs or drug dose decrease by 30 % maintained for at least 2 weeks) is associated with a small cognitive decline, especially in persons with dementia [13]. The MINOR clinical trial that enrolled elderly patients with the symptoms of hypotension has analyzed the possibilities of controlled hypotensive drug discontinuation based on the ABPM (ambulatory blood pressure monitoring) evaluation. A significant decrease in the number of drugs administered (-28.6 %; P <0.001) and a decreased rate of hypotension symptoms was confirmed in the DS group vs. the control group (64.9 % vs. 20 %) (P <0.001) [14]. 17.8 % patients had their hypotensive drugs discontinued within 12 weeks in the observational trial that enrolled 13,096 long-term care facility residents using hypotensive drugs. The cumulative 2-year hospitalization rate with the stroke or myocardial infarction was similar among residents that continued treatment or underwent DS [15].

However, one cannot state that the data obtained were unanimous. For example, in the DANTON study that enrolled 205 subjects randomized into the groups of hypotensive treatment discontinuation (n=101) or continuing regular hypotensive treatment (n=104), serious adverse events (AEs) during the 16-week follow-up were observed in 36 % (treatment discontinuation) and 24 % (regular therapy) patients, with the adjusted hazard ratio of 1.65 [95 % CI 0.98–2.79]. Authors concluded that hypotensive treatment discontinuation was not safe and beneficial enough to recommend it in elderly persons with dementia [16].

Observational studies have showed that 3 out of 4 patients indicated less strict drug therapy do not discontinue cardiovascular or antidiabetic drugs [17], which may lead to the risk of preventable AEs. Several obstacles were detected for the DS of cardiometabolic drugs [18]. Physicians had difficulties with their decisions due to the lack of evidence regarding potential benefits and risks of discontinuing cardiometabolic drugs. Besides, sufficient communicative skills and tools have not been developed to involve elderly and fragile patients into the discussion of potential benefits and risks [19]. Patients possibly evaluate the benefits and harm of hypotensive treatment differently based on their values, preferences, and specific circumstances [20]. Thus, DS should include the mutual decisions made with the patients and their caregivers. The final objective is to optimize patient care by weighing the advantages and drawbacks of continuing treatment individually for each patient.

The Dutch Multicomponent CO-DEPRESCRIBE Program was started in 2024 with the purpose of educating communications concerning the discontinuation of cardiometabolic drugs in elderly patients within the primary care settings. The program aim is to let physicians initiate and arrange comprehensive consultations (accounting for the potential benefits and risks of discontinuing cardiometabolic drugs, accounting for the functional status, attitude, and the patient's drug treatment experience) in patients aged 75 years and over regarding the discontinuation of cardiometabolic drugs [21].

Deprescribing Algorithm

The protocol for hypotensive drug discontinuation based on the CEASE model [22] was proposed in 2015 and includes several steps:

C (**current drugs**) — current drug therapy of the patient and indications to the drug use;

E (elevated risk) — evaluation of the drugs administered for the risk of adverse effects;

A (assess) — assessment of the benefit-risk ratio for each drug;

S (sort and prioritise) — ranking the priorities of drug discontinuation depending on the benefits, harm, discontinuation simplicity, and patient preferences;

E (eliminate) — DS and patient condition monitoring after the drug discontinuation.

The modern algorithm of controlled hypotensive drug discontinuation presumes several key steps, focusing on the patient characteristics and thorough monitoring of BP and adverse effects.

First Step: Identification of Patients with a High Risk of Adverse Events (AEs)

Adverse effects of hypotensive treatment includes hypotension, syncope, falls, fractures, acute kidney injury, and electrolyte disorders [23, 24]. The largest relative association with hypotensive treatment in randomized clinical trials was established by BP decrease (hypotension and syncope). Several conditions and factors may lead to a higher risk of adverse events (Table 1).

Accounting for the complex EH treatment in elderly patients and multiple AE risk factors, it is feasible to evaluate individual risks using special tools that can help in making physician decisions. The STRATIFY-Falls tool to evaluate the risk of hospitalization or death resulting from serious falls within the next 1, 5, 10 years uses the model that includes age, gender, ethnicity, history of falls, stroke and multiple sclerosis, senile asthenia, and drug use [25]. This tool provides the personalized evaluation of the AE risk which may directly correlate with the cardiovascular risk. However, this tool has limitations when used among patients with a very high risk of adverse events, and no threshold has been defined for a risk that can be considered sufficiently high to justify DS.

Second Step: BP Evaluation

Before discontinuing treatment, it is important to confirm that the patient's BP is controlled below the recommended values (<150 mm Hg in patients over 80 years, <140 mm Hg in those aged 75–79 years) [9]. Russian EH guidelines lack statements about such values, while the regular evaluation of the status and AEs is recommended along with an individual approach in patients with impaired self-care abilities and dementia [25].

In elderly patients with EH and syncope, hypotensive drug discontinuation with systolic BP elevation by 12 mm Hg and the absolute 24-hour MBP elevation to 134 mm Hg prevented falls, which, according to authors, was an optimal DS target [26].

Third Step: DS Group Identification

To determine the candidate drugs for discontinuation, one should thoroughly analyze the current drug regimen using STOPP (Screening Tool of Older Person's Prescriptions) / START (Screening Tool to Alert Doctors to Right Treatment) criteria (Version 3, 2023) [27] and Beer's criteria of the American Geriatric Society [28]. STOPP/START criteria were developed as a tool to detect potentially non-recommended or irrationally administered drugs, as well as to detect the so-called "missed" administrations, i.e. those with sufficient efficacy data in a specific disease, but which were not administered earlier due to any cause. An Expert Group (11 experts from 8 European countries) has harmonized the third version that contains already 133 STOPP and 57 START criteria [28]. The number of published studies ¬using STOPP/START criteria is stably growing since 2008, reflecting their practical clinical significance in many countries [17].

STOPP criteria include drug products potentially not recommended for use in patients aged 65 years or older, when the risks of their use overweigh the expected benefits. START criteria include drug products to be considered if they were not administered earlier regardless of contraindications and if the clinical status of the elderly patient is not "end-of-life", i.e. not presuming the focus on palliative pharmacotherapy. It is presumed that

Table 1. *Risk factors for adverse events during antihypertensive treatment in the elderly*

Risk factors for adverse events (AE)	The case for deprescribing
Advanced age	Age-related changes in pharmacokinetics and pharmacodynamics predispose to the development of AE. Polymorbidity and polypharmacy are accompanied by a high risk of drug interactions and AE.
Dementia	The high risk of syncope and falls is exacerbated by sedatives and antipsychotics. Anticholinesterase inhibitors may cause bradycardia, especially with beta blockers.
Chronic kidney disease	Impaired drug excretion leads to an increased risk of adverse events and acute kidney injury.
History of AE	A history of previous AE determines a high risk of future complications.
Low blood pressure	Patients with SBP <120 mmHg are at risk of hypoperfusion and syncope-associated AE/
Severe frailty	High risk of adverse events that may lead to hospitalization, decreased autonomy.
Polypharmacy	Polypharmacy may be justified and even in patients with a high risk of AE or inadequate when the risk of AE exceeds the benefit. It is necessary to establish the priority of prescribing medications.

the physician administering drugs analyzes all specific contraindications to their administration before recommending the pharmacotherapy to an elderly patient.

STOPP/START criteria are grouped by organ systems, including additional sections devoted to DPs that increase the risk of falls in elderly patients, use of analgesics and DPs with antimuscarinic/anticholinergic properties, and immunization.

If the indications to DS of hypotensive drugs have been confirmed, it is recommended to discontinue them in the order reverse to the treatment recommended [9]. Drugs not recommended for elderly persons, i.e. loop diuretics, aldosterone antagonists, centrally acting hypotensive drugs, peripheral vasodilators, alpha-blockers, may be discontinued first. Concerning other drugs, beta-blockers are considered for discontinuation first, followed by thiazides or thiazide-like diuretics, or ACE inhibitors/angiotensin-II receptor blockers, and (finally) calcium channel blockers [24].

Fourth Step: Drug Discontinuation And Thorough Monitoring of Results

The DS process for hypotensive drugs is individual, although a practical algorithm exists [24]:

Doses of the following drug classes are discontinued/reduced (in the order preferred): diuretics (thiazides/thiazide-like, i.e. hydrochlorothiazide, indapamide) is the most common group to be discontinued; calcium channel blockers; ACE inhibitors or angiotensin-II receptor blockers; beta-blockers were discontinued less common due to comorbidities (CAD, AFib).

The DS procedure is selected at the physician's discretion — complete discontinuation of a single drug or its 25–50 % dose reduction.

During the discontinuation process, hypotensive drugs may be discontinued one by one with 4-week intervals.

Regular follow-up is required with the evaluation of AEs associated with the drug discontinuation (uncontrollable EH, palpitations, edema after discontinuing diuretics) along with BP measurement. If systolic BP remains below 150 mm Hg in 12 weeks, deprescribing is considered successful. If BP has become uncontrollable, one should consider the possibility of a repeated administration of a drug discontinued earlier in a lower dose (if possible) or recommend other non-drug approaches to blood pressure reduction.

The OPTIMISE (Optimising Treatment for Mild Systolic Hypertension in the Elderly) trial showed that the total AE rate in the DS and standard treatment groups was similar (12.1 % and 12.5 %, respectively (p=0.92) [7]. The DANTON (Deprescribing and Adverse events in New Users of Two or More Old-age Negative Agents) trial demonstrated that the AE (BP fluctuations, tachycardia, edema) rate in the setting of hypotensive drug DS was 10–15 %. 18–25 % patients required complete or partial resumption of the discontinued drug within 6–12 months after DS [16].

DS studies did not present detailed data on the association of specific AEs and the discontinuation of specific hypotensive drug classes. However, based on the general pharmacology principles, one can define expected AEs during the DS process by the drug classes.

Conclusion

The concept of hypotensive drug DS is new, and many practical issues required further analysis in randomized controlled trials to determine the long-term effects on important clinical results and the quality of life of elderly patients. It should be underscored that hypotensive drug discontinuation is a sphere with limited evidence and very few clinical trials evaluating long-term clinical effects. This review has summarized the current data on benefits and risks of hypotensive drug discontinuation in elderly patients, describing the practical DS algorithm.

Table 2. *Adverse events potentially associated with discontinuation of specific classes of antihypertensive drugs*

Drug classes	Potential adverse events after discontinuation
Diuretics	Increased blood pressure, edema (due to decreased sodium excretion). Hypokalemia (if the diuretic is discontinued in patients with initially low potassium).
Calcium channel blockers	Reflex tachycardia (due to decreased vasodilation). Deterioration of blood pressure control (especially in patients with initially high pulse pressure).
ACE inhibitors/sartans	Increased edema (rare if calcium channel blockers were continued in treatment). Increased creatinine (if there was a decrease in glomerular filtration rate and ACE inhibitors/sartans played a nephroprotective role).
Beta blockers	Tachycardia, increased blood pressure (if indicated — coronary heart disease, atrial fibrillation). Exacerbation of angina (in patients with coronary heart disease). Consider reducing the dose first before completely discontinuing the drug to avoid recurrent adrenergic hypersensitivity.

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КРАТКИЙ ОБЗОР ИСТОРИИ РАЗВИТИЯ ФАРМАКОЛОГИЧЕСКОЙ АНТИГИПЕРТЕНЗИВНОЙ ТЕРАПИИ

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A Brief Overview of The History of The Development of Pharmacological Antihypertensive Therapy

Резюме

На протяжении многих десятилетий сердечно-сосудистые заболевания занимают лидирующую позицию в структуре смертности во всем мире. Имеются данные, что общее число сердечно-сосудистых заболеваний удвоилось за последние 30 лет, а число смертей от них выросло на 65 % за это же время. Вместе с тем увеличивающаяся распространенность артериальной гипертензии как важнейшего фактора риска сердечно-сосудистых заболеваний представляет собой глобальную проблему всемирного здравоохранения. В такой ситуации актуален вопрос антигипертензивной терапии, её качества. Сохраняется потребность в дальнейших исследованиях новых классов антигипертензивных препаратов. В статье кратко обсуждается эволюция взглядов на патогенез артериальной гипертензии, поэтапное внедрение в широкую клиническую практику препаратов, снижающих артериальное давление. Также в статье приведены новые группы препаратов и последние тенденции в лечении артериальной гипертензии.

Ключевые слова: *история медицины, кардиология, гипертоническая болезнь, антигипертензивные препараты*

Конфликт интересов

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

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Abstract

For many decades, cardiovascular diseases have been the leading cause of death worldwide. There is evidence that the total number of cardiovascular diseases has doubled over the past 30 years, and the number of deaths from them has steadily increased by 65 % over the same time. At the same time, the increasing prevalence of arterial hypertension as the most important risk factor for cardiovascular diseases is a global problem for world health. In this situation, the issue of antihypertensive therapy and its quality is relevant. There is still a need for further research into new classes of antihypertensive drugs. The article briefly discusses the evolution of views on the pathogenesis of arterial hypertension, the gradual introduction of drugs that lower blood pressure into widespread clinical practice. The article also presents new groups of drugs and the latest trends in the treatment of arterial hypertension.

Key words: *history of medicine, cardiology, hypertension, antihypertensive drugs*

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EH — essential hypertension, BP — blood pressure, BBs — beta-blockers, CCBs — calcium channel blockers, DBP — diastolic blood pressure, ACEIs — angiotensin-converting enzyme inhibitors, siRNA — small interfering RNA, RAAS — renin-angiotensin-aldosterone system, RH — resistant hypertension, SBP — systolic blood pressure, CVDs — cardiovascular diseases, CHF — chronic heart failure

Introduction

When no blood pressure (BP) measurement devices existed, its elevation was suspected based on indirect signs: cardiomegaly, pulse tension, second cardiac tone accent over the aorta. For the first time BP was measured by an English physician S. Gales in 1733: during the experiment, he determined the height of the blood column in a glass tube inserted into the carotid artery of the horse. The first accurate BP evaluation in a human was arranged invasively by the surgeon Febvre in 1856 [1]. In 1905, the Russian surgeon N.S. Korotkov proposed an auscultation method of BP measurement; this technique has been used globally for over 100 years thanks to its simplicity and comfort.

Such studies have laid a foundation for analyzing pathological BP alterations. Currently we know about a mosaic theory of essential hypertension pathogenesis as a complex of various system effects and BP regulation pathways, which explains a constant search for efficient methods of affecting the maximum number of pathogenetic mechanisms by analyzing and synthesizing new drugs from various groups, dose optimization, and drug combinations. This awareness was not always present: the medical and scientific society has cleared a long way to arrive at the current treatment level. Starting from the 20th century, the development of hypotensive therapy may be analyzed using a time scale illustrating the rate with which new hypotensive agents become available in the clinical practice of modern physicians (**Figure 1**), while changes in pharmacotherapeutic BP lowering strategies with time are presented in **Table 1**.

The concept of normal BP level has also been altered for quite a long time. Currently, a trend to strict BP control prevails. Based on the opinions of American Heart Association and American College of Cardiology, the modern target BP level for adults with confirmed hypertension is SPB <130 mm Hg, DBP <80 mm Hg [2]; however, in 1960s BP was considered elevated when reaching values over 160/110 mm Hg, while the medical society debated whether one should decrease elevated BP, as the latter one was considered an inevitable and, thus, significant component of the body aging process.

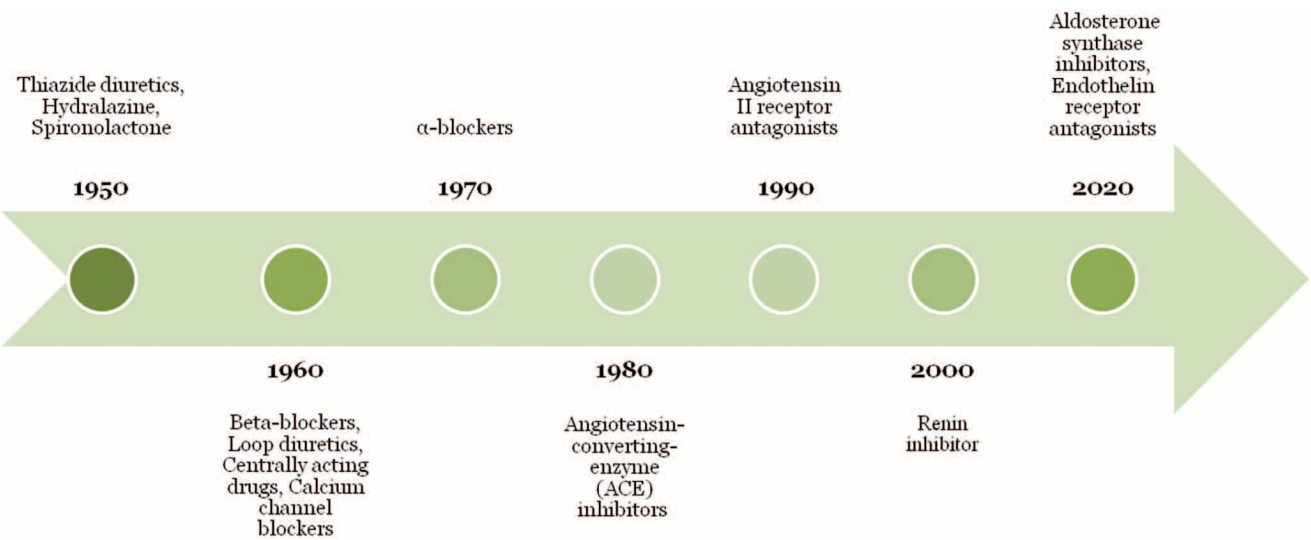

Figure 1. *Chronology of the introduction of different groups of antihypertensive drugs into clinical practice for the first time*

Table 1. Pharmacotherapeutic strategies for the treatment of arterial hypertension in a historical context

Stage	Means	Features
Antiquity and the Middle Ages	Bloodletting, herbal and animal remedies, dietary changes	Low efficiency, health hazard
Beginning of the 20th century	Nitrates, sodium nitroprusside, mercury diuretics, sedatives	Large number of side effects, toxicity, poorly predicted hypotensive effect
Mid 20th century	Ganglionic blockers, α-blockers and centrally acting drugs, acetazolamide, thiazide and loop diuretics, first beta-blockers and calcium channel blockers	The search for more effective and safer means continues; many representatives of these groups have remained relevant to this day
The turn of the 20th-21st century	ACE inhibitors, Angiotensin II receptor antagonists, latest generations of beta-blockers and calcium channel blockers, renin inhibitor	Greater efficacy and safety; significant reduction in mortality from cardiovascular diseases; accumulation of scientific research data
Modernity	Active use of combinations of antihypertensive drugs from different groups	Emphasis on an individual approach to the treatment of high blood pressure, on low doses of drugs used, on the impact on various links in the pathogenesis of hypertension; continued search for means in accordance with scientific discoveries and the development of pharmacology

Pharmacological Agents Used for Decreasing Blood Pressure

Depressive (sedative) drugs

At the beginning of the 20th century, understanding a significant role of sympathetic regulation in the pathogenesis of essential hypertension (EH) led to the search for methods to affect it as one of the treatment principles. Significant attention was paid to the emotional condition of patients with hypertension. The founder of the Russian electrocardiography L.I. Fogelson wrote: "Medications should be used to decrease the nervous system excitability and to decrease the tone of peripheral arteries. Bromides and valerian drugs, luminal act well as general tranquilizers, decreasing the excitability of the autonomous nervous system centers" [3]. In his article "Hypertension (experience of the analysis of its origin)", D.D. Pletnev, one of the teachers of A.L. Myasnikov, stated that "warm "indifferent" baths, bromides, valerian drugs are beneficial" in the treatment of essential hypertension [4]. In his monumental monograph "Essential hypertension", G.F. Lang also underlined the role of luminal in "decreasing the excitability of both autonomous hypothalamic centers and the brain cortex", as well as mentioning the barbituric acid compound in the treatment of essential hypertension with artificial intermittent or continuous sleeping [5].

Drugs based on natural agents

The role of vascular tone as one of the pathogenetic aspects in EH urged to consider those substances that were known for a long time to affect the vascular tone. Thus, plant extracts containing poisonous alkaloids and causing the vascular collapse among other effects, have been known from ancient times. Considering plants as a ready-to-use drug product, one cannot avoid alkaloid-containing drugs, that became the most popular in the middle of the 20th century due to the unsatisfactory prior therapy and significant progress in the chemical industry. Salsoline was a vasodilating agent used in essential hypertension ("early disease with unstable blood pressure"). Salsoline was an isoquinoline derivative, an alkaloid derived from aerial parts of the Asian plant Richter's saltwort. Due to the emergence of more efficient agents, by 1981 the USSR Ministry of Health excluded salsoline and its combinations from the drug product nomenclature. A bright representative of plant-derived alkaloids, reserpine (a sympatholytic agent isolated from Rauwalfia serpentina), was synthesized artificially by R.B. Woodword in 1956 [6]. Reserpine had multiple adverse effects, including angina worsening. A Soviet biochemist V.A. Dadali developed a drug product raunatine based on the same Rauwalfia alkaloids — its sedative effects were less significant than in reserpine, while it was not inferior in hypotensive effects. An opium alkaloid papaverine known for approximately two centuries was also popular in the 20th century as a hypotensive agent, just like another spasmolytic drug bendazole. Up till the present time, bendazole, papaverine and their combination can be found on the pharmaceutical market. These drugs have not been supported with clinical evidence, but are characterized by a large number of adverse effects, including decreased myocardial contractility and cardiac output, delayed cardiac conductivity (even with complete AV-block), and significant autonomous disorders. Ergotamine isolated in 1918 from the mixture of ergot (parasitic fungus) alkaloids can be rightly considered a precursor of alpha-blockers [7].

Diuretics

Pathological effects of fluid excess in EH pathogenesis led to the attempts of using diuretics. Since ancient times, a search of agents to relieve edema continued; based on empiric observations, edema relief also led to BP decrease. The following substances were used in previous centuries with diuretic purposes: mineral mercury compounds; sea onion infusion; rockberry (bear berry) leaves containing an arbutine glycoside with diuretic effects. Thiazide diuretics were created only by the end of 1950s, but they have proven their high efficacy specifically in the treatment of EH. The largest ALLHAT hypotensive treatment trial (42,000 patients) arranged in more than 600 North American hospital for 8 years, starting in 1994, demonstrated a high efficacy of a thiazide-like diuretic chlorthalidone in the prevention of cardiovascular complications, which was not inferior to angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) [8].

Central hypotensive drugs

The effects of neural regulation in the structure of EH pathogenesis often led to the attempts of analyzing the effects of a specific substance by inhibition or mimetic effects on specific receptors, with subsequent BP alteration directly or indirectly. Thus, clonidin, an imidazole derivative (centrally acting drug), was developed in 1960s as a decongestant; however, its hypotensive properties were almost always observed. As a hypotensive drug, clonidine was priorly used for several decades in the USSR and other countries. The adverse sedative effect of clonidine caused by the activation of α2-adrenoceptors located in the locus ceruleus initiated the development of drugs with more selective effects. Currently second-generation selective agonists of imidazole I1 receptors (moxonidine, rilmenidine) are widely available — these don't have adverse effects of clonidine, but rather provide pleiotropic features (decreased insulin resistance, lipid metabolism regulation, neuroprotection, effects on inflammation and cellular proliferation processes, etc.) [9]. The originator of this group, methyldopa, is included into the List of Vital and Essential Drugs (as of 2025), being one of a few agents approved for use in pregnancy.

Beta-blockers

The physiological effects of adrenal gland extracts on the cardiovascular system were first described at the end of the 19th century. Meanwhile, in 1898 John Jacob Abel obtained a crystalline substance from these extracts with the ability to increase BP; he called it epinephrine ("above the kidney") [10]. Several decades of studies enabled to prove the effects of catecholamines on myocardium and to discover adrenoceptors. 60 years later, in 1958, the first beta-blocker (BB) dichloroisoproterenol was synthesized [11], although it was refuted due to significant intrinsic sympathomimetic activity. At the beginning of 1960s, a group of British investigators managed to synthesize propranolol. In 1964, after the publication in The Lancet, propranolol became the first-in-the-world BB to be successfully used in oral and parenteral dosage forms in clinical practice [12]. Practolol was the first cardioselective drug synthesized at the end of 1960s, but it was discontinued due to adverse effects (sclerosing peritonitis, pleurisy, keratoconjunctivitis). It has been noted that as the BB selectivity enhances, its effect concerning beta1-adrenoceptor blockade also increases. Selectivity is a dose-dependent feature, however the rate of adverse effects also increases with the dose. Due to this, decades were spent to search for highly selective BBs. This resulted in the synthesis of latest-generation BBs, including metoprolol, nebivolol, bisoprolol [13]. After the meta-analysis of L. Lindholm et al., BBs have lost the leading roles in EH pharmacotherapy. When comparing the effects of BBs with placebo or no treatment, no differences were observed in the myocardial infarction and mortality rate, while the relative stroke risk decreased twice; thus, BBs are administered only in the presence of additional indications [14].

Calcium channel blockers

In 1959 F. Dengel synthesized a papaverine analogue with negative inotropic and chronotropic effects. The substance was initially called iproveratril, then verapamil [15]. The drug was initially developed as a BB, but subsequently a feature of blocking the calcium ion flux via the slow transmembrane channels was discovered for this substance. In general, CCBs represent a heterogenous group of drug products. They differ in their chemical structure, pharmacokinetics, and pharmacodynamics, features of adverse effects, and contraindications to their use. Several authors call verapamil, nifedipine, and diltiazem first-generation drugs. CCBs have quickly reached stable positions in cardiology. Short-term effects of the first-generation drugs and a wide range of therapeutic plasma levels led to unstable vasodilating effects, variable BP and heart rate. Not all attempts to develop new CCBs were successful. For example, mibefradil, a representative of a new (in 1980s) selective T-type CCB subgroup, had a high hypotensive activity, but was not compatible with more than two dozens drugs metabolized by the P450 cytochrome 2D6 and 3A4 systems. Drugs accumulated in hazardous concentrations due to inhibitory mibefradil effects, causing the abdominal muscle necrosis, acute kidney injury, severe bradycardia [16]. CCBs have additional advantages (metabolic neutrality, anti-atherosclerotic,

anti-thrombotic, anti-ischemic effects, etc.). Currently the latest-generation CCB group includes such dihydropyridine derivatives as amlodipine and lercanidipine, which are successfully used in modern hypotensive therapy in Russia.

Non-standard peripheral vasodilator

Agents causing peripheral vasodilation due to direct relaxation of smooth vascular muscles have been an attractive group for a long time regarding their hypotensive effects. Pinacidil history is worth describing. This drug was not associated with other hypotensive agents used in clinical structures neither by the mechanism of action nor by the structure. Pinacidil belongs to a new (for 1980s) class of drugs called "potassium channel openers", acting via potassium efflux, hyperpolarizing cellular membranes, leading to the decreased intracellular calcium levels and finally to the relaxation of smooth vascular muscles. The problem of pinacidil was in frequent adverse effects resulting from its basic peripheral vasodilating activity, i.e. headache, edema, palpitations, tachycardia. These effects required treatment discontinuation or the addition of drugs from other groups [17].

Renin-angiotensin-aldosterone system blockers

More and more empiric evidence about the role of kidneys in BP regulation had accumulated by the beginning of the 20th century. Physicians attempted to treat elevated BP with macerated kidneys; features of renal and hepatic extracts prepared similarly were compared. Hypotensive effects were not detected in the latter ones [5]. However, additional data indicated that the significant amount of favorable results from the use of renal extracts in hypertension is explained by their pyrogenic effects [18]. Substances with doubtful purity caused inflammatory reactions and fever. In 1942 P. Korkoren et al. neutralized the pressor effects of angiotonin (hypertensin), also known today as angiotensin [19]. In the middle of 1960s S. Ferreira verified the angiotensin-converting enzyme [20]; the development of its inhibitors first led to the emergence of teprotide — a short-acting polypeptide extracted from the poison of the Brazilian snake jararacucu (with a multitude of adverse effects), but in 1977 the first ACEI captopril was synthesized and implemented into clinical practice. 1977 is considered the starting year for successful pharmacological blockade of the renin-angiotensin-aldosterone system (RAAS). In 1980 the therapeutic arsenal was enriched by enalapril — a second-generation drug and a long-acting ACEI. Saralazine was synthesized 2 years before teprotide — that was a peptide, the first representative of the angiotensin II receptor blocker (ARB) class, which development subsequently was much slower than that of ACEIs. Further non-peptide ARBs with the affinity to type 1 receptors started to be widely used in the treatment of EH, chronic heart failure (CHF), and chronic renal disease since the onset of 1990s [21]. In 2002 the arsenal of cardiologists was enriched by a new group with another RAAS-blocking mechanism: FDA approved the first oral direct renin inhibitor — aliskiren. Subsequently this drug circulation was prohibited, including in Russia. The ALTITUDE clinical trial demonstrated that the addition of aliskiren to standard RAAS-blocking therapy in patients with type 2 diabetes mellitus and a high risk of cardiovascular and renal events may be harmful [22]. RAAS blockers have become ubiquitous in clinical practice [23]. Clinical Guidelines "Essential hypertension in adults" (2024) list valsartan + sacubitril (a combination already used in the treatment of CHF) as a new hypotensive drug. This combination of an ARB decreasing RAAS hyperactivation and sacubitril (a neprilysin-blocking enzyme) provides additional BP lowering and may exhibit organoprotective properties, in particular decreased stiffness of major arteries in systolic EH and additional natriuresis [24].

Fixed combinations

Accounting for the multipathogenetic theory of EH pathogenesis, currently combined hypotensive treatment is justified with the possible physiological and pharmacological interactions between drugs from different classes, more intensive BP lowering, and better tolerability, prognosis and survival effects compared to monotherapy. The trend to low-dose combinations has been forming. It should be noted that the first fixed hypotensive drug combinations emerged in the beginning of 1960s. They were represented by various substances, including methyldopa + hydrochlorothiazide; hydrochlorothiazide + potassium-sparing diuretics; reserpine + hydralazine + hydrochlorothiazide (see above).

On the topic importance and pharmacokinetics features

Based on the evaluations of the Global Disease Burden (GBD) 2019 study that included all available data sources on the incidence, prevalence, lethality, mortality, and health hazards for the population of 204 countries and territories within the period from 1990 to 2019, the following statistical conclusions were made. Total cardiovascular disease (CVD) cases almost doubled from 271 million (95 % uncertainty interval [UI]: 257–285 millions) in 1990 to 523 million (95 % UI: 497–550 million)

in 2019, while the number of CVD deaths increased from 12.1 million (95 % UI: 11.4–12.6 million) in 1990, reaching 18.6 million (95 % UI: 17.1–19.7 million) in 2019 [25]. It is evident that the need for new hypotensive drugs is still here. Besides the issues of patient cure and compliance, some pharmacokinetic features are also typical for specific drug groups. For example, angiotensin II may form using pathways omitting the angiotensin-converting enzyme (chymases, CAGE, catepsine G, elastase, tonin), thus leading to pathological processes in organs and tissues that cannot be completely eliminated only by the ACEI administration [26].

Active trends

Lately a large number of variable studies have been devoted to the analysis of significance of small interfering RNA (siRNA). Cardiological markers and new-generation drug products based on siRNA are deemed prospective options. This drug group will be used for parenteral administration once in several months, which can significantly enhance the compliance. Zilebesiran is one of such developed drugs, which represents a siRNA inhibiting the angiotensinogen gene transcription in the liver [27].

New hypotensive drug classes were recently developed and tested among patients with resistant hypertension (RH) to be used after the inefficacy of three or more BP-lowering agents. Spironolactone has been administered recently to resolve RH, as excessive aldosterone synthesis is considered one of the RH mechanisms. Highly selective aldosterone synthase inhibitors (bacdrostat, lorundrostat) represent a new drug class. Some investigators fear that aldosterone synthase is highly similar to the enzyme initiating cortisol synthesis, and aldosterone synthase blockade may be associated with adrenal failure. However, the preclinical use of bacdrostat was associated with decreased aldosterone, but not cortisol levels [28].

An endothelin receptor blocker aprocitentan was authorized in 2024. Just like for aldosterone synthase inhibitors, RH is an indication for its use. Aprocitentan is a variably acting antagonist of both endothelin receptor types (A and B), so the drug affects not only the vascular tone, but also the stimulation of endothelial NO synthesis. Endothelin receptor antagonists are well-known for the successful treatment of pulmonary hypertension, with promising results also shown for essential hypertension [29].

Conclusion

Hypotensive treatment has undergone multiple changes and evolutionary steps, following the paths of understanding the disease pathogenesis, possibilities of effects with decreasing the risks of adverse events, increasing the life expectancy and quality of life. The majority of drug products was discarded due to new discoveries in pathophysiology and pharmacology. Currently studies are active on the management of EH and associated risks, expanding the clinical arsenal and getting closer to the era of the actual personalized medicine.

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НЕАЛКОГОЛЬНАЯ ЖИРОВАЯ БОЛЕЗНЬ ПЕЧЕНИ И ВОЗМОЖНОСТИ ЕЕ ТЕРАПИИ (ОБЗОР)

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Non-Alcoholic Fatty Liver Disease and Possibilities of Its Therapy (Review)

Резюме

НАЖБП является актуальной междисциплинарной проблемой, учитывая ее высокую распространенность во всем мире, а также роль в развитии и прогрессировании кардиометаболических нарушений, онкологических заболеваний. В обзоре проанализированы современные данные, касающиеся эпидемиологии, механизмов развития неалкогольной жировой болезни печени и современных возможностей ее терапии. Проблема НАЖБП хорошо изучена. При этом публикуются новые данные, касающиеся механизмов ее развития, влияния на другие метаболически ассоциированные заболевания. Это доказывает, что необходим дальнейший поиск новых схем лечения таких пациентов, с целью улучшения прогноза и снижения кардиометаболических рисков. Особое внимание в обзоре было уделено возможностям гепатопротективной терапии при стеатозе печени.

Ключевые слова: *неалкогольная жировая болезнь печени, лечение, гепатопротекторы, средиземноморская диета*

Конфликт интересов

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Abstract

NAFLD is an urgent multidisciplinary problem, given its high prevalence worldwide, as well as its role in the development and progression of cardiometabolic disorders and cancer. The review analyzed current data regarding epidemiology, mechanisms of development of non-alcoholic fatty liver disease and current possibilities of its therapy. The problem of NAFLD is well understood. At the same time, new data are published regarding the mechanisms of its development, the impact on other metabolically associated diseases. This proves that a further search for new treatment regimens for such patients is necessary in order to improve the prognosis and reduce cardiometabolic risks. Particular attention in the review was paid to the possibilities of hepatoprotective therapy for hepatic steatosis.

Key words: *non-alcoholic fatty liver disease, treatment, hepatoprotectors, Mediterranean diet*

Conflict of interests

The authors declare no conflict of interests

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NAFLD — non-alcoholic fatty liver disease, MAFLD — metabolic-associated fatty liver disease

Introduction

According to the modern concepts, non-alcoholic fatty liver disease (NAFLD) is an important interdisciplinary problem. Pathogenetically it is often associated with obesity, diabetes mellitus, cardiovascular diseases, and even hepatocellular carcinoma [1, 2].

NAFLD is currently in the lead among all liver diseases [3]. For example, based on the Russian ESSE RF-2 study, fatty liver disorders were detected in 38.5 % males and 26.6 % females [4]. In comparison, it is reported in almost 33 % European citizens, while in Asian countries this parameter does not exceed 18 % [4]. The global prevalence in the general population is somewhat variable, ranging from 6.3 to 33 % [3, 5]. Accounting for the fact that NAFLD verification requires morphological confirmation in the majority of cases, one can propose that these values might be significantly higher.

It is important to underline that fatty liver disease increases the risk of mortality not only from liver diseases (cirrhosis, hepatocellular carcinoma), but also from other associated diseases, i.e. diabetes mellitus, cardiovascular diseases [3].

Despite the prolonged and thorough NAFLD analysis, the current issue of possible drug therapy remains debatable. Studies aimed at searching for optimum treatment protocols of this disease that could lead to the fatty liver regression and cardiometabolic risk decrease are actively ongoing.

Review purpose: analyzing data concerning epidemiology, mechanisms of non-alcoholic fatty liver disease, and its modern treatment options.

Materials and Methods

Russian and foreign publications for the topic analyzed were searched in PubMed, RINC, and eLibrary databases with the use of the following keywords: non-alcoholic fatty liver disease, obesity, cardiovascular risks, treatment, hepatoprotective agents, Mediterranean diet. The information from literature reviews, articles, meta-analyses published within the latest 10 years was analyzed. Information selection criteria: scientific articles in peer-reviewed journals reflecting modern approaches to the NAFLD issue, with specific descriptive statistics. Highly cited articles from leading journals were in priority.

In this review we analyzed the changes in the scientific NAFLD paradigm (etiology, pathogenesis) and also discussed modern approaches to its treatment.

NAFLD Issue and Modern Approach to It

The issue of NAFLD has been analyzed for a long time. In 1849 the Austrian pathologist Carl von Rokitansky detected that the fatty liver dystrophy was directly associated with overweight [6, 7]. Further on, H. Taler (1962) detected hepatic alterations typical for persons abusing alcohol in patients without the toxic component [8]. In 1980 the German scientist Yurgen Ludwig from the Mayo clinic (USA) along with his colleagues formulated the common term "non-alcoholic steatohepatitis" [9]. In 2000 American hepatologists proposed the term "non-alcoholic fatty liver disease". Meanwhile, the Russian physicians started using the latter term only in 2002 [10, 11].

In 2020, a new term "Metabolic-associated fatty liver disease" (MAFLD) was proposed [3, 12]. With the new term scientists underline the association of the fatty liver disease with the metabolic dysfunction; diagnostic criteria were also developed for this diagnosis.

In 2023 the International Expert Group on behalf of the Liver Associations proposed a new nomenclature for the fatty liver disease — Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD). This term presumes hepatic steatosis in combination with at least one cardiometabolic risk factor (obesity, diabetes mellitus, hypertension, dyslipidemia). This terminology has been adopted in the Russian Federation, and it is recommended to use new optimized diagnostic criteria. Nevertheless, medical documents still operate designations adopted in ICD-10 [3].

Currently it is considered that non-alcoholic fatty liver disease is a chronic liver disease associated with

metabolic dysfunction, excessive accumulation of lipids (triglycerides) in the hepatic parenchyma, that leads to multiple complications affecting other organs and systems [2, 3].

Pathogenesis of NAFLD and Associated Conditions

Currently two non-alcoholic fatty liver disease forms are reported — steatosis and steatohepatitis. It was considered earlier that NAFLD always started with steatosis. A "two-hit" concept proposed by Day C.P. and James O.F. was a long-term concept supporting this theory. The researchers explained that the first hit was due to the deposition of enhanced triglyceride amounts in the hepatic parenchyma. The second step was associated with cytokine and toxic liver overload, leading to cellular inflammation [13, 14]. Currently steatosis and steatohepatitis are considered independent NAFLD variants according to the "multiple-hit" theory. The latter explains that the disease develops in genetically predisposed patients under the effects of multiple environmental factors. The "multiple-hit" concept defines the whole multifaceted NAFLD pathogenesis. This presumes insulin resistance, imbalance between adipokines and cytokines, dietary issues, enhanced intestinal permeability, etc. [3, 15, 16].

Impaired insulin sensitivity is one of the key mechanisms promoting fatty liver dystrophy and the metabolic syndrome. This promotes metabolic disorders, leading to the increased production of free fatty acids (FFAs). For example, it is well-known that adipocytes produce about 60 % FFAs. Thus, the association of obesity and NAFLD is made clear [3, 15, 16]. β-oxidation of FFAs is impaired due to their excessive amounts entering the liver. Mitochondrial dysfunction provokes oxidative stress. This leads to decreased synthesis and secretion of low-density lipoproteins, which leads to the imbalance between FFA influx and disposal. This leads to the accumulation of triglycerides in the hepatocyte, which lipolysis again forms FFAs that directly injure hepatocytes [3]. Oxidative stress leads to the formation of reactive oxygen species and activation of lipid peroxidation mechanisms, provoking hepatocyte injury [3, 15, 16].

Intestinal flora also plays a huge role in the development of NAFLD. Impaired microbiome leads to the overuse of protective liver mechanisms, which in turn enhances the production of inflammatory markers (i.e. cytokines). This induces inflammation and fibrosis in the liver parenchyma. Intestinal flora also actively participates in the metabolism of bile acids which mediate the sensitivity of tissues to insulin [3, 17].

As a result of all mechanisms described above, chronic inflammation develops, which leads to the activation of Kupffer cells, stellate and fat-storing cells. They start active collagen production. This leads to hepatitis progression and further fibrosis.

Besides processes in the liver, NAFLD activates the mechanism of development and progression of cardiovascular diseases, chronic kidney disease, with the increased risk of malignancies [18]. Systemic inflammation is key to these conditions. For example, it is well-known that proatherogenic lipoproteins are excessively produced in NAFLD. This leads to enhanced thrombogenesis and vascular injury [3, 18]. Gluconeogenesis and glucose depoing processes are impaired in steatosis, with subsequent decrease in tissue sensitivity to insulin and possible onset of diabetes mellitus. It has also been confirmed that endocrine disorders (gynecomastia, infertility, decreased libido, testicular atrophy) may emerge with the prolonged fatty liver alterations [18].

NAFLD Treatment

The scientists' opinions have changed not only towards NAFLD and mechanisms, but also its treatment. Accounting for the multifaceted etiology and pathogenesis of this disease, the treatment should be complex, safe, and efficient [3].

The whole NAFLD treatment is essentially based on three milestones — physical activity, diet, and drug therapy.

Various groups of drug products and their combinations have been proposed while analyzing the issue of NAFLD. The key fact is that physical activity and diet have always been playing the foremost role in the treatment of liver diseases.

Diet is of utmost importance in NAFLD. Some scientists have considered that quick weight loss is required with the decreased amount of carbohydrates in the diet and consumption of larger fat amounts [19]. Others have proposed the interval diet ("healthy fasting") [19].

In 2016, the European Association of Liver Diseases, Diabetes Mellitus, and Obesity developed the main diet principles in those conditions. Gradual weight loss (5–10 % from baseline) can be achieved by decreasing the amount of calories consumed daily; limiting fatty foods and increasing the amount of complex carbohydrates, plant fibers, and proteins; eliminating toxic alcohol doses and fructose-rich products [20].

Currently the Mediterranean diet takes the lead among all diets used for the treatment of NAFLD [21].

The main principles of this diet are reflected in the so-called correct nutrition pyramid [21]. Products recommended for daily consumption are located at the pyramid base. The closer to the apex, the less should those food products be present in the weekly diet. Physical activity supports the pyramid. It should be selected

individually, accounting for the features of each patient. Moderate-tempo aerobic exercises are the most preferable ones [22, 23].

The Mediterranean diet is beneficial as it can not only decrease the body weight, but also maintain the results achieved within a prolonged time period. This diet type may lead to the recovery of metabolic disorders, which is especially important in liver disorders. Several scientific articles have demonstrated that this diet induces the regression of inflammatory and fibrous alterations in the parenchyma, as well as decreasing cardiometabolic risks [23]. Summing up the aforementioned facts, weight loss is the main goal of non-medication treatment. With that, physical exercises promote not only weight normalization, but also the normalization of metabolic processes. Some articles have also demonstrated that physical exercises decrease the fat contents in hepatocytes [23]. Systematic reviews and meta-analyses have established that adequate physical activity may lead to decreased lipid amounts in hepatocytes even in the absence of significant weight loss [24]. For example, a study conducted in 2017 enrolled 115 patients with NAFLD. All patients undertook aerobic exercises for 30–60 minutes 2–3 times a week for 6 months. The amount of hepatic fat was evaluated afterwards. The results showed that the amount of hepatic lipids decreased by 24.4 % [24].

Currently various groups of drugs are used in the treatment of NAFLD — from herbal drugs to bile acids and succinic acid derivatives. This variety of medications is associated with the multifaceted pathogenesis of hepatic steatosis. However, unfortunately, one can state that no universal drug potentially affecting all NAFLD mechanisms has been developed yet.

Hepatoprotective drugs are the main ones in the treatment of NAFLD [3]. The purpose of their administration is to slow down the progression of pathological processes directly in the hepatic tissue. The following effects are expected from hepatoprotective drugs: anticholestatic, antioxidant, antifibrotic, immune-modulating, etc. [3]. Many of them have multidirected effects and positively affect the cardiovascular system, restore carbohydrate and lipid metabolism disorders [3, 26, 27].

A large number of drugs with various mechanisms of action currently belong to this group. These include bile acid metabolites, a fixed combination of inosine + meglumine + nicotinamide + succinic acid + methionine (Remaxol), ursodeoxycholic acid, alpha-tocoferol acetate (vitamin E), ademethionine, etc. Every drug has its own evidence base [3].

Being a lipophilic antioxidant, vitamin E can be used in the treatment of NAFLD. The mechanism of its action presumes that due to the inhibition of hydroperoxide production it breaks the chain reaction of lipid peroxidation and promotes the elimination of free radicals [27].

It has been proven that the antioxidant ability of hepatocytes is depleted in chronic liver diseases [3]. It has been shown that the daily use of vitamin E in the dose of 800 international units decreases the severity of steatosis and inflammation [27]. Several articles demonstrated positive effects of using this drug in the form of cytolysis reduction, decreased inflammation activity, although no effects on liver fibrosis were confirmed [3, 27, 28]. In 2005 the meta-analysis showed that the use of large vitamin E doses increased the risks of mortality from other causes [28]. Those data were refuted later by other investigators [27, 28]. Currently the feasibility and safety of this drug still remains debatable, which limits its use.

A fixed combination of inosine + meglumine + nicotinamide + succinic acid + methionine (Remaxol) provides all effects expected from hepatoprotective drugs, including hepatoprotective, anticholestatic, antioxidant effects. Each Remaxol component plays its important role [3, 29].

Succinic acid directly affects the correction of mitochondrial dysfunction, which is the basic step of NAFLD pathogenesis. This is achieved due to antioxidant and antihypoxic effects of this component [29–31].

Nicotinamide (vitamin PP) is a source of nicotinamide-adenine-dinucleotide and nicotinamide-adenine-dinucleotide phosphate, which are coenzymes for many enzymes participating in oxidation-reduction reactions. Nicotinamide also participates in the metabolism of carbohydrates, normalizes the bowel function [30, 31].

Methionine is an essential amino acid required for growth maintenance and nitrogen equilibrium in the body. It is also used for the synthesis of choline required for the production of phospholipids. Methionin also participates in depleting the neutral fat deposits in the liver [30, 31].

Inosine has antihypoxic effects, enhances the energy balance in the whole body, participates in carbohydrate metabolism, enhances the activity of the Krebs cycle enzymes [30, 31].

Due to the unique multicomponent composition, Remaxol affects the main steps in the NAFLD pathogenesis; thus, it can be considered a universal hepatoprotective drug, which may be used as monotherapy.

Its positive effects on cholesterol metabolism have been demonstrated in several investigations [31, 32]. It is important to note that Remaxol can not only decrease the total cholesterol and triglyceride levels, but can also promote the increase in high-density lipoprotein levels. Several studies have demonstrated that the treatment with this drug leads to quick elimination of asthenic and dyspeptic syndromes [32]. In 2021, a multicenter open comparative trial was conducted among 317 patients to compare the effects of ademethionine and Remaxol.

The patients' general condition, laboratory parameters (cytolysis and cholestasis markers), lipid metabolism were evaluated. As a result, both drugs demonstrated positive results. However, in several parameters Remaxol was superior to ademethionine, e.g. concerning the decrease in pruritus severity, along with a quicker drop in bilirubin levels [31].

Ademethionine is a natural substance of the human body synthesized in the liver from L-methionine and adenosine triphosphoric acid. It is required for the synthesis of glutathione, which is considered a very important cellular antioxidant. If glutathione levels in the body decrease (e.g., in chronic liver diseases), the damaging effects of free radicals worsen. In turn this leads to mitochondrial dysfunction, hepatocellular apoptosis, and even possibly to hepatocellular carcinoma [33].

It is well-known that depressive disorders (increased irritability, fatigability, malaise, sleep disorders) are common in chronic liver diseases. The role of ademethionine in the elimination of asthenic syndrome has been demonstrated in several studies [33]. 18 controlled trials showed that the antidepressive effect of this drug had a similar efficacy to chloropiramine, minaprine, and imipranine [33]. Accounting for the latter fact, ademethionine is considered the drug of choice in such clinical situations.

Ursodeoxycholic acid is currently widely used in liver diseases, including NAFLD. It has been proven that this drug decreases inflammation, inhibits fibrosis progression, improves the lipid profile parameters [34, 35]. In 2018, a multicenter "Uspekh" trial enrolling 207 patients with NAFLD was arranged. All patients were administered an ursodeoxycholic acid drug for 6 months in a standard dose of 15 mg/kg of body weight. As a result, cytolysis was improved along with cholesterol metabolism parameters, while steatosis and fibrosis severity decreased as well [34, 35]. The role of ursodeoxycholic acid in lipophagy is currently being actively discussed.

Not only hepatoprotective drugs, but also those aimed at correcting comorbidities are currently used in the treatment of NAFLD. For example, glucagon-like peptide 1 analogues (liraglutide, semaglutide) and sodium-glucose co-transporter 2 inhibitors (ipragliflozin, dapagliflozin) are used in type 2 diabetes mellitus [3]. These drugs lead to weight loss, decreased insulin resistance and cytolysis levels, as well as diminish lipogenesis de novo [3, 36]. If NAFLD is combined with dyslipidemia and cardiovascular diseases, HMG-CoA-reductase inhibitors (statins) can be justified to achieve the target low-density lipoprotein levels. Several studies have demonstrated that statins induce the regression of steatosis, inflammation, and liver fibrosis [37, 38]. If HMG-CoA-reductase inhibitors are not tolerated or not efficient, ezetimib is recommended [39]. Fenofibrates are administered to decrease the cardiovascular risks and severity of cytolysis [3, 40].

One should also separately note a group of patients with NAFLD combined with obesity. It is well-known that weight loss promotes the regression of steatosis severity and steatohepatitis activity [41]. Patients not responding to non-medication treatment (diet, dosed physical activity) are administered drug products for the treatment of obesity [3]. For example, liraglutide or orlistat that promote weight loss facilitate the patient compliance with dietary recommendations and help to develop new dietary habits [42]. If lifestyle modifications and pharmacotherapy do not provide positive effects, bariatric surgery is recommended. The results of meta-analysis confirm positive effects of bariatric interventions on the course of non-alcoholic fatty liver disease. 88 % patients demonstrated the regression in steatosis and steatohepatitis severity, with fibrosis regression in 30 % patients [3, 42]. Indications to surgical interventions are defined individually for each patient by the interdisciplinary physician team.

The nuclear transcription factor modulators (e.g., farnesoid X receptor [FXR]) form a prospective direction in the treatment of NAFLD. Obeticholic acid (FXR stimulator) promotes the decreased bile acid levels, also improving other metabolic processes (e.g., gluconeogenesis and lipogenesis) [12, 43].

A new target drug Resmetirom (thyroid hormone receptor agonist) is currently authorized in the USA for the treatment of patients with NAFLD. The MAESTRO-NASH study demonstrated that the latter drug not only decreased the disease activity, but also led to hepatic fibrosis regression [44]. This drug has not been authorized in Russia yet.

Conclusion

Non-alcoholic fatty disease is a chronic multisystemic disease with a multifaceted pathogenesis, characterized by the high global prevalence and associated with the development of other comorbid conditions.

The treatment of this disease should be complex, with the use of medication and non-medication methods. It should lead to the regression of hepatic steatosis, while also decreasing cardiometabolic risks.

The role of Remaxol effects on the course of non-alcoholic fatty liver disease is currently being actively analyzed. The results of recent studies have demonstrated good drug tolerability with its high efficacy concerning the decreased liver enzyme levels, cholesterol metabolism normalization, elimination of dyspeptic signs. This fact enables us to not only include Remaxol into NAFLD treatment protocols in order to decrease the risk of fibrosis progression and the number of complications, but also to consider it for use as monotherapy.

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ТЕЧЕНИЕ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ В РАННЕМ ПЕРИОДЕ ПОСЛЕ КАТЕТЕРНОЙ КРИОБАЛЛОННОЙ АБЛАЦИИ ПРИ ПАРОКСИЗМАЛЬНОЙ И ПЕРСИСТИРУЮЩЕЙ ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ

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Course of Chronic Heart Failure in the Early Period Following Catheter Cryoballoon Ablation in Paroxysmal and Persistent Atrial Fibrillation

Резюме

Цель. Изучить течение хронической сердечной недостаточности при пароксизмальной и персистирующей фибрилляции предсердий в раннем периоде после операции катетерной криобаллонной аблации устьев легочных вен. **Материал и методы.** Шестьдесят семь пациентов (средний возраст 65,07 ± 7,72 лет, 31(46,3 %) мужчин) с фибрилляцией предсердий и хронической сердечной недостаточностью разделены на 2 группы: I — пароксизмальная, II — персистирующая фибрилляция предсердий. Все пациенты получили первичную криобаллонную аблацию по стандартной методике. До и через 3 месяца после операции проводились тест 6-минутной ходьбы, оценка качества жизни по Миннесотскому опроснику, уровня N-терминального фрагмента прогормона мозгового натрийуретического пептида, эхокардиография. **Результаты.** Уровень N-терминального фрагмента прогормона мозгового натрийуретического пептида (NT-proBNP) был ниже в группе I — 151,00 [65,50; 249,00] против 513,00 [355,25; 948,00] нг/л (p <0,001) в группе II. Группа II отличалась большими размерами левого предсердия: передне-задний размер 40,00 [37,00; 43,00] мм (p=0,018), индекс объема левого предсердия 35,00 [31,00; 43,00 мл/м^2 (p=0,023), правого предсердия: 38,00 [36,00; 40,00] мм (p=0,001) и левого желудочка. Фракция выброса левого желудочка была ниже в группе II — 55,00 [50,50; 58,00] против 60,00 [57,00; 62,00] % (p <0,001). Внутригрупповой анализ изменений в динамике после КБА показал: в группе I улучшение качества жизни и увеличение дистанции 6-минутной ходьбы с 411,0 [377,0; 482,5] до 455,0[420,0 –515,0] метров (p=0,001). У пациентов группы II в динамике отмечено: увеличение расстояния 6-минутной ходьбы с 424,00 [390,00; 500,75] до 470,00 [410,00 — 551,50] метров (p < 0,001), значимое снижение уровня NT-proBNP с 513,00 [355,25; 948,00] до 153,00 [73,50 — 171,00] нг/л (p<0,001), уменьшение размеров левого предсердия, правого желудочка, систолическое давление в легочной артерии, увеличение фракция выброса левого желудочка с 55,0 [50,5; 58,0] до 60,0 [55,0 — 60,0] % (p=0,004). **Заключение.** У пациентов с персистирующей фибрилляцией предсердий, которые исходно имели более тяжелое течение хронической сердечной недостаточности, через 3 месяца после операции криобаллонной аблации устьев легочных вен отмечалось улучшение функционального статуса, повышение толерантности к ходьбе, уменьшение размеров левого предсердия, правого желудочка, систолического давления в легочной артерии, увеличение фракции выброса левого желудочка, снижение уровня

NT-proBNP в сыворотке крови. У пациентов с пароксизмальной фибрилляции предсердий проведенная катетерная криобаллонная аблация устьев легочных вен способствовала повышению толерантности к физической нагрузке и улучшению качества жизни.

Ключевые слова: *фибрилляция предсердий, сердечная недостаточность, качество жизни, криобаллонная аблация, эхокардиография, фракция выброса левого желудочка, NT-proBNP*

Конфликт интересов

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

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Abstract

Aim. Study the course of chronic heart failure with paroxysmal and persistent atrial fibrillation (AF) during the early period after catheter cryoballoon ablation of pulmonary vein. **Material and Methods.** Sixty-seven patients (mean age 65.07 ± 7.72 years, 31 (46.3 %) men) with atrial fibrillation and heart failure were divided into two groups: Group I — paroxysmal AF and Group II — persistent AF. All patients underwent primary cryoballoon ablation using standard technique. Before operation and three months post-operation, tests included six-minute walk test, Minnesota Living with Heart Failure Questionnaire, measurement of N-terminal pro-brain natriuretic peptide, and echocardiography. **Results.** The NT-proBNP level was lower in Group I — 151.00 [65.50;249.00] ng/L versus 513,00 [355.25; 948.00] ng/L in Group II (p <0.001). Group II demonstrated larger left atrial dimensions: left atrial diameter 42.50[40.25;45.00] mm (p=0.018), indexed left atrial volume 40.00 [37.50;46.65] mL/m^2 (p=0.023), right atrial diameter 43.00 [40.25;45.75] mm (p=0.001) and left ventricular. Left ventricular ejection fraction was lower in Group II — 55.00 [50.50;58.00] % versus 60.00 [57.00;62.00] % (p <0.001). Within-group analysis showed that Group I improved the quality of life and an increased 6-minute walk test distance from 411.0 [377.0;482.5] meters to 455.0 [420.0–515.0] meters (p=0.001). For Group II, dynamic changes revealed an increase in 6-minute walk test distance from 424.00 [390.00;500.75] to 470.00 [410.00–551.50] meters (p<0.001), a significant drop in NT-proBNP level from 513.00 [355.25;948.00] to 153.00 [73.50–171.00] ng/L (p<0.001), reduction in left atrial dimensions, right ventricular size, systolic pulmonary artery pressure, and an increase in left ventricular ejection fraction from 55.00 [50.50;58.00] % to 60.00 [55.00–60.00] % (p=0.004). **Conclusion.** Patients with persistent atrial fibrillation, who initially had more severe chronic heart failure, experienced an improvement in their functional status, increased walking endurance, reduction in left atrial and right ventricular dimensions, as well as systolic pulmonary artery pressure, along with an increase in left ventricular ejection fraction and a decrease in NT-proBNP levels, 3 months after cryoballoon ablation. Patients with paroxysmal atrial fibrillation benefited from cryoballoon ablation through enhanced physical activity tolerance and improved quality of life.

Key words: *atrial fibrillation, heart failure, quality of life, cryoballoon ablation, echocardiography, left ventricular ejection fraction, NT-proBNP*

Conflict of Interest

The authors declare that this work, its topic, subject matter, and content do not affect any competing interests.

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Compliance with the principles of ethics

The study protocol was approved by the local ethics committee of Federal State Autonomous Educational Institution of Higher Education «N.I. Pirogov Russian National Research Medical University» of the Ministry of Health of the Russian Federation (Minutes No230 dated 28.06.2023). Approval and protocol procedure was obtained according to the principles of the Declaration of Helsinki. Written consent was obtained from the patients for publication of relevant medical information and all of accompanying images within the manuscript.

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AAT — antiarrhythmic therapy, LAVI — left atrial volume index, CBA — cryo-balloon ablation, EDV — end-diastolic volume, EDS — end-diastolic size, LA — left atrium, IVC — inferior vena cava, RV — right ventricle, LAAPS — left atrial anteroposterior size, SPAP — systolic pulmonary artery pressure, PVO — pulmonary vein ostia, LVEF — left ventricular ejection fraction, NYHA FC — functional class of congestive heart failure based on the New York Heart Association classification, AFib — atrial fibrillation, CHF — chronic (congestive) heart failure, CHFpEF — chronic heart failure with preserved ejection fraction, CHFmrEF — chronic heart failure with moderately reduced ejection fraction, CHFrEF — chronic heart failure with reduced ejection fraction, EchoCG — echocardiography, EHRA — European Heart Rhythm Association scale for the assessment of atrial fibrillation symptoms, MLHFQ — Minnesota Living with Heart Failure Questionnaire, NT-proBNP — N-terminal fragment of the brain natriuretic peptide hormone, TAPSE — tricuspid annular plane systolic excursion, 6MWT — 6-minute walking test

Introduction

Atrial fibrillation (AFib) and chronic (congestive) heart failure (CHF) are a serious burden for public health, causing high mortality and morbidity, negatively affecting the quality of life and prognosis in patients [1]. CHF is diagnosed in 22.5 % patients with paroxysmal AFib, 44 % patients with persistent AFib, and 56 % patients with permanent AFib. AFib prevalence increases in parallel with the CHF functional class (FC), reaching 45 % in FC III-IV [2, 3].

For a long time, the issue of the preferable management for patients with AFib remained debatable. The latest trials, i.e. EAST-AFNET 4 [4], RAAFT-2 [5], EARLY-AF [6], have demonstrated the advantages of a sinus rhythm (SR) recovery and maintenance strategy, including with the use of ablation methods. Catheter ablation as a first-line therapy in persistent AFib has a smaller evidence class (IIb) than that for the paroxysmal one (I) [7]. In 2024, a Consensus was published by the European Heart Rhythm Association concerning the catheter and surgical ablation in AFib. This document contains the systematic review of 11 randomized clinical trials (RCTs) devoted to the selection of the AFib treatment method in patients with chronic heart failure with reduced ejection fraction (CHFrEF), which has demonstrated the benefits of interventional procedures over the antiarrhythmic therapy (AAT), concerning the improved quality of life, decreased hospitalization and mortality rate, decreased AFib burden, increased ejection fraction (EF), prevention of CHF progression [8].

The study was aimed at analyzing the CHF course in paroxysmal and persistent AFib in the early period after the cryo-balloon ablation (CBA) of pulmonary vein ostia (PVO).

Materials and Methods

A total of 67 patients with paroxysmal and persistent AFib and CHF were included into the single-center prospective study. Subjects were aged 41 to 76 years (65.15±7.76), including 36 (53.7 %) females.

Study inclusion criteria:

Symptomatic paroxysmal or persistent AFib.

Confirmed heart failure.

Primary catheter ablation.

Patient's informed consent.

Study exclusion criteria:

Left atrial anteroposterior size (LAAPS) exceeding 5.0 cm based on echocardiography (EchoCG) criteria. LA appendage thrombosis based on contrast-enhanced cardiac computed tomography or transesophageal EchoCG; implanted devices (permanent pacemaker, implantable cardioverter-defibrillator [ICD], cardiac resynchronization therapy [CRT]); moderate and severe mitral and aortic heart diseases (or those requiring surgical correction); uncorrected thyroid dysfunction; current malignancy, end-stage renal disease, moderate or severe anemia or thrombocytopenia; acute infectious diseases; acute heart failure or decompensated CHF; myocardial infarction and/or coronary revascularization within the prior 3 months; infectious endocarditis, myocarditis, pericarditis, pulmonary embolism; acute cerebrovascular accident within the prior 6 months.

Before the surgical intervention, all patients underwent the assessment of the functional status using the 6-minute walking test (6MWT), the quality of life using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), as well as the test for levels of N-terminal fragment of the brain natriuretic peptide hormone (NT-proBNP) and echocardiography (EchoCG). Linear and volumetric parameters, LVEF, tissue Doppler parameters, diastolic dysfunction degree were assessed during EchoCG. 24-hour ECG monitoring (Miocard-Holter-2 24-hour ECG Monitoring System; manufacturer: Scientific Research Institute of Medical Device Construction ESN LLC) was provided to all patients 3 months after the intervention to assess arrhythmias and heart blocks. In patients with ejection fraction ≥50 %, H2FPEF, HFA-PEFF scales, and (if indicated) the diastolic stress-test was used to verify chronic heart failure with preserved ejection fraction (CHFpEF). CHF was diagnosed based on Clinical Guidelines on the Management of Patients with Chronic Heart Failure (2024) [9]. All patients underwent the catheter cryo-balloon ablation (CBA) based on the procedure adopted in the hospital, with the achievement of the isolation of pulmonary vein ostia and without any additional occlusive interventions. Under local anesthesia with novocaine and total intravenous anesthesia (fentanyl, midazolam, propofol), the right internal jugular vein and the right femoral vein were punctured with subsequent insertion of hemostatic introducers. Multipolar diagnostic electrophysiological catheters were installed in the coronary sinus and the right ventricle. Under fluoroscopy guidance, the interatrial septum was punctured; heparin was administered intravenously for the prevention of intraoperative thromboembolic complications (target values of activated partial thromboplastin time: 300–350 seconds). The transseptal introducer was inserted into the left atrial cavity. The transseptal introducer was switched for the Polar Sheath 12F delivery system (Boston Scientific, USA) on a diagnostic guidewire 150–270 cm long. After inserting the PolarX cryo-balloon catheter (Boston Scientific, USA) into the left atrial cavity, cryo-interventions were sequentially arranged in the left superior, left inferior, right inferior, and right superior pulmonary veins (240 seconds long). Before each exposure, the pulmonary vein occlusion with the balloon catheter was confirmed by the fluoroscopic injection of

the contrast drug into it. The electric isolation of pulmonary veins was confirmed by the disappearance of the electrical activity in the muscle cuff of each pulmonary vein recorded using a PolarMap diagnostic circular catheter (Boston Scientific, USA) Additional non-occlusive interventions outside of pulmonary veins were not conducted. If atrial fibrillation was preserved after all interventions, electrical cardioversion was applied to restore the sinus rhythm. After completing the surgical intervention, patients were routed into the intensive care unit. After hemopericardium exclusion, anticoagulant therapy was resumed 4 hours after the surgery. Regardless of the CHA2DS2-VASC score, all patients were administered direct oral anticoagulants for at least 3 weeks before and 8 weeks after the surgery based on the Clinical Guidelines for the Treatment of Atrial Fibrillation and Flutter (2020) [10]. Vitamin K antagonists were not used.

The study was arranged in accordance with the Good Clinical Practice standards and the Declaration of Helsinki principles. The study was approved by the Local Ethics Committee of the N.A. Pirogov Russian National Research Medical University, Protocol No. 230 dated June 28, 2023. The written informed consent was obtained from all subjects before the study enrollment.

The statistical analysis was conducted using the StatTech v. 4.8.0 software (StatTech LLC, Russia). Quantitative parameters were evaluated for the compliance with normal distribution using the Shapiro-Wilk test. Quantitative parameters, which selective distribution corresponded to the normal one, were described using the mean arithmetics (M) and standard deviations (SD). 95 % confidence interval (95 % CI) limits were defined for the mean values for representativeness. In the absence of normal distribution, quantitative data were described using the median (Me) and lower/upper quartiles [Q1 — Q3]. For the comparison of two groups in the quantitative parameter, which distribution in each group corresponded to the normal one, the Student's t-test was used provided the dispersions were equal. For the comparison of two groups in the quantitative parameter, which distribution was abnormal, the Mann-Whitney U-test was used. When comparing normally distributed quantitative parameters calculated for two linked samples, the paired Student's t-test was used. When comparing quantitative parameters with abnormal distribution in two linked groups, the Wilcoxon test was used. The Pearson's x2 test was used to compare qualitative parameters. Differences were considered statistically significant with $p<0.05$.

Results

Based on the study design, before CBA patients were divided into two groups depending on the AFib form: Group I — paroxysmal, n=45 (67.2 %), mean age 67.0 years, 16 males (35.6 %); Group II — persistent, n=22 (32.8 %), mean age 65.0 years, 15 males (68.2 %). No patients with long-standing persistent AFib (>1 year) were included into the study. Patients in groups differed by gender: Group I had 16 (35.6 %) males and 29 (64.4 %) females, Group II had 15 (68.2 %) males and 7 (31.8 %) females (p=0.012). Groups were similar in the age (p=0.505), body mass index (BMI) — 29.89 and 30.84 kg/m2 (p=0.372), comorbidities: essential hypertension (EH) — in 45 (100 %) patients from Group I and in 21 (95.5 %) from Group II (p=0.328); coronary artery disease (CAD) — 4 (8.9 %) in Group I, 5 (22.7 %) in Group II (p=0.160), type 2 diabetes mellitus — 3 (6.7 %) in Group I, 1 (4.5 %) in Group II (p=1.000), hypertrophic cardiomyopathy (HCM) — 1 (2.9 %) in Group I, 1 (7.1 %) in Group II (p=0.503), estimated glomerular filtration rate (eGFR) — 67.00 [60.00–75.00] mL/min/1.73 m2 in Group I, 71.00 [61.75–79.75] mL/min/1.73 m2 — in Group II (p=0.224).

All patients with essential hypertension were administered hypotensive therapy and achieved target blood pressure values. CHF medications were similar in both groups. Patients with CHFrEF were on quadruple therapy in maximum tolerated doses for at least 3 months before the surgical intervention: sacubitril/valsartan 200 mg/day, spironolactone 25 mg/day, bisoprolol 5 mg/day, dapagliflozin 10 mg/day. Differences were detected in the antiarrhythmic therapy: patients in Group used Class IC drug and beta-blockers more often, while amiodarone prevailed in Group II (Table 1).

The majority of patients from both groups had CHF FC II (NYHA) (p=0.717). The EHRA class reflecting the degree of AFib symptom severity was higher in Group I patients, but no significant differences between groups were observed (p=0.441) (Table 2).

Patients with preserved EF were predominant in both groups. In Group II, 5 (22.7 %) patients demonstrated reduced or moderately reduced LVEF, while in Group I, 3 (6.7 %) patients had moderately reduced EF. When comparing detected CHF phenotypes by EF, no statistically significant differences were established between groups (p=0.070). Groups were not statistically different in the parameters describing quality of life and 6-minute walking distance test, as well as points in H2FPEF and HFA-PEFF scales. NT-proBNP levels were significantly lower in Group I (151.00 ng/L, $p<0.001$). Among EchoCG parameters, Group II had significantly larger cardiac chamber sizes, including the anteroposterior left atrial size, left atrial volume index, right atrial and left ventricular sizes. LVEF was significantly lower in Group II (55.00 %, $p<0.001$). Thus, more severe CHF course was observed in Group II patients, which manifested with significantly elevated levels of the myocardial stress biomarker (NT-proBNP) and severe structural-hemodynamic deviations based on EchoCG data (Table 2).

Table 1. *Drug therapy before CBA*

Drug therapy n (%)	Group I (Paroxysmal AF) n=45	Group II (Persistent AF) n=22	p
Class I C antiarrhythmic drugs (propafenone, lappaconitine hydrobromide)	19 (42,2)	1 (4,8)	0,002*
Amiodarone	9 (20,0)	14 (63,6)	<0,001*
Sotalol	9 (20,0)	7 (31,8)	0,363
Beta-adrenergic blockers	27 (60,0)	7 (31,8)	0,030*
ACE inhibitors	22 (48,9)	10 (45,5)	0,792
Angiotensin II receptor antagonists	19 (42,2)	6 (27,3)	0,289
ARNI	1 (2,3)	3 (13,6)	0,100
SGLT-2	12 (26,7)	9 (40,9)	0,271
Mineralocorticoid receptor antagonists	18 (40,0)	10 (45,5)	0,793
Loop diuretics	1 (2,2)	0 (0,0)	1,000

Abbreviations: AAD — antiarrhythmic therapy, ACE — angiotensin-converting enzyme, ARNI — angiotensin receptor and neprilysin inhibitors, SGLT-2 — sodium-glucose cotransporter type 2 inhibitors

Table 2. *Data of patients with paroxysmal and persistent AF before CBA*

Indicator	Group I (Paroxysmal AF) n=45	Group II (Persistent AF) n=22	p
Men, %	35,6	68,2	0,012*
Age, years	67,00 [61,75; 72,00]	64,00 [61,00; 70,00]	0,505
NYHA FC CHF, n (%) Class I Class II Class III	 19 (48,2) 24 (53,3) 2 (4,4)	 8 (36,4) 12 (54,5) 2 (9,1)	0,717
Phenotype of CHF, n (%) CHFrEF CHFmrEF CHFpEF	 0 (0,0) 3 (6,7) 42 (93,3)	 2 (9,1) 3 (13,6) 17 (77,3)	0,070
MLHFQ, points	30,3 (±15,65)	23,52 (±13,81)	0,100
6MWT,	411,00 [377,00; 482,50]	424,00 [390,00; 500,75]	0,962
NT-proBNP, ng/l	151,00 [65,50; 249,00]	513,00 [355,25; 948,00]	<0,001*
EHRA класс, n (%) I IIa IIb III	 4 (8,9) 14 (31,1) 26 (57,8) 1 (2,2)	 1 (4,5) 11 (50,0) 10 (45,5) 0 (0,0)	0,441
LV EF , %	60,00 [57,00; 62,00]	55,00 [50,50; 58,00]	<0,001*
LA AP diameter, mm	40,00 [37,00; 43,00]	42,50 [40,25; 45,00]	0,018*
LAVI, ml/m²	35,00 [31,00; 43,00]	40,00 [37,5; 46,65]	0,023*
EDV, ml	87,00 [78,00; 109,00]	98,00 [89,25; 121,00]	0,008*
EDD, cm	4,5 [4,30 — 4,90]	4,91 [4,60 — 5,10]	0,033*
RV, mm	29,0 [26,0 — 31,0]	30,6 [29,0 — 31,0]	0,069
IVC, mm	17,0 [14,0; 19,0]	18,0 [15,0; 22,0]	0,187
TAPSE, cm	2,20 [2,00; 2,30]	2,00 [1,82; 2,20]	0,299
sPAP, mmHg	30,00 [25,00 — 34,00]	31,00 [25,00 — 38,00]	0,581
E/e’	9,50 ± 2,36 (8,67 — 10,32)	9,64 ± 2,79 (8,29 — 10,98)	0,847

Note: Data are presented as M ± SD or Me [Q1; Q3] depending on the type of distribution. * — $p < 0.05$ was considered statistically significant.
Abbreviations: AF — atrial fibrillation, NYHA FC CHF — functional class of chronic heart failure according to the New York Heart Association, EHRA — European Heart Rhythm Association Atrial Fibrillation Symptom Rating Scale, CHFrEF — heart failure with reduced ejection fraction, CHFmrEF — heart failure with moderately reduced ejection fraction, CHFpEF — heart failure with preserved ejection fraction, MLHFQ — Minnesota Living with Heart Failure Questionnaire , 6MWT -Six-minute walk test, NT-proBNP — N-terminal pro-brain natriuretic peptide , LV EF — left ventricular ejection fraction, LA AP diameter — Left atrial anteroposterior diameter, LAVI — Left atrial volume index, EDV — End-diastolic volume, EDD — End-diastolic diameter, RV — Right ventricular diameter, IVC — Inferior vena cava diamete, TAPSE — Tricuspid annular plane systolic excursion, sPAP — Systolic pulmonary artery pressure, E/e’ — the ratio of the transmitral E peak to the tissue myocardial Doppler e’.

Statistically significant differences were detected between groups in the antiarrhythmic therapy administered after the surgery: in Group II 16 (72.7 %) patients were administered amiodarone, 6 (27.3 %) — sotalol, while in Group I 17 (37.8 %) used propaphenone, 9 (20.0 %) — amiodarone, 9 (20.0 %) — sotalol, 6 (13.3 %) — metoprolol, 4 (8.9 %) — lappaconitine hydrobromide (Table 3).

Patients were re-examined 3 months after CBA. The intra-group follow-up analysis of parameters before and after the CBA intervention demonstrated the following significant changes: in Group I MLHFQ points decreased, which reflected the improvement in the patient's quality of life; the distance in the 6-minute walking test increased as well. Among EchoCG parameters, only the diameter of the inferior vena cava (IVC) decreased from 17.0 [14.0; 19.0] to 15.0 [13.0–17.5] mm (p=0.047). No changes were observed in LVEF — 60.0 [57.0; 62.0] and 59.0 [56.0–61.0] % (p=0.831); left atrial anteroposterior size (LAAPS) — 40.00 [37.0; 43.0] and 39.0 [36.0–42.0] mm (p=0.948); left atrial volume index (LAVI) — 35.00 [31.00–43.00] and 34.50 [27.0–38,8] mL/m^2 (p=0,274); RV 29.1 [26.0–31.0] and 29.0 [27.0–30.0] mm (p=0.460); SPAP — 30.16 [25.0–34.0] and 30.0 [26.5–33.5] mm Hg (p=0.557).

The following statistically significant changes were detected among Group II patients: increased distance during the 6-minute walking test, significantly decreased NT-proBNP levels (Table 4). When evaluating EchoCG parameters, the statistically significant LVEF increase was verified, along with the significant decrease in linear and volumetric parameters of the left atrium and right ventricle, SPAP, IVC diameter (Figure 1).

Table 3. *Antiarrhythmic therapy in patients with paroxysmal and persistent AF after CBA*

Drug therapy	Group I (Paroxysmal AF) n=45	Group II (Persistent AF) n=22	p
Amiodarone	9 (20,0 %)	16 (72,7 %)	p<0,001
Sotalol	9(20,0 %)	6 (27,3 %)	p=0,542
Metoprolol	6 (13,3 %)	0	p=0,167
Propaphenone	17 (37,8 %)	0	p<0,001
Lappaconitine hydrobromide	4 (8,9 %)	0	p=0,249

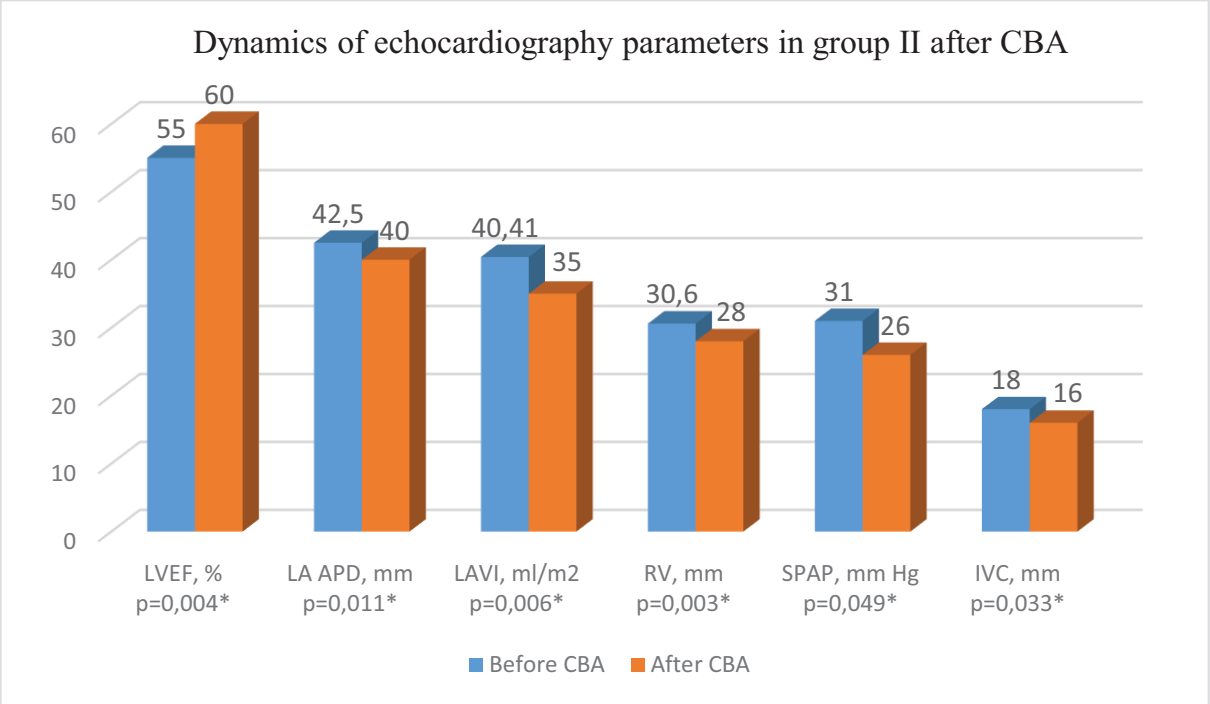

Figure 1. *Dynamics of echocardiography parameters in group II 3 months after CBA*

Abbreviations: LVEF — left ventricular ejection fraction, LA APD — left atrial anterior-posterior dimension, LAVI — left atrial volume index, RV — right ventricle, IVC — inferior vena cava, TAPSE — tricuspid annular systolic excursion, SPAP — pulmonary artery systolic pressure

Table 4. Data from patients with paroxysmal and persistent AF 3 months after CBA

	Group I			Group II		
Indicator	Before CBA	After CBA	p	Before CBA	After CBA	p
MLHFQ, points	30,3 (±15,65)	19,50 [6,25–41,0]	0,032*	23,52 (±13,81)	15,00 [6,50-23,00]	0,168
6MWT, meter	411,0 [377,0; 482,5]	455,0[420,0 –515,0]	<0,001*	424,00 [390,00; 500,75]	470,00 [410,00 — 551,50]	<0,001*
NT-proBNP, ng/l	151[65,5;249]	91,50 [46,30 — 219,75]	0,216	513,00 [355,25; 948,00]	153,00 [73,50 — 171,00]	<0,001*
EDV, ml	87,0 [78,0; 109,00]	85,00 [75,5–97]	0,122	98,00 [89,25; 121,00]	105,00 [94,00 — 120,00]	0,258
EDD, cm	4,64 (±0,41)	4,50 [4,3 — 4,9]	0,171	4,91 (±0,52)	4,80 [4,65 — 5,05]	0,529
TAPSE, cm	2,20 [2,0; 2,30]	2,11 ± 0,25 (2,03–2,19)	0,344	2,00 [1,82; 2,20]	2,19 ± 0,36 (2,01 — 2,37)	0,409
E/e’	9,50 ± 2,36	8,80 ± 2,48	0,078	9,64 ± 2,79	8,96 ± 3,44	0,358

Note: Data are presented as M ± SD or Me [Q1; Q3] depending on the type of distribution. * — p < 0.05 was considered statistically significant.
Abbreviations: MLHFQ — Minnesota Living with Heart Failure Questionnaire, 6MWT -Six-minute walk test, NT-proBNP — N-terminal pro-brain natriuretic peptide, LV EF — left ventricular ejection fraction, LA AP diameter — Left atrial anteroposterior diameter, LAVI — Left atrial volume index, EDV — End-diastolic volume, EDD — End-diastolic diameter, TAPSE — Tricuspid annular plane systolic excursion, E/e’ — the ratio of the transmitral E peak to the tissue myocardial Doppler e’

AFib paroxysms were observed in 6 (13.3 %) patients in Group I and 1 (4.5 %) patients in Group 2 (p=0.412) within the first 90 days during the blinded period after the CBA. Based on the 24-hour ECG monitoring, 3 months later AFib paroxysms were reported in 4 (8.9 %) patients only in Group I; accounting for a small number of patients with relapsing AFib, no statistically significant differences were confirmed between groups (p=0.294).

Thus, increased exercise tolerance was reported both in the paroxysmal and persistent AFib groups 3 months after the catheter cryo-balloon ablation. The quality of life gradually significantly improved in patients with paroxysmal AFib. Patients with persistent AFib had significantly decreased NT-proBNP and improved structural-hemodynamic EchoCG parameters: decreased linear and volumetric parameters of the left atrium and right ventricle, systolic pulmonary artery pressure, inferior vena cava, with the increasing left ventricular ejection fraction, thus reflecting the improved CHF course.

Concerning adverse events in the early post-CBA period, transient phrenic nerve paralysis was reported in 1 patient from Group I (2.9 %), non-fatal ACVA developed 36 days after the surgery in 1 patient from Group I (2.9 %), with further complete compensation of neurological deficit. A post-puncture hematoma not requiring additional interventions was observed in 1 patient from Group I (2.9 %).

Discussion

Catheter ablation (CA) as a rhythm control strategy significantly improves survival, decreases the rate of repeated hospitalizations, promotes the sinus rhythm maintenance, preserved cardiac function, and improves the quality of life in patients with AFib and CHF [11]. Optimal CA strategy for patients with persistent atrial fibrillation (persAFib) and heart failure (HF) remains unclear. In the CRYO4PERSISTENT AF study [12] enrolling 101 patients with persistent AFib without CHF after the cryo-balloon ablation, the quality of life improved: mean standardized SF-36 Physical Health parameter improved by 7.1 points (from 46.9 to 53.9 points; p<0.0001), while the Psychic Health parameter improved by 3.3 points (from 47.3 to 50.6 points; p=0.008). In our study the quality of life improvement was demonstrated in patients with paroxysmal AFib, while no significant changes were detected in patients with persistent AFib.

CA benefits in patients with AFib and CHF were demonstrated by S.A. Virk et al. [13]: the meta-analysis of 6 RCTs compared the results of CA and drug therapy in 772 AFib patients with the mean LVEF parameter 30±9 % and a predominantly persistent AFib. CA vs. drug therapy was accompanied by a larger improvement in LVEF (mean difference in absolute parameter increment between groups 5.67 %; p<0.001), larger mortality decrease by 48 % (p=0.001), increased distance in the 6-minute walking test (MD 25.12 m; 95 % CI, 0.59–49.65; p=0.04), and an improved quality of life with a larger MLHFQ score decrease (MD 9.03; 95 % CI, 2.48–15.59; p=0.007). In our study patients with persistent AFib after CBA also demonstrated improved LVEF, improved exercise tolerance, although no significant quality of life improvement was confirmed.

In the RAFT-AF trial [14], 411 patients with CHF with preserved or reduced EF, with over 90 % patients suffering from persistent AFib, were distributed into the ablation-based rhythm control group (n=214) and the rate control group (n=197). LVEF increased in the ablation group by 10.1±1.2 % vs. 3.8±1.2 %, p=0.017; the distance in the 6-minute walking test increased by 44.9±9.1 m vs. 27.5±9.7 m, p=0.025; meanwhile,

NT-proBNP levels decreased by 77.1 % vs. 39.2 %, p<0.0001. The MLHFQ questionnaire demonstrated a more significant improvement in the quality of life in the ablation-based rhythm control group (p=0.0036). Data from our study also demonstrate positive changes of LVEF, cardiac cavity remodeling, NT-proBNP levels, distance in the 6-minute walking test in patients with persistent AFib after CBA.

The trial of A. Pott [15] that enrolled 414 patients with AFib after the primary cryo-balloon ablation, with 137 (33 %) diagnosed with persistent atrial fibrillation, 113 (27.3 %) had CHFrEF (mean LVEF 38.4±10.8 %), while 301 (72.7 %) had preserved left ventricular ejection fraction; LVEF increased from 38.4±10.8 % to 52.5±17.2 % (p<0.001), symptoms associated with HF regressed, and NYHA FC of CHF decreased within the first 12 months after CBA, while the hospitalization rate decreased. In our study the group of patients with persistent AFib had more patients with LVEF <50 % than in the paroxysmal AFib group, and the former one demonstrated significantly increased ejection fraction with the improvement of the functional patient status.

Conclusion

The presented study demonstrates that patients with persistent atrial fibrillation and a more significant pathological myocardial remodeling along with the high myocardial stress level marker at baseline had significantly positive changes in parameters characterizing chronic heart failure 3 months after the catheter cryo-balloon ablation: improved functional status, increased exercise tolerance, decreased left atrial and right ventricular sizes, SPAP, increased left ventricular ejection fraction, decreased NT-proBNP levels. CBA promoted increased exercise tolerance and improved quality of life in patients with paroxysmal atrial fibrillation.

It is scheduled to continue patient follow-up and evaluate the parameters analyzed 12 months after the surgery, which can provide the assessment of long-term alterations in the heart failure course.

Limitations of this study include a small sample size and a short follow-up period (3 months).

Вклад авторов:

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Author Contribution:

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

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КЛИНИКО-ЛАБОРАТОРНАЯ ХАРАКТЕРИСТИКА И ЛЕТАЛЬНОСТЬ У ПАЦИЕНТОВ С ЦИРРОЗОМ ПЕЧЕНИ

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Clinical and Laboratory Characteristics and Mortality in Patients with Liver Cirrhosis

Резюме

Цель исследования: представить клинико-лабораторную характеристику и оценить частоту 28-дневной летальности у пациентов с циррозом печени (ЦП). **Материалы и методы:** в исследование включено 137 пациентов (средний возраст 51±11, 75 (54,7 %) мужчин) с ЦП. Диагноз устанавливался на основе клинических и лабораторно-инструментальных данных. Согласно шкале органной дисфункции CLIF-C OF-score пациентов разделили на две группы: основная группа (n=72, средний возраст 52±11, 37 (51,4 %) мужчин)) — с наличием острой печеночной недостаточности на фоне хронической (ACLF) и группа сравнения (n=65, средний возраст 49±11, 38 (58,5 %) мужчин)) — с декомпенсированным циррозом печени (декЦП) без ACLF. Оценивались клинические показатели, маркеры воспаления, уровень аммиака, лактата, прогностические шкалы, 28-дневная летальность. Статистический анализ данных проводился с использованием программы IBM SPSS 26. **Результаты:** Среди пациентов с ЦП 72 (52,6 %) пациента имели декЦП, а 65 (47,4 %) — ACLF, преобладала алкогольная этиология заболевания (52,8 % и 63,1 % соответственно). Пациенты с ACLF характеризовались значимо более тяжелой печеночной, почечной дисфункцией, системным воспалением и высокими баллами всех прогностических шкал (p <0,001). 28-дневная летальность составила 9,7 % в группе декЦП и 27,7 % — в группе ACLF, достигая 71,4 % при ACLF 3. Анализ выживаемости показал значительные различия между группами (Log-Rank p <0,001). **Заключение:** установлена высокая распространенность ACLF среди госпитализированных пациентов с ЦП. Использование шкалы CLIF-C OFs позволяет эффективно стратифицировать пациентов по степени риска, что имеет важное значение для определения тактики ведения и своевременного направления в специализированные центры.

Ключевые слова: *цирроз печени, острая печеночная недостаточность на фоне хронической (ACLF), декомпенсация цирроза печени*

Конфликт интересов

Соавтор статьи Никитин И.Г. является членом редакционной коллегии журнала «Архивъ внутренней медицины». Статья прошла принятую в журнале процедуру рецензирования. Никитин И.Г. не участвовал в принятии решения о публикации этой статьи.
Соавтор статьи Ильченко Л.Ю. является главным редактором журнала «Архивъ внутренней медицины». Статья прошла принятую в журнале процедуру рецензирования. Решение о публикации статьи было принято редакционной коллегией без участия главного редактора.
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Abstract

Background: To present clinical and laboratory characteristics and assess 28-day mortality in patients with liver cirrhosis (LC). **Materials and Methods:** The study included 137 patients (mean age 51±11; 75 (54,7 %) males) with LC. The diagnosis was established based on clinical, laboratory, and instrumental data. According to the CLIF-C OF organ dysfunction score, patients were divided into two groups: the main group (n=72, mean age 52±11; 37 (51,4 %) males) — with acute-on-chronic liver failure (ACLF), and the comparison group (n=65, mean age 49±11; 38 (58,5 %) males) — with decompensated liver cirrhosis (DC) without ACLF. Clinical parameters, inflammatory markers, ammonia and lactate levels, prognostic scores, and 28-day mortality were assessed. Statistical analysis was performed using IBM SPSS 26. **Results:** Among patients with LC, 72 (52,6 %) had DC and 65 (47,4 %) had ACLF. Alcohol-related etiology was predominant (52,8 % and 63,1 %, respectively). Patients with ACLF were characterized by significantly more severe hepatic and renal dysfunction, systemic inflammation, and higher scores on all prognostic scales (p <0,001). The 28-day mortality rate was 9,7 % in the DC group and 27,7 % in the ACLF group, reaching 71,4 % for ACLF grade 3. Survival analysis showed significant differences between the groups (Log-Rank p <0,001). **Conclusion:** A high prevalence of ACLF was established among hospitalized patients with LC. The use of the CLIF-C OFs scale allows for effective risk stratification of patients, which is important for determining management tactics and timely referral to specialized centers.

Key words: *liver cirrhosis, acute-on-chronic liver failure (ACLF), decompensated liver cirrhosis*

Conflict of interests

Co-author of the article Nikitin I.G. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article has passed the peer-review procedure adopted by the journal. Nikitin I.G. did not participate in the decision to publish this article.

Co-author of the article Ilchenko L.Yu. is the editor-in-chief of the journal «The Russian Archives of Internal Medicine». The article has passed the peer-review procedure adopted by the journal. The decision to publish the article was made by the editorial board without the participation of the editor-in-chief.

The authors did not declare any other conflicts of interest

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Conformity with the principles of ethics

The study protocol was approved by the Local Ethics Committee of N.I. Pirogov Russian national research medical university (Approval No. 235, December 18, 2023). Informed consent was obtained from all patients who participated in the study.

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ALD — alcoholic liver disease, ALT — alanine aminotransferase, AST — aspartate aminotransferase, EV — esophageal varices, GGT — gamma-glutamyl transpeptidase, DLC — decompensated liver cirrhosis, EMIAS — Common Medical Information-Analytical System (Russia), GIB — gastrointestinal bleeding, UTI — urinary tract infection, INR — international normalized ratio, NASH — non-alcoholic steatohepatitis, NLI — neutrophil-lymphocyte index, AHF — acute hepatic failure, HE — hepatic encephalopathy, ROPIP — Russian Society for Liver Diseases, CRP — C-reactive protein, SBP — spontaneous bacterial peritonitis, MBP — mean blood pressure, CLD — chronic liver diseases, LC — liver cirrhosis, ALP — alkaline phosphatase

Introduction

Liver cirrhosis (LC) is a common disease representing a terminal stage of the chronic liver disease, associated with high mortality.

The LC-associated mortality is 2.4 % of the global mortality, with two million deaths annually (11th global cause of death) [1, 2].

LC develops over several stages: Stages 0–2 of compensated LC, when the portal pressure gradually increases in the absence of clinical signs or with mild signs; Stage 3 of LC, manifesting with the first episode of bleeding from esophageal varices (EV); Stage 4 of LC, characterized by the emergence of ascites and its worsening, an episode of hepatic encephalopathy (HE); Stage 5 of recurrent decompensated LC (DLC) [3, 4].

These conditions significantly increase the rate of patient hospitalization and intrahospital mortality within the range of 10 to 50 % [5].

However, the patient management with “terminal cirrhosis”, including severe complications (recurrent/refractory ascites, infections, renal or another extrahepatic organ dysfunction) and the possible emergence of acute hepatic failure (AHF) within the setting of the chronic one, or Acute-on-chronic liver failure (ACLF), is an important issue still remaining in clinical practice [6].

Renal and extrahepatic organ dysfunction is observed in ACLF with systemic inflammation and a very high 28-day mortality [7]. In the meta-analysis presented, the global ACLF prevalence among patients hospitalized with LC is 35 % [8].

Despite the generally recognized ACLF diagnostic criteria, data on the prevalence and features of this syndrome in the Russian population remain limited.

Study objective: presenting clinical & laboratory characteristics, determining the 28-day mortality rate in patients with liver cirrhosis.

Study materials and methods

The study was approved by the Local Ethics Committee of FSAEI HE N.I. Pirogov Russian National Research Medical University (Pirogov University) (Protocol No. 235 dated December 18, 2023) and arranged at the Clinical Base of the State Budget Healthcare Institution "V.M. Buyanov City Clinical Hospital" (SBHI V.M. Buyanov CCH), G.I. Storozhakov Department of Hospital Therapy of the Institute of Clinical Medicine, within the period from October 2023 to April 2025.

According to the Clinical Guidelines of Russian Society for Liver Diseases (ROPIP), the diagnosis of LC was established based on the clinical and laboratory-instrumental signs of intrahepatic portal hypertension with signs of hepatic failure or without them [9].

Inclusion criteria: males and females aged 18 to 75 years with LC that signed the informed consent for the study participation and anonymous publication of results.

Non-inclusion criteria: severe decompensated somatic extrahepatic diseases; psychic diseases; a malignancy detected in the patient before or during the hospitalization; patients not signing the informed consent.

This study was a prospective cohort study that enrolled 137 patients (76 males and 61 females, mean age 50 [42–58] years), with predominantly alcoholic liver cirrhosis (79; 57.7 %). The patients were examined within the first three days of hospitalization. The patient's condition severity was determined using the following scales: Child-Turcotte-Pugh (CTP) [10], Model for End-Stage Liver Disease (MELD) [11], Model for End-Stage Liver Disease-Sodium (MELD-Na) [12], Maddrey Discriminant Function (MDF) [13], Sequential Organ Failure Assessment (SOFA) [14].

The organ dysfunction was evaluated using the CLIF Consortium Organ Failure score (CLIF-C OF-score) [15], which helped to divide patients into two groups: ACLF (**main group**) and DLC (**comparison group**) (Table 1).

The ACLF group was divided into ACLF 1, ACLF 2, ACLF 3 subgroups based on the organ dysfunction severity. Such design helped to evaluate differences in mortality and features between patients with the different degrees of the hepatic failure severity.

The following inflammatory response markers were evaluated: C-reactive protein (CRP), neutrophil-lymphocyte index (NLI; a ratio of absolute neutrophil count to absolute lymphocyte count) [16].

HE severity was evaluated based on clinical signs using the West-Haven score and the ammonia levels in capillary blood (microdiffusion method; PocketChem BA PA-4140, Japan) [17].

28-day mortality was selected as a primary endpoint in accordance with the international standards of prognosis evaluation in patients with ACLF established in the CANONIC trial [7]. This period is critical for determining the short-term prognosis and decisions on the liver transplant. 28-day mortality was determined from the moment of the patient hospitalization into the inpatient department. The outcome was evaluated on Day 28 of follow-up. The information about the patient's vital status after discharging was clarified using the Common Medical Information-Analytical System (EMIAS, Russia).

Data were statistically processed using the IBM SPSS 26 software. The distribution normality was evaluated

Table 1. *The CLIF-C OFs for patients with cirrhosis of the liver*

Organ/system		Subscore		
		1	2	3
Liver, bilirubin, μmol/L		<103	103 до 205	≥205,2
Kidneys, creatinine, μmol/L		<177	177 до 309	≥309 or RRT
Brain — West-Haven grade for HE		0	1-2	3-4
Coagulation, INR		<2	2,0 до 2,5	≥2,5
Circulatory, MAP		≥70	<70	Use of vasopressors
Respiratory	PaO2/FiO2	>300	≤300, но >200	≤200
	SpO2/FiO2	>357	≤357, но >214 >214 and ≤357	≤214

Note. RRT- renal replacement therapy; HE — hepatic encephalopathy; INR — International Normalized Ratio; MAP — Mean Arterial Pressure; PaO2, partial pressure of arterial oxygen; FiO2 — fraction of inspired oxygen; SpO2 — pulse oximetric saturation

using the Kolmogorov-Smirnov test. Descriptive statistics were presented using the median and the 25th;75th percentiles for quantitative variables; rates and proportions in the sample for qualitative variables. The Mann-Whitney U-test was used to compare quantitative data in two non-associated samples. The non-parametric Kruskall-Wallis test was used for multiple comparisons of quantitative data in non-linked samples; aposteriori comparisons were provided using the Dunn's test with the Holm's adjustment. Percent proportions during the analysis of quadrupole tables and multipole contingency tables were analyzed using the Pearson's chi-square test. Survival was analyzed using the Kaplan-Meier method. The survival distribution was compared using the log-rank test. Survival diagrams were constructed for graphical data presentation.

The significance level (p) was in general below 0.050 in all comparisons described.

Results

Based on the CLIF-C OF score, 72 (52.6 %) of 137 patients were diagnosed with DLC, while 65 (47.4 %) had AHF within the setting of chronic failure (ACLF). Groups were similar by gender (p=0.856) and age (p=0.128). Among patients with ACLF, those with ACLF 1 predominated (n=41; 63.1 %), while other type — ACLF 2 (n=17; 26.2 %) and ACLF 3 (n=7; 10.7 %) — were less common.

The most common factors provoking the condition worsening in DLC (n=72) were infections (n=20; 27.8 %), alcohol abuse (n=17; 23.6 %), and gastrointestinal bleeding (GIB) (n=9; 12.5 %). The combined effects of several factors were observed in 16 cases (22.2 %); the cause was not determined in 8 patients (11.1 %).

The main ACLF triggers (n=65) included alcohol consumption (n=27; 41.5 %) and the combination of several factors (n=28; 43.1 %); GIB (n=4; 6.2 %) and infections (n=3; 4.6 %) were less common. ACLF cause was not determined in 2 patients (3.1 %). The groups analyzed also did not differ in the severity of edema and ascites as a cause of hospitalization (p=0.238).

The rate of repeated hospitalizations was higher among patients with ACLF (46; 74.2 %) vs. DLC (42; 65.6 %), however, no statistically significant difference was confirmed.

The leading etiological role in LC in both groups belonged to the alcoholic liver disease (ALD): 38 (52.8 %) in DLC and 41 (63.1 %) in ACLF (Table 2). Patients with the mixed etiology of chronic liver diseases (CLDs) formed a significant proportion of cases: ALD + viral infection — 14 (19.4 %) DLC and 8 (12.3 %) ACLF) and ALD + non-alcoholic steatohepatitis (NASH) — 14 (19.4 %) DLC, 15 (23.1 %) ACLF). The "viral infection + NASH" combination was reported only in the DLC group (n=3 [8.3 %]).

See Tables 3 and 4 for specific clinical-morphological and laboratory patient characteristics.

The degree of anemia severity correlated with the increased organ dysfunction severity in ACLF (p=0.05), with the lowest hemoglobin levels observed in ACLF 3.

Patients with ACLF also had significantly larger white blood cell counts (9.8 [7.5–13.2]; 7,9 [5.6–11.2] x10^9/L, p=0.009), CRP levels (34 [16–52.8]; 25 [9.6–48.3] mg/L, p=0.05), and NLI (4.4 [2.5–7.5]; 2.9 [2.1–5.5], p=0.004) vs. the DLC group. The NLI level demonstrated a trend to increasing with the ACLF severity (ACLF 1: 3.8 [2.3–6.7]; ACLF 2: 4.9 [2.2–7.0]; ACLF 3: 4.9 [1.0–7.7]; p=0.023).

ACLF was characterized by significantly higher levels of total bilirubin (p<0.001), AST (p=0.008), and ALP (p=0.036) vs. patients with DLC. The AST/ALT ratio was higher in ACLF. Bilirubin levels significantly increased with ACLF progression (p<0.001).

The protein-synthetic liver function, i.e. the total protein (p=0.05) and albumin (p=0.05) levels, were lower in the ACLF group. The lowest values were reported in ACLF 3 (total protein 56 g/L, albumin 24 g/L, p=0.015).

The capillary blood ammonia level reflecting the detoxifying hepatic function was significantly higher in patients with ACLF vs. the DLC group (p=0.048), increasing in association with the organ dysfunction severity (ACLF 1: 148 [101–195]; ACLF 2: 125 [87–186]; ACLF 3: 196 [172–199] μmol/L; p=0.017).

When evaluating the renal function, higher creatinine levels were reported in ACLF vs. DLC (p=0.016),

Table 2. *Etiology of liver cirrhosis among patients with decompensated cirrhosis (DC) and ACLF*

Etiology of Cirrhosis	DC (n=72), n (%)	ACLF (n=65), n (%)	p-value
ALD	38 (52,8)	41 (63,1)	0,234
ALD + viral infection	14 (19,4)	8 (12,3)	0,267
ALD + NASH	14 (19,4)	15 (23,1)	0,609
Viral infection + NASH	6 (8,3)	0 (0)	0,014

Note: Data are presented as n (%). Group comparison was performed using Fisher's exact test due to expected frequencies <5. ALD — alcoholic liver disease; NASH — non-alcoholic steatohepatitis DC — decompensated cirrhosis; ACLF — acute-on-chronic liver failure.

Table 3. *Comparative clinical and laboratory characteristics of patients with decompensated cirrhosis (DC) and acute-on-chronic liver failure (ACLF)*

Indicator / Reference range	Overall cohort n=137	DC n=72	ACLF n=65	P value
Gender, n (%) males females	 62 (45,3) 75 (54,7)	 38 (52,8) 34 (47,2)	 38 (58,5) 27 (41,5)	0,856
age	50 (42-58)	51,5 (44,3-59,0)	48,0 (51,0-58,0)	0,128
Readmissions, n (%)	88 (69,8 %)	42 (65,6 %)	46 (74,2 %)	0,295
Ascites on admission, n (%)	101 (79, 5 %)	48 (84,2 %)	53 (75,7 %)	0,238
Hemoglobin, 130–170 г/л	109 (90-126)	116 (94-134)	103 (87-118)	**0,010**
Platelets, 150–340×10^9 /л	122 (88-161)	123 (88-164)	121 (76-161)	0,674
Leukocytes, 4–10×10^9 /л	9.0 (6,4-12,3)	7,9 (5,6-11,2)	9,8 (7,5-13,2)	**0,009**
CRP, 0,1–7 мг/л	29 (14-51)	25 (9,6-48,3)	34 (16-52,8)	**0,05**
NLR 1–2	3,6 (2.3-6,4)	2,9 (2,1-5,5)	4,4 (2,5-7,5)	**0,004**
Total protein, 65–85 г/л	67 (59-71)	68 (63-71)	64 (57-72)	**0,05**
Albumin, 35–55 г/л	28 (24-32)	28 (26-33)	27 (23-32)	**0,05**
Total bilirubin, 1,7–20,5 мкмоль/л	108 (36-268)	49 (27-100)	272 (165-467)	**<0,001**
Direct bilirubin, 0,9–5 мкмоль/л	53 (17-142)	27 (16,5-52,5)	143 (79-210)	**<0,001**
ALT, 0–32 МЕ/л	42 (20-73)	35 (19-63)	48 (27,3-77,5)	**0,048**
AST, 5–34 МЕ/л	111 (62-184)	88 (45-173)	140 (82,5-189)	**0,008**
GGT, 0–73 МЕ/л	182 (77-679)	153 (45-643)	249 (96-715)	0,064
ALP, 64–306 МЕ/л	335 (227-501)	295 (201-478)	359 (277-578)	**0,036**
Creatinine, 71–115 мкмоль/л	89 (72-124)	87 (72-108)	103 (71-177)	**0,016**
Lactate, 0,5 до 2,2	2,7 (1,8-4.4)	1,6 (1,5-2,3)	3,4 (2,5-5,4)	**0,001**
INR, 0,85–1,2	1,6 (1,3-2,1)	1,47 (1,29-1,77)	1,86 (1,41-2,46)	**<0,001**
Ammonia, 8–60 мкмоль/л	149 (109-205)	146 (113-219)	149 (101-196)	**0,048**

Note: Data are presented as median (25th; 75th percentile) for continuous and n (%) for categorical variables. Continuous variables were compared using the Mann-Whitney U test. Data for 'Previous hospitalizations' and 'Ascites at admission' were available for 126 and 127 patients, respectively. CRP — C-reactive protein; NLR — neutrophil-to-lymphocyte ratio; ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGT — gamma-glutamyl transferase; ALP — alkaline phosphatase; INR — international normalized ratio.

reaching the maximum in ACLF 3 (p=0.003). Lactate was also significantly higher in the ACLF group (p=0.001), with its peak levels in ACLF 3.

INR was significantly higher in the ACLF group (p<0.001), with its values increasing in correlation with the ACLF severity (p<0.001).

All the analyzed prognostic scores (MELD-Na, MDF, SOFA, CLIF-C OFs, Child-Pugh) presented in Table 5 significantly differed in ACLF vs. patients with DLC (p<0.001 for all patients), as well as in different ACLF stages (ACLF 3 > ACLF 2 > ACLF 1; p<0.001).

Kaplan-Meier curves were constructed for the survival analysis. Statistically significant differences were detected in the 28-day survival between the groups of patients with DLC, ACLF 1, ACLF 2, and ACLF 3 (Log-Rank p<0.001). The features of curve changes demonstrated their significant divergence, which was the clearest in the ACLF 3 group (Fig. 1).

The mean maximum life expectancy in DLC was 26.7±0.5 days; 95 % CI 25.6–27.7; the minimum one was reported in ACLF 3 patients — 13±3.4 days; 95 % CI 5.6–20.4.

The 28-day mortality in patients with DLC did not exceed 9.7 % (7/72), while in patients with ACLF it reached 27.7 % (18/65); (ACLF 1: 24.4 % (10/41), ACLF 2: 17.6 % (3/17), ACLF 3: 71.4 % (5/7).

To detect factors directly associated with 28-day mortality, the comparative analysis of clinical & laboratory parameters and data from prognostic scales was arranged between the survived (n=112) and deceased (n=25) patient groups (Table 6). The proportion of patients with ACLF in the deceased group was significantly higher (18 [72.0 %] vs. 47 [42.0 %] among survived subjects; p=0.007). And, on the contrary, decompensated patients without ACLF predominated among survived patient (65 (58.0 %) vs. 7 (28.0 %) among deceased ones; p=0.007).

Table 4. *Comparative clinical and laboratory characteristics by different stages of ACLF*

Indicator	ACLF 1 (n=41)	ACLF 2 (n=17)	ACLF 3 (n=7)	P value
Gender, n (%)				
males	27 (65,9 %)	8 (47,1 %)	3 (42,9 %)	
females	14 (34,1 %)	9 (52,9 %)	4 (57,1 %)	
age, лет	48 (41-58 %)	47 (41-57 %)	50 (34-57 %)	0,498
Ascites on admission, n (%)	27 (75,0 %)	17 (100,0 %)	4 (100,0 %)	0,090
Readmissions, n (%)	30 (76,9)	13 (81,3)	3 (42,9)	0,181
Hemoglobin, 130–170 г/л	110 (93-123)	93 (83-103)	90 (64-106)	0,005
Platelets, 150–340×10⁹ /л	112 (66-160)	126 (100-162)	132 (70-146)	0,801
Leukocytes, 4–10×10⁹ /л	8,7 (6,8-11,1)	12,1 (9,7-14,8)	12,4 (9,6-25,0)	0,001
CRP, 0,1–7 мг/л	29,7 (16-51)	38,4 (12-48,4)	48 (31-84)	0,106
NLR 1–2	4,2 (2,6-6,5)	5,0 (2,8-6,4)	4,9 (2,0-8,6)	0,023
Total protein, 65–85 г/л	67 (59-73)	64 (57-70)	56 (48-62)	0,015
Albumin, 35–55 г/л	28 (24-34)	27 (23-31)	24 (20-26)	0,015
Total bilirubin, 1,7–20,5 мкмоль/л	260 (117-431)	316 (216-444)	635 (209-640)	<0,001
Direct bilirubin, 0,9–5 мкмоль/л	101 (40-198)	138 (111-206)	199 (145-208)	<0,001
ALT, 0–32 МЕ/л	60 (28-74)	43 (18-80)	62 (43-77)	0,151
AST, 5–34 МЕ/л	147 (71-187)	141 (108-183)	130 (96-195)	0,052
GGT, 0–73 МЕ/л	330 (121-735)	194 (88-517)	156 (74-248)	0,222
ALP, 64–306 МЕ/л	359 (283-580)	381 (340-562)	278 (129-504)	0,044
Creatinine, 71–115 мкмоль/л	89 (69-177)	89 (78-160)	177 (125-349)	0,003
Lactate, 0,5 -2,2	3,0 (2,5-4,4)	3,6 (1,8-7,1)	4,9 (2,6-8,2)	0,008
INR, 0,85–1,2	1,57 (1,32-2,08)	2,30 (1,86-2,83)	2,57 (2,09-3,71)	<0,001
Ammonia, 8–60 мкмоль/л	125 (87-186)	148 (101-195)	196 (172-199)	0,017

Note: Data are presented as median (25th; 75th percentile) for continuous and n (%) for categorical variables. Overall comparison of continuous variables across the three groups was performed using the Kruskal-Wallis test. CRP — C-reactive protein; NLR — neutrophil-to-lymphocyte ratio; ALT — alanine aminotransferase; AST — aspartate aminotransferase; GGT — gamma-glutamyl transferase; ALP — alkaline phosphatase; INR — international normalized ratio.

Table 5. *Comparison of prognostic scales and outcomes*

Scale	DC (n=72)	ACLF (1,2,3) (n=65)	p-value[1]	ACLF1 (n=41)	ACLF2 (n=17)	ACLF3 (n=7)	p-value[2]
MELD-Na	18 (13-23)	28 (24-33)	<0,001	26 (22-29)	30 (26-35)	37 (31-42)	<0,001
MDF	33 (31-45)	58 (40-100)	0,002	43 (35-78)	67 (51-102)	103 (92-134)	0,001
SOFA	4 (2-5)	6 (5-7)	<0,001	5 (4-6)	6 (5-7)	10 (7-12)	<0,001
CLIF-C OFs	7 (7-8)	9 (8-11)	<0,001	9 (9-9)	11 (10-11)	13 (12-14)	<0,001
Child-Pugh class, n (%)							0,012
– A	2 (2,8 %)	0	<0,001	0	0	0	NA
– B	26 (36,1 %)	7 (11,1 %)		7 (17,9 %)	0	0	1-3 =0,023
– C	44 (61,1 %)	56 (88,9 %)		32 (82,1 %)	17 (100 %)	7 (100 %)	1-3 =0,046
28-day mortality, %	7 (9,7 %)	18 (27,7 %)	0,007	10 (24,4 %)	3 (17,6 %)	5 (71,4 %)	0,05

Note: Data are presented as median (25th; 75th percentile) for scores and n (%) for Child-Pugh class. p-value[1] denotes comparison between DC and ACLF (1-3) groups. p-value[2] denotes overall comparison across ACLF 1, 2, and 3 groups (Kruskal-Wallis test for scores and Chi-square for Child-Pugh class). MELD-Na — MELD-Sodium; MDF — Maddrey discriminant function; SOFA — Sequential Organ Failure Assessment; CLIF-C OFs — CLIF Consortium Organ Failure score.

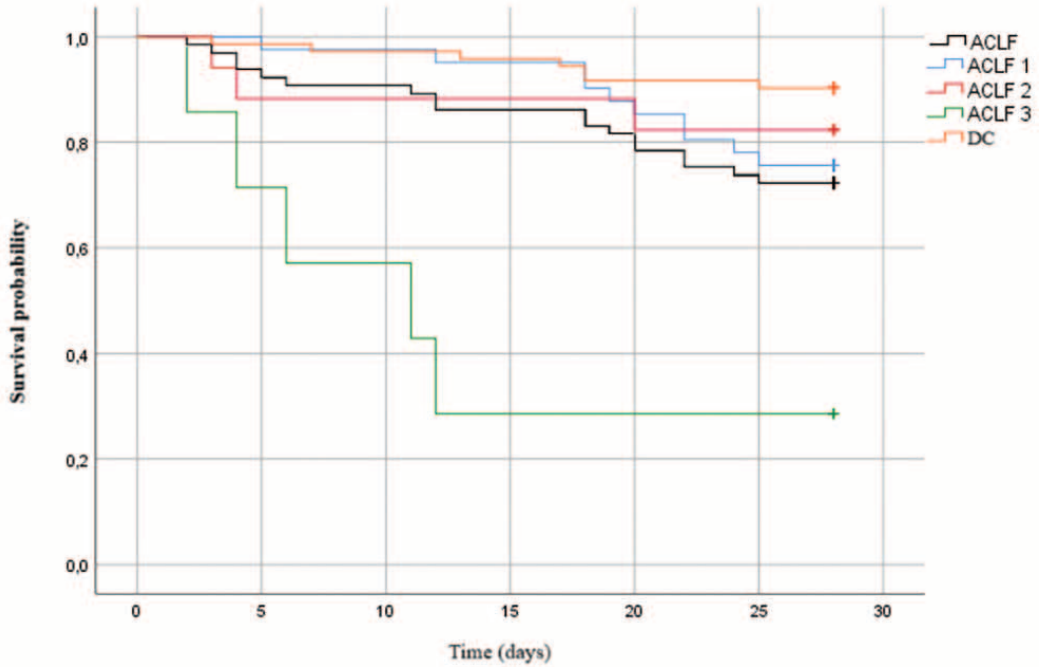

Figure 1. *28-day survival of patients with ACLF and DC*
Abbreviations: ACLF — acute-on-chronic liver failure; DC — decompensated cirrhosis without ACLF.

The age and gender of patients with LC did not differ in the deceased and survived groups (p>0.05). When evaluating oxygenation and hemodynamics parameters among the deceased patients, a decreased SpO_2/FiO_2 index (457.00 [452.00; 466.00] vs. 461.00 [461.00; 466.00]; p=0.001) and a lower mean blood pressure (81.00 [71.50; 91.50] mm Hg vs. 87.00 [80.00; 93.00] mm Hg among survived patients; p<0.001) were reported.

The following laboratory abnormalities were reported: white blood cells (9.70 vs. 8.62×10^9/L; p=0.025), NLI (5.73 vs. 3.26; p=0.034), CRP (48.00 vs. 25.50 mg/L; p<0.001), hyperbilirubinemia (252.0 vs. 97.0 μmol/L; p<0.001), AST (143.0 vs. 108.0 U/L; p=0.046), ALT (47.0 vs. 39.0 U/L; p=0.018); hyperlactatemia (3.40 vs. 2.50 mmol/L; p=0.040) — among the deceased and survived patients with LC, respectively.

One should also underline a larger rate of various infectious complications in the deceased patient group. Thus, urinary tract infections (UTIs) were detected in 16 (69.6 %) deceased vs. 35 (32.1 %) survived patients with LC (p=0.001). However, the rate of pneumonia and spontaneous bacterial peritonitis (SBP) in the groups analyzed did not differ (p>0.05).

Besides, when calculating prognostic scales, significant differences were also reported in the deceased vs. survived group**:** MELD (26.0 vs. 20.0; p=0.001), MELD-Na (26.0 vs. 22.0; p=0.001), Child-Pugh (score: 12.0 vs. 11.0; p=0.001; Class C: 92.0 % vs. 70.0 %; p=0.023), SOFA (5.0 vs. 4.0; p=0.025), CLIF-SOFA (9.0 vs. 8.0; p=0.002), CLIF-C OFs (9.0 vs. 8.0; p=0.001).

Discussion of results

Clinical & laboratory parameters of patients with DLC and ACLF were comparatively analyzed. Patient groups with DLC and ACLF were uniform and did not differ in gender or age.

Among patients hospitalized into the inpatient department with events of decompensated LC, a high rate of ACLF reaching 47 % was confirmed — this exceeds the values obtained in the European population (22.6 %) [7].

Decompensated LC as a cause of inpatient hospitalization is caused by various factors (late hospitalization, untimely referral, alcohol abuse).

The profile of DLC and ACLF triggers significantly differed**:** if isolated causes (infection, alcohol, GIB) were typical for DLC, while ACLF developed mainly due to the combination of these factors.

In both groups ALD was the most common cause of LC, which confirms the importance of alcoholization as a leading factor of CLDs.

Based on the meta-analysis published in 2023, the prevalence of ALD constitutes 3.5 % of the global population, with 5-year mortality rates reaching 50 %. With that, the prevalence of alcoholic LC is 0.3 %, with variable rates in different regions: 3.0 % in Europe, 3.6 % in the Western-Pacific region, 7.0 % in the United States of America [18].

The proportion of deaths caused by alcohol consumption in Russia is approximately 18 %, which corresponds to the 5th place among 180 countries [19].

Table 6. *Clinical and laboratory characteristics of deceased and surviving patients with liver cirrhosis*

Parameter	Deceased (n=25)	Survivors (n=112)	p-value
age, лет	50,0 [46,0; 58,0]	50,0 [42,0; 58,0]	0,085
gender, male (n(%))	14 (56,0 %)	61 (54,5 %)	0,889
Clinical indicators			
ACLF (n(%))	18 (72,0 %)	47 (42,0 %)	**0,007**
DC, (n(%))	7 (28,0 %)	65 (58,0 %)	**0,007**
Readmissions	12 (54,5 %)	76 (73,1 %)	0,085
Ascites	15 (78,9 %)	86 (79,6 %)	0,946
MAP, мм рт.ст.	81,00 [71,50; 91,50]	87,00 [80,00; 93,00]	**<0,001**
SpO_2/FiO_2	457,00 [452,00; 466,00]	461. 00 [461,00; 466,00]	**0,001**
UTI (n(%))	16 (69,6 %)	35 (32,1 %)	**0,001**
Pneumonia (n(%))	4 (16,0 %)	10 (9,1 %)	0,306
SBP (n(%))	2 (10,5 %)	21 (27,6 %)	0,120
Scale			
MELD	26,0 [21,0; 33,0]	20,0 [15,0; 26,0]	**0,001**
MELD-Na	26,0 [24,0; 34,0]	22,0 [16,0; 28,0]	**0,001**
DF	67,0 [43,0; 94,0]	43,0 [32,5; 79,0]	0,114
CPT класс C (n(%))	23 (92,0 %)	77 (70,0 %)	**0,023**
CPT класс B (n(%))	2 (8,0 %)	31 (28,2 %)	**0,034**
SOFA	5,0 [4,0; 7,0]	4,0 [3,0; 6,0]	**0,025**
CLIF-SOFA	9,0 [8,0; 12,0]	8,0 [6,0; 9,0]	**0,002**
CLIF-C OFs	9,0 [8,0; 11,0]	8,0 [7,0; 9,0]	**0,001**
CLIF-C ACLF	43,0 [0,0; 55,0]	0,0 [0,0; 44,0]	**0,001**
Laboratory parameters			
Hemoglobin, г/л	109,00 [88,50; 126,75]	111,00 [92,25; 123,50]	0,895
Leukocytes, $\times 10^9$/л	9,70 [8,00; 12,00]	8,62 [5,90; 12,60]	**0,025**
NLR	5,73 [2,86; 8,71]	3,26 [2,18; 5,75]	**0,034**
Lactate, ммоль/л	3,40 [2,50; 5,60]	2,50 [1,70; 4,23]	**0,040**
Total bilirubin, мкмоль/л	252,0 [135,0; 505,0]	97,0 [34,0; 237,0]	**<0,001**
ALT, Ед/л	47,0 [34,0; 90,0]	39,0 [19,0; 71,0]	**0,018**
AST, Ед/л	143,0 [87,0; 184,0]	108,0 [57,0; 183,0]	**0,046**
CRP, мг/л	48,00 [33,00; 67,00]	25,50 [12,00; 48,00]	**<0,001**
Ammonia	184 [144; 223]	142 [102; 196]	0,068

Note: Data are presented as median (25th; 75th percentile) for continuous and n (%) for categorical variables. Comparisons were made using the Mann-Whitney U test for continuous and Chi-square test for categorical variables. ACLF — acute-on-chronic liver failure; DC — decompensated cirrhosis; MAP — mean arterial pressure; UTI — urinary tract infection; SBP — spontaneous bacterial peritonitis; MELD — Model for End-Stage Liver Disease; MELD-Na — MELD-Sodium; DF — Discriminant Function; SOFA — Sequential Organ Failure Assessment; CLIF-SOFA — CLIF-SOFA score; CLIF-C OFs — CLIF Consortium Organ Failure score; CLIF-C ACLF — CLIF-C ACLF score

With that, chronic alcohol abuse is the most common cause of LC. Less frequently the etiology of CLDs among the patients examined by us was associated with a combination of several factors, i.e. alcohol, viral hepatitis, metabolic disorders.

The key role in the development of ACLF belongs to the systemic inflammatory reaction, which mechanism is still not fully clear. Modern data define the two main pathways leading to the immune response dysregulation and progressive inflammation [20].

The first pathway is associated with bacterial translocation and subsequent activation of Toll-like receptors (TLRs) [21] in immune cells via the interactions with pathogen-associated molecules (PAMPs) [22], e.g. bacterial lipopolysaccharides. This causes the formation of proinflammatory molecules, inducing the systemic inflammatory response.

The second pathway includes the release of damage-associated molecular patterns (DAMPs) by the altered hepatocytes [22], which leads to similar effects, as these molecules also bind to TLRs and other receptors, thus stimulating immune cells. The prolonged activation of these mechanisms leads to the constant proinflammatory response in patients with LC.

Besides, patients with cirrhosis and ACLF demonstrate impaired reactions to PAMPs due to immune exhaustion and endotoxin tolerance, which in turn is also caused by immunodeficiency associated with LC. This imbalance leads to the enhanced susceptibility to infectious complications. Ethanol enhances the sensitivity of hepatocytes to apoptosis, which potentiates their synergistic damaging effects with the bacterial lipopolysaccharide.

UTIs were significantly more common in our study in the deceased patient group, followed by pneumonia and SBP.

Although inflammation plays an important prognostic role in patients with ACLF, the modern laboratory evaluation of the inflammatory response is difficult, mainly due to the absence of a possible routine evaluation of cytokines outside of scientific institutions [23].

Due to the fact that systemic inflammation is a pivotal part of the ACLF pathogenesis, the search for available early markers of this condition is an important objective.

A systemic inflammation parameter, NLI, is one of such markers of the cellular immunity activation. The normal NLI range is 1 to 2; values over 3.0 or below 0.7 are considered abnormal in adults [24].

According to the CANONIC trial, CRP levels in the blood of patients with ACLF are significantly higher than in patients without organ dysfunction. Undoubtedly, the contribution of the infectious trigger is evident, however, when excluding patients with the confirmed infection, statistically significant differences in CRP levels are preserved between groups with or without infectious complications [7], which confirms the importance of immune dysregulation typical for ACLF.

Patients with ACLF demonstrated higher levels of liver dysfunction parameters, including bilirubin, INR, AST, ALP levels, as well as the decreased protein-synthetic function and hemoglobin levels, confirming the progressive organ failure.

Our study results have demonstrated that the mean life expectancy in patients with decompensated LC was 26 days, which significantly exceeded this parameter in the ACLF 3 group (13 days). This underlines the required early detection, timely treatment of cirrhosis complications, and the importance of evaluating disease stages for the outcome prediction.

In our study 28-day mortality in the DLC group was 9.7 %, in ACLF 1 — 24.4 %, while in ACLF 2 — 17.6 %, and ACLF 3 — 71.4 %. These results correlate with parameters in the CANONIC trial arranged based on the analysis of 1343 inpatients with LC from 21 European countries, while the mortality increased correlating with the organ dysfunction severity, i.e. 22.1 % in ACLF 1, 32 % in ACLF 2, 76.7 % in ACLF 3), while it was 4.7 % in the DLC group [7]. Mortality in ACLF was associated with the multi-organ failure, thus transferring patients to the high-risk group. The isolation of this patient group is possible thanks to the timely use of standard scales, which is currently not implemented into routine practice. Besides, limited therapeutic capabilities mostly aimed at symptomatic treatment also promote poor outcomes.

In our study we used scales to evaluate the condition of patients with LC (CTP, MELD, MELD-Na), as well as those evaluating the organ dysfunction (CLIF-SOFA, CLIF-C OFs, CLIF-C ACLF).

Thus, the CANONIC trial helped to develop an organ dysfunction assessment scale CLIF-SOFA [7]. In 2014 Jalan R. et al. showed that the accuracy of the CLIF-C OF simplified scale is similar to that of CLIF-SOFA in predicting the mortality among patients with LC [15]. The CLIF-C ACLF advantage is that the white blood cell count is also checked to assess the level of inflammation. According to multiple studies, CLIF-SOFA, CLIF-C OF, and CLIF-C ACLF are superior to CTP, MELD, and MELD-Na in the accuracy of predicting short-term and long-term mortality among patients with ACLF [7, 15, 25].

Using CLIF-C OFs, CLIF-SOFA scales helps to define a patient group with a high mortality risk.

MELD and SOFA demonstrated their efficacy in the assessment of the patient condition concerning the mortality prediction. However, one should note that each scale has its own limitations and should be used in conjunction with clinical data and individual patient features.

The comparative analysis of patients by the 28-day outcomes (Table 6) has provided significant evidence of the multi-organ failure severity and mortality risk factors in our cohort, which is confirmed by significantly higher scores in all scales assessing the multi-organ failure (SOFA, CLIF-SOFA, CLIF-C OFs, CLIF-C ACLF; $p<0.05$ for all scores).

Conclusion

Our study demonstrated a high rate of ACLF (47.4 %) in patients with LC, which exceeded parameters recorded in the European population (35 %). A combination of provoking factors prevailed among the main triggers leading to ACLF, while infections were the main cause of decompensated LC, which underscores the importance of their prevention, early screening, and timely treatment.

Patients with ACLF were characterized by significantly more severe hepatic failure, renal dysfunction, systemic inflammation, and higher scores in all predictive scales.

In our study, the use of CLIC-C OF as a key tool for ACLF assessment and determining the mortality risk has demonstrated a high predictive value, helping not only to differentiate patients with decompensation and ACLF ($p<0.001$), but also to detect differences between ACLF 1-3. This scale use in clinical practice will promote the timely patient referral to the specialized treatment, including liver transplant centers.

Вклад авторов:

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Тараки Б.М.: сбор и анализ данных, статистическая обработка материала, написание текста.

Адамова И.Г.: сбор и анализ данных, статистическая обработка материала

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Петренко Н.В.: участие в разработке концепции и дизайна исследования

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Contribution of Authors

All the authors made a significant contribution to the preparation of the work, read and approved the final version of the article before publication

Taraki B.M.: data collection and analysis, statistical processing of data, text writing

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Ilchenko L.Yu.: concept and design of the study, text editing, approval of the final text of the article

Fedorov I.G.: data collection, literature review

Totolyan G.G.: design of the article and accompanying materials

Petrenko N.V.: concept and design of the study

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МОЛОДАЯ ПАЦИЕНТКА С СИНДРОМОМ АЛЬПОРТА И ТЕРМИНАЛЬНОЙ ПОЧЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ. КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

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Young Patient with Alport Syndrome and End-Stage Renal Disease. A Clinical Observation

Резюме

Синдром Альпорта (СА) — генетически детерминированное заболевание, обусловленное нарушениями в генах, кодирующих альфа-3/4/5 цепи коллагена IV типа. Данный тип коллагена является важнейшим структурным компонентом базальных мембран клубочка, сетчатки и внутреннего уха, поэтому генетические мутации при данном заболевании приводят к поражению почек, нарушениям зрения и слуха. В зависимости от типа мутации, клиническая картина СА варьирует от бессимптомного снижения функции почек до раннего развития терминальной хронической почечной недостаточности (тХПН), утраты слуха и нарушения зрения. При этом, СА является одной из наиболее распространенных причин семейной протеинурии в популяции.

Исторически данное заболевание рассматривалось в качестве болезни детского возраста и чаще — мужского пола, хотя в настоящее время его распространенность среди женщин достаточно высока. Женский пол сопряжен с более мягким течением и поздним развитием осложнений, включая характерные нарушения зрения, слуха и тХПН. По данным J.P. Jais et al. (2003), тХПН наблюдается к 45 годам у 12% пациенток с х-сцепленным вариантом СА. Таким образом, раннее возникновение тяжелых проявлений является относительно редким, что приводит к недостаточной настороженности в отношении генетически обусловленных заболеваний почек, позднему проведению генетического тестирования и несвоевременному началу лечения, в том числе — трансплантации. В настоящее время проблема выявления, терапевтического и оперативного лечения СА остается сложным в решении вопросом.

В данной статье представлен клинический случай диагностики и ведения молодой пациентки с х-сцепленным COL4A5 вариантом СА, осложнившимся ренопаренхиматозной артериальной гипертензией и ранним прогрессированием до тХПН, что потребовало проведения заместительной почечной терапии и последующей трансплантации почки. Динамическое 2,5-летнее наблюдение показало значительное улучшение состояния органов-мишеней на фоне своевременного проведенного лечения.

Ключевые слова: *синдром Альпорта; х-сцепленное наследование, мутация гена COL4A5; терминальная почечная недостаточность; трансплантация почки; ингибиторы ангиотензин-превращающего фермента*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

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Abstract

Alport syndrome (AS) is a genetically determined disease caused by abnormalities in the genes encoding alpha-3/4/5 chains of type IV collagen. Collagen IV is the most important structural component of the glomerular basement membranes, retina and inner ear, therefore, genetic mutations in this disease lead to kidney damage, vision and hearing impairment. Depending on the type of mutation, the clinical features of AS vary from asymptomatic decrease to early development of end-stage renal disease (ESRD), hearing loss and blindness. At the same time, AS is one of the most common causes of familial proteinuria in the population. Historically, this disease was considered a pediatric disease and more common in males, although currently its prevalence among women is high. The female sex is associated with a milder course and late development of complications, including vision and hearing impairment and ESRD. According to J.P. Jais et al., ESRD is observed by the age of 45 in 12% of patients with the x-linked variant of AS. Early onset of severe manifestations is quite rare, which leads to insufficient diagnosis of genetically determined kidney diseases, late genetic testing and initiation of treatment, including transplantation. Currently, the problem of detection, therapeutic and surgical treatment of AS remains a difficult issue to resolve.

This article presents a clinical case of diagnosis and management of a young patient with the x-linked COL4A5 variant of AS, complicated by renal parenchymal hypertension and early progression to ESRD, which required renal replacement therapy (dialysis) and kidney transplantation. The subsequent 2.5-year follow-up showed a significant improvement in the condition of target organs against the background of timely treatment.

Key words: *Alport syndrome, x-linked inheritance, COL4A5 gene mutation, end-stage renal disease, kidney transplantation, angiotensin converting enzyme inhibitors*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Young Patient with Alport Syndrome and End-Stage Renal Disease. A Clinical Observation» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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EH — essential hypertension, BP — blood pressure, Ab — antibody, CSs — corticosteroids, PW — posterior wall, ACEIs — angiotensin-converting enzyme inhibitors, LV — left ventricle, LA — left atrium, IVS — interventricular septum, AS — Alport syndrome, ABPM — ambulatory blood pressure monitoring, GFR — glomerular filtration rate, CKD — chronic kidney disease, ESRD — end-stage renal disease, EchoCG — echocardiography

Introduction

Alport syndrome (AS) is a genetically determined disease caused by mutations in genes coding α-chains of type IV collagen that represent the most important component of basal membranes. AS prevalence is approximately 1:2000 and differs in various regions, with higher prevalence in Northern European countries [1]. The X-linked disease variant caused by mutations in the gene coding the α5-chain of type IV collagen (COL4A5) is the most common one, as it is detected in over 80% patients with this disease [2, 3].

Type IV collagen is a main structural component of basal membranes, playing a significant role in cellular proliferation and differentiation, activation of migration processes, and maintenance of adhesion of various cell types [4]. Clinical AS manifestations may be variable: detection of the pathogenic COL4A5 mutation variant is associated with a larger probability of anomalies of the glomerular basement membrane, hearing loss, lenticonus, posterior subcapsular cataract, and macular retinopathy. Some patients with X-linked AS resulting from the partial deletion of the COL4A5 gene or the neighboring COL4A6 gene develop diffuse leiomyomatosis — smooth muscle tumors of the esophagus, trachea, bronchi, and female genitals [5].

During the early disease stage, persistent hematuria is detected in all male patients and approximately 95% females, as well as proteinuria [6–8]. End-stage renal disease (ESRD) requiring dialysis and renal transplant is the disease outcome. According to the results of Gillion

V, et al. (2018), the mean age of ESRD emergence in patients with different AS variants was 26 years, while the transplant age was 28 years (range: 11–12 to 71–73 years) [9]. With that, the risk of progression to ESRD in females with X-linked AS and heterozygous COL4A5 reaches 12 % by the age of 45, 30 % by the age of 60, and 40 % by the age of 80 [10, 11]. Renoparenchymatous hypertension is another significant complication, which often develops in childhood or adolescence within the setting of progressive glomerulonephritis and accelerates renal fibrosis [12].

The genetic testing for the COL4A5 gene mutations is the main diagnostic method for the X-linked AS variant and further determination of approaches to treatment — from medications to renal transplant in patients with ESRD [6]. This clinical case describes a patient with an X-linked COL4A5 AS variant complicated by renoparenchymatous hypertension and requiring renal transplant.

Clinical Case Study

The female patient K., 22 years old, was hospitalized into the University Clinical Hospital (UCH) No. 1 of the Sechenov University (Moscow) in February 2025. She was followed up by outpatient clinics with complaints of unstable blood pressure (BP), palpitations during physical exertion. The family history was significant for hematuria in the patient's mother, grandmother, and grandgrandmother. The first changes in the patient's urinalysis were detected in 2005 at the age of 3 years (Table 1). With that, based on the examination results (renal ultrasound (US) and urography), the size and function of kidneys corresponding to the age norm.

In 2006 (at the age of 4 years) repeated tests demonstrated proteinuria, hematuria (even total), leukocyturia — the patient was hospitalized for additional examination with the preliminary diagnosis of the urinary tract infection or metabolic nephropathy. The US revealed slight asymmetry of kidney sizes (right: 93×35 mm; left: 86×30 mm). In September 2007 red-brown urine emerged within the setting of an acute respiratory viral infection (ARVI). Renal biopsy was not arranged, however accounting for the clinical signs, family history, and laboratory data, the preliminary diagnosis of hereditary nephritis was established. Treatment with corticosteroids (CSs) was started, but lacked a positive effect.

Hematuria (from minimum to total) and proteinuria persisted within the period from 2007 to 2019. The patient was hospitalized annually, in 2013 she started using an angiotensin-converting enzyme inhibitor (ACEI) enalapril with nephroprotective purposes. With that, hematuria and proteinuria episodes persisted, and later enalapril was discontinued. To verify the diagnosis, the blood tests were arranged for anti-double-stranded DNA antibodies (Abs), C3 and C4 complement components, anti-myeloperoxidase Abs, anti-proteinase 3 Abs, antimitochondrial Abs (detected in a diagnostically insignificant titer).

In 2019 the patient was hospitalized into the National Medical Research Center (NMRC) of the Children's Health (Moscow), where CKD was diagnosed (anemia, uremia, hyperuricemia, with the creatinine level of 159 μmol/L). Renal biopsy was conducted diagnostically on April 22, 2019 (focal-segmental glomerulosclerosis was confirmed). Despite the CS treatment administered, her condition continued to worsen progressively: by January 23, 2020 the creatinine level reached 178.0 μmol/L. On January 30, 2020, accounting for the unfavorable family history, the molecular-genetic testing was arranged with the confirmed pathogenic (heterozygous) variant of chrX:g.107938061_107938064de in the COL4A5 gene, which, according to the Online Mendelian Inheritance in Man (OMIM) database, corresponded to AS with X-linked dominant inheritance. Thus, the following diagnosis was established: Alport syndrome. Focal-segmental and global glomerulosclerosis. Chronic kidney disease (CKD) 3B, Grade A3.

Table 1. *Dynamics of urine and biochemistry blood tests parameters*

Urine test								
Year / Parameter	2005-06.2006	11.2006-12.2006	09.2007	2019	2021	2022 (after transplantation)	2024	2025
Proteinuria, g/l	0,132-0,165	0,2	0,099	1,456	-	0,17	0,048	0
RBC/HPF	15-18	total	4-8	total	-	-	5-8	0
WBC/HPF	-	-	До 10	-	-	-	15-20	7-10
Biochemistry blood test								
Creatinine, μmol/l	N	N	N	136-178	1096-1269	110	115	116
Urea, mmol/l	N	N	N	-	38,2-38,4	6	6,28	7,35

Note. RBC — red blood cells, HPF — high powered field, WBC — white blood cells

In April 2021, the patient's condition deteriorated significantly: along with unstable BP, she developed severe headache (the patient started taking non-steroidal anti-inflammatory drugs: ketorolac, ibuprofen, maximum 3 tablets daily) and fine tremor in upper extremities. In October 2021 creatinine and urea levels increased (Table 1), while hemoglobin level dropped to 76 g/L. Blood transfusions were arranged, erythropoietin and iron drugs were added to treatment with positive effects: hemoglobin levels increased to 97 g/L. After the discharge, CRF events progressed with the emergence of mineral-bone disorders, secondary hyperparathyroidism. Due to the first-detected regular episodes of BP elevation (to 225/130 mm Hg), the diagnosis of hypertension was established, and the following outpatient hypotensive treatment was administered: bisoprolol and nifedipine, although the patient did not take those medications regularly. Echocardiography (EchoCG) revealed left ventricular (LV) hypertrophy (1.2 cm) with the left atrial (LA) dilation (4.2 cm), pericardial effusion (5–6 mm). The US demonstrated significant diffuse alterations in the renal parenchyma — signs of nephrosclerosis (right kidney: 79×29 mm; left kidney: 79×29 mm), renal cysts. Glomerular filtration rate (GFR) decreased to critical values (4 mL/min/1.73 m2), while urea levels increased to 38.3 mmol/L. Hemodialysis sessions started from October 12, 2021. Accounting for the persistent BP elevation episodes, hypotensive treatment was corrected: losartan and nifedipine were administered. See Figure 1 for the patient's condition time scale.

Accounting for the patient's age and absence of severe concomitant diseases, the renal transplant was approved. The patient received the right kidney transplant from the postmortem donor on November 12, 2022. The transplant function was immediate. Creatinine (110 μmol/L) and urea (6 mmol/L) levels stabilized in the postoperative period. The following immunosuppressive therapy was selected: tacrolimus 12 mg, mycophenolic acid 720 mg twice daily, methylprednisolone 16 mg. Positive follow-up with the persistent BP normalization at the level of 120–130/80 mm Hg was confirmed during the inpatient treatment and after discharge (hypotensive treatment was discontinued). Due to the satisfactory transplant function for over a year, in 2024 the arteriovenous fistula for hemodialysis was closed surgically. Based on the transplant US, the kidney was sized 112×42 mm (Figure 2).

During the follow-up, the LV wall thickness decreased (interventricular septum (IVS): 0.90–0.95 cm; posterior wall (PW): 0.9 cm); the LA cavity shrunk to 2.9 cm. Since May 2023, the patient again developed unstable BP with maximum levels reaching 140–150/90 mm Hg; enalapril 5 mg/day was added to the outpatient treatment, however the therapy was discontinued spontaneously. Accounting for the persistent BP elevation episodes, in February 2025 the patient visited for the first time the cardiologist of the Sechenov University Clinical Center, after which she was hospitalized for the first time to the Cardiology Department No. 1 of UCH No. 1 (Moscow) for additional examination and treatment selection.

Physical examination: the patient's condition remained satisfactory; edema was not detected. During lung auscultation, vesicular breathing was detected in all pulmonary regions, with no rales. Regular heart rhythm, clear cardiac tones were auscultated. Heart rate (HR) 86 beats per minute. BP 145/95 mm Hg. SpO2 98 %. No dysuric signs were reported. The lumbar punch sign was negative. Laboratory tests: the hemoglobin level was within normal limits (125 g/L), creatinine (116 μmol/L) and urea (7.35 mmol/L) levels were moderately increased, with the estimated GFR of 58 mL/min/1.73 m2.

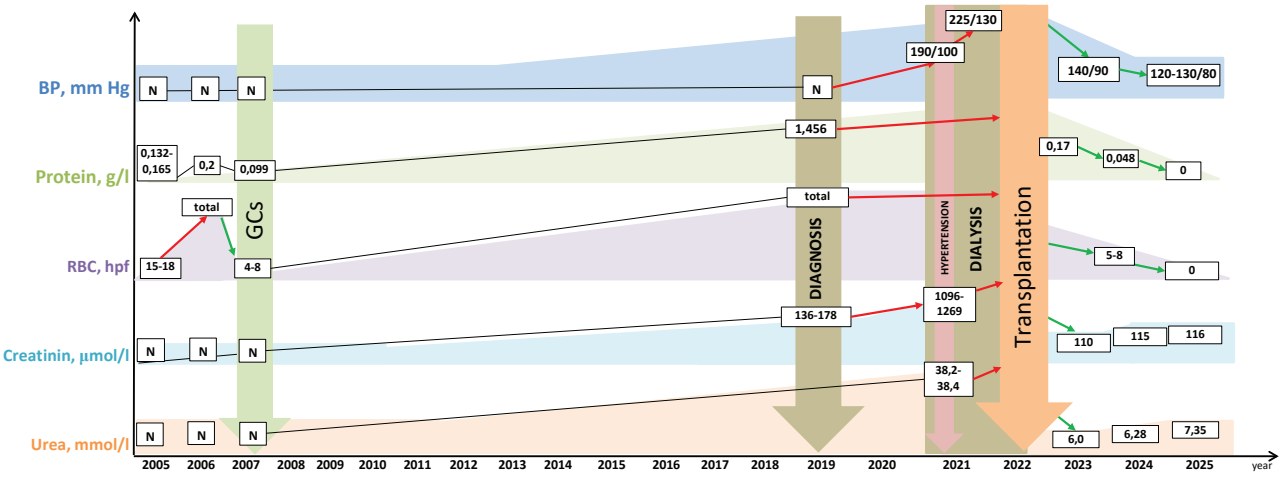

Figure 1. *Patient's condition before and after kidney transplantation*
Note. BP — blood pressure, RBC — red blood cells, GCs — glucocorticoids

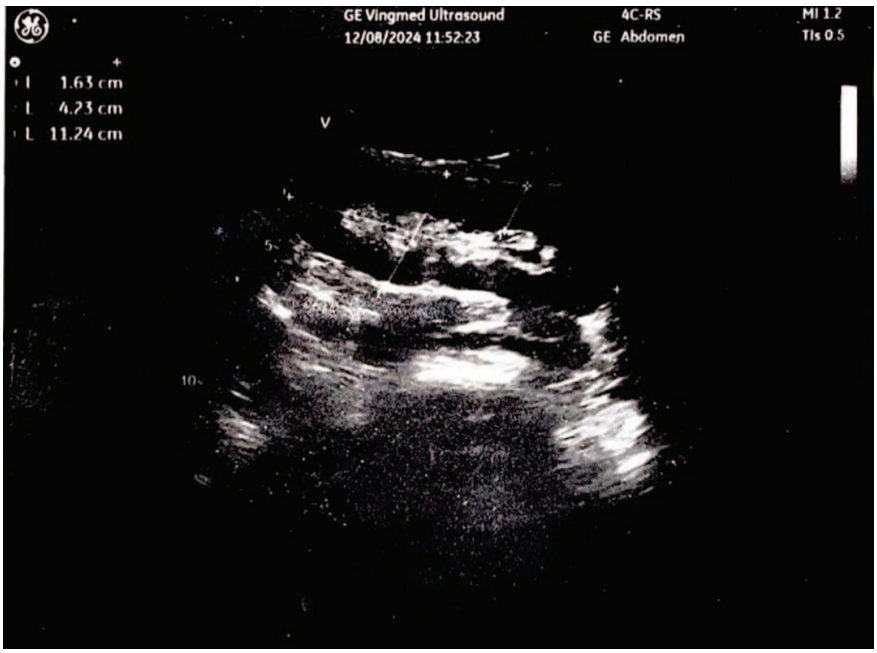

Figure 2. *Ultrasound of transplanted kidney*

Echocardiography (EchoCG): sizes of cardiac cavities, LV wall thickness was within normal limits (IVS: 0.9–0.95; PW: 0.9 cm). The systolic function was not impaired (LV ejection fraction 60 %). Diastolic dysfunction signs were not detected. Holter electrocardiography (ECG) monitoring: main sinus rhythm, no significant arrhythmias and blocks were reported. According to the ambulatory blood pressure monitoring (ABPM) data, persistent systolo-diastolic hypertension was detected during the whole monitoring period (Figure 3).

According to the renal US data, kidney sizes were decreased to 56×20 mm (right) and 55×18 mm (left), with the maximum parenchymal thickness of 4 mm.

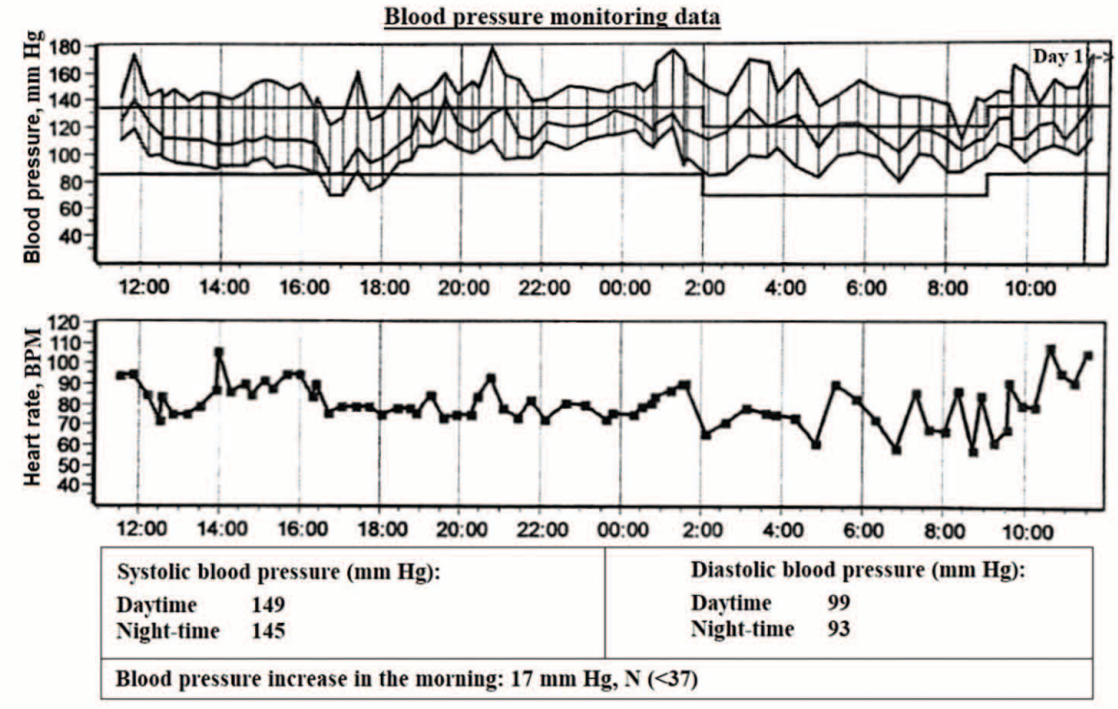

Figure 3. *Patient's blood pressure monitoring data*

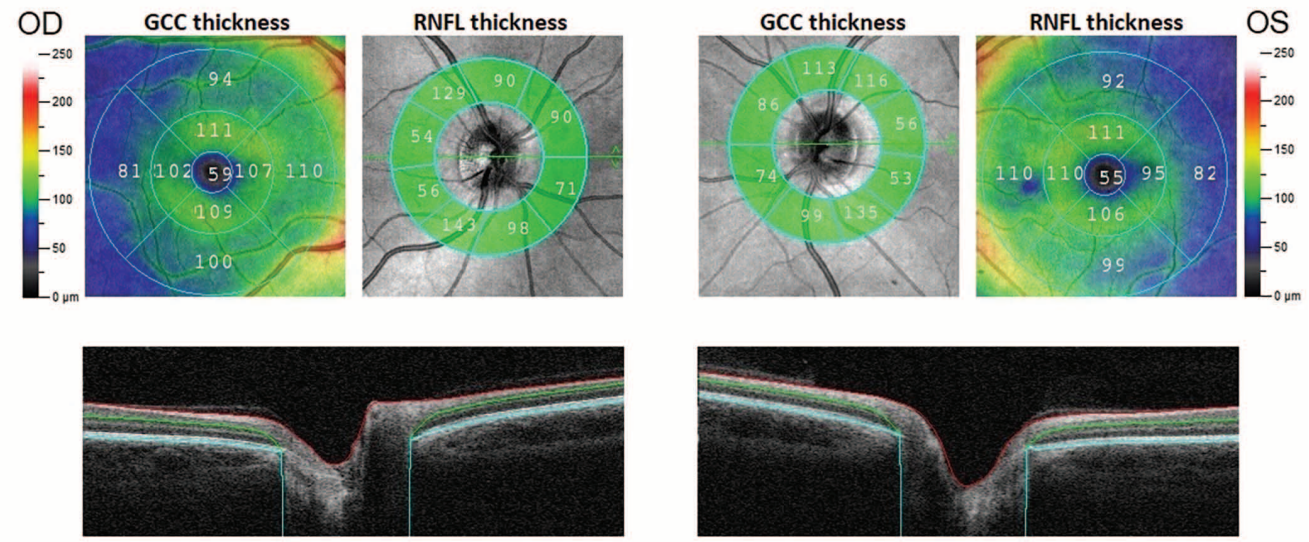

Figure 4: Patient's optical coherence tomography data.
OD — right eye; OS — left eye; GCC — ganglion cell complex; RNFL — retinal nerve fiber layer

The donor kidney was sized about 115×43 mm, with two marginal cysts sized 12 and 9 mm. Accounting for the ABPM data (persistently unstable BP with elevations to 179/120 mm Hg), as well as with cardionephroprotective purposes, therapy was supplemented with perindopril (4 mg in the morning) with BP level monitoring. During the inpatient treatment, BP dropped to 125–130/80 mm Hg, with good tolerability and therapy compliance; thus, this treatment regimen was continued.

To detect retinal vascular alterations as part of AS and renoparenchymatous hypertension, optic coherent tomography (OU) was arranged: nuclear and plexiform layers were preserved, the external limiting membrane was patent and continuous. The "retinal pigmented epithelium — Bruch's membrane" complex was normal. The choroid was normal (Figure 4).

Based on the clinical & instrumental data obtained, the following final clinical diagnosis was established:

Main disease: Alport syndrome, COL4A5 X-linked dominant type. Left kidney transplant from the postmortem donor with the transplanted ureter stenting (December 11, 2022). Creation of the arteriovenous fistula (October 18, 2021), surgical closure of the fistula on July 9, 2024.

Complications: Focal-segmental glomerulosclerosis (renal biopsy arranged in 2019). CKD C5 (renal replacement therapy with long-term hemodialysis since October 2021 till November 2022) with the outcome of CKD 3A (eGFR (CKD-EPI, 2011 modification) 57.53 mL/min/1.73 m^2), A1. Donor kidney cysts. Grade 3 secondary renoparenchymatous hypertension (controlled). High cardiovascular risk. Severe anemia transforming to mild anemia.

As the patient's condition stabilized, she was discharged under the follow-up of nephrologist, cardiologist, general practitioner at place of residence. Upon discharge, recommendations on the lifestyle modification were given, while the nephroprotective and hypotensive therapy (perindopril 4 mg/day), immunosuppressive therapy (tacrolimus 5 mg/day, mycophenolic acid 360 mg twice daily, prednisolone 5 mg/day), gastroprotective therapy (omeprazole 20 mg/day) was continued. Subsequently, after the treatment start, serum creatinine and potassium levels were monitored for 3 weeks (with no trends to increasing). After 3 months of follow-up, the patient's condition remained stable, not deteriorating within the setting of drug therapy. According to the BP measurements during follow-up visits and BP self-control, BP normalized at levels <130/80 mm Hg, which corresponded to target levels based on the Clinical Guidelines of the Ministry of Health of Russia and KDIGO Guidelines [13–15].

Clinical Case Discussion

A familial case of hemorrhagic nephritis was first described by S. Alport almost a century ago, in 1927 [16]. The analysis of the collagen structure in the glomerular basement membrane enabled to determine the pathophysiological mechanisms of this syndrome subsequently [17]. The following typical pathomorphological AS signs were established: altered thickness of the glomerular basement membrane, accelerated loss of podocytes or fusion of their processes [18, 19]. Most frequently those alterations form signs typical for the minimal change disease, focal-segmental glomerulosclerosis, or mesangioproliferative glomerulonephritis [2].

Structural alterations lead to microhematuria in 98 % female patients, manifesting with the combination of hematuria and proteinuria in 73 % cases [20]. Clinical AS manifestations may be different, and despite the fact that in the majority of cases persistent microhematuria is the only disease symptom, while ESRD may develop at a rather early age, which corresponds to the disease course in the patient described [21]. In the clinical case presented, the molecular-genetic testing was arranged rather late despite the family history, typical clinical signs, and renal biopsy data (focal-segmental and global glomerulosclerosis), which delayed the diagnosis.

The clinical case presented demonstrates the modern capabilities of therapeutic and surgical management of a young patient with an X-linked AS variant with a COL4A5 gene mutation. In this mutation type, hearing loss, lenticonus, retinopathy, and focal-segmental glomerulosclerosis more commonly manifest already in the adult years [6]. Based on the existing data, females with heterozygous mutations are not "benign carriers" and may have various disease outcomes, even with progression to ESRD [22]. It has been confirmed that the risk of its development is significantly higher in males, increasing with age in both genders: by the age of 40, ESRD affects ~90 % patients, by the age of 60 — 30 % female patients with AS [11, 23, 24]. Although the female gender is usually considered a factor of more favorable prognosis in COL4A5 X-linked AS variant, in our clinical case renal failure progression in the patient lead to early (at the age of 18) ESRD and its complications (renoparenchymatous hypertension, severe nephrogenic anemia, secondary hyperparathyroidism, mineral bone disorders) with subsequent hemodialysis and transplantation of the right kidney from the post-mortem donor. During the post-transplant period, eGFR increased and urea levels normalized within the shortest period possible, which confirms the efficacy of that intervention. Nevertheless, despite the patient's condition stabilization up till the present time, constant and prolonged monitoring of laboratory parameters and renal condition is required after the transplant, as it will help to minimize the risk of possible complications, timely starting the treatment if they emerge.

Sensorineural hearing loss of variable severity and visual disorders (corneal opacities, macular retinopathy, anterior lenticonus, cataracts) is often observed in patients with the X-linked AS form [25–27]. Besides, hypertension developing in several patients with hypertension also promotes intimal thickness and hyaline degeneration of the vessel wall. These structural rearrangements form the basis for the further development of hypertensive retinopathy [28]. In our clinical case the patient lacked hearing disorders, pathological alterations of the basal membrane, and retinal angiopathy, which was confirmed by the optical coherent tomography-angiography (2025).

The basal membrane lesions in the retina and internal ear are common, but not mandatory AS manifestations. In females with X-linked AS hearing loss and visual abnormalities are less common than in males, affecting ~28 and 15 % patients, respectively [11, 29]. According to Yamamura T. et al. (2017), only 4 (1.5 %) of 275 examined patients developed specific ocular lesions [20]. In our clinical case the absence of secondary retinal alterations was most likely associated with the young age of the patient and a short-term history of hypertension, hypotensive treatment administered, and timely renal transplant.

The absence of extrarenal manifestations (hearing loss, visual disorders) is not a criterion to exclude the diagnosis of AS. Genetic testing is the key step in AS recognition that allows to avoid diagnostic errors [30]. Accounting for the risk of ESRD both in patients and their offsprings, the detection of AS in the young age is defining for the prognosis in such patients [6]. Renal transplant is the only curative treatment method for patients with ESRD. With that, the risk of graft rejection in patients with AS does not differ from that in patients with CKD of other origin; thus, the renal transplant is considered a method of choice in the treatment of this pathology [31].

The selection of hypotensive treatment mainly is mainly supported by the treatment tolerability and achievement of target BP levels [14, 15]. Accounting for the ambiguous recommendations regarding the selection of a specific drug group for the treatment of young patients that have received a transplant, as well as baseline BP levels of 140–150/90 mm Hg, this patient was recommended monotherapy with the drug from the ACEI group. Accounting for the achievement of the target BP value (120–130/80 mm Hg) and good treatment tolerability along with high compliance, it was decided to abstain from subsequent administration of the combined hypotensive treatment to avoid decreasing the systolic BP to ≤120 mm Hg, which can lead to hypoperfusion of vital organs and associated adverse effects [14]. Besides, it has been shown that early administration of ACEIs or angiotensin receptor blockers is safe and efficient to decrease proteinuria, stabilize BP levels, slow the progression of renal failure, and increase the life expectancy in patients with AS [32]. Based on this, timely renal transplant and subsequent administration of ACEIs for the treatment of renoparenchymatous hypertension in this patient was justified and can promote the improvement not just in the quality of life, but also in the survival [33].

Conclusion

Thus, the Alport syndrome course differs due to the variety of clinical manifestations, including secondary renoparenchymatous hypertension. Early ESRD is also

possible in females with the X-linked autosomal-dominant COL4A5 variant of this disease, with the possible absence of significant ear and eye lesions. At the same time, timely complex treatment may prevent further development of severe organ lesions, leading to a more favorable variant of the disease course.

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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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ГИПЕРРЕНИНОВАЯ АРТЕРИАЛЬНАЯ ГИПЕРТЕНЗИЯ — ТРУДНОСТИ ДИФФЕРЕНЦИАЛЬНОГО ДИАГНОЗА. КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

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Hyperreninic Arterial Hypertension — Difficulties in Differential Diagnosis. Clinical Observation

Резюме

Вторичные формы артериальной гипертензии (ВтАГ) характеризуются наличием конкретной потенциально устранимой причины повышения артериального давления (АД), более высокими его значениями, нередко рефрактерностью к гипотензивной терапии и большей распространенностью среди лиц молодого возраста. Диагностика ВтАГ предполагает поиск причин по принципу «от простого к сложному» на амбулаторном и стационарном этапах обследования. В статье описан клинический случай 44-летней женщины без факторов риска АГ, госпитализированной по поводу гипертонического криза на фоне неконтролируемой АГ. Была проведена многоэтапная лабораторная и инструментальная диагностика для исключения почечной, эндокринной, сосудистой патологии. Высокие значения ренина при нормальных показателях других гормонов надпочечников, гипофиза, щитовидной и паращитовидной желез послужили основанием для поиска ренальной и экстраренальной ренинпродуцирующей опухоли, результатом которого стала постановка диагноза гипергениновой эссенциальной АГ. В статье приводится классификация ВтАГ с перечнем рекомендованных диагностических мероприятий, принципы терапии гипергениновой АГ, имеющие практическое значение для терапевта, врача общей практики, эндокринолога, нефролога.

Ключевые слова: *вторичная артериальная гипертензия, эндокринная АГ, гипергениновая АГ, ренинома, селективный забор крови из почечных вен, диагностика, лечение*

Конфликт интересов

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

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Abstract

Secondary arterial hypertension (SAH) is characterised by the presence of a specific potentially treatable cause of hypertension, higher blood pressure (BP) values, often refractory to hypotensive therapy, and higher prevalence in young adults. Diagnosis of VtAH involves searching for causes according to the principle 'from simple to complex' at the outpatient and inpatient stages of examination. The article describes a clinical case of a 44-year-old woman without risk factors for AH, hospitalised for hypertensive crisis on the background of uncontrolled AH. Multistage laboratory and instrumental diagnostics was performed to exclude renal, endocrine, vascular pathology. High values of renin with normal values of other hormones of adrenal, pituitary, thyroid and parathyroid glands were the basis for searching for renal and extrarenal renin-producing tumours, which resulted in the diagnosis of hyperrenin essential AH. The article presents the classification of VtAH with a list of recommended diagnostic measures, principles of therapy of hyperreninic AH, which are of practical importance for the therapist, general practitioner, endocrinologist, nephrologist.

Key words: *secondary arterial hypertension, endocrine AH, hyperreninemic AH, reninoma, selective renal vein blood sampling, diagnosis, treatment*

Conflict of interests

The authors declare no conflict of interests

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Hyperreninic Arterial Hypertension — Difficulties in Differential Diagnosis. Clinical Observation» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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EH — essential hypertension, SH — secondary hypertension, BP — blood pressure, CNS — central nervous system, ECG — electrocardiogram, HR — heart rate, EF — ejection fraction, CAD — coronary artery disease, BMI — body mass index, RR — respiratory rate, HRT — hormone replacement therapy, 5-HIAA — 5-hydroxy-indole-acetic acid, RAAS — renin-angiotensin-aldosterone system, IHC — immunohistochemistry, ANF — antinuclear factor, ANCA — anti-neutrophil cytoplasmic antibodies, anti-dsDNA — anti-double-stranded DNA antibodies, anti-Scl-70 — anti-scleroderma 70 antibodies, ARBs — angiotensin II receptor blockers, MRAs — mineralocorticoid receptor antagonists, US — ultrasound, MSCT — multispiral computed tomography, MRI — magnetic resonance imaging, PET-CT — positron emission tomography — computed tomography, AC — abdominal cavity, ELISA — enzyme-linked immunosorbent assay, CVS — cardiovascular system, DP — drug product, ACEIs — angiotensin-converting enzyme inhibitors, HREH — high-renin essential hypertension

Introduction

Secondary (symptomatic) hypertension (SH) is a type of hypertension, which is defined as being caused by an identifiable root cause [1].

Secondary hypertension is diagnosed in 5–25 % cases of all hypertensions [1]. Primary or essential hypertension (EH) does not require the additional search for causes, unlike the secondary one — when the latter is suspected, other conditions that can trigger stable BP elevation should be excluded. Such conditions include renoparenchymatous and renovascular diseases, endocrine diseases affecting any endocrine gland and/or dysregulating its function, CNS diseases (both focal and diffuse), drug-induced hypertension, vascular anomalies. An important aspect of hypertension etiology verification is a possibility of its complete or partial regression in specific clinical situations, including with curative surgeries.

One of the most typical SH signs is a young age of the patient (with the exception of renovascular hypertension in elderly as a result of atherosclerotic renal artery stenosis). The inefficacy of optimal drug therapy, true resistance in middle-aged and elderly patients make the clinician expand the range of diagnostic investigations to search for additional causes of stably elevated BP. Ignoring clinical SH markers threatens to

lead to a high risk of cardiovascular complications at any age.

The prevalence of SH causes varies in specific age groups. Thus, among young persons the most common pathologies causing malignant hypertension include thyroid disorders, fibromuscular dysplasia, renal parenchyma and urinary tract disorders (interstitial nephrities, glomerulopathies [including diabetic one], renal amyloidosis, urolithiasis, infrarenal chronic obstruction) [2]. Adrenal lesions are more common among persons aged 40 to 64 years [1]. Unfortunately, the obstructive sleep apnea syndrome is underestimated in this age group as a SH cause [3].Major drug products triggering BP elevation in the young cohort and among middle-aged persons definitely include non-steroidal anti-inflammatory drugs with their nephrotoxic effects. The following drugs are used less commonly in the population, but also cause hypertension: corticosteroids; oral contraceptives; nasal adrenomimetics; psychic stimulators (amphetamine, cocaine, MDMA); immunosuppressive drugs with vasospastic effects (cyclosporine, tacrolimus); licorice (stimulating mineralocorticoid receptors).

Hereby we present a clinical case of hypertension in a young female that required a detailed differential-diagnostic search for SH.

Clinical Case Study

The female patient M., 44 years old, a lawyer and a teacher, felt discomfort in the left heart of the chest (burning sensation) not associated with physical exertion, along with BP elevation to 160/106 mm Hg, tachycardia (112 bpm) on September 24, 2023. 3 days before the hospitalization, the patient for the first time developed significant general weakness, episodes of elevated BP accompanied by flushing, feverish sensation, anorexia, nausea and diarrhea. Due to inefficient hypotensive treatment and the general condition worsening, the patient was hospitalized via the ambulance to the intensive care unit of the L.A. Vorohobov CCH No. 67 with the diagnosis "Uncontrollable hypertension. Target BP values not achieved". ECG: sinus rhythm, HR 79/min, right axis deviation; negative troponin test (troponin I 0.024 ng/mL). EchoCG: cardiac contractility was preserved (EF 62 %), heart chambers were not dilated; no significant valvular lesions were detected. After BP stabilization, the patient was transferred to the Department of Cardiology with the following diagnosis: "CAD: first-detected angina. Grade 3 essential hypertension. Hypertensive crisis dated September 24, 2023". The mortality risk was assessed as low (GRACE 38 points), coronary angiography was not conducted, but repeated echocardiography, ambulatory BP monitoring, Holter ECG monitoring were scheduled. During the treatment with enalapril (2.5 mg twice daily), target BP values were achieved, however significant weakness persisted. Blood tests demonstrated hypokalemia (2.48 mmol/L) twice, which required the administration of a glucose-potassium-insulin mixture (400 mL of 5 % glucose solution + 40 mL of 4 % potassium chloride solution + 8 insulin units, three times) and a mineralocorticoid receptor antagonist (spironolactone 25 mg; due to persistent hypokalemia, the dose was increased to 50 mg daily).

Accounting for the young age and suspected SH, the patient was counseled by the employees of the Department of Acad. A.I. Nesterov Faculty Therapy Department of N.I. Pirogov RSRMU to clarify its causes.

The history collection revealed that the first BP elevation developed during the first pregnancy initiated by the in vitro fertilization at the age of 34 years (the preparation period was not complicated). The pregnancy was accompanied by eclampsia and HELLP-syndrome, while hereditary thrombophilias and antiphospholipid syndrome were excluded. After the delivery (via cesarean section at the term of 31 weeks), persistent hypertension was preserved; the patient took hypotensive therapy (perindopril 5 mg + indapamide 1.25 mg) and isoptin 250 mg (half a tablet). The second pregnancy emerged 4 years later spontaneously and was also accompanied by eclampsia. Two healthy children were born as a result. After the second delivery, BP elevated to 145/98 mm Hg, and the patient tolerated that poorly. The attending physician administered her amlodipine 5 mg + losartan 100 mg daily. Due to early natural menopause at the age of 41, the patient had been taking Femostone (dydrogesterone 10 mg + estradiol 1 mg) for 3 years. 3 months before the hospitalization, the patient suffered from a severe distress (simultaneous death of several relatives), and hypertension became critical with maximum numbers of 160/110 mm Hg, accompanied by nausea, vomiting, and diarrhea during the high BP levels. No electrolyte disorders were reported before the hospitalization.

Physical examination in the cardiology department: satisfactory condition, clear consciousness.Skin and mucous membranes are of normal color, with preserved turgor; no cyanosis or edema were detected. BMI 19.5 kg/m^2. Peripheral lymph nodes were not palpated. The clear pulmonary sound was detected during pulmonary percussion; vesicular breathing with no rales was auscultated in lungs. RR 18/min, O2 saturation 96 %. Systolic blood pressure in both arms 118 and 120 mm Hg; diastolic BP 72 and 75 mm Hg; HR 64/min. During

cardiac percussion, heart borders were not dilated. Cardiac auscultation: weak S1 at the apex, with a soft systolic murmur irradiating to the left axillary region; split S2 over the aorta. The abdomen was not distended, soft and non-tender on palpation; the liver and spleen were not enlarged based on percussion results. Urination: 1.5–2 L/day. Endocrine system: thyroid gland consistency was elastic, it was not enlarged (WHO Grade 0) and non-tender on palpation. Parathyroid glands, adrenal glands, the pancreas were not palpated. Ocular symptoms were negative.

Standard laboratory tests detected the decrease in levels of total protein to 54.1 g/L (N 66.0–83.0); urea to 1.62 mmol/L (N 2.80–7.20); creatinine to 44.4 μmol/L (N 49.0–90.0). The sodium level was 139 mmol/L (N 136–145 mmol/L), the fasting blood glucose level was 4.2 mmol/L (N 3.5–5.5 mmol/L). Persistent hypokalemia (2.8 mmol/L) was worth noting. Lipid profile: total cholesterol 4.3; LDL 1.59; HDL 2.1; triglycerides 1.8 mmol/L. Urinalysis was normal, lacking albuminuria.

The differential diagnosis was arranged between EH and SH caused by thyroid, renoparenchymatous, renovascular, adrenal disorders, and drug-induced hypertension, including estrogen-induced hypertension (Table 2).

Accounting for laboratory capabilities of the department, levels of thyroid hormones, ACTH, renin, cortisol, aldosterone, parathyroid hormone were tested; the contrast-enhanced MRI of the abdominal cavity was arranged as well. TSH, free T3 and T4 levels were normal; adrenal hormones: serum and salivary cortisol, serum aldosterone (after discontinuing hypotensive therapy with angiotensin-2 receptor blockers and mineralocorticoid receptor antagonists a day before) levels were also normal, while ACTH levels were mildly decreased. The low-dose dexamethasone suppression test was negative. Hypercortisolism and hyperaldosteronism were excluded. Renin levels were 10-fold higher than reference values (Table 1).

Holter ECG monitoring demonstrated supraventricular and ventricular extrasystoles; the heart rate variability was normal, with average daily HR 70 bpm. Ambulatory BP monitoring (September 26, 2023) revealed that the daytime BP profile corresponded to borderline diastolic hypertension with maximum BP values of 156/104 mm Hg; nocturnal BP profile was normotensive with maximum BP values of 127/82 mm Hg; BP variability was within the reference range, while the mean daily pulse BP was normal. The Doppler renal ultrasound demonstrated a left-sided accessory artery overlying the main one, connected to the upper renal

Table 1. *Hormonal status of the patient 'pituitary-adrenal' over time.*

	26.09.23	30.09	04.10	17.10	26.10	02.11.23	Reference values
ACTH	6,9		8,6	9,6		12,9	7,2-63,3 pg/ml
Plasma Renin	>300	252,3	400	445		150,6	2,8-39,9 μIU/mL
Aldosterone		230		lying 180 sitting 457			69,8-1085,8 pmol/l
Potassium	2,8	3,4	4,6	3,92		4,12	3,5-5,1 mmol/l
Sodium	139	142	145	143		142	136-145 mmol/l
Serum Cortisol	394,8		374	428		402	177 — 629 nmol/l
Free plasma methanephrine			0,32	0,2			0-0,49 nmol/l
Plasma Chromagranin A			55,55	45			0 — 100 mcg/ml
Serum Serotonin					0,24		0,22-2,05 mmol/l
Vanillylmindal acid					3,3		1,4-6,5 VMA mg/day
Homovanilic acid					3,1		1,4-8,8 HVA mg/day
5-HIAA (5-hydroxyindolacetic acid)					2,48		2-7 5-HIAA mg/day

segment; the parenchymal echogenicity was normal, with the normal corticomedullary differentiation; contours of both kidneys were clear and smooth. The contrast-enhanced MRI of the abdominal cavity was arranged on September 27, 2023: no pathologies were detected. The patient reached BP values of 120/75 mm Hg while taking valsartan 40 mg twice daily and amlodipine 5 mg once daily; she was discharged with the diagnosis "Grade 2 secondary hypertension (renin-induced). Premature menopause, permanent HRT (Femostone 10 mg + 1 mg)", and the recommendation to continue treatment and to consult the endocrinologist.

The next step presumed the exclusion of pheochromocytoma and paraganglioma (extraadrenal pheochromocytoma). Outpatient tests were arranged for free plasma metanephrins, plasma chromogranin A — their levels were normal. The search for an endocrine hypertension associated with renin secretion (reninoma; Robertson-Kihara syndrome) or an ectopic renin-secreting tumor (in lungs, pancreas, Fallopian tubes) was continued. The (static) scintigraphy of adrenal glands and kidneys, brain MRI (in the pituitary gland area) was recommended. If MRI, contrast-enhanced CT of the abdominal cavity, kidneys and adrenal glands, chest to exclude a small-sized reninoma had yielded doubtful/negative results, it would have been recommended to arrange the selective blood collection from renal veins to determine the renin level ratio bilaterally and in the inferior vena cava in a specialized department.

On October 20, 2023, the patient was counseled by the nephrologist in FSBI V.I. Kulakov SMRC OGP. BP 120/70 mm Hg, serum renin was elevated (400 mmol/L), metanephrines/normetanephrines, TSH were normal; C3, C4 complement levels were normal; creatinine clearance 53 mL/min, microalbuminuria 5 mg/L, urine density not decreased, potassium 3.92 mmol/L. Nephrologist counseling: "The origin of nausea and vomiting episodes with the normal BP values remains unclear; migrenologist counseling recommended". On October 24, 2024 the patient was counseled in the Scientific Center for Endocrinology, where the steroid serum profile was determined (multisteroid test using the tandem mass-spectrometry liquid chromatography (HPLC-MS/MS) method) — no pathological alterations; potassium 3.92 mmol/L (normal); renin level significantly increased (428 mmol/L). The following diagnosis was established: "Premature ovarian exhaustion, drug-induced subcompensation". Endocrine hypertension? Reninoma? Carcinoid syndrome?" The following tests were arranged for the diagnosis of neuroblastoma, pheochromocytoma, carcinoids and other neuroendocrine tumors: MSCT of kidneys; blood tests for Chromogranin A, serotonin; 24-hour urine for 5-HIAA, i.e. epinephrine, norepinephrine, dopamine, serotonin levels. The patient was counseled by the gynecologist: burning sensation in the back of the head, shoulder, chest, chills, nausea were considered menopausal signs; the dose of Femostone 2 was increase (dydrogesterone 10 mg + estradiol 2 mg). Contrast-enhanced MSCT of the abdominal cavity, kidneys, and adrenal glands was arranged on September 28, 2023 — no pathologies were detected.

On October 26, 2023, the following tests were obtained: serum serotonin 0.24 μmol/L (N 0.22–2.05 μmol/L); catecholamine metabolites in 24-hour urine — vanillylmandelic acid (final catecholamine metabolite) 3.3 mg/day (N 1.4–6.5 VMA mg/day); homovanillic acid (final dopamine metabolite) 3.1 mg/day (N 1.4–8.8 HVA mg/day); 5-HIAA (5-hydroxy-indole-acetic acid, major serotonin metabolite) 2.48 (N 2–7 5-HIAA mg/day); serum Chromogranin A (marker of the neuroendocrine tissue and other neuroendocrine tumors) 1.47 μg/mL (N 0–100 μg/mL). Additionally, levels of folic acid (7 nmol/L; N 7–39.7 nmol/L) and cyanocobalamine (478 pg/mL; N 197–771 pg/mL) were determined. Combined hypotensive treatment (losartan 50 mg twice daily; spironolactone 25 mg/day; bisoprolol 2.5 mg/day) was recommended and demonstrated positive effects; potassium was to be monitored every 3 months. Follow-up (November 2, 2023): plasma renin levels were still elevated (150 mmol/L), most likely due to MRA therapy and the addition of beta-blockers. Renal MR-angiography was arranged on November 6, 2024 — no pathological alterations. Thus, the renin-producing tumor was excluded, and the final diagnosis was formulated as follows: "Essential hypertension, hyper-renin form, Stage 1, target BP levels achieved, CVS risk 4 % (low risk as per the SCORE scale)".

The follow-up demonstrated a favorable disease course within 2 years, the patient's well-being remained normal; the Scientific Center for Endocrinology specialist recommended permanent administration of the selected hypotensive treatment with BP and pulse monitoring, annual laboratory-instrumental examinations, and follow-up by the cardiologist and endocrinologist.

Discussion

The diagnosis of symptomatic hypertensions in real clinical practice is arranged based on the "simple to complex" principle, with the order of examinations determined by the proposed SH type. Table 2 lists *screening methods* for the diagnosis and *advanced examinations*, depending on the SH type.

Table 2. *Screening methods and methods of in-depth diagnosis of SAH [1]*

SAH Variants	The main reasons	Diagnostic methods
Renault-parenchymal	– Chronic Pyelonephritis – Acute/chronic glomerulonephritis – Polycystic kidney disease – Obstructive nephropathy – Tubulo-interstitial nephritis, including medicinal – Systemic connective tissue diseases with kidney damage – Kidney dysplasia – Congenital anomalies and scarring	– Blood test for creatinine and urea, uric acid, – general urinalysis with leukocyte formula, urine analysis according to Nechiporenko, Zimnitsky, – daily albuminuria, daily proteinuria, creatinine from daily urine, daily uricosuria, GFR (calculated formula CKD-EPI, creatinine clearance according to the Rehberg-Tareev test), – ANF, ANCA, ATdsDNA, AT to Scl-70, serum IgA, immunoelectrophoresis of serum and urine proteins – Duplex examination (ultrasound of the renal arteries) (assessment of blood flow in the renal arteries), CT native, static and/or dynamic renal scintigraphy – Nephrobiopsy with IHC* including congo-mouth staining – Consultation with a nephrologist
Renovascular	– Fibromuscular dysplasia – Atherosclerosis of the renal arteries – Large cysts located at the gates of the kidney – Kidney tumor – Vasculitis of large vessels	– Duplex examination (ultrasound of the renal arteries) — peak blood flow rate> 2 m/sec (normally up to 1 m/sec) – MR angiography (3D with gadolinium) – CT aortography, angiography of the renal arteries – CT OBP with contrast
Pathology of the thyroid gland	Hypothyroidism Hyperthyroidism	Stage I — blood TSH level (ELISA) Stage II — free T4 and total T3 – ultrasound, thyroid scintigraphy
Pheochromocytoma	A tumor originating from the chromaffin cells of the adrenal glands that secrete one or more catecholamines: adrenaline, norepinephrine, dopamine	– Fractionated methanephrines (free and conjugated) in blood plasma, in daily urine (with the elimination of drugs that affect these parameters [see section "Drugs capable of causing hypertension" and [1*]) (ELISA) [4], – Direct serum renin, plasma renin activity – Serum Aldosterone and potassium – ACTH – Serum serotonin – Vanillylmindic acid, homovanilic acid and 5-OIC in daily urine – Chromogranin A of serum – Ultrasound of the kidneys and adrenal glands with Doppler, -MSCT, MRI of the adrenal glands, thoracic and abdominal cavities with contrast – PET-CT with fluorodeoxyglucose or Gallium isotope 68
Hypercorticism	Endogenous Exogenous	– Free cortisol: in blood serum, in saliva sample in the evening or in daily urine (double determination) – Suppressive test with 1 mg dexamethasone – ACTH, prolactin, serum somatostatin – Ultrasound of the kidneys and adrenal glands with Doppler, -MSCT, MRI of the adrenal glands, thoracic and abdominal cavities with contrast – PET-CT with fluorodeoxyglucose or Gallium isotope 68
Primary hyperaldosteronism	Conn's syndrome	– Potassium in blood serum – Serum Aldosterone – Renin activity in blood plasma — against the background of withdrawal of ace inhibitors, ARA, AMCR – Ultrasound of the kidneys and adrenal glands with Doppler, -MSCT, MRI of the adrenal glands, thoracic and abdominal cavities with contrast – PET-CT with fluorodeoxyglucose or Gallium isotope 68

Table 2. *(The end)*

SAH Variants	The main reasons	Diagnostic methods
Reninoma	Renin-producing kidney tumor or extrarenal localization, Multiple endocrine neoplasia	– Direct serum renin, plasma renin activity – Serum Aldosterone and potassium – ACTH – Ultrasound of the kidneys and adrenal glands with Doppler, – MSCT, MRI of the adrenal glands, thoracic and abdominal cavities – Selective blood sampling from the renal veins with lateralization and the inferior vena cava – PET-CT with fluorodeoxyglucose or Gallium isotope 68
Pathology of the parathyroid glands	Hyperparathyroidism	– Total and ionized serum calcium, parathyroid hormone – Ultrasound, scintigraphy of the thyroid and parathyroid glands, – PET-CT scan
Obstructive sleep apnea syndrome	ntermittent night snoring, sleep apnea, nocturia, sleep disorders, daytime drowsiness, morning headache, obesity	Epworth Sleepiness Scale questionnaire; pulse oximetry during sleep
Pathology of the central nervous system (neurogenic arterial hypertension)	Tumors, injuries, encephalitis, polio, focal ischemic lesions, large malformations of cerebral vessels	– CT scan of the skull – MRI of the brain, including in the cerebral mode
Medicines, food, and beverages that can cause hypertension	Hormonal contraceptives; corticosteroids; sympathomimetics; mineralocorticoids; cocaine; foods containing tyramine or monoamine oxidase inhibitors; nonsteroidal anti-inflammatory drugs; cyclosporine; erythropoietin; acetaminophen, methyldopa, tricyclic antidepressants, monoamine oxidase inhibitors, sympathomimetics, catecholamine reuptake inhibitors, mesalamine/sulfasalazine, phenoxybenzamine, levodopa, anesthetics, L-DOPA, high-dose diuretics, rauwolfia alkaloids (reserpine), theophylline, nitroglycerin, caffeine, ethanol	

Notes: * IHC — immunohistochemical study, ANF — antinuclear factor, ANCA — antineutrophil cytoplasmic antibodies, ATdsDNA — antibodies to double-stranded DNA, AT to Scl–70 — antibodies to scleroderma 70, ARA — angiotensin II antagonists, AMCR — antagonists of mineralcorticoid receptors, ultrasound — ultrasound examination, MSCT — multispiral computed tomography, MRI magnetic resonance imaging tomography, PET-CT positron emission tomography.
[1*] Do not smoke 4 hours before the study, 3 days before the analysis, exclude tea, coffee, cocoa, cola and energy drinks, bananas, pineapples, avocados, tomatoes, eggs, cheese, chocolate, vanillin-containing products (pastries, confectionery), beer from the diet [4].

When compiling diagnostic algorithms, one should account for the fact that "classic" hormones directly affecting the vascular tone and the circulating blood volume include hormones from various adrenal gland regions (cortisol, norepinephrine, epinephrine, aldosterone). Thus, hypercortisolism (increased cortisol levels) should be evaluated using the low-dose dexamethasone suppression test. Meanwhile, epinephrine and norepinephrine are short-living molecules, so the diagnosis should be based on 24-hour urine for nor- and metanephrines; the test is especially informative if urine samples are collected after the hypertensive crisis. Aldosterone levels should be ideally evaluated together with the plasma renin activity upon achieving the target serum potassium level range.

Speaking about thyroid hormones (thyroxine and triiodothyronine), one should mention their significant cardiotonic and vasodilating effects. However, they can cause BP elevation only in predisposed patients with a baseline increase in vascular tone. Hypothyroidism may also provoke hypertension, as the vascular tone increases despite negative chronotropic and inotropic effects. It is well-known that BP elevation in both hyper- and hypothyroidism is not significant, and it is not a leading clinical sign.

Hyper-renin EH is characterized by high renin plasma levels within the setting of normal aldosterone levels, persistent BP elevation, and is diagnosed by excluding a true secondary renin-induced hypertension due to a renin-producing tumor [5]. The combination of hyperreninemia and hypokalemia led to thorough patient examination.

Reninoma is a benign tumor arising from the smooth muscle cells of afferent arterioles of the juxtaglomerular

apparatus producing increased renin levels, which in turn leads to secondary hyperaldosteronism and hyperkalemia [6]. It is diagnosed in adolescents and young adults. The classic symptom triad includes hypertension, increased plasma renin activity, and hypokalemia, all of which were observed in our patient for a prolonged period [7]. This type of renin-mediated hypertension is often accompanied by a prolonged history of migraine-like headache and drowsiness; it is rather sufficiently treated with drugs suppressing the activity of the renin-angiotensin-aldosterone system (RAAS) — thus, it might not be diagnosed, masquerading as a "migraine" or EH. Other relatively common symptoms include nausea, polyuria, polydipsia [8].

Imaging methods might not identify a small tumor (it is usually located superficially in the renal cortex), so it is still important to arrange an invasive selective blood collection from renal veins with lateralization (and the inferior vena cava) along with testing for renin levels in various blood samples — the closer to the renin hyperproduction source, the more probable is the tumor location; renin lateralization ratio >1.5 is maximally close to the source and region of a suspected surgical intervention.

An important aspect of the RAAS hormone hyperproduction is to exclude the use of RAAS inhibitors for at least 3 days before the laboratory test, which was not followed in the clinical case discussed (with the non-invasive diagnosis, 3 days are sufficient, while the selective blood collection from renal veins requires 2 weeks) [9]. The very-low-salt diet (<40 mmol/day) is also recommended for 4 days [9]. During this period, it is feasible to switch the drugs to alpha-blockers, calcium channel blockers, central drugs, supporting them with potassium drugs. The blood collection for plasma renin and renin activity should be arranged at room temperature maximally quickly to avoid in vitro renin activation and false-positive elevated results [10].

A Wilms tumor (nephroblastoma) is a malignant renin-producing renal tumor that is highly malignant, but more common in childhood and adolescence [6]. Multiple endocrine neoplasia is one of the prognostically unfavorable causes of renin hyperproduction.

Renin-secreting extrarenal tumors include lung carcinoma, pancreatic adenocarcinoma, Fallopian tube adenocarcinoma, with single clinical cases of vascular invading reninoma with lung metastases. If the renin-dependent tumor is suspected, PET/PET-CT with fluorodeoxyglucose is highly sensitive and specific, while PET scan with Gallium-68 is even more sensitive.

After a thorough patient examination, accounting for the favorable follow-up (no hypertension progression, preserved RAAS blocker effect), a high-renin essential hypertension (HREH) was concluded in her. Plasma renin levels widely vary in patients with EH. When analyzing the renin status in middle-aged persons with hypertension (both treated and untreated) of unknown origin in a Russian study, every fourth patient demonstrated significantly elevated renin (>39.9 μIU/mL) vs. 67 % patients with normal renin levels [2]. It is interesting to note that HREH is more common in younger persons, especially males, with hypersympathetic activation and mildly decreased circulating plasma volume; it may also form in response to the administration of angiotensin-converting enzyme inhibitors, angiotensin-2 receptor blockers, or mineralocorticoid receptor antagonists (as seen in the case presented).

Hyper-renin EH treatment includes standard regimens with the use of the aforementioned hypotensive drugs, as well as direct renin inhibitors (aliskiren) [5]. If adrenoblockers are used, alpha-blockers are preferable, with subsequent possible addition of beta-blockers to avoid paradoxical BP elevation with beta-receptor blockade. To correct resistant hypertension, bilateral sympathectomy of renal arteries using the radiofrequency ablation method is efficient provided the tumor resection is not possible [11].

Conclusion

A high-renin variant of essential hypertension requires a thorough search for the initial cause of renin hyperproduction, especially in young persons. Renal, adrenal, and extrarenal sources of renin synthesis justify a multi-step diagnosis of serum RAAS component levels with specific blood collection conditions (exclusion of drugs and food products for 3 days before the test), otherwise false-positive results may misinterpret the data. Multidisciplinary approach is complex for this patient, as it is difficult to implement in outpatient settings and requires high patient compliance with diagnosis and treatment.

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ОПЫТ ПРИМЕНЕНИЯ КОЛХИЦИНА ПРИ БОЛЕЗНИ СТИЛЛА, РЕФРАКТЕРНОМ К СТАНДАРТНОЙ ТЕРАПИИ

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Experience Of Colchicine Administration in Refractory Still's Disease

Резюме

Болезнь Стилла (БС) — это редкое хроническое аутовоспалительное заболевание, проявляющееся развитием высокой пиковой лихорадки, поражением суставов в виде артралгий и артритов и возникновением макулопапулезной сыпи лососевого цвета. В рекомендациях EULAR (The European Alliance of Associations for Rheumatology) 2024 г. унифицированы критерии диагностики БС, включающие лихорадку ≥39°C (102,2°F), периодическое появление эритематозной сыпи, поражение опорно-двигательного аппарата, нейтрофильный лейкоцитоз, повышение острофазовых показателей — С-реактивного белка (СРБ) и скорости оседания эритроцитов (СОЭ) и ферритина. При возможности определения уровней S100 или интерлейкина (ИЛ) 18, их повышенные значения будут указывать в пользу БС. Также изменены подходы к лечению БС с назначением генно-инженерных биологических препаратов (ГИБП) групп ингибиторов ИЛ-1 или ИЛ-6 при неэффективности глюкокортикоидов (ГК), применение метотрексата рассматривается в случае невозможности инициации терапии ГИБП.

Представленный клинический случай посвящен своевременной диагностике БС и резистентности к стандартной терапии ГК (включая пульс-терапию) и метотрексатом (МТХ). В связи с недостаточной доступностью ГИБП на основании имеющегося опыта назначения колхицина при БС в научной литературе, пациентке модифицирована терапия с добавлением колхицина в дозе 1 мг внутрь в сутки, после назначения которого отмечена регрессия клинический проявлений и нормализация острофазовых показателей.

Данный клинический опыт демонстрирует возможность использования колхицина в качестве альтернативы ГИБП для снижения активности заболевания при рефрактерности БС к терапии ГК и МТХ.

Ключевые слова: *болезнь Стилла, генно-инженерные биологические препараты, колхицин, глюкокортикоиды, метотрексат, воспаление*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Пациент дал согласие на опубликование данных лабораторных и инструментальных исследований в статье «ОПЫТ ПРИМЕНЕНИЯ КОЛХИЦИНА ПРИ БОЛЕЗНИ СТИЛЛА, РЕФРАКТЕРНОМ К СТАНДАРТНОЙ ТЕРАПИИ» для журнала «Архивъ внутренней медицины», подписав информированное согласие

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Abstract

Still's disease (SD) is a rare chronic autoinflammatory disease manifested by the development of high peak fever, joint involvement (arthralgias and arthritis), and the appearance of a salmon-colored maculopapular rash. The 2024 EULAR guidelines unified the diagnostic criteria for Still's disease including fever ≥39°C (102.2°F), recurrent erythematous rash, musculoskeletal involvement, neutrophilic leukocytosis, and elevated CRP and ferritin. If S100 or interleukin (IL)18 levels can be determined, their elevated values will point in favor of SD. Also, treatment strategy have been modified with the administration of biologics of IL-1 or IL-6 inhibitors if glucocorticoids (GCs) are ineffective, and the use of methotrexate (MTX) is considered if biologic therapy cannot be initiated.

This case report focuses on the situation of timely diagnosis of SD and resistance to standard therapy with GCs (including pulse therapy) and MTX. Due to insufficient availability of biologics, based on the existing experience of colchicine prescription in SD in the scientific literature, the patient's therapy was modified with the addition of colchicine at a dose of 1 mg orally per day, after the administration of which regression of clinical manifestations and normalization of acute-phase markers were noted.

This clinical experience demonstrates the feasibility of colchicine administration as an alternative to biologics to reduce disease activity if SD is refractory to GC and MTX therapy.

Key words: *Still's disease, biologics, colchicine, glucocorticoids, methotrexate, inflammation*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article « Experience Of Colchicine Administration in Refractory Still's Disease » for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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ABT — antibiotic therapy, BP — blood pressure, ALT — alanine aminotransferase, ANA — antinuclear antibodies, ANF — antinuclear factor, AST — aspartate aminotransferase, ACPA — anti-citrullinated peptide antibodies, SD — Still's disease, DMARDs, disease-modifying antirheumatic drugs, AOSD — adult-onset Still's disease, >ULN — over the upper limit of normal, SBHI CR — State Budget Healthcare Institution of the Crimea Republic, BAs — biological agents, CSs — corticosteroids, IL — interleukin, CT — computed tomography, LDH — lactate dehydrogenase, MTX — methotrexate, NSAIDs — non-steroidal anti-inflammatory drugs, AC — abdominal cavity, PC — pelvic cavity, PIPs — proximal interphalangeal joints, RCH — Republican Clinical Hospital, RCT — randomized clinical trial, RF — rheumatoid factor, MAS — macrophagal activation syndrome, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein, US — ultrasound, TNF-α — tumor necrosis factor α, RR — respiratory rate, HR — heart rate, JIA — juvenile idiopathic arthritis, JSIA — juvenile systemic idiopathic arthritis, GS — gastroscope, EULAR — The European Alliance of Associations for Rheumatology, ILAR — International League of Associations for Rheumatology, CARRA — The Childhood Arthritis and Rheumatology Research Alliance, PRINTO — Pediatric Rheumatology International Trials Organization, ACR30 — American College of Rheumatology 30, SDAS — Still's Disease Activity Score, SMS — Systemic Manifestation Score, SFS — Systemic Feature Score, mPoS — Modified Pouchot-Activity Score, JAK — Janus kinase

Introduction

Still's disease (SD) is a rare chronic autoinflammatory disease manifesting with high peaking fevers, joint involvement (arthralgia or arthritis), and salmon-pink maculopapular rash. Heterogenous disease signs are associated with a variable combination of clinical manifestations [1, 2].

For the first time juvenile systemic idiopathic arthritis (JSIA) was described by Sir George Still at the end of the 19th century, while the adult-onset SD (AOSD) was first described in 1971 by Eric Bywaters. The incidence of SD is 1 per 100,000 population, with the peak incidence in persons aged 16 to 35 years [3, 4, 5].

Due to the common pathogenetic mechanisms, these disease form were defined as a single pathological process, but were also considered specific nosological units with the variable age onset.

According to the 2024 European Alliance of Associations for Rheumatology (EULAR) guidelines, JSIA and AOSD have been compiled into a single disease form of SD [1, 5, 6, 7]. Due to heterogenous clinical manifestations and rarity of this syndrome, quick SD diagnosis is difficult, which has been an obstacle for unification and compilation of diagnostic SD criteria.

Classification criteria of ILAR (International League of Associations for Rheumatology), CARRA (The Childhood Arthritis and Rheumatology Research Alliance), PRINTO (Pediatric Rheumatology International Trials Organization) were known earlier in rheumatological practice. To optimize and accelerate SD diagnosis, 2024 EULAR recommendations have included supportive clinical manifestations for the identification of patients with SD:

- Fever (usually undulating) with body temperature reaching ≥39 °C (102.2 °F), lasting at least 7 days;
- Periodic rash usually coinciding with fever peaks, localized predominantly on the torso. The rash is usually erythematous (salmon-pink), although

other rash types (e.g., urticarial) may be observed — this does not contradict the diagnosis;
- Musculoskeletal lesions (arthralgia/myalgia). Arthritis is an additional, but not mandatory diagnostic criterion — it can develop during the disease [1, 7];
- Neutrophilic leukocytosis, elevated serum C-reactive protein (CRP) and ferritin levels.

It has been additionally defined that significant elevation of interleukin (IL) 18 and/or S100 inflammatory protein (e.g., calprotectin) levels in the blood serum significantly enhances the accuracy of SD diagnosis, thus it is recommended to determine them if possible. The examination aiming to exclude malignancies, infections, other immune-mediated and monogenic autoinflammatory disorders should be arranged in parallel [1, 8].

Updated 2024 EULAR guidelines on SD patient management also reflect changes in the therapeutic tactics, i.e.:

1) to decrease the duration of systemic corticosteroid (CS) use, it is essentially recommended to use IL-1 and IL-6 inhibitors to achieve and maintain treatment targets due to the potent efficacy evidence.
2) IL-1 or IL-6 inhibitors should be started as soon as possible after establishing the diagnosis;
3) Clinical remission should be achieved within 3–6 months without using CSs to discontinue biological agents (BAs) [4].

Based on the EULAR expert opinion, the efficacy of synthetic disease-modifying anti-rheumatic drugs (DMARDs) has been studied insufficiently in SD. In a single randomized clinical trial (RCT) (arranged among patients with juvenile idiopathic arthritis (JIA)) methotrexate (MTX) was not superior to placebo even at the low response threshold based on American College of Rheumatology 30 (ACR30) criteria [9]. Traditionally DMARDs are used in patients with severe joint lesions [10]. In several observational studies patients treated with MTX or MTX combinations with BAs demonstrated response [11]. MTX may be used with steroid-sparing purposes [12]. Despite the fact that IL-1 and IL-6 inhibitors are currently designated as the drugs of choice, MTX should be considered if the former drugs are not available [13]. However, the real anti-inflammatory MTX effect in SD remains debatable, which requires further search for new anti-inflammatory agents to decrease the severity of clinical manifestations accounting for the financial and logistic feasibility in general [12].

In some patients (17–32 %) insufficient treatment response was achieved with the decreased clinical and laboratory activity after administering high CS doses and traditional DMARDs [2, 4, 14]. In such scenario, SD is considered resistant to standard DMARD treatment. Accounting for the heterogenous clinical SD manifestations, the probability of inflammation spread with the involvement of vital organs and systems (pleurisy, pericarditis, hepatomegaly, splenomegaly, myocarditis), as well as the possibility of SD progression to life-threatening conditions, including macrophagal activation syndrome (MAS), timely administration of adequate inflammatory treatment is required with the achievement of low SD activity or remission [15]. Due to financial and logistic difficulties, treatment with IL-1 or IL-6 inhibitors is not always possible, which requires the search for efficient, safe, and economically feasible alternative for BAs [16].

A collision with the issue of mandatory decrease in SD activity, achievement of disease activity control and preventive measures concerning the emergence of MAS within the setting of deficient BA availability has led to the decision on treatment intensification with the administration of colchicine in addition to MTX and CS in the clinical case presented.

Objective: demonstration of colchicine efficacy with the resistant SD course as an alternative to BAs.

Clinical Case Report

The female patient O., 32 years old, was hospitalized into the Department of Rheumatology of the State Budget Healthcare Institution of the Crimea Republic (SBHI CR) N.A. Semashko Republican Clinical Hospital (RCH) complaining of severe pain in metacarpophalangeal, proximal interphalangeal joints of hands (mostly in the right hand), wrist, ankle, and both shoulder joints; pain in the cervical spine; swelling of small joints in both hands, crepitation during motions in joints of lower extremities; morning stiffness for over 2 hours, significant general weakness, body temperature elevation to 37.2–38.0 °C (without signs of acute respiratory viral infections), periodic rash on lower extremities and buttocks.

Medical history: the disease started on January 22, 2025 with the emergence of erythematous & macular rash, sore throat, scratchy feeling in the throat. 4 days later, the patient noted more severe fever (~38 °C) and visited the general practitioner at place of residence; she was counseled by the otorhinolaryngologist and diagnosed with catarrhal tonsillitis. The following antibiotic therapy (ABT) was administered: azithromycin 500 mg/day, ceftriaxone 1.0 g intramuscularly twice daily. During 5 days of therapy, febrile fever persisted,

while pain and swelling emerged in the small joints of hands (Fig. 1), wrist, shoulder, and ankle joints; maculopapular rash spread to the skin of legs, thighs, buttocks, and forearms — it was accompanied by mild itching (Fig. 2). Sore throat and swallowing discomfort significantly improved, although lymphadenopathy of anterior cervical lymph nodes emerged. The common blood count detected leukocytosis (16×10^9/L) with neutrophilic left shift and elevated erythrocyte sedimentation rate (ESR) to 35 mm/h, C-reactive protein (CRP) to 71 mg/L. ABT was adjusted, with one drug switched to levofloxacin 500 mg twice daily orally. No clinical effects were observed within 3 days of therapy; laboratory tests demonstrated worsening, with leukocytosis elevation to 26×10^9/L and ESR to 51 mm/h, CRP — to 171 mg/L; elevated transaminase levels (aspartate aminotransferase (AST) — 82 U/L, alanine aminotransferase (ALT) — 96 U/L). The urinalysis demonstrated transient proteinuria (~0.3 g/day).

Due to the treatment inefficacy, the patient on her own visited the outpatient rheumatologist at place of residence on February 5, 2025 — the diagnosis of undifferentiated arthritis was established, and the following drugs were administered: methylprednisolone 16 mg once daily orally; meloxicam 15 mg once daily orally. The patient noted positive effects during the treatment administered — the rash disappeared, the joint syndrome improved, and the fever diminished to subfebrile values. Laboratory monitoring (February 13, 2025) revealed positive changes, with CRP levels dropping to 40.26 mg/L; blood test for rheumatoid factor (RF) — 14.1 IU/mL (N<14 IU/mL), antinuclear factor (ANF; HEp2-line) — 1:320 with the granular nuclear fluorescence, AC-2,4 (N<1:80). On February 21, 2025, the patient was counseled by the outpatient rheumatologist of SBHI CR N.A. Semashko RCH, where SD was suspected for the first time; the blood test for IL-18 was proposed as a clarifying SD marker. While adjusting treatment, it was recommended to increase methylprednisolone dose to 20 mg, MTX was administered in the initial dose of 10 mg weekly parenterally in combination with folic acid 5 mg weekly and laboratory parameter monitoring; the inpatient treatment was scheduled in the Department of Rheumatology SBHI CR N.A. Semashko RCH for the diagnosis verification and therapeutic management correction.

Upon the admission into the inpatient department on February 25, 2025, physical examination demonstrated mildly impaired general condition, with the body temperature of 37.3 °C. The skin was of physiological color, dry, without rash. Mobile, moderately tender anterior cervical lymph nodes up to 2 cm in diameter were palpated, not adhering to surrounding tissues. The thyroid gland was not enlarged. Vesicular breathing with no rales was auscultated in lungs; respiratory rate (RR) 16/min, SaO_2 97 %. Body weight: 69 kg.

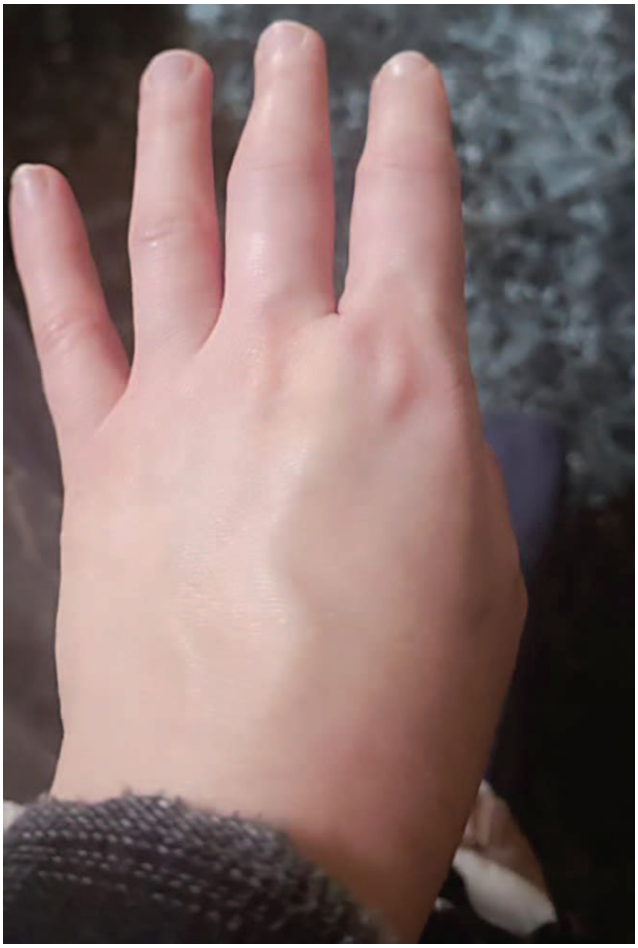


Figure 1. *Arthritis of the small joints of the hands*

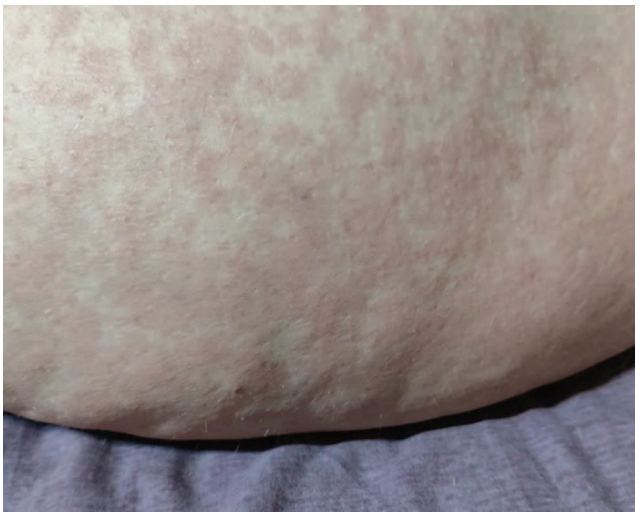


Figure 2. *Maculopapular rash on the thighs*

The chest percussion revealed normal cardiac sizes within the age limits. Pathological murmurs were not auscultated, although cardiac tones were muffled. The cardiac rhythm was regular. Blood pressure (BP) 130/70 mm Hg in both arms. Heart rate (HR) 80 beats per minute. The tongue was moist and clean. The abdomen was soft, not enlarged, non-tender on palpation. Peritoneal irritation signs were negative. The liver was not enlarged. The spleen was palpated and enlarged (14×7 cm). The lumbar punch sign was negative bilaterally. No peripheral edema was detected. Urination and defecation were normal. The urination was free, not difficult or painful. The stool was normal, without pathological inclusions, with bowel movements once or twice daily. Meningeal signs were negative.

Examination of joints in upper extremities: tenderness and swelling during the palpation of right shoulder, both wrist joints, second proximal interphalangeal joints (PIPs) in both hands; positive hand compression test bilaterally; positive Dowborn arch test in the upper third of the right arm. Examination of joints in lower extremities: tenderness and defiguration of both ankle joints.

Blood tests at the moment of hospitalization: Hb 98 g/L, white blood cells 13.6×10^9/L (74.7 % neutrophils), platelets 275×10^9/L, ESR 35 mm/h, AST 37.1 U/L, ALT 19.9 U/L, CRP 48.2 mg/L, RF 12.8 IU/mL, ANF (HEp-2) 1:320, anti-cyclic citrullinated peptide antibodies (ACPA) <5 IU/mL (N<5 IU/mL). Urinalysis parameters were within the reference range.

Before hospitalization, malignancies were excluded in the patient using the ultrasound (US) of abdominal cavity (AC) and kidneys, which demonstrated echographic signs of moderate splenomegaly; US of pelvic organs did not reveal pathological alterations. Computed tomography (CT) of the chest did not demonstrate focal and infiltrative pulmonary lesions. X-ray of feet (anteroposterior view): signs of polyarthritis of distal feet joints, Grade 1 hallux valgus. X-ray of hands: signs of periarticular osteoporosis in 2nd to 5th metacarpophalangeal and 2nd to 5th PIPs, corresponding to signs of Grade 1 arthritis. Echocardiography: no signs of pericarditis, valvular lesions detected. Gastroscopy: signs of congestive gastrobulbopathy, duodenogastric reflux, Grade 1–2 cardia insufficiency, chronic distal reflux esophagitis.

The patient was examined by the hematologist — Grade 1 chronic iron deficiency anemia was diagnosed, lymphoproliferative processes were excluded.

Based on the clinical & laboratory data, the preliminary diagnosis was established:

“Main disease: Still’s disease, early stage, high activity (DAS28-CRP=5.94, DAS28-ESR=6.07), X-ray stage 1, FC II.

Concomitant diseases: Chronic gastritis, remission. Grade 1 chronic iron deficiency anemia”.

Due to the insufficient efficacy, methylprednisolone dose was increased to 24 mg once daily orally; with the purpose of further CS dose decrease, the patient had her methotrexate dose increased to 15 mg weekly in combination with folic acid 5 mg weekly orally in inpatient conditions.

Next day after the hospitalization, the patient had a recurrent body temperature spike to 38.5 °C, worsening pain in peripheral joints, and the emergence of erythematous-macular rash on the skin of the face and neck (Fig. 3, 4). It was decided to assess the profile of antinuclear antibodies and antiphospholipid antibodies, C3/C4 complement components to exclude the systemic connective tissue disorder, as well as to modify the treatment with methylprednisolone pulse therapy (250 mg No. 3 intravenously).

Inpatient laboratory tests revealed preserved CRP (45.6 mg/L), lactate dehydrogenase (LDH) (664 U/L; N=135–214 U/L), and ferritin (285 μg/L; N=13.00–150.00 μg/L) levels. The blood test (immunoblotting) did not reveal antinuclear (ANA) and antiphospholipid antibodies; C3 and C4 levels were within the reference range. Significantly elevated IL-18 levels were demonstrated: >1000 pg/mL (0–270 pg/mL). The patient underwent the follow-up USAC: splenomegaly (140×70 mm) with the normal spleen structure was confirmed. The repeated echocardiography did not reveal pathological valvular lesions.

Based on the detected clinical symptoms (sore throat and scratchy feeling in the upper airways, non-erosive arthritis, erythematous-macular rash, relapsing febrile fever, splenomegaly) and results of laboratory tests (significantly elevated acute-phase reactants — ESR, CRP, ferritin, leukocytosis), as well as a significantly elevated Still's disease marker (IL-18), the following final clinical diagnosis was established:

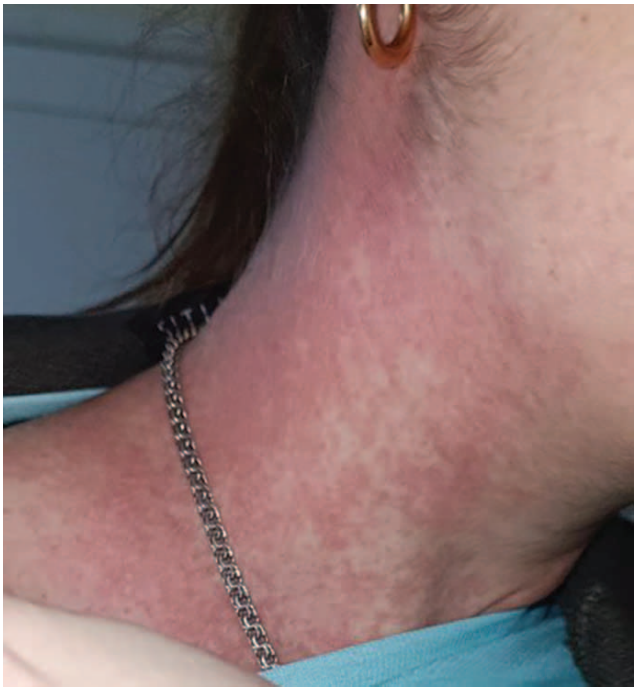
"Main disease: Still's disease, early stage, high activity (DAS28-CRP=5.94, DAS28-ESR=6.07, SDAS=7, mPoS=8, SMS=5, SFS=7), X-ray stage 1. FC II.

Concomitant diseases: Chronic non-erosive gastritis, remission. Congestive gastrobulbopathy. Duodenogastric reflux. Grade 1-2 cardia insufficiency. Chronic distal reflux esophagitis. Grade 1 chronic iron deficiency anemia".

According to the EULAR-2024 guidelines, the Still’s syndrome was evaluated using the validated scales (adapted from [4, 17]) (Table 1).

The following indices were determined in the patient: SDAS=7, mPoS=8, SMS=5, SFS=7 (i.e. high disease activity).

With the following treatment administered: CS 24 mg/day, methotrexate 15 mg weekly, pulse therapy with methylprednisolone (250 mg No. 3, IV infusion) — the patient's condition improved with the body temperature normalization (36.8 °C), rash and joint syndrome regression. After the pulse therapy, positive laboratory changes were noted in the patient: CRP levels decreased to 20.2 mg/L, hemoglobin levels elevated to 116 g/L, ESR decreased to 40 mm/h, ALT and AST levels normalized (23 and 30 U/L, respectively).



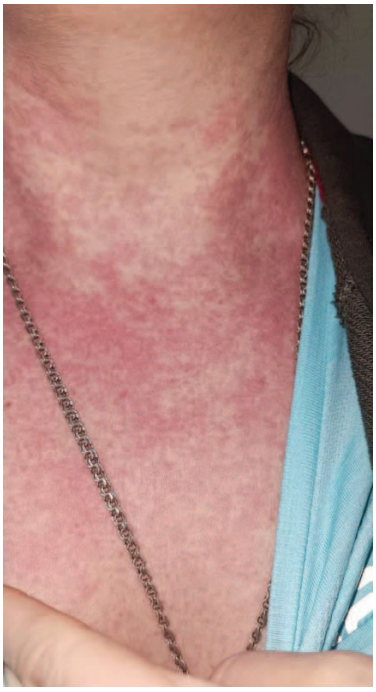


Figure 3, 4. *Erythematous and macular rash on the neck*

Table 1. *Approved scales for assessing BD activity*

Manifestations	SDAS[1]	mPoS[2]	SMS[3]	SFS[4]
Daily or night fever of 37.5–38°C (99.5-100.3°F)	-	-	1	1 ✓
Daily/nighttime fever of 38–39°C (100.4-102.1°F)	-	1 ✓	2 ✓	
Daily/nighttime fever of 39–40°C (102.2-103.9°F)	1		3	
Daily/nighttime fever above 40°C (>104°F)			4	
Muscle pain (myalgia)	-	1 ✓	-	-
>2 swollen joints (inflammatory synovitis)	1 ✓	1 ✓	-	-
Rash in Still's disease (not on the face, confirmed by a doctor)	1 ✓	1 ✓	1 ✓	1 ✓
Weight loss (>10 % of body weight)	1	-	-	-
Sore throat (current or within the past 2 weeks)	1 ✓	1 ✓	1 ✓	-
Pleurisy or pleural effusion		1		
Pericarditis or pericardial effusion	1	1	1	1
Pneumonitis (according to X-ray data)		1		
Peritonitis		-		
Generalized lymphadenopathy	1 ✓	1 ✓	1 ✓	1 ✓
Hepatomegaly or splenomegaly		1 ✓	1 ✓	1 ✓
Elevated liver enzymes (AST[5] or ALT[6] > 1,5 times above the LNL[7])	1 ✓		-	-
Elevated CRP[8] level (>20 mg/l)		-	-	1 ✓
Elevated ESR[9] (>50 mm/h)	1 ✓	-	-	1 ✓
Elevated ferritin (>500 μg/mL)		1 ✓		-
Increased platelet count (>600 × 10^3/μl)	-	-	1	1
Increased white blood cell count (>12,5 × 10^3/μl)	1 ✓	1 ✓	-	1 ✓
Anemia (haemoglobin <9 g/dl)	-	-	1	1

***Notes:** [1] SDAS — Still's Disease Activity Score, [2] SMS — Systemic Manifestation Score, [3] SFS — Systemic Feature Score, [4] mPoS — Modified Pouchot-Activity Score, [5] AST — aspartate aminotransferase, [6] ALT — alanine aminotransferase, [7] LNL — limit of the normal level, [8] CRP — C-reactive protein, [9] ESR — erythrocyte sedimentation rate.

Table 2. *Chronological scale of clinical and laboratory changes*

Data	Clinical changes	Laboratory and instrumental studies of indicators
22.01.2025	• Maculopapular rash • A feeling of tickling in the throat	
25.01.2025	• Body temperature rise to 38C • Contacting a therapist • Catarrhal angina has been diagnosed • ABT[1] is prescribed: azithromycin 500 mg 1 r/day orally and ceftriaxone 1.0 g 2 r / day by injection intramuscularly	
30.01.2025	• Body temperature preservation • Arthritis of small joints of hands, wrist, shoulder and ankle joints • The spread of maculopapular rash on the lower legs, thighs, forearms in combination with itching § • Replacement of ABT with Levofloxacin 500 mg 2p/day with subsequent use within 3 days	• Leukocytes — 16×10⁹/l (N=4-9×10⁹/l) • ESR[2]-35 mm/h (N=2-15 mm/h) • CRP[3]-71 mg/l (N<5,0 mg/l)
03.02.2025	• Lack of positive dynamics	• Leukocytes — 26.4×109/l (N=4-9×10⁹/l) • ESR-51 mm/h (N=2-15 mm/h) • CRP -171 mg/l (N<5,0 mg/l) • ALT[4] — 96 U/l (N<34 U/l), AST[5]-82 U/l (N<31 U/l) • Proteinuria-0,3 g/l (N<0,14 g/l)
05.02.2025	• Consultation with a rheumatologist • "Undifferentiated arthritis" was diagnosed • Treatment: methylprednisolone 16 mg/day, Meloxicam 15 mg/day	
13.02.2025	• Positive dynamics • The disappearance of the rash • Reducing the severity of arthritis	• Leukocytes — 12,3 ×10⁹/л (N=4-9×10⁹/l) • ESR — 38 mm/h (N=2-15 mm/h) • CRP — 40,2 mg/l (N<5,0 mg/l) • RF[6] — 14,1 IU/ml (RF<14,0 IU/ml) • ANA-Hep2[7] — 1:320 (AC-2,4)
21.02.2025	• Rheumatologist's consultation, dose increase • Correction of therapy: – escalation of the dose of methylprednisolone to 20 mg 1 r / day orally – initiation of MTX[8] 10 mg once a week parenterally	
25.02.2025	• A condition of moderate severity • Fever 37.3 C • Lymphadenopathy of the anterior cervical lymph nodes • Splenomegaly • Arthritis of the right shoulder, both wrist joints, II PIP[9] of both hands, both ankle joints • Preliminary diagnosis: "Still's disease, early stage, high degree of activity (DAS28-CRP=5.94[12], DAS28-ESR[13]=6.07), radiological stage 1, FC II» Correction of therapy: escalation of methylprednisolone to 24 mg per day orally, MTX — up to 15 mg once a week parenterally in combination with folic acid 5 mg	• Leukocytes — 13,6×10⁹/l (neutrophils — 74,7 %, pratelets — 275×10⁹/l) • ESR — 35 mm/h (N=2-15 mm/h) • CRP — 48,2 mg/l (N<5,0 mg/l) • RF — 12,8 IU/ml (RF<14,0 IU/ml) • ACPA[10] — <5 IU/ml (N<5,0 IU/ml) • AST — 37,1 U/l (N<31 U/l), ALT — 19,9 U/l (N<34 U/l) • IL-18[11] — >1000 pg/ml (<270 pg/ml) • Renal/abdominal ultrasound: moderate splenomegaly • X-ray of the hand bones: signs of stage 1 arthritis • Hematologist: chronic iron deficiency anemia grade 1, lymphoproliferative process excluded
26.02.2025	• Fever up to 38.5°C • Increased joint pain • Appearance of erythematous-macular rash on the face • Diagnostics: assessment of the antinuclear antibody and antiphospholipid antibody profile, complement components C3 and C4 to exclude systemic connective tissue disease • Modification of therapy: pulse therapy with methylprednisolone 250 mg № 3 intravenously by drip • The final clinical diagnosis: • "Primary: Still's disease, early stage, high activity (DAS28-CRP=5.94, DAS28-ESR=6.07, SDAS=7, mPoS=8, SMS=5, SFS=7), radiological stage 1. FC II.	• CRP — 45,6 mg/l (N<5,0 mg/l) • LDH[14] — 664 U/l (N=125-220 U/l) • Ferritin — 285 mkg/l (N=10-150 mkg/l) • Abdominal ultrasound: splenomegaly
03.03.2025	• Sore throat • Recurrence of rash in the décolleté, upper and lower extremities • Fever 37.8°C • Therapy adjustment: add colchicine at a dose of 1 mg orally once daily	• CRP — 20,2 mg/l (N<5,0 mg/l) • CBC[15]: haemoglobin — 116 g/l (N=120-140 g/l), ESR — 40 mm/h (N=2-15 mm/h) • ALT — 23 U/l (N<31 U/l), AST — 30 U/l (N<34 U/l)
07.03.2025	• Fever — 36.8C • Regression of maculopapular rashes and arthritis, reduction in the severity of sore throat, leveling of lymphadenopathy	• CRP — 8,82 mg/l (N<5,0 mg/l) • CBC: ESR — 26 mm/h (2-15 mm/h), leukocytes — 10,1×10⁹/l
04.04.2025	• No complaints • Treatment: MTX 15 mg once a week parenterally, methylprednisolone 16 mg orally with subsequent de-escalation to 4 mg, colchicine 1 mg once a day orally	• CRP — 3,39 mg/l (N<5,0 mg/l) • ESR — 15 mm/h (N=2-15 mm/h) • Ferritin — 139 ng/ml (N=11,0 до 306,8 ng/ml)

*** Notes.** [1] ABT — antibacterial therapy, [2] ESR — erythrocyte sedimentation rate, [3] CRP — C-reactive protein, [4] ALT — Alanine aminotransferase, [5] AST — Aspartate aminotransferase, [6] RF — Rheumatoid factor, [7] ANA-HEp2 — Antinuclear Antibodies HEp-2 Substrate, [8] MTX — methotrexate, [9] PIP — proximal inter-phalangeal (PIP) joints, [10] ACPA — anticitrullinated peptide antibodies, [11] Interleukin 18 — IL-18, [12] DAS28-CRP — Disease activity score 28 — CRP, [13] DAS28-ESR — Disease activity score 28 — ESR, [14] LDH — lactate dehydrogenase, [15] CBC — common blood count.

However, 3 days after methylprednisolone administration the patient developed a scratchy feeling in the throat, recurrent rash in the V-neck area, on the skin of upper and lower extremities, fever (37.8 °C). Due to the resistant disease course, the rheumatologist team decided to administer colchicine (1 mg once daily orally) for 28 days.

During colchicine treatment, the patient's body temperature normalized (36.8 °C), maculopapular rash and arthritis regressed, the scratchy feeling in the throat improved, lymphadenopathy disappeared. 14 days after the start of colchicine therapy, laboratory tests demonstrated CRP level decrease to 8.82 mg/L, ESR — to 26 mm/h, white blood cells — to 10.1×10^9/L.

Positive clinical & laboratory trends were also preserved during the next days. Within 28 days after hospitalization, clinical signs did not recur, while levels of CRP (3.39 mg/L; N<5 mg/L), ESR (15 mm/h), and ferritin (139 ng/mL) normalized. The follow-up USAC detected the preserved splenomegaly (~140 mm long). Further methylprednisolone dose tapering was recommended (4 mg every 14 days to 16 mg), followed by the rheumatologist counseling with the purpose of tapering the CS dose to the supportive one. It was also recommended to continue methotrexate 15 mg weekly in combination with folic acid 5 mg, colchicine 1 mg for 3 months with the monitoring of CBC, urinalysis, creatinine, urea, ALT, AST, glucose, CRP.

See Table 2 for changes of clinical & laboratory parameters during the whole treatment selection period.

Discussion

The pathogenesis of autoinflammatory diseases affects the congenital immune system; several pathologies are characterized by the activation of inflammasomes with subsequent IL-1β production [18]. It should be noted that clinical signs of SD are somewhat similar to the manifestations of autoinflammatory diseases.

In its turn, colchicine is widely used in rheumatology in the treatment of gout, familial Mediterranean fever, and Behcet's disease [19]. The drug action principle is based on the inhibition of chemokines, neutrophils, and endothelial cell adhesion molecules [21]. A recent study has shown that colchicine inhibits the assembly of the inflammasome complex by affecting the transport of the apoptosis-associated SPEC-like protein and the protein caspase recruiting domain [18, 20]. These data allow to propose that colchicine may modulate the inflammasome-mediated proinflammatory cascades, which defines the review of the treatment concept for colchicine-sensitive inflammatory conditions.

The Practical Guidelines for Rheumatologists concerning SD published by the British Rheumatology Society [21] traditionally include CS, MTX, azathioprine, and hydroxychloroquine as anti-inflammatory treatments used in SD. If the disease is resistant to therapy administered, treatment can be modified with the administration of IL-1 (canakinumab, anakinra) or IL-6 (tocilizumab) inhibitors; tumor necrosis factor α (TNF-α) inhibitors may be considered, although the priority is given to IL-1 and IL-6 inhibitors [21]. Colchicine is not listed as a possible therapeutic option in SD.

A review by Gerfaud-Valentin M. et al. [22] notes that TNF-α inhibitors may be used in chronic polyarticular resistant SD, predominantly in systemic lesions; however, the efficacy of tumor necrosis factor α inhibitors is limited in time, while switching from one drug to another is efficient approximately in 50 % cases. Based on Efthimiou P. et al. [23], patients with arthritis without systemic manifestations, lower IL-18 and ferritin levels in the blood serum are more likely to demonstrate positive effects during the tumor necrosis factor α inhibitor use, while switching inside this drug group does not lead to positive effects.

IL-6 levels are significantly elevated in active SD; this cytokine is considered a target in case of SD resistant to standard treatment [24]. The use of tocilizumab, a humanized anti-IL-6 receptor antibody that blocks membrane-bound and soluble IL-6 receptors in SD resistant to CSs, DMARDs, TNF-α inhibitors, and cyclosporine, has demonstrated positive effects regarding arthritis and systemic manifestations [24].

IL-1 inhibitors play a pivotal role among BAs regarding efficacy. Treatment with IL-1 inhibitors is significantly more efficient in patients with SD resistant to traditional treatment [25]. Quick start of IL-1 blocking therapy is associated with better disease outcomes and optimal patient retaining in the inpatient department [26, 27]. The response to IL-1 inhibitors is quick and stable, which allows patients to taper CS doses. It is important that the inefficacy of the first IL-1 inhibitor does not exclude the achievement of therapeutic effects with the use of another IL-1 inhibitor. Besides, IL-1 inhibitors have demonstrated a satisfactory safety profile in the SD treatment [28, 29].

The use of a Janus-kinase (JAK) inhibitor tofacitinib led to disease remission and CS dose tapering in 14 cases of resistant SD [30].

Despite a large spectrum of BAs that have demonstrated positive effects in resistant SD, IL-1 and IL-6 inhibitors are leading in the efficacy [31]; the results of clinical trials for canakinumab and tocilizumab in systemic SD manifestations have showed that these

treatment methods cannot completely decrease the risk of the macrophagal activation syndrome, even with sufficient disease control [32].

A review of Bindoli et al. [33] analyzed the efficacy and safety of SD and MAS treatment, and colchicine was considered a possible therapeutic option along with CS, intravenous immune globulin based on the experience of V. Myachikova et al. [35]. However, the experience of using colchicine in patients with SD is sparse. The focus of authors' attention was concentrated on the possibility of using BAs, in particular IL-1 (canakinumab, anakinra, rilonacept) and IL-6 (tocilizumab) inhibitors [34].

The first data on the efficacy of colchicine in combination with non-steroid anti-inflammatory drugs (NSAIDs) in patients with SD and serositis were published in the study of V. Myachikova et al. [34]. When analyzing the medical charts of patients that used colchicine as an additional drug in the setting of pericarditis, the effects were achieved not only concerning pericarditis, but also regarding other manifestations, i.e. arthritis/arthralgia, rash, leukocytosis, inflammatory markers. More than 50 % patients achieved complete disease remission, 15 % patients achieved partial response, and approximately 20 % patients did not respond to therapy. Based on the author's view, due to favorable safety profile colchicine may become an evident alternative in the first line of treatment of systemic SD with serositis. Besides, one should note rather low colchicine costs and its availability, thus making it possible to use as an alternative to CSs, MTX, and BAs [35].

Tomoyuki Asano et al. used colchicine in patients with SD resistant to TNF-α or IL-6 inhibitors. In our clinical case colchicine demonstrated efficacy concerning the decreased severity of SD symptoms in a patient resistant to CSs and BAs; thus, it can be also positioned as an alternative to BAs — IL-1 and TNF-α inhibitors [19].

Accounting for the high BA costs and the risk of adverse reactions (increased infection rate), colchicine is a good alternative for decreasing the inflammatory process activity in patients with SD, if the timely BA treatment is impossible due to the time and financial constraints.

Our experience of adding colchicine to MTX and CS in the treatment of SD led to the complete regression of clinical symptoms, including systemic ones, as well as to the persistent control of laboratory inflammatory markers. Due to high CRP levels at the disease onset, systemic manifestations, high SD activity, and resistance to standard treatment, this patient was in an evident risk group for MAS. The addition of colchicine to MTX and CS helped to reach the complete remission along with the prevention of MAS, a life-threatening SD complication. Based on the positive experience of using colchicine as a DMARD in combination with MTX and CS, this therapy regimen may become a robust and efficient BA alternative in resistant SD, if BAs are not available or contraindicated.

Conclusions

This clinical experience of using colchicine in a patient with AOSD has demonstrated colchicine efficacy in SD resistant to CS, as well as the possibility of its use as an alternative to costly BAs (i.e. IL-1 and IL-6 inhibitors).

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