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ВЫБОР МЕЖДУ ФИКСИРОВАННЫМИ ДОЗИРОВАННЫМИ КОМБИНАЦИЯМИ АНТИГИПЕРТЕНЗИВНЫХ СРЕДСТВ И ИХ СВОБОДНЫМИ КОМБИНАЦИЯМИ В ЛЕЧЕНИИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

O.S. Levchenkova, R.R. Galimulina, B.R. Komev, K.D. Zagnet

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Choice Between Free Combination of Antihypertensive Agents and Fixed Dosed Combinations in the Treatment of Arterial Hypertension

Резюме

Большинству пациентов с артериальной гипертензией требуется более одного антигипертензивного лекарственного препарата для достижения целевого уровня артериального давления. Некоторым пациентам рекомендуют антигипертензивные схемы, состоящие из нескольких таблеток. Другим — лечение с помощью фиксированных дозированных комбинаций в одной таблетке. Анализ литературы реферативных баз elibrary и PubMed по публикациям в период с 2014 по 2024гг, касающейся выбора двухкомпонентных комбинированных антигипертензивных средств, содержащих ингибитор ренин-ангиотензин-альдостероновой системы (РААС) и тиазидный/тиазидоподобный диуретик или блокатор кальциевых каналов, показал, что использование фиксированных дозированных комбинаций (ФДК) антигипертензивных средств и прием одной таблетки один раз в день улучшает приверженность лечению и ускоряет контроль артериального давления (АД). Хотя стоимость ФДК антигипертензивных средств, содержащих ингибитор РААС и тиазидный/тиазидоподобный диуретик или блокатор кальциевых каналов, чаще выше этих же средств, взятых по отдельности, применение фиксированных комбинаций, повышая приверженность пациента терапии, обладает клиническим преимуществом по критерию эффективности снижения АД. С другой стороны, использование свободной комбинированной терапии в двух разных таблетках, когда их прием разбит в течение суток, иногда может давать более устойчивый антигипертензивный эффект в течение 24 часов. Доказательства эффективности контроля АД для ФДК зачастую экстраполируются с данных о свободных комбинациях. Кроме того, ФДК характеризуются меньшей выявляемостью возможной неэффективности одного из компонентов. Ассортимент ФДК и представленных в них соотношений дозировок компонентов расширяется, но выбор среди свободных комбинаций по-прежнему шире. В перечне жизненно необходимых и важнейших лекарственных препаратов за 2024 год отсутствуют ФДК антигипертензивных средств, что исключает возможность их получения на льготной основе и создает возможность для производителя устанавливать на них произвольные цены. Несмотря на то, что в последнее время научное сообщество рекомендует в качестве стартовой терапии использование ФДК антигипертензивных средств в силу лучшего соблюдения режима применения, а значит клинической эффективности и экономической целесообразности, нельзя сказать, что не осталось места для свободных комбинаций антигипертензивных средств в лечении артериальной гипертензии. Выбор врача, частота назначения, доля закупок ФДК в РФ, обзор их потребления требует дальнейшего анализа.

Ключевые слова: *артериальная гипертензия, фиксированные дозированные комбинации антигипертензивных средств, свободная комбинация антигипертензивных средств*

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Abstract
Most patients with arterial hypertension require more than one antihypertensive drug for blood pressure target achievement. Some patients are recommended for a multi-pill antihypertensive regimen, others — treatment with fixed dosed combinations in one tablet. Analysis of elibrary and PubMed publications in the period mostly from 2014 to 2024 concerning the choice of two-component combined antihypertensive agents containing renin-angiotensin system inhibitor and diuretic or calcium channel blocker, revealed that fixed-dose combinations (FDC) use and taking one tablet once a day improves adherence to treatment and facilitates blood pressure control. Although the cost of FDC containing the renin-angiotensin-aldosterone system inhibitor and a thiazide/thiazide-like diuretic or calcium channel blocker is in most cases higher than the same drugs taken separately, the use of fixed combinations, increasing patient adherence to therapy, has clinical advantage in terms of the effectiveness of lowering blood pressure, which confirms their economic feasibility. On the other hand, the use of free combination therapy in two different tablets, when taken separately during the day, can sometimes provide a more sustained antihypertensive effect over 24 hours. Evidence of the effectiveness of blood pressure control for FDCs is often extrapolated from data on free combinations. In addition, FDCs are characterized by less detection of possible ineffectiveness of one of the components. The range of FDCs and the dosage ratios of the components presented in them is gradually expanding, but the choice among free combinations is still wider. In addition, the list of vital and essential drugs (VED) for 2024 does not contain FDCs for antihypertensive drugs, which excludes the possibility of free receiving them on a preferential basis and gives the opportunity for the manufacturer to set prices for them. Despite the fact that recently the scientific community has recommended the use of FDC antihypertensive drugs as initial therapy due to better compliance with the regimen, and therefore clinical effectiveness and economic feasibility, it cannot be said that there is no space left for free combinations of antihypertensive drugs in the treatment of arterial hypertension. The choice of doctor, frequency of prescription, share of purchases of the FDCs in the Russian Federation, review of their consumption requires further analysis.

Key words: *arterial hypertension, fixed dosed combinations of antihypertensive agents (two-drug single-pill), free-equivalent combination of antihypertensive drugs*

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AH — arterial hypertension, AHD — antihypertensive drug, BP — blood pressure, CCB — calcium channel blocker, ARB — angiotensin II receptor blocker, ACEi — angiotensin-converting enzyme inhibitor, IHD — ischemic heart disease, RAAS — renin-angiotensin-aldosterone system, SBP — systolic blood pressure

Introduction

Control of blood pressure (BP) with achievement of the target levels and prevention of complications is a clinical objective of arterial hypertension (AH) management in adults. According to the World Health Organisation (WHO), the incidence of AH is very high. Over the past 30 years, the number of people with AH has doubled and makes 1.28 billion people [1, 2]. The majority of people with AH are asymptomatic, that is why this pathology is called a silent killer. Without adequate medicinal treatment, AH can affect target organs where BP is elevated: first, it is the heart where the risk of left ventricular hypertrophy, remodelling with myocardium fibrosis and dysfunction, angina, and myocardial infarction exists. Second, the brain with cerebrovascular complications. Third, eye retina with possible retinopathy. Fourth, kidney with progressing renal insufficiency. Annually, AH claims the lives of 9.4 million people. BP is considered elevated if the systolic and diastolic values exceed 140 and 90 mm Hg, respectively. According to the 2022 clinical recommendations for the drug therapy of arterial hypertension, the majority of patients with AH (except for patients with BP < 150/90 mm Hg and patients over 80 years of age, patients with senile

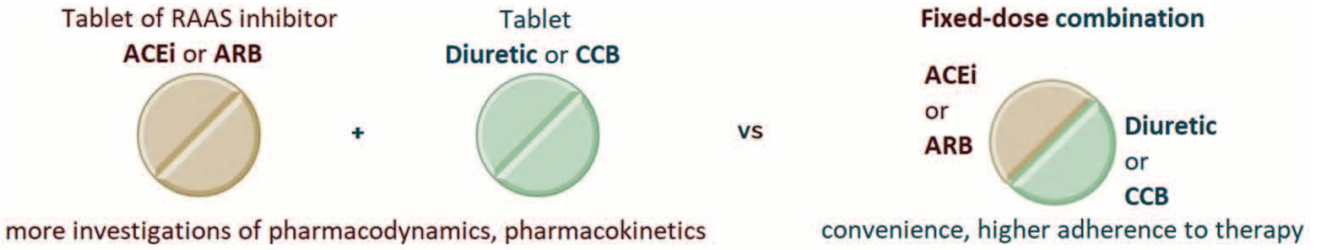

Figure 1. *The choice of combined two-component antihypertensive therapy*
Note: RAAS — renin-angiotensin-aldosterone system, ACEi — angiotensin-converting enzyme inhibitor, ARB — angiotensin II receptor blocker, CCB — calcium channel blocker

asthenia) are prescribed a combination of antihypertensive drugs as their initial treatment [1, 2].

Advantages of combined AH therapy include potentiation of component activity, slowing down counterregulatory mechanisms of BP elevation, better acceptability of the treatment, and efficient prevention of target organ damage [3, 4]. All these aspects are typical of sound combinations of antihypertensive agents, mostly of angiotensin-converting enzyme inhibitors (ACEi) and thiazid/thiazid-like diuretics (TD/TLD) or angiotensin II receptor blockers (ARB) (antagonists) with TD/TLD. Also, these are combinations of ACE inhibitors with calcium antagonists — dihydropyridine calcium channel blockers (CCB) or combinations of ARB and CCB. Once AH has been diagnosed, the physician has to choose between these combinations following the current recommendations; they are first-line therapy [2]. These antihypertensive agent groups can be combined in one tablet and are a part of a majority of fixed-dose combinations (FDC) registered in Russia, or they can be prescribed as two separate tablets (Fig. 1).

A number of recent studies demonstrate that drug therapy compliance and BP control are better in patients taking FDC than in patients taking free combinations of antihypertensive agents [5-7]. At the same time, in the real-life clinical practice, physicians sometimes prefer components of combined antihypertensive drug therapy in two separate tablets. This study seeks to identify whether it is justified for the compliant patients and whether free combinations of antihypertensive agents are still used as the first-line therapy.

Combined antihypertensive therapy

Monotherapy instead of a combined therapy is one of the causes of poor control of BP in the general population of AH patients. An important aspect is selection between fixed (one tablet) and free (two tablets) combinations of antihypertensive agents.

Over the past decades, a number of large-scale randomised studies demonstrated the efficacy of a two-component combination of RAAS inhibitor and a thiazide/thiazide-like diuretic or calcium channel blockers (CCB) in various populations. This choice is challenging; it requires justification and is a common example of the so-called Good Prescribing, when the adequate combined drug therapy prescribed to a specific patient ensures the highest efficacy and safety. The ACCOMPLISH study compared a combination of ACEi benazepril and CCB amlodipine with a combination of benazepril and hydrochlorothiazide (diuretic) in the reduction of the primary combined endpoint of cardiovascular events and cardiovascular mortality. A combination of RAAS inhibitor and CCB demonstrated higher efficacy in reduction of the rate of cardiovascular complications, whereas a combination with a diuretic showed positive results in patients with cardiovascular insufficiency and also in African American patients [9].

When a two-component therapy is insufficient to achieve the target BP values, standard doses of a three-component antihypertensive therapy are used (with possible use of FDC, including ACEi/ARB+CCB+diuretic). According to the State Register of Medicinal Products, four such FDCs are available on the Russian market: two combinations with ACE inhibitors (lisinopril/perindopril) plus amlodipine and indapamide, and two combinations with ARB (valsartan/telmisartan) plus amlodipine and hydrochlorothiazide. Currently, studies are ongoing to evaluate three-component FDCs with low doses of components (telmisartan/amlodipine/indapamide doses (mg): 10/1.25/0.625 and 20/2.5/1.25 vs. two-component FDC of the above antihypertensive agents [10].

In refractory (resistant) hypertension, four-component therapy is possible: a three-component FDC and one antihypertensive agent from the list of second-line drugs. The prospects of using a four-component combination, i. e. very low doses of four antihypertensive agents in one tablet (doses which are four times lower than the average doses of each component): irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and a beta-blocker bisoprolol 2.5 mg [11, 12]) require further studies, since the efficacy of this therapy was

evaluated in the QUARTET study in comparison with irbesartan 150 mg monotherapy; comparison with a two-component FDC is required: irbesartan and indapamide with irbesartan and amlodipine. The study, where irbesartan was replaced with candesartan 2 mg and all other components were the same as in the QUARTET study (amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg), did not demonstrate any significant difference in the clinical efficacy and safety vs. controls (candesartan 8 mg + amlodipine 5 mg daily starting from week 6) [13]. In 2013, a four-component FDC was registered in Russia, which is marketed under the brand name Hypotef (Syntez LLC), containing enalapril 5 mg, vinpocetine 2.5 mg, indapamide 0.75 mg, and metoprolol 25 mg. This FDC contains the average doses of the ACE inhibitor and beta-blocker, while indapamide and vinpocetine are in a lower dose compared to when taken individually. Vinpocetine corrects cerebrovascular disorders, it is not a classical CCB, but its mechanism of action involves calcium antagonism. The FORSAGE study demonstrated comparable efficiency and tolerability of this combination vs. patients who were treated with full doses of antihypertensive agents (ACEi/ARB+diuretic/CCB/beta-blocker), as well as the promising outlook of its use in patients with AH and dyscirculatory encephalopathy [14, 15].

Rate of prescription, share and cost of two-component antihypertensive FDC

Studies conducted in different countries seek to evaluate the rate of prescription by doctors of a drug combination in one tablet as initial combined therapy, according to the recent recommendation of the European Society of Hypertension. Bryan A.S., et al. (2023) report that in the USA only one third of adult patients with AH are treated with FDC [16]. A German study to analyse the use of the current recommendations on the drug treatment of hypertensive patients in 2016–2020 recorded high rates of non-compliance with the recommendations in Germany regarding prescription of antihypertensive FDC. Almost two years after the publication of ESC/ESH 2018 Recommendations on Hypertension Management, in 2020 only 10.9 % of prescribed antihypertensive drugs were FDC, evidencing poor use of the current recommendations on drug treatment of arterial hypertension [17]. At the same time, a cost-benefit analysis of an initial two-component antihypertensive therapy demonstrated that, taking into account direct healthcare costs, quality-adjusted life years (QALY) and 10-year additional economic efficiency coefficient, in 10 years the use of FDC will yield extra 0.028 quality-adjusted life years without any significant investments, vs. monotherapy. A two-component FDC is economically more viable than a free combination of equivalent doses of individual tablets (additional economic efficiency coefficient $57 000/increase in QALY) [16]. Therefore, the more active use of FDCs in routine clinical practice is required in order to improve prognosis for patients with AH.

In Russia, an analysis was performed of the data on antihypertensive agent sales in 2018 in pharmacies across 10 districts of the Far East Federal Region. The study showed that the highest share of FDC was in the Amur Region (15.3 %) and Zabaikalye Territory (13.5 %). The lowest share was recorded in the Sakhalin (5.3 %) and Magadan (6.6 %) Regions. The most popular fixed dose combinations in the Far East Federal Region are balanced combinations of ACEi and diuretics or CCB, as well as ARB with diuretics [18]. For sure, the share of antihypertensive FDC in pharmacies and the rate of prescription by doctors who regularly deal with AH, grows with every passing year, including Russia. A questionnaire survey among primary care providers in the Voronezh Region demonstrated that medical professionals (MP) prefer FDC with ACEi+diuretic (72 % of MPs) vs. the earlier Russian PIFAGOR IV study (2013), where this combination was chosen in 33 % of cases. Compared to the PIFAGOR IV study, healthcare providers preferred ACEi+CCB (46 %) (PIFAGOR IV study: 24 %), ARB+diuretic (36 % vs. 28 %) [19].

According to literature, one disadvantage of free combinations in AH management is higher cost of treatment, since FDC are cheaper than individual agents [20]. However, the opinion that the reduced cost of treatment is partially associated with lower cost of combined products vs. cost of individual components [21] was not confirmed in the majority of cases when we compared retail prices of two-component antihypertensive products in pharmacies (data from at least 5 pharmacies) in Smolensk in May 2024 (Table 1). For instance, the average retail price of FDC containing perindopril and indapamide, marketed under the brand name Noliprel A Forte, is twice as high as the total average price of its components from the same manufacturer (Servier). At the same time, there are FDC (e.g., azilsartan medoxomil with chlortalidone (brand name: Edarbyclor), where the average price is almost the same as the total price of individual components. The cost of AH therapy comprises direct and indirect costs; however, for some patients, the price of drugs in pharmacies can be a deciding factor.

For reference: the annual cost of FDC therapy for one patient in Germany was significantly higher than therapy with the same combinations of two tablet

Table 1. *Comparison of average retail prices for some fixed-dose combinations (FDCs) containing RAAS inhibitor and diuretic or calcium channel blocker with prices for the same combinations in different tablets*

N	FDC: component INN, dosage, number of dosage units, brand name (manufacturer), price per package	Component 1 ACEi or ARB: INN, dosage, number of dosage units, brand name (manufacturer), price per package	Component 2 Diuretic or CCB: INN, dosage, number of dosage units, brand name (manufacturer), price per package
1.	ACEi perindopril 5 mg, diuretic indapamide 1,25 mg, # 30 *Noliprel A Forte (Servier)* Average price: 954,4 RUB	perindopril 5 mg, # 30 *Prestarium A (Servier)* Average price: 259,9 RUB	indapamide 1,5 mg, # 30 *Arifon retard (Servier)* Average price: 211 RUB Average combination price 470,9 RUB
2.	ACEi ramipril 5 mg, diuretic indapamide 1,25 mg, # 30 *Konsilar-D24 (Vertex)* Average price: 672,4 RUB	ramipril 5 mg, # 28 *Ramipril vertex* Average price: 167 RUB	indapamide 1,5 mg, # 30 *Indapamide vertex* Average price: 32 RUB Average combination price 199 RUB
3.	ACEi enalapril 10 mg, CCB lercanidipine 10 mg, #28 *Lerkamen Duo (Berlin-Chemie/Menarini)* Average price: 666,5 RUB	enalapril 10 mg, # 30 *Berlinpril (Berlin-Chemie/Menarini)* Average price: 132,7 RUB	lercanidipine 10 mg, # 28 *Lerkamen (Berlin-Chemie/Menarini)* Average price: 463,8 RUB Average combination price 596,5 RUB
4.	ACEi lisinopril 10 mg, CCB amlodipine 5 mg, # 30 De-kriz (MEDISORB) Average price: 343,6 RUB	lisinopril 10 mg, # 30 *Lisinopril medisorb* Average price: 135,5 RUB	amlodipine 5 mg, # 50 *Amlodipin medisorb* Average price: 80 RUB Average combination price 215,5 RUB
5.	ARB valsartan 80 mg, diuretic hydrochlorothiazide 12,5 mg, # 28 *Co-diovan (Novartis Pharma)* Average price: 2504,8 RUB	valsartan 80 mg, # 28 *Diovan (Novartis Pharma)* Average price: 2035,5 RUB	hydrochlorothiazide 25 mg, # 20 *Gipotiazid (Sanofi Rossija)* Average price: 94,4 RUB Average combination price 2129,9 RUB
6.	ARB azilsartan medoxomil 40 mg, diuretic chlorthalidone 12,5 mg, # 28 *Edarbi-Klo (Takeda Island Limited)* Average price: 1225,4 RUB	azilsartan medoxomil 40 mg, # 28 *Edarbi (Takeda Island Limited)* Average price: 952,2 RUB	chlorthalidone 12,5 mg, # 30 *Dikardplus (Ipca Laboratories Limited)* Average price: 227,8 RUB Average combination price 1183 RUB
7.	ARB candesartan 16 mg, CCB amlodipine 10 mg, # 30 *Giposart A (Akrikhin)* Average price: 618,8 RUB	candesartan 16 mg, # 30 *Giposart (Akrikhin)* Average price: 485,5 RUB	amlodipine 10 mg, # 30 *Amlodipine (Vertex)* Average price: 65 RUB Average combination price 550,5 RUB
8.	ARB telmisartan 40 mg, CCB amlodipine 5 mg, # 28 Telzap AM (Sanofi Russia) Average price: 502,8 RUB	telmisartan 40 mg, # 30 *Telzap AM (Sanofi Russia)* Average price: 464 RUB	amlodipine 5 mg, # 30 *Amlodipine (Vertex)* Average price: 65 RUB Average combination price 528 RUB

(ramipril/ amlodipine: EURO 230 vs. EURO 134; candesartan/amlodipine: EURO 339 vs. EURO 235) [22].

A higher price of antihypertensive FDCs from the same manufacturer in Russia in comparison to the total cost of the same doses of individual components is partially due to a higher demand for FDC, since the doctors are under regulatory pressure to prescribe FDCs. To a greater extent, this is a result of the absence of these FDCs in the list of vital and essential medicines. In the Russian Federation, price control applies only to the drugs which are included in the list of vital and essential medicines (Art. 60 of Federal Law No. 61 as amended on 30/01/2024, On Circulation of Medicines, and Decree of the RF Government No. 865, On State Control of Prices for Vital and Essential Medicines); only medicines in this list are subject to the manufacturer's maximum sale price, specific wholesale and retail mark-ups. The prices for medicines, not included in the list of vital and essential medicines (in this case — antihypertensive FDC), are determined by the manufacturer.

Selection of the most optimal two-component combinations of antihypertensive agents: FDC or free combinations

1) Combination of an ACEi and a diuretic. A combination of an ACEi and TD/TLD is the most common in AH management due to its high efficiency, protection of target organs, adequate safety and tolerability, ability of ACEi to prevent diuretic-mediated hypopotassaemia [23].

An earlier large-scale retrospective study in patients with AH evaluated compliance with ACEi and TD. One year after initiation of hydrochlorothiazide-only therapy, 70 % of patients withdrew from further therapy, whereas when an FDC of TD and ACEi was prescribed, the number of patients withdrawing from antihypertensive therapy was twice as low [24]. In the study, fixed combinations were compared to TD monotherapy; and no comparisons were made with ACEi monotherapy and with a free combination of ACEi and TD in various tablets.

A retrospective cohort study in 13,350 subjects aged 66 years and over in Ontario, with a follow-up period of up to 5 years, compared patients treated with fixed combinations of ACEi and TD/TLD with patients taking individual antihypertensive agents. Comparison of results before the first case of treatment withdrawal (when there were no differences in compliance between groups) did not reveal any significant intergroup difference in clinical results [25]. The use of FDC was associated with better compliance (70 % with FDC vs. 42 % with individual tablets) [25].

A randomised, 8-week prospective cross-section study in two groups, conducted in Nigeria in 2018 in adult patients with AH who were treated with ACEi lisinopril and TD hydrochlorothiazide monotherapy or with FDC, demonstrated that, by the end of week 8, both regimens achieved significant reduction in BP vs. baseline values; there were no cases of proteinuria in both groups; however, compliance was better with the use of FDC [26].

One of the most popular and common FDCs of ACEi with a thiazide-like diuretic is a combination of a lipophilic prodrug perindopril with indapamide. In Russia, this combination is distributed just under 19 trade names, for instance, Noliprel which is presented in three doses: Noliprel A (perindopril/indapamide 2.5 mg/0.625 mg), Noliprel A Forte (perindopril/indapamide 5 mg/1.25 mg), Noliprel A Bi-Forte (perindopril/indapamide 10 mg/2.5 mg), thus making it possible to individually select a dose [27].

In their study, the staff of A. I. Evdokimov Moscow State University of Medicine and Dentistry discuss advantages of the Russian combined medicine — Konsilar-D24, which is a fixed combination of ACEi ramipril 5 mg and TLD indapamide 1.25 mg, primarily better compliance among patients with AH [21]. The study of this FDC continued with the CONSONANCE 2023 program; for the first time, the therapy efficacy was evaluated after home-based BP monitoring, taking into account drug effects for the long-term BP variability and patient well-being using the EuroQol visual and analogue scale. The target clinical BP levels of < 140/90 mm Hg after 2 weeks were achieved in 74.9 % of patients, after 6 months — 99.4 % of patients. The target home-based BP levels of < 135/85 mm Hg after 2 weeks were achieved in 75.7 % of patients, after 6 months — 91.1 % of patients [28].

2) Combination of an ARB and a diuretic. An equally important, and also an alternative, combination with ACEi, especially in case of their individual intolerance (dry cough, angioedema), is ARB with TD/TLD [29].

Telmisartan (ARB) possesses high affinity to AT_1 receptors and more than any other sartans affects peroxisome proliferator-activated receptors γ (PPARγ), at a dose recommended for AH therapy, which can be of importance in case of concomitant insulin resistance, type 2 diabetes mellitus and metabolic syndrome. PPARγ activation boosts adiponectin production and facilitates anti-inflammatory, anti-oxidative effects on vessel walls, thus having angioprotective activity and reducing the risk of atherosclerotic processes.

Currently, the following doses of the FDC of telmisartan and hydrochlorothiazide are marketed in Russia: telmisartan 40 mg+hydrochlorothiazide 12.5 mg, telmisartan 80 mg+hydrochlorothiazide 12.5 mg, telmisartan 80 mg+hydrochlorothiazide 25 mg, as well as the FDC of telmisartan and indapamide: telmisartan 40 mg+indapamide 1.5 mg and telmisartan 80 mg+indapamide 1.5 mg [30].

Also, an FDC containing ARB azilsartan medoxomil with diuretic chlortalidone is of interest [31], which is available only in two doses: azilsartan 40 mg and chlortalidone 12.5 or 25 mg. Chlortalidone is a 1st generation thiazide-like diuretic with a long-lasting effect (24–48 h vs. 6–12 h for hydrochlorothiazide). That is why a comparison of the two combinations of azilsartan medoxomil with chlortalidone (FDC Edarbyclor) and hydrochlorothiazide demonstrated that the combination of azilsartan medoxomil with chlortalidone possesses higher antihypertensive efficiency and comparable safety vs. the combination with hydrochlorothiazide [29]. In a comparative study of the FDC azilsartan medoxomil with chlortalidone (Edarbyclor 40/12.5 mg) and a free combination of azilsartan medoxomil with indapamide retard (Edarb 40 mg+indapamide retard 1.5 mg) in patients with AH, after 12 weeks 88 % of patients in the first group and 72 % of patients in the second group reached target clinical BP; the first group demonstrated higher antihypertensive effects on clinical and 24-hour peripteral BP, as well as normalisation of 24-hour systolic BP [32].

3) Combination of ACEi and CCB. First studies of the combination of fixed doses of ACEi enalapril and dihydropyridine calcium channel blocker lercanidipine showed that the FDC is more potent in BP reduction than enalapril 20 mg monotherapy or lercanidipine 10 mg monotherapy [33].

A comparative analysis of AH management using a free combination of ACEi perindopril and CCB amlodipine and FDC Prestans during 12 months compared changes in BP values, including BP variability, target organ remodelling criteria. By the end of week 4, the target BP values were observed in 87.5 % and 87.1 % of patients in both groups vs. baseline. Diastolic BP and nocturnal systolic BP were lower in patients taking FDC. One year after therapy initiation, the group of patients treated with a free combination of perindopril with amlodipine still demonstrated changes in target organ remodelling parameters: glomerular filtration rate, microalbuminuria, ankle-brachial index, which is a result of poorer compliance, more frequent withdrawals from one of the prescribed antihypertensive agents for 1–3 days, as well as dose modifications by patients [34]. The need for a wider dose range has been satisfied with a fixed dose combination of perindopril with amlodipine sold under the brand name Dalneva, which is available in four perindopril/perindopril dose combinations: 4/5, 8/5, 4/10, and 8/10 mg, which is very useful for the real-life clinical practice [5]. A study by Simonyi G., et al. (2017) comparing the stability of a year-long AH therapy with free combinations and FDC demonstrated that the actual rate of therapy withdrawal was approximately two times higher with free doses vs. FDC [35].

A comparison of the efficacy of FDC and a free combination of ramipril and amlodipine in patients with AH also demonstrated better compliance and the degree of the nephroprotective and angioprotective effects in the FDC group vs. a free combination [36, 37]. A combination of ACEi and CCB is seen as a promising option in the therapy of patients with AH and concomitant COVID-19, it being a result of efficient correction of endothelial dysfunction. It appears that perindopril not only increases the bradykinin levels and boosts the activity of endothelial NO-oxidase, but it also decreases the rate of endothelial cell apoptosis, while amlodipine acts as an antioxidant [5, 38].

4) A combination of ARB and CCB is not indicated in cardiovascular comorbidities with conduction abnormalities: bradycardia, atrioventricular blocks, but is a combination of choice in concomitant ischemic heart disease, myocardial hypertrophy, migraines.

The VICTORY II study assessed the efficacy and safety of an FDC containing valsartan and amlodipine in achievement of target BP levels in newly diagnosed or uncontrolled AH. During a 3-month period with monthly valsartan/amlodipine dose titration, the target AH levels were achieved in a majority of patients with good tolerability. Also, FDCs reduced albuminuria, vascular endothelium dysfunction and improved erectile function and quality of life [39]. The use of medical services and the costs incurred by the patients in the FDC group treated with valsartan/amlodipine, as compared to their free combinations, were 16–20 % lower. In particular, they had fewer hospital admissions, outpatient visits and ambulance calls [40].

In a study conducted at the Kazan Medical University, patients treated with an FDC of losartan and amlodipine showed significantly higher reduction in the values of 24-hour BP monitoring vs. losartan and hydrochlorothiazide. It is assumed that an FDC containing CCB is preferable in patients with reduced nocturnal BP [41].

When an FDC of candesartan and amlodipine and their free combinations were used, the number of patients who were treated with and withdrew from the therapy with these drugs within 2 months after therapy initiation was comparable. However, after 3 months, the

rate of therapy discontinuation was higher in patients taking a combination of two tablets vs. FDC; after 12 months, the difference between the groups was even bigger [42].

A comparison of the comorbidity risk factor (all-cause mortality and all-cause hospitalisation) showed that the FDC regimen, in particular combinations of valsartan/amlodipine, candesartan/amlodipine, had advantages vs. free antihypertensive combinations. Thus, FDC regimens are associated with a lower rate of cardiovascular events and lower all-cause mortality in the clinical practice [43].

Market analysis of two-component antihypertensive FDCs containing a RAAS inhibitor and diuretic/calcium channel blocker

In order to analyse the Russian market of antihypertensive agents, we studied the number of trade names of two-components FDCs, based on the INN of ACEi/ARB in the National Register of Medicines. Below are RAAS inhibitors in descending order of their presence in FDC (in brackets, the first digit means the number of INN combinations with various diuretics and calcium channel blockers; the second digit is the number of their trade names):

1) enalapril (4/16)> lisinopril (3/15)> ramipril (3/7)> perindopril (2/25)>
captopril (1/2)> zofenopril (1/1) ≈ trandolapril (1/1) ≈ fozinopril (1/1) ≈ quinapril (1/1)> spirapril (0/0) ≈ cilazapril (0/0);
2) telmisartan (3/15)> valsartan (3/19)> losartan (2/22)> candesartan (2/6)> olmesartan medoxomil (2/3)> azilsartan medoxomil (2/2) ≈ irbesartan (2/2)> eprosartan (1/1).

In general, prolonged-release antihypertensive FDCs should be preferable in order to ensure a 24-hour effect after a single administration. Less common are products with such diuretics as indapamide; there is only one combination with diuretic chlortalidone (azilsartan medoxomil+chlortalidone). More common are FDCs with a shorter-action diuretic hydrochlorothiazide (especially among 2-component FDCs containing sartans).

The majority of FDCs containing CCB include dihydropyridine derivative amlodipine. There is one FDC containing lercanidipine: enalapril+lercanidipine, and one FDC containing nitrendipine: enalapril+nitrendipine. An FDC with a non-dihydropyridine CCB verapamil is available only in one drug from a non-Russian manufacturer.

An analysis of the market depth, i.e. availability of FDCs with ratios of various component doses, requires a more thorough study. It should also be taken into account that the availability of antihypertensive FDCs mentioned in the National Register of Medicines can significantly differ from the assortment in pharmacies of various constituent territories of the Russian Federation.

Discussion and conclusion

Currently, the most common initial drug therapy of AH is a combination of two products. The recommendations of the International Society of Hypertension (ISH) state that the optimal option is a combination of a RAAS inhibitor (ACEi or ARB) with a CCB in the majority of patients, while a fixed combination of an ACEi or ARB with a diuretic is advisable in elderly people with a history of stroke or transient ischaemic attack, with signs of chronic cardiac failure, and a history of CCB intolerance [39]. Selection of a specific initial regimen of AH therapy depending on the clinical picture is presented in Table 2.

The use of a combined therapy, which is synergetic and complementary, increases a share of patients achieving the recommended target BP values, as well as ensures protection against target organ damage and reduces the risk of side effects and cardiovascular events [46]. An important matter is the selection between a fixed combination in one tablet and a combined therapy in two different tablets.

Combined antihypertensive products in the form of FDCs improve BP control and compliance among patients with AH. Despite the fact that the FDC assortment is gradually growing, a 2-year study in the USA showed that three out of five hypertensive adults treated with 2 classes of antihypertensive agents use a regimen, which as of January 2023 was not commercially available in the form of an equivalent FDC [47]. These results demonstrate that the available FDC assortment does not meet the clinical needs of the target population [48]. On the one hand, the available FDCs are not complete; on the other hand, they overlap and duplicate one another due to a wide range of generic products [47]. Besides, FDCs are not often used as a first-line antihypertensive therapy, despite the increasing volume of evidence and scientific recommendations [49]. According to the literature, patients, whose initial therapy was usually FDCs, were younger and had fewer comorbidities. A multivariate analysis demonstrated that in patients with a history of myocardial infarction or stroke, healthcare providers prefer a more flexible therapy and free combinations of antihypertensive agents [42].

Table 2. *Choice of fixed-dose combinations (FDC) containing RAAS inhibitor and a diuretic or calcium channel blocker for arterial hypertension [2, 7, 44, 45]*

Comorbidities	Preferred FDC	Alternative
angina pectoris	ACEi (primarily perindopril or ramipril) + **CCB**	ARB (primarily valsartan or candesartan) + **CCB**
myocardial infarction	ARB + **CCB**	ACEi + **CCB/TD**
chronic heart failure	ACEi + **TD/TLD**	ARB + **TD/TLD**
left ventricular hypertrophy	ARB + **CCB**	ACEi + **CCB**
atrial fibrillation	ACEi/ARB + **CCB non-dihydropyridine (non-DHP), e.g. verapamil**	ACEi/ARB + **CCB dihydropyridine (DHP)**
coronary and carotid atherosclerosis, dyslipidemia	ACEi + **CCB**	ARB + **CCB**
cerebrovascular disease	ARB + **TLD/ CCB**	ACEi + **TLD**
metabolic syndrome	ACEi/ ARB + **CCB**	ACEi/ARB + indapamide
type 2 diabetes mellitus	ACEi/ ARB + **CCB**	ACEi/ARB + indapamide
proteinuria / microalbuminuria	ACEi/ ARB + **TD/TLD**	ACEi/ARB + **CCB**
chronic kidney disease	ACEi/ ARB + **loop diuretic**	ACEi/ARB + **TD/TLD**
peripheral artery disease	ARB + **CCB**	ACEi + **CCB**
intolerance to ACE inhibitors (dry cough, which is more common for women, patients of the Negroid and Mongoloid races, smokers, patients with concomitant bronchopulmonary pathology)	ARB + **CCB**	ARB + **TD/TLD**
patients with multiple **drug allergies, bronchial asthma, COPD**	ARB + **CCB**	ARB + **TD/TLD**

Note. CCB — dihydropyridine calcium channel blocker, ARB — angiotensin II receptor blocker, ACEi — angiotensin-converting enzyme inhibitor, TD — thiazide diuretic, TLD — thiazide-like diuretic

In addition to the patient convenience, better compliance, ease of prescription and better achievement of target BP values, advantages of a combined antihypertensive drug therapy with FDCs include prevention of the probability of irrational combinations [27]. At the same time, advantages of free combinations of antihypertensive agents include more individualised selection of drug doses (however, the range of FDC doses and assortment grow from year to year), the possibility to cancel or replace one component of the combination with another one, the possibility of taking combination components at various times during the day, which can yield a more stable 24-hour antihypertensive effect (for instance, a RAAS blocker is taken in the morning and a CCB — before bed) [8, 50].

Going back to the main advantage of FDC, that is, better compliance, it is worth mentioning that no therapy will ever be efficient, unless the patient takes the prescribed medicines in a correct order, correct dose and required number of times. FDCs once daily improve compliance. Currently, there are FDCs which contain not only antihypertensive agents, but also components to correct the main risk factors of AH and its complications. For example, in order to simplify the drug therapy regimen in concomitant dyslipidemia and metabolic syndrome, statins were added to one tablet with antihypertensive agents. Two ACEi-containing FDCs are currently available in Russia: lisinopril/perindopril+amlodipine+statin (rosuvastatin/atorvastatin), and one ARB-based combination:

losartan+amlodipine+statin (rosuvastatin). In a study comparing a three-component FDC of olmesartan/amlodipine/rosuvastatin in one tablet at a dose of 20/5/5 mg (group 1) and 20/5/10 mg (group 2) vs. FDC of olmesartan/amlodipine at a dose of 20/5 mg (group 3), the primary endpoint was the difference in the changes in cholesterol and low-density lipoprotein (LDL) levels 8 weeks after the baseline in 3 groups of patients with AH and a low or moderate cardiovascular risk. Achievement of LDL cholesterol of < 5.6 mmol/L after 8 weeks was statistically different between the groups (65.8 %, 86.7 %, and 6.3 %, respectively). Results for total cholesterol, triglycerides, HDL, apolipoprotein B, etc. were better in groups treated with FDCs containing rosuvastatin; no serious adverse drug reactions (ARD) were reported in any group [51]. A meta-analysis of 18 actual clinical studies with the total number of 20,463 subjects revealed a statistically significant correlation between the use of FDCs with statins and improvement in compliance, lower BP and total cholesterol in hypertensive patients in the high-risk group [52].

Generally, an idea of using all required medicines in one tablet to prevent and correct cardiovascular risk factors (not only statins, but also antiplatelets for thrombosis prevention, folic acid for homocysteinemia correction, etc.) has been actively developing [53] and is at the edge of polypharmacy, which brings about sound scepticism. First, there is a risk of taking unnecessary drugs and excessive control of very low levels of BP and LDL cholesterol. Second, there are pharmacokinetic drug-drug interactions in multi-component (4 and more components) FDCs, with subsequent changes in therapy efficacy and unpredictable incidence of ARDs. Third, some healthcare providers want to emphasise a non-drug correction of risk factors.

When evaluating the pharmacoeconomic advantages and reduction in the cost of FDC therapy, it is assumed that the costs for patients treated with adequate FDC regimens is lower than with the use of free combinations. In particular, they have fewer hospital admissions, outpatient visits and ambulance calls [27]. However, in a meta-analysis by Mallat S.G., et al. (2016), analysing 7 randomised clinical studies comparing efficiency of BP control with FDCs and free antihypertensive combinations, the authors concluded that the designs of these studies are not adequate in terms of methodology, that is why their results do not confirm and do not rule out significant difference between a fixed and free combined therapy of AH [39]. Besides, evidences gathered in clinical studies of free combinations are often projected on fixed combined therapy, which is a doubtful extrapolation.

At the same time, the START study analysed data from 57,998 AH patients: 15,349 patients were treated with ramipril/ amlodipine, 10,801 — with valsartan/amlodipine, 1,026 — with candesartan/amlodipine in one tablet or several similar tablets. All groups treated with FDC had reliably lower all-cause mortality, reliably higher therapy tolerability, lower incidence of events with cardiovascular complications vs. a combination of several tablets [56]. These results confirm the recommendations of the European Society of Cardiology/European Society of Hypertension and International Society of Hypertension, recommending using combinations in one tablet and more active introduction of FDC to routine clinical practice.

A systemic review by Parati G., et al. (2016) discusses a number of potential advantages of FDC vs. free combinations of equivalent drugs: lower tablet load, lower healthcare costs and use of resources, reduction in clinical inactivity by healthcare providers and better therapy compliance [54]. However, none of the studies measured compliance through drug monitoring (drug quantification in blood and urine); instead, indirect methods to count tablets were used, such as a share of days covered or drug possession factor, which can overestimate compliance, although, in the long-term, these methods allow for efficient measurements. Also, studies which demonstrated similar compliance between DC and free combinations of two tablets were mostly prospective, and patients were regularly and closely followed-up. Because of better compliance, studies of the positive effect of FDC vs. combinations of two tablets were retrospective.

The 2024 list of vital and essential medicines contains a combination of ARB valsartan with inhibitor neprilysin sacubitril (Uperio), used in the management of chronic cardiac failure. There are no antihypertensive FDCs including a RAAS inhibitor and a diuretic or CCB; patients cannot get them at a discounted price and healthcare providers can choose to prescribe free combinations of antihypertensive agents.

FDCs are associated with some limitations which should be assessed in clinical practice: fewer cases of potential inefficiency of one of the components, a narrower range of component doses, relative limitation of an increase in the dose of one of the drugs irrespective of the other one, or adaptation of the dose of one drug to some circumstances (reduction of the diuretic dose in case of fever or diarrhoea), a higher risk of complications in non-compliant patients [49, 55].

Therefore, optimal fixed dose combinations help both healthcare providers and AH patients to achieve and maintain the life-long target BP. FDCs should be preferable. At the same time, currently there are a number of

circumstances, where combined antihypertensive therapy in two different tablets can be used. Further studies of pharmacoepidemiological and pharmacoeconomic aspects of the two-component antihypertensive therapy in Russia are required.

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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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Zagnet K.D.: critical review of the article, editing a manuscript

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МЕТОД УСИЛЕННОЙ НАРУЖНОЙ КОНТРПУЛЬСАЦИИ В КЛИНИЧЕСКОЙ ПРАКТИКЕ

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The Method of Enhanced External Counterpulsation in Clinical Practice

Резюме

Хронические неинфекционные заболевания представляют важную медико-социальную проблему для системы здравоохранения. Оптимальная фармакотерапия не всегда оказывается достаточно эффективной, а применение хирургических методов лечения возможно не у всех больных. Кроме того, важным звеном комплексного ведения таких пациентов является дозированная физическая активность, однако у большинства из них низкая толерантность к нагрузкам не позволяет их осуществлять, запуская порочный круг, приводящий к снижению функционального резерва организма. В данном случае полезным может быть использование немедикаментозных методов лечения, например, усиленной наружной контрпульсации. Настоящий обзор посвящен анализу литературных данных о возможностях использования данного метода, что имеет существенное значение в клинической практике.

Ключевые слова: *хронические неинфекционные заболевания, усиленная наружная контрпульсация, немедикаментозные методы лечения*

Конфликт интересов

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

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Abstract

Chronic non- infectious diseases represent an important medical and social problem for the healthcare system. Optimal pharmacotherapy is not always effective enough, and the use of surgical treatment methods is not possible in all patients. In addition, an important link in the comprehensive management of such patients is dosed physical activity, however, in most of them, low exercise tolerance does not allow them to exercise, starting a vicious circle that leads to a decrease in the functional reserve of the body. In this case, the use of non-pharmacological treatment methods, for example, enhanced external counterpulsation, may be useful. This review is devoted to the analysis of literature data on the possibilities of using this method, which is important in clinical practice.

Key words: *chronic non- infectious diseases, enhanced external counterpulsation, non-pharmacological treatment methods*

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IHD — ischaemic heart disease, CPST — cardiopulmonary stress test, ECP — external counterpulsation, DM — diabetes mellitus, CVD — cardiovascular diseases, EECP — enhanced external counterpulsation, LV EF — left ventricle ejection fraction, CNCD — chronic non-communicable diseases, COPD — chronic obstructive pulmonary disease, CRD — chronic respiratory diseases, CCI — chronic cardiac insufficiency, 6MWT — 6-minute walk test

Introduction

Chronic non-communicable diseases (CNID) are one of the global problems all over the world due to their high incidence, poor prognosis (incapacitation and death) and negative impact on the quality of patients' lives [1]. Almost a half of the world population have at least one chronic condition [2]. According to the Russian Society for the Prevention of Noncommunicable Diseases [3], the most common CNCD are cardiovascular diseases (CVD), malignancies, chronic respiratory diseases (CRD), and diabetes mellitus (DM). These conditions deplete the functional reserves of the human body and reduce the intensity of compensatory and regenerative responses.

Currently, pharmacological and surgical treatment strategies have been actively developing, and they can improve the well-being of such patients. However, it is worth mentioning that even the optimal drug therapy in such patients is not always efficient enough, and surgery is possible not in all patients. Besides, in recent decades, physical exercises have been widely used for the management of patients with CNCDs. A systematic overview [4], comprising results from 85 meta analyses on 22 various chronic conditions, demonstrated that graduated exercises are a safe way to boost physical and functional capabilities in patients with CNCDs. It means aerobic training, strength training, combined exercises with weight, as well as a majority of other training protocols, typical for a specific condition of the body. Still, not all patients can do exercises due to poor tolerance and long-lasting hospitalisations, thus bringing about a vicious circle of muscle dysfunction resulting in body de-training and depletion of its functional reserves. Such cases require additional non-drug therapies, one of which is enhanced external counterpulsation (EECP), which allows patients not only to boost their motor performance, but can also be used together with physical exercises.

Background of the method

The external counterpulsation (ECP) method has been used in the clinical practice since recently. The term "counterpulsation" appeared just in the second half of the 20th century. It was used in 1962 for the first time to describe a mechanism of fast reverse movement of the blood in the aorta. Then the new method was tested in an experiment in dogs. Cuffs were placed on the lower extremities of animals, then air was pumped to increase the diastolic pressure in the aorta. Some time later, these experiments were used to create the first device for ECP in humans as an alternative to intra-aortic balloon counterpulsation, which is an invasive and technically sophisticated method. First ECP devices used only two cuffs; later, the addition of a buttock cuff enhanced the haemodynamic efficacy of the method, hence the name of the method.

A modern EECP device comprises an electronic control unit, compressor, air hoses, couches, fitted cuffs for patient's shanks, hips and buttocks, electrodes to synchronise the device with the patient's ECG and finger photoplethysmograph (Fig. 1).

EECP mechanism of action

During the diastolic phase, the air is quickly and consistently pumped from the cuff from the bottom up (from shanks to buttocks), which compresses arterial vessels. The resulting reverse arterial blood flow and increased diastolic pressure in the aorta facilitate an increase in perfusion pressure in arterial vessels and better organ perfusion. Before systole, cuffs are deflated; therefore, blood from the heart is pumped to partially empty vessels with lower resistance, reducing the afterload [5].

The EECP mechanism of action includes haemodynamic, neurohumoral and tissue effects (Table 1).

Haemodynamic effects are associated with increased diastolic coronary blood flow, increased venous return

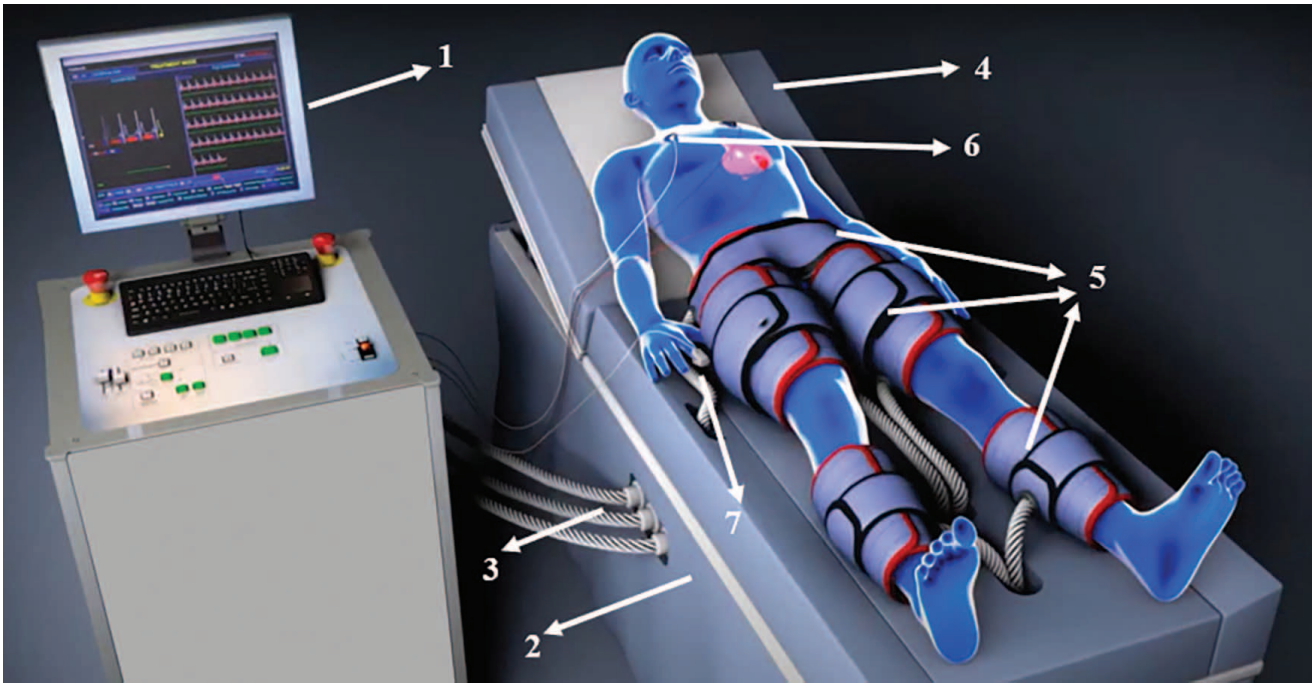

Figure 1. *Device for enhanced external counterpulsation*
Note: 1 — electronic control unit; 2 — compressor; 3 — air hoses; 4 — couch; 5 — cuffs; 6 — electrodes; 7 — finger photoplethysmography

Table 1. *Effects of enhanced external counterpulsation*

Hemodynamic	Vascular	Tissue
- Increased diastolic coronary blood flow; - Improvement of systemic microcirculation; - Reduction of postload on the heart; - Increased venous return;	- Improvement of the elastic properties of blood vessels (reduction of stiffness); - Improvement of endothelial function; - Formation of collaterals (angiogenesis); - Slowing down the progression of atherosclerosis;	- Improvement of metabolic activity in tissues; - Increased tissue resistance to ischemia; - Increased insulin sensitivity;

to the heart, better system microcirculation, as well as reduced afterload to the heart. The haemodynamic effect of EECP is based on an increase in perfusion pressure in coronary arteries during the diastole and lower resistance to the cardiac output during left ventricle systole [6].

Vascular effects are due to better elastic properties of vessels and endothelial function, formation of collaterals and slowing down of atherosclerosis progression. It has been found out that EECP improves athrombogenic activity of the vascular wall, increases antitrombin III and plasminogen levels, and reduces antioxidant tissue-type plasminogen activator inhibitor levels [7]. Also, EECP causes an increase in nitrogen oxide levels and reduction in endothelin 1 levels [8], as well as contributes to neoangiogenesis activation. This effect is possible due to shear stress in vessel endothelial cells, resulting from friction between a blood layer and vessel wall. Faster blood flow in arteries during compression of lower limbs increases this value and stimulates release of various vasoactive substances (α-actin, von Willebrand factor, basic fibroblast growth factor, hepatocyte growth factor, vascular endothelial growth factor, and nitrogen oxide) [9-11].

Tissue effects are associated with better metabolic activity in tissues, better tissue resistance to ischaemia and insulin sensitivity.

This review presents results of an analysis of the literature data for 1998–2024 from PubMed, RSCI (Russian Science Citation Index), Scopus on the use of EECP in clinical settings. The following keywords were used: external counterpulsation, non-drug treatment,

rehabilitation. These scientific researches describe the capabilities of this method in various conditions, as well as discuss possible mechanisms of positive effect from EECP, which is of importance in clinical practice and further studies.

Use of the method in clinical practice

In clinical settings, EECP was used for the first time in patients with chronic cardiac insufficiency (CCI) [12] and ischaemic heart disease (IHD) [13]. In the Russian clinical recommendations on stable IHD, EECP is recommended for the management of refractory (both to drug therapy and surgery) angina (grade of recommendation A, level of evidence 2) [13]. In the European clinical recommendations, EECP is suggested for the management of symptoms in patients with severe angina, which is refractory to optimal drug therapy and revascularisation (grade of recommendation IIb, level of evidence B) [14]. Currently, EECP is included in the standards of management of patients with stable IHD [15] and CCI [16].

The method is unique since it is cost-effective and can be used in outpatient settings, therefore, it is available for a majority of patients. Also, EECP does not require a high level of body training, that is why the method can be used to treat patients who are not able to do exercises. In Russia, EECP has been included into territorial programs of compulsory health insurance for patients with IHD. At the same time, poor awareness of this method among healthcare providers and patients and inadequate availability of required equipment at the hospitals are still a problem.

Indications for EECP

Stable IHD (refractory angina) is the main indication for the use of this method, including cases where surgical revascularisation is not possible.

Also, EECP has proven to be effective in the management of patients with other conditions (including CCI, acute ischaemic cerebrovascular event, cognitive disorders, central retinal artery occlusion, inner ear diseases, ischaemic erectile dysfunction, obliterating diseases of lower limb arteries, chronic obstructive pulmonary disease), so the use of this method in these conditions is justified [17].

Contraindications to EECP

Despite the efficiency and safety, EECP has a number of contraindications [18, 19]:

- a history of thrombophlebitis and/or phlebitis;
- stage 2–3 pulmonary hypertension;
- decompensated cardiac insufficiency;
- myocardial infarction within the last three months;
- instable angina;
- uncontrolled arterial hypertension;
- haemorrhagic conditions (blood-clotting disorder with the international normalised ratio of > 2.0 or prothrombin time > 15 s);
- severe cardiac valve pathology;
- critical ischaemia of lower extremity arteries;
- abdominal and/or thoracic aortic aneurysm;
- irregular and tachysystolic atrial fibrillation, frequent ventricular extrasystoles, heart rate of > 135 or < 35 bpm);
- cardiac catheterisation within the last two weeks;
- surgery within the last six weeks;
- pregnancy.

Use of EECP in cardiology

As mentioned earlier, the capabilities of EECP are widely used in CVD management, and the effects of this procedure are studied most in this group of patients. The first large-scale study was MUST-EECP [20], which demonstrated the positive effect of a course of EECP in reduction of the number of angina episodes, thus in reduction in the need for nitroglycerine products, as well as longer physical exercise tolerance and the time to segment depression of ≥ 1 mm during the stress test. According to V. Singh et al. (2018) [21], 163 patients participating in the study also experienced reduction in clinical signs of IHD. According to R. Subramanian et al. (2005) [22], patients with CCI have elevated left ventricle ejection fraction (LV EF) after a course of EECP: from 46.40 ± 15.88 % to 50.05 ± 13.20 % ($p < 0.001$). Similar results were described in a study by A. Sardari et al. (2016) [23]: after a course of EECP, LV EF increased from 42.65 ± 11.82 % to 44.26 ± 11.86 % ($p < 0.001$). In addition to increased LV EF, EECP improves exercise tolerance. It was demonstrated in a study by E. Wu et al. (2013) [24], where exercise tolerance was evaluated using the 6-minute walk test (6MWT). Following EECP, the distance walked by patients increased by 7 %, from 410 m to 439 m ($p < 0.001$). The long-term effects of EECP on the structural and functional parameters of heart and vessel condition, exercise tolerance, and quality of life of patients with stable IHD with CCI, were studied in the Russian EXCEL study [25]. 120 patients were randomly divided into three groups of 40 subjects; two groups were treated with an optimal drug therapy plus EEPC once every six or 12 months, while the third group had placebo counterpulsation. During a 12-month follow-up period, groups 1 and 2 demonstrated better cardiac performance (LV EF increased

from 40.6 ± 7.5 to 47.5 ± 10.2 % and from 41.3 ± 6.8 to 43.9 ± 10.3 %, respectively), as well as better exercise tolerance during 6MWT (distance walked increased by 44.5 % and 24.9 %, respectively) and improved quality of life, as evidenced by specialised questionnaires. These positive changes lasted for the entire study, i.e. 36 months [26].

Also, patients with IHD often have peripteral artery conditions, which are a relative contraindication to EECP. However, a study by B. Thakkar et al. (2010) [27] demonstrated safety of the method in such patients, provided they do not have signs of critical ischaemia of lower extremities. In another study [28], a course of therapy (35 EECP sessions) in patients with obliterating atherosclerosis of lower limb arteries resulted in significant reduction in leg pain, calf muscles myotonia and chills in feet. Also, this category of patients demonstrated a significant increase in the rheographic index of shanks and feet (by 23.9 % and 23.2 %, respectively), longer distance of pain-free walking (in controls, an increase in distance was 64.5 ± 25.1 m ($p < 0.05$), while in the EECP group the distance increased by 250 ± 31.2 m ($p < 0.05$)), and a higher ankle-brachial index in the anterior and posterior tibial artery (by 31.4 and 35.2 %, respectively ($p < 0.05$). In this case, the positive effect of EECP was a result of endothelial effects.

Often, patients with IHD have arterial hypertension, when endothelial cells are damaged. A study by J. Liang et al. (2021) [29] demonstrated positive effects of EECP: reduction in systolic (133.2 ± 4.9 mm Hg vs. 139.3 ± 6.4 mm Hg, $p < 0.05$) and diastolic (83.4 ± 4.5 mm Hg vs 89.5 ± 7.6 mm Hg, $p < 0.05$) blood pressure and better reparative capability of endothelial cells.

Use of EECP in pulmonology

As far as the use of EECP in patients with CRDs is concerned, the studies are scarce and mechanisms of positive effects are understudied. The largest study is the study by M. Zhao et al. (2020) [30] to evaluate the effects of EECP on exercise tolerance of healthy volunteers and patients with chronic obstructive pulmonary disease (COPD). This randomised clinical trial enrolled 72 subjects aged 27 to 82 years of age who were randomly assigned to two groups: EECP group and non-EECP group. Depending on the highest oxygen consumption, groups with normal exercise tolerance, low exercise tolerance and COPD (symptoms, risk factors and the ratio of 1 second forced expiratory volume to forced vital capacity of < 70 %) were assigned as well. To evaluate the efficiency of a 15-session EECP, cardiopulmonary stress test (CPST) results obtained before and after the course were used. The study showed a considerable improvement in the anaerobic threshold of oxygen consumption, highest oxygen consumption, aerobic pulse threshold, anaerobic threshold of training load, metabolic equivalent of the anaerobic threshold, and highest metabolic equivalent in all subgroups of the EECP group vs. non-EECP group ($p < 0.05$). It has been demonstrated that EECP improves exercise tolerance, which is very important for patients with COPD. Although this study did not evaluate the pulmonary function, a small sampling study showed positive changes in the pulmonary function of patients with COPD who underwent a course of EECP. Another US clinical study conducted in 2021 [31] evaluated the efficiency of EECP in the management of long COVID-19. The study enrolled 16 patients with confirmed long COVID. Of note, in addition to

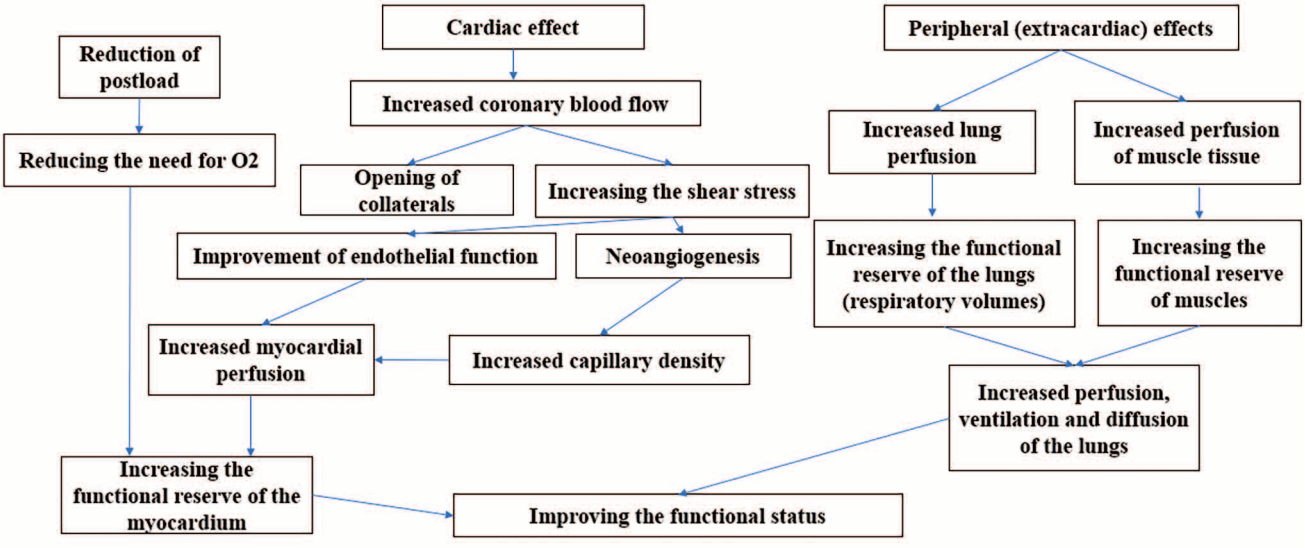

Figure 2. *Mechanism of action of enhanced external counterpulsation in chronic respiratory diseases*

long COVID, these patients had comorbidities, such as IHD and/or arterial hypertension. All patients had 15 to 35 EECP sessions. After a course of therapy, exercise tolerance (6MWT) was significantly better (the distance increased by 200.00 ± 180.14 m, p = 0.002) vs. baseline. Also, 44 % of study subjects noted improvement in their dyspnoea (Rose scale), 63 % of subjects had better angina functional status (Canadian Cardiovascular Society classification). A recent pilot study conducted at the Sechenov University [32] also showed the efficiency of EECP in patients with CRDs. The study enrolled 30 subjects aged 35 to 74 years of age with severe and moderate ventilation disorders without comorbidities. All patients had a 20-session course of EECP. Unlike other studies, in addition to CPST and 6MWT, EECP efficiency was for the first time evaluated using body plethysmography and a study of diffusing lung capacity. A course of therapy resulted in significant positive changes in lung capacity: 18 % increase in the total lung capacity, mostly due to the lung capacity, which grew by 24 % (p < 0.001). It is worth noting that there were no significant changes in diffusing lung capacity. CPST showed a significantly higher anaerobic threshold, ventilation reserve and exercise tolerance (p < 0.001). There is also a description of EECP use in post-COVID syndrome management [33]. In October 2020, a 38-year-old otherwise healthy woman had COVID-19 infection without pneumonia. Once a majority of symptoms had resolved, she was still complaining of dyspnoea during exercises, weakness and headache. The symptoms persisted for three months, then the patient had one-hour long EECP sessions three times per week. After 10 days of the therapy, the patient noted improvement in her dyspnoea; five weeks later, she reported that she had the pre-disease physical performance.

The primary points of EECP application in patients with CRDs can be: impaired lung perfusion and diffusing capability, reduced muscular strength and endurance, increased muscular fatigue, and impaired diaphragmatic mobility. Respiratory muscle dysfunction, together with limb muscle dysfunction, is a significant problem in patients with CRDs; it contributes to the development and persistence of respiratory insufficiency [34]. Thus, the mechanism of EECP action in CRDs (Fig. 2) is likely to be a result of better perfusion of the lung tissue (improperly ventilated alveolar and bronchiolar areas), diaphragm and other respiratory muscles. M. Melin et al. (2018) [35] demonstrated that EECP can induce a response by skeletal muscle cells and increase expression of their growth factors, thus increasing muscle metabolism and ability to oxygenate muscles. These mechanisms facilitate better functional reserve of the body, which decreases in this group of diseases.

Use of EECP in endocrinology

According to study results, EECP has positive effect on glycaemic control in patients with DM2. Studies by P. Sardina et al. (2016) [36, 37] confirm that in two weeks after a course of 35 sessions, fasting glycaemia, postprandial glycaemia and glycated haemoglobin levels dropped by 12.0, 13.5, and 19.6 %, respectively. The positive change in insulin resistance index HOMA-IR after a course of EECP was –31.1 %. Also, a significant reduction in pro-inflammatory cytokine levels and advanced glycation end product lasted up to 6 months after a course of therapy. Besides, a number of studies [38, 39, 40] demonstrated positive effect of EECP on DM complications, such as diabetic retinopathy and diabetic nephropathy.

Use of EECP in neurology

Studies demonstrate improvement in cerebral blood flow and artery collateralisation in the ischaemic area after a stroke following EECP [41], so that this method can be used for the management of neurological patients. Better cerebral perfusion contributes to better metabolism of neurons and glial cells, as well as remyelination, and can affect motor function recovery in patients with upper limb palsy [42]. According to G. Kozdağ et al. (2013) [43], EECP facilitates improvements in all cognitive areas, except for verbal and visual memory tests. Q. Zhou et al. (2004) [44] were the first to notice that, among 33 patients with Parkinson's disease treated with EECP, 87.9 % demonstrated improvement in symptoms, probably due to better cerebral blood flow, which, in turn, improved performance of various neurotransmitters and receptors in dopaminergic neurons in the substantia nigra of the brain stem. Also, EECP improved insomnia due to better cerebral blood flow and modulation of respective neurotransmitters [45].

Use of EECP in ophthalmology

A retrospective analysis by Chinese scientists [46] showed positive effects of EECP in combination with drug therapy in patients with ischaemic eye diseases and stenotic carotid artery. Another study [47] demonstrated that EECP increased the mean blood velocity, end diastolic and peak systolic blood flow in ophthalmic arteries and central retinal artery in patients with ischaemic neuropathy of the optic nerve, and improved vision and haemodynamic parameters.

Use of EECP in otorhinolaryngology

In a study by C. Offergeld et al. (2000) [48], EECP therapy in patients with acute persistent hearing loss and tinnitus resulted in better blood flow in carotid

arteries (by 19 %) and better blood flow in spinal arteries (by 11 %). Besides, 47 % of patients reported tinnitus improvement, 28 % of patients noted better hearing, which lasted for a year after the therapy.

Use of EECP in urology

A study by S. Froschermaier et al. (1998) [49] reported for the first time about significantly increased peak systolic blood flow in cavernous artery and subsequent improvement in erectile function, which lasted for over 6 months. Another study by W. Lawson et al. (2007) [50] demonstrated EECP efficiency in ischaemic erectile dysfunction management in patients with refractory angina. Comparison of the values of the International Index of Erectile Function before and after EECP showed improved erectile function (p = 0.003), satisfaction with sexual intercourse (p = 0.009) and overall satisfaction (p = 0.001). Considering that currently erectile dysfunction is treated mostly with phosphodiesterase type 5 inhibitors, which are contraindicated in patients with IHD taking nitrates, this method can be a useful alternative.

The main characteristics of EECP studies are presented in Table 2.

Table 2. *Characteristics of the EECP research*

Research	Nosology	Research design, n	Endpoints	Results
MUST-EECP (1999) [20]	CHD	Randomized, blind, placebo-controlled; n=139; 8 weeks	The duration of physical activity and the time to ST segment depression ≥1 mm, the average daily number of angina attacks and the use of nitroglycerin	An increase in the time to ST segment depression ≥1 mm (p=0,01) compared to the baseline and placebo group. Episodes of angina pectoris were less frequent in the active EECP group compared with placebo (p <0.05)
Singh et al. (2018) [21]	CHD with or without diabetes mellitus type 2	Non-randomized, uncontrolled; n=163; 12 months.	Severity of angina pectoris according to the CCS classification, severity of dyspnea on the MRC scale, indicators of glycemic control (fasting glycemia and HbA1c)	A decrease in the severity of angina pectoris and the severity of shortness of breath, a decrease in fasting glycemia and HbA1c (p < 0.001)
Subramanian et al. (2005) [22]	CHD, CHF	Non-randomized, uncontrolled; n=72; 8 weeks	LVEF, CASP, AI	An increase in LVEF compared to the baseline level after the course of EECP (p <0.001). A decrease in CASP, AI with normal blood pressure, an increase in CASP, AI with low blood pressure and left ventricular dysfunction (p <0.05)
Sardari et al. 2018 [23]	CHD, CHF	Non-randomized, uncontrolled; n=34; 7 weeks	LVEF, duration of physical activity, workload	After the course of EECP, LVEF, maximum workload and duration of physical activity increased compared to the baseline level (p <0.001)
Wu et al. (2013) [24]	CHD	Non-randomized, uncontrolled; n=34; 6 months	Exercise tolerance (6MWT), quality of life (SF-36), severity of angina pectoris according to the CCS classification	After the course of EECP, exercise tolerance increased compared to the baseline level, quality of life improved and the severity of angina pectoris decreased (p <0.001)
EXCEL (2024) [25]	CHD, CHF	Randomized, placebo-controlled; n=120; 36 months	Exercise tolerance (6MWT), quality of life (MLHFQ and SF-36), functional parameters of the vascular bed (capillaroscopy) and heart (LVEF), adverse cardiovascular clinical outcomes	An increase in exercise tolerance, quality of life, functional parameters of the vascular bed and heart (p < 0.05) compared with the baseline and placebo group, as well as a decrease in the incidence of adverse outcomes

Table 2. Continued

Research	Nosology	Research design, n	Endpoints	Results
Badtieva et al. (2019) [28]	Obliterating atherosclerosis of the vessels of the lower extremities	Non-randomized, controlled; n=68; 7 weeks	The frequency of characteristic complaints, the pain-free walking distance, the state of peripheral hemodynamics, the ankle-shoulder index	A decrease in the severity of symptoms in the EECP group, an increase in the pain-free walking distance, an improvement in peripheral hemodynamics and an increase in the ankle-shoulder index ($p < 0.05$)
Liang et al. (2021) [29]	Arterial hypertension of the 1st degree	Randomized, controlled; n=40; 7 weeks	Blood pressure, FDV, EPC	A decrease in systolic and diastolic blood pressure, an increase in the value of FDV and an improvement in EPC function ($p < 0.05$)
Zhao et al. (2020) [30]	COPD	Randomized, controlled; n=72; 3 months	Physical endurance: anaerobic threshold oxygen uptake, maximum oxygen uptake, anaerobic threshold impulse, anaerobic threshold metabolic equivalent and maximum metabolic equivalent (CPST)	Compared with the baseline and the control group, indicators of physical endurance increased ($p < 0.05$)
Sathyamoorthy et al. (2021) [31]	Long-Covid	Non-randomized, uncontrolled; n=16; 5 months	Exercise tolerance (6MWT), severity of shortness of breath on the Rose scale, DASI activity index, quality of life (SAQ and PHQ-9), fatigue (PROMIS), severity of angina pectoris according to the CCS classification	After the course of EECP, exercise tolerance increased compared to the baseline level ($p=0.002$), the severity of shortness of breath decreased, the indicators of the DASI activity index, quality of life improved and the severity of angina pectoris decreased ($p < 0.001$)
Nikolaeva et al. (2023) [32]	Chronic lung diseases with ventilation disorders	Non-randomized, uncontrolled; n=30; 4 weeks	Pulmonary volumes, lung diffusion capacity, exercise tolerance (CPST, 6MWT)	After the course of EECP, an increase in total lung capacity was observed, and exercise tolerance increased compared to the baseline level ($p < 0.001$). There was no significant dynamics in the diffusion capacity of the lungs
Sardina et al. (2016) [36, 37]	Diabetes mellitus type 2	Randomized, controlled; n=30; 3 and 6 months	Fasting plasma glucose, postprandial glycemia, HbA1c	A decrease in glycemic control indicators compared to the baseline level and the control group ($p < 0.05$)
Yang et al. (2013) [46]	Ischemic ophthalmopathy	Non-randomized; controlled; n=65; 2 months	Visual acuity, visual fields and optical hemodynamics	Improvement of visual acuity, visual fields and optical hemodynamics compared to baseline and control group ($p < 0.05$)
Zhu et al. (2015) [47]	Front ischemic optic neuropathy	Non-randomized, uncontrolled; n=16; 2 weeks	The average blood flow rate, peak systolic velocity and final diastolic velocity in the ocular artery and central retinal artery, the value of intraocular pressure, visual fields and visual acuity	An increase in the blood flow rate in the ocular artery and central retinal artery, a decrease in intraocular pressure, an increase in visual fields and visual acuity ($p < 0.05$)

Table 2. The end

Research	Nosology	Research design, n	Endpoints	Results
Offergeld et al. (2000) [48]	Diseases of the inner ear	Non-randomized, uncontrolled; n=33; 12 months	The volume of blood flow in the internal carotid arteries and in the vertebral arteries, the intensity and/or appearance of noise and the audibility threshold (audiogram)	An increase in blood flow in the internal carotid arteries and in the vertebral arteries, a decrease in the intensity and/or appearance of tinnitus, an increase in the hearing threshold ($p < 0.05$)
Froscher-maier et al. (1998) [49]	Erectile dysfunction	Non-randomized, uncontrolled; n=13; 3 weeks	Penile rigidity, peak systolic blood flow and erection quality	Increased penile rigidity, peak systolic blood flow and erection quality ($p < 0.05$)
Lawson et al. (2007) [50]	CHD, erectile dysfunction	Non-randomized, uncontrolled; n=120; 7 weeks	International Index of Erectile Function, DASI activity index	Improvement of erectile function ($p < 0.05$) and DASI activity index. There were no significant changes in orgasmic function and sexual desire

Note: EECP — enhanced external counterpulsation; CHD — coronary heart disease; CHF — chronic heart failure; CASP — central aortic systolic pressure; AI — augmentation index; FDV — flow-dependent vasodilation; EPC — endothelial progenitor cells; COPD — chronic obstructive pulmonary disease; LVEF — left ventricular ejection fraction; CPST — cardiopulmonary stress test; 6MWT — 6-minute walking test

Conclusion

EECP has been used as a support therapy for decades, and it has proven its efficiency and safety in management of various diseases. In recent years, great achievements have been made in understanding the physiological mechanisms of its effects for the body in some CNCDs, including IHD, CCI, DM2, COPD, etc. Nonetheless, a lot of aspects of this method in clinical settings are still unclear and require further studies in order to assess EECP capabilities and evaluate long-term effects. Also, a range of indications is growing. A promising area is the study of EECP efficiency in CNCDs, such as systemic connective tissue disorders and kidney diseases.

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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ОЦЕНКА УРОВНЯ NT-PROBNP У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ В ВОЗРАСТЕ 80 ЛЕТ И СТАРШЕ В ЗАВИСИМОСТИ ОТ НАЛИЧИЯ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ И СИНДРОМА СТАРЧЕСКОЙ АСТЕНИИ

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Assessment of the Level of NT-proBNP in Patients with Arterial Hypertension Aged 80 Years and Older, Depending on the Presence of Heart Failure and Senile Asthenia Syndrome

Резюме

Цель. Оценить информативность N-концевого промозгового натрийуретического пептида (NT-proBNP) для диагностики хронической сердечной недостаточности (ХСН) в зависимости от наличия синдрома старческой астении (ССА) у пациентов с артериальной гипертензией (АГ) 80 лет и старше. **Материал и методы.** 320 пациентов с АГ в зависимости от наличия ХСН и ССА были распределены в группы: 1А группа — пациенты с АГ, ССА и ХСН (n=84), 1Б группа — пациенты с АГ, ССА без ХСН (n=77), 2А группа — пациенты с АГ, ХСН без ССА (n=84), 2Б группа — пациенты с АГ без ХСН и без ССА (n=75). ССА выявляли по опроснику «Возраст не помеха». Уровень NT-proBNP определяли в сыворотке крови иммуноферментным методом. Для определения порогового значения маркеров применили ROC-анализ. **Результаты**. У пациентов с АГ и ССА без ХСН концентрация NT-proBNP в крови выше в 2,3 раза (p=0,003) по сравнению с пациентами с АГ без ССА и без ХСН, что свидетельствует о влиянии ССА на уровень NT-proBNP. У пациентов с АГ и ХСН без ССА уровень NT-proBNP в 4,3 раза выше в сравнении с пациентами с АГ без ССА и без ХСН (p<0,001), у которых концентрацию NT-proBNP отмечали ниже порогового уровня (106,2 пг/мл). У пациентов с АГ и ССА и ХСН регистрировали наибольшие значения концентрации NT-proBNP, которые в 2,9 раза (p<0,001) выше, чем у «хрупких» пациентов с АГ без ХСН и в 1,5 раза выше чем у «крепких» пациентов с АГ и ХСН (p<0,001). Рассчитан новый пороговый уровень NT-proBNP для диагностики ХСН у пациентов с АГ и ССА в возрасте 80 лет и старше — 365,9 пг/мл. **Заключение.** Для диагностики ХСН у пациентов с АГ 80 лет и старше без ССА маркер NT-proBNP является информативным, так как, согласно полученным данным, его уровень не зависел от возраста пациентов. При применении NT-proBNP для выявления ХСН у пациентов с АГ и ССА 80 лет и старше следует использовать рассчитанный пороговый уровень маркера (365,9 пг/мл), поскольку у этих пациентов концентрация NT-proBNP повышена, независимо от наличия ХСН.

Ключевые слова: *хроническая сердечная недостаточность, синдром старческой астении, возраст 80 лет и старше, NT- proBNP*

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Abstract

Objectives. To evaluate the informativeness of the N-terminal brain-promoting natriuretic peptide (NT-proBNP) for the diagnosis of chronic heart failure (CHF), depending on the presence of senile asthenia syndrome (SSA) in patients with arterial hypertension (AH) 80 years and older. **Materials and Methods.** 320 patients with hypertension, depending on the presence of CHF and SSA, were divided into groups: group 1A — patients with hypertension, SSA and CHF (n=84), group 1B — patients with hypertension, SSA without CHF (n=77), group 2A — patients with hypertension, CHF without SSA (n=84), group 2B — patients with hypertension without CHF and without SSA (n=75). The CSA was identified by the questionnaire "Age is not a hindrance". The level of NT-proBNP was determined in blood serum by enzyme immunoassay. ROC analysis was used to determine the threshold value of markers. **Results.** In patients with hypertension and SSA without CHF, the concentration of NT-proBNP in the blood is 2.3 times higher (p=0.003) compared with patients with hypertension without SSA and without CHF, which indicates the effect of SSA on the level of NT-proBNP. In patients with hypertension and CHF without SSA, the level of NT-proBNP is 4.3 times higher compared with patients with hypertension without SSA and without CHF (p<0.001), in whom the concentration of NT-proBNP was noted below the threshold level (106.2 pg/ml). In patients with hypertension and SSA and CHF, the highest concentrations of NT-proBNP were recorded, which are 2.9 times (p<0.001) higher than in "fragile" patients with hypertension without CHF and 1.5 times higher than in "strong" patients with hypertension and CHF (p<0.001). A new threshold level of NT-proBNP has been calculated for the diagnosis of CHF in patients with hypertension and SSA aged 80 years and older — 365.9 pg/ml. **Conclusion.** For the diagnosis of CHF in patients with hypertension 80 years and older without CSA, the NT-proBNP marker is informative, since, according to the data obtained, its level did not depend on the age of the patients. When using NT-proBNP to detect CHF in patients with hypertension and SSA 80 years and older, the calculated threshold marker level (365.9 pg/ml) should be used, since in these patients the concentration of NT-proBNP is increased, regardless of the presence of CHF.

Key words: *chronic heart failure, senile asthenia syndrome, age 80 years and older, NT-proBNP*

Conflict of interests
Co-author of the article Chesnikova A.I. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Chesnikova A.I. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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Conformity with the principles of ethics
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AH — arterial hypertension, NUP — natriuretic peptides, FS — frailty syndrome, CCF — chronic cardiac failure, NT-proBNP — N-terminal pro brain natriuretic peptide

Introduction

Chronic cardiac failure (CCF) is one of the most relevant problems of the modern healthcare. It is worth mentioning that the incidence of CCF increases with age. Elderly people (65 years old and over) make 80 % of patients with CF [1]. CCF in elderly people worsens prognosis significantly, and 1-year and 5-year mortality rates in people over 80 years old are 19.5 % and 24.4 %, respectively [2]. Early identification of adverse events in patients with CVDs, including CCF development and decompensation, is essential. However, diagnosis of cardiac insufficiency in elderly patients can be challenging due to low specificity of symptoms, and special attention should be paid to ECG results and blood cardiac markers [3]. Currently, measurement of natriuretic peptide (NUP) levels in included into the diagnostic algorithms for CCF and is an essential test method to make a diagnosis; and their high value in prognosis and risk classification in patients with CF has been repeatedly proven in numerous clinical trials [4,5]. Of note, besides a number

of advantages (easy and accessible tests, high prognostic significance), NUPs have drawbacks, such as highly variable values, which depend on sex, age and comorbidities [6]. Also, the use of NUP in elderly people with CCF is challenging because of higher biomarker levels due to comorbidities and ageing with a number of geriatric syndromes. Patients with CCF are more susceptible to senile asthenia (SA) than the general population; SA is an independent predictor of re-hospitalisations and mortality in this category of patients. Approximately 20 % of patients with CCF have senile asthenia syndrome, while 50 % have pre-asthenia [7]. SA diagnosis can become an integral component of the management plan for elderly and old patients with CCF. Strategies of CCF diagnosis and prognosis, clinical symptoms, as well as structural and functional heart re-modelling in patients with AH depending on the presence or absence of FS, remain understudied.

The objective of this study was to evaluate the informative value of N-terminal pro brain natriuretic peptide (NT-proBNP) in diagnosis of CCF depending on the presence of frailty syndrome (FS) in patients with arterial hypertension (AH), who are 80 years old and over.

Materials and Methods

This study was a cross-sectional study. The study meets the standards and principles of the Declaration of Helsinki. The study was approved by the Ethics Committee at the Federal State Budgetary Educational Institution of Higher Education Rostov State Medical University of the Ministry of Health of Russia (minutes No. 13/19 dated 05/09/2019). The patients were enrolled in the study after they signed a written voluntary informed consent form. Patients were recruited in outpatient settings in Rostov-on-Don. The total number of subjects was 320 patients with AH aged at least 80 years old (56.9 % were women and 43.1 % were men); the mean age was 85.8 ± 4.5 years.

Inclusion criteria: age of at least 80 years old; AH, grade IIA–IIB CCF and FC II–IV. Exclusion criteria: haemodynamically significant heart diseases, implanted electrocardiostimulator, a history of ischaemic heart disease (absence of typical clinical presentation, past medical history, ST segment depression or elevation on ECG and Holter ECG, area of hypo- and akinesia on Echo CG), acute cerebrovascular accident or transient ischaemic attack within past 6 months, malignancies, severe liver condition (transaminase levels 3xUNL or more) or severe kidney condition (GFR ≤ 30 mL/min).

Depending on the presence of CCF and FS, all patients were divided into four clinical groups: group 1A — patients with AH, FS and CCF (n = 84), group 1B — patients with AH, FS and without CCF (n = 77), group 2A — patients with AH, CCF and without FS (n = 84), group 2B — patients with AH and without CCF and FS (n = 75).

AH was diagnosed on the basis of the past medical history and results of office blood pressure (BP) measured under the method developed by S. N. Korotkov.

CCF was diagnosed on the basis of symptoms and clinical signs, cardiac failure marker (NT-proBNP) levels and ECG findings in accordance with the national clinical guidelines for CCF diagnosis and management [4]

FS was diagnosed with the help of the "Age is no disqualification" questionnaire; patients who scored ≥ 3 points underwent a brief battery of physical function tests [8].

Serum NTproBNP levels in study subjects were measured with ELISA test.

A form was filled out for each patient, specifying risk factors, comorbidity, current therapy, physical examination results, laboratory and instrumental test results, as well as scale and questionnaire scores.

Study results were statistically processed using STATISTICA 12.0 (StatSoft Inc., USA), SPSS 21.0, MedCalc (version 9.3.5.0).

The representative sample size, characterising the general population in terms of FS rates, was calculated as follows:

$$n= (z_{\alpha}^2\, p*q)/\Delta^2, \text{ where}$$

n is the number of observations in the sample; z_{α} is type I error (at a = 0.05); p is the incidence of the attribute in the population; q is the reverse event rate; D is the margin of sampling error

The incidence of all test parameters was checked for normality using Shapiro — Wilk test. Since the incidence of test parameters in the sample was both normal and other than normal, then the data were presented using both mean selective value, error of mean (M±σ) and median and interquartile range (Me [Q1; Q3]). Qualitative variables are presented as absolute (n) and relative (%) values. Groups were compared using Yates corrected χ2 for qualitative attributes and Mann — Whitney U test for quantitative attributes for two independent groups. The four groups of patients were compared using Kruskal — Wallis ANOVA. The critical significance level of the zero statistical hypothesis was $p_{mg} < 0.05$. Evaluations of the diagnostic efficiency of the methods and identification of the diagnostic cut-off were performed using ROC-analysis with calculation of sensitivity and specificity, odds ratio, as well as ROC-curve plotting and area under ROC-curve evaluation.

Results

Clinical characteristics of subjects are presented in Table 1. All patients in the clinical groups had a very high cardiovascular risk; AH duration exceeded 20 years.

A comparative analysis of CCF stage distribution demonstrated the lack of any statistically significant difference between patients, irrespective of FS (p> 0.05).

Table 1. *Clinical characteristics of the patients included in the study*

Indicator \ Group	1A group (AH + CHF + SAS, n=84)	1B group (AH + SAS without CHF, n=84)	2A group (AH + CHF without SAS, n=77)	2B group (AH without SAS and without CHF, n=75)	Pairwise comparison of groups	$p_{мг}$/ p_{mg}
Age, years	84,9±4,8	84,2±4,1	85,7±5,9	86,4±5,7	p_1=0,937 p_2=0,848 p_3=0,839 p_4=0,962	0,852
Gender (f/m), n (%)	44/40 (52,4/47,6)	41/43 (48,8/51,2)	38/39 (49,4/50,6)	38/37 (50,7/49,3)	p_1=0, 953 p_2=0,871 p_3=0, 639 p_4=0,597	0,872
HTN stage II, n (%)	-	6 (7,1)	-	4 (5,3)	p_4=0,861	-
HTN stage III, n (%)	84 (100)	78 (92,9)	77 (100)	71 (94,7)	p_1=0,634 p_2=0,739 p_4=0,906	0,945
Left ventricular ejection fraction, %	44,0 [42,4;47,3]	52,8 [50,6;55,4]	59,2 [57,8;60,5]	62,2 [60,6;63,9]	p_1<0,001 p_2=0,813 p_3=0,002 p_4=0,009 p_5=0,092	0,004
CHF stage IIA, n (%)	73 (86,9)	-	71 (92,2)	-	p_3=0,314	-
CHF stage IIB, n (%)	11 (13,1)	-	6 (7,8)	-	p_3= 0,428	-
CHF II FC, n (%)	24 (28,6)	-	32 (41,6)	-	p_3=0,041	-
CHF III FC, n (%)	52 (61,9)	-	35 (45,5)	-	p_3=0,036	-
CHF IV FC, n (%)	8 (9,5)	-	10 (12,9)	-	p_3=0,382	-
Anemia, n (%)	20 (23,8)	9 (10,7)	12 (15,6)	10 (13,3)	p_1=0,033 p_2=0,172 p_3=0,237 p_4=0,341	0,193
Atrial fibrillation, n (%)	42 (50,0)	25 (29,8)	19 (24,7)	13 (17,3)	p_1=0,003 p_2=0,313 p_3<0,001 p_4=0,082	<0,001
Chronic kidney disease, n (%)	56 (66,67)	48 (57,14)	31 (40,26)	24 (32)	p_1=0,203 p_2=0,293 p_3<0,001 p_4=0,001	<0,001
Type 2 diabetes mellitus, n (%)	26 (31)	15 (17,9)	19 (24,7)	12 (16)	p_1=0,042 p_2=0,199 p_3=0,386 p_4=0,778	0,089
BMI, kg/m^2	23,4 ± 2,1	28,2±0,4	32,1 ± 2,0	30,3±0,4	p_1=0,062 p_2=0,319 p_3=0,029 p_4=0,823	0,481
Obesity, n (%)	8 (9,88)	14 (16,67)	18 (23,37)	11 (14,66)	p_1=0,236 p_2=0,563 p_3=0,032 p_4=0,206	0,582
Dyslipidemia, n (%)	47 (55,95)	58 (69,05)	46 (59,74)	55 (73,33)	p_1=0,076 p_2=0,079 p_3=0,614 p_4=0,571	0,080
Hemoglobin, g/L	110±14*•	123±6	122±9	125±8	p_1=0,020 p_2=0,452 p_3=0,034 p_4=0,547	0,013

Table 1. (The end)

Group / Indicator	1A group (AH + CHF + SAS, n=84)	1B group (AH + SAS without CHF, n=84)	2A group (AH + CHF without SAS, n=77)	2B group (AH without SAS and without CHF, n=75)	Pairwise comparison of groups	p_{MG}/ p_{mg}
Red blood cells, $\times10^{12}$/ L	4,1±0,8	4,2±0,6	4,0±0,5	4,5±0,7	p_1=0,620 p_2=0,492 p_3=0,716 p_4=0,937	0,482
Glycemia, mmol/L	5,2±0,31	5,1±0,26	5,3±0,28	5,0±0,35	p_1=0,784 p_2=0,592 p_3=0,847 p_4=0,286	0,981
Urea, mmol/L	5,7±0,21	6,1±0,37	5,9±0,42	6,0±0,36	p_1=0,482 p_2=0,291 p_3=0,582 p_4=0,637	0,934
Creatinine, μmol/L	126±0,79	110±0,83	104±0,94	101±0,77	p_1=0,691 p_2=0,482 p_3=0,593 p_4=0,791	0,158
Estimated glomerular filtration rate, ml/min/1.73m^2	54,4±2,13*•	72,3±2,37	75,7±2,08	73,6±2,68	p_1=0,027 p_2=0,491 p_3=0,041 p_4=0,285	0,031
Uric acid, μmol/L	393,2±4,39*	370,3±4,67	380,5±4,0	369,6±4,63	p_1=0,015 p_2=0,782 p_3=0,451 p_4=0,991	0,113
ALT, U/L	22±2,7	23± 3,3	21± 2,1	22± 1,9	p_1=0,835 p_2=0,621 p_3=0,423 p_4=0,815	0,729
AST, U/L	27±3,2	24±2,8	25±3,1	23±2,5	p_1=0,581 p_2=0,371 p_3=0,514 p_4=0,148	0,725
Total bilirubin, mmol/L	13±1,5	15±1,8	15±1,4	14±1,7	p_1=0,571 p_2=0,491 p_3=0,281 p_4=0,623	0,381

Note: AH — arterial hypertension, HTN — hypertension, BMI — body mass index, SAS — senile asthenia syndrome, CHF — chronic heart failure;
p_1 — differences between groups 1A and 1B; p_2 — differences between groups 2A and 2B; p_3 — differences between groups 1A and 2A; p_4 — differences between groups 1B and 2B;
p_5 — differences between groups 1B and 2A; p_{mg} — multi-group comparison; * — p — differences between groups 1A and 1B, p <0,05; • — p — differences between groups 1A and 2A, p <0,05; the differences are statistically significant when p <0,05.

The evaluation of CCF FC in the study groups showed a higher incidence of FC III CCF with FS (by 16.4 %, p = 0.036) and FC II CCF in patients without FS (by 13 %, p = 0.041). The lowest LV EF was observed in frail patients with AH and CCF; the values were statistically different from the same parameter in frail patients with AH without CCF (p < 0.001) and non-frail patients with AH and CCF (p = 0.002). CCF duration was 8.4 ± 3.6 years.

An analysis of the clinical characteristics demonstrated that frail patients with AH and CCF had concomitant AFib (by 29.3 %, p = 0.003), anaemia (by 13.1 %, p = 0.033) and type 2 DM (by 17.6 %, p = 0.042) more often that frail patients with AH and without CCF.

It is worth noting that patients with AH, CCF and FS had twice as high rates of AFib (p < 0.001) and 26.4 % more CCF (p < 0.001) as compared to patients with AH and CCF and without FS. Non-frail patients with AH and CCF, on the other hand, had a higher BMI vs. frail patients with AH and CCF (p = 0.029), and 2.4-fold number of obese patients (p = 0.032). Also, frail patients without CCF had more cases of CKD (by 25.14 %) (p = 0.001) vs. non-frail patients without CCF.

An analysis of laboratory values showed that frail patients with AH and CCF (subgroup 1A) had higher levels of uric acid (p = 0.015) vs. frail patients with AH and without CCF (subgroup 1B) and statistically lower levels of GFR and Hb vs. frail patients without

CCF (p = 0.027, p = 0.020) and non-frail patients with CCF (subgroup 2A) (p = 0.034, p = 0.041), respectively (Table 1). It can be a result of a comorbidity, particularly CCF, and the effect of FS, which is associated with reduced active muscle body weight and reduced intensity of metabolic processes. There were no intergroup differences in biochemistry parameters (p > 0.05). Mean biochemistry values were within reference ranges, indicating compensated somatic functions.

Statistically significant differences (p_{mg} < 0.001) (Table 2) were demonstrated by an intergroup comparison of NT-proBNP concentrations in the study groups.

Of note, non-frail patients with AH and without CCF had lower serum NT-proBNP concentrations, with the mean values being below the threshold level of 125 pg/mL (Fig. 1).

When non-frail patients with AH (group 2A) had CCF, they also had expectedly higher NT-proBNP levels (4.3-fold, p < 0.001) vs. non-frail patients with AH and without CCF (group 2B).

An evaluation of FS effects on NT-proBNP levels included an intergroup comparison of values of patients with AH in groups 1B and 2B, i.e. with or without FS, respectively. It has been established that in patients with AH and FS and without CCF (group 1B), blood NT-proBNP concentrations were 2.3 times higher (p = 0.003) than in patients with AH and without CCF and FS (group 2B), making it possible to see the FS effects on the levels of this marker.

Results of an intergroup analysis of NT-proBNP concentrations in patients with AH and CCF, but without FS (group 2A) and AH and FS, but without CCF (group 1B) indicate statistically higher effects of CCF on NT-proBNP levels (460.2 pg/mL vs. 244.5 pg/mL, p < 0.001) as compared to effects of FS.

It is worth noting that a combination of FS and CCF in patients with AH (group 1A) was associated with the highest NT-proBNP concentrations, which were 2.9 times higher (p < 0.001) than the same parameter in the group of patients with AH and FS, but without CCF (group 1B), and 1.5 times higher than the marker levels in patients with AH and CCF, but without FS (group 2A) (p < 0.001).

A gender analysis of serum NT-proBNP concentrations demonstrated no statistically significant differences between men and women in each group (p > 0.05) (Table 3).

Table 2. *Analysis of NT-proBNP serum levels in patients included in the study*

Group / Marker	1A group (AH + CHF + SAS, n=84)	1B group (AH + SAS without CHF, n=84)	2A group (AH + CHF without SAS, n=77)	2B group (AH without SAS and without CHF, n=75)	Pairwise comparison of groups	$p_{мг}$/ p_{mg}
NT-proBNP, pg/ml	697,9 [606,2 — 837,3]	244,5 [187,2– 300,2]	460,2 [341,2–531,7]	106,2 [55,7–173,8]	p_1<0,001 p_2<0,001 p_3<0,001 p_4=0,003 p_5<0,001	<0,001

Note: AH — arterial hypertension, SAS — senile asthenia syndrome, CHF — chronic heart failure; NT-proBNP N-terminal propeptide of B-type natriuretic hormone; p_1 — differences between groups 1A and 1B; p_2 — differences between groups 2A and 2B; p_3 — differences between groups 1A and 2A; p_4 — differences between groups 1B and 2B; p_5 — differences between groups 1B and 2A; p_{mg} — multi-group comparison; the differences are statistically significant when p <0,05.

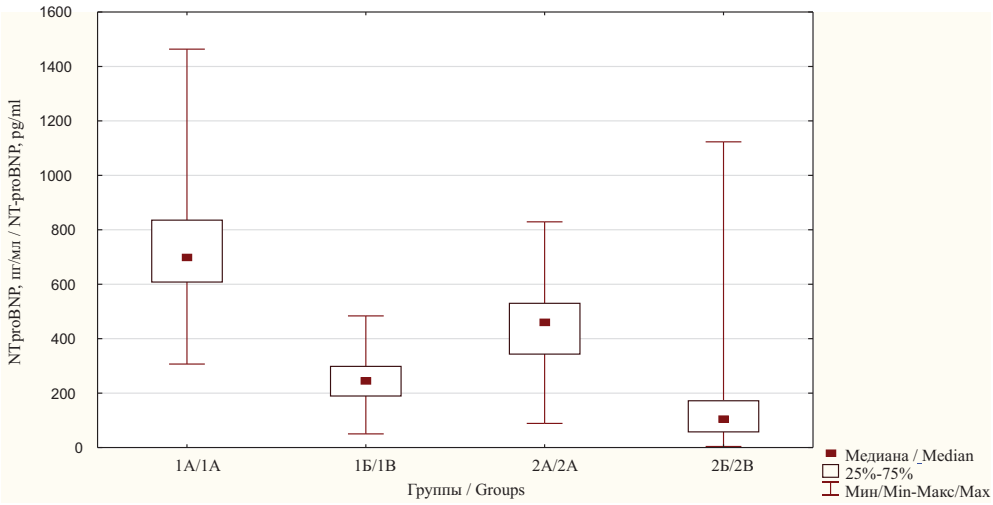

Figure 1. *Median, interquartile range and range of NT-proBNP concentration in blood serum in patients of the studied groups*

Note: NT-proBNP — N-terminal propeptide of the B-type natriuretic hormone

Table 3. *Analysis of NT-proBNP serum levels in patients included in the study, depending on gender*

1A group (n=84)			
Gender/Marker	Women (n=44)	Men (n=40)	$p_{1A\ wom\ -1A\ men}$
NT-proBNP, pg/ml	793,0 [643,0 — 988,2]	658,3 [539,4 — 792,1]	0,92
1B group (n=84)			
Gender/Marker	Women (n=43)	Men (n=41)	$p_{1B\ wom\ -1B\ men}$
NT-proBNP, pg/ml	281,4 [216,1 — 320,2]	215,7 [161,5 — 267,3]	0,90
2A group (n=77)			
Gender/Marker	Women (n=38)	Men (n=39)	$p_{2A\ wom\ -2A\ men}$
NT-proBNP, pg/ml	474,1 [416,2 — 554,5]	428,6 [264,1 — 511,4]	0,91
2B group (n=75)			
Gender/Marker	Women (n=37)	Men (n=38)	$p_{2B\ wom\ -2B\ men}$
NT-proBNP, pg/ml	71,2 [51,4 — 191,3]	126,4 [83,9 — 163,3]	0,89
	$p_{1A\ wom\ -1B\ wom} < 0,001$ $p_{1A\ wom\ -2A\ wom} < 0,001$ $p_{1B\ wom\ -2B\ wom} < 0,001$ $p_{2A\ wom\ -2B\ wom} < 0,001$ $p_{1A\ wom\ -2B\ wom} < 0,001$	$p_{1A\ men\ -1B\ men} < 0,001$ $p_{1A\ men\ -2A\ men} < 0,001$ $p_{1Б\ men\ -2B\ men} = 0,004$ $p_{2A\ men\ -2B\ men} = 0,002$ $p_{1A\ men\ -2Б\ men} < 0,001$	
$p_{мг}$ / p_{mg}	$p_{mg\ wom} < 0,001$	$p_{mg\ men} < 0,001$	

Note: NT-proBNP — N-terminal propeptide of natriuretic hormone B-type; p — differences between women and men of groups 1A, 1B, 2A, 2B; p_{mg} — multi-group comparison; p_{mg} of women, p_{mg} of men — confidence probability of multiple comparison of groups 1A, 1B, 2A, 2B among women and men, accordingly, using the analysis of variance and the Kraskell-Walis criterion

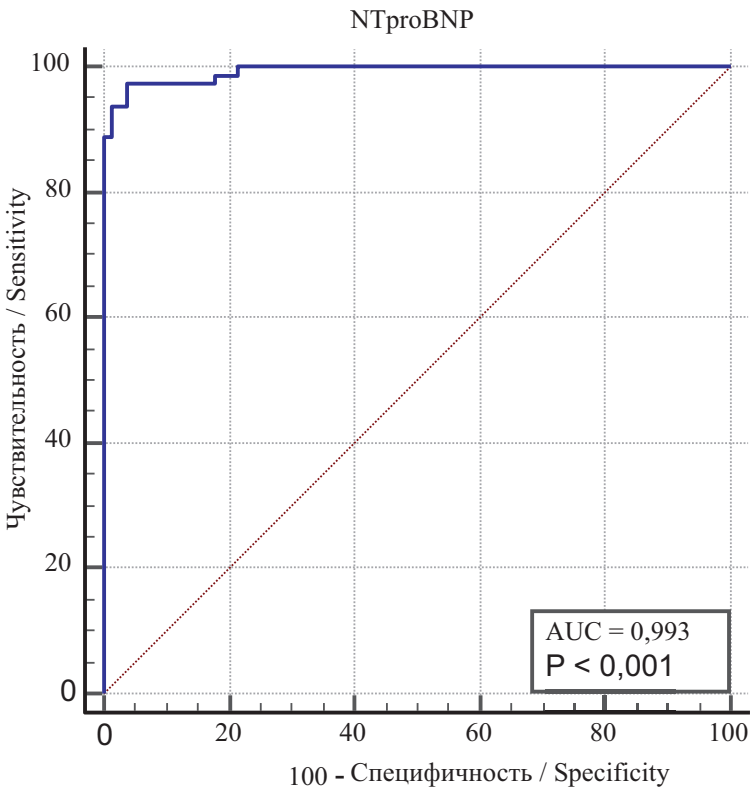

Figure 2. *ROC-curve of compliance of diagnostic sensitivity and specificity of NT-proBNP concentration for the diagnosis of CHF in patients with hypertension and senile asthenia syndrome*

Note: AH — arterial hypertension, SAS — senile asthenia syndrome, CHF — chronic heart failure; NT-proBNP N-terminal propeptide of B-type natriuretic hormone

However, both frail women with CCF and frail men with CCF had highest NT-proBNP values vs. both frail women and frail men without CCF and non-frail women and non-frail men with CCF ($p_{mg\ women} < 0.001$, $p_{mg\ men} < 0.001$).

ROC-analysis was used to identify the threshold value. Diagnostic sensitivity and diagnostic specificity values were used to plot a performance curve (ROC-curve). An important aspect of the ROC-analysis was identification of the cut-off point. In addition to visual assessment of ROC-curve location of the plot, the area under ROC-curve (AUC) was calculated for the unbiased identification of the diagnostic efficiency of the method. The closer the AUC value to one, the higher the diagnostic test ability to identify a disease [9].

Given that frail patients with AH and without CCF had higher NT-proBNP levels, the focus of the study was on the determination of the threshold value of NT-proBNP for CCF diagnosis in patients with AH and FS. Its blood concentration, corresponding to the highest values of diagnostic sensitivity and specificity (cut-off point) in the diagnosis of CCF with presence/absence of FS, was 365.9 pg/mL. When this level is achieved and exceeded, a diagnostic decision on CCF is taken with 97.5 % sensitivity and 96.2 % specificity ($p < 0.001$).

AUC value for NT-proBNP in patients with AH and FS for CCF diagnosis was 0.993 ± 0.004 (CI: 0.965–1.0) ($p < 0.001$), indicating the excellent quality of the model (Fig. 2).

Discussion

It is well known that NTproBNP concentrations increase with age, both in men and women. At the same time, the level of this hormone in elderly people over 75 years of age (especially in women) can be 4 times higher than in younger patients [10]. It is associated both with comorbidities (diabetes mellitus, arterial hypertension, chronic obstructive pulmonary disease, atrial fibrillation) and impaired renal function [11].

In some patients, no adequate increase in NUP values is observed, despite increased filling pressure in the left heart. To the contrary, obese patients have significantly lower blood NT-proBNP concentrations vs. patients with lower body weight [12].

It has been reported that, in patients with CCF and preserved LF EF, NTproBNP levels can remain within the normal range, and it is observed approximately in three–four patients with verified CCF and preserved LF EF out of ten [13].

Of note, in this study, non-frail old patients with AH had the mean NT-proBNP level within the normal range (< 125 pg/mL), irrespective of sex and age. A higher level of this marker in elderly and old patients with CCF in works by other researchers can be explained by the fact that no evaluation of FS presence was performed. In this study, this is FS that impacts NT-proBNP levels in patients over 80 years old with AH and without CCF.

Available data coincide with the results of the study by Yao S et al., which demonstrated the association between higher plasma NUP levels and a higher risk of FS and pre-asthenia in elderly people [14].

This study shows that in frail patients over 80 years of age with AH, but without CCF, the mean NT-proBNP concentration was above 125 pg/mL, and it enabled us to see FS effects on the marker concentration.

Inflammation is known to play an essential part in the development not only of cardiovascular diseases, but it also contributes to pathogenesis of senile asthenia. Patients with senile asthenia have higher levels of such markers of inflammation as WBC, interleukin 6, C-reactive protein, blood coagulation factor VIII, fibrinogen, D-dimer, and tumour necrosis factor-α [15]. The inflammatory nature of senile asthenia has also been proven in Women's Health and Ageing I and II study, where a higher risk of senile asthenia with an increase in the number of inflammatory diseases [16] was reported. It should also be noted that the rate of increase in proinflammatory mediator concentrations correlates with NT-proBNP levels [4].

Another connecting mechanism between senile asthenia and a higher NT-proBNP concentration can be endothelial dysfunction. Results of Toledo Study for Healthy Ageing showed that patients with FS had impaired endothelial function when evaluated on the basis of asymmetric dimethyl arginine [17]. Also, the results correlate with results from the study by Y. Wang et al., where endothelial dysfunction was associated with higher NT-proBNP levels, larger left atrium (myocardium remodelling) and fibrosis [18].

A higher NT-proBNP concentration (> 125 pg/mL) was reported both in non-frail patients with CCF and frail patients without CCF. However, a comparative analysis demonstrated statistically higher effect of CCF on increased NT-proBNP levels vs. effects of FS.

Non-frail patients with CCF had higher NT-proBNP concentrations (> 125 pg/mL), similar to younger patients.

A combination of CCF and FS in old patients with AH was associated with the highest NT-proBNP concentration among the groups, indicating potentiation of CCF and FS effects.

Given higher NUP concentrations in patients with FS, the NT-proBNP level was calculated, which reliably shows the presence of CCF in patients over 80 years of age with AH and FS. In patients with AH and FS, higher NT-proBNP levels of over 365.9 pg/mL enable confirming CCF.

A gender analysis of serum NT-proBNP concentrations in the study groups demonstrated the lack of statistically significant differences between men and women.

Conclusions

The results allow drawing a conclusion that, in diagnosing CCF in patients over 80 years of age with AH, but without FS, NT-proBNP is an informative marker, because the results show that its concentrations were independent of the patient age. When using NT-proBNP for identification of CCF in patients over 80 years of age with AH and FS, the calculated threshold level (365.9 pg/mL) should be used, since these patients have an elevated NT-proBNP concentration, with or without CCF.

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Чесникова А.И.: разработка концепции и дизайна, сбор, анализ и интерпретация данных, проверка критически важного интеллектуального содержания, окончательное утверждение для публикации, автор ответственен за все аспекты работы

Contribution of the 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
Safronenko V.A.: concept and design development, data collection, analysis and interpretation, justification and writing of the manuscript, final approval for publication, the author is responsible for all aspects of the work

A.I. Chesnikova: concept and design development, data collection, analysis and interpretation, verification of critical intellectual content, final approval for publication, the author is responsible for all aspects of the work

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ЭХОГРАФИЧЕСКАЯ ВЕРИФИКАЦИЯ И КЛИНИЧЕСКОЕ ЗНАЧЕНИЕ ПАТОЛОГИИ ОКОЛОСУСТАВНЫХ СТРУКТУР ПРИ ОСТЕОАРТРИТЕ КОЛЕННОГО СУСТАВА

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Sonographic Verification and Clinical Significance of the Features of Surrounding Structures in Knee Osteoarthritis

Резюме

Актуальность. Остеоартрит (ОА) коленного сустава — одно из самых распространенных заболеваний, наиболее значимым клиническим проявлением которого является хронический болевой синдром. Известно о низкой корреляции между рентгенологической стадией ОА и интенсивностью болей. Прежде всего, это объясняется разнообразием источников болевого синдрома, среди которых важное значение имеет патология многочисленных околосуставных структур (ОС). На сегодняшний день вклад этого вида патологии в клиническую картину ОА изучен недостаточно, в первую очередь в связи с тем, что перечень и частота этих поражений до сих пор не описаны. **Цель** — описание патологии основных околосуставных структур у пациентов с различными рентгенологическими стадиями первичного ОА коленного сустава по данным клинического и ультразвукового исследования. **Материалы и методы**. В наблюдательное поперечное исследование в настоящий момент включено 88 пациентов, обратившихся на амбулаторный прием ревматолога по поводу остеоартрита коленного сустава в период с 2021-2023 гг. В ходе исследования оценено 110 коленных суставов с использованием клинического и ультразвукового методов. **Результаты:** наиболее частыми околосуставными УЗ-изменениями независимо от рентгенологической стадии были тендопатия сухожилий «гусиной лапки» (57,3 %), киста Бейкера (45,5 %), фиброз жирового тела Гоффа (40 %) и лигаментопатия медиальной коллатеральной связки (36.4 %). Выявлена значимая корреляция между количеством изменений по данным УЗИ и рентгенологической стадией (ρ=0,45 [95 % ДИ: 0,28; 0,59], p <0,001), а также между ВАШ и количеством выявленных УЗ-изменений (ρ=0,29 [95 % ДИ: 0,11; 0,46], p=0,002). Кроме того, продемонстрировано, что поздние стадии ОА ассоциированы с бóльшим количеством изменений (p <0,001). **Заключение**. Изменения околосуставных структур имеются у большинства пациентов с остеоартритом коленного сустава; их количество коррелирует с величиной ВАШ, рентгенологической стадией ОА. Детализация этих изменений, их клиническая значимость и патогенетический вклад в прогрессирование ОА КС требуют дальнейшего изучения.

Ключевые слова: *остеоартрит, коленный сустав, околосуставная патология*

Конфликт интересов

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

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Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract
Background: Osteoarthritis (OA) of the knee joint is one of the most dangerous diseases, the most significant manifestation of which is chronic pain syndrome. There is a low correlation between the radiographic stage of OA and pain progression. First of all, this is a variety of pain syndromes, among which is the pathology of periarticular structures (AS). To date, the contribution of this type to the clinical picture of OA has been sufficiently studied, primarily due to the fact that the list and frequency of these lesions have not yet been described. **Aim:** to describe the basis of the main periarticular structures in patients with different radiographic stages of knee OA according to ultrasound data. **Materials and methods:** The observational study has currently included 88 patients who had an outpatient appointment with a rheumatologist for knee osteoarthritis between 2021 and 2023. The study assessed 110 knee joints using clinical and ultrasound techniques. **Results:** The most common periarticular ultrasound changes, regardless of radiographic stage, were pes anserine tendinopathy (57.3 %), Baker's cyst (45.5 %), fibrosis of the severe Hoffa body (40 %) and ligamentopathy of the medial collateral ligament (36). ,4). %). A significant correlation was found between the number of changes according to ultrasound and the radiological stage (ρ=0.45 [95 % CI: 0.28, 0.59], p <0.001), as well as between the VAS and the definition of identified ultrasound changes (ρ= 0.29 [95 % CI: 0.11, p=0.002); In addition, it was shown that late stages of OA are associated with a greater content of changes (p <0.001). **Conclusion:** Changes in periarticular structures are present in most patients with knee osteoarthritis; their number correlates with the VAS value and radiographic stage of OA. Details of these changes, their clinical significance and pathogenetic contribution to the progression of knee OA require further study.

Key words: *osteoarthritis, knee joint, knee pain*

Conflict of interests
The authors declare no conflict of interests

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Conformity with the principles of ethics
The study was approved by the LEC of the N.I. Pirogov Russian National Research Medical University (protocol No. 213 dated December 13, 2021). Patients were included in the study after signing written informed voluntary consent.

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OA — osteoarthritis, KJ — knee joint, PAS — periarticular structures, CR — clinical recommendations

Introduction

According to the WHO, at least 1.71 billion people all over the world have musculoskeletal diseases, which are a significant cause of disability.[1] The most common joint condition is osteoarthritis (OA). In 2017 in Russia, the incidence of OA exceeded 4.3 mln people,[2] and the primary disease incidence grows annually. [34] About 73 % of patients with osteoarthritis are aged over 55 years old.[5] The most common location is the knee joint (KJ).[5]

It is currently believed that KJ OA is associated not only with progressive degeneration of the articular cartilage and subchondral bone, but also with significant changes in other structures, including components of the periarticular soft skeleton.[6] Therefore, KJ OA involves the joint as a whole and not its individual tissues.

Periarticular structures in the KJ are numerous and versatile. Given no clear anatomic boundaries and a strict listing of periarticular structures in the KJ, they include at least 5 ligaments, 9 tendons, 1 fascia structure and a variable amount of bursa (8 to 13), as well as fatty pads.[7, 8] Thus, there are a number of organs near the KJ, which are expected to be a part of the pathological processes in OA and can be a source of pain. Obviously, verification of a pain source in a specific patient is a necessary condition for efficient therapy.

However, involvement of periarticular structures (PAS) in KJ OA is still understudied. Recent studies have been focusing mainly on the study of processes in intraarticular tissues. At the same time, there are a very few studies of periarticular pathologies, which are based on small samples and take into account changes

in individual PAS.[9–12] The currently available data do not allow getting an idea of which PAS, how and how often are damaged in patients with KJ OA.

OA diagnostics is based on clinical parameters or their combinations with X-ray observations.[13] The existing criteria allow making a diagnosis, but they do not provide for a possibility to find out the source of pain in a specific patient, i.e. they do not create conditions for patient-specific therapy. In particular, the role of PAS pathology in the clinical presentation of OA is not discussed in any version of the current CRs. At the same time, being the main diagnostic method, X-ray examinations do not visualise PAS.

By contrast, ultrasound is a highly informative method of PAS evaluation.[14–16] Besides, ultrasound is popular due to its swiftness, accessibility, no radiation exposure, possibility to performed targeted examination in the place of pain, and stress tests. The examination can be repeated, also for the evaluation of therapy efficiency.

Therefore, the **objective** of this study is to describe PAS pathology in patients with primary KJ OA depending on the X-rate stage, using clinical and ultrasound methods.

Materials and Methods

The study enrolled patients over 50 years old, diagnosed with primary KJ OA in accordance with the classification criteria of the American College of Rheumatology.[17] OA was staged using the Kellgren — Lawrence X-ray classification.[18] Pain syndrome intensity was evaluated using VAS. To study PAS pathology, knee ultrasound was performed using Alpinion Ecube 8 with multifrequent linear 3–12 MHz sensors. Evaluation included all RASs which could be visualised, in the anterior, medial, lateral, and posterior knee joint areas: patellar tendon, kneecap ligament, Hoffa's fat pad in the anterior section of the joint; medial collateral ligament, pes anserinus tendons — in the medial section; lateral collateral ligament, biceps femoris tendon, distal iliotibial tract, popliteal muscle tendons — in the lateral section; semimembranosus muscle tendons — in the posterior section of KJ. Also, all sections of the joint were assessed for cysts and bursitis.

Identification of key ultrasound changes

Ultrasound results demonstrated that patients had signs of tendon pathology, ligament pathology, bursitis, as well as changes in Hoffa's fat pad. Changes were evaluated on a grey scale, with axial and transverse scanning, and were compared to a reference area. All ultrasound examinations were performed using same equipment, same method by same experienced specialist.

Following an ultrasound examination, a tendon pathology is diagnosed on the basis of the following changes:[16, 19] homogeneously or focally hypoechogenic signal in tendon, tendon thickening, loss of the normal fibrillar drawing pattern, signs of peritendinitis (swelling, oedema and hyperaemia of soft tissue surrounding the tendon). Also, possible presence of vascularisation, hyperechoic inclusions, and signs of partial rupture was taken into account.

A ligament pathology was a change in the ligament: thickening, hypoechogenic signal, loss of normal pattern, presence of inclusions and vascularisation, signs of partial rupture.[16 19]

Baker's cyst is an anechogenic, non-vascular lump with liquid contents, clear contour, variable size, located between the inner head of the calf muscle and semimembranosus muscle.[20]

Bursitis is an abnormal anechogenic or hypoechogenic extraarticular mass between tissue layers. On ultrasound, the mass can be squeezed, depending on location [21]. Knee bursas are observed in all sections and located between various structures (between bone and tendon, between tendon and ligament, etc.) [22]

Hoffa's fat pad is located below the kneecap, posteriorly to the kneecap ligament and anteriorly to femoral condyles. This is an intracapsular, but extrasynovial structure.[23] The most common conditions in patients were Hoffa's fat pad fibrosis, which manifested as changes in the normal structure of the fatty tissue and appearance of diffuse areas with increased echogenicity.

Statistical Analysis

Statistical analysis and visualisation of the obtained data were performed in R 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics for categorial variables is presented as an absolute and relative frequencies; while for quantitative variables — as a mean (± standard deviation) and median (1st–3rd quartiles) values.

Associations of quantitative variables were analysed with the help of Spearman rank correlation (ρ) with a respective 95 % confidence interval (95 % CI). Correlation was statistically significant at $p < 0.05$.

Results

The study included 88 patients: 71 (80.7%) women and 17 (19.3%) men aged 50 to 83 years old (mean age was 66.9 (±7.7) years). 110 knee joints were examined, of which 22 (20%) cases of X-ray stage 1, 41 (37.3%) — stage 2, 45 (40.9%) — stage 3, and 2 (1.8%) cases of stage 4.

Table 1 shows that the most common periarticular ultrasound changes (irrespective of X-ray stage) were pathologies of pes anserinus structures (tendon pathology, enthesopathy, pes anserinus bursitis) — 59.1%, Baker's cyst (45.5%), Hoffa's fat pad fibrosis (40%) and ligament pathology in the medial collateral ligament (36.4%), while the most uncommon changes were observed in infrapatellar bursa, biceps tendon and kneecap ligament (Fig. 1). Besides, changes in some PAS were not observed at all. For instance, there were no cases of prepatellar bursitis and tendon pathology of semimembranosus muscle tendon.

Thus, the most common changes were observed in anterior, medial and posterior section of the joint, irrespective of OA stage. Changes were reported in all PAS types: in tendons, ligaments, bursa, as well as in Hoffa's fat pad. Quite common was a combination of several changes in one knee joint (up to 6 changes). The overall number of changes grew statistically with a higher OA stage ($p < 0.001$). Currently, the small sample size prevents from identifying the correlation between OA stage and individual changes in PAS. Available data show that the list of involved structures remains constant irrespective of the stage, and there were no stage-specific changes.

Statistical data processing showed a significant correlation between the number of changes on ultrasound and X-ray stage ($\rho = 0.45$ [95% CI: 0.28; 0.59], $p < 0.001$), between VAS score and the number of identified ultrasound changes ($\rho = 0.29$ [95% CI: 0.11; 0.46], $p = 0.002$). Also, comparative analysis revealed that stage 3–4 OA is associated with a larger number of changes ($p < 0.001$, Fig. 2,3).

Table 1. *General characteristics of the list, frequency and number of ultrasound changes depending on the radiological stage (n=110).*

Characteristics	All joints n=110	1-2 grade n=63	3-4 grade n=47	p
Number of changes in one knee joint according to ultrasound*	2 (1-3) 2 (0-6)	2 (1-3) 2 (0-5)	3 (2-4) 3 (0-6)	**<0,001**
0 (n, %)	9 (8,2%)	6 (9,5%)	3 (6,4%)	
1	29 (26,4%)	25 (39,7%)	4 (8,5%)	
2	26 (23,6%)	15 (23,8%)	11 (23,4%)	
3	31 (28,2%)	14 (22,2%)	17 (36,2%)	
4	8 (7,3%)	2 (3,2%)	6 (12,8%)	
5	5 (4,5%)	1 (1,6%)	4 (8,5%)	
6	2 (1,8%)	0 (0%)	2 (4,3%)	
Pes anserine tendons tendopathy/enthesopathy	55 (50%)	28 (44,4%)	27 (57,4%)	0,189
Pes anserine bursitis	10 (9,1%)	4 (6,3%)	6 (12,8%)	0, 286
Baker's cyst	50 (45,5%)	26 (41,3%)	24 (51,1%)	0, 325
Hoffa's fat pad fibrosis	44 (40%)	18 (28,6%)	26 (55,3%)	0, 005
Hoffa's fat pad inflammation	2 (1,8%)	0 (0%)	2 (4,3%)	<0,001
Medial collateral ligament ligamentopathy	40 (36,4%)	15 (23,8%)	25 (53,2%)	0,002
Lateral collateral ligament ligamentopathy	3 (2,7%)	2 (3,2%)	1 (2,1%)	0,741
Popliteus tendinopathy	20 (18,2%)	9 (14,3%)	11 (23,4%)	0,288
Iliotibial band changes	7 (6,4%)	3 (4,8%)	4 (8,5%)	0,421
Quadriceps tendinopathy	7 (6,4%)	2 (3,2%)	5 (10,6%)	0,157
Patellar ligament ligamentopathy	3 (2,7%)	2 (3,2%)	1 (2,1%)	0,573
Biceps femoris tendinopathy	2 (1,8%)	0 (0%)	2 (4,3%)	0,18
Infrapatellar bursitis	1 (0,9%)	1 (1,6%)	0 (0%)	0,7

***Comments:** the number of changes in one knee joint is presented as median (Q1-Q3), median (minimum-maximum), respectively.

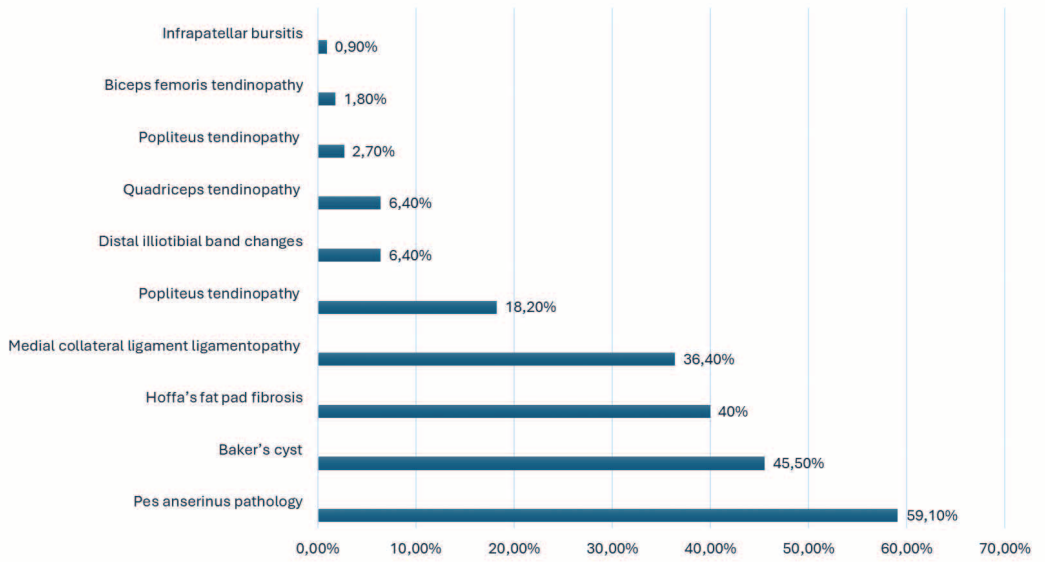

Figure 1.
Frequency of ultrasound changes regardless of the osteoarthritis grade

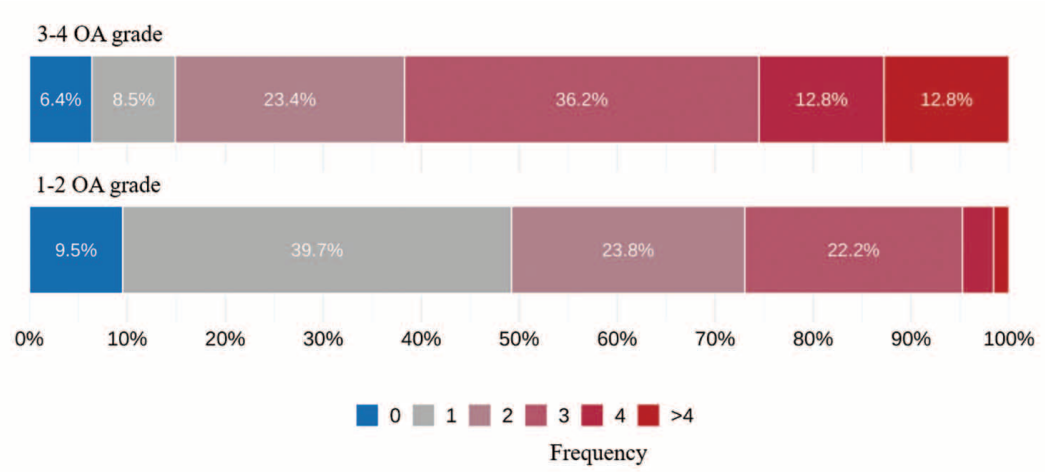

Figure 2.
Number of ultrasound changes depending on the radiographic stage.
Comments: No changes — more often at 1-2 grades, one change — much more often at 1-2 grades, 3 or more changes were present more often at 3-4 grades

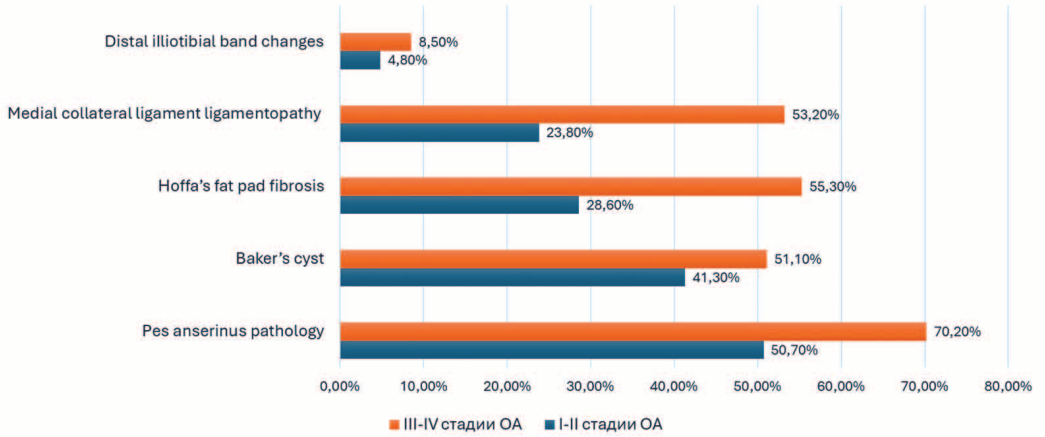

Figure 3.
Frequency of main ultrosound changes depending on the radiographic stage.
Comments: all changes were significantly more often detected at more progressive OA stages

Discussion

It is well known that changes in various PAS are often found in patients with KJ OA, and recently it had been confirmed, also due to the wide-spread use of musculoskeletal ultrasound. Nevertheless, the problem of periarticular involvement in KJ OA is undermined both in routine clinical practice and scientific research. Inadequate state of exploration of the problem of periarticular involvement is seen in clinical recommendations for OA: none of the versions describe this pathology; it means it is beyond the list of diagnostic and therapeutic objectives.

The current articles on the ultrasound verification of PAS pathology discuss just selected changes, which, according to the authors, are the most important: usually, these are pes anserinus bursitis, Baker's cyst and certain tendon pathologies.[9–12] In this article, we examined all PASs, which are suitable for ultrasound imaging; in other words, we have conducted the most comprehensive examination. The absolute majority of our patients had a pathology of this or that PAS, where all PASs were involved; and the list of such problems is quite typical.

The most common problems identified were pes anserinus conditions. According to our data, pes anserinus bursitis is quite a rare condition (9.1 % of cases), unlike other articles, where the incidence of this condition is significantly higher (20–46 %).[24, 25] However, we noted that pes anserinus tendon pathology and enthesopathy were more common than bursitis (50 % of cases); and they did not always coincide with bursitis. It is interesting to note that, despite the abundance of sources dedicated to ultrasound verification of bursitis, pes anserinus tendon pathology and enthesopathy are outside the research interest. Nonetheless, our data show that pes anserinus tendon pathologies and enthesopathies are the most commonly identified PAS changes, and this fact requires additional studies and interpretation.

Another common abnormality in our patients was changes in Hoffa's fat pad — fibrosis (40 %) — and, less common, signs of inflammation (2 %). Currently, Hoffa's fat pad is being actively studied, because it has been shown that this organ greatly influences KJ OA progression. On the other hand, Hoffa's fat pad undergoes pathological changes as well: patients with KJ OA are known to have inflammation and fibrosis of Hoffa's fat pad tissue.[26, 27] These changes can be visualised on ultrasound;[28] however, we could not find any studies where sonographic changes in Hoffa's fat pad of patients with KJ OA were taken into account. Nevertheless, in our patients, these changes were very common, indicating the need for evaluating their clinical significance.

According to the modern idea, KJ OA is thought to primarily affect the medial part of the joint,[29] where major morphological and clinical events indeed take place. In this context, it was surprising to see a relatively considerable involvement of the structure lying in the lateral and posterior sections: in the examined patients, tendopathy of popliteal muscle tendon was diagnosed in 18.2 %, taking the fifth place in the frequency of PAS changes.

A tendon pathology is usually a result of a long-term tendon overload[30] and, in addition to its clinical significance, it indicates persistent dysfunction of the respective muscle. Muscle dysfunctions in patients with KJ OA have been actively discussed; however, in a majority of cases, they related to femoral muscles,[31–33] while the shank muscle conditions (more specifically, popliteal muscle) are mentioned just in a few studies.[34, 35] The interest to the state of tendons in patients with KJ OA has been recently stimulated by the growing amount of sonographic examination data; however, the subject of research in this case is usually tendons of the musculus quadriceps femoris,[36] while popliteal muscle tendons are left unstudied. In this context, the results of our research imply that changes in popliteal muscle and its tendons in patients with KJ OA require through evaluation.

The study has limitations. The absence of a control group could have limited our conclusions.

Conclusions

PAS damages are the least studied area of pathological changes in KJ OA. At the same time, PAS is a potential source of pain and an area of therapeutic intervention in OA. Our study demonstrates the high incidence and versatility of PAS changes and confirms that they contribute greatly to the clinical presentation of OA, being an important source of pain. The correlation between the pain syndrome intensity, OA stage and the number of periarticular changes indicates that this pathology is a significant component of the clinical presentation and pathologic response in OA and should be treated as a sign and not as a set of concomitant conditions. Detailed examination of these changes, their clinical significance and pathogenic contribution to KJ OA progression are a perspective area of further studies.

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Скрипниченко Э.А.: концепция и дизайн статьи, обзор публикаций по теме, написание первого варианта статьи, научное редактирование и переработка, утверждение финального варианта

Лялина В.В.: концепция и дизайн статьи, обзор публикаций по теме, научное редактирование и переработка, утверждение финального варианта статьи

Приписнова С.Г.: научная консультация, выполнение УЗИ, интерпретация УЗ-изменений, редактирование и переработка статьи, утверждение финального варианта

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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

Skripnichenko E.A.: concept and design of the article, scientific editing and revision, review of literature, writing the first draft of the article, approval of the final version of the article

Lyalina V.V.: concept and design of the article, scientific editing and revision, review of literature, approval of the final version of the article

Pripisnova S.G.: scientific consultation, ultrasound examination, interpretation of ultrasound changes, editing and revision of the article, approval of the final version

Valery G. Golubev: scientific editing and revision, approval of the final version of the article

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ТРУДНОСТИ ДИАГНОСТИКИ ПАЦИЕНТА С ЛИХОРАДКОЙ НЕЯСНОГО ГЕНЕЗА

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Difficulties in Diagnosing a Patient with Fever of Unknown Origin

Резюме

Лихорадка неясного генеза представляет собой сложный для дифференциальной диагностики синдром. При отсутствии ключевого признака, который мог бы указать на причину состояния дальнейший диагностический поиск становится затруднительным. Осложняет диагностику многообразие причин и отсутствие единого алгоритма обследования. В представленном клиническом случае описывается пациентка 53 лет, с длительной лихорадкой более 1.5 месяцев, болевым синдромом в области лица. При амбулаторном наблюдении причина выяснена не была. На стационарном этапе проведено комплексное обследование по всем классам причин. Выявленные изменения щитовидной железы и наличие тиреотоксикоза позволили поставить диагноз подострого тиреоидита. Согласно данным литературы, подострый тиреоидит является одной из редких причин лихорадки неясного генеза. Назначение глюкокортикостероидов позволило достигнуть полного регресса клинических симптомов к 4 суткам. Через 5 месяцев достигнут субклинический гипотиреоз. Нозологический подход и междисциплинарное взаимодействие способствовали верной тактике и благоприятному исходу заболевания.

Ключевые слова: *лихорадка неясного генеза, подострый тиреоидит*

Конфликт интересов

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Abstract

Fever of unknown origin is a difficult syndrome for differential diagnosis. Absence of a key feature, variety of causes and the lack of single examination algorithm makes difficult further diagnosis. The presented clinical case describes a 53-year-old patient with a prolonged fever of more than 1.5 months, pain syndrome in the facial area. During outpatient monitoring, the cause was not clarified. At the inpatient stage, a comprehensive examination was conducted for all classes of causes. The revealed changes in the thyroid gland and thyrotoxicosis made it possible to diagnose subacute thyroiditis. According to the literature, subacute thyroiditis is one of the rare causes of fever of unknown origin. Prescription of glucocorticosteroid made it possible to achieve complete regression of clinical symptoms in 4 days. After 5 months, subclinical hypothyroidism was achieved. The nosological approach and multidisciplinary interaction contributed to the correct tactics and a favorable outcome of the disease.

Key words: *fever of unknown origin, subacute thyroiditis*

Conflict of interests

Co-author of the article Adasheva T.V. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Adasheva T.V. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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FUO — fever of unknown origin, GCS — glucocorticosteroids, CRP — C-reactive protein, ESD — erythrocyte sedimentation rate, CT — computer tomography, TTH — thyrotropic hormone, free T3 — free triiodothyronine, free T4 — free thyroxine, GCA — giant cell arteritis

"The true knowledge is the knowledge of causes"
Galileo Galilei

For the first time, fever of unknown origin (FUO) was mentioned in 1930 in a report by a US hospital. Scientists described a follow-up of 173 patients starting from 1913, who were discharged with the diagnosis "fever of unknown origin".

In 1961, R.G. Petersdorf and P.B. Beeson proposed the first official definition of fever of unknown origin: "A fever of over 100.9 F (38.3 ˚C) in some cases, persisting without a diagnosis for three weeks, despite one week of inpatient examinations" [1].

30 years later, Durack D.T. and Street A.C. modified this definition: undefined diagnosis after three visits to the doctor or a 3-day inpatient examination [2].

It is important to note that the body temperature can vary by 0.7 ˚C depending on the place of measurement. In Europe and the USA, temperature is usually measured in the oral cavity or rectum, while in Russia, the most common is axillary crease. Therefore, criteria of FUO can be temperature less than 38.3 ˚C.

The aetiology of FUO includes five groups of the most common causes: infections (40 %), tumours (20 %), inflammatory connective tissue diseases (20 %), returned traveller diseases, and other (10 %). Statistically, 10 % of patients remain undiagnosed (Table 1).

The diagnostic search includes four steps (Fig. 1): identification of an additional sign, provisional hypothesis, additional diagnostic investigations, data interpretation, and comparison with the clinical case [4].

Currently, there isn't any universal diagnostic algorithm of FUO. During the past two decades, several diagnostic search designs were proposed; all of them have different structure and content. For instance, the algorithm by Roth A. and Basello G. (Fig. 2), which was presented in 2003, is more structured, more branched; unlike other variants, it provides for separate sets of examinations depending on the estimated ICD code. According to the algorithm proposed by Varghese et al. [6] in 2010, the first step includes a general medical examination, which is available in a majority of medical institutions; if no cause is found, then the second step follows, which is hi-tech examinations. Despite differences, these algorithms follow the principle of accessibility, stage-by-stage approach and cost-effectiveness. However, all algorithms are based on the personal experience of their authors and are not evidence-based.

During the diagnostic search, it is recommended to use symptomatic therapy only, namely antipyretics. Antibacterial therapy is indicated only in severe intoxication, haemodynamic disorders, signs of DIC-syndrome, neutropenia, and positive procalcitonin test. If system connective tissue disorders are suspected, test therapy with glucocorticosteroids (GCS) can be initiated, with

Table 1. *Causes of fever of unknown origin (adapted from Wright WF, Auwaerter PG. Fever and Fever of Unknown Origin: Review, Recent Advances, and Lingering Dogma. Open Forum Infect Dis. 2020 May 2;7(5):ofaa132. doi: 10.1093/ofid/ofaa132. PMID: 32462043; PMCID: PMC7237822.) [3]*

Category	Common	Uncommon
Infectious diseases	Mycobacterium tuberculosis (mainly extrapulmonary), endocarditis, culture-negative Epstein-Barr virus infections, cytomegalovirus infections	Bartonellosis (mainly Bartonella henselae), brucellosis, occult abscesses, salmonellosis, urinary tract infections, acute HIV, Hepatitis A, B, and E, Human herpesvirus-6, Human herpesvirus-7, bone and joint infections
Neoplastic diseases	Lymphoma (Hodgkin and non-Hodgkin), leukemia, solid-organ tumors (renal cell carcinoma and melanoma)	Myelodysplastic syndrom, colonic adenocarcinoma, multiple myeloma, gastric carcinomas, mesothelioma, Castleman's disease
Inflammatory diseases	Adult-onset Still's disease, systemic lupus erythematosus, polymyalgia rheumatica, temporal arteritis, inflammatory bowel disease	Rheumatoid arthritis, polyarteritis nodosa, sarcoidosis, granulomatosis with polyangiitis, Kawasaki's disease
Returnes travelers	Malaria, Dengue virus	Pulmonary infection, urinary tract infectoins, hepatitis A,B, and E, rickettsial deseases, leptospirosis, schistosomiasis, gnathostomiasis, cysticercosis, typhoid, acute HIV, tuberculosis
Miscellaneous	Medication / drug fever, chronic pulmonary embolism, hyperthyroidism, hematoma	Subacute thyroiditis, hypoadrenalism, necrotizinf lymphadenitis, periodic fevers (genetic), hemophagocytic lymphohistiocytosis, factitious fever.

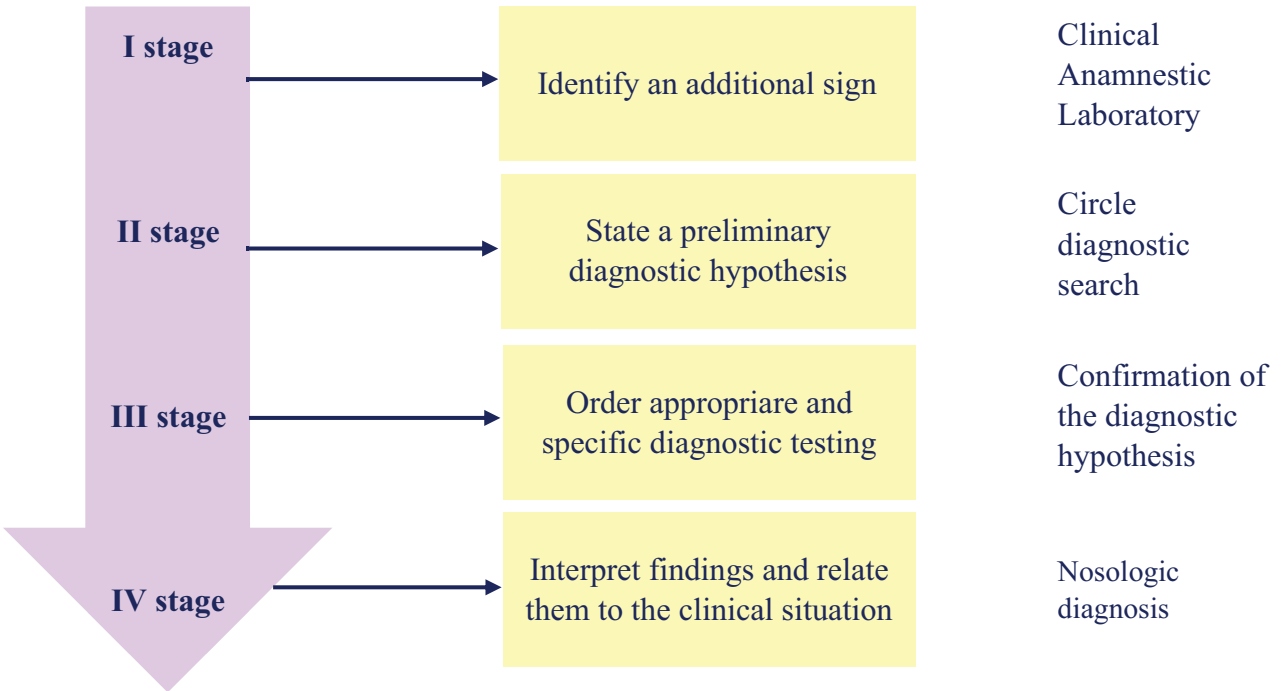


Figure 1. *Diagnostic search scheme of FUO (adapted from Dvoreckij L.I. Fever of unknown origin: an eternal clinical intrigue. Moscow, MEDpress-inform. 2019; 138 p. [In Russian]) [4]*

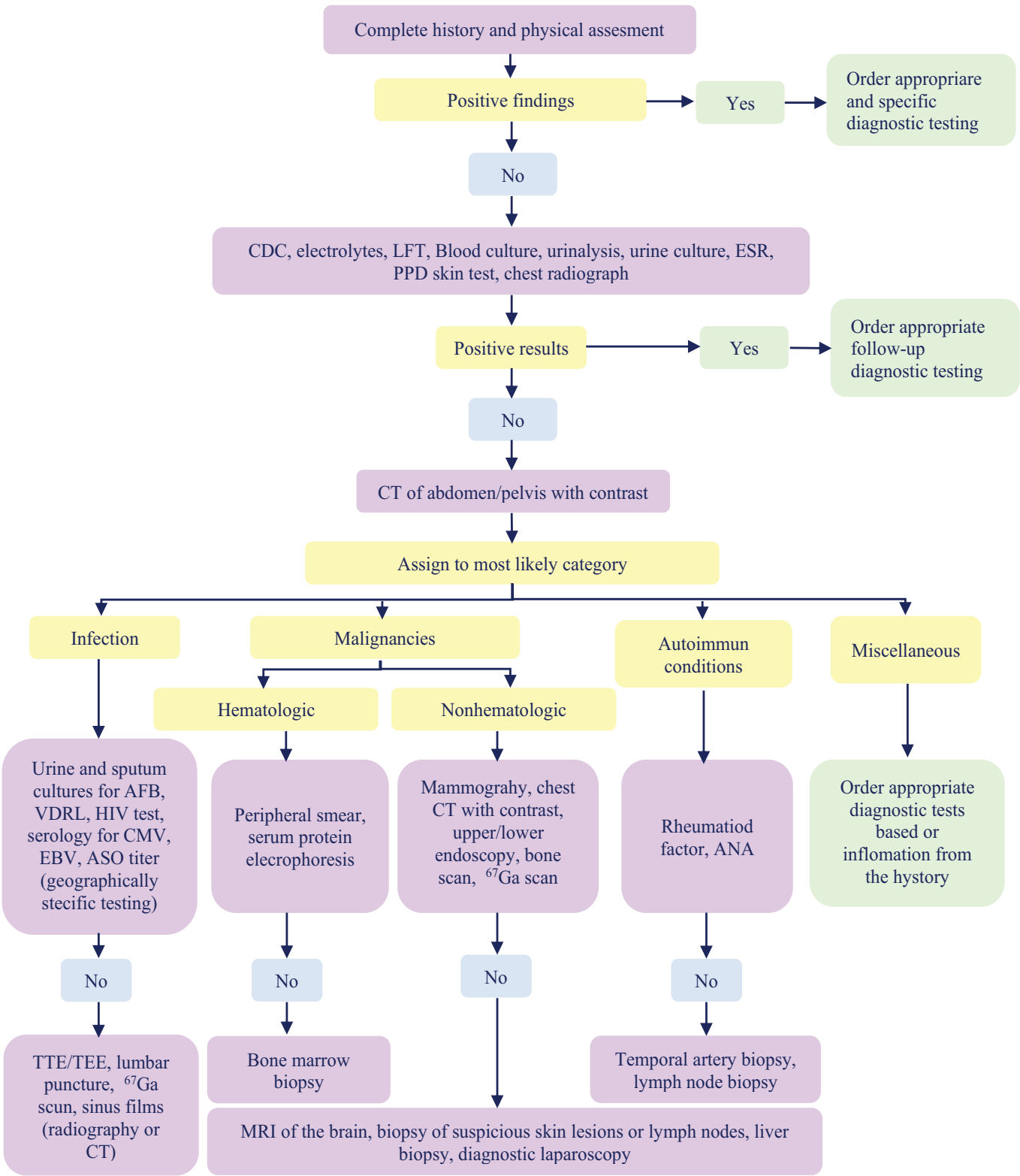


Figure 2. *Algorithm for the diagnosis of fever of unknown orogin Roth A., Basello G., 2003 (adapted from из Roth AR, Basello GM. Approach to the adult patient with fever of unknown origin. Am Fam Physician. 2003 Dec 1; 68(11): 2223-8. PMID: 14677667) [5]*

Note: CBC — complete blood count; LFT — liver function test; ESR — erythrocyte sedimentation rate; PPD — purified protein derivative; CT — computed tomography; AFB — acis-fast bacilli; HIV — human immunodeficiency virus; CMV — cytomegalovirus; EBV — Epstein-Barr virus; ASO — antistreptolysin-O antibodies; TTE — transthoracic echocardiography; TTE — transesophageal echocardiography; MRI — magnetic resonance imaging

efficiency assessment in 48–72 hours; if the therapy is inefficient, GCS should be discontinued.

If the cause of FUO is still unknown despite a comprehensive examination, case follow-up and laboratory monitoring are recommended, provided the patient is stable.

CASE STUDY

Patient M., 53 years old. On 17 April, she was admitted to the Department of Internal Medicine at the hospital of the Central Union of Consumer Cooperatives of the Russian Federation. The patient was complaining of a fever of 37.2–37.5 ˚C rising to 39.0 ˚C every 4–5 days for 1.5 months; pain on the left side of her face, increased fatigue, weakness, atony, apathy, irritability, poor concentration and attentiveness.

Medical history. The patient considers herself ill for four months, when psychoemotional stress caused exacerbation of recurrent neuritis of her left fifth cranial nerve, a condition, which the patient has had for the last five years, with annual recurrences; the condition is managed with pregabalin. The present episode of exacerbation manifests with headaches and pain on the left side of her face; the patient took pregabalin 600 mg and acyclovir, with no effect.

Early in February, the pain spread to the left temporal region and left eye area (Table 2).

Late in February, the patient had a high fever (39.5–39.9 ˚C) for three days; then it was a moderate fever (38.0–38.9 ˚C) for two weeks. Later, the patient had a subfebrile fever (37.2–37.5 ˚C) for 1.5 month, with rises in the body temperatures to 39.0 ˚C every 4–5 days (Fig. 3).

Over a period of two months, the patient repeatedly sought medical help. Outpatient examinations: ultrasound examination of neck, supraclavicular, subclavicular, axillary, and groin lymph nodes; paranasal sinus X-ray; consultation by a dentist — no pathologies.

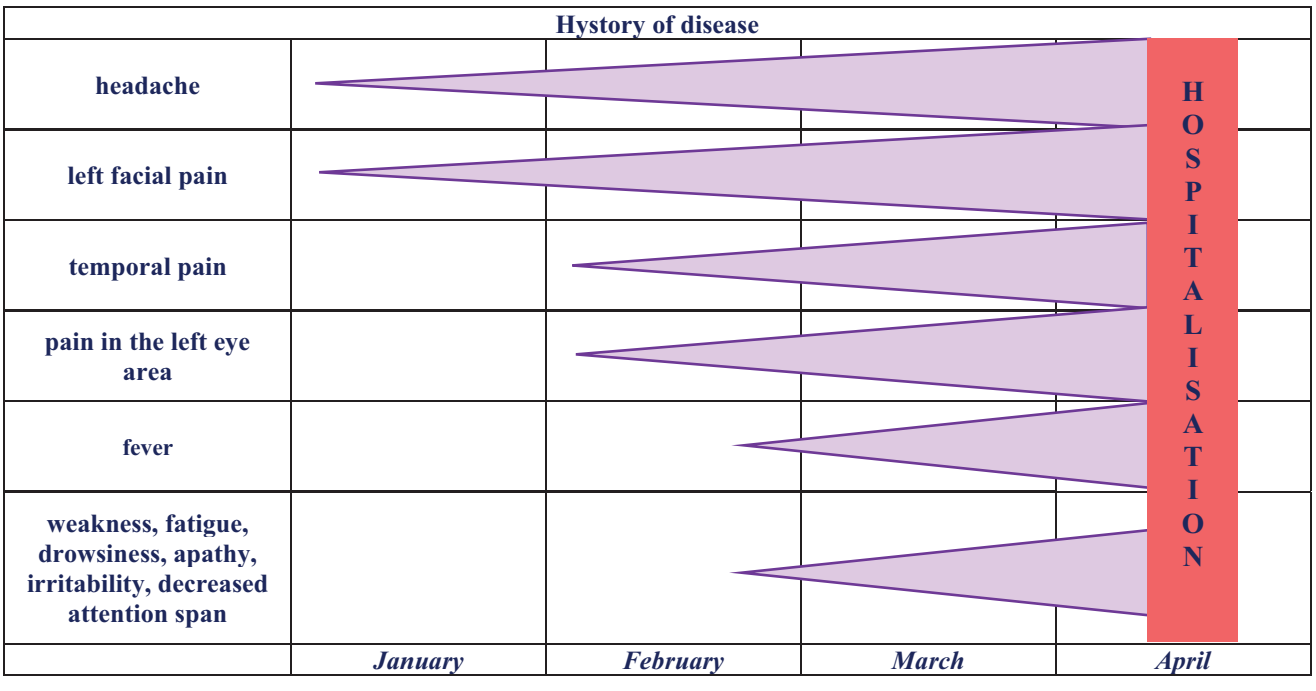
22 March: ultrasound examination of the thyroid gland, salivary glands, neck and submandibular lymph nodes. Echo signs of palpable abnormalities of the thyroid gland (13x10x7 mm, 15x13x9 mm, 12x10x9 mm) Thi-RADS 3–4 and diffuse changes in the right thyroid lobe, hyperplasia of the right paratracheal lymph node (6x5x4 mm) and moderate hyperplasia of two right submandibular lymph nodes (12x11x8 mm, 20x18x8 mm).

23 March: complete blood count — unremarkable; elevated ESR up to 38 mm/h; CRP (hsCRP) — up to 7.1 mg/L, TTH: 1.55 IU/L (normal range: 0.4–4.0 IU/L).

Biopsy of thyroid gland lumps: areas of colloid goitre with proliferated thyroid epithelial cells (Bethesda Category II — benign).

Past history. Type 2 diabetes mellitus from 2013; continuously takes insulin glargine 14 units once daily, metformin 1,000 mg twice daily. Recurrent neuritis of the left fifth cranial nerve from 2017. Positive family history for type 2 diabetes mellitus on her mother's side; her mother is followed-up to thyroid nodule. No bad habits. No history of allergies. Continuously takes atenolol 25 mg. The patient denies any trips outside the Moscow Region during the last six months. Any contact with contagious patients: denies. Any contact with animals, rodents, birds, animal raw materials: denies.

Table 2. *Dynamics of clinical symptoms*



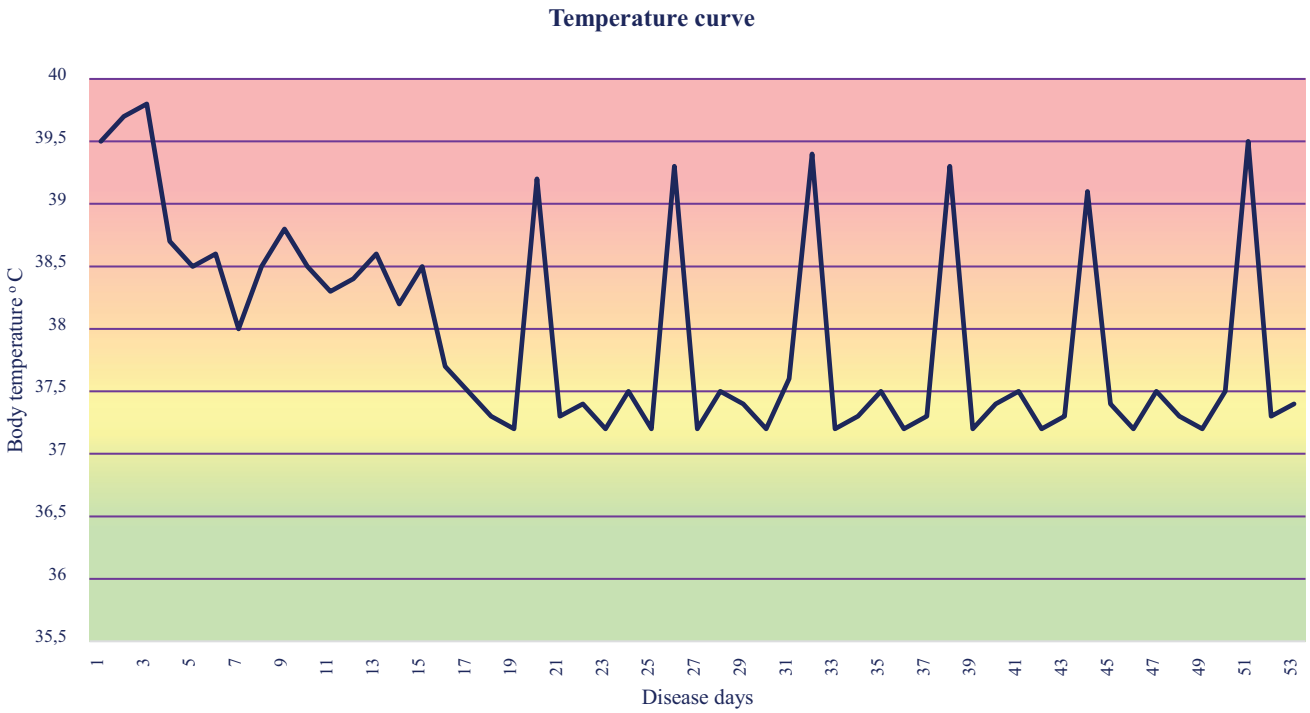


Figure 3. *Dynamics of the patient's body temperature outside the hospital*

Initial examination results dated 17 April: moderately severe condition; body temperature: 37.5 ° C. The oropharynx is not hyperaemic. Palpable enlarged submandibular lymph nodes on the left side. Respiratory rate: 19/min, vesicular respiration, without rales, SpO2: 98 %. Clear, rhythmic heart tones without any murmur; HR: 105 bpm; BP: 130/80 mm Hg; the thyroid gland is not enlarged, slightly painful. The patient is lucid, sensible, cooperative, emotionally labile. Other organs and systems: no abnormal changes.

Medical history and physical examination did not reveal any additional diagnostic sign. Examinations of the first-line diagnostic search: general clinical examinations, taking into account available outpatient examination and tests.

ECG dated 17 April: regular sinus rhythm. HR: 109 bpm. Sinus tachycardia. Horizontal CEA (cardiac electrical axis).

Complete blood count dated 17 April: HB — 112 g/L, EBC — 3.98 mln/μL, platelets — 372 ths/μL, WBC — 7.88 ths/μL, NEU — 60.3 % (4.75 ths/μL), LYMPH — 29.2 % (2.30 ths/μL), MONO — 7.7 % (0.61 ths/μL), EOS — 2.3 % (0.18 ths/μL), BAS — 0.5 % (0.04 ths/μL), HCT — 33.9 %, ESR — 105 mm/h.

Blood biochemistry dated 17 April: ALT — 10 U/L, AST — 10 U/L, albumin — 40 g/L, glucose — 7.7 mmol/L, creatinine — 64 μmol/L, urea — 5.7 mmol/L, total protein — 72 g/L, hsCRP — 69.8 mg/L, glycated Hb — 8.7 %, calcitonin — 1.8 pg/mL.

Urinalysis, ultrasound examination of abdomen, kidneys, pelvis, EcoCG: no abnormal changes.

At this stage, no clinically significant changes were observed, which would help to identify the key sign It was concluded that chest, abdominal, retroperitoneal and pelvic CT (with IV contrast) was required. The examination did not identify any meaningful pathologies of the chest, abdomen, or pelvis. However, structure inhomogeneity and contrast accumulation by thyroid parenchyma were reported.

Given the available information, changes in the thyroid gland revealed by the biopsy (taking into account normal hormone levels) were interpreted as signs of multinodal colloid goitre.

At this stage, examination results did not make it possible to choose a certain group of diseases. Initial examinations for all categories of diseases have been performed.

Blood test for autoimmune markers dated 18 April: rheumatoid factor — < 20.0 IU/mL, antinuclear antibodies (ANA IIFT, HEp-2) — <1:160 titer.

Blood test for infections dated 18 April: EBV virus DNA — negative; type 6 herpes simplex virus — negative.

In order to rule out a septic process, blood test for procalcitonin (0.03 ng/mL) and blood culture for sterility (no microflora growth) were performed.

Examinations: paranasal sinus CT, mammography, esophagogastroduodenoscopy, fibrocolonoscopy — no clinically significant changes.

Repeated blood tests dated 24 April showed the following abnormalities: Hb — 109 g/L, HCT — 32.9 %, ESR — 99 mm/h, albumin — 34.5 g/L, CRP — 60.4 mg/L.

Since there was no key sign, and CT changes in the thyroid gland were reported, TTH levels were measured: < 0.0083 IU/L (23 March: 1.55 IU/L).

The key sign was identified — thyrotoxicosis, which was not observed one month earlier. Follow-up examinations of the thyroid gland were performed.

Blood test dated 25 April: TTH receptor antibodies — 1.0 IU/L (negative); free T3 — 5.5 pmol/L (3.0–5.6 pmol/L); free T4 — 33.05 pmol/L (9.00-19.05 pmol/L).

Thyroid ultrasound (Fig. 4) as compared to 22 March demonstrated an enlarged thyroid gland: right lobe — 19×18×47 mm→23×20×55 mm, left lobe — 18×16×43 mm→18×18×50 mm, isthmus — 3 mm→5 mm, volume: 12 cm^3→20.1 cm^3. Parenchyma: mixed echogenicity, marked diffuse heterogeneity,

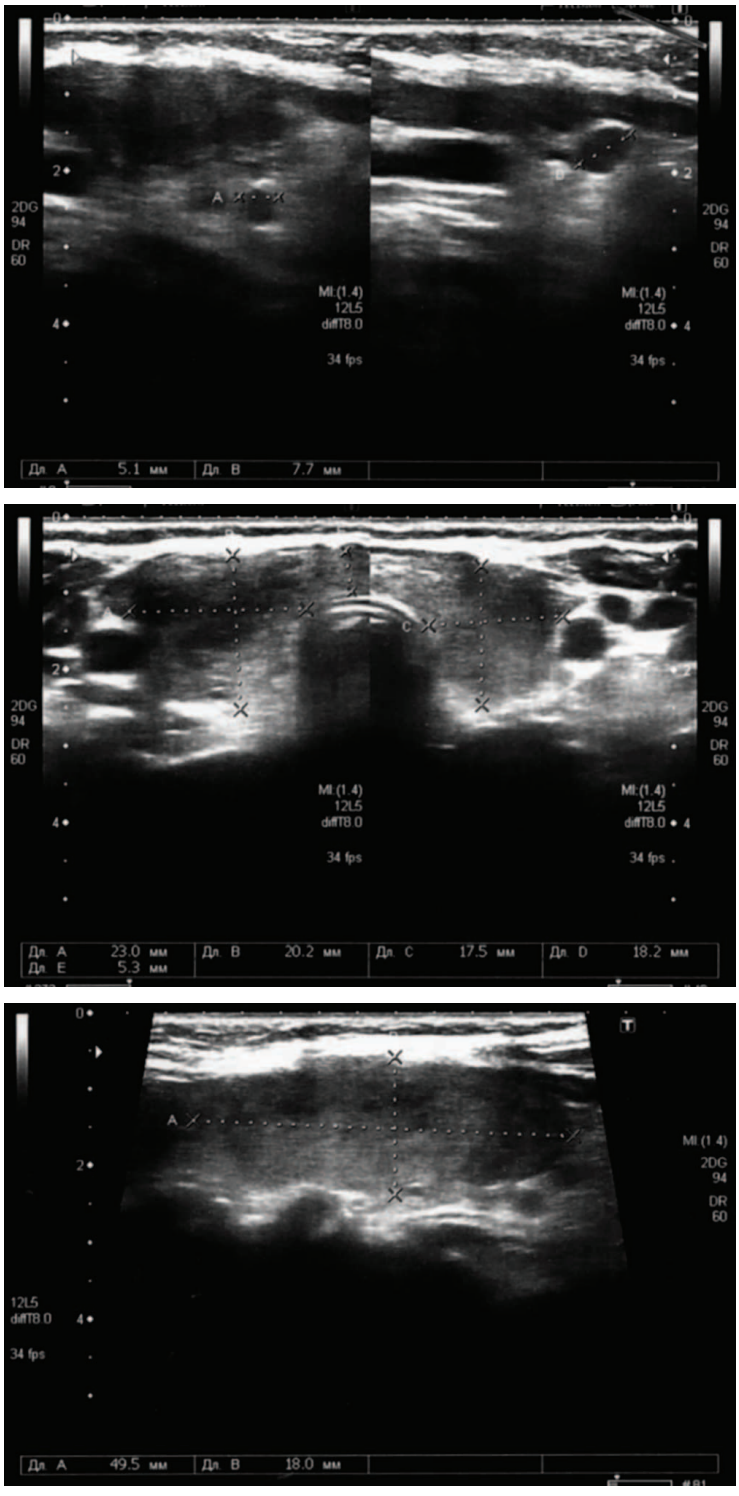


Figure 4. *Thyroid ultrasound 25.04*

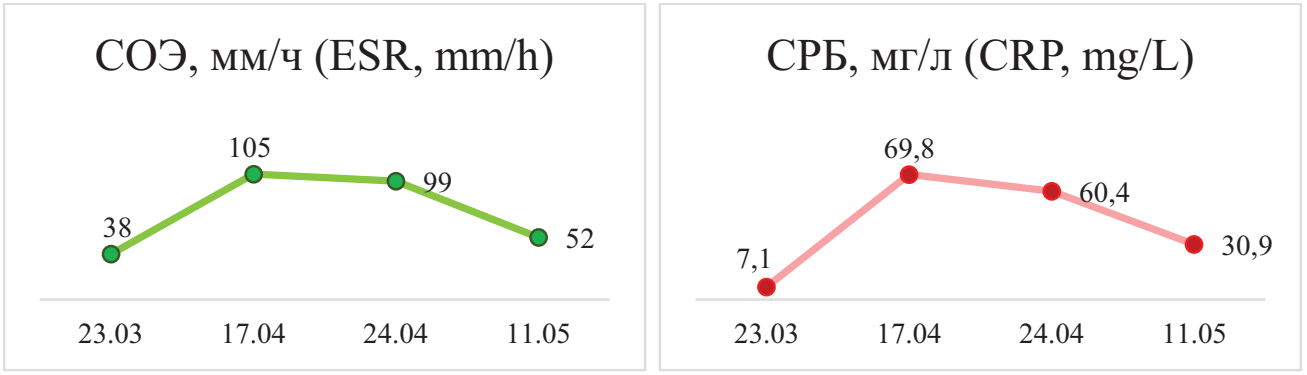


Figure 5. *Dinamics ESR and CRP over the observation period*

more in the right lobe, with large areas of decreased echogenicity in the whole lobe. The lower body of the right lobe: the above-mentioned hypoechoic node with even, unclear edges cannot be differentiated due to the overall lobe heterogeneity. The above-mentioned areas of reduced echogenicity along the posterior surface with uneven, unclear edges and without enhanced blood flow, which were interpreted as Thi-RADS 4, have now amalgamated with the large areas. In the central segment there is an isoechoic node with even, unclear edges, 15×13×9 mm.

The patient was consulted by an endocrinologist; the following diagnosis was made on the basis of laboratory and instrumental test results: severe subacute thyroiditis.

Laboratory tests showed thyrotoxicosis syndrome, pain syndrome, accelerated ESR syndrome, typical ultrasound changes in the thyroid gland.

According to the clinical recommendations for the management of acute and chronic thyroiditis [7], the patient had a prednisolone challenge test, i.e. test therapy: prednisolone 20 mg once daily. On day 2 of therapy, the body temperature normalised; on day 3, weakness, apathy, irritability resolved; and on day 4, the pain syndrome resolved completely.

An analysis of the clinical, laboratory and instrumental data as well as medical history confirm the diagnosis of severe subacute thyroiditis:

- Palpatory tenderness of the thyroid gland
- Fever
- Thyrotoxicosis syndrome
- Accelerated ESR syndrome without leukocytosis
- Enlarged thyroid gland, areas of decreased echogenicity, migration of these areas on ultrasound
- Positive prednisolone challenge test.

Final diagnosis: Severe subacute thyroiditis. Type 2 diabetes mellitus, target HbA1c of less than 7.0 % has not been achieved. Mild normocytic, normochromic anaemia.

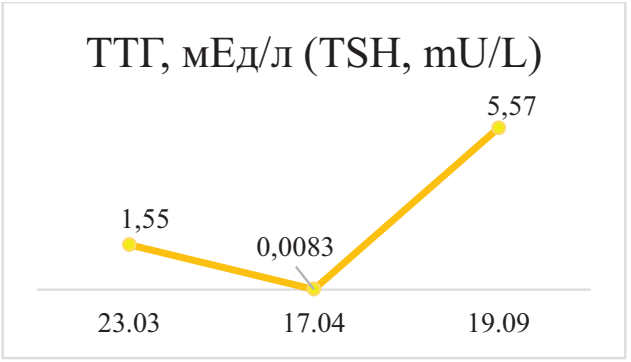


Figure 6. *Dynamics of thyroid-stimulating hormone levels during the observation period*

The patient was discharged with improvements and was given the following recommendations:

- Prednisolone 20 mg once daily, weekly follow-up complete blood counts (including ESR); once ESR has normalised, prednisolone dose should be reduced by 2.5 mg (1/2 tablet) every week until complete withdrawal
- Atenolol 25 mg once daily (in the morning)
- Insulin glargine 14 units once daily
- Metformin 1,000 mg twice daily (in the morning and before bed)
- Empagliflozin 10 mg once daily
- Omeprazole 20 mg twice daily.

1.5 months later, the patient started reducing prednisolone dose, and by the end of August, she withdrew from it completely. According to laboratory blood tests, in mid-September the patient had asymptomatic hypothyroidism, which corresponds to the hypothyroid phase of destructive (subacute) thyroiditis: TTH — 5.57 IU/L (0.4–4.0 IU/L), free T3 — 5.14 pmol/L (3.0–5.6 pmol/L), free T4 — 10.81 pmol/L (9.0–19.05 pmol/L).

Discussion

The peculiarities of this clinical case are the rare incidence of this pathology, lack of unified management recommendations and long diagnostic search due to uncharacteristic clinical manifestations.

There is literature evidence of FUO caused by subacute thyroiditis, where local symptoms and signs of impaired thyroid function are not primary aspects. In FUO, pain syndrome can be mild or can be absent; in some cases, patients recalled short-term pain or discomfort in the neck area, which is not typical of the traditional course of subacute thyroiditis.

In this case, pain syndrome has an atypical location.

Symptoms of thyrotoxicosis were unclear, which can be a result of beta-blockers inhibiting manifestation of thyrotoxicosis (non-selective beta-blockers have a more pronounced effect).

Also, the diagnostic process was challenging due to the available outpatient data of thyroid data examinations and absence of any clinical signs for a follow-up examination. According to the clinical recommendations on thyroid disorders, TTH levels are monitored every eight to 12 weeks. An examination performed in March showed euthyroid state; however, the thyrotoxic phase of destructive thyroiditis set in within one month. Ultrasound results made it possible to monitor changes in the thyroid gland, including signs typical of subacute thyroiditis (migration of hypoechoic cloud-shaped areas).

Of note, available data of thyroid gland examinations hindered diagnostic search; pain syndrome and initial examination results were misinterpreted. It is likely that outpatient blood tests and thyroid ultrasound were performed at the early stage of disease, i.e. at the beginning of destructive thyrotoxicosis (Fig. 7), when the thyroid function had not yet responded to the existing inflammation and starting thyrocyte destruction. Also, ultrasound results were not pathognomonic for subacute thyroiditis; and they could be interpreted only during the follow-up (migration of hypoechoic cloud-shaped areas).

In this case, differential diagnosis with giant cell arteritis (GCA) was required. The patient had typical pain location. However, upon examination the patient did not present with typical changes in her temporal areas (temporal artery bulging and a clearer contour, palpatory tenderness of skin of the head and temporal region); also, there were no symptoms of muscle involvement (myodynia, alternating mandibular claudication), etc.

A positive effect of GCS is typical for both diseases; however, in GCA, higher doses of GCS are used for approximately 24 months; any attempts to reduce the dose or discontinue GCS can cause a relapse. In this case, 1.5 months after therapy initiation, laboratory values normalised, and two months later, the therapy was discontinued completely. The patient's condition did not deteriorate, while thyroid hormone levels corresponded to subclinical hypothyroidism, which correlates with stage 3 subacute thyroiditis (transient thyroiditis).

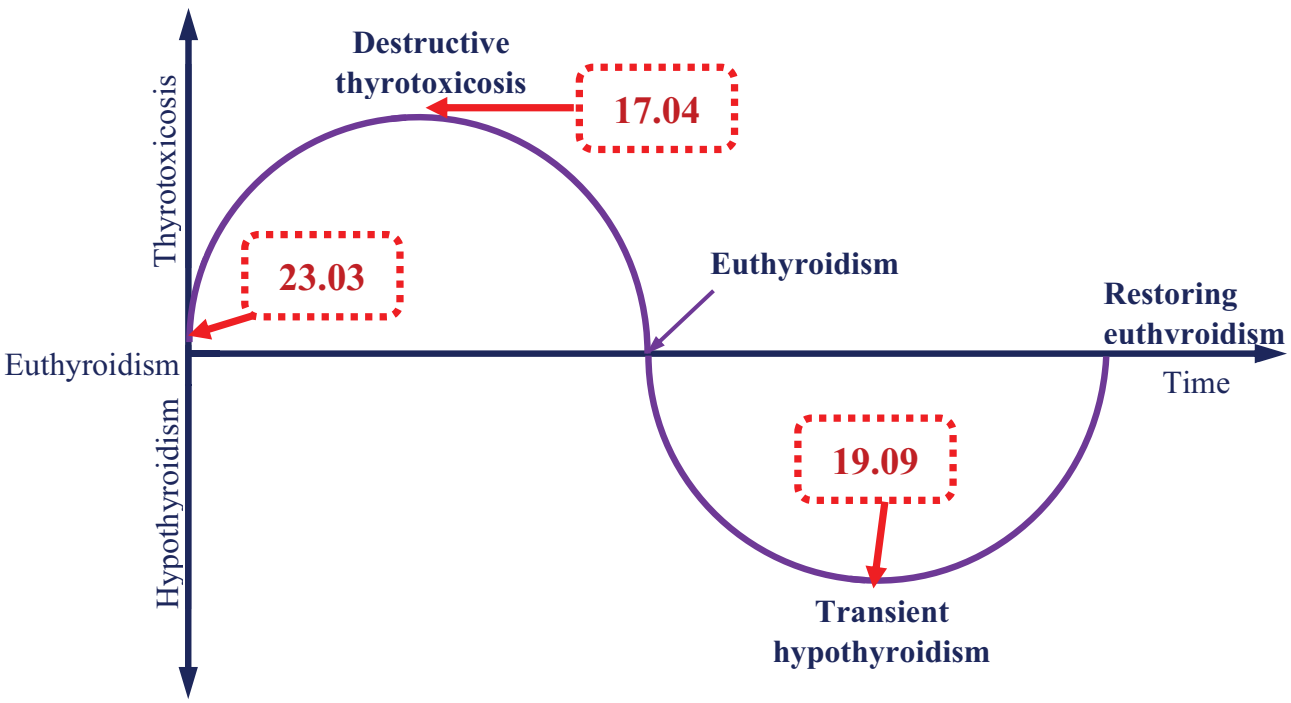


Figure 7. *Stages of subacute thyroiditis*

Conclusion

This clinical case demonstrates challenges of management of patients with fever of unknown origin. Versatile causes, belonging to various areas of medicine, usually an atypical clinical presentation of the disease disguised by FUO, poor awareness among healthcare providers of the causes (including rare cases, such as subacute thyroiditis) and diagnosis of this condition, lack of clinical recommendations on the management of such patients, hinder diagnostic search and extend the time needed to make a diagnosis.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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LMNA-КАРДИОМИОПАТИЯ ПРИ МЫШЕЧНОЙ ДИСТРОФИИ ЭМЕРИ-ДРЕЙФУСА

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LMNA-Cardiomyopathy in Emery-Dreifuss Muscular Dystrophy

Резюме

Мышечная дистрофия Эмери-Дрейфуса — редкое заболевание, возникающее вследствие генетического дефекта белков ядерной оболочки, чаще эмерина и ламина А/С. Заболевание проявляется медленно прогрессирующей слабостью лопаточно-плечевой и тазово-перонеальной групп мышц, миодистрофией, первичной контрактурой суставов, а также кардиомиопатией с нарушениями ритма и проводимости. Сердечно-сосудистые осложнения и жизнеугрожающие аритмии — основная причина смерти таких пациентов в молодом возрасте. В зависимости от ведущих симптомов и наследственного анамнеза больные попадают в поле зрения разных клиницистов — неврологов, кардиологов, аритмологов, ортопедов, — часто недостаточно информированных о данном заболевании, что препятствует диагностике, своевременной профилактике и лечению осложнений. В данной статье рассмотрены данные эпидемиологии, патофизиологии, особенности течения, диагностики, подходы к ведению сердечно-сосудистой патологии при прогрессирующей мышечной дистрофии Эмери-Дрейфуса с развитием LMNA-кардиомиопатии. А также представлен клинический случай данного заболевания.

Ключевые слова: *Эмери-Дрейфуса, кардиомиопатия, ламинопатия, LMNA, мышечная дистрофия*

Конфликт интересов

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

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Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Emery-Dreifuss muscular dystrophy is a rare disease resulting from a genetic defect in nuclear envelope proteins, most commonly in emerin and lamin A/C. The disease is characterized by slowly progressing weakness of the scapular-brachial and pelvic-peroneal muscle groups, myodystrophy, primary joint contracture and cardiomyopathy with rhythm disorders and conduction abnormalities. Cardiovascular complications and life-threatening arrhythmias are the main cause of death in such patients at a young age. Depending on the leading symptoms and family history, patients are under the care of different specialists. Unfortunately, neurologists, cardiologists, cardio surgeons and orthopedics are not well informed about this rare condition and thus the disease tends to be not diagnosed in time. This article examines the data of epidemiology, pathophysiology, features of the course, diagnosis, approaches to the management of cardiovascular pathology in progressive Emery-Dreyfus muscular dystrophy with the development of LMNA cardiomyopathy. A clinical case of this disease is also given.

Key worlds: *Emery-Dreifuss, cardiomyopathy, laminopathy, LMNA, muscular dystrophy*

Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «LMNA-Cardiomyopathy in Emery-Dreifuss Muscular Dystrophy» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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AV — atrioventricular, SCD — sudden cardiac death, DCMP — dilated cardiomyopathy, LTVT — life-threatening ventricular tachyarrhythmia, ICD — implantable cardioverter defibrillator, CMP — cardiomyopathy, MAPK — mitogenic-activated protein kinase, MRI — magnetic resonance imaging, ACVA — acute cerebrovascular accident, CF — cardiac failure, CVC — cardiovascular complications, CRT– cardiac resynchronisation therapy, AF — auricular fluttering, TEC — thromboembolic complication, LV EF — left ventricle ejection fraction, AFib — atrial fibrillation, Holter ECG — Holter electrocardiography monitoring, CCF — chronic cardiac failure, EDMD — Emery — Dreifuss muscular dystrophy, ECG — electrocardiography, ECS — electrocardiostimulator, EchoCG — echocardiography

Introduction

In the 1960s, two neurologists — E. E. Emery and F. Dreifuss — identified a unique group of patients with a hereditary muscular-cardiac-articular syndrome. When compared to the previously described Duchenne — Becker muscular dystrophies, the clinical course of this condition was more benign [1]. The syndrome was called Emery — Dreifuss muscular dystrophy (EDMD). The following symptom triad is typical for this dystrophy:

1. Slowly progressing dystrophies and weakness of scapular, shoulder and fibular muscles, which usually manifest at the age of 3 to 15 years old. The ability to walk independently is lost in extreme cases [2].
2. Early contractures in elbow flexors, Achilles tendon flexors and neck extensors. The latter are often observed during the first decade of life, but get worse and cause discomfort in adolescence [3].
3. Clinically, heart involvement manifests during the 2nd or 3rd decade of the patient's life. The most often manifestations are atrial and ventricular tachyarrhythmia, conduction abnormalities, cardiomyopathy (CMP) with developing cardiac failure (CF). The incidence of CF can exceed 60 % in patients over 50 years of age with *LMNA* gene mutations [4]. Cardiac manifestations can precede skeletal muscle weakness. If compared to the general population, female EDMD carriers have a higher risk of cardiovascular complications (CVC) even in the absence of marked neural and muscular symptoms [1].

Pathogenesis

The pathogenesis of EDMD is associated with protein-coding genes: emerin — gene *EMD*, lamin — *LMNA*, nesprin 1 — *SYNE1*, nesprin 2 — *SYNE2*, H-like protein 1 factor — *FHL1*, transmembrane protein 43 — *TMEM43*. They correspond to the specific EDMD subtypes: EDMD 1 (gene *EMD*), EDMD 2 (*LMNA*), EDMD 3 (*LMNA*), EDMD 4 (*SYNE1*), EDMD 5 (*SYNE2*), EDMD 6 (*FHL1*), EDMD 7 (*TMEM43*) (Fig. 1) [5,6].

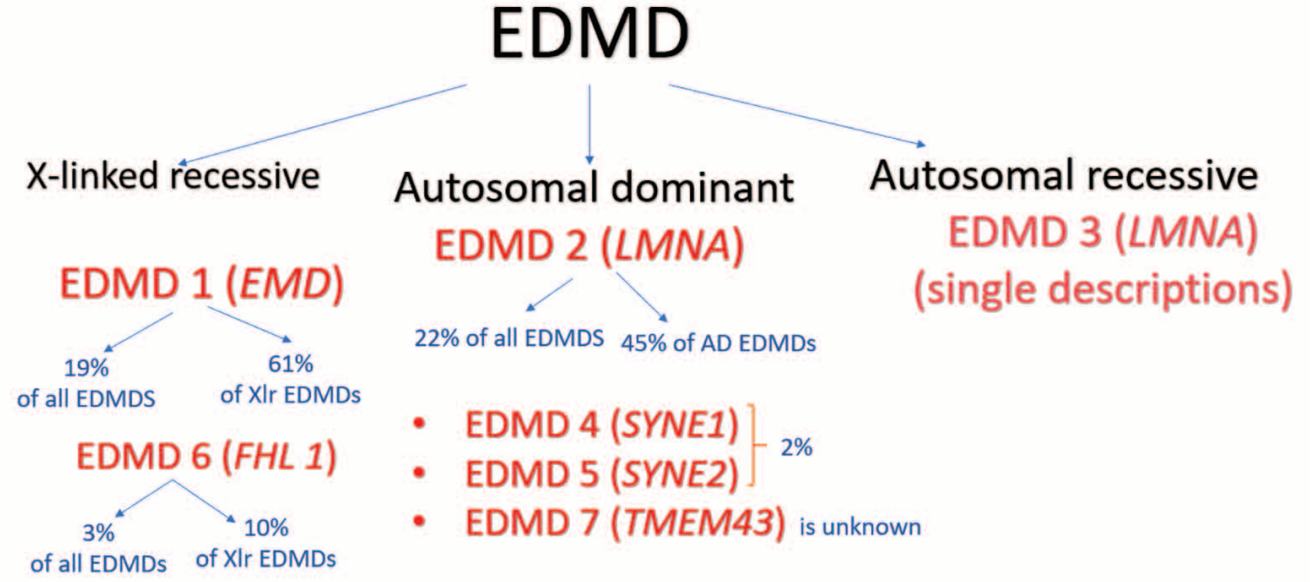

Figure 1. *7 genetic variants of Emery-Dreifuss muscular dystrophy.*
Note: EDMD — Emery-Dreifuss muscular dystrophy, EMD — emerin protein genes, LMNA — lamin protein gene, SYNE1, SYNE2 — genes of proteins nesprin-1, nesprin-2, respectively, FHL1 — gene factor H-like protein 1, TMEM43 — transmembrane protein 43. Xlr — X-linked recessive, AD — autosomal dominant

According to the Online Mendelian Inheritance in Man (OMIM) database, genes *SUN1, SUN2*, which encode homonymous proteins of the internal nuclear membrane, and *TTN* (titin-encoding gene) are also potentially associated with EDMD phenotype [7]. Mutations in genes *LMNA* and *EMD* are the most common causes of EDMD; they account for approximately 40 % of EDMD cases [2].

In 1986, when the first gene *EMD* responsible for the disease development was discovered, the molecular era of EDMD diagnostics began. Mutation in this gene causes impaired production of emerin, with the X-linked mode of inheritance [6,8].

In 1999, it was discovered that EDMD 2 is related to gene *LMNA*, localised on the long arm of chromosome 1 (q11–q230. Mutations in this gene cause defects in the structure and function of lamin A/C and clinical manifestations of EDMD; usually, the mode of inheritance is autosomal dominant [6,9].

Lamins A/C and emerin are nuclear membrane proteins and components of the nuclear lamina, which participates in the maintenance of the cellular architecture and is a frame for other factors, which participate in deoxyribonucleic acid replication, chromatin organisation and transcription [10]. Atrioventricular (AV) node cells, which do not contain lamin A, demonstrate increased nuclear deformity and apoptosis [11]. A cascade to destroy pacemaker cells and cardiac cells is triggered, resulting in gradual replacement of the myocardium with fibrous and fatty tissue. The process usually starts in atria, then involves AV node and, finally, ventricles (Fig. 2) [2].

Lamin A/C defect is characterised with a wide clinical variability, genetic heterogeneity, variety of phenotypes. In addition to EDMD2, mutations in gene *LMNA* are responsible for the development of over a dozen of diseases — laminopathies, involving various tissues (skeletal muscles, myocardium, fatty tissue, peripheral nerves), both individually and systemically (premature ageing syndrome) [12]. Cardiac manifestations of laminopathies are versatile: dilated CMP (DCMP), restrictive CMP, conduction abnormalities, atrial fibrillation/fluttering (AFib/AF), malignant ventricular arrhythmias [13,14].

Potential mechanisms of LMNA-CMP pathogenesis:

- Haploinsufficiency (one gene copy is not enough for normal protein function, where inactivation of even one of the two alleles can cause disease), which results in early death of AV node cardiac cells.
- Abnormal chromatic organisation.
- Abnormal activation of mTOR path (rapamycin target in mammals — serine/threonine kinase, participating in control of cell growth and proliferation).
- Abnormal activation of the platelet growth factor path, which results in impaired calcium metabolism [15-17].

Very often, the degree of cardiac involvement in EDMD does not correlate with the muscle weakness progression. Patients with a mild skeletal muscle damage can have severe conduction abnormalities, requiring an implantable electrocardiostimulator (ECS). Individuals with gene *LMNA* mutations often have severe DCMP and life-threatening rhythm and conduction abnormalities [18].

EPIDEMIOLOGY

This disease is rare; it affects 0.39 per 100,000 (1 per 250,000) people (Table 1) [19,20].

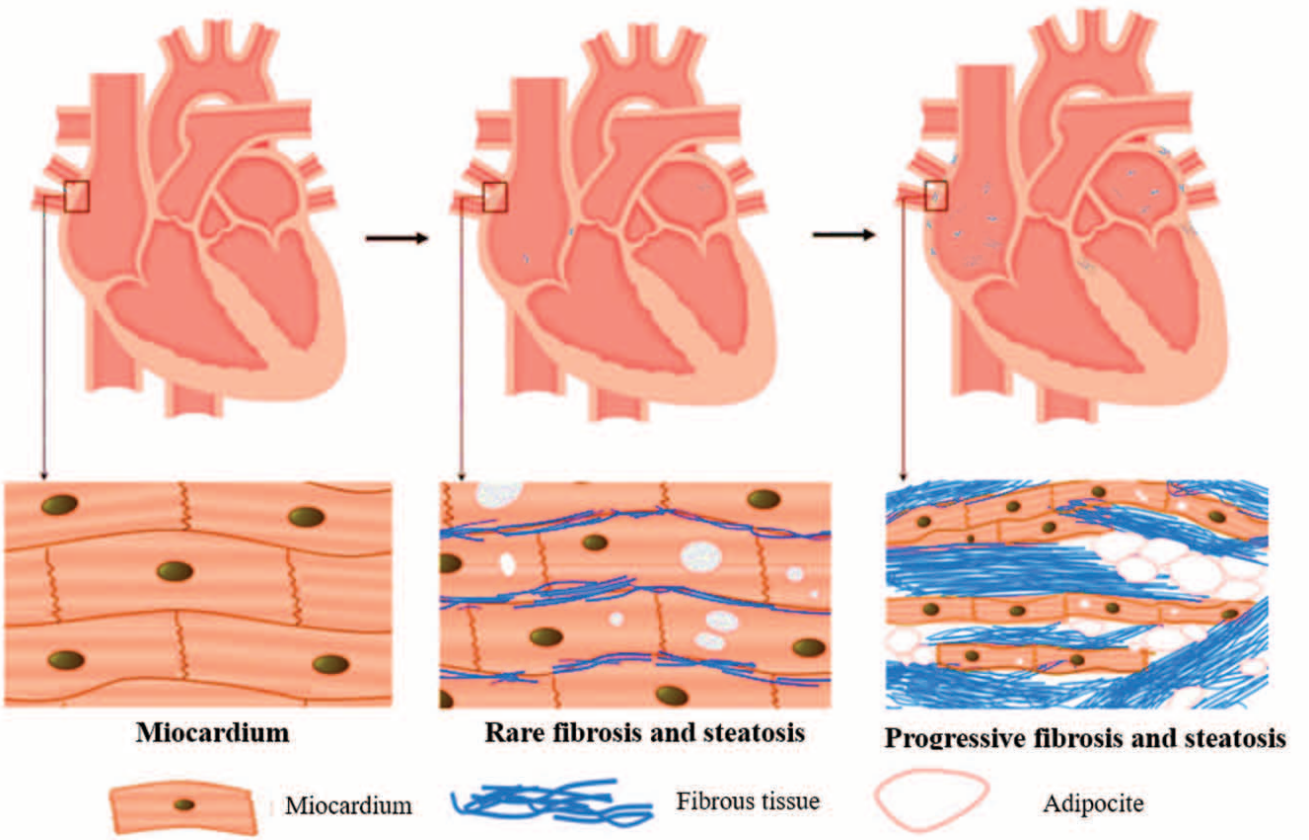

Figure 2. *Replacement of atrial myocardium by fibrosis and adipose, which can eventually affect atrioventricular node and ventricle [2]*

Table 1. *The prevalence of various types of EDMD [5,20].*

Types	Frequency of occurrence
EDMD 1	0.13 — 0.2 per 100 thousand 19 % of all EDMD
EDMD 2	22 % of all EDMD
EDMD 3	10 registered cases
EDMD 4	2 % of all EDMD
EDMD 5	
EDMD 6	3 % of all EDMD
EDMD 7	is unknown

Note: EDMD — Emery-Dreifuss Muscular Dystrophy

Diagnosis

EDMD diagnosis can be challenging due to the low incidence of this condition and similarity with other muscle dystrophies and laminopathies [13, 21].

If a muscle dystrophy is suspected, electroneuromyography and muscle biopsy are indicated; however, in EDMD and other laminopathies, results of these examinations are usually non-specific [14, 22].

An important marker of muscle dystrophies is high creatine phosphokinase levels, which can vary from normal values to 5–15-fold increase over the upper limit of normal. In patients with mostly heart involvement, creatine phosphokinase levels are within the normal range. In other words, increased creatine phosphokinase levels can be useful for the diagnosis, but normal levels do not rule out EDMD [2].

Skeletal muscle imaging can be a useful additional diagnostic tool. EDMD is characterised with scapular, shoulder and fibular muscle hypotrophy, while compensatory hypertrophy of muscles in other locations is not typical. Muscle imaging observations can contribute to the diagnosis of various muscle dystrophies [23-25].

All patients with EDMD should undergo a thorough examination of their cardiovascular system, including physical examination, ECG and Echo-CG, as well as Holter ECG monitoring [2, 14, 26-28].

ECG abnormalities in EDMD patients include atrial arrhythmias, AV arrhythmias, AV blocks. Common events are tachyarrhythmias: AFi, AF, other supraventricular and ventricular arrythmias [2]. Progressive conduction abnormalities up to complete transverse block are a common observation [29, 30].

Lazarte J., et al. (2022), who analysed the data from the UK Genetic Biobank using whole-genome sequenc-

ing (n = 185,990), found out 1,167 (0.63 %) patients with various gene *LMNA* mutations. The demonstrated the correlation between defects in lamin A/C protein and arrhythmias (AFib, bradyarrhythmias, ventricular arrhythmias, DCMP and CF (risk ratio (RR) = 2.21; p < 0.001). The incidence of arrhythmias or CMP was 43 per 1,000 person-years among carriers of defective gene *LMNA*, and 6.38 per 1,000 person-years among other, p < 0.001 [31].

EchoCG in EDMD can show DCMP. Signs of ventricular dystrophy from fibrosis can be observed. A common observation is enlarged atria as compared to ventricles, especially at early stages of diagnosis [26, 32].

Very often, magnetic resonance imaging (MRI) of the heart in patients with EDMD is not possible due to the presence of ECS.

Myocardium biopsy can show advanced atrial fibrosis, which causes EDMD. A study involving 8 patients with EDMD 2 showed the absence of any marked displacing fibrosis at Gd-enhanced MRI [32]. Heart MRI is usually used to visualise ventricles and is not widely used for atrial visualisation because adequate image resolution in thin-wall atria is impossible. In Duchenne muscular dystrophy, MRI is recommended for identification of ventricle myocardial fibrosis, which is an early sign of myocardial involvement preceding systolic dysfunction [33].

The gold standard in the diagnosis of EDMD is genetic testing, although currently it is not included in mandatory medical insurance programs. The majority of genetic tests are a sequencing analysis of a set of EDMD-associated genes, using NGS (next-generation sequencing) [34, 35].

Risk of sudden cardiac death

There are no specific scales to calculate the risk of sudden cardiac death (SCA) in patients with LNMA-CMP. In 2019, a validated scale to assess a 5-year risk of life-threatening ventricular tachyarrhythmia (LTVT) in laminopathies was developed (https://lmna-risk-vta.fr) [36]. Predictors are independent risk factors: male sex, gene *LMNA* mutation, AV block of grade 1 or above, unstable ventricular tachycardia and left ventricle ejection fraction (LV EF) of < 45 % [37]. In this scale, the 5-year estimated risk threshold of ≥ 7 % can predict 96.2 % of LTVT [36].

Wahbi K., et al. (2019) demonstrated that in patients with laminopathies (n = 444, of which 65 had EDMD), 19.3 % (n = 86) had LTVT (3.9 % of the annual morbidity; 95 % confidence interval (CI): 3.03–4.69) over a mean follow-up period of 3.6 years. Among patients with LTVT, 36 % (n = 31) had an implantable cardioverter defibrillator (ICD), 16 % (n = 14) had SCD [36,38].

Nakajima K., et al. (2018) showed that among 110 patients with gene *LMNA* mutations (60 families with laminopathies), 20 % were diagnosed with chronic CF (CCF) with LV EF of < 50 % during the first visit and in 52 % over a period of 5 years. Malignant ventricular arrhythmias (persistent ventricular tachycardia, ventricular fibrillation, SCD, ICD activation were diagnosed in 18 % during the first visit and in 42 % over a period of 5 years. 26 families (43 % of patients with laminopathies) had SCD events. Over the 5-year follow-up period, 17 deaths were recorded (19 % of patients with laminopathies), including SCD — in 4 (4 %), death caused by CF progression — in 13 (14 %), acute cerebrovascular accident (ACVA) — 1 (1 % of patients with laminopathies). It demonstrates a very unfavourable prognosis in LMNA-CMP [35,37,39].

Management

Management of patients with *LMNA*-CMP and EDMD 1 includes:

- Prevention and therapy of CVC.
- Prevention of skeletal myopathy progression, including rehabilitation exercises, mobility support and rehabilitation.
- Contracture surgery [13].

Management of patients with heart damage depends on the clinical presentation and complications.

Patients with CCF

In 2017, information appeared on the drug therapy of CF in EDMD and other neuromuscular conditions; it was concluded that the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are justified. Restricted use of beta blockers due to a high rate of AV blocks was mentioned [25,27].

In 2023, data were published on the efficacy of angiotensin II receptor antagonists and neprilysin inhibitors, sodium-glucose linked transporter 2 (SGLT-2) inhibitors in CCF in patients with *LMNA*-CMP. Reverse remodelling of left ventricle with the use of these products has been demonstrated in patients with isolated *LMNA*-DCMP [14].

Risks of TEC

One study in patients with laminopathies (n = 76) demonstrated a high incidence of atrial arrhythmias, especially AFib, which often precede ventricular dysfunction. The risk of thromboembolic complications (TEC) in patients with various abnormal variants of gene *LMNA*, including EDMD 2, is higher than in other DCMP (n = 224) (RR = 4.8, 95 % CI: 2.2-10.6; p < 0.05) [40].

Tremblay-Gravel M., et al. concluded that the high rate of AFib and higher risks of TEC in patients with *LMNA* gene mutations are a result of internal atrial myopathy [41]. Therefore, it is essential to follow the recommendations for AFib and AT in such patients. The efficiency of antithrombotic prevention in EDMD has not been studied; however, a high risk of cardioembolic strokes requires adequate prevention [42,43].

Heart rhythm and conduction abnormalities: ICD, ECS, CRT

According to the recommendations of the American Heart Association, ECS implantation is indicated in patients with EDMD with any grade of AV block, including grade one block, because of progression to complete AV block [44].

Currently, there are no clear recommendations on the use of antiarrhythmic drugs and ablation for ventricular arrhythmia in patients with *LMNA*-CMP. Given the location of substrate and a high risk of arrhythmia recurrence, no ablation for ventricular arrhythmia is indicated in these patients [45]. Sidhu K., et al. followed up patients with *LMNA*-CMP with implantable cardioverter defibrillators for primary (n = 27) or secondary (n = 16) prevention for two years. The incidence of ventricular tachycardias was significantly higher in patients with ICDs implanted for secondary prevention (28 ± 40.9 vs. 3.6 ± 7.3 episodes per 100 patient-years; $p < 0.001$) [46].

In patients with LMNA-EDMD, cardiac resynchronisation therapy (CRT) is also used, although due to its rareness the efficacy and safety in EDMD is understudied [44]. Sidhu K., et al. conducted a retrospective analysis of CRT results in patients with *LMNA*-CMP (n = 105, mean age: 51 ± 10 years). The factor, indicating positive response to CRT, was an increase in LV EF of ≥ 5 % in six months after implantation. Six months after CRT, the mean change in LV EF was 4 ± 9 %. Positive effects of CRT were observed in 38 % and were associated with a lower baseline LV EF (≤ 45 %) or high pre-CRT pacing rates (≥ 50 %) of the right ventricle in patients with an implanted ECS. In patients, who underwent CRT in strict compliance with the recommendations of the European Society of Cardiology (class I), the rate of response was 61 %. Median expected difference in survival without cardiovascular events in SRT responders was 1.3 year ($p = 0.04$). Thus, it has been demonstrated that in patients with LMNA-CMP CRT contributes to improved systolic function of LV, provided there are clear indications for implantation and survival rates [47].

Heart transplantation

Heart transplantation was described in patients with EDMD with terminal CF [48, 49]. However, heart transplantation or implantation of devices, which support LV function, in LMNA-CMP usually is not performed due to arrhythmogenic complications [48].

Promising pathogenetic methods of LMNA-CMP therapy

Currently, new promising treatment methods for patients with laminopathies have been investigated, which is possible to better diagnosis of this pathology [50]. Animal models are used to study a possible impact on mitogenic-activated protein kinase (MAPK), the pathological potential of which has been proven to increases in *LMNA gene mutations*. MAPK inhibitors have demonstrated favourable effects in mice models. In 2023, phase 2 clinical trial of low-molecular selective inhibitor of MAPK p38a — ARRY-371797 (PF-07265803) — was completed. The study evaluated the impact of the medicinal product on the functional performance of the patient and cardiac function in patients with *LMNA*-associated DCMP. Patients (n = 36) with NYHA class II–III CF were treated with ARRY-371797 100 or 400 mg twice daily for 48 weeks. The investigational medicinal product demonstrated positive results: increased functional performance of the patients and reduced concentrations of natriuretic peptide. In other words, MAPK p38a inhibition with this medicinal product can bring about a new therapeutic approach in the management of *LMNA*-CMP. Currently, a double-blind randomised placebo-controlled phase 3 study (REAL-DCM) is ongoing, which evaluates the impact of ARRY-371797 therapy on the functional performance, cardiac biomarkers and quality of life of patients with LMNA-DCMP [51].

Case Study

Until the age of 3 years old, the patient had been developing according to her age. Since the age of 3 years old, the patient had progressing gait disorder, shank and foot muscle weakness (Fig. 3). Spinal muscular atrophy was diagnosed. Then myopathy symptoms slowly progressed. Since the age of 8 years old, the patient had elbow contractures. At 11 years old, the patient started using a wheel-chair. At 14 years old, she also started having ankle joint contractures, at 20 years — knee and hip contractures, mostly on her right side.

In 2008, when the patient was 24 years old, she was diagnosed with paroxysmal AFib (150–160 bpm) for the first time. Initially, the patient had occasional paroxysm episodes once every half-year, which were treated with amiodarone. After a while, AFib episodes were more frequent; in 2015 to 2016, she was treated with cordarone, which resulted in thyrotoxicosis; for two years, she was treated with tyrosol. Since 2018, the patient has had permanent AFib. Due to a villus rectal polyp and potential haemorrhagic complications, the patient decided to withdraw from anticoagulants. Since she had acute essential oedema as a reaction to metoprolol succinate, the patient refused to take other beta blockers and was treated with ivabradine 5 mg.

At the age of 27 years old, in 2011, the patient underwent a clinical genealogical examination and DNA testing: c.745C> T mutation in gene *LMNA* was diagnosed. Hereditary history: her father had had similar symptoms since the age of two years old, and died at 27 years old from an acute cerebrovascular accident. Taking into account phenotype data, a hereditary history and DNA testing results, the following diagnosis was made: Progressing Emery — Dreifuss muscular dystrophy, autosomal dominant mode of inheritance.

Figure 3. *Patient's photo to 4 years old: she is able to walk independently, the beginning of manifestations of muscle weakness (All materials are posted with the patient's consent)*

In 2016, ECG showed grade 1 AV block. Holter ECG showed periods of asystole of over 3 s. SA node weakness (tachybradycardia syndrome) was diagnosed. An ECS was implanted.

In 2017, the patient had elevated BP (up to 200/110 mm Hg); losartan 25 mg daily was prescribed (the patient does not tolerate angiotensin converting enzyme inhibitors due to cough). June 2018: dizziness, speech disorder (dysarthria), progressing neurological symptoms — motor aphasia and moderate right-side hemiparesis. Brain CT did not show any focal lesions in the brain substance; an area of bilateral ischaemia was observed during follow-up; an ischaemic stroke was diagnosed in the vertebrobasilar system and left medial cerebral artery system. Brain CT in 2020 showed cystogliotic changes in cerebellar hemispheres and left fronto-temporal lobe. Anticoagulant therapy was recommended.

In June 2023, emergency ECS operation was reported: flat battery, broken atrial electrode. A two-chamber ECS BIOTRONIK in DDD-60 mode was re-implanted.

In September 2023, when the patient was 40 years old, she visited a cardiologist, complaining of irregular heart beat, burning pain on the left side of her chest when BP elevates to 150/100 mm Hg without any exercise stress; the episodes were managed with nitroglycerine or resolved on their own within 5 minutes. On physical examination, the overall condition was satisfactory. She is a wheel-chair user, can transfer herself to the bedside toilet and eat without assistance (Fig. 5). Skin and visible mucosa: pale, physiologically wet.

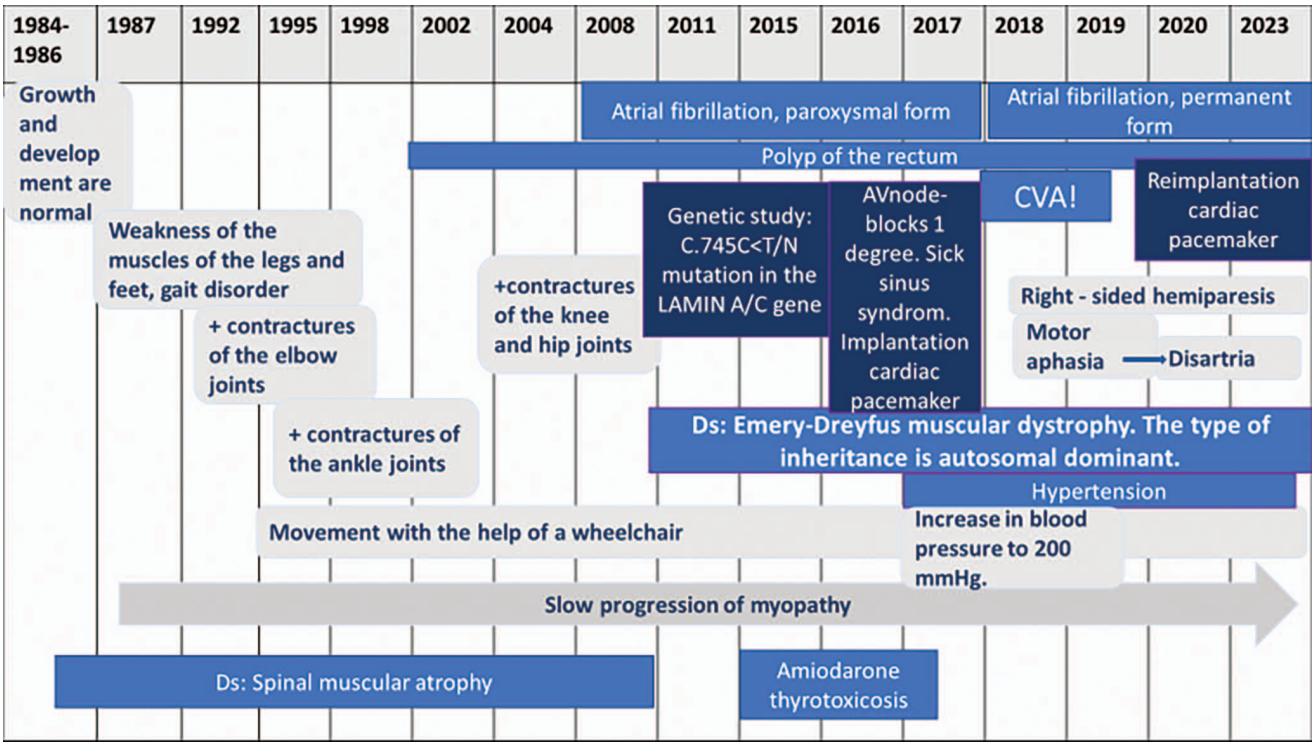

Figure 4. *Patient's anamnesis*

Body mass index: 11 kg/m^2. Neurologically: mildly flattened nasolabial fold on the right side, loss of hearing on the right, moderate dysarthria with tongue muscle atrophy. Quadriparesis with marked hypotrophy of pelvic and peroneal muscles, shoulder girdle muscles (winged shoulder blades) and muscles of proximal section of the upper and lower limbs. Diminished strength in proximal sections of her arms to 3 points, right hand — to 3 points, left hand — to 4 points, proximal and distal muscles of legs — to 3 points, with abnormal talipes varus. Elbow flexion contractures — to 110, right knee contractures — to 90, left knee contractures — to 140. Tendon reflexes are triggered by biceps on both sides, all other — by torpid. Rankin scale: 4 points. Breathing is unaided, clear, auscultatory weaker in the lower sections of the lungs on both sides. Oxygen saturation is 98 %. Region of the heart: visually unremarkable. Auscultation findings: muffled heart tones, irregular rhythm, systolic murmur in the tricuspid valve plane extending to the right axillary space and aggravating on inhalation. HR is 69 bpm, without pulse deficit. Blood pressure: 115/65 mm Hg. Abdomen is soft, painless, symmetric and engaged in respiration. Bowel movements are regular, unremarkable. Urination is unaided. No dysuria

Figure 5. *Patient's photo 40 years old (All materials are posted with the patient's consent)*

Blood biochemistry is remarkable for low-density lipoprotein levels of 2.3 mmol/L, which is outside the target range with a very high risk of CVCs in this patient (< 1.4 mmol/L). Total creatine phosphokinase level of 27 U/L is within the reference range, which is not exceptional for patients with EDMD (normal range: < 165 U/L). NTproBNP: 145 pg/mL (normal range: < 125 pg/mL, in CCF: < 300 pg/mL).

ECG shows AV rhythm, from 3rd complex — ECS rhythm; HR: 69 bpm, changes in the myocardium in the lower wall of left ventricle (Fig. 6).

EchoCG results for the period from 2017 to 2023 (Table 2) show reduced left ventricle volume, enlarged atria, higher systolic pressure in pulmonary artery, progressing tricuspid regurgitation as a result of impaired coaptation of the leaflets because of ECS (Fig. 7a, 7b).

Taking into account the complaints, past history, clinical presentation, instrumental and clinical test results, the following diagnosis can be made in this patient:

Primary disease: Progressing Emery — Dreifuss muscular dystrophy, autosomal dominant mode of inheritance; genetic testing dated 2011: mutated c.745C> T in gene LMNA, associated with LMNA-CMP.

Comorbidity: Controlled grade 3 arterial hypertension, very high risk of CVCs. Type IIB dyslipidaemia.

Complications: 1. SA node weakness (tachybradycardia syndrome). Grade 1 AV block. Permanent ECS from 2016, ECS BIOTRONIK reimplanted in June 2023 in DDD-60 mode.

2. Steady atrial fibrillation. EHRA IIA. CHA2DS2-VASC 4 points. HAS-BLED: 3 points.

3. Sequellae of past ischaemic ACVA in the vertebrobasilar system and left medial cerebral artery system in 2018; cardioembolic pathogenetic variant.

Using MOGES classification, this LMNA-CMP variant can be presented as follows [26]:

$$\mathbf{M}_{\text{ND[AF, AVB]}}\mathbf{O}_{\text{HM}}\mathbf{G}_{\text{AD}}\mathbf{E}_{\text{G LMNAc.745C<T/N}}\mathbf{S}_{\text{A-I.}}$$

MORAL-STAGE classification [52]:

$$\mathrm{M}_{\text{ND[AVB, AF]}}\mathrm{O}_{\text{H+M}}\mathrm{R}_{\text{LVTA(SCD) — 11,9 %, HF — 3.9 %-1 y.o.; 10.2 % — 3 y.o.}}$$
$$\mathrm{A}_{27}\mathrm{L}_{1}\,\mathrm{S}_{1\text{-}1}\mathrm{T}_{\text{S[AF+PM]}}\,\mathrm{A}_{\text{AF+AVB}}\mathrm{G}_{\text{AD}}\mathrm{E}_{\text{G LMNAc•745C<T/N}}$$

This patient faces a high risk of CCF: 3.9 % within 1 year, 10.2 % within 3 years. A 5-year risk of life-threatening ventricular tachyarrhythmias is 12.6 %.

The patient is recommended to continue antihypertensive therapy (losartan 50 mg daily), anticoagulant therapy (apixaban 2.5 mg twice daily). Ivabradine 5 mg was replaced with nebivolol 2.5 mg daily. Cholesterol-lowering therapy (pitavastatin 4 mg daily) was added.

Thus, the patient has the symptom triad typical for EDMD. A thorough past history evaluation and physical examination showed slowly progressing symptoms of muscle weakness and hypotrophy, early joint contractures, as well as rhythm and conduction abnormalities.

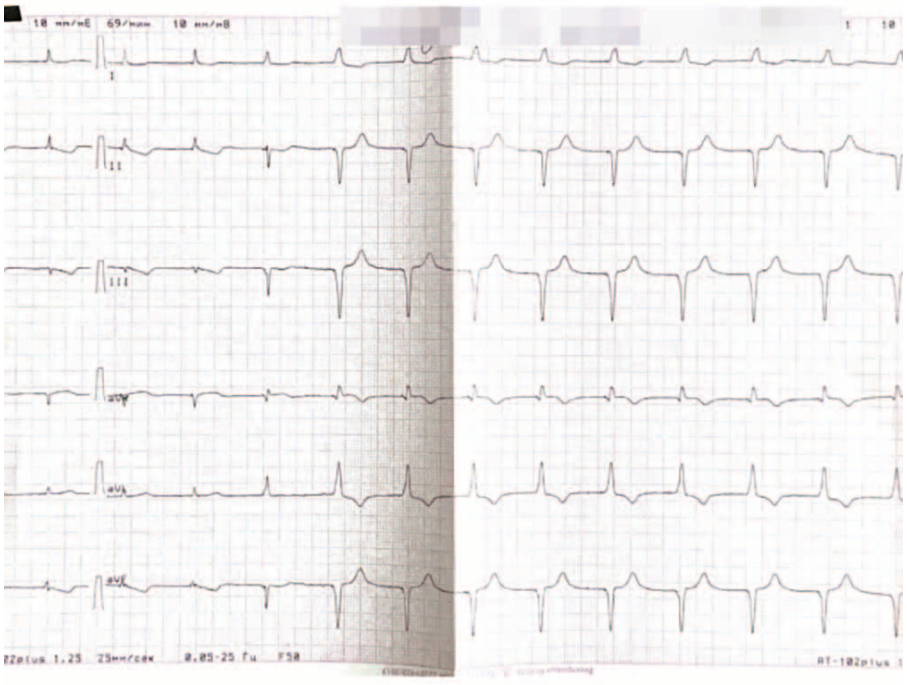

Figure 6. *ECG from September 2023*

Table 2. *Echocardiography parameters from 2017 to 2023*

Echo parameter	2017	2020	2023
IVSTd, cm	0.7	0.8	0.55
LV PWTd, cm	1.0	0.8	0.55
LV EDV, ml	79	-	46
LV ESV, ml	32	-	15
LV EF, %	60	69	66
LV ESD, cm	3.8	2.1	2.51
LV EDD, cm	4.2	3.6	4.59
RA, cm RA V, ml	3.9x3.6 33	4.0x3.5 44	4.54x4.79 59
LA, cm LA V, ml	3.3 38	3.6 40	3.75 57
RV EDD, cm	2.5	2.5	2.37
PASP, mm Hg	28	33	39
Doppler ECHO	MR I TR II PR I	MR I TR II PR I	MR I TR III PR I

Note: IVSTd — thickness of the interventricular septum in the diastole; LV — left ventricle, PWTd — thickness of the posterior wall in the diastole; EDV — end-diastolic volume; ESV — end-systolic volume ; EF — ejection fraction; ESD — end-systolic dimension; EDD — end-diastolic dimension; RA — right atrium; LA — left atrium; V — volume; RV — right ventricle; PASP — systolic pressure of the pulmonary artery; MR — mitral regurgitation, TR — tricuspid regurgitation, PR — pulmonary regurgitation

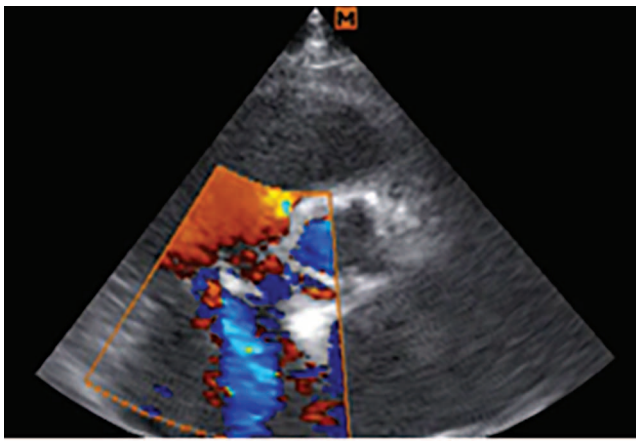

Figure 7a. *Parasternal short axis view. Color Doppler mapping mode. Tricuspid regurgitation (Blue flow)*

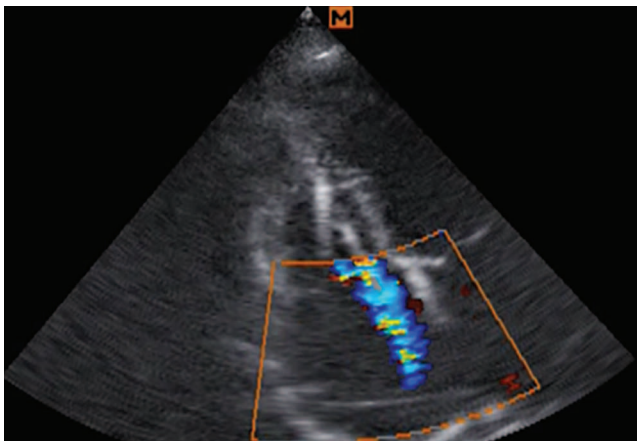

Figure 7b. *Apical four-chamber view. Color Doppler mapping mode. Tricuspid regurgitation (Blue flow)*

Therefore, a genetical cardioneurological disease was suspected; genetical testing was performed, the results of which enabled us to make the final diagnosis of EDMD with resulting LMNA-CMP.

Conclusion

Type 2 Emery — Dreifuss muscular dystrophy and other laminopathies are rare conditions; their common sign is *LMNA* gene mutation with similar phenotypes of cardiac involvement — LMNA-CMP.

A case study is described, and the clinical course of the disease is presented; CMP is defined and classified according to the latest recommendations of the European Society of Cardiology, MOGES, MORALSTAGE; risks of CCF and SCD for this patient were calculated.

Despite an inadequate level of knowledge of rare genetic conditions, patient management should take into account generally accepted strategies of CVC prevention, i.e. timely anticoagulant therapy in AFib to prevent TEC, taking into account high risks of conduction abnormalities, LTVT, SCD; early use of ECS/ICD/CRT should be considered to preserve the quality of life and improve prognosis. Management of patients with EDMD and LMNA-CMP requires a multidisciplinary team of specialists: neurologist, cardiologist, arrhythmia and rehabilitation specialists, GP, orthopaedist, genetic specialist, etc.

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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Kovaleva A.A.: concept development, writing the text of the article, data collection and processing of the material, communication with the patient, providing illustrations, interaction with the editorial board in the process of preparing the publication and printing

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Comments from the patient

I was born in Penza; I moved to Moscow when I was 23 years old and have been living there for 15 years. I attended the Penza Branch of the International Independent University of Environmental and Political Sciences to become a psychologist, but then I did not pursue my profession. At one point, I realised that I did not want to hear complaints of absolutely healthy and successful people. I moved beyond and in 2016 was qualified as a stylist. This year, I've learnt the basics of a profession, which gains popularity day by day — SMM specialist. I also organised concerts in child care homes on my own. Later it became my profession, and I was a project manager in a charitable trust for 15 years.

I've been a wheel-chair user since the age of 11. I have a genetic condition — muscle dystrophy, but it has never prevented me from communicating with people. When a child, I was on friendly terms with all children around me. We used to play together, sneak to nursery to get apples, and ride on a merry-go-rounds. We had a happy childhood!

I could not accept the wheel-chair and myself in it for over a year, although my transition to the wheel-chair was gradual. Some time later, I realised that I had no choice. Even those in a wheel-chair can have an interesting and happy life.

To those who have never been in a wheel-chair, I would like to remind: we are not different! We just need more comfort. We are happy when you do not take our parking spaces, when you do not step on the toilet seats in accessible toilets.

If you see someone in a wheel-chair, do not be afraid to ask if they need help. Do not stop children when they take interest in disabled people. Just be ready to explain to your child that we move around differently. Be more sensitive and do not be afraid to show your love.

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ТЯЖЕЛОЕ СОЧЕТАННОЕ ПОРАЖЕНИЕ ПОЧЕК У ВИЧ-ИНФИЦИРОВАННОЙ ПАЦИЕНТКИ, ПОЛУЧАВШЕЙ АНТИРЕТРОВИРУСНУЮ ТЕРАПИЮ (КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ)

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Severe Combined Kidney Injury in an Hiv-Infected Patient Receiving Antiretroviral Therapy (Clinical Observation)

Резюме

Спектр почечной патологии у лиц, инфицированных вирусом иммунодефицита человека (ВИЧ), многообразен. Успешное применение антиретровирусной терапии (АРВТ) сопряжено с нефротоксическим эффектом некоторых препаратов. Представляем клиническое наблюдение тяжелого сочетанного поражения почек — хронической и острой болезни почек (ХБП, ОБП) — у пациентки с ВИЧ-инфекцией стадия 3 (субклиническая), длительно принимавшей трехкомпонентную схему АРВТ (комбинированный препарат с фиксированной дозой рилпивирина гидрохлорид, тенофовира дизопроксил фумарат, эмтрицитабина (~~эвиплер~~)) и имевшей на момент начала лечения нормальную почечную функцию (расчетная скорость клубочковой фильтрации 69 мл/мин/1,73м^2). У пациентки регистрировалось постепенное нарастание креатинина крови, она не наблюдалась нефрологом, ей не проводилась коррекция АРВТ. Через два года зарегистрированы артериальная гипертензия и гиперазотемия (креатинин крови 718 мкмоль/л). С учетом постепенного нарастания креатинина крови и длительного проведения АРВТ диагностирован хронический тубулоинтерстициальный нефрит, ХБП 5 ст., начата заместительная почечная терапия перитонеальным диализом. Через 9 мес. отмечено стойкое снижение и стабилизация креатинина крови в диапазоне 210-190 мкмоль/л, что свидетельствовало о перенесенной ОБП. Представленное наблюдение демонстрирует возможность развития тяжелого сочетанного поражения почек — ХБП и ОБП при проведении АРВТ у ВИЧ-инфицированной пациентки. Регулярный мониторинг функции почек и динамическое наблюдение нефрологом необходимы для предотвращения и своевременного выявления повреждения почек у ВИЧ-инфицированных пациентов и коррекции АРВТ.

Ключевые слова: *вирус иммунодефицита человека (ВИЧ), антиретровирусная терапия, хроническая болезнь почек, острое повреждение почек/острая болезнь почек*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Kidney injury in patients infected with the human immunodeficiency virus (HIV) has a diverse spectrum. Some antiretroviral therapy (ART) drugs have nephrotoxic effects. We present a clinical case of severe combined kidney injury — chronic kidney disease (CKD) and acute kidney disease (AKD) — in a patient with HIV infection. She was on long-term treatment with a fixed-dose combination of rilpivirine, tenofovir, and emtricitabine and had normal pre-treatment renal function (estimated glomerular filtration rate 69 mL/min/1.73m^2). There was gradual increase in blood creatinine, but the patient did not visit a nephrologist and the ART was not changed. The patient was admitted to the nephrology department two years later because she had arterial hypertension and hyperazotemia (blood creatinine 718 μmol/l). Diagnosis: chronic tubulointerstitial nephritis, CKD G5 taking into account the gradual increase in blood creatinine during long-term ART. The patient was treated with peritoneal dialysis. There was persistent decrease and stabilization of blood creatinine (210-190 μmol/l was) which indicated in AKD. The presented observation demonstrates that ART in an HIV-infected patient can lead to the development of severe combined chronic and acute kidney injury. HIV-infected patients receiving ART require regular monitoring of renal function and follow-up by a nephrologist

Key words: *Human immunodeficiency virus (HIV), antiretroviral therapy, chronic kidney disease, acute kidney injury/acute kidney disease*

Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article « Severe Combined Kidney Injury in an Hiv-Infected Patient Receiving Antiretroviral Therapy» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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BP — blood pressure; ART — antiretroviral therapy; HIV — human immunodeficiency virus; ATN — acute tubular necrosis; AKI — acute kidney injury; AKD — acute kidney disease; PD — peritoneal dialysis; eGFR — estimated glomerular filtration rate; CKD — kidney disease; CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration

Introduction

The incidence of kidney damage in patients with human immunodeficiency virus (HIV), depending on a geographic region, varies a lot, while kidney diseases are versatile. These include glomerular renal pathologies: less common classic HIV-associated nephropathy and more common immunocomplex renal pathologies, manifesting as polymorphous morphological changes in renal tissue, as well as tubulointerstitial and vascular kidney damage. A renal pathology can be primary, caused by direct cytopathic effects of HIV on renal tissue, or mediated by continuous antigen challenge, production of anti-HIV antibodies, and formation of immune complex deposits in kidneys. Secondary renal pathologies are associated with a comorbid pathology, concurrent infectious and non-infectious diseases, antiretroviral therapy (ART), and therapy with other categories of nephrotoxic drugs. Clinical manifestations of a primary and secondary kidney pathology in HIV are similar and include acute nephritic and/or nephrotic syndrome, impaired renal function, arterial hypertension [1, 2].

So far, the large scale use of ART has secured significant success in HIV management. Development of a variety of antiretroviral agents has changed both the course of HIV infection (which is now chronic) and disease prognosis. At the same time, successful use of ART in HIV patients brought about new nephrological problems, related mostly to nephrotoxic effects of some antiretroviral agents and an increase in the incidence of non-infectious pathologies associated with chronic kidney disease (CKD): arterial hypertension, diabetes mellitus, other vascular diseases. ART can cause various kidney conditions: acute kidney injury (AKI), acute and chronic tubulointerstitial nephritis, crystal-induced intrarenal obstruction, tubulopathy; less common — Fanconi's anemia, renal diabetes insipidus, stone disease [3-6].

A serious renal pathology, the incidence of which in HIV patients is growing due to the active use of ART, is AKI. According to recently published meta-analyses and systematic reviews, the incidence of AKI in HIV patients in China was 12.5 %, while in Africa the figure was twice as high (23.35 %) [7, 8]. In a number of cases, signs of AKI are persistent for a long time, evidencing the development of acute kidney disease (AKD). AKI, AKD and CKD often go hand-in-hand: CKD can precede acute kidney injury or can develop after AKI/AKD. The relative risk of AKI/AKD in CKD patients with HIV is high. AKI/AKD in HIV patients is associated with

life-threatening complications and is the most significant cause of hospitalisation and mortality. The development paths of an acute renal pathology have been understudied; however, studies in this area demonstrate that the predisposing factors include HIV, poor control of HIV infection, elderly age, low Hb levels, side effects of ART, and comorbidities.

One of AKI/AKD variants in HIV patients undergoing ART is acute tubulointerstitial nephritis. It is caused by an immune-mediated reaction to an antiviral drug. The diagnostic criterion of acute tubulointerstitial nephritis is high blood creatinine levels, either isolated or together with clinical symptoms — fever, abdominal or lower back pain, eosonophilia and eosinophiluria, sometimes persistent aseptic leukocyturia. In some cases, acute tubulointerstitial nephritis can be complicated by concomitant acute tubular necrosis (ATN). Morphological examination of a renal biopsy material shows signs of interstitial inflammation and tubulitis [9, 10]. Usually, symptoms of renal injury regress after drug discontinuation, and blood creatinine levels normalise within several weeks. Some patients, however, had irreversible changes — gradual reduction in kidney function, probably due to transformation of acute tubulointerstitial nephritis to chronic tubulointerstitial nephritis.

The close connection between HIV infection and ART with renal pathology indicates the need for strict nephrological control and regular monitoring of the renal function in HIV positive patients. However, the real-life clinical practice shows that not all HIV patients, including those undergoing ART, are referred to a kidney specialist or regular nephrological check-ups. The following case study of a female HIV patient undergoing combined ART, which resulted in a complex kidney damage — CKD and AKI/AKD — confirms the narrative.

Case Study

Patient S., born in 1963. No family history of kidney diseases. Previous diseases: tonsillectomy, acute infectious hepatitis, left axillary lipoma excision, tooth implants. Pregnancies: 2 (delivery — 1, abortion — 1). Bad habits: occasional smoker (1–2 cigarettes/day). Allergies: denies. COVID-19 vaccinated.

The patient has a long history of moderate arterial hypertension, with elevations in blood pressure (BP) up to 140–150/90–100 mm Hg; she occasionally takes antihypertensive drugs (losartan, nifedipine). She has been followed up by an endocrinologist due to hypothyroidism, which was diagnosed several years ago, and takes levothyroxine sodium 75 μg daily.

According to the patient, at the age of 56 years old, she was diagnosed with HIV, stage 3 (subclinical stage), when she was undergoing examination for a surgery (lipoma excision). She was prescribed a three-component ART: two nucleoside/nucleotide reverse transcriptase inhibitors (emtricitabine 200 mg, tenofovir disoproxil fumarate 300 mg) in combination with a non-nucleoside reverse transcriptase inhibitor (rilpivirine hydrochloride 27.5 mg) (Eviplera, 1 tablet daily). Two weeks after ART initiation, the patient experienced oedema and joint pain in her upper and lower extremities. She underwent inpatient treatment in a hospital at the place of her residence for primary generalised osteoarthritis. Complete blood count: Hb 151 g/L, WBC $5.5x10^9$/L, ESR 25 mm/h. Urinalysis: unremarkable. Biochemical blood count: creatinine 82 μmol/L, estimated glomerular filtration rate (eGFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula 69 mL/min/1.73 m^2, urea 5.0 mmol/L, uric acid 435 μmol/L, total protein 81 g/L, cholesterol 4.7 mmol/L, glucose 4.9 mmol/L, bilirubin 10 μmol/L, AST 28 U/L, ALT 43 U/L, CRP 196 mg/L. Liver and kidney ultrasound: hepatomegalia, fatty hepatosis, diffuse changes in pancreas and kidneys. Hand X-ray: signs of small joint arthrosis. The patient was treated with dexamethasone (1 mg daily per os), prednisolone (25 mg daily with dose tapering until complete discontinuation), non-steroidal anti-inflammatory drugs, with positive changes: oedema and arthralgia resolved.

The patient is followed up by the specialists from the AIDS and Infectious Diseases Center. Continued ART with Eviplera; a routine laboratory examination was performed: CD4+ T lymphocytes are consistently over 200 cells/μL, HIV RNA is below 4,000 copies/mL. The patient noted a gradual increase in creatinine levels to 90–150–200 μmol/L (eGFR 61–33–24 mL/min/1.73 m^2); no changes in ART regimen; the patient failed to come to an appointment to the kidney specialist.

Significant deterioration in condition was observed 2 years after ART initiation: rising weakness, epigastrium and mesogastrium pain, nausea, repeated episodes of vomiting, persistently elevated BP up to 170/100 mm Hg. The patient was examined by GP, who diagnosed exacerbation of chronic pancreatitis; minor increase in blood alpha-amilase to 127 U/L (normal range: 28–100 U/L). Consultation by an infection disease doctor and laboratory tests. Complete blood count: Hb 132 g/L; WBC 6.7×10^9/L; platelets 235×10^9/L; biochemical blood count: creatinine 718 μmol/L, urea 18 mmol/L. Eviplera was replaced with dolutegravir 50 mg daily and doravirine 100 mg daily. The patient was consulted by a kidney specialist and referred to hospitalisation to the dialysis ward.

Upon admission, her condition was moderately severe. Height 167 cm, weight 70 kg (body mass index 27.3 kg/m^2). BP 150/90 mm Hg. Clear rhythmic heart tones; 76 bpm. Diuresis 1.5 L/day. Complete blood count: moderate anaemia, normal white blood cell differential; urinalysis: specific gravity: 1,008, protein: 0.5 g/L; WBC, RBC: 1 per HPF. Biochemical blood count confirmed hyperazotaemia; metabolic acidosis was diagnosed: pH 7.23, bicarbonate 17.6 mmol/L, lactic acid 0.7 mmol/L. Kidney ultrasound: kidney position and shape are normal, the size is within the normal range

(length 198 mm, width 51 mm), with even, clear margins; parenchyma is moderately echogenic, up to 16 mm thick, the layer differentiation is preserved; the vascular pattern is moderately depleted and traceable up to the capsule; the collecting system is not dilated; no stones were observed. Doppler sonography of renal vessels: no signs of stenosis.

Taking into account gradually increasing serum creatinine levels after long-lasting ART with nephrotoxic drugs, it was established that the condition had deteriorated because of chronic tubulointerstitial nephritis, stage 5 CKD. A peritoneal catheter was installed, and the patient was included in the automated peritoneal dialysis (PD) program: 20 L daily with low-osmolarity and medium-osmolarity solution. A peritoneal equilibration test using the ratio between creatinine concentration in dialysate and plasma (dialysate creatinine/plasma creatinine = 0.53) established moderately low transport properties of the peritoneum. The PD program was consistently adequate for the clearance of nitric metabolites and liquids: total urea clearance 2.3–2.5/week, total creatinine clearance 63–83 mL/week, ultrafiltration 0.5–0.7 L/day, residual diuresis 1.0–1.2 L/day. Changes in laboratory test results of patient S. are presented in the table.

Patient's condition during PD remained satisfactory. Weight: 70 kg, stable. BP 130–135/80–85 mm Hg on combined antihypertensive therapy (losartan 50 mg daily, amlodipine 5 mg daily, bisoprolol 5 mg daily). Three months after PD initiation, the patient experienced elevation of serum cholesterol levels to 8.1 mmol/L, low density lipoprotein cholesterol to 4.6 mmol/L, triglycerides to 5.0 mmol/L, reduction in high density lipoprotein cholesterol to 0.83 mmol/L. Rosuvastatin 5 mg daily was prescribed (safety of rosuvastatin was evaluated in the AURORA study in patients undergoing haemodialysis [11] and in a study of PK profile in patients undergoing PD [12]). ART remained the same according to the infection disease doctor's recommendations. After nine months of PD therapy, the following results were observed: reduction in blood creatinine and urea levels, regression of anaemia, normalised serum phosphorus, low density lipoprotein cholesterol and triglycerides reduced to 3.5 mmol/L and 4.1 mmol/L, respectively; high density lipoprotein cholesterol levels reached 1.1 mmol/L. Hydrodiuresis, proteinuria of 320 mg daily, normal urinary sediments were observed. The PD program was terminated. The patient was discharged from the dialysis ward with the following diagnosis: Primary disease. Drug-induced chronic tubulointerstitial nephritis. Chronic kidney disease, C4, A3. Hypertensive disease, stage 3, uncontrolled arterial hypertension. Dyslipidemia. Proteinuria. Cardiovascular risk 4 (very high). Target BP: below 130/80 mm Hg. Comorbidities: HIV infection, stage 3 (subclinical). Condition after acute kidney disease and peritoneal dialysis. Primary hypothyroidism, medicated compensation.

Table. *Dynamics of laboratory examination results of patient S.*

Blood parameter	Before starting peritoneal dialysis	Peritoneal dialysis treatment, months				After peritoneal dialysis treatment, months				
		1	3	6	9	1	3	6	12	18
Hemoglobin, g/L	114	95	105	121	125	123	141	146	145	136
Leucocytes, ×109/L	5,9	6,6	7,6	9,2	8,7	8,1	8,7	7,8	8,8	7,2
Platelets, ×109/L	347	355	336	459	278	394	327	326	304	300
Potassium, mmol/L	4,0	3,8	4,0	4,5	4,4	4,4	4,5	4,7	4,4	5,1
Total protein, g/L	77	70	76	81	73	73	77	84	76	82
Albumin, g/L	39	38	41	41	40	39	47	49	45	47
Creatinine, μmol/L	570	481	455	359	233	186	180	186	167	201
Urea, mmol/L	18,8	18,4	19,1	8,9	8,1	5,0	6,0	6,3	7,2	9,3
Uric acid, μmol/L	284	389	300	323	334	335	376	409	347	354
Alanineaminotransferase, U/L	19	10	15	11	13	17	15	14	15	31
Aspartateaminotransferase, U/L	8	6	9	7	8	10	9	11	9	20
Cholesterol, mmol/L	5,2	5,8	8,1	8,3	8,7	7,6	6,0	4,9	4,6	4,8
Calcium total, mmol/L	2,45	2,2	2,62	2,61	2,51	2,46	2,47	2,59	2,57	2,35
Phosphorus, mmol/L	1,38	1,65	1,53	1,62	1,23	1,27	1,19	1,27	1,15	1,32
Glucose, mmol/L	5,3	4,4	5,3	6,0	6,1	5,8	5,2	6,1	5,4	5,1

The patient was provided with recommendations on renoprotective therapy to eliminate/mitigate primary modifiable risk factors associated with progressive kidney dysfunction:

- Reduction of protein intake to 0.5–0.6 g/kg/day; replacement of some animal proteins with vegetable protein; sodium chloride intake of max. 5 g/day, potassium — max. 2–3 g/day, phosphorus — max. 800–1000 mg/day due to intake of animal proteins with the phosphorus/protein ratio of max. 12–14 mg/kg, and elimination of products with phosphate-containing additives, as well as purine-rich products.
- Strict BP monitoring with the target BP of 125/75 mm Hg: intake of antihypertensives (losartan 50–100 mg daily, bisoprolol 5 mg daily).
- Dyslipidemia correction: atorvastatin 20 mg daily (monitoring of changes in fats, ALT and AST, creatine phosphokinase activity).

Dispensary observation by a kidney specialist and at the dialysis centre was recommended as well, with quarterly complete and biochemical blood counts (Hb, creatinine, urea, uric acid, blood electrolytes, albumin, ferritin/transferrin saturation, parathyroid hormone).

During the first year after PD discontinuation, blood creatinine stabilised; however, it remained persistently high — 186–167 μmol/L (eGFR: 24–28 mL/min/1.73 m^2); remaining biochemical blood parameters normalised; diuresis: 3.1 L/day; urinalysis: specific gravity: 1,006, protein: 0.1 g/L, WBC, RBC: 1 per HPF. One and a half years (May 2024) after PD discontinuation, further reduction in kidney function was observed (creatinine: 201 μmol/L, eGFR: 23 mL/min/1.73 m^2); dyslipidemia: low density lipoprotein cholesterol: 2.4 mmol/L, high density lipoprotein cholesterol: 1.05 mmol/L, triglycerides: 3.3 mmol/L. Renoprotective therapy and follow-up by a kidney specialist continued.

The patient is being followed up by an infection disease doctor. Recent examination results (May 2024): CD4+ T-lymphocytes: 1,116 cells/μL (42 %), viral load: less than 40 copies/mL; ART regime remains the same: doravirine 100 mg daily and dolutegravir 50 mg daily.

Discussion

Currently, CKD is one of the most common non-infectious comorbidity in chronically ill HIV patients who undergo combined ART. This situation necessitates regular monitoring and examination of HIV positive patients by a kidney specialist; however, this patient came onto the radar of a specialist two years after ART initiation when she already had severe hyperazotaemia. Did the patient have CDK caused by arterial hypertension when she was diagnosed with HIV infection? Likely not, since two weeks after inpatient ART initiation she had normal urinalysis results and eGFR of > 60 mL/min/1.73 m^2, however, she did not undergo any albuminuria examinations.

CKD development and progression in HIV patients is associated with a combination of factors, including: (1) socio-demographic factors, (2) factors directly related to HIV, (3) non-infectious comorbidity, (4) coinfections, and (5) side effects from drugs [13]. Patient observation shows that ART has the primary role in the development of renal insufficiency. Susceptibility to kidney damage during ART increases (1) with a certain physical status: in this case, this is female sex, presence of arterial hypertension and, later, a history of AKD; (2) clinical characteristics of HIV infection: progression with a reduction in CD4+ T lymphocytes and increased viral load, not observed in this patient; and (3) the use of some therapy regimens: concomitant use of several nephrotoxic drugs for a long period of time. This is the latter factor (the use of a combined product containing tenofovir disoproxil fumarate, which is very nephrotoxic due to its renal elimination and weak ability to bind with plasma proteins, and rilpivirine, which causes tubular dysfunctions) led to renal insufficiency in this patient [4, 14].

Studies show that inclusion of tenofovir disoproxil fumarate in ART regimens can cause serious nephrotoxic side effects: chronic tubulointerstitial nephritis with reduced eGFR, toxic damage to proximal tubules and ATN, Fanconi's anaemia, nephrogenic diabetes insipidus. The probability of renal dysfunction in patients treated with tenofovir increases in elderly people with anaemia, lower baseline eGFT and higher viral load [6, 10, 15, 16]. Although the patient did not have these risk factors except for the age of over 50 years old, she developed a complex kidney injury. Gradual increase in creatinine levels and high azotaemia levels at admission were highly indicative of the development of chronic tubulointerstitial nephritis and CKD. Patient follow-up and partially recovered renal function with long-lasting peritoneal dialysis give reasons to assume concomitant severe ATN and development of AKD. It is highly probable that kidney biopsy would have made it possible to diagnose a combination of CKD and AKD; however, due to the patient's serious condition, the need for urgent dialysis and no clinical justification of the procedure in tenofovir-associated kidney injury, no biopsy was performed [17]. Thus, long-lasting ART with nephrotoxic drugs in this HIV positive patient resulted in CKD, which caused AKD. CKD is confirmed by persistent loss of kidney function after AKD resolved. It is highly likely that early detection of an increase in blood creatinine and ART regimen adjustments would have resulted in complete regression of kidney injury or would have prevented AKD and further progression of CKD.

The years-long real-life clinical experience and study results are convincing: HIV infection, ART and kidney pathologies are closely related [1, 2, 5, 13, 17]. During primary diagnosis of HIV infection and ART planning, patients have their kidney injury markers (urinary sediment, albuminuria/proteinuria), baseline kidney function (eGFR) and risk factors of a kidney disease assessed.

In normal kidney function and no risk factors, nephrological examinations are performed on a yearly basis; in impaired kidney function, presence of risk factors, as well as ART with tenofovir or atazanavir, assessments are performed two to four times a year. In addition to examination of kidney function and kidney damage markers, BP, carbohydrate and lipid metabolism are monitored [13, 17].

HIV patients with diagnosed CKD require joint follow-up by an infection disease doctor and kidney specialist. The infection-related component of joint follow-up of such patients includes correction and adequate selection of an ART regimen taking into account kidney function. In patients with significantly decreased eGFR, combined nephrotoxic antiviral agents with a fixed active ingredient dose are inadvisable. The nephrological strategy depends on the cause of CKD, degree and rate of kidney function impairment, and the nature of concomitant complications typical of CKD. The renoprotective therapy has an important role to play; it is designed to slow down CKD progression and prevent development of cardiovascular pathologies and other complications. In addition to general recommendations (diet), the renoprotective therapy in HIV patients is somehow different. It requires maintaining a target BP of 125/75 mm Hg, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, irrespective of BP values, as well as statins in patients with a high cardiovascular risk [17-19].

Conclusion

HIV patients undergoing ART with nephrotoxic agents are at a higher risk of kidney damage — CKD and AKI/AKD. Regular laboratory monitoring and follow-up by a kidney specialist will facilitate early detection of kidney dysfunction and timely ART adjustments, thus ensuring recovery of kidney function, prevention of AKI/AKD, as well as prevention of progression and CKD complications.

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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

Vetchinnikova O.N.: design development, scientific consultation, writing and editing the text of the manuscript, review of publications on the topic of the article, interaction with the editors in the process of preparing the publication for publication

Suslov V.P.: review of publications on the topic of the article, writing a clinical case

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