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RATIONAL ANTIHYPERTENSIVE THERAPY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

Abstract

Background. The relationship between obstructive sleep apnea (OSA) and hypertension is well known. In numerous studies, obstructive sleep apnea was found to be an independent predictor of the development of resistant hypertension (RH), and the severity of apnea directly correlated with the severity of RH with the exception of such confounders as age, obesity, and gender. **The objective** of this publication is to present a new strategy and modern approaches of drug and non-pharmacological therapy of resistant hypertension in patients with OSA with the possibility of their implementation in real clinical practice. **Conclusion.** Currently, for a practitioner, the therapy of the patient with OSA and RH is a serious clinical task. A new rational therapeutic strategy for the treatment of such patients includes a combination of three-component drug therapy and non-pharmacological continuous positive air pressure therapy (CPAP therapy). A reasonable duration of CPAP therapy should exceed 12 weeks. The proposed strategy for the treatment of patients with OSA + RH has the highest efficiency in achieving target blood pressure levels and significantly reduces the risks of fatal cardiovascular events.

Keywords: *antihypertensive therapy, obstructive sleep apnea, resistant hypertension, CPAP therapy.*

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AHT — antihypertensive therapy, CAs — calcium antagonists, CCBs — calcium channel blockers, ARBs — angiotensin II receptor blockers, AHI — apnea-hypopnea index, ACEIs — angiotensin-converting enzyme inhibitors, OSA — obstructive sleep apnea, ARF — acute respiratory failure, RAAS — renin-angiotensin-aldosterone system, RH — resistant hypertension, RCTs — randomized clinical trials, SNS — sympathetic nervous system.

Introduction

There is now a clinical definition of obstructive sleep apnea (OSA), which was achieved through consensus among pulmonologists, cardiologists and sleep medicine professionals.

Obstructive sleep apnea (OSA) is a heterogeneous parasomnia (sleep-related) disorder characterized by pharyngeal collapses (respiratory pauses longer than 10 sec) during sleep period with preserved respiratory efforts, frequent nocturnal desaturations (reduced arterial oxygen saturation) and daytime signs (excessive sleepiness, hypertension, cardiac arrhythmias, insulin resistance, metabolic disorders) varying in time and intensity and associated with the severity of the disease (Figure 1) [1]. The severity of the disease is described by the total number of events of pharyngeal narrowness (hypopnea) and occlusion (apnea) per 1 hour of sleep-state monitoring (Apnea-Hypopnea Index, AHI). AHI higher than 5 events/hour corresponds to the onset of the disease. AHI of 5 to 15 events/hour corresponds to mild disease, AHI of 15 to 30 events/hour — to moderate disease, and AHI over 30 events/hour — to severe disease [2].

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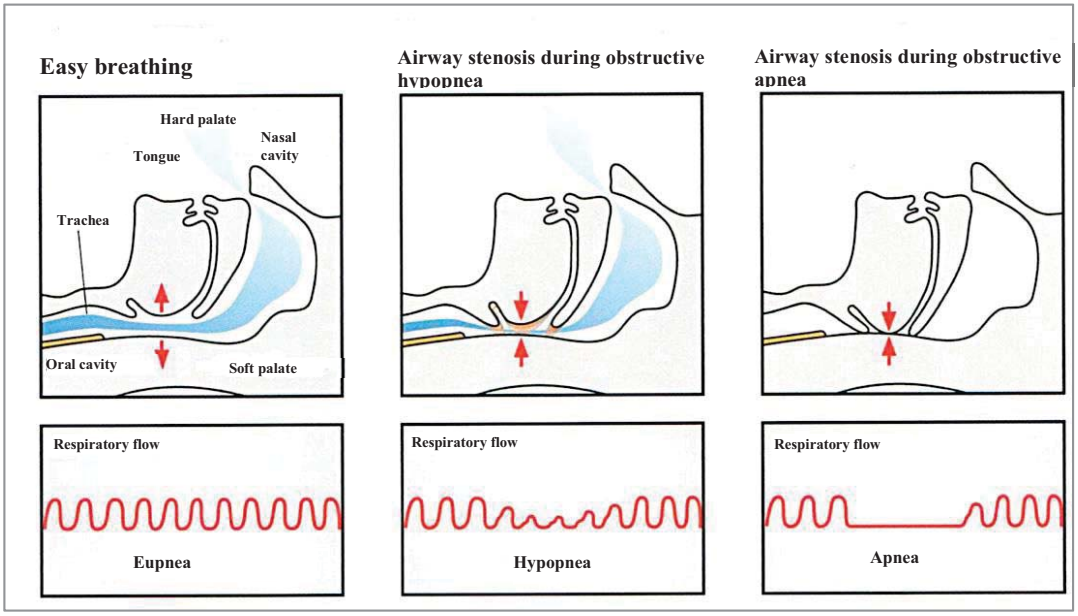

Figure 1. *The mechanism of development of sleep apnea-hypopnea with a decrease in oropharynx muscle tone during sleep (adapted from Bradley T.D., Floras J.S. Sleep apnea and heart failure: Part I: obstructive sleep apnea. Circulation. 2003; 107: 1671–8)*

The relationship between OSA, risk factors for vascular diseases, metabolic disorders and vascular diseases was described in major prospective clinical studies [3, 4]. Moreover, it was found that sleep apnea was an independent predictor of the development of hypertension, and OSA severity correlated to the blood pressure (BP) level when adjusted for age, obesity and gender [5]. Logan et al. (2001) first verified resistant hypertension (RH) in patients with obesity and apnea. Currently, OSA is considered to be the most common cause of resistant hypertension (RH), in which changes in lifestyle and rational combination therapy using adequate doses of at least three antihypertensive drugs, including diuretic, fail to achieve the target BP [6, 7].

According to the current randomized clinical trials (RCT), the percentage of patients with OSA among all patients with RH reaches 64 % (Figure 2) [8].

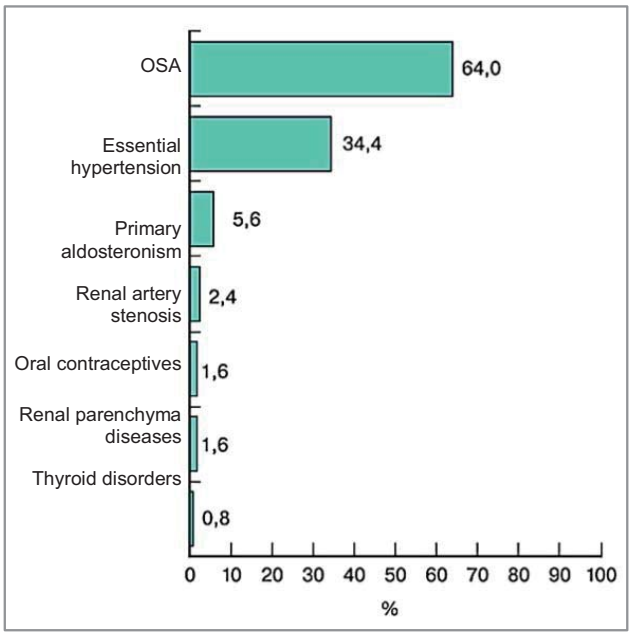

Figure 2. *Basic clinical conditions associated with the development of RH (adapted from Pedrosa R.P. et al. Hypertension. 2011 Nov; 58 (5): 811–7)*

1. RH development mechanisms in patients with OSA

It has been found that sleep fragmentation as a result of frequent nocturnal arousals in OSA patients has an active impact on blood pressure through the activation of the sympathoadrenal system, renin-angiotensin-aldosterone system (RAAS) and neurohumoral regulation as a whole [9].

Hypoxemic stimuli, hypercapnic reactions, hypoxemia/reoxygenation cycles triggered by apnea episodes significantly increase the activity of the sympathetic nervous system (SNS). Chronic stimulation of SNS is directly associated with the development and worsening of hypertension in OSA patients, thus forming resistance to antihypertensive therapy [10–12].

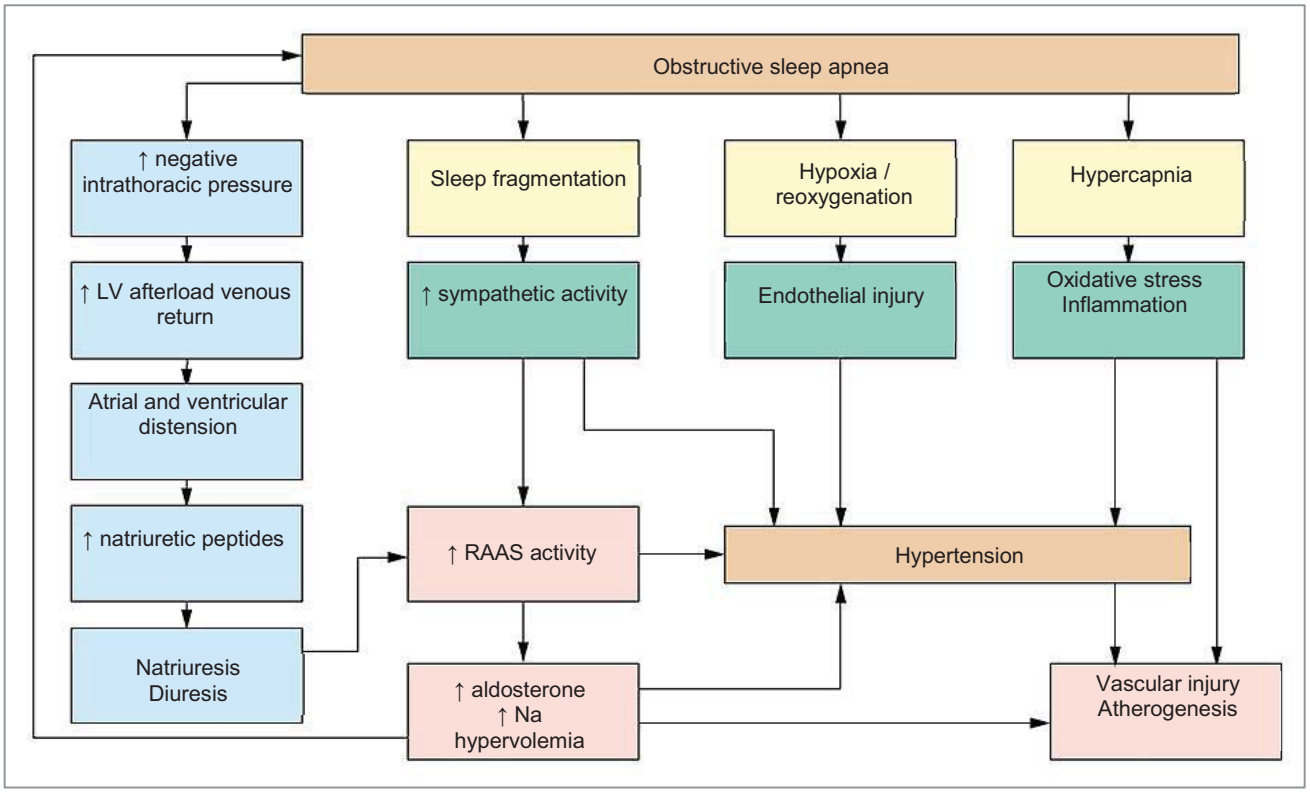

Figure 3. *Diagram of the main pathogenetic links of RH development in patients with OSA (adapted from Malyavin A.G., Babak S.L., Adasheva T.V. et al., Diagnostics and Management of Patients with Resistant Arterial Hypertension and Obstructive Sleep Apnea (Clinical Recommendations). Therapy. 2018; 1 (19): 4–42)*

The major pathogenetic elements of the SNS imbalance in OSA patients include:

1. **Reduced stroke volume** in apnea events due to the increase in negative intrathoracic pressure. The result is carotid sinus zone activation, which activates the vasomotor center and increases sympathetic impulses. As a result, baroreflex zone damage occurs, including due to the impact of hypoxia/reoxygenation cycles. Reduced baroreflex sensitivity to hypotension is the most common phenomenon observed in OSA patients, which is effectively resolved by continuous positive air pressure therapy (CPAP-therapy) [13, 14].
2. **Hypoxia and hypercapnia** that stimulate medulla oblongata and peripheral aortic and sinocarotid chemoreceptors. Activated chemoreceptors stimulate the vasomotor center, which, in turn, increases sympathetic activity and reduces parasympathetic activity (as a result, BP and HR increase). It has been found that the activity of chemoreceptors was of key importance in the development of systemic hypertension in OSA patients [15].
3. **Termination of stretching of pulmonary receptors** during inspiration and, as a consequence, inhibition of the central sympathetic activity (pulmonary baroreflex).
4. **Cortical arousals (sleep fragmentation)** and the resulting increase in sympathetic activity and reduction in vagal tone/
5. **Vibration effect of regular snoring** leads to the direct damage of carotid arteries and impairs the baroreflex function and chemoreceptor stimulation, which promotes structural failures and accelerates atherosclerotic vascular disease [16].

Pharyngeal collapses are associated with the activation of RAAS. As a result, hypernatremia and fluid retention are observed in OSA patients, more often in lateral pharyngeal (parapharyngeal) segments, aggravating the severity of apnea and activating the RAAS. Assessment of the role of angiotensin II and aldosterone in patients with OSA + hypertension performed in the meta-analysis by Jin Z.N., Wei Y.X. (2016) established the direct impact of OSA on RAAS system, with drug resistance formed through activation of neurohumoral

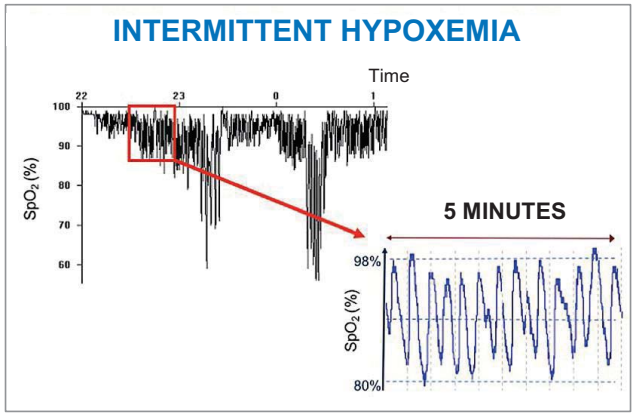

Figure 4. *An example of cyclic desaturation (rapid SpO_2 change) in a patient with severe OSA. In a short period of time (5 minutes), a sharp drop in saturation (80 %) occurs with a rapid return the parameter to a normal value (own data)*

systems. Moreover, renin in OSA patients did not significantly differ from normal values, while aldosterone correlated to both apnea severity and drug resistance intensity [14].

Recurrent hypoxia/reoxygenation cycles in OSA are similar to ischemia/reperfusion in coronary insufficiency by their ability to stimulate the formation of reactive oxygen species (ROS) and cause oxidative injury processes (Figure 4) [17].

Furthermore, hypoxia activates nuclear transcription factors, including nuclear factor kB (NF-kB), tumor necrosis factor alpha (TNF-α) and interleukin-8 (IL-8). They play the leading role in the development of endothelial injury and chronic vascular inflammation. Hypoxic stimuli promote production of endothelin, its cyclic changes in recurrent (intermittent) hypoxia at night. It is clear that the activation of oxidative stress, inflammation, endothelial dysfunction in patients with OSA + RH accelerates vascular injury processes, with increased vascular wall stiffness, early development of atherosclerosis, which substantially increases the risk of cardiovascular events [18].

2. RH diagnosis in patients with OSA

Hypertension in OSA patients has a number of clinical and functional features, which are found when taking medical history, as well as during office and 24-hour blood pressure monitoring:

1. High incidence of isolated diastolic hypertension.
2. High variability of BP with reduced cardiac rhythm variability.
3. Change in the daily profile of BP with increased number of non-dippers and night-peakers.

Increase in blood pressure in the early morning hours is well traced by the example of 24-hour BPM recording of one of our patients with OSA + RH (Figure 5).

Such results of 24-hour BPM require a practitioner to take measures to identify the causes of BP changes in the early morning hours, which can be expressed as two fundamental rules:

1. When examining RH patients, questionnaires with highly sensitive prognosis of OSA (STOP BANG, NoSAS, ESS) should be used;
2. If clinical markers of OSA are detected, apnea should be verified by polygraphy or polysomnography.

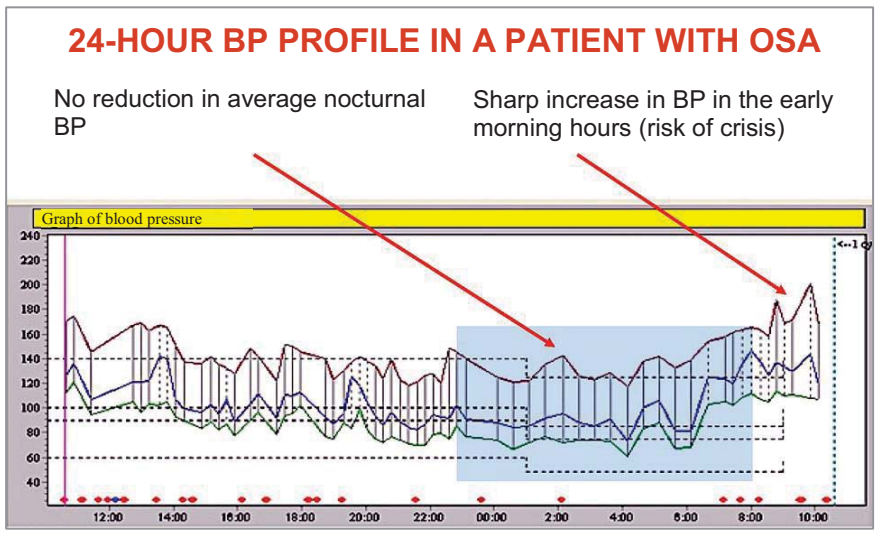

Figure 5. *An example of an increase of the blood pressure level in early morning hours in a patient with OSA + RH when performing 24-hour BPM (own data)*

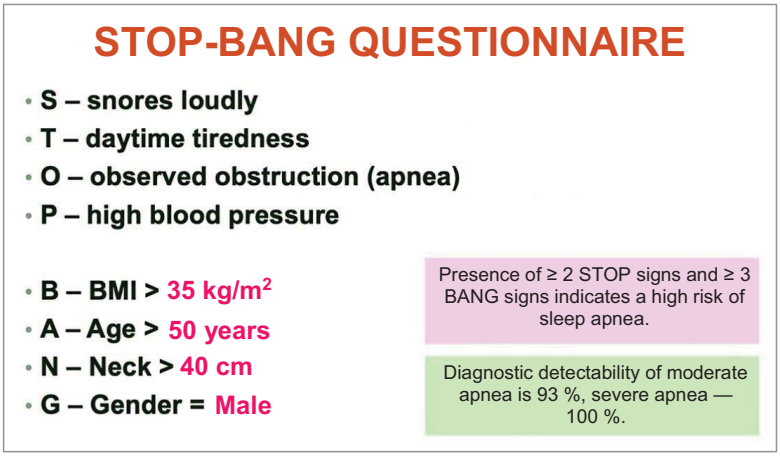

Figure 6. *STOP-BANG Questionnaire for predicting OSA (adapted from Chung F., Abdullah HR, Liao P. STOP-BANG questionnaire: a practical approach to screen for obstructive sleep apnea. Chest. 2016 Mar; 149 (3): 631–638)*

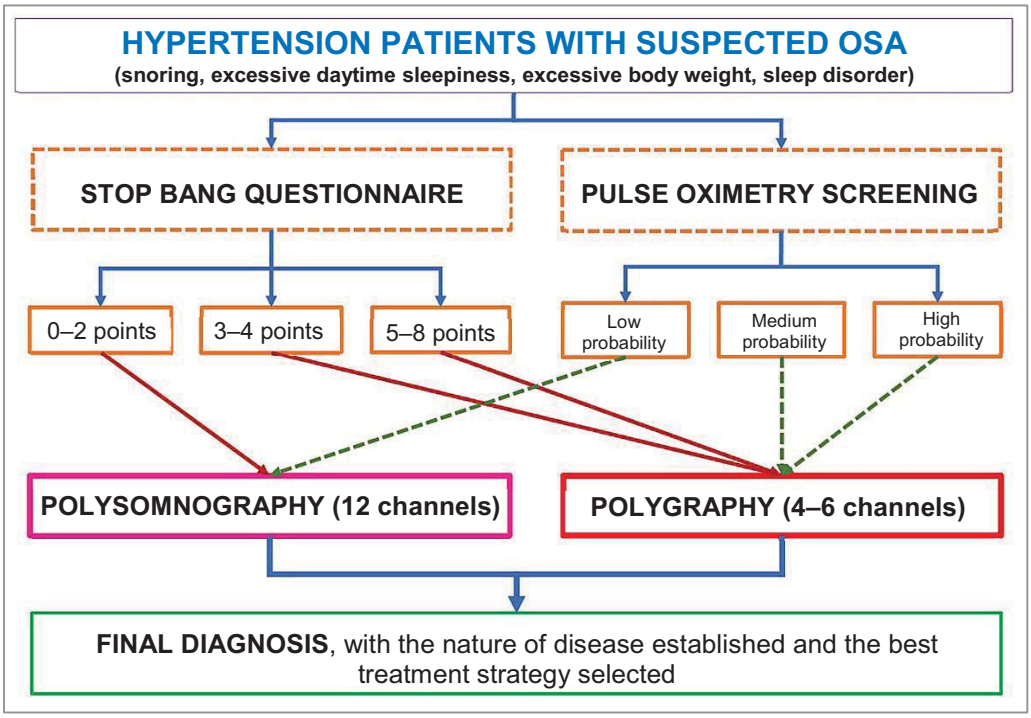

Figure 7. *Diagnostic procedure of OSA in patients with RH (adapted from Malyavin A.G., Babak S.L., Adasheva T.V. et al. Diagnostics and Management of Patients with Resistant Arterial Hypertension and Obstructive Sleep Apnea (Clinical Recommendations). Therapy. 2018; 1 (19): 4–42)*

The most reasonable and validated prediction scale for general practitioners is the STOP-BANG questionnaire (Figure 6) [19]. In fact, the use of this scale excludes the possibility of error in the subjective assessment of OSA markers by a practitioner.

In case of high risk of OSA according to the interviewing results, it is useful to perform the nocturnal polygraphy. Present-day diagnostic systems make it possible to perform respiratory monitoring on an outpatient basis, in an environment familiar to the patient, without disturbing his/her sleep process (Figure 7).

3. Therapeutic strategy for RH treatment in patients with OSA

The modern treatment strategy for RH patients with diagnosed OSA certainly includes a set of pharmacological and non-pharmacological methods:

1. Changing lifestyles (body weight loss, low-salt diet, alcohol restriction, aerobic exercise);
2. Antihypertensive therapy (AHT);
3. Non-pharmacological methods of treatment aimed at restoring upper airways patency (positioning treatment, surgical aids, intraoral applicators, CPAP-therapy).

3.1. Rational antihypertensive therapy (AHT)

Principles of rational and reasonable therapy of RH in OSA patients are based on the major pathogenetic mechanisms of the development of hypertension and clinical and functional characteristics of sleep apnea itself [20]:

1. Using drugs with the longest antihypertensive effect to control BP during night hours.
2. Adhering to chronotherapy principles, with shifting of drug administration to evening time for better BP control in patients with pathologic 24-hour profile of blood pressure (non-dippers, night-peakers).
3. Prescribing additional short- and medium-acting drugs before bedtime to prevent nocturnal shifts in blood pressure.
4. As a control of effect of antihypertensive therapy, 24-hour BPM should be used to assess the BP reduction at nighttime.
5. Using fixed combinations of antihypertensive drugs to improve adherence to the therapy.

β-blockers

Despite the lack of comprehensive data on the use of β-blockers in RH associated with OSA, the administration of this class of drugs in combination regimens is justified based on their effect on pathogenetic mechanisms of hypertension in OSA (inhibiting sympathetic activity and normalizing control over autonomic nervous system). Atenolol is the most widely studied β-blocker in patients with OSA. There are relative contraindications to the use of non-selective β-blockers (propranolol), as their negative effect on the patency of upper airways was demonstrated earlier [21].

RAAS antagonists

Data on the action of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs, sartans) are contradictory and associated with different levels of renin, angiotensin II, aldosterone in various severity of OSA. Some studies show their benefit, while others demonstrate their lesser effect or effect comparable to other drugs. However, given that the most patients with OSA + RH have significant carbohydrate and lipid metabolism disorders, RAAS blockers (ACEIs, ARBs) with the maximum organoprotective effects are the compulsory therapeutic strategy [22].

Diuretics

According to the clinical guidelines of the Russian Scientific Medical Society of Physicians concerning the management of patients with OSA + hypertension, the optimization of diuretic therapy using the combinations of thiazid/loop diuretic + spironolactone forms the basis for therapy of RH, especially associated with OSA. Significant decrease in apnea severity and BP reduction in OSA patients with uncontrolled hypertension was found when using intensive diuretic therapy with metolazone (5 mg) and spironolactone (50 mg). Moreover, there were reduced fluctuations of nocturnal fluid volumes in lower extremities, neck volume and decreased severity of apnea [23, 24].

Calcium antagonists

Calcium channel blockers (CCBs), or calcium antagonists (CAs), belong to one of five classes of antihypertensive drugs recommended as first-line treatment of hypertension. This class of drugs is often included in combination regimens in resistant hypertension. However, there are several potentially negative mechanisms of action of calcium antagonists in OSA patients:

- By suppressing the hypoxic vasoconstriction of pulmonary vessels, CCBs promotes the existence of hypoxia. Such action was found first in patients with acute respiratory failure (ARF) when administering nifedipine;
- When using CCBs, fluid can accumulate in lower limbs due to vasodilation and activation of capillary filtration, especially in an upright position. During sleep (at night), it moves to the upper half of the body and lungs causing the characteristic edema of parapharyngeal tissues.

It is obvious that increasing CCBs doses is undesirable in patients with OSA + RH. They should be discontinued at the first sign of fluid accumulation in lower limbs [25].

3.2. Non-pharmacological treatment methods (CPAP-therapy)

Therapy with continuous positive airway pressure (CPAP-therapy) is recognized as one of the most effective strategies of OSA treatment (Figure 8) [26]. Special benefits from CPAP-therapy have been established for the patients with OSA + RH.

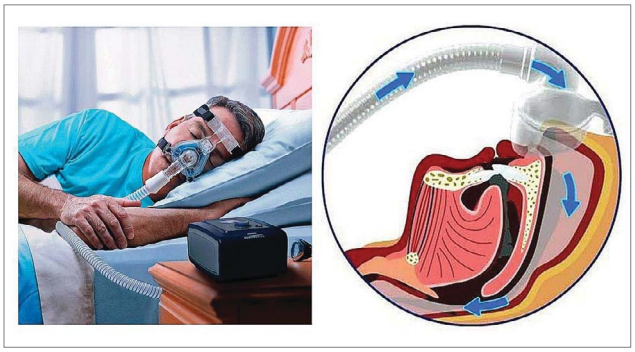

Figure 8. *Schematic representation of the CPAP therapy mechanism of action. The stabilization of pressure in upper airways during inhalation and exhalation eliminates the possibility of the development of airway occlusion (sleep apnea) in a patient at night. CPAP therapy is carried out through a nasal mask at home (adapted from Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal 1 (8225): 862-5)*

Meta-analysis of 28 RCTs has revealed considerable reduction in BP on CPAP-therapy even after excluding such factors as the severity of OSA and the existence of daytime sleepiness [27].

Of particular interest is the HIPARCO (randomized, multicenter, open-label, parallel-group) study involving OSA patients with moderate to severe RH. After 12 weeks of therapy, the combination correction (drug therapy + CPAP) led to significantly expressed reduction in BP (average daily DBP and average BP). The combination correction resulted in normalized circadian rhythm of BP: the percentage of non-dippers reduced by 10 %. There was a positive correlation between the use of CPAP-therapy and its antihypertensive effect. Linear regression analysis showed BP reduction by 1.3 mm Hg per every additional hour of CPAP-therapy [28].

Comparison of drug therapy regimens with combination correction, including CPAP-therapy, made it possible to conclude on the obvious advantage of the latter due to the normalization of blood pressure (average daily DBP and average BP), circadian rhythm, resolution of hypertension resistance and reduction of risks of fatal cardiovascular events in OSA patients with moderate to severe RH [29, 30].

Conclusion

In real clinical practice, the management of a patient with OSA and resistant hypertension represents a serious problem due to the sophisticated diagnostic algorithm. We tried to systematize and analyze the existing knowledge on the causes and consequences of hypertension resistance in OSA patients. In our opinion, only the doctor who is well experienced in causal relationships between OSA and hypertension, and possesses knowledge of the modern combination pharmacotherapy and non-pharmacological methods of sleep apnea correction, can successfully plan the treatment strategy. This is a multidisciplinary problem requiring clinicians to go beyond the scope of their profession.

The current rational therapy of patients with OSA + RH includes a combination of three-component drug therapy and non-pharmacological CPAP-therapy. To achieve a long-lasting positive effect, the duration of CPAP-therapy should exceed 12 weeks. Resolving OSA and hypertension resistance during combination therapy significantly reduces risks of fatal cardiovascular events in the group of patients concerned.

Conflict of interests

The authors declare no conflict of interests.

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CARDIORENAL SYNDROME IN PATIENTS WITH HEART FAILURE AS A STAGE OF THE CARDIORENAL CONTINUUM (PART 2): PROGNOSIS, PREVENTION AND TREATMENT

Abstract

Cardiorenal syndrome in patients with heart failure is a regular link of cardiorenal continuum. Doctors of various specialties may encounter patients with cardiorenal syndrome: general practitioners, cardiologists, nephrologists, resuscitators, anesthetists, cardiac surgeons, etc. The currently definition, classification, pathogenesis, diagnosis and epidemiology of cardiorenal syndrome in patients with heart failure were presented in the first part of our review. In the second part, prognosis, approaches to the prevention and treatment of cardiorenal syndrome in patients with heart failure are discussed. They include treatment of cardiovascular pathology and heart failure in accordance with current guidelines for the prevention of episodes of acute and decompensated chronic heart failure; diet; quitting smoking and drinking alcohol, weaning off nephrotoxic drug administration; body weight, blood pressure and glycemia control; use of angiotensin converting enzyme inhibitors, angiotensin receptor antagonists or angiotensin receptors and neprilisin inhibitors (ARNI), statins; reducing of the abdominal pressure, and others. It is necessary to develop and introduce new approaches to nephroprotection in patients with cardiorenal syndrome, which is possible with the joint work of a multidisciplinary team.

Key words: *cardiorenal continuum, cardiorenal syndrome, chronic heart failure, acute heart failure, chronic kidney disease, acute kidney injury, glomerular filtration rate, albuminuria, prognosis, mortality, survival, diagnosis, nephroprotection, prevention, treatment, angiotensin converting enzyme inhibitor, angiotensin receptor antagonist, angiotensin receptor and neprilisin inhibitor (ARNI)*

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ASA — acetylsalicylic acid, BMI — body mass index, CRS — cardiorenal syndrome, NUPs — natriuretic peptides, ADHF — acute decompensated chronic heart failure, AKI — acute kidney injury, AHF — acute heart failure, RF — renal failure, RCS — randomized clinical studies, GFR — glomerular filtration rate, HF — heart failure, CRT — cardiac resynchronization therapy, LVEF — left ventricular ejection fraction, FC (NYHA) — functional class, CKD — chronic kidney disease, CHF — chronic heart failure

Cardiorenal syndrome (CRS) is a typical link in cardiorenal continuum. It is a condition when a patient has heart failure (HF) and renal failure (RF) at the same time. CRS is reported in 32-90.3 % of HF patients. There are acute and chronic types of CRS in HF. Acute CRS is acute kidney injury (AKI) in acute heart failure (AHF) or decompensated chronic HF (ADHF) [17, 25, 73, 78, 116].

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Chronic CRS is the development of chronic kidney disease (CKD) in chronic heart failure (CHF) [81]. The prognostic significance of CRS, approaches to CRS and kidney injury progression prevention in HF patients are discussed in this part of the review.

Prognostic significance of impaired renal function, albuminuria and renal hemodynamics in HF patients

The importance of renal function as a prognostic factor in HF has been underestimated or ignored for a long time. In randomized clinical studies (RCS), emphasis was placed on cardiovascular events and mortality, while renal outcomes were either reported as safety endpoints or were not evaluated at all [39].

The prognostic significance of serum concentrations of creatinine in patients with CHF was demonstrated for the first time in the middle 1990s [50, 92]. In 2000, Hillege et al. calculated glomerular filtration rate (GFR) in patients with CHF NYHA III–IV and left ventricular ejection fraction (LVEF) of less than 35 % enrolled in PRIME-II study [66]. They showed that GFR is an independent predictor of the total and cardiovascular mortality, even more potent than NYHA FC and LVEF [53, 71, 72]. This was confirmed by numerous international and Russian studies [9, 11, 18, 19, 49].

It was found that both baseline serum creatinine and its increase during hospitalization (deterioration of renal function) were associated with longer hospitalization duration, frequency of hospitalization, and mortality [54, 89, 111]. Gottlieb et al. showed that it is observed even in case of increase in creatinine concentration by 0.1 mg/dL (8.8 μmol/L). Smith et al. demonstrated that increase in serum concentration of creatinine by 0.2 mg/dL (17.7 μmol/L) or more during hospitalization is associated with the increase of risk of death within 6 months by 67 % and rehospitalization probability by 33 % [127]. Its increase by ≥0.3 mg/dL (or 26.5 μmol/L), which is currently a criterion for AKI diagnosis when it occurs within 48 hours, made it possible to predict in-hospital mortality at 81 % sensitivity and 62 % specificity, and hospitalization duration of more than 10 days at 64 % sensitivity and 65 % specificity [62]. Moreover, the increase in creatinine concentration during hospitalization was a more potent mortality predictor as compared to its baseline level [127].

In the meta-analysis of 7 studies involving CHF patients (n=16,106) and 2 studies involving AHF patients (n=54,305), Smith et al. revealed an increase in risk of long-term mortality in severe kidney injury (GFR<53 mL/min/1.73 m^2) by 56 %. Furthermore, deterioration of renal function was associated with an increase in mortality within 6 months by 47 % [126]. The meta-analysis conducted by Damman et al. (n=18,634) showed that the deterioration of renal function leads to the increase in mortality risk by 61 % and rehospitalization risk by 30 % within 2–6 months of follow-up [41].

In their meta-analysis of 20 prospective studies, 5 subanalyses of clinical studies and 17 retrospective observational studies involving patients with acute HF (n=275,832, with the observation period of 1 month to 8 years, in most cases — 6 months to 1 year), Butler et al. confirmed that kidney injury and deterioration of renal function (in most studies, creatinine concentration increased by ≥0.3 mg/dL (26.5 μmol/L) during hospitalization) are related to in-hospital, long-term mortality, rehospitalization frequency, combined hospitalization/death endpoint, and length of stay in hospital [22, 30, 37, 52, 54, 83, 84, 89, 91, 103, 106–108, 127, 140]. Heywood et al. demonstrated that worsening of renal dysfunction is associated with higher necessity for cardiopulmonary resuscitation, mechanical ventilation and ultrafiltration [70]. Forman et al. found that worsening of renal function led to a twofold increase in the likelihood of major complications, such as cardiogenic shock, myocardial infarction, stroke, sepsis, significant hypotension and atrial fibrillation [54].

Predictors of deterioration of renal function during hospitalization in CHF are male gender, baseline serum creatinine >1.5 mg/dL (132.6 μmol/L), uncontrolled hypertension (systolic BP>200 mm Hg), HR>100 beats/min, crackles appearing outside basal areas of lungs [89], atrial fibrillation [37], age, and concomitant diabetes mellitus [54, 62]. Predictors of reduced renal function in HF within 6 months following examination are vascular pathology (acute cerebrovascular accidents and transient ischemic attacks, peripheral

vascular diseases, renal artery stenosis, abdominal aortic aneurysm diagnosed at the time of enrollment to the study), treatment with thiazide diuretics and baseline serum urea over 9 mmol/L [42]. There were no significant differences in percentages of the maximum recommended dose of ACE inhibitors, which was administered at the baseline and during observation, in patients with decreased and increased GFR [43]. Initially prescribed doses of diuretics did not differ in patients with increased and decreased GFR, although 6 months later, the doses of diuretics were significantly higher in patients with deterioration of renal function as compared to patients without it [42].

Valente MA et al. conducted a study involving 120 patients having clinically stable CHF with LVEF <45 % and mainly NYHA FC II and III, the follow-up period was 3 years, the combined endpoint included all-cause mortality, heart transplantation and hospitalization for decompensated HF. This study demonstrated the equal prognostic significance of the following GFR determination methods: based on ^{125}I-iothalamate clearance, calculation using the formula of MDRD, CKD-EPI serum cystatin C, CKD-EPI creatinine and serum cystatin C, and the Cockcroft-Gault formula [7]. The study conducted earlier by Zamora E. et al. (2011), which involved 925 patients with CHF, also compared the predictive significance of the CKD-EPI, MDRD and Cockcroft-Gault formulae. However, the prediction of risk of death proved to be the most exact for the Cockcroft-Gault formula, while the CKD-EPI and MDRD formulae demonstrated similar predictive efficacy [7]. The meta-analysis of 25 prospective studies for risk stratification in HF patients based on GFR (irrespective of LVEF) has shown that the CKD-EPI formula provides the best risk stratification as compared to the MDRD [7].

In addition to blood creatinine and GFR, poor prognosis in CHF patients is associated with albuminuria irrespective of their levels. The CHARM sub-study (n=2,310) showed accurate independent worsening of prognosis for the combined endpoint (total mortality, cardiovascular mortality and hospitalization for ADHF) in HF patients and microalbuminuria or macroalbuminuria (RR: 1.43 (1.21–1.69); p<0.0001 and 1.75 (1.39–2.20); p<0.0001, respectively) [22][7]. The GISSI-HF sub-study (n=2,131) also confirmed the role of micro- and macroalbuminuria as a predictor of total mortality in CHF patients with LVEF 33±9 % (RR = 1.42 (1.11–1.81); p=0.005 and RR=1.70 (1.16–2.50); p=0.006) [7]. In the Russian population, micro- and macroalbuminuria (A2 and A3) also negatively affected prognosis in patients with CHF: mortality of patients with albuminuria was significantly higher as compared to patients without it [65, 129].

Renal blood flow figures are also related to with prognosis. Ennezat PV et al. were the first to demonstrate the negative prognostic value of renal resistance indices in patients with CHF. This was confirmed in other foreign and domestic studies [7]. Moreover, the prognostic significance of reduced volumetric renal blood flow in CHF was demonstrated in the Russian population [9, 12].

Thus, the prognosis in HF patients is associated with impaired renal function, albuminuria and renal hemodynamics. This may be due to that the existence of renal dysfunction reflects the severity of HF. Moreover, renal dysfunction is related to insufficient elimination of toxic substances, such as oxidized catecholamines, uremic factors and uric acid, increased cardiac pre- and afterload, anemia, disturbed calcium-phosphorus metabolism and other metabolic processes, which may also contribute to the worsening of prognosis in this patient population [42, 126].

Cardiorenal syndrome prevention and treatment in HF patients

In accordance with pathogenetic mechanisms for the development of cardiorenal syndrome, and current guidelines for management of patients with HF, CKD, AKI, the following approaches can be used to prevent the development and progression of cardiorenal syndrome in HF patients.

1. HF therapy in accordance with current guidelines [1, 5, 114]. Since ADHF episodes predispose to the development of AKI, subsequent development and progression of CKD [39], it is crucial, with the aim of nephroprotection, to prescribe adequate therapy of HF according to current guidelines in order to prevent and reduce incidence of decompensations [38]. In most patients, it should include

ACE inhibitors / angiotensin receptor antagonists, beta-blocking agents, diuretics, mineralocorticoid receptor antagonists. If the above combination is ineffective, ACE inhibitors / angiotensin receptor antagonists may be replaced with sacubitril/valsartan in systolic blood pressure >100 mm Hg, ivabradine may be added in sinus rhythm with HR ≥70, and cardiac resynchronization therapy (CRT) may be considered at QRS ≥130 msec. In this case, to prevent episodes of hypovolemia and hypotension, which promote the development of AKI, it is necessary to start the drug therapy with minimum doses, and slowly titrate and adjust doses in accordance with GFR values [5, 6, 8, 13].

2. Diet. Low-salt diet (salt <6 g/day, sodium <2.4 g/day), low-protein diet (1 g/kg/day in CKD Stages 1–2, and 0.6–0.8 g/kg/day in CKD Stages 3a–4), replacement of animal proteins with plant proteins, which put lesser stress on kidneys (soy proteins have lesser negative impact on renal hemodynamics, and also effect nephro-, cardioprotective and antisclerotic action), low-potassium diet (>4 g/day in CKD Stages 1–2, and 2–4 g/day in CKD Stages 3a–4), and low-phosphate diet (1.7 g/day in CKD Stages 1–2, and 0.8–1.0 g/day in CKD Stages 3a–4) have proved to be effective in preventing the progression of CKD [10, 14, 15].

3. Smoking cessation, because smoking is a dose-dependent risk factor for the reduction of GFR and the development of microalbuminuria [110, 136].

4. Limitation of alcohol consumption [15, 16, 90].

5. Elimination or minimization of modifiable risk factors for the development and progression of CKD. Nephrotoxic drugs, including non-steroidal anti-inflammatory drugs (NSAIDs), nephrotoxic antibiotics, contrast agents, food supplements (including Thai Herbs, Fat Burners, weight-gainer shakes), which may negatively affect the renal function, should be avoided.

The administration of even small doses of acetylsalicylic acid (ASA), as well as other NSAIDs, in CHF patients is associated with worsening of outcome, as these drugs block the synthesis of prostaglandins, which prevent the negative impact of neurohumoral activation, and weaken the effect of drugs for CHF treatment — ACE inhibitors, diuretics, spironolactone, carvedilol [3, 23, 55]. Prescription of ASA is associated with the higher frequency of hospitalization for worsening CHF [98]. This indicates that NSAIDs should be avoided in CHF (except for prescribing ASA at the early stage to 8 weeks after suffering myocardial infarction), particularly when there is renal dysfunction [4]. If antiplatelet therapy is required, ASA may be indicated to be replaced with clopidogrel [48].

It should be borne in mind that, starting from CKD Stage 3b, the effectiveness of thiazide diuretics is reduced and the risk of their side effects grows, therefore, loop diuretics should be preferred [8]. Moreover, aldosterone antagonists are strictly contraindicated in GFR <30 mL/min/1.73 m^2 due to the risk of aggravated renal dysfunction and hyperkalemia, and in GFR 30–60 mL/min/1.73 m^2 they should be used with caution at a dose of no more than 25 mg/day, with close monitoring of on-treatment blood potassium and creatinine 7 days following the beginning of therapy or dose change, subsequently on a weekly basis for up to 1.5 months, and then once every 4 months [8, 16, 123].

Cardiac glycosides in CRS patients should be prescribed with great caution, only when there is atrial fibrillation [8]. GFR should be taken into account when prescribing digoxin, since the elimination of digoxin decreases with reduced GFR, and serum concentration of digoxin should be maintained at <0.8 ng/mL [104]. For safety purposes, it is not recommended to start treatment in CRS patients with loading doses, and low doses should be used as maintenance doses, i. e., 0.125 mg, probably every other day [123].

6. Maintaining the body mass index (BMI) within the range of 20–25 kg/m^2 through adjusted dietary calories and sufficient physical activity (30 min aerobic activities at least 4–5 times a week), since the increase of BMI >25 kg/m^2 even in young healthy individuals is associated with a higher risk of end-stage chronic renal failure [74].

7. Close blood pressure monitoring. The target BP is <140/90 mm Hg at optimal EAM <10 mg/g (A0), and <130/80 mm Hg at higher albuminuria (A1–A4). In this case, it is very important to avoid the reduction in systolic BP <120 mm Hg in order to prevent the decrease of renal blood flow [15, 79, 95, 138, 139].

8. Close glycemia monitoring. The target glycated hemoglobin (HbA1c) level depends on age and existing complications (Table 1); in most patients, it is <7 % [8].

Table 1. *The target level of glycated hemoglobin in patients with cardiorenal syndrome [8]*

HbA1c target, %	Age, years		
	Young adults <45	Middle age ≥45<70	Elderly (≥70) or life expectancy <5 years
Absence of macrovascular complications and/or hypoglycemia risk	<6.5 %	<7.0 %	<7.5 %
Presence of macrovascular complications and/or hypoglycemia risk	<7.0 %	<7.5 %	<8.0 %

9. Prescribing ACE inhibitors/ARBs/ARNIs [20]. Nephroprotective action of ACE inhibitors and ARBs is due to the fact that they increase renal blood flow through the dilation of afferent arterioles and increase in cardiac output, and block negative renal effects of angiotensin II, including proliferation and hypertrophy of mesangial cells [118]. In case of long-term administration of ACE inhibitors/ARBs, the dilation of efferent arterioles prevents hyperfiltration and reduces albuminuria [69]. All this leads to slower progression of CKD and reduced risk of end-stage CRF.

ACE inhibitors were contraindicated for a long time with blood potassium over 5 mmol/L and creatinine over 220 μmol/L (2.5 mg/dL). In the analysis of 20902 Medicare participants over 65 years of age with systolic dysfunction (LVEF < 40%), the reduction in mortality within 1 year in the course of treatment with ACE inhibitor was more significant in patients with serum creatinine >265 μmol/L (3mg/dL) as compared to patients with creatinine concentration ≤265mg/dL (37% and 16%, respectively) [55]. In light of this, "there is no specific level of creatinine, at which ACE inhibitors are contraindicated" [69, 75-77, 80]. According to most experts, ACE inhibitors or angiotensin II receptor antagonists may be prescribed in serum creatinine <6 mg/dL (528 μmol/L) and GFR≥20 mL/min. However, renal artery stenosis should be excluded before starting treatment. In patients with GFR<30 mL/min/1.73 m², treatment should be started in a hospital, where creatinine and potassium can be analyzed on a daily basis and agents for treating acute RF are available [44, 94, 100]. Patients with GFR ≥30 mL/min/1.73m² should be analyzed for serum creatinine and potassium and GFR 7 days following the first administration and dose increase, subsequently once a week for up to 1.5 months, and then once every 4 months [16]. If, in the course of treatment, creatinine concentration has increased by less than 50% and remains below 266 μmol/L, GFR — above 25 mL/min/1.73m², potassium — below or equal to 5.5 mmol/L, no changes in the therapy with ACE inhibitors or ARBs are required. In case of more pronounced changes in blood concentrations of creatinine and/or potassium, ACE inhibitor/ARB doses should be reduced twice, and creatinine and potassium should be controlled in 1 week. When blood concentration of potassium increases to >5.5 mmol/L, creatinine increases by over 100% or above 310 μmol/L, GFR decreases to <20 mL/min/1.73m², RAAS blockers should be discontinued and nephrologist consultation is required (Table 2). ACE inhibitors and ARBs should be interrupted in case of scheduled administration of contrast agents, preparation to colonoscopy, or before major surgical interventions [2, 8].

The combination of ACE inhibitor and ARB reduces EAM and BP better than isolated use of any of these groups of medications, but does not

Table 2. *Management of patients with changes in serum creatinine concentration / glomerular filtration rate on the background of angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) [8]*

Increasing of serum creatinine, %	Serum creatinine, μmol/l	Glomerular filtration rate, ml/min/1,73 m²	Serum potassium, mmol/l	Changes in the dose of ACEI / ARB
<50 %	<266	>25	<5,5	Not required
50-100 %	266-310	20-25	-	Decreasing of the dose 2 times, control after 1 week
>100 %	>310	<20	>5,5	Drug's withdrawal

prevent the combined endpoint: doubling of creatinine, dialysis dependence or death [96]. In light of this, the combination of ACE inhibitor and ARB is not recommended at present.

Sacubitril/valsartan, a drug of the new ARNI class, includes ARB and neprilysin inhibitor. Neprilysin is a neutral endopeptidase that cleaves natriuretic peptides (NUPs), bradykinin, and other peptides. Inhibition of neprilysin leads to increased blood levels of NUPs, increased urine output, natriuresis, improved myocardial relaxation, and decreased secretion of renin and aldosterone [64, 117]. In PARADIGM-HF study, sacubitril/valsartan reduced cardiovascular mortality and frequency of hospitalizations for HF 20%, and all-cause mortality 15% better than enalapril [13, 88].

Subanalysis of findings from the PARADIGM-HF study (n=1,872) has shown that GFR decreased significantly less in the course of treatment of CHF patients with impaired LVEF with sacubitril/valsartan as compared to enalapril: by 1.61 and 2.04 mL/min/1.73m^2/year, respectively ($p<0.001$). However, the increase in albumin/creatinine ratio was higher with sacubitril/valsartan as compared to enalapril: by 1.2 mg/mmol and 0.9 mg/mmol, respectively ($p<0.001$) [40]. Similar data were obtained during the PARAMOUNT study in patients with preserved LVEF [134]. Moreover, in the PARADIGM-HF study, hyperkalemia was rarer among patients who received mineralocorticoid receptor antagonists in the course of treatment with sacubitril/valsartan as compared to enalapril [46].

10. Lipid-lowering therapy. To slow down atherosclerosis and renal fibrosis, which promote the development of CKD, statins are indicated. According to the meta-analysis of 50 studies (n=30,144), at various stages of CKD, statins significantly reduced daily proteinuria, although they had no considerable effect on GFR. Positive effects of statins did not depend on the stage of CKD [128]. The GREACE study showed improved renal filterability in CHF patients who received atorvastatin. Nevertheless, in accordance with the current guidelines, since statins do not affect the selected (solid) endpoints, it is not recommended at present to initiate therapy with statins in CHF, although such therapy may be continued in patients with CHF of ischemic etiology [7]. Perhaps, it is particularly important to continue treatment with statins in patients with CRS.

11. Reducing abdominal pressure. Paracentesis with fluid evacuation to relieve the symptoms can be considered for patients with ascites. By reducing abdominal pressure, this procedure can partially increase renal filtration pressure and GFR [1, 10, 105, 114, 133].

Potential approaches to nephroprotection in CRS

In addition to the above, a number of other approaches to nephroprotection in CRS were and are still being intensively studied.

Nesiritide

Nesiritide is a synthetic form of brain natriuretic peptide (BNP). Experimental studies have shown its favorable effect on kidneys [124]. However, its diuretic action was less pronounced in CHF patients as compared to healthy individuals. Effects of nesiritide on renal plasma flow, urine output and sodium excretion were comparable to the placebo [135]. Under its influence, GFR did not increase even in patients in whom this drug produced natriuretic and diuretic effect [97, 135]. In the FUSION II study, nesiritide (infusions 1-2 times a week for 12 weeks) caused an increase in serum creatinine by 0.5 mg/dL (44 μmol/L) [94, 141]. In their meta-analysis, Sackner-Bernstein et al. found that the risk of death within 30 days was higher in patients receiving nesiritide as compared to the placebo group. The study conducted by Peacock et al. showed that, as compared to placebo, the probability of rehospitalization within 30 days was 57% lower in the patients receiving nesiritide, and the duration of rehospitalization was 2.6 times shorter. The meta-analysis of seven large randomized controlled studies performed by Arora et al. demonstrated that the relative risk of death within 30 and 180 days was not significantly different in the nesiritide and placebo groups [112]. The ROSE study, which involved 360 patients with decompensated HF and GFR of 15 to 60 mL/min/1.73m^2, did not reveal any advantages of nesiritide (0.005 mcg/kg/min) as compared to placebo in regard to congestion and GFR [33]. Tachycardia and hypotension were reported in many patients. In light of this, the use of nesiritide in patients with CRS is limited [114, 133].

Vasopeptidase inhibitors

In theory, vasopeptidase inhibitors may have a clinical advantage over ACE inhibitor in patients with CHF. The first drug of the group, omapatrilat, blocked 3 enzymes: ACE, aminopeptidase P and neprilysin [109]. However, it often led to allergic reactions, therefore, is not recommended for administration [88]. The drug of the ARNI class, which contains neprilysin inhibitor, is described above.

Vasopressin receptor antagonists

Antagonists of renal (V2) vasopressin receptors increase urine output and aquaresis (excretion of water without electrolyte loss), and allow resolving hyponatremia either in the presence or absence of HF [51, 59]. A number of studies showed the potent aquaretic effect of tolvaptan without damage to the kidneys in patients with ADHF [56]. The SALT study demonstrated that this drug is effective and safe in patients with HF and hyponatremia. In the EVEREST study (n=4,133), reduction in body weight and intensity of clinical symptoms was higher in the patients hospitalized for HF, who received tolvaptan, as compared to the control group; however, there was no favorable effect on mortality, including cardiovascular mortality, and frequency of hospitalization for HF [57, 85, 88, 112]. Other studies showed no advantages of vasopressin antagonists (tolvaptan, conivaptan) for renal function as compared to furosemide in patients with CHF [21, 36, 87, 104, 121]. The meta-analysis performed by Sen J. et al. based on data obtained in 17 studies (n=1,597) did not find any differences concerning changes in GFR and serum creatinine among control groups and tolvaptan group [122]. There is no justification to prescribe these drugs for nephroprotection in patients without hyponatremia [114].

Adenosine A1 receptor blockers

As noted above, increased plasma adenosine is observed in HF patients, which reduces cortical blood flow in kidneys and sodium excretion. Selective adenosine A1 receptor blockers (BG9719, KW3902 — rolofylline) increase urine output and natriuresis. Gottieb et al. demonstrated that BG9719 in combination with furosemide increased urine excretion and caused no changes in GFR as compared to the placebo [60-62]. In another study, rolofylline led to significant increase in GFR by 32% and in renal plasma flow by 48% [47, 58]. However, in the PROTECT placebo-controlled randomized study (n=2,033), rolofylline did not improve clinical outcomes and serum creatinine in patients hospitalized for ADHF, having GFR 20-80 mL/min/1.73 m^2, as compared to the placebo. Moreover, neurological complications were more common in the rolofylline group [99, 103, 113, 137]. Another pilot study also confirmed the neutral effect of rolofylline on renal function [63]. Administration of rolofylline for nephroprotection in CHF is not justified at present.

Endothelin receptor blockers

In two VERITAS studies, intravenous infusion of endothelin receptor blocker tezosentan, despite its more favorable hemodynamic effect, failed to improve acute HF symptoms, change short- and long-term disease prognosis, or prove the nephroprotective action of the drug as compared to the placebo [102, 131].

Guanylate cyclase activators and stimulators

It has been shown that soluble guanylate cyclase activators and stimulators (BAY 58-2667, cinaciguat; HMR1766, ataciguat; BAY 1021189/MK-1242, vericiguat; BAY 63-2521, riociguat; BAY60-4552, nelociguat) also reduce pre- and afterload and increase cardiac output in HF animals, increase sodium excretion, with preservation of glomerular filtration[87, 120]. These drugs, including their nephroprotective action, are currently being studied in HF patients [86].

Iron and erythropoietin preparations

Correction of anemia in CHF leads to increased exercise tolerance, reduced intensity of clinical symptoms, but has no effect on survival [17, 24, 88, 101]. In some studies, erythropoietin preparations had cardioprotective effect through suppression of apoptosis, oxidative stress and inflammation, reduced infarction area, increased angiogenesis and prevented

arrhythmias [29]. Nephroprotective effect of erythropoetin and its analogues was proven [32], but they led to hypertension , which negatively affected the overall outcome. Darbepoetin alfa, a stimulator of erythropoietin synthesis, does not improve prognosis in HF patients with reduced LVEF and mild to moderate anemia, but results in thromboembolic complications. Therefore, it is not recommended [1, 5, 114]. In some studies, correction of anemia with iron preparations increased oxidative stress [27, 82]. The nephroprotective effect of iron and erythropoietin preparations in patients with CRS has not been proven, and their administration for nephroprotection is not recommended at present [1].

Relaxin

Relaxin 2, a natural peptide that participates in adaptation of the female body to pregnancy, is a potent renal vasodilator [35]. The RELAX-AHF study showed significantly reduced dyspnea (primary endpoint), improved GFR and decreased total mortality within 180 days (secondary endpoints) in patients with decompensated HF who received serelaxin (human recombinant relaxin 2) as compared to the placebo [130]. Moreover, administration of serelaxin reduced intensity of congestion and the need for intravenous diuretics [93]. The subsequent RELAX-AHF-EU study did not confirm the drug effect on the primary endpoint (death + HF worsening), for which reason further studies and the manufacture of the drug, which is potentially prospective for CRS treatment, were suspended.

Cardiac resynchronization therapy

Perfusion in CHF can be improved using cardiac resynchronization therapy (CRT). In one study, CRT increased GFR by 2.7 mL/min/1.73m^2 in the subgroup of patients with GFR of 30–60 mL/min/1.73m^2 [28]. This issue needs thorough examination.

TNF-α inhibitors

Given the role of inflammation in the genesis of HF and kidney injury, there was an idea to use TNF-inhibitors (infliximab and etanercept) for the treatment of heart failure, but the ATTACH, RECOVER and RENASSAINCE (RENEWAL) studies had disappointing results. Despite the reduced plasma concentrations of the highly sensitive C-reactive protein and IL-6, the lack of effect on prognosis or increased mortality were reported in the course of treatment with these drugs [34, 96]. However, there is no sufficient information on renal function in these studies [39].

Effect on oxidative stress

Despite the fact that the role of oxidative stress in the development of CRS has been proven, the potential therapeutic effect on this component of pathogenesis remains understudied. Clinical studies did not demonstrate any effect of treatment with antioxidants (vitamins E, C), which can be explained by the lack of specificity in their mechanism of action. Currently, animal studies are conducted for selective blockers of different oxidative stress pathways: NADPH oxidase inhibitors (S17834, gp91ds-tat) and mitochondrial antioxidant (MitoQ) [7].

Denervation of renal arteries

Given the role of sympathoadrenal system activation in the genesis of kidney injury in HF, sympathetic denervation of renal arteries was assumed as one of potential approaches to the management of CRS patients. However, given that the SYMPLICITY HTN-3 study identified no advantages of renal artery denervation as compared to a sham procedure, the importance of this treatment method is rather doubtful [26].

Compression therapy for lymphatic drainage

In lower limb swelling resistant to diuretic therapy, compression therapy may be appropriate to provide for lymphatic drainage and fluid return from intercellular spaces to blood streams [132]. The renal effect of that has not been studied.

Mechanical circulatory support

In most HF patients with reduced LVEF and CRS, renal function improved after implanting mechanical circulatory support (MCS) devices [67, 119]. The worst renal function before the devices were implanted was associated with the poor

prognosis [31]. Moreover, in patients who received MCS as a bridge to kidney transplantation, post-transplantation renal function correlated to that observed following the initiation of MCS [45, 125]. However, the use of MCS is associated with future complications, such as infection, bleeding and thrombosis, and may not be considered as treatment of CRS [133].

The existing approaches to nephroprotection in patients with CHF are summarized in Table 3. Areas for further studies on the issue are as follows: 1) epidemiological data, including data on AKI in HF; 2) understanding of CRS pathogenesis; 3) feasibility of using a biomarker panel for diagnosis and management of CRS; and 4) development of new approaches to nephroprotection [115].

Table 3. *Approaches to nephroprotection in patients with HF (with changes as per [38, 68, 133])*

The purpose of the treatment	Existing approaches	Possible/future approaches
Modification of risk factors for renal dysfunction	Prevention of CH decompensation Careful titration of doses of the drug, depending on renal function Diet Quitting smoking, drinking alcohol Limitation of nephrotoxic effects, incl. drugs Control of hypertension Avoidance of hypotension Glycemia control Maintain optimal BMI Careful monitoring of fluid balance, urine excretion	Allopurinol SGLT2 Physical exercise
Hemodynamic disorders	Adequate diuretic therapy ACE inhibitors / ARB / ARNI Cardiac resynchronization therapy Mechanical circulatory support Heart and / or kidney transplantation	Vasopressin V2 Receptor Antagonists Calcium Sensitizers Endothelin receptor antagonists Luso-inotropic agents (istaroxime) Heart myosin activators Relaxin-2
Neurohumoral activation	ACE inhibitors / ARB / ARNI β-blockers	FGF-23 Receptor Blockers Adenosine A1 receptor antagonists Direct renin inhibitors Physical exercise Renal artery denervation
Atherosclerosis, endothelial dysfunction, coagulation and vascular&platelet hemostasis disorders, thromboembolic complications	Statins Antiplatelet therapy Anticoagulants	Nitrogen oxide Physical exercise Endothelin receptor antagonists
Malnutrition, inflammation, oxidative stress, cachexia	Nutritional support Physical exercise	Ghrelin Antioxidants Anti-inflammatory drugs
Uremia	Peritoneal dialysis / hemodialysis	Removal of toxins by high-flow hemofiltration and / or new absorbents
Anemia, iron deficiency	Iron	Diet Anti-hepcidin therapy Carnitine Erythropoietin preparations
Mineral and bone disorders [14]	Diet Preparations of the active form of vitamin D Selective Vitamin D Receptor Activators Phosphate binding agents Calcimimetics	FGF-23 Receptor Blockers Antibodies to FGF-23

Note: ARB — angiotensin receptor blocker, ARNI — angiotensin receptor and neprilysin antagonist, ACE — angiotensin converting enzyme, BMI — body mass index, FGF — fibroblast growth factor, SGLT2 — type 2 sodium-glucose transporter inhibitors

Thus, cardiorenal syndrome is a regular component of cardiorenal continuum [115]. It is reported in most patients with CHF. Doctors of various specialties may encounter patients with cardiorenal syndrome: general practitioners, cardiologists, nephrologists, resuscitators, anesthetists, cardiac surgeons, etc. In order to prevent and slow down progression of kidney injury, treatment according to the current guidelines for HF, CKD and AKI should be recommended for patients with CHF. There is need to develop and introduce new approaches to nephroprotection, which is possible with the collaborative work of a multidisciplinary team.

Conflict of interests

The authors declare no conflict of interests.

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THE ROLE OF ALDOSTERONE IN THE DEVELOPMENT OF ATRIAL FIBRILLATION: MODERN UNDERSTANDING OF THE PROBLEM

Abstract

The literature review presents modern understanding of the role of aldosterone in the development and maintenance of atrial fibrillation. It is shown that the hormone takes part at all stages of the electrophysiological and structural atrial remodeling, contributing to the formation of the arrhythmia substrate. It was noted that negative effects of aldosterone in the myocardium are realized not only due to its high systemic production but also because of its direct synthesis in the atrial tissues. Increased expression of mineralocorticoid receptors in cardiomyocytes also play important role in the development of atrial fibrillation. It is demonstrated that hyperaldosteronemia can be a cause as well as an effect of atrial fibrillation. The episode of arrhythmia is characterized by neurohormonal activation, increased intramyocardial aldosterone synthesis and high mineralocorticoid receptor expression. This contributes to the further progression of atrial remodeling and creates conditions for the arrhythmia recurrence.

Key words: *aldosterone, atrial fibrillation, remodeling, renin-angiotensin-aldosterone system, genetic polymorphism*

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ACE — angiotensin-converting enzyme, AT2 — angiotensin 2, LV — left ventricle, MCR — mineralocorticoid receptors, RAAS — renin-angiotensin-aldosterone system, AF — atrial fibrillation

Atrial fibrillation (AF) is still one of the most common cardiac rhythm disorders. Its incidence reaches 1 % in the general population and exceeds 7 % in individuals over 60 years of age [1]. Disturbed hemodynamics and thromboembolic complications associated with repeated AF episodes lead to considerable expenses on treatment, lower quality of patients' life and higher mortality [2].

Despite the progress made in understanding the electrophysiological mechanisms of the development and maintenance of AF, the pathogenesis of this arrhythmia remains understudied. It is an undisputable fact that the development and maintenance of this arrhythmia is closely related to structural atrial changes, which are largely due to the excessive activity of renin-angiotensin-aldosterone system (RAAS) [3–5]. Higher activity of RAAS contributes to the development of inflammation, fibrosis, and oxidative stress in cardiomyocytes [3]. The pathogenic effect of RAAS hyperactivity was long associated primarily with the action of angiotensin-2 (AT2). Numerous experimental studies [6, 7] confirmed that this hormone had a number of proarrhythmic effects, such as activation of calcium currents through L-type channels, suppression of potassium flows, inhibited conduction of atrioventricular node, increased release of noradrenaline in atria, stimulation of fibrosis and systemic inflammation, etc. However, studies conducted in recent years [8–12] suggest that the majority of

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detrimental effects of RAAS, which were previously explained exclusively by the action of AT2, in fact can be attributed to the excessive activity of the end effector of the system, i. e., aldosterone.

Aldosterone role and metabolism in the body

Views on the role and metabolism of aldosterone in the body have changed considerably in recent years. According to the classic concept [13], aldosterone is an adrenal cortex hormone, the receptors of which are located in the kidneys, and its primary effect involves maintaining a constant volume of fluid in the body. However, information has been accumulated recently on the extraadrenal production of aldosterone (in the myocardium, vascular wall, adipose tissue, pancreatic cells and even brain), and its receptors were found far beyond the kidneys [14, 15]. It has been shown that the action spectrum of this hormone is not limited to influence on water-salt metabolism, but is represented by a wide variety of pathogenic effects.

RAAS serves as the principal mechanism for regulation of aldosterone secretion. Renin is synthesized in juxtaglomerular cells. It acts on angiotensinogen protein produced by the liver to form angiotensin-1, which has a poor vasoconstrictive effect. Then, under the influence of the angiotensin-converting enzyme (ACE) secreted in proximal renal tubules and lungs, angiotensin-1 turns into the potent vasoconstrictor AT2. The latter, in its turn, has a stimulating effect on the adrenal cortex, thus activating the secretion of aldosterone [16].

Along with AT2, sodium and potassium ions are the most important stimulators of aldosterone synthesis. An increase in potassium level just by 2 ppm increases the aldosterone level by 25 %. Adrenocorticotropic hormone, dopamine, endothelin, serotonin, vasopressin, and acetylcholine participate less in the stimulation of hormone synthesis. Agents inhibiting the production of aldosterone are atrial natriuretic peptide, heparin, and androgens [14, 16].

Almost all aldosterone is contained in the blood in free form. Under normal conditions, its plasma concentration depends mainly on the quantity of sodium taken with food, time of the day and body position. The minimum hormone level is observed in the morning and in prone position, and the maximum level — in the afternoon and in a vertical position (sitting, standing). Low salt intake leads to increased blood concentrations of the hormone, and excessive salt intake — on the contrary, to reduced blood concentrations. Plasma level of aldosterone decreases with age [16].

Aldosterone begins to act only after being bound to special protein structures — mineralocorticoid receptors (MCR). Numerous studies have shown that these receptors are scattered all over the body: along with classical epithelial MCR located in renal cells, they are found in cardiomyocytes, endotheliocytes, salivary and sweat glands, fibroblasts, monocytes, macrophages, adipose tissue cells and neurons [15, 17]. Both adrenal mineralocorticoid hormones — aldosterone and deoxycorticosterone — have high and almost equal affinity to MCR. However, the majority of the latter is contained in the blood in inactive form. Therefore, MCR are activated primarily owing to aldosterone. MCR can also be stimulated by glucocorticoids, particularly, cortisol. Although its affinity to MCR is slightly less than that of aldosterone, the plasma level of cortisol far exceeds the concentration of aldosterone. Therefore, it is cortisone that binds MCR in some tissues (pituitary gland, myocardium) [18].

Like all corticosteroid hormones, aldosterone has two mechanisms of action [19]. Genomic, or slow, mechanism is related to intercellular penetration of the hormone molecule and its binding to nuclear receptors with subsequent stimulation of synthesis of effector proteins. Effects induced by this interaction develop in hours or days. They include myocardial fibrosis, inflammatory reactions in vascular walls, development of edema syndrome, tissue remodeling, and apoptosis of cardiomyocytes [20]. Quick, or non-genomic, route of cell signaling transduction is mediated by interaction with membrane receptors, and includes activation of various kinase cascades. As this process does not require protein synthesis, the effect develops within minutes following interaction. Examples of a non-genomic mechanism include electrical myocardium remodeling, vasoconstriction, development of oxidative stress [21].

Primary physiological effects of aldosterone consist in maintaining water-salt balance in the human body [19]. Once in the bloodstream, aldosterone interacts with MCR of epithelial cells of distal tubules and renal collecting tubules, leading on the one hand to

increased reabsorption of sodium and fluid retention, and on the other hand to enhanced excretion of potassium and magnesium. Sodium-retarding effect of aldosterone plays a key role in maintaining homeostasis in the presence of hypovolemia.

In recent years, conclusive evidence has been obtained, showing that the action spectrum of aldosterone lies far outside the limits of the narrow range of "renal" effects. Systemic or local hyperproduction of the hormone causes a number of pathological effects [19–24]:

- sodium retention, loss of potassium and magnesium;
- endothelial dysfunction;
- myocardial and vascular wall inflammatory changes;
- reduced arterial compliance;
- AT2 vasoconstrictive action potentiation;
- catecholamine action potentiation;
- increased platelet aggregation;
- increased lipids;
- dulled baroreceptor response;
- oxidative stress induction;
- impaired function of ion channels in cells and repolarization processes;
- enhanced formation of collagen in organs and tissues;
- left ventricular (LV) hypertrophy;
- LV diastolic dysfunction;
- reduced heart rate variability;
- activated tumor growth factor β1;
- impaired glucose tolerance;
- insulin resistance.

Many of these effects play a key role in the development and progression of various cardiovascular diseases, including atrial fibrillation.

Aldosterone role in AF development and maintenance

Although the role of excessive activity of RAAS in AF development is no longer in doubt, the importance of aldosterone in the development and maintenance of this arrhythmia is only just being studied. Indirect evidence of that was obtained as early as 2005 by Milliez P. et al. [25], who showed that the risk of AF in patients with primary hyperaldosteronism was 12 times higher than in the general population. Further clinical studies [26, 27] found that blood level of aldosterone increased during an AF episode and decreased following sinus rhythm restoration. Experimental data obtained later showed that the blockade of aldosterone receptors contributes to the suppression of atrial fibrosis processes and prevents AF development [28].

It is assumed that pathological myocardial effects of aldosterone occur not only through its systemic hyperproduction, but also because of direct synthesis of the hormone in atrial tissues. It is reported [29] that local levels of AT2 and aldosterone are higher in patients with AF as compared to individuals with sinus rhythm. Moreover, the extent of local production of RAAS products varies in different categories of patients with AF and depends on the type of underlying disease. The existence of AF in patients with mitral stenosis is associated with high levels of both local and circulating AT2 and aldosterone, while the key role in AF development in mitral insufficiency belongs to local RAAS hyperactivity [30].

By combining experimental and clinical study data, Tsai C-T et al. [31] significantly expanded the existing understanding of mechanisms of adverse effects of aldosterone. Researchers have shown that the most important negative properties of the hormone are related not even mainly to its local hyperproduction in atrial tissue, but result from excessive expression of MCR. They have demonstrated that even in equal intra-atrial aldosterone level in patients with sinus rhythm and AF, MCR expression in the latter increases considerably. In their subsequent experiments based on atrial cardiomyocytes, the authors found that the increased expression of MCR is induced by quick depolarization occurring in AF. Exposure of cells with spironolactone weakens these processes.

Reasons for increased production of aldosterone in AF remain largely understudied. It is not clear whether AF itself induces synthesis of aldosterone or, on the contrary, overproduction of this hormone "triggers" mechanisms of arrhythmia development and maintenance. Analyzing literature data and findings of own studies [26, 27], it seems that the occurrence of AF may indirectly contribute to the development of hyperaldosteronism.

In particular, it is well known [32] that an AF episode is accompanied by pronounced neurohormonal activation: increased levels of AT2 and catecholamines, which are potent stimulators of aldosterone synthesis. Increase in AT2 concentration

during an AF episode (by increasing ACE expression) and the number of its receptors leads to not only higher adrenal production of aldosterone and its higher plasma levels, but also promotes excessive intramyocardial production of the hormone.

It is interesting that the impact of AT2 on the level and activity of aldosterone is not a one-way process: the latter, in its turn, potentiates negative effects of AT2. Synergism of AT2 and aldosterone has been confirmed by many experimental studies [33]. So, when working with smooth muscle cells, negative effects caused by AT2 (oxidative stress, apoptosis) were partially mitigated by exposing the cells to spironolactone, a MCR antagonist.

Aldosterone can activate type 1a AT2 receptors by increased phosphorylation of several signaling proteins (ERK1/2, JNK, NF-kB, etc.). AT2, in its turn, can stimulate nuclear MCR receptors. Both effectors of RAAS activate a number of factors in a synergic manner, which leads to the induction of cardiac hypertrophy and fibrosis processes, systemic inflammation and hypercoagulation [34].

Thus, the development of AF in itself clearly leads to higher systemic and local production of aldosterone. In its turn, the persistence of such hyperaldosteronism promotes the occurrence of all negative effects typical for this hormone: fibrosis, inflammation, and cardiomyocyte apoptosis. This leads to further atrial remodeling, forming a substrate for AF recurrences and thereby "completing the vicious circle".

Mechanisms of aldosterone-mediated atrial remodeling

For the development of AF, a triggering mechanism (trigger) is required, and for its maintenance — a certain atrial substrate. The arrhythmia substrate forms as a result of the so-called atrial remodeling [35, 36]. Detailed mechanisms of the process have not been fully elucidated yet. At the moment, electrical (electrophysiological), contractile and structural atrial remodeling has been identified [37].

Electrical remodeling is a set of intra- and extracellular changes in the myocardium, which result in the impairment of its electrophysiological properties [37]. Changes in the functions of ion channels, transporters and receptors lead to the impairment of depolarization and post-depolarization processes, development of atrial conduction heterogeneity, and consequently, the occurrence of re-entry waves and triggering activity, predisposing to AF. Preservation of AF further contributes to the progression of electrophysiological remodeling. High atrial contraction rate in arrhythmia leads to calcium overload of the atrial myocardium, which poses a threat to cell viability and triggers a number of compensatory mechanisms aimed at reducing its intracellular flow (inactivation of L-type calcium channels). Consequently, the atrial action potential duration and effective refractory period become shorter, which contributes to AF preservation. Electrophysiological remodeling induced by AF occurs quickly (usually within several days), but at the same time it is a fast reversible process after sinus rhythm is restored [38]. Contractile atrial remodeling occurs within the same time periods as electrophysiological remodeling. Reduction in intracellular calcium concentration at a high atrial contraction rate results in decreased contractility of atrii [38].

If arrhythmia persists for over 7 days, contractile remodeling transforms into structural remodeling, when different disturbances in myocardial cell and tissue structures occur [38]. At the cellular and tissue levels, structural remodeling is expressed as apoptosis, cellular degeneration, inflammatory changes, fibroblast proliferation, and at the macrolevel — as atrial hypertrophy and dilation. Many structural changes are irreversible and, ultimately, result in the development of permanent AF.

Role of aldosterone in electrical atrial remodeling

Numerous studies have shown that aldosterone is the most important mediator in electrical atrial remodeling. Mechanisms of such an effect are under discussion. Some assume that one of them is mediated through non-genomic effect of the hormone, i. e., the oxidative stress induction. Aldosterone directly stimulates the formation of reactive oxygen intermediates in the myocardium, which leads to the destruction of membrane components, with formation of lipid peroxidation products [10].

The other, more complex route is mediated by hyperproduction under the exposure of nuclear factor kappa B (NF-kB) aldosterone [39, 40]. This protein is one of the main transcriptional agents responsible for adaptive responses of cells. It represents the family of cytoplasmic proteins, which, when stimulated, pass into the free state, moving

to the nucleus where they exhibit activity binding to promoters of over 100 genes. NF-kB plays an important role in cellular proliferation, apoptosis, inflammatory and autoimmune responses, as it regulates the expression of genes involved in these processes. One of the important effects of NF-kB is its participation in regulating the function of ion channels. Stimulated formation of this protein under the influence of aldosterone leads to disturbed transmembrane ion fluxes, thus contributing to electrical atrial remodeling [40, 41].

Aldosterone-dependent electrical atrial remodeling can also be caused by calcium overload of cardiomyocytes. In the study conducted by Lalevée N. et al. [42], aldosterone increased calcium flux through T-type ion channels, without affecting L-type ion channels. This resulted in the overloading of cardiomyocytes with calcium, inducing the electrical atrial remodeling. The effect of aldosterone on calcium metabolism in cardiomyocytes was also confirmed by Sakamuri S. S. et al. [43]. The authors showed that the use of MCR antagonists can prevent the calcium overload of cardiac cells. This information helps explain the ineffectiveness of calcium channel blockers in preventing electrical remodeling and understand why the drugs failed in the clinical studies on AF prevention: they block L-type calcium channels, while aldosterone acts through T-type channels, i. e., the so-called escape phenomenon occurs.

Calcium metabolism disorders caused by aldosterone can, in turn, trigger a chain of other pathologic processes. In the section of human atrial cells, it was demonstrated that tachy-induced overload of atrial cells with calcium causes oxidative stress, cellular degeneration and mitochondrial dysfunction in them. It leads further to cellular apoptosis and contractile dysfunction [44].

Thus, the role of aldosterone in the induction of electrophysiological disorders in atrial cells is now obvious. However, it should be noted that electrical remodeling is a complex and multifactorial process, and despite all the studies conducted in this area, there are still more questions than answers. It is hard to say whether the findings of said studies can be fully extrapolated to the general population of patients with AF. In some publications, the effect of aldosterone on electrical remodeling processes was assessed only on the basis of cellular models, while the majority of patients enrolled in the conducted clinical studies had valvular AF (developed with an underlying severe mitral or aortic valve condition) and were subject to surgical intervention. At the same time, mechanisms of the effect of this hormone on electrophysiological processes in the myocardium in non-valvular AF remain unclear.

Aldosterone role in structural atrial remodeling

At the tissue level, structural atrial remodeling manifests itself in several processes: myocardial fibrosis, inflammatory changes, cardiomyocyte hypertrophy and apoptosis [45]. Current studies confirm that aldosterone participates in these processes [19].

There is more and more information available, showing that aldosterone is a key mediator for atrial fibrosis [46, 47]. Myocardial fibrosis is a pathologic process characterized by the destruction of the normal structure of cardiomyocytes and subsequent excessive deposition and accumulation of extracellular matrix proteins (collagens and fibronectins), which form the basis of connective tissue, in the destructed cardiomyocytes.

Underlying molecular mechanisms of this phenomenon are not entirely clear. Some assume that the trigger effect of aldosterone in myocardial fibrosis processes is implemented through a number of ways. Firstly, the hormone has a direct growth-stimulating impact on fibroblasts, and in this case the excessive expression of intramyocardial MCR plays the most important role in the implementation of profibrotic effects. The interaction between aldosterone and MCR leads to the stimulated production of types 1A and 3A collagen, transforming growth factor β1, alpha-type smooth muscle myosin and other fibrotic agents. In long-term and persistent hyperaldosteronism, the accelerated proliferation of collagen- and fibronectin-producing fibroblasts is observed. Eventually, it leads to the pronounced stimulation of perivascular fibrosis processes in intramyocardial vessels of atrii [48].

The other mechanism consists in the effect of aldosterone on the fibrinolysis system. It has been proven that the hormone affects a number of plasminogen inhibitors and activators, in particular, type 1 plasminogen activator inhibitor (PAI-1) and tissue-type plasminogen activator (t-PA) [49, 50]. Distortion of the PAI-1/t-PA ratio leads to the development of imbalance in the fibrinolysis system and coagulation system. It is well known [50] that PAI-1 and

t-PA are synthesized primarily by the vascular endothelium. Hyperaldosteronism-induced endothelial dysfunction results in disturbed participation of the endothelium in the regulation of fibrinolysis processes and the activation of myocardial fibrosis. The inhibitory action of aldosterone on the fibrinolysis system also promotes fibrosis processes. By suppressing the production of plasmin from plasminogen, aldosterone contributes to the accumulation of the extracellular matrix.

The fibrosing effect of the hormone can be mediated by the induction of inflammation, arteriolar necrosis and cardiomyocyte apoptosis [50]. Substitutive fibrosis processes develop subsequently in place of dead cells.

There is also a number of other potential, but less studied mechanisms. Rombouts K. et al. [51] say that aldosterone can inhibit the activity of collagenase, an enzyme participating in collagen catabolism processes. S. Johar et al. [52] demonstrate that aldosterone is a mediator of AT2-induced atrial fibrosis, while the use of spironolactone inhibits these effects of AT2.

Along with fibrosis, inflammatory changes in the atrial myocardium also play a role in the genesis of the structural remodeling of atrii. It is noted that AF often develops in patients after coronary artery bypass graft surgery, with the maximum incidence observed on day 2 or 3 following the surgery and coincides with peak blood concentrations of inflammatory markers (C-reactive protein, leucocytes, and interleukins). The level of C-reactive protein and incidence of arrhythmia episodes are substantially reduced by preventive application of glucocorticosteroids and other drugs having anti-inflammatory action in patients who underwent cardiac surgery and unoperated patients with AF [53]. This hypothesis has also been confirmed histologically [54]: microscopy of atrial issue in patients with AF often reveals inflammatory infiltration even when there are no other organic heart diseases.

It has been shown that aldosterone potentiates local inflammation processes in the endothelium of small and medium coronary vessels, as well as in perivascular areas of the myocardium. Even physiological concentrations of aldosterone in MCR-expressing cardiomyocytes cause rapid increase in the activity of genes involved in inflammation processes [55].

Pro-inflammatory effect mechanisms of the hormone are diverse [56]. First of all, the induction of inflammation is started by reactive oxygen intermediates. It is well known that the formation of hydrogen superoxide and peroxide leads to the activation of various pro-inflammatory transcription factors — protein-1 activator, NF-κB, etc. The activation of the latter subsequently results in the formation of different adhesion molecules, chemokines and inflammatory cytokines. In the experiment, systemic administration of aldosterone increased NADPH oxidase concentrations in macrophages, heart, vessels and kidneys [57]. *In vitro*, aldosterone activated chemoattractant lymphocyte factor, interleukin-16, antigen-4 associated with cytotoxic T-lymphocytes (CTLA4) and other inflammation mediators [58]. *In vivo*, aldosterone administration in rats increased the cardiac expression of intercellular adhesion molecules, cyclo-oxygenase-2, osteopontin and led to inflammatory changes in arteries involving perivascular macrophages. At the same time, the administration of MCR blockers in animals prevented such an inflammatory reaction. In kidneys, the administration of aldosterone caused perivascular leucocytic infiltration and increased expression of osteopontin and interleukins 1 and 6 [59].

Thus, there is no doubt about the role of aldosterone in the genesis of inflammatory changes in the myocardium.

While the effect of aldosterone on atrial tissues is only just being studied, the fact that this hormone is a key factor of structural ventricular remodeling is no longer in doubt [39]. Ventricular hypertrophy and fibrosis occurring in this case result in the increased stiffness of the left ventricle, the development of its diastolic dysfunction, subsequent hemodynamic atrial overload and occurrence of conditions for AF development.

There is no doubt that aldosterone takes part in the development of LV hypertrophy. It has been shown that aldosterone concentration in patients with hypertension significantly correlates to the mass index of its myocardium [39]. In patients with aldosterone-secreting adenomas, LV hypertrophy, which is reversible following tumor resection, is observed [59].

One of the best understood pathogenetic mechanisms of the development of LV hypertrophy against the background of hyperaldosteronism is associated with the hypertensive effect of the hormone. Sodium retention and increased circulatory

volume as a result of excessive production of aldosterone naturally leads to a rise of blood pressure, LV overload and compensatory gain in its myocardial weight [19].

However, there is emerging evidence that the hormone can stimulate hypertrophy processes, irrespective of the extent of its hypertensive effect. According to Tomaschitz A. et al. [60], aldosterone level in patients with mild and moderate hypertension who had LV hypertrophy was significantly higher than in patients with a comparable degree of hypertension but without LV hypertrophy. In experimental studies, aldosterone in the presence of sodium chloride stimulated myocardial fibrosis and hypertrophy, irrespective of blood pressure level [61].

By interacting with epithelium receptors of baroreflex areas, aldosterone contributes to their hyposensitization and impairment of blood pressure control mechanisms [61]. In this way, the hormone can modulate local sympathetic cardiac activity and indirectly affect the development of LV hypertrophy. Genetic factors affect the rate and degree of myocardial hypertrophy development as well. There is evidence that the gene responsible for aldosterone synthesis belongs to the group of genes, the expression of which determines the polygenic inheritance of LV hypertrophy [60].

With respect to the stimulating effect the hormone has on hypertrophy processes, the expected question arises whether such an effect is limited to the ventricular myocardium, or covers atrii as well. This question was answered in the experimental work by Reil J.-C. et al. [11], where osmotic minipumps, which supply aldosterone at a rate of 1.5 mg/h, were implanted subcutaneously in 11 rats of the treatment group. The control group included 9 native rats. Standard electrocardiogram, AF inductivity and atrial pressure were analyzed in the animals following 8 weeks of observation *in vivo*. Then, isolated hearts were assessed for LV function and atrial conduction, and epicardial mapping was performed. Histologic examination of tissues was also conducted. The results showed that neither systolic, nor diastolic LV function, as well as atrial pressure, changed in the animals that received aldosterone. At the same time, longer P-wave, increased overall time of atrial activation, and impaired local conduction were observed in them. Histologic differences consisted in the development of hypertrophy of atrial cardiomyocytes and their fibrosis in the treatment group. This model proves conclusively that aldosterone has a direct effect on the atrial myocardium, including hypertrophy processes therein.

Aldosterone synthase gene polymorphism as a risk factor for AF

As is known, the most common causes of AF are ischemic heart disease and hypertension, and, rarer, valvular heart disease [1]. However, sometimes clinicians have to deal with family cases of arrhythmia or observe early onset of the disease in the absence of clear cardiac and extracardiac causes, which allows suspecting the genetic nature of the disease [62].

There is now data showing that the primary genetic determinant of non-familial AF forms is polymorphism of the RAAS genes [63]. The role of the terminal effector of the system, i. e., aldosterone, in the development and progression of myocardial remodeling is also determined to a considerable extent by genetic factors. In particular, the key enzyme participating in synthesis of the hormone is aldosterone synthase, for the primary structure of which the *CYP11B2* gene is responsible. Polymorphism of the fifth region of the gene has been examined most of all. The DNA region in the regulatory area of the *CYP11B2* gene where cytosine (C) in the -344th position is replaced with thymine (T) is designated as genetic marker C(-344)T. There are 3 potential genotypes of this fragment: C/C, C/T, T/T [64].

Some assume that the activity of aldosterone, and hence the intensity of its pathogenic effects, may depend on polymorphism of C(-344)T. According to recent studies [65, 66], the presence of T-allele (rs1799998 polymorphism) is associated with hypertension, chronic kidney disease and cardiac hypertrophy.

Data on the interrelation between C(-344)T polymorphism and AF development still remains contradictory. Amir R. E. et al. [67] examined the relationship between different genotypes of the enzyme and the risk of AF in 178 patients with LV systolic dysfunction. Arrhythmia was diagnosed in 57 (32 %) patients. The genetic study found that -344 CC genotype is a potent predictor of AF: almost half (45 %) of the patients with this genotype had arrhythmia, while in individuals with -344 TT and TC types it was reported cumulatively only in 27 % of cases ($p = 0.02$). Multivariate

regression analysis has shown that, after age and the size of the left atrial, -344 CC genotype was the most potent independent predictor of AF (odds ratio: 2.59, 95 % CI: 1.68–3.98, p = 0.02).

Other researchers, in contrast, have found a relationship between the presence of T-allele of aldosterone synthase C(-344)T gene and the development of AF. Sun X. et al. [68] did not find any significant impact of the gene polymorphism on the risk of AF development or recurrence. ACE (I/D) genotype has become the determining genetic factor for the development of arrhythmia. According to these and some other researchers [69], C(-344)T polymorphism in the aldosterone synthase gene is not directly related to the risk of AF, but is associated with the development of structural atrial remodeling.

Convincing results have been obtained in the meta-analysis that included 2,758 patients with AF from six different studies [69]. The authors found that the presence of C-allele in C(-344)T gene of *CYP11B2* substantially increases the risk of AF (odds ratio: 1.26, 95 % CI: 1.11–1.42, p = 0.0002).

Finally, a recent large-scale meta-analysis of 12 studies involving 5,466 patients confirmed that C(-344)T polymorphism with presence of T-allele (rs1799998) is closely related to a higher risk of AF in the general population (odds ratio: 1.29, 95 % CI: 1.08–1.54, p = 0.005), and its highest predictive value is typical for East Asians and individuals with hypertension and heart failure [66].

Still, the ambiguity of the available information on the contribution of aldosterone synthase C(-344) T gene polymorphism to the development of AF makes it necessary to conduct further studies in this area.

Conclusion

The excessive activity of aldosterone undoubtedly plays a role in the development and maintenance of AF. The hormone takes part in all the stages of electrophysiological and structural atrial remodeling, promoting the formation of arrhythmia substrate. The occurring disorders are not only the result of hemodynamic changes in cardiac chambers, but also the consequence of the direct action of aldosterone on the atrial myocardium.

The adverse myocardial effects of the hormone occur not only through its systemic hyperproduction, but also because of direct synthesis of the hormone in atrial tissues. Increased expression of MCR plays a major role in the development of AF.

Hyperaldosteronism can be a cause as well as the effect of AF. An episode of arrhythmia is characterized by pronounced neurohormonal activation, accompanied by an increase in intramyocardial synthesis of aldosterone and expression of its receptors. This contributes to further atrial remodeling, by creating conditions for arrhythmia recurrences and thereby "completing the vicious circle".

The data obtained helps to shed light on AF development mechanisms and the role of aldosterone in them. Further study of pathogenic effects of the hormone and their pathways may contribute to the discovery of new therapeutic approaches to the treatment of arrhythmia.

Conflict of interests

The authors declare no conflict of interests.

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DYNAMICS OF CHARACTERISTICS OF RESPIRATORY FUNCTION FOR THE DEVELOPMENT OF CORONARY HEART DISEASE IN PATIENTS WITH CHRONIC OBSTRUCTIVE LUNG DISEASE

Abstract

Chronic obstructive pulmonary disease (COPD), along with cardiovascular disease, belongs to the leading chronic non-infectious diseases of our time, which, occurring in comorbidity, lead to the development of severe complications, which aggravate each other. **Objective:** to determine the methods of diagnosis and prevention of coronary events in patients with COPD living in the northern latitudes based on the dynamic assessment of the parameters of respiratory function. **Materials and methods**. During five years, extended instrumental examination (body plethysmography, echocardiography) was provided in 182 patients with COPD (mean age 65.0±1.2 years) within the study. Coronary events during prospective follow-up were recorded in 66 patients (mean age 65.0±1.2 years). **Results:** in a cohort of 976 patients with COPD, the number of patients with moderate bronchial obstruction (54 %) was 6 times higher than the number of patients with severe bronchial obstruction (8.6 %) ($p<0.001$). During the five-year progression of impairments of volume and speed parameters of respiratory function was registered period in patients with isolated COPD (n=116). It should be noted that the course of COPD in this sample of patients was associated with a predominant decrease in restrictive function parameters, and manifested in the form of a decrease in the expiratory reserve volume (ERV) by 20.6 % ($p=0.004$). In patients with COPD, constituting a risk group for the development of coronary events, there was no significant dynamics of respiratory function parameters for five years ($p>0.05$). Patients with lower values of volume parameters of respiratory function, such as ERV and inspiratory capacity (IC), showed a recorded coronary event during the five-year follow-up period ($p<0.05$). The greatest number of coronary events among patients of moderate and high risk with COPD was recorded in the first 3 years of follow-up, among patients of very high risk — evenly over 5 years. Coronary events were associated with periods of exacerbation of the underlying disease ($p<0.05$). Their incidence rate (myocardial infarction, angina, and coronary death) for five years in patients with COPD with very high, high and moderate coronary risk was 33.9 %, 10.5 %, 1.52 %, respectively. Using stepwise discriminant analysis, it was found that the leading prognostic markers of coronary events in patients with COPD living in the northern latitudes are the data of echocardiography (end-diastolic dimension of the left ventricle, pulmonary artery systolic pressure) and body plethysmography (ERV). **Conclusion.** Body plethysmography and echocardiography must be provided in all patients with COPD to identify silent restrictive respiratory function disorders at the first stage of the disease. Given the low level of diagnosis of COPD in Russia, a long asymptomatic course of the disease, and the development of COPD after 10 years of living in the North, according to the literature, it is recommended to conduct an annual body plethysmography as a screening method of examination of all smokers living in the northern latitudes. Thus, the use of body plethysmography with a targeted assessment of volume parameters, as well as echocardiography, allows to identify groups of patients at risk of coronary events and, thereby, to carry out timely prevention of the latter among patients with COPD.

Key words: *chronic obstructive pulmonary disease, respiratory function, ischemic heart disease, comorbidity*

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IC — inspiratory capacity, IHD — ischemic heart disease, EDD_{LV} — left ventricular end-diastolic dimension, MEFR — maximum expiratory flow rate, FEV_1 — forced expiratory volume in 1 second, ERV — expiratory reserve volume, PASP — pulmonary artery systolic pressure, HF — heart failure, CVDs — cardiovascular diseases, COPD — chronic obstructive pulmonary disease, ECG — electrocardiogram

Chronic obstructive pulmonary disease (COPD) is one of the leading chronic non-contagious diseases. It has been established that the primary cause of death among the patients with COPD is not only respiratory failure but also cardiovascular diseases (CVDs) that are very widespread in the world today as well [1, 2, 3]. Patients suffering from COPD are at 2 to 3 times higher risk of cardiovascular mortality [4]. In the northern regions this risk is 5 to 6 times higher [5] and contributes approximately 50 % of the total number of deaths [4]. According to Kerry Schnell et al., comorbidity with underlying COPD is the rule rather than the exception, since 96.4 % of patients with COPD aged 45 and older have at least one concomitant disease [6]. Findings of studies conducted by domestic and foreign therapists and pulmonologists show that 85 % of patients with COPD have essential hypertension involving target organs, 64 % — coronary atherosclerosis; 19 % — a past history of ischemic stroke; 21 % — confirmed thromboembolism of pulmonary arteries; 39 % — excess fat deposits, etc. [7]. The main types of CVDs in case of COPD, according to Correia L. et al., include ischemic heart disease (IHD), hypertension and heart failure (HF). According to European researchers, the incidence of COPD and IHD in patients of older age groups is 62 %; the mortality rate in case of comorbidity of the two conditions exceeds 50 %. Patients with newly diagnosed COPD have 5.5 times higher incidence rate of myocardial infarction as compared to the general population, and 3 times higher incidence rate of CVA [3, 8].

In view of some shared components of pathogenesis, particular features of a clinical picture form in cardiorespiratory comorbidity accompanied with mutual aggravation syndrome [9]. According to modern views, great importance for the development and progression of COPD and CVDs is attached to the disruption of the functioning of the cellular component of immune system, phagocyte and cytokine systems. Due to hemodynamic stress, free-radical oxidation, systemic inflammation and imbalance in the proteinases–inhibitors system, patients with COPD show early formation of endothelial dysfunction, change in collagen and elastin metabolism in vascular walls, damage to cellular and molecular structures, activation of procoagulant and growth factors in a vessel wall, which lead to its destructuration and fibrosis [10, 11]. Owing to hypertrophy and hyperplasia of endothelium and subendothelium in response to hypoxia developed over time, intima and media thickening occurs in the vascular wall, which results in the disruption of its functional activity, progression of hypertrophy and hyperplasia of smooth muscle cells, an increase in the content of collagen and elastin [12]. Endothelium dysfunction and vascular remodeling worsen steadily even in the stable course of COPD, contributing to development and progression of a coronary disease. Progressive hypoxemia aggravates COPD as well as comorbid CVDs.

Numerous studies show the relationship between the decrease in the forced expiratory volume in 1 second (FEV_1) and increased development of IHD [13–22]. In patients with mild and moderate COPD, the risk of cardiovascular mortality increases by 28 % with every 10 % of decrease in FEV_1 [2, 18]. It has been established that the primary factors, which determine changes in FEV_1 in patients with COPD during long-term follow-up include smoking status, frequency of exacerbations, appropriate therapy and therapeutic compliance [23–25, 27]. When selecting an approach for management of patients with COPD and cardiac comorbidity, there is need to bear in mind the cumulative risk of potential complications, especially for the elderly [2, 21, 22].

The search for effective methods to prevent and treat conditions with a multimorbidity/comorbidity is one of the most critical medical and social challenges due to the increase in life expectancy

of the population and the number of patients with comorbidities. Early diagnosis of IHD in COPD patients remains relevant. However, it is complicated due to the similarity of the symptoms, low diagnostic value of routine electrocardiogram (ECG) examination, peculiarities of clinical signs when one disease leaves another in "the shadow" [22–24, 26].

Thus, early diagnosis and prevention of cardiovascular diseases in COPD through the search for the most informative risk factors for their development remain relevant. The identification of such risk factors should be referred to predictive medicine, which is one of components of the modern 5P model of medicine.

Study objective: to identify methods for diagnosing and preventing coronary events in patients with COPD, who live in northern latitudes, based on dynamic assessment of respiratory function parameters.

Materials and Methods

Over a five-year period of observation, 976 patients with COPD (mean age: 60.7±0.35 years) were treated at the Surgut Hospital. The ratio of male to female patients was 5:1, n=820 (84 %) and n=156 (16 %), respectively. The mean age of the patients was comparable (females — 61.1±0.94 years, males — 60.7±0.37 years) (p=0.671).

The inclusion criterion was the presence of confirmed COPD (Global Initiative for Chronic Obstructive Lung Disease, GOLD, 2011, 2014). Exclusion criteria were IHD confirmed at the beginning of the study, other concomitant respiratory diseases, cancer and hematologic diseases, end-stage kidney or liver failure, chronic heart failure of 3 and 4 NYHA classes, and diabetes mellitus types 1 and 2.

From among 976 patients, of which 19 patients (2 %) reached the fatal endpoint (coronary death) [25], 182 patients were randomized to undergo extended instrumental examination for five years. Duration of COPD was 8.6±0.23 years. Duration of living in northern regions was 29.9±0.5 years. In the course of prospective observation of the group, changes in the key morphofunctional parameters of respiratory and cardiovascular systems were assessed. As a result, predictors of coronary events were identified. Non-fatal events including acute (myocardial infarction) and chronic forms of IHD (angina, silent myocardial ischemia, cardiac rhythm disorder, heart failure) newly diagnosed in patients during the observation period were reported in 66 patients (control group) of 182 (mean age: 65.0±1.2 years) (60 males (mean age: 63.0±1.1 years) and 6 females (mean age: 74.0±0.8 years) (p<0.01)). It is worth noting that no fatal coronary events were reported in the control group. The treatment group included 116 patients (at the ratio of 5:1: 96 males (mean age: 60.9±1.2 years) and 20 females (mean age: 54.9±2.7 years) (p=0.140)). It should be noted that during the prospective observation of over 182 patients, the development of coronary events (IHD), in particular, was assessed. The clinical diagnosis of IHD in the course of dynamic observation was confirmed based on the generally accepted diagnostic standards using the appropriate laboratory and instrumental examination, according to the International Classification of Diseases, 10th Edition, as well as based on the criteria of the WHO Expert Committee and the Russian Society of Cardiology guidelines (2006, 2007, 2008, 2011).

The main study methods included: the interview method (recording of complaints, medical history), physical examination (measuring of blood pressure (BP), identifying leading clinical syndromes of COPD and IHD), laboratory tests (complete blood count, biochemical analysis), instrumental examination methods (body plethysmography, echocardiography performed as per standard methods). Coronary risk was identified in all patients at the baseline as per the Systematic Coronary Risk Evaluation (SCORE), taking into account gender, age, systolic blood pressure, total cholesterol, and smoking status. A relative risk score was applied to young persons. The term coronary risk was used, first of all, with consideration for the exact translation of the SCORE title; and second, due to the fact that the assessment covered the incidence of coronary events and peculiarities of coronary disease course with underlying COPD. According to the European Guidelines on cardiovascular disease prevention in clinical practice, all the patients were divided into groups at moderate (up to 5 % as per the SCORE), high (5–9 % as per the SCORE), and extremely high (over 10 % as per the SCORE) risk.

Statistics were processed using Microsoft Excel 2007, IBM SPSS Statistics 22. The Student's *t*-test was used for inter-group differences (the data distribution equality was assessed by the Kolmogorov-Smirnov test), and the Pearson's c^2-test and *z*-test were applied in the analysis. Coronary events over the observation period were recorded by the Kaplan-Meier analysis. The latter were predicted using stepwise discriminant analysis. The expiratory reserve volume was taken as a grouping factor.

Results and Discussion

In the cohort of 976 patients with COPD, the number of patients with moderate bronchial obstruction (54 %) was 6 times as much as those with extremely severe one (8.6 %) (p<0.001). The least proportion of patients had mild bronchial obstruction (4.2 %) (p<0.001). One in three study patients had severe COPD (33.2 %) (p=0.004). Among females, patients with moderate bronchial obstruction prevailed (71.8 %), as compared to males (50.7 %) (p=0.014). Severe COPD was predominant among males (36.1 %) in contrast to female with COPD, among whom this severity was reported only in one in five cases (18.0 %) (p=0.005) (Table 1).

The average annual incidence of exacerbations that require hospitalization in COPD patients was 1.6±0.1. Females experienced exacerbations rarer (1.3±0.1) than males (1.6±0.1) (p=0.046), which is associated with less pronounced bronchial obstruction. So, the average annual number of exacerbations in severe and extremely severe COPD was 1.8±0.0 and 1.8±0.0, respectively, which was much greater than in mild COPD, i. e., 1.2±0.0 (p<0.001). The worsening of bronchial obstruction and exacerbations of COPD result in the development and progression of cardiovascular diseases [2, 26, 27]. Moderate bronchial obstruction among the study patients was reported in one in two patients in the treatment group (54 %, n=62) and the control group (50 %, n=33) (p>0.05)). Extremely severe bronchial obstruction was reported rarer (8.6 %, n=10 (treatment group); 7.3 %, n=5 (control group) (p>0.05)) (p<0.001). Mild severity was observed in the least number of patients (4.2 %, n=5) (treatment group); 3.8 %, n=3) (control group) (p>0.05). Severe bronchial obstruction was reported in one in three patients (33.2 %, n=39 (treatment group); 38.9 %, n=25 (control group)) (p>0.05).

When analyzing expiratory function parameters in COPD patients without any reported coronary event over the five-year period of observation (n=116), it was established that FEV_1 was decreased in males with COPD by 30.0%, and in females — by 26 %, indicating the severity of bronchial obstruction in this patient population. Females showed greater inspiratory capacity (IC) (%) (p=0.050). Tiffeneau index in males decreased by 9.5 %, and in females — by 4.6 %. Analysis of characteristics of

Table 1. *Bronchial obstruction in patients with COPD (n = 976)*

Parameter	All patients n=976 abs. (%)	Male n=820 abs. (%)	Female n=156 abs. (%)	p	χ^2
	1	2	3		
I (FEV_1 >70 %)	40 (4.2 %)	32 (4.0 %)	8 (5.1 %)	p_{1-2}=0.935 p_{1-3}=0.724 p_{2-3}=0.647	χ^2_{1-2}=0.007 χ^2_{1-3}=0.125 χ^2_{2-3}=0.209
II (FEV_1 70–50 %)	528 (54.0 %)	416 (50.7 %)	112 (71.8 %)	p_{1-2}=0.451 **p_{1-3}=0.042** **p_{2-3}=0.014**	χ^2_{1-2}=0.569 **χ^2_{1-3}=4.120** **χ^2_{2-3}=6.044**
III (FEV_1 50–30 %)	324 (33.2 %)	74 (36.1 %)	28 (18 %)	**p_{1-2}<0.001** **p_{1-3}=0.005** **p_{2-3}=0.005**	**χ^2_{1-2}=97.722** **χ^2_{1-3}=7.864** **χ^2_{2-3}=7.788**
IV (FEV_1 <30 %)	84* (8.6 %)	19* (9.2 %)	8* (5.1 %)	**p_{1-2}<0.001** p_{1-3}=0.233 p_{2-3}=0.104	**χ^2_{1-2}=28.153** χ^2_{1-3}=1.483 χ^2_{2-3}=2.649

Note: the significance of differences between patients with COPD by the χ^2 test

patency of respiratory tract at different levels identified no differences between males and females. The maximum expiratory flow rate $(MEFR)_{25}$ was reduced in males by 46.7 %, and in females — by 65.6 % (p=0.063); $MEFR_{50}$ was decreased in males by 59.4 %, and in females — by 51.5 % (p=0.633).

Among 66 COPD patients with IHD diagnosed during the observation period, mixed respiratory function impairments with predominant obstructive changes were found (Table 2).

At the beginning of the study, only several volumetric lung parameters were different between the COPD patients and those with COPD and confirmed IHD. So, the minimum values of ERV, IC and PEFR were found in males with COPD with reported coronary events (p<0.05).

Over the five-year period, the worsening of respiratory function impairments concerning its volumetric and velocity parameters was reported in patients suffering from COPD only (n=116). It should be noted that the progress of COPD in this number of patients was associated primarily with the reduction in restrictive parameters presented as ERV decrease by 20.6 % (p=0.004) (Figure 1).

Table 2. *Respiratory function in patients with COPD and IHD at the beginning of the study (M±m) (n=66)*

Parameter (unit)	COPD and IHD Male n=60	COPD and IHD Female n=6	U	p
Vital Capacity (VC_{max}) (%)	76.44±2.50	74.11±7.56	168	p>0.05
Forced VC (%)	73.20±2.51	71.30±12.80	180	p>0.05
FEV_1 (%)	47.93±2.52	57.14±14.91	171	p>0.05
Tiffeneau index (%)	61.16±2.15	51.47±3.78	126	p>0.05
$MEFR_{25}$ (%)	20.79±1.28	16.43±0.01	54	p>0.05
$MEFR_{50}$ (%)	45.5±5.6	43.2±3.1	52	p>0.05
Inspiratory capacity (%)	78.33±3.95	115.69±24.24	**90**	**p<0.05**
Expiratory reserve volume (%)	59.43±4.32	70.24±7.74	**92**	**p<0.05**
Peak expiratory flow rate (%)	43.96±2.48	46.95±6.15	**135**	**p<0.05**

Note: p — the reliability of differences in performance between patients with COPD and IHD of male and female is determined by the U-test

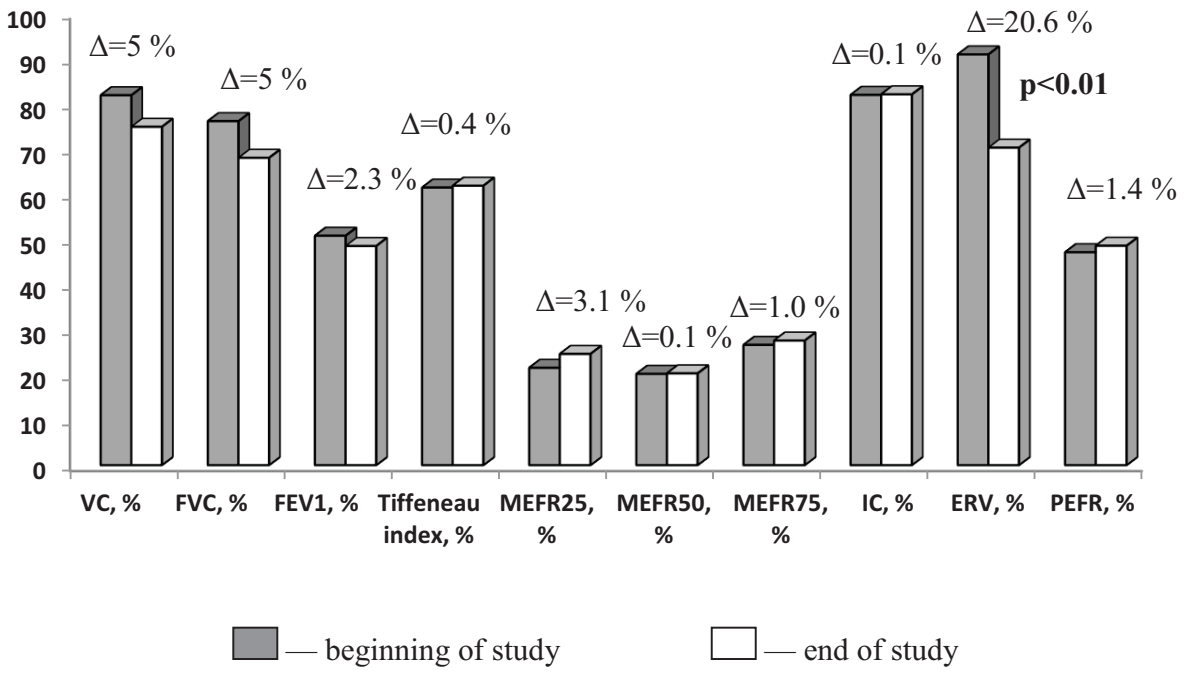

Figure 1. *Dynamics of respiratory function parameters in patients with chronic obstructive pulmonary disease (n=116)*

Table 3. *Five-year dynamics of main parameters of respiration function in patients with COPD and IHD (M±m) (n=66)*

Index (unit)	COPD and IHD (beginning of the study) n=66	COPD and IHD (end of the study) n=66	W	ρ
VC_{max} (%)	78.14±2.86	76.44±2.50	–0.502	0.616
FVC (%)	73.02±2.93	73.20±2.51	–0.275	0.783
FEV_1 (%)	47.72±2.76	47.93±2.52	–0.590	0.555
Tiffeneau Index (%)	58.60±2.24	57.88±2.09	–0.543	0.587
Inspiratory capacity (%)	80.15±3.92	78.33±3.95	–0.465	0.642

Note: ρ — the reliability of differences in patients with COPD and IHD at the beginning of the study and after 5 years was determined by the W-criterion. The differences are not significant

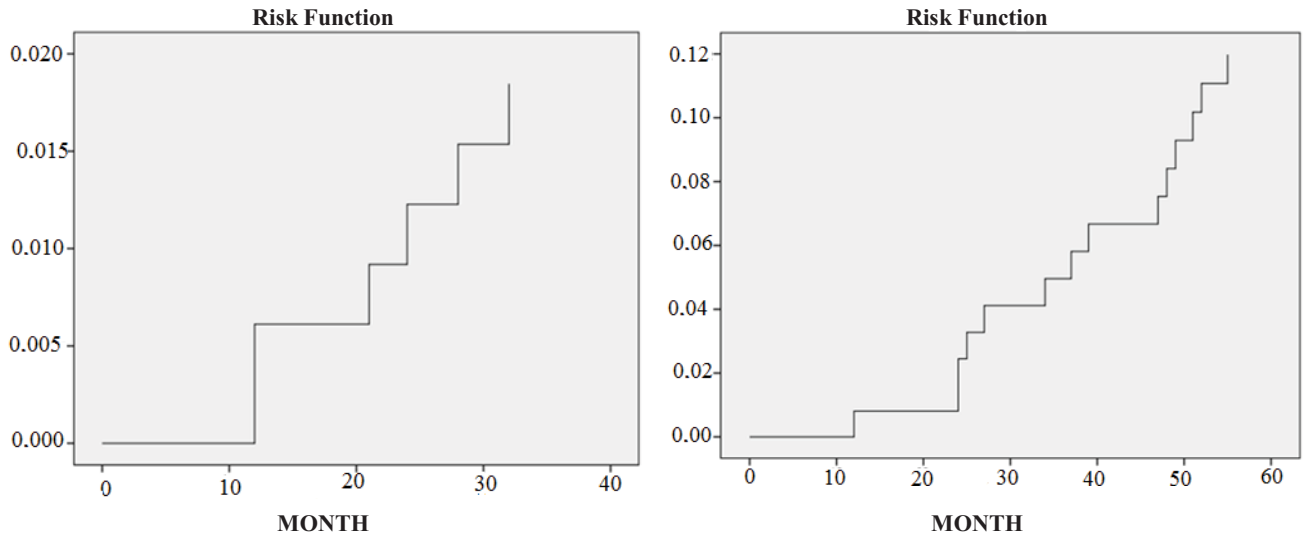

Figure 2. *Coronary events in patients with COPD during the observation period (moderate (left) and high (right) coronary risk)*

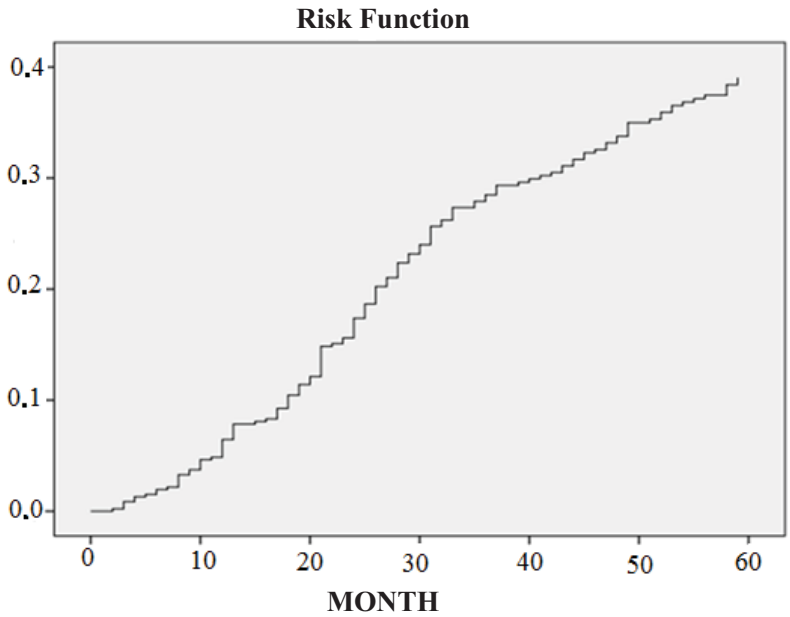

Figure 3. *Coronary events in patients with COPD during the observation period (very high coronary risk)*

In COPD patients making up the risk group for coronary events, no significant changes in respiratory function parameters were observed over five years (Table 3).

Most coronary events among COPD patients at moderate and high risk were reported during the first 3 years of observation, among patients at extremely high risk — evenly throughout 5 years. Coronary events were accompanied by the underlying disease exacerbations and more often were reported in the autumn-winter period. Their incidence (myocardial infarction, angina, coronary death) in COPD patients at extremely high, high and moderate coronary risk over five years was 33.9 %, 10.5 %, 1.52 %, respectively [22] (Figures 2, 3).

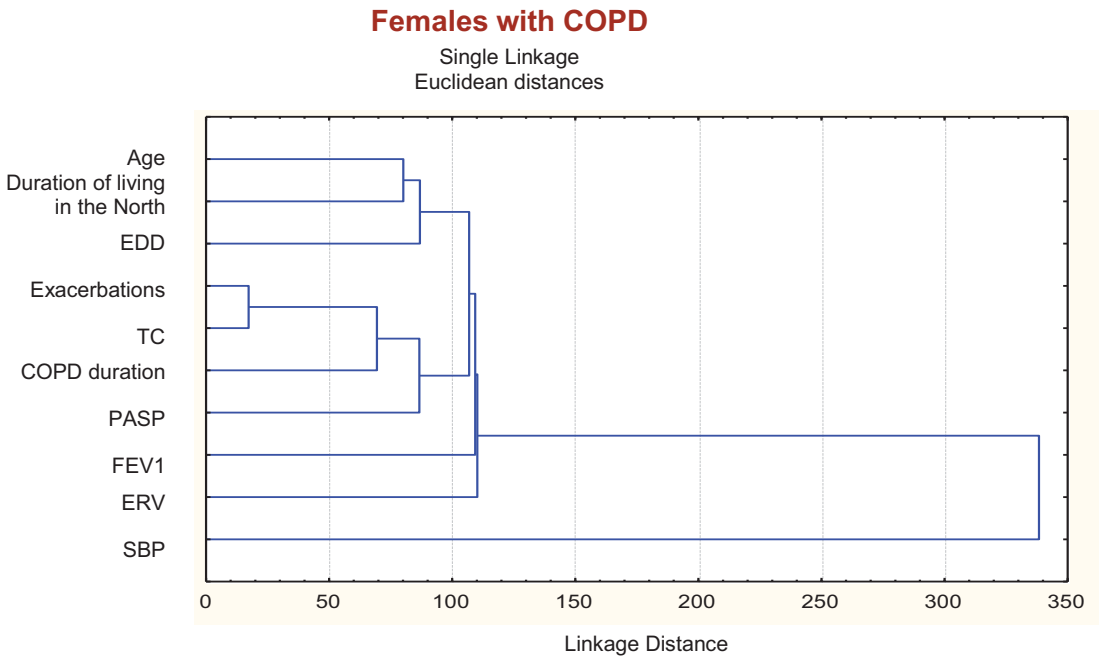

Figure 4. *Clusters of risk factors for coronary events in female patients with COPD*

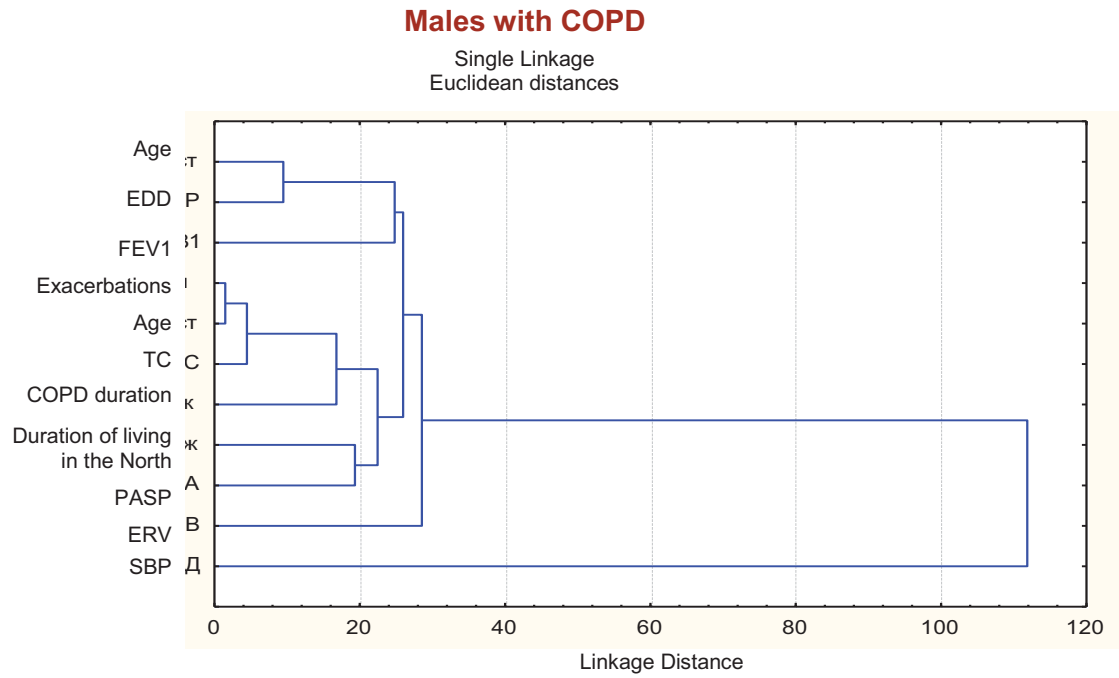

Figure 5. *Clusters of risk factors for coronary events in male patients with COPD*

The extended (body plethysmography, echocardiography) instrumental examination makes it possible to predict the risk of coronary events in COPD by identifying a high-risk group. Using stepwise discriminant analysis, it has been established that the key predictive markers of coronary events in the COPD patients living in northern latitudes are echocardiography data (left ventricular end-diastolic dimension (EDD_{LV}), pulmonary artery systolic pressure (PASP), most important for females (Figure 4)) and body plethysmography data (expiratory reserve volume (ERV), which is the most important for males (Figure 5)). The annual frequency of COPD exacerbations that required hospitalization was associated with the incidence of reported coronary events ($p<0.05$) both among males and females suffering from COPD.

Thus, the use of echocardiography and body plethysmography with the target assessment of volumetric parameters makes it possible to identify risk groups for coronary events and thereby prevent them in a timely manner.

Conclusion

There are a lot of studies that confirm the relationship between cardiovascular mortality and progressive worsening of obstructive respiratory function impairments, the main marker of which is FEV_1 [13–15, 19–21, 24–27]. However, in our view, when predicting coronary events in COPD patients, the progressive aggravation of volumetric respiratory function parameters, and consequently the progression of restrictive respiratory function impairments, is underestimated. The study of respiratory function in COPD patients has established that patients with lower volumetric respiratory function parameters, such as ERV (%), IC (%), had confirmed IHD over the five-year observation period ($p<0.05$). It is interesting that obstructive respiratory function impairments remained relatively stable over time. This suggests the need to perform body plethysmography in all COPD patients as an obligatory examination in order to identify latent restrictive respiratory function impairment at the very beginning of the disease. Endothelial dysfunction and vascular remodeling, which progressively worsen even during stable COPD, contribute to the development and progression of latent left ventricular failure, as evidenced by left ventricular myocardium remodeling [21–23], which undoubtedly leads to a coronary condition.

We have proved that COPD first manifests in patients after 20 and more years of living in the North. However, given the low diagnosis level of COPD in Russia and long asymptomatic progress of the disease, it may happen that using body plethysmography as screening of all smokers, COPD signs would be identified after a shorter period. Several authors have concluded that changes in lungs occur after 10 years of living under conditions of northern latitudes [1]. Thus, in the North, cardiorespiratory remodeling in patients with COPD includes permanent obstructive respiratory function impairment and reduction in lung volume, which, along with other risk factors, contributes to the development of coronary events.

Conflict of interests

The authors declare no conflict of interests.

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MOLECULAR BASES OF MUSCULAR DEFINITION: THE ROLE OF MYOSTATIN AND PROTEINKINASE β IN PROGRESSION OF PROTEIN-ENERGY WASTE IN PATIENTS ON HEMODIALYSIS

Abstract

Improving the nephrology service and increasing the availability of hemodialysis create the prerequisites for a deeper analysis of associated complications and diseases. One of the main clinical condition that worsen the patient's prognosis is protein-energy wasting (PEW), which is manifested by loss of muscle mass, strength and performance of skeletal muscles, which also leads to a decrease in quality of life, and often to disability and death. **The objective:** To assess the relationship between myostatin and protein kinase β as markers of the catabolic cascade, and the signs of PEW in dialysis patients. **Materials and methods:** Eighty patients were enrolled in the study (47 men and 33 women); the median age was 51.7 ± 11.6 years. All patients had CKD 5D and were on chronic hemodialysis for an average duration of 33.5 (0.5; 236) months. Clinical examination, anamnestic data collection and muscle strength measurement via hand dynamometry were provided in all patients. The serum levels of MSTN and AKT were determined by enzyme immunoassay (ELISA Kit, USA). Statistical analysis was carried out using Microsoft Office (USA) and Statistica-10.0 (StatSoft Inc., USA) software packages. **Results:** A dependence of the local increase in the skinfold thickness with an increase in the MSTN level, as well as a decrease in the thickness of the subcutaneous fatty tissue with a decrease in AKT ($p = 0.03$) was detected. We proposed a muscle catabolism index for assessing the degree of muscle degradation. It had a statistically proven association with degree of PEW and its clinical signs. The analysis of the effect of systemic inflammation markers on MSTN did not give significant results. However, in the subgroup with elevated AKT on the background of the activation of anabolic processes, we observed a decrease in β2-microglobulin and an increase in serum iron ($p = 0.04$). In the subgroup with a high level of MSTN, higher concentrations of parathyroid hormone (PTH) were determined. We found a direct correlation between the increase in protein kinase β and the annual PTH fluctuation ($r = 0.83$, $p = 0.01$). **Conclusion:** In our study, we found that in patients with CKD 5D on chronic hemodialysis, the activity of myostatin and protein kinase β varies. This leads to an increase in protein degradation over the processes of synthesis, which creates prerequisites for the development of sarcopenia. Taking into account the data obtained, further study of the intermolecular interactions of these markers in the catabolic cascade of muscle proteins is of research interest.

Key words: *chronic kidney disease, protein-energy wasting, sarcopenia, myostatin, protein kinase β*

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AKT — protein kinase β; ISRNM — International Society of Renal Nutrition and Metabolism; MSTN — myostatin; PEW — protein-energy wasting; MTCI — muscle tissue catabolism index; PTH — parathyroid hormone; CKD — chronic kidney disease; CRF — chronic renal failure

Introduction

Improving nephrology service and increasing the accessibility of hemodialysis as a method of renal replacement therapy create the conditions for a more detailed analysis of complications and diseases associated with it. One of the main clinical conditions that significantly worsen the patient's prognosis is protein-energy wasting (PEW) and the development of muscle mass loss, decrease of strength and performance of skeletal muscles, referred to as sarcopenia, on the background of uremic intoxication. These changes lead to the deterioration of quality of life and often to disability and death. [3].

The International Society of Renal Nutrition and Metabolism (ISRNM) identifies sarcopenia as a clinical manifestation of PEW [7]. According to the latest data, 20–70 % of patients with CKD on hemodialysis suffer from complications associated with PEW [1]. According to ISRNM guidelines, the main criteria in the diagnosis of PEW are: low body weight, including a reduction in fat mass and BMI; decrease in muscle mass (based on mid-arm circumference, double X-ray absorptiometry, bioelectrical impedance analysis) or changes in blood creatinine; reduced protein/energy intake; detection of biochemical markers of protein catabolism [10].

A slight but persistent imbalance between protein synthesis and its degradation in patients with kidney diseases causes a significant loss of protein. At present, there are no perfect methods to prevent muscle atrophy caused by chronic renal failure (CRF). However, mechanisms have been identified that regulate the metabolism of muscle protein. Their study will create conditions for the development of therapeutic approaches aimed at the pharmacological correction of intermolecular relationships in the muscle metabolism pathway and will allow controlling this process.

One of the main catabolic pathways that cause the degradation of muscle proteins is the activation of the ubiquitin-proteasome system, which operates through myostatin and protein kinase β [13].

Myostatin (MSTN) is a member of the transforming growth factor-beta family, whose catabolic effects are due to the activation of Smad2/Smad3 signaling molecules and the blocking of protein kinase β (AKT) phosphorylation on the one hand. As a result, signal transmission through the IGF-1/PI3K/AKT pathway is disrupted, the level of the active factor FoxO1 increases and the genes associated with atrophy are activated [11]. On the other hand, the myostatin signal in the AKT-mTOR pathway blocks endogenous protein synthesis, also leading to the development of muscle atrophy. Another effect of MSTN overexpression is the development of fibrosis [9] and the suppression of the activity of satellite cells involved in muscle fiber repair processes [5].

The mechanisms of muscle tissue degradation described can be initiated by complications of chronic renal failure: metabolic acidosis, defective insulin signaling, inflammation, uremic intoxication, hormonal imbalance, hypodynamia, and abnormal appetite regulation.

The objective of our study was to assess the relationship between myostatin and protein kinase β, as markers of the catabolic pathway, and PEW manifestations in patients on hemodialysis.

Materials and Methods

The study involved 80 subjects, 47 men and 33 women; the median age was 51.7 ± 11.6 years. All patients had CKD 5D and were treated with chronic hemodialysis for a mean duration of 33.5 (0.5; 236) months. Anamnestic data was collected, an anthropometric evaluation of the upper and lower extremities was carried out (the diameter and the circumference of the mid-arm, wrist, neck, thigh; the subcutaneous skinfold thickness in the biceps, triceps, above and below the scapula, in the iliac region were measured). Muscle strength was measured by hand dynamometry (DMER-120-0.5, Russia). The PEW stage was evaluated using a complex method in G. L. Bilbrey

and T. L. Cohen modification [1]. MSTN and AKT serum concentrations were determined by enzyme-linked immunoassay using the Myostatin ELISA Kit (USA), Protein Kinase B Beta ELISA Kit (USA). Statistical data analysis was performed using Microsoft Office (USA) and Statistica-10.0 (StatSoft Inc., USA) software packages.

The statistical significance of mean difference was determined using Student's t-test when the sample distribution was normal, and using Mann-Whitney test when the sample distribution deviated from a normal distribution. Correlation analysis was carried out using the Pearson coefficient when the trait distribution was normal and using Spearman coefficient when the trait distribution deviated from a normal distribution. A single- and multifactor linear regression analysis was performed. Parametric analysis of variance was performed using ANOVA analysis, Levene's test, and Brown-Forsythe test. Differences were considered statistically significant with $p<0.05$.

Results

We noted a high prevalence of PEW in the study group: manifestations of muscle atrophy varying in degree were discovered in 90 % of the subjects. At the same time, most of the disorders were related to mild and moderate degree of PEW (61.25 % and 27.5 %); a significant protein imbalance was detected in 1 patient. Correlation dependence was found between the combined attribute of the presence of PEW and the decrease in muscle strength. We divided the data obtained into three subgroups, where 0 is the absence of a decrease in muscle strength, 1 is a decrease in muscle strength of the hand or leg, 2 is a decrease in the muscle strength of both limbs (Table 1).

The mean MSTN value in the study group was 8.47 ± 1.27 ng/ml, the mean AKT value was 3.15 ± 2.15 ng/ml, ranging from 0.08 to 11.6 ng/ml, and the distribution in both cases did not differ from normal. The ANOVA analysis and the Brown-Forsythe test made it possible to

Table 1. *Correlation of the combined attribute of the presence of PEW and the decrease in muscle strength with clinical parameters*

Clinical parameters	r, Spearman
Gender (male — 0, female — 1)	0.30*
Dynamometry on a fistula-free hand, N	–0.50*
Dynamometry on the left hand, N	–0.50*
Dynamometry on the right hand, N	–0.50*
Decreased hand muscle strength	0.37*
Test with raising the leg, sec	0.37*
Reduced leg muscle strength	–0.62*
The degree of decrease of the muscle strength of the limbs	0.75*

Note: *— $p<0.05$

Table 2. *The values of clinical parameters (M ± SD) in subgroups depending on the level of MSTN*

Parameter	MSTN		SS	SS error	MS error	F	p
	≤8.49 ng/ml	>8.49 ng/ml					
Lymphocytes, 10^3 cells/μl	1.58 ± 0.5	1.54 ± 0.5	0.001	7.94	0.10	0.01	0.91
Transferrin, g/l	1.9 ± 0.45	1.8 ± 0.36	0.05	5.9	0.08	0.71	0.40
Ferritin, μg/l	386 ± 367	366 ± 263	79,042	4,241,027	55,803	1.42	0.24
Serum iron, g/l	10.5 ± 2.9	10.5 ± 3.6	2.7	396	5.1	0.53	0.47
Albumin, g/l	41.8 ± 2.3	41.7 ± 2.3	0.01	173	2.22	0.005	0.94
HbA1c, %	5.9 ± 1.2	7.5 ± 1.1	0.03	4.44	0.64	0.04	0.84
β2-MCG, ng/ml	119 ± 32	125 ± 29	0.30	39,883	511	0.0006	0.98
CRP, mg/l	124 ± 26	118 ± 42	2,438	60,401	774	3.15	0.07

distribute quantitative traits into two subgroups depending on the myostatin value. The concentrations of parathyroid hormone (PTH) were higher in the subgroup with a high MSTN value, which indicates a possible activation of the catabolic pattern of muscle metabolism in patients with CKD 5D on the background of secondary hyperparathyroidism. Regarding the increase in protein kinase β, a correlation was found with the annual PTH fluctuation (r = 0.83, p = 0.01). In the subgroup with high PTH fluctuation, a more pronounced decrease in PTH value was observed during the observation period (–123 ± 12 versus 11 ± 18 ng/ml, p = 0.021), as well as more frequent prescription of hormone replacement therapy (38.5 % versus 11.1 %, p = 0.04).

When assessing the effect of non-specific markers of systemic inflammation on blood myostatin concentration, no statistically significant results were obtained. (Table 2).

However, an increase in serum iron and a decrease in β2-microglobulin were observed in the subgroup with an elevated AKT value on the background of the activation of anabolic processes (Table 3).

When assessing the effect of anthropometric measurements on the MSTN value, it was found that an increase in its concentration (above the median ≥8.49 ng/ml) was associated with an increase in the skinfold thickness above the biceps and in the iliac region (Fig. 1, Fig. 2). At the same time, in patients with a low AKT value, there was an increase in the skinfold thickness above the biceps more than the mean value (Fig. 3). These data indicate the activation of lipid metabolism in the regions discussed with an increase in catabolic processes in muscle tissue.

Table 3. *The values of clinical parameters (M ± SD) in subgroups depending on the level of AKT*

Parameter	AKT		SS	SS error	MS error	F	p
	≤2.55 ng/ml	>2.55 ng/ml					
Lymphocytes, 10^3 cells/μl	1.6 ± 0.5	1.5 ± 0.5	0.18	7.8	0.09	1.88	0.17
Transferrin, g/l	1.86 ± 0.4	1.81 ± 0.4	0.007	6.4	0.08	0.09	0.77
Ferritin, μg/l	327 ± 255	427 ± 366	67,467	4,125,783	54,286	1.25	0.27
Serum iron, g/l	10.3 ± 2.5	14.7 ± 3.8	20.3	380	4.9	4.2	0.04
Albumin, g/l	41.9 ± 2.2	41.6 ± 2.4	0.19	174	2.2	0.08	0.77
HbA1c, %	5.9 ± 1.2	7.5 ± 1.1	0.03	4.44	0.64	0.04	0.84
β2-MCG, ng/ml	119 ± 32	125 ± 29	0.30	39,883	511	0.0006	0.98
CRP, mg/l	124 ± 26	118 ± 42	2,438	60,401	774	3.15	0.07

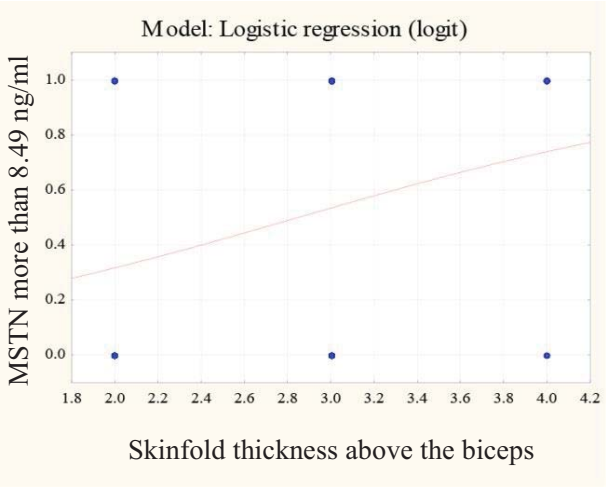

Figure 1. *The probability of the myostatin level increase, depending on the skinfold thickness above the biceps*

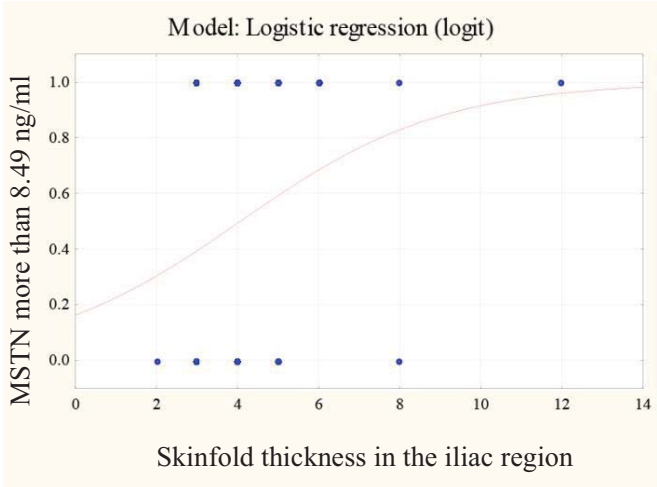

Figure 2. *The probability of the myostatin level increase, depending on the skinfold thickness in the iliac region*

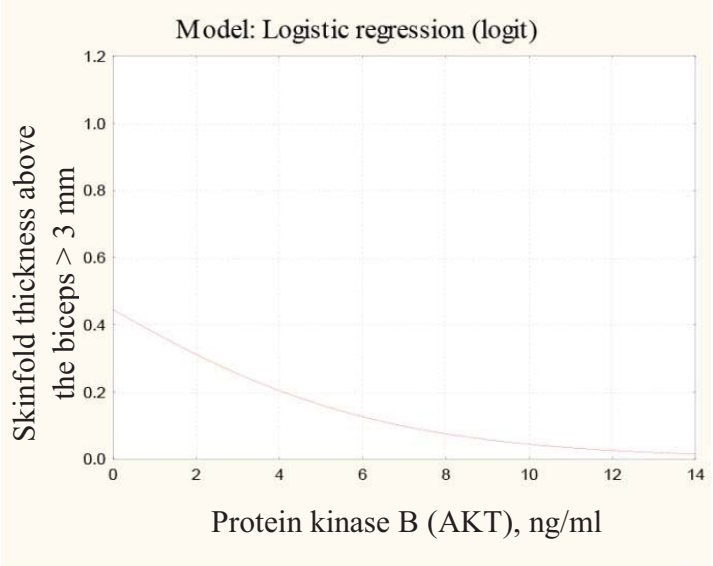

Figure 3. *The skinfold thickness above the biceps depending on the level of AKT*

When studying the association between MSTN and protein kinase β, a relationship was established between these biomarkers. We have proposed a muscle tissue catabolism index (MTCI), which is calculated by the ratio of MSTN to AKT. It can be a basis for indirect determination of the direction of skeletal muscle metabolism in patients with CKD 5D. We separated the patients into three subgroups: 0 — low MTCI, which is determined by the prevalence of anabolic processes (low myostatin, high AKT), 1 — moderate MTCI, protein synthesis and degradation processes are balanced (low myostatin, low AKT or high myostatin, high AKT), 2 — high MTCI, in which degradation of muscle proteins significantly prevails over their synthesis (high MSTN, low AKT).

According to the regression analysis, there was an increase in the proposed coefficient with an increase in the stage of PEW (Fig. 4).

In our study, the link between parameters of muscle strength decrease and the catabolic markers being studied is statistically significant only for an increase in myostatin ($\chi^2 = 4.15$, $p = 0.041$). However, the use of MTCI allows defining pathogenetic interactions more clearly. Thus, a decrease in muscle strength along with an increase in MTCI was noted in 91 %

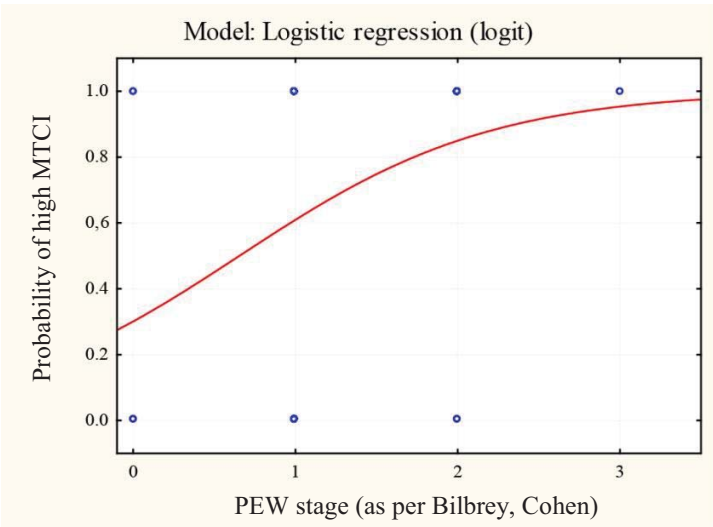

Figure 4. *The regression equation and the graphic representation of the probability of the MTCI increase depending on the stage of PEW*

Table 4. *Values of parameters (M ± SD) depending on the presence of PEW and MTCI*

Parameter	no PEW			PEW		
	MTCI					
	0	1	2	0	1	2
Dynamometry of muscle strength on a fistula-free hand, N	41.8 ± 30	39.0 ± 19	23.2 ± 7.4	37.7 ± 13	36.2 ± 13	32.7 ± 11
	SS = 595, MS = 119, F = 2.81, ρ = 0.022					

of cases, versus 63 % in its absence (χ^2 = 3.67, ρ = 0.048). ANOVA analysis and statistical significance assessment using the Levene's test allows to perform a quantitative analysis of traits in subgroups depending on the presence or absence of PEW and the degree of MTCI (Table 4).

Discussion

Dissociation in the processes of protein kinetics in end-stage CRF is associated not only with nutritional deficiency, as previously thought, but also with impaired synthesis and degradation of proteins [6]. In the case of CKD-induced muscle atrophy, the prevalence of protein degradation processes is more important than a decrease in the synthesis [12]. Such changes in muscle tissue are characterized by the development of PEW, accompanied by a decrease in the mass and function of muscle fiber [8].

One of the leading roles in maintaining skeletal muscle homeostasis is played by myostatin and protein kinase β [2], the activity of which is determined by a number of exogenous and endogenous factors, in particular, vitamin D imbalance and the development of secondary hyperparathyroidism [4]. At the same time, metabolic acidosis and systemic inflammatory response on the background of uremia can also have a trigger effect on the system of muscle proteolysis [5].

As shown by our study, the activity of the discussed biomarkers changed in patients with CKD who received therapy with chronic hemodialysis, resulting to the prevalence of protein degradation over synthesis processes, which creates the conditions for the development of sarcopenia.

Detection of the serum MSTN and AKT concentrations, as well as the coefficient of their intermolecular interaction, can serve as an additional minimally invasive method for diagnosis of PEW and indirect assessment of the severity of sarcopenia in patients with CKD 5D.

Conclusion

The effect of elevated myostatin and low protein kinase β levels on the parameters of muscle strength in patients with CKD 5D has been determined. The dependence of changes in these factors in the anthropometric assessment of the skinfold thickness in various body segments was determined, which may be related to the processes of fibro-adipogenesis in muscle fiber.

The original muscle tissue catabolism index developed can be used in a comprehensive assessment of the nutritional status in CKD patients, who receive long-term hemodialysis.

Further study of the intermolecular interactions of MSTN and AKT in the catabolic pathway of muscle proteins is of research interest. In particular, the question of the intracellular determination of the biomarkers discussed, as well as the integrative role of the mTOR serine-threonine protein kinase in muscle tissue metabolism in patients with CKD and sarcopenia, requires in-depth study.

Conflict of interests

The authors declare no conflict of interests.

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THE CONDITION OF THE CARDIOVASCULAR SYSTEM IN PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS

Abstract

The **objective** of the study was to evaluate the state of the cardiovascular system, systemic inflammation markers and oxidant/|antioxidant balance in patients with relapsing-remitting multiple sclerosis. **Material and methods.** The study included 45 patients with relapsing-remitting multiple sclerosis (17 men and 28 women), aged 28 [24; 32] years, disease duration of 5.5 [2; 7] years. The control group included practically healthy patients, aged 30 [25; 33] years. Patients with multiple sclerosis were examined neurologically using the Expanded Disability Status Scale. Instrumental methods included a comprehensive assessment of the cardiovascular system (24-hour ECG monitoring and 24-hour blood pressure monitoring with determination of the daily vascular wall stiffness, and echocardiography). Laboratory methods included complete blood count and biochemical analysis, including lipid profile, glycemia, and C-reactive protein determination. The parameters of oxidative stress (acyl hydroperoxide) and antioxidant protection (glutathione peroxidase, superoxide dismutase) were studied; a marker of endothelial dysfunction (vascular cellular adhesion molecule-1) was analyzed. **Results.** In the group of patients with multiple sclerosis, there was an increase in C-reactive protein and vascular cellular adhesion molecule-1 in comparison with the control group ($p < 0.001$). The parameters of oxidative stress and antioxidant protection were significantly increased ($p < 0.001$). According to the results of 24-hour blood pressure monitoring the variability of systolic blood pressure and diastolic blood pressure during daytime hours was reduced in comparison with the control group, ($p < 0,026$) and ($p < 0.002$), respectively. The parameters of daily vascular wall stiffness in the group of patients with multiple sclerosis were significantly increased ($p < 0.001$). According to the results of 24-hour ECG monitoring, no heart rhythm disorder was detected in both groups. In the group of patients with relapsing-remitting course of multiple sclerosis, an increase in the number of supraventricular extrasystoles was detected in comparison with the control group ($p < 0.005$). The main parameters of echocardiography were within normal values, no significant differences between the groups were found. **Conclusion.** The study showed that multiple sclerosis patients are at risk of developing cardiovascular diseases and require increased attention to prevent their development.

Key words: *multiple sclerosis, cardiovascular diseases, oxidative stress, antioxidant protection, endothelial dysfunction, vascular wall stiffness.*

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BP — blood pressure, AHP — acyl hydroperoxides, GPO — glutathione peroxidase, DBP — diastolic blood pressure, MS — multiple sclerosis, SBP — systolic blood pressure, 24-hour BPM — 24-hour blood pressure monitoring, SOD — superoxide dismutase, CRP — C-reactive protein, CVD — cardiovascular diseases, ECG HM — Holter ECG monitoring, HR — heart rate, ECG — electrocardiogram, Echo-CG — echocardiography, EDSS — Expanded Disability Status Score, VCAM-1 — vascular cell adhesion molecule-1.

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Multiple sclerosis (MS) is one of the biggest challenges facing modern neurology, and it occupies a special place among demyelinating diseases as the most prevalent one [1]. This disease mostly affects young people who lead an active working and social life [2, 3]. MS is a multifactorial disease where viral infection, genetic predisposition, as well as extrinsic factors, including environmental factors play a key role in its initiation and development [3]. Worldwide prevalence of MS is about 2.3 million people, although this figure continues to rise [4]. Prevalence of MS in Russia varies from 30 to 100 cases per 100,000 people [5].

The course of MS and its clinical symptoms are extremely diverse and labile. At the present time, MS is classified according to the activity of pathologic process reflected by the type of disease [3, 5]. Relapsing-remitting clinical course is reported in 85–90 % of patients at the onset of MS. It is characterized by distinct exacerbations alternating with remission. The primary pathogenetic mechanism of relapsing-remitting MS is immunopathological reactions [3, 6].

With an increase in overall life expectancy of patients with MS, it is necessary to consider risk data on potentially preventable diseases [7, 8]. Identification of a risk of cardiovascular diseases (CVD) in patients with MS is essential in optimizing patient management and assessment of the course of the disease. Comorbidity in MS can affect life quality, the course and approaches to treatment of the disease. There is contradictory data on the risk of cardiovascular morbidity in MS. On the one hand, a number of studies have shown that MS is a risk factor for cardiovascular pathology [8–12]. Other researchers have not found any statistically significant relationship among different types of MS and the risk of CVD [6, 13–16]. Several literary sources describe MS treatment methods with cardiotoxic effect [8, 11].

Study objective: to study the condition of the cardiovascular system in patients with relapsing-remitting multiple sclerosis, with assessment of vascular injury markers and oxidant/antioxidant balance.

Materials and methods

The study included 45 patients (17 males and 28 females) aged 28 [24; 32] years who had suffered from relapsing-remitting MS diagnosed in accordance with the international McDonald criteria (2010), with the disease duration of 5.5 [2; 7] years, the annual incidence of exacerbations of 0.8 [0.38; 1] (Group 1). The control group (Group 2) included 15 individuals (10 females and 5 males) of comparable age (30 [25; 33] years) without clinical signs of nervous system diseases, i.e., apparently healthy individuals.

None of the study patients and control individuals had a history of CVD, diabetes mellitus, ischemic heart disease (IHD), or hypertension.

Patients with multiple sclerosis were examined neurologically with rating of disability according to the Expanded Disability Status Score (EDSS), a 10-point severity scale obtained by assessing separate neurological areas. This figure was 2.54 [1; 3.5] points.

Patients of both groups underwent general clinical examination: complete blood count and biochemical analysis, including lipid profile (total cholesterol, triglycerides, high- and low-density lipoproteins), glycemia, and high-sensitivity C-reactive protein (CRP). The following parameters were also identified: endothelial dysfunction marker (vascular adhesion molecule-1 (VCAM-1)), oxidative stress (acyl hydroperoxides (AHP)) and antioxidant defense (superoxide dismutase (SOD) and glutathione peroxidase (GPO)) indices.

Daily blood pressure monitoring (24-hour BPM) was performed using BpLab portable monitors capable of identifying the 24-hour vascular wall stiffness (mean PWVao).

Holter ECG monitoring (ECG HM) was performed using Microvit MT-101/200 Holter ECG monitoring system (SCHILLER, Switzerland). The analyzed parameters included basic rhythm, medium, maximum and minimum heart rate (HR) for 24 hours, presence of pauses, number of extrasystoles, and ST segment dynamics.

Central hemodynamics was studied by echocardiography (Echo-CG) using Vivid 7 Expert echocardiograph (GE Medical Systems) according to

the generally accepted method. Wall thickness, left ventricular (LV) cavity dimension, left atrial (LA) longitudinal size were assessed from the parasternal access along the LV long axis. Diastolic thickness of interventricular septum (IVST, cm) and left ventricular posterior wall (LVPW, cm), left ventricular end-diastolic (EDD, cm) and end-systolic diameters (ESD, cm), left ventricular end-diastolic (EDV) and end-systolic volumes (ESV) were measured. Also, left ventricular ejection fraction (EF, %) was assessed according to Simpson's rule. Left ventricular mass (LVM) was calculated by the formula of R.B. Devereux et al. Left ventricular mass index (LVMI) was calculated based on LVM indexed to the body surface index of the examined patient (S, m^2). LVMI was calculated to assess the left ventricular hypertrophy (LVH), with the upper limit of normal of 95 g/m^2 for females and 115 g/m^2 for males.

Statistical processing and analysis of the data obtained were performed using SPSS 22.0 software. The type of data distribution was identified by the Kolmogorov — Smirnov test. Sampling was described using the median, the first and third quartiles, as the data was not primarily normally distributed. The comparison in the groups was performed using the Mann — Whitney test. Differences were considered significant with $p < 0.05$.

Results and discussion

Patients from both groups were comparable on basic anthropometric and general clinical parameters. Clinical and laboratory characteristics of MS patients and control group patients are shown in **Table 1.**

All of the patients had normal office blood pressure (BP), with no anamnestic signs of hypertension.

According to the results of 24-hour BPM, no statistically significant difference was found in day- and night-time BP in both groups. Comparison of 24-hour BPM figures in groups 1 and 2 is provided in **Table 2.**

The BP variability assessment draws attention to the significant reduction in variability of daytime systolic blood pressure (VarSBP) in MS patients as compared to the control group ($p < 0.026$). However, these figures were within the normal range. A similar trend was found when assessing the variability of daytime diastolic blood pressure (VarDBP) in MS patients as compared to the control group ($p < 0.002$).

A number of studies show data on the relationship between blood pressure variability and cardiovascular complications. On the one hand, it was noted that the increase in BP variability contributes to the development of endothelial dysfunction due

Table 1. *Clinical and laboratory characteristics of patients with relapsing-remitting MS (group 1) and patients of the control group (group 2)*

Parameter	Group 1, n = 45	Group 2, n = 15	P
Age, years	28 [24; 32]	30 [25; 33]	0.282
BMI	22.75 [20.5; 23.7]	24.66 [20.76; 26.32]	0.021
Total cholesterol, mmol/l	4.1 [3.8; 4.33]	4.33 [3.87; 4.68]	0.2
Triglyceride, mmol/l	1.3 [0.89; 1.63]	0.88 [0.67; 1.3]	0.03
HDL, mmol/l	1.4 [1.088; 1.6]	1.48 [1.17; 1.67]	0.497
LDL, mmol/l	2.31 [1.73; 2.69]	2.39 [2.2; 2.79]	0.272
Total protein, g/l	72 [68; 74.25]	74 [70; 78]	0.185
Creatinine, μmol/l	72.5 [60.75; 83]	72 [64; 78]	0.821
Urea, mmol/l	4.35 [3.725; 4.925]	4.1 [3.7; 4.7]	0.712
Total bilirubin, μmol/l	17 [14; 19]	12 [8.7; 15.2]	0.012
ALT, U/l	24 [21; 28.25]	11 [9; 17]	0.001
AST, U/l	22 [19; 26.25]	15 [11; 17]	0.001
Glucose, mmol/l	4.55 [4.2; 5.1]	4.7 [4.5; 4.9]	0.382

Note: ALT — alanine aminotransferase, AST — aspartate aminotransferase, BMI — body mass index, HDL — high-density lipoprotein, LDL — low-density lipoprotein, p — significance of differences (Mann — Whitney test).

Table 2. *Parameters of 24-hour blood pressure monitoring in patients with relapsing-remitting MS (group 1) and patients of the control group (group 2)*

Parameter	Group 1, n = 45	Group 2, n = 15	P
Mean daytime SBP, mm Hg	117 [110; 127.25]	115 [106; 123]	0.96
Variability of daytime SBP, mm Hg	10 [8; 13]	13 [10; 17]	0.026
Mean daytime DBP, mm Hg	73 [67; 78]	75 [70; 82]	0.314
Variability of daytime DBP, mm Hg	9 [7; 10]	10 [9; 16]	0.002
Mean nighttime SBP, mm Hg	107 [97.5; 117]	101 [92; 118]	0.519
Variability of nighttime SBP, mm Hg	10 [8; 12]	9 [7; 12]	0.19
Mean nighttime DBP, mm Hg	66 [58.25; 71]	64 [56; 71]	0.933
Variability of nighttime DBP, mm Hg	8 [7; 9]	8 [7; 12]	0.665
Degree of nighttime decrease in SBP, %	7.75 [4.2; 11.11]	13 [6; 14]	0.15
Degree of nighttime decrease in DBP, %	9.655 [4.79; 16.42]	18 [11; 22]	0.017
Mean 24-hour SBP, mm Hg	115 [107; 124.25]	111 [102; 121]	0.718
Mean 24-hour DBP, mm Hg	71.5 [64.9; 76]	73 [65; 78]	0.788

Note: DBP — diastolic blood pressure, SBP — systolic blood pressure, ρ — significance of differences (the Mann — Whitney test).

to suppressed production of nitric oxide and effect on vascular intima, which, in turn, can result in atherogenesis [17]. On the other hand, patients with high variability show increased activity of the sympathetic nervous system, as a result of which vascular tone increases, especially during morning hours, which leads to a higher risk of cardiovascular complications [10, 18–19].

Considering the study data (reduced blood pressure variability in MS patients as compared to the control group), it can be assumed that the decrease of BP variability in MS shows the lack of effect of the above-mentioned mechanisms on the risk of development of cardiovascular complications.

According to the night-time reduction in diastolic blood pressure (DBP night), most MS patients showed insufficient reduction in diastolic blood pressure (DBP) (non-dippers), and normal nighttime DBP (dippers) prevailed in the control group ($\rho < 0.017$).

There are literary data on the increased nighttime activity of sympathoadrenal system in patients with impaired 24-hour BP profile. It has been established that non-dippers had disturbed circadian rhythm of the autonomic nervous system activity, higher nighttime activity of the sympathetic nervous system, as well as inadequate activity of the parasympathetic nervous system [20].

Changes in the circadian rhythm of BP in patients with relapsing-remitting MS, who have normal BP figures, require separate study, since, according to the Ohasama study (1997, 2002), non-dippers without essential hypertension are characterized by higher risk of cardiovascular mortality, which is comparable to the relative risk for dippers with essential hypertension and can be even greater.

The assessment of 24-hour vascular wall stiffness can be used as screening to detect preclinical atherosclerosis and identify high cardiac risk groups. A number of studies show that persistent increase in pulse velocity in hypertension and other CVD is associated with high cardiovascular risk and adverse outcome [9, 16, 17, 21].

In our study, 24-hour vascular wall stiffness figures were significantly higher in MS patients as compared to the control group: mean PWVao: 9.2 [8.5; 9.8] m/sec and 7 [6.4; 7.8] m/sec, respectively ($\rho < 0.001$). However, these figures were within the normal range.

In assessing the Holter ECG monitoring (ECG HM) data, the average daily, minimum, and maximum HR figures were within the normal range. No significant difference was found in both groups. What is noticeable is that the level of supraventricular arrhythmia is higher in MS patients as compared to the control group ($\rho < 0.005$). The number of ventricular extrasystoles (VES) did not exceed the normal limit; there were no significant differences between the

Table 3. *Parameters of systemic inflammation, endothelial dysfunction, oxidative stress and antioxidant protection in patients with relapsing-remitting MS (group 1) and patients of the control group (group 2)*

Parameter	Group 1, n = 45	Group 2, n = 15	P
CRP, mg/l	1.1 [0.49; 2.28]	0.6 [0.3; 0.8]	0.001
VCAM-1, ng/ml	590 [412.18; 894.75]	446.7 [385.3; 542.7]	0.017
AHP, nmol/mg	6.05 [4.55; 7.6]	3.45 [2.84; 4.61]	0.001
SOD, UA/g	1,633 [951.5; 1,916]	1,487.8 [1,285.3; 1,634.1]	0.001
GPO, UA/g	82.4 [74.2; 88.38]	46.3 [36.4; 62.4]	0.001

Note: AHP — acyl hydroperoxides, CRP — C-reactive protein, GPO — glutathione peroxidase, SOD — superoxide dismutase, VCAM-1 — vascular cell adhesion molecule-1, p — significance of differences (the Mann — Whitney test).

groups. No significant changes were found for ST segment in both groups. The increased level of supraventricular arrhythmia in MS patients reflects an imbalance in the sympathetic/parasympathetic regulation.

According to echocardiography, left atrial longitudinal dimension, left ventricular linear dimensions (ESD, EDD, IVS, LVPWT, EDV, ESV) and LV systolic function indices (EF) were within the normal range in both groups. LVM and LVMI also did not exceed threshold values both in MS patients and in the control group. No statistically significant differences in the above-mentioned figures were found in both groups.

The leading role in the pathogenesis of multiple sclerosis belongs to immune inflammation, activated oxidative stress and impaired antioxidant defense mechanisms. In MS, humoral immunity is activated, activity of macrophages is higher. As a result, non-specific mechanisms of phagocytosis become active and oxidative stress develops in nerve and glial cells, which leads to the destruction of myelin sheath of axons and reduction in their number [3, 22–24].

Non-clinically significant increase of CRP was found in the group of patients with relapsing-remitting MS as compared to the control group ($p < 0.001$). Comparative characteristics of the study groups according to the markers of systemic inflammation, endothelial dysfunction and oxidant/antioxidant system are presented in **Table 3.**

Comparison of the two groups showed a significant increase of endothelial dysfunction marker of VCAM-1 in MS patients ($p < 0.017$). This increase is associated with more pronounced endothelial injury processes in patients with multiple sclerosis, which developed under the effect of oxidative stress, which results in endotheliocytes being activated and adhesion molecules being expressed [25, 26].

Oxidative stress was assessed based on AHP, and was higher in MS patients as compared to the control group ($p < 0.001$). Antioxidant defense indicators were also significantly higher in MS patients as compared to the control group: GPO ($p < 0.001$), SOD ($p < 0.001$).

Thus, in MS patients, the activation of antioxidant systems occurs in response to the increased oxidative stress, with the formation of the oxidant/antioxidant balance at a new level. These processes are typical for the early stages of various diseases, including cardiovascular pathology. It has been established that, in patients with progressive MS, oxidant/antioxidant imbalance occurs in response to the continuous production of reactive oxygen intermediates due to inhibited activity of antioxidant enzymes [27, 28].

Conclusions

Based on the examination performed when comparing patients with relapsing-remitting MS and the control group, the average daily BP figures are within the normal range, without significant differences between the groups. There are no statistically and clinically significant differences in morphofunctional characteristics of the cardiovascular system (Echo-CG and ECG HM).

Increase in oxidative stress (AHP), antioxidant defense (SOD, GPO), CRP, endothelial dysfunction marker (VCAM-1) is observed in MS patients,

which demonstrates the systemic damaging effect of reactive oxygen intermediates and activation of antioxidant defense, with the development of systemic inflammation and endothelium dysfunction.

Increased vascular wall stiffness is reported in MS patients, despite the absence of day- and nighttime SBP and DBP abnormalities, which demonstrates increased risk of cardiovascular complications in these patients.

Considering the study results, markers of a higher risk of developing cardiovascular diseases were found in patients with MS, thus indicating the need to pay special attention to this group of patients to develop strategies for prevention and early diagnosis of a cardiovascular pathology. At the same time, the systemic pathology of small vessels may be one of pathogenetic mechanisms of multiple sclerosis and may increase with the disease progression [21, 24].

Conflict of interests

The authors declare no conflict of interests.

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RETROPERITONEAL FIBROSIS (ORMOND'S DISEASE): CLINICAL CASE

Abstract

Retroperitoneal fibrosis (Ormond's disease) is a nonspecific inflammatory process in the retroperitoneal tissue with the formation of fibrous tissue that causes compression of the ureter and other adjacent structures. The disease is rare: its incidence is about 1 per 200 thousand people. This explains little knowledge about the disease, the absence of a real standard of patient's management with the determination of drug therapy and the most effective method of surgical treatment. The prognosis is determined by the activity of the disease with the development of urinary tract obstruction and the occurrence of renal failure and other complications. The article presents a clinical case of a 40-year-old patient suffering from Ormond's disease. In this case, the initial treatment to remove retroperitoneal fibrosis was undertaken by surgeons 5 months after the onset of the disease. Drug therapy was started 10 months later, when the final diagnosis was made using immunohistochemistry, and the progression of the disease developed (the retroperitoneal fibrosis area increased). On the background of immunosuppressive therapy, a decrease of the severity of retroperitoneal fibrosis was noted, however, it was not possible to achieve the full effect, most likely due to the late start of treatment and the irreversible fibrosis formed in this connection. Treatment was also complicated by the persistently recurring urinary tract infection. The best method of treatment in this situation (with persistent obstruction of the ureter and the risk of renal damage worsening) can only be surgical treatment aimed at restoring adequate urodynamics. Based on the presented clinical case, we can make the following conclusions: Ormond's disease (retroperitoneal fibrosis) needs further study and development of standards for the management of such patients; immunosuppressive, which can prevent the development of irreversible fibrosis, therapy should be prescribed as soon as possible; and, in advanced stages of the disease, treatment should be comprehensive, including both drug and surgical treatment.

Key words: *retroperitoneal fibrosis, Ormond's disease, immunosuppressive therapy*

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CT — computed tomography; USD — urinary stone disease; MRI — magnetic resonance imaging; MSCT — multislice computed tomography; RPF — retroperitoneal fibrosis; USS — ultrasound scanning; CRF — chronic renal failure

Retroperitoneal fibrosis (posterior peritoneal fibrosis, periurethral fibrosis, retroperitoneal granuloma, Ormond's disease) is a non-specific inflammatory process in the retroperitoneal tissue with the formation of fibrous tissue, causing gradual compression of adjacent structures. Retroperitoneal fibrosis (RPF) is the most common name for this disease. For the first time, a disease, which is characterized by proliferation of dense fibrous tissue in retroperitoneal fat and causing obstruction of the ureter, was described by Ormond, the urologist from Baltimore, in 1948.

RPF is a rare disease, with an incidence about 1 in 200 thousand people. It is usually diagnosed in patients between 30 and 60 years of age [2]. Men are affected twice as often as women. Mortality

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depends on the severity of obstruction and associated complications.

There is primary (idiopathic) and secondary RPF. Autoimmune mechanisms play the leading role in the development of idiopathic RPF. Secondary RPF is a consequence of various pathological conditions and diseases (cancer, infections, chronic inflammation of the liver, intestines, pancreas and female genital organs, spinal tuberculosis, toxic effects of certain drugs, etc.) [1, 7]. The primary idiopathic form is about 60–70 %, and the secondary form ranges from 30 to 40 % of all cases in the Russian Federation [7].

Usually, RPF begins in the retroperitoneal tissue surrounding the iliac vessels, at the site of their intersection with the ureter (at the site of L4–L5). Fibrosis extends gradually to the sacral promontory and to the kidney hilum. The process is bilateral in 30 % of cases. The vessels and the ureter are involved in the process so intimately that it is impossible to determine the border between adventitia and fibrous tissue. Diffusely growing scar tissue compresses the ureters first of all, then the inferior vena cava, the aorta and its main arteries are involved in the process. The disorder of urine flow through the ureter leads to an increase in intrapelvic pressure and the development of hydronephrosis, pyelonephritis, urinary stone disease (USD), renovascular hypertension, and ultimately to chronic renal failure (CRF) and renal scarring. In rare cases, RPF causes intestinal obstruction, obstruction of venous and arterial vessels.

The clinical picture depends on the stage, activity and extent of the process. The disease develops slowly, gradually progressing. There are three periods in the course of the disease: 1 — period of onset and development of the disease; 2 — period of the disease activity when the proliferating cellular and fibrous processes surround the retroperitoneal structures. 3 — period of contraction of fibrous mass with compression of the structures involved.

The first complaint is a constant dull pain localized in the lower back, abdomen, hypochondria with radiation to the groin, genitals, lower limbs. In the early stage of the disease, moderate fever, leukocytosis, and an increase in ESR are often observed. Symptoms due to compression of tubular retroperitoneal structures: hydroureteronephrosis, pyelonephritis, hypertension, CRF can follow the initial complaints in various terms: from 1 month to 2 years. Partial or complete obstruction of the ureters is observed in 75 % — 85 % of patients, oliguria or anuria is observed in 40 % of patients.

To confirm the diagnosis of RPF, intravenous urography is traditionally used, which allows to detect a triad of symptoms indicating the presence of this disease: hydronephrosis with dilated tortuous upper segment of the ureter; medial deviation of the ureter and external compression of the ureter. Recently, ultrasound scanning (USS), computed tomography (CT) and magnetic resonance imaging (MRI) of the abdominal organs and retroperitoneal space have been used in case of RPF to clarify the diagnosis, which allow to detect a space-occupying lesion, assess its extension, and monitor time-related changes during treatment. Multislice CT (MSCT) with contrast enhancement, as well as MRI are the most informative in the diagnosis of RPF and complement each other. MSCT with contrast enhancement allows to differentiate RPF from the aortic aneurysm, reveal the involvement of the arteries (lower mesenteric, testicular and vertebral), kidneys and ureters, and rule out enlargement of lymph nodes. MRI is superior to CT in differentiating between inflammatory tissue and mature fibrosis and can help to determine malignancy [3]. However, the final diagnosis can only be made on the basis of biopsy [4]. Differential diagnosis of the malignant and benign disease is performed using multiple deep biopsies, and, in some cases, only after laparotomy and open biopsy of this mass, followed by immunohistochemistry.

At the present time, there is no real standard of treatment for RPF; there is no clear definition of the role of drug therapy and the most effective method of surgical treatment [2]. Conservative treatment depends largely on the cause of the disease. Discontinuation of medication often leads to recovery, if the use of the drugs was the cause of the RPF. Treatment of malignant diseases is carried out in accordance with their cell type. Idiopathic RPF is often treatable with glucocorticoids and adjunctive immunosuppressive and antifibrotic agents [5, 6]. If necessary, anti-inflammatory, antibacterial therapy, detoxification, and symptomatic therapy are employed. If there is no effect from conservative

therapy, a surgical intervention is often required to release the ureters and other structures from dense connective tissue in order to reduce their obstruction.

The rarity of the condition and the difficulty of diagnosing RPF are a frequent cause of late onset and prolonged ineffective treatment of patients for the manifestations of various diseases and complications: hypertension, cancer, chronic colitis, cholecystitis, pancreatitis, gastric and duodenal ulcers, urinary stone disease, acute pyelonephritis, hydronephrotic kidneys, anuria, CRF, etc. In this clinical case, physicians faced similar challenges, which determined the lack of efficacy of conservative therapy.

Clinical Case

The patient K., 43 years of age, first complained of nagging pain in the left lumbar region, mostly at rest and at night, in January 2015 (at the age of 40). Since the pain arose after the removal of the intrauterine device, the patient was examined by gynecologist and received antibacterial therapy without effect. Body temperature was 37.0 °C. Stool and urination disorders, as well as menstrual cycle disorders were not observed. In March 2015, ultrasound scanning, followed by an MRI scan, performed at the Saratov City Clinical Hospital No. 2, revealed a soft tissue lesion measuring 55×33×82 mm, located in the retroperitoneal space, surrounding the aorta and adjacent to the inferior vena cava. Its structure was heterogeneous due to areas with fluid signal characteristics, irregular contours with moderately pronounced perifocal edema of retroperitoneal tissue. The uterus had normal dimensions, was unremarkable.

In April 2015, a dense, circumscribed, mobile lesion measuring 100×60 mm was revealed during laparotomy. It was located in the projection of the inferior vena cava and aorta, from the lower edge of the pancreas to the bifurcation of the vessels and was adhered to the duodenal inferior horizontal part and the anterior wall of the inferior vena cava. On the left, the lesion was surrounding the aorta and the left iliac vessels. Histological study of the lesion suggested the presence of fibrous histiocytoma. In May 2015, CT scan of the abdominal and retroperitoneal organs was performed at the N. N. Blokhin Russian Cancer Research Center, which confirmed the presence of a retroperitoneal lesion measuring 55×40×70 mm, with indicated localization, surrounding the aorta circumferentially (the aortic lumen was narrowed to 1.2 cm) and the inferior vena cava along its anterior surface. The lesion was removed; its histological structure corresponded to the retroperitoneal neurofibroma with pronounced secondary changes: (hyalinosis of stroma, lymphoid infiltration, accumulation of xanthoma cells).

Discomfort persisted in the lower abdomen in the postoperative period. Body weight loss of 15 kg and periodic increase in BP to 145–160/100 mm Hg were observed. The patient took captopril as needed. CT on September 2015 revealed a band of infiltration measuring 3–4 mm in thickness and 60 mm in length at the site of the lesion described previously, surrounding the aorta like a cuff up to its bifurcation, and extending by up to 20 mm to the proximal segments of the iliac arteries. Hepatomegaly was discovered. No other abnormalities were revealed during CT and USS.

Given the lack of treatment, follow-up CT carried out at N. N. Blokhin RCRC in February 2016 revealed negative time-related changes: an increase of thickness (up to 13 mm) and length (up to 70 mm) of the lesion that was extending to the common iliac vein and the upper third of the left ureter, causing dilation of its proximal parts to 8 mm and pyelectasis measuring up to 23 mm. Nephrostomy was performed in the left side, an immunohistochemical study was performed, according to the results of which the diagnosis was changed to idiopathic RF (Ormond's disease). Taking into account the outflow disorder in the left ureter detected during angiography, a stent was inserted into the left ureter, and the nephrostomy tube was closed. Follow-up and treatment by the rheumatologist were recommended.

Over the next 2 years, the patient was regularly (once every 3–5 months) followed-up at the Departments of Rheumatology and Urology of the Saratov Regional Clinical Hospital where she was undergoing USS, CT of the abdominal and retroperitoneal organs, as well as duplex ultrasound of the abdominal and retroperitoneal vessels and general clinical laboratory tests. Treatment

with Metypred (24 mg with a gradual decrease to 8 mg), D-penicillamine 250 mg/day, Coronal 2.5 mg/day was prescribed. Occasionally, the patient noted the appearance of turbid urine with meat slops color. Proteinuria, with a maximum of 1.45 g per day, bacteriuria, massive leukocyturia, and hematuria were revealed. Repeated catheterization of the left ureter with stent replacement (every 3–5 months) was performed; antibacterial therapy was prescribed with a short-term effect. In May 2016, she reported that the nephrostomy tube fell out without adverse effects. From the beginning of this conservative therapy, a gradual decrease in the RPF thickness from 13 mm (February 2016) to 4 mm (July 2017) has been observed: Figure 1. During the following year, no further positive changes were observed despite continued treatment. The length of the lesion did not change significantly.

In March 2018, the patient developed a partial ptosis of the upper eyelid on the right, after that D-penicillamine was canceled, a CT scan of the head was performed taking into account the possible development of a tumor of the orbit in this disease, but this abnormality was not revealed. Since the eyelid function has fully recovered after the discontinuation of D-penicillamine, we considered ptosis as an adverse reaction to this drug with the development of myasthenia gravis. Instead of D-penicillamine, methotrexate was prescribed at low doses (10 mg per week). The lack of further positive changes regarding the RPF, persistent ureteral obstruction with the development of hydronephrosis of the left kidney, and recurrent urinary tract infection were the basis to recommend surgical treatment to the patient, aimed at restoring the patency of the left ureter.

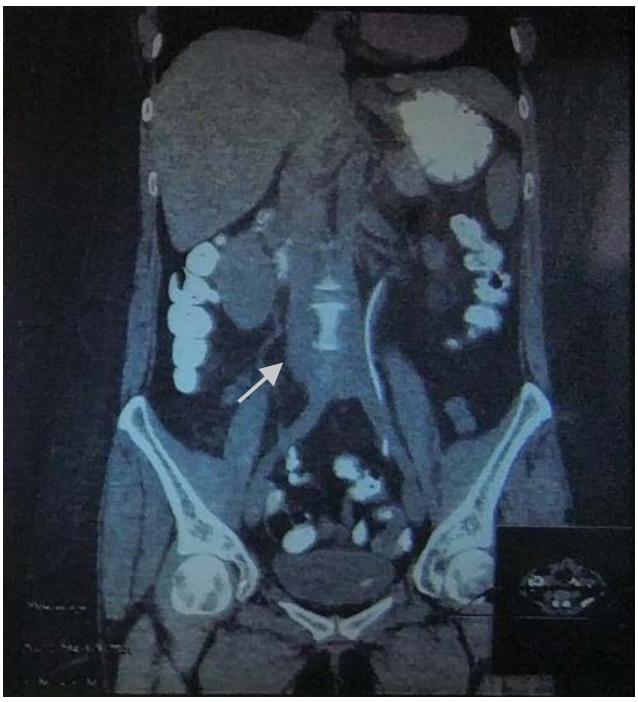

Figure 1. *Retroperitoneal Fibrosis (October, 2016)*

Discussion

The low incidence of RPF in the population and associated difficulties in obtaining statistically significant results, the lack of sufficient experience of individual clinical centers in the diagnosis and management of patients led to the lack of a unified approach to the treatment of patients with this condition. Some authors begin with glucocorticoids and other drugs and, in the lack of effect, resort to surgical treatment. Others opt for a surgical procedure immediately, and then prescribe or do not prescribe drug therapy.

In this case, the initial treatment (removal of RPF) was undertaken by surgeons. Drug therapy was started only 10 months after the surgery (one year after the first symptoms of the disease appeared), when the final diagnosis was made and the progression of the disease became apparent (an increase in the lesion thickness from 3–4 mm to 13 mm and in its length from 60 mm to 70 mm with dilation of the proximal left ureter and the development of pyelectasis).

With immunosuppressive therapy, some positive changes were observed (a decrease in RPF thickness up to 4 mm), however, late diagnosis of the disease and, accordingly, delayed start of treatment did not allow achieving the full effect, apparently due to the development of irreversible fibrosis. Recurrent urinary tract infection limiting the possibility of long-term immunosuppressive therapy in adequate doses was a factor aggravating the treatment.

Thus, the rarity and little knowledge of Ormond's disease caused delayed diagnosis and untimely medical therapy; surgical treatment without subsequent immunosuppressive therapy does not prevent the progression of the disease; although

delayed and insufficient (due to urinary tract infection) drug therapy caused a decrease in RPF, it did not result in its complete elimination, thus creating the risk of further disease progression and the need for repeated surgical intervention.

Conclusions

1. Ormond's disease (retroperitoneal fibrosis) needs further study and development of standards for the management of patients with this condition
2. Immunosuppressive therapy should be prescribed as soon as possible to prevent the development of irreversible fibrosis
3. In advanced stages of the disease, treatment should be comprehensive, including both medical therapy and surgical intervention.

Conflict of interests

The authors declare no conflict of interests.

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SEPSIS LIKE A SEVERE COMPLICATION OF AUTOIMMUNE LIVER DISEASE IN GASTROENTEROLOGICAL PATIENTS

Abstract

In the article, we present features of clinical pattern and treatment of patients with ulcerative colitis associated with primary sclerosing cholangitis and autoimmune hepatitis. Course of disease was complicated by bacterial cholangitis, sepsis, and multiple organ failure. Pathogenetic features of autoimmune disorder in liver and bowel diseases are described. The role of bacterial translocation in primary immune disorder development and in inflammatory syndrome maintenance is described. Differential diagnosis challenges in primary and secondary cholangitis are described. Features of management of patients in critical condition are reviewed in the article. The role of glucocorticosteroids in sepsis treatment is sketched. Modern guidelines for the management of patients with overlap syndrome are highlighted. Patient D. was admitted to the intensive care unit of the hospital with a clinical pattern of shock and systemic inflammatory response syndrome. Exacerbation of ulcerative colitis complicated by infection on the background of primary sclerosing cholangitis and autoimmune hepatitis was diagnosed. This condition led to sepsis and multiple organ failure. Despite intensive care treatment, there was a progressive worsening of the patient's state until clinical death. Resuscitation procedures within 6 minutes were successful. Multiple areas of necrosis have developed on the limbs because of multiple organ failure and intensive treatment with vasopressors. Glucocorticosteroids in combination with antibacterial agents were prescribed despite sepsis with ulcerative colitis exacerbation and cytolysis syndrome. On the thirtieth day of hospital stay, patient D. was transferred from the intensive care unit to the gastroenterology department, where the treatment was continued. Because of the treatment provided, signs of multiple organ failure, infectious complications, exacerbation of ulcerative colitis and primary sclerosing cholangitis regressed. The patient was regularly followed-up.

Key words: *ulcerative colitis, primary sclerosing cholangitis, autoimmune hepatitis, sepsis, glucocorticosteroids*

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BP — blood pressure, AIH — autoimmune hepatitis, 5-ASA — 5-aminosalicylic acid, BT — bacterial translocation, IBD — inflammatory bowel disease, GCS — glucocorticosteroids, BMI — body mass index, ABS — acid-base status, CT — computed tomography, MRCPG — magnetic resonance cholangiopancreatography, MOF — multiple organ failure, PSC — primary sclerosing cholangitis, RGA — Russian Gastroenterological Association, BOS — bacterial overgrowth syndrome, CRP — C-reactive protein, SIRS — systemic inflammatory response syndrome, UDCA — ursodeoxycholic acid, HR — heart rate, UC — ulcerative colitis, CLIF-C ACLF — Chronic liver failure consortium Acute on chronic liver failure

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Introduction

Currently, there is a steady increase in the number of patients with ulcerative colitis (UC) and, as a consequence, with associated conditions. According to available epidemiological data, the prevalence of the disease is 505 per 100,000 people [1]. The social and economic significance of this pathology is also determined by the presence of a morbidity peak attributable to persons of working age from 20 to 30 years.

UC is a chronic disease of the colon, characterized by immune inflammation of its mucous membrane [2]. In addition, there are many extra-intestinal manifestations of the disease, aggravating the course and prognosis. Among them, liver diseases play a special role.

The proven association of UC and primary sclerosing cholangitis (PSC) is demonstrated in the phenotypic classification of the latter. The study of UC confirmed that the variant with liver damage differs from the isolated form of the disease [3]. In 5% of patients with autoimmune bowel disease, there are signs of liver disorder. UC associated with PSC is characterized by a milder course, a pronounced lesion of the proximal colon and the remaining almost intact rectum [3]. In turn, liver damage sometimes manifests itself before the onset of the clinical picture of UC in the form of a moderate increase in serum cholestasis enzymes.

Another variant of association of UC with liver damage is autoimmune hepatitis (AIH), which is detected in 1–5% of patients. Increase of cytolysis enzymes, detection of autoantibodies, hypergammaglobulinemia in patients can serve as evidence of this disease.

In some cases, clinical and laboratory signs of the above-described liver diseases are combined, in which case this condition is called autoimmune overlap: PSC with signs of AIH.

Clinical case

On 04.08.18, patient D., 34 years old, was urgently delivered by ambulance service to the Moscow City Clinical Hospital after V. M. Buyanov with a referral diagnosis of hypotension of unknown origin. He was admitted to the intensive care unit with complaints of fever up to 39 °C, jaundice of the skin and sclera, pronounced weakness.

He considers himself sick since December 2014, when he first noticed signs of weakness, reduced tolerance to the usual physical activity (playing football and fighting without rules), pulling pain in the right hypochondrium, liquid blood-streaked stool up to 4 times a day. In outpatient settings, increased activity of enzymes of cytolysis and cholestasis, which was the reason for hospitalization in the Central Research Institute of Gastroenterology, Moscow, was revealed. According to the results of the examination, the patient was diagnosed with: PSC with signs of autoimmune hepatitis (AIH), moderate biochemical activity. UC with total involvement, of minimal activity. Therapy with ursodeoxycholic acid (UDCA) 1,500 mg/day, 5-aminosalicylates (5-ASA) 3 g/day, glucocorticosteroids (GCS) 40 mg/day was started, during which a positive change was noted. After discharge, patient D. continued to engage in heavy physical activity, diet was not followed; the recommended therapy was not adhered to.

Subsequently, the patient was repeatedly hospitalized at the Loginov Moscow Clinical Scientific Center due to UC attacks caused by noncompliance with the diet, recommended therapy and exercise regimen. There was a progression of the disease and deterioration of the clinical picture with each subsequent hospitalization. The patient noted current deterioration from August 2018, which was the reason for hospitalization.

In the intensive care unit, the patient's condition was regarded as severe. Fever was up to 39 °C. Position of the body due to severe weakness was forced lying on a gurney. The patient was conscious, euphoric, sluggish, inhibited, oriented in space, time and person. Skin was intensely jaundiced, dry, distal limbs were cold, cyanotic. Lymph nodes were not palpable. There were phenomena of respiratory failure — tachypnea at rest with respiratory rate of 30 per minute. Auscultatory breathing was bronchial, heard symmetrically throughout all lung fields, weakened in the lower parts, rales were not heard. Hypotension (BP — 60/40 mm Hg), tachycardia (HR — up to 100 beats/min), heart tones were rhythmic, muffled; heart murmurs during auscultation were not heard. Tongue was dry, covered

with a coat. Abdomen was soft and painless during palpation. The liver was 10×10×9 cm according to Kurlov's method, indurated, non-tender; its lower edge was sharp. The lower pole of the spleen was located in the depth of the hypochondrium on the left side. Peritoneal signs were not observed. Peristalsis was heard. The rate of diuresis is reduced, Pasternatsky's symptom is negative on both sides.

The dynamics of analyses for the period of hospitalization is presented in Table 1. Because of the auscultatory picture, right-sided community-acquired lower lobe pneumonia was suspected. High levels of hepatic enzymes and creatinine were evidence of severe hepatic and renal failure. Taking into account tachypnea, tachycardia, hypotension, fever, as well as an elevated level of C-reactive protein (CRP) and procalcitonin, the development of sepsis was not excluded. According to the integrated scale Chronic liver failure consortium — acute on chronic liver failure (CLIF-C ACLF) — 39 points. Infusion, antibacterial, anticoagulant therapy was started; hemodynamics was supported by administration of vasopressors, and humidified oxygen was injected through nasal cannulas.

Rectosigmoscopy with biopsy was conducted, and its results identified a UC attack (Mayo index — 10 points) [4].

In a day spent in the intensive care unit, the patient's condition deteriorated sharply. There was a progression of the phenomena of multiple organ failure (MOF): cardiovascular — requiring vasopressor support with a tendency to escalate dosages; respiratory — with the development of decompensated shifts of acid-base state (ABS), low oxygen saturation; hepatic — with an increase in the level of bilirubin, enzymes of cholestasis and cytolysis; renal — clinically manifested by decreased rate of diuresis to oliguria and increased azotemia parameters (Table 1). Due to the increase in MOF phenomena and metabolic disorders, the patient was put on mechanical ventilation.

The patient's condition on 06.08.18 was regarded as extremely severe. Due to the lack of efficacy of antibiotic therapy, the drugs were repeatedly changed, including macrolides, semi-synthetic penicillins and cephalosporins protected by sulbactam, oxazolidones, glycopeptides, antifungal agents. Vasopressor, infusion, sedative, gastroprotective therapy, correction of metabolic disorders and prevention of thromboembolic complications were also carried out.

Despite intensive therapy, on 08.08.18 the patient's condition is regarded as agonal with transition to clinical death. Extended resuscitation was carried out, after 6 minutes of which sinus rhythm was restored, BP — 80/40 mm Hg, HR — 160 beats/min.

Table 1. *Dynamics of the main laboratory parameters in patient D.*

Показатели	04.08.18	05.08.18	08.08.18	10.08.18	16.08.18	26.08.18	17.09.18
Hemoglobin (130-170 г/л)	116	118	88	107	118	101	114
Erythrocytes (4.28-5.78*10^{12} /л)	3.47	3.36	2.50	2.89	3.43	3.06	3.13
Leukocytes (3.9 — 10.9*10^{9} /л)	10.70	47.20	30.20	49.50	21.60	28.60	21.60
Platelets (150-340*10^{9} /л)	444	203	24	59	35	305	562
AST (5-34Е/л)	354	562	814	559	379	270	119
ALT (0-32Е/л)	324	376	429	412	258	214	248
GGTP (9-39Е/л)	2259	1975	820	1239	420	716	745
Alkaline phosphatase (64-306Е/л)	2502	1346	1205	753	1688	1509	1402
Total bilirubin/Conjugated bilirubin (0.86-5.0мкмоль/л) 1.7-20.5 мкмоль\л	82/47	112/79	205/100	233/197	274/161	292/178	146
Creatinine (71-115мкмоль/л)	196	176	121	133	72	73	70
CRP 0.1-7.0	-	-	325.9	124,8	-	-	-
Procalcitonin (0.05-0.50 нг/мл)	13.38	33.04	-	7.59	-	-	-

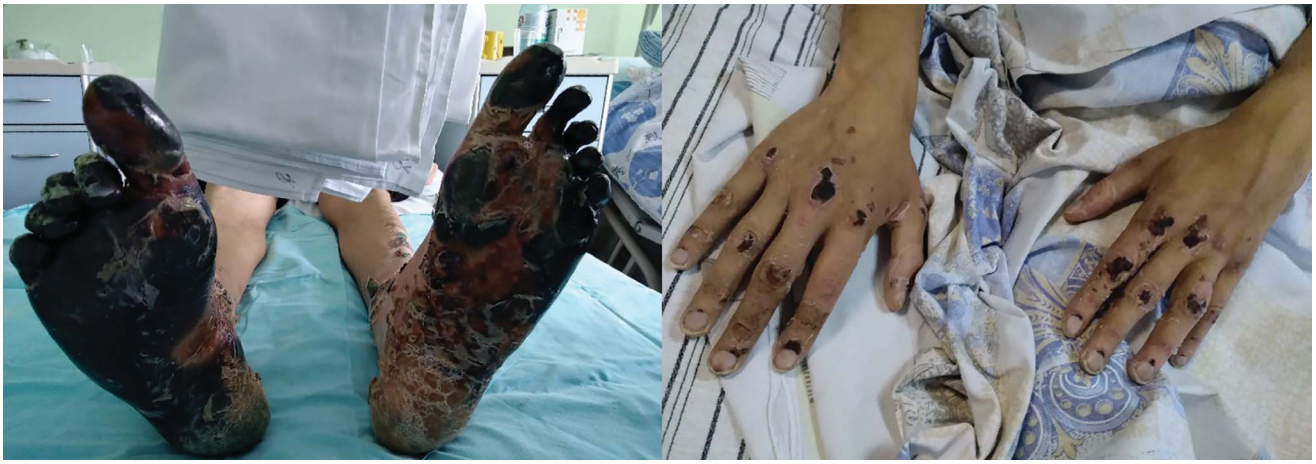

Figure 1. *Condition of the lower and upper extremities of patient D. on the 12th day of stay in the intensive care unit*

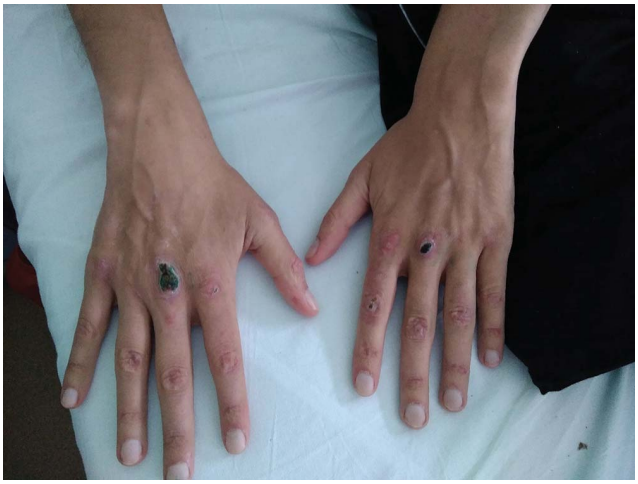

Figure 2. *The condition of the lower and upper extremities of patient D. at discharge*

With further observation, the patient's condition was regarded as stable and severe. On chest CT from 10.08.18 — pattern of bilateral polysegmental pneumonia. A bronchoscopy with airway hygiene was performed with further microbiological examination of washings (in bronchial washings — Enterococcus faecium, Klebsiella pneumoniae).

On the 12th day of staying in the intensive care unit, the patient's condition was severe, without negative change; the patient was conscious, available to limited contact. On the distal phalanges of the fingers of the lower and upper extremities, multiple areas of necrosis were determined (Photo 1). The high level of cholestasis enzymes, CRP, conjugated bilirubin and insufficient efficacy of antibiotic therapy did not allow to exclude bacterial cholangitis, which was the reason for selective cannulation of the large duodenal papilla for bile sampling. In a bacteriological study, Acinetobacter species and Klebsiella pneumoniae were determined in bile, and therapy with tigecycline, meropenem was prescribed taking into account sensitivity. During treatment, positive changes were noted: normalization of body temperature, regression of respiratory failure (pneumonia at resolution phase), reduction of cholestasis in the blood (Table 1).

On the 22nd day, due to the continuing activity of UC (diarrhea up to 5 times a day, blood admixture in feces, leukocytosis), the Medical Council decided to prescribe to patient D. GCS-prednisolone at a dose of 140 mg/day by intravenous bolus. Two days later, the patient was transferred to self-breathing with minimal support with humidified oxygen.

From Day 30, patient D. continued treatment in the Department of Gastroenterology, intravenous GCS was replaced by oral one (Metypred) at a dose of 24 mg/day; positive changes in laboratory parameters were noted (Table 1). In addition, signs of MOF, infectious complications, exacerbation of UC and PSC regressed. The Mayo index was 2 points.

At discharge, the patient was limited in activity, as trophic changes on the skin of the limbs were preserved (Photo 2). A recommendation was made to continue taking UDCA, 5-ASA, GCS (with tapering course), additional enteral nutrition, and protective diet. The patient continued dynamic follow-up; after 2 months the condition was apparently improved.

Discussion

A clear relationship between UC and PSC is shown by high frequency (70–90%) of association [5]. At the genetic level, UC susceptibility loci were identified, that may be associated with PSC [5]. The latter is characterized by a number of specific complications (bacterial cholangitis, cholelithiasis, bile duct strictures, cholangiocarcinoma).

The phenomenon of bacterial translocation (BT), which provides the key to understanding the relationship between these states, deserves attention. There are two ways of bacteria migration through the intestinal wall: transcellular pathway and directly through the intercellular space of enterocytes [6].

The primary link in the mechanism of bacterial translocation is bacterial overgrowth syndrome (BOS). However, there is a need for a second, but no less important, element of the pathological process — disturbed immune response of the macroorganism. Patients with UC showed changes in the phagocytic immunity [7] and elevated levels of proinflammatory cytokines [8].

The research results do not allow to eliminate the etiological role of microbiota as one of the factors of induction and maintenance of inflammatory process in the intestine and liver.

There are microorganisms that are more predisposed to translocation, perhaps due to their better ability to adhere to the intestinal epithelium. These are, first of all, gram-negative bacteria — Escherichia coli, Klebsiella pneumoniae, and enterococci. In our observation, the association of Acinetobacter species and Klebsiella pneumoniae was found in the bile of the patient, which does not contradict well-known ideas about the etiological role of microorganisms in the formation of bacterial cholangitis.

It should be noted that there are difficulties in diagnosing bacterial cholangitis in patients with IBD/PSC. A classic sign of acute cholangitis is the Charcot triad — pain in the upper right quadrant of the abdomen and epigastrium, accompanied by chills and rapidly developing mechanical jaundice. However, the clinical picture of PSC can mask the signs of bacterial cholangitis. So abdominal pain occurs in 35% of cases, jaundice — in 30%; fever — only in 17% of cases [9, 10]. Manifestations of general intoxication syndrome may be due to exacerbation of UC, as well as the development of cholangiocarcinoma [11]. The increase in cholestasis is also possible due to the development of morphofunctional changes in hepatocytes in sepsis [12].

Among the instrumental methods of examination, ultrasonography and endoscopy play an important role. Signs of biliary hypertension in the form of bile duct dilation above the level of the obstacle always reliably indicate the mechanical nature of cholestasis, but thickening and/or focal expansion was also noted in PSC. A mandatory element of instrumental diagnosis in patients with jaundice and cholangitis is endoscopic examination. The absence of bile in the intestine and signs of papillitis may indicate the mechanical nature of jaundice. Endoscopic retrograde cholangiopancreatography has long been the gold standard of diagnosis [13, 14]. However, this procedure has a number of complications — the development of pancreatitis and sepsis [15]. According to the recommendations of both the European and Russian society for liver research, as well as of American College of Gastroenterology, the first line method is MRCPG [13–15].

Currently, the role of invasive methods of examination remains important during the diagnostic and treatment procedures. Our patient underwent selective cannulation of the large duodenal papilla for bile collection for bacteriological study, the results of which diagnosed the bacterial nature of cholangitis, which confirms the difficulties of diagnosis between primary and secondary cholangitis in real clinical practice.

Reduced compensatory capacity of the body due to UC, autoimmune liver disease, severe hypoproteinemia led to the aggravation of the cascade of pathological reactions — activation of macrophages, neutrophils, vascular endothelium, and, as a consequence, to the hyperproduction of cytokines with the development of organ dysfunction (MOF, sepsis). An important role is given to the definition of strategy for the management of such conditions, the detection of MOF syndrome, the diagnosis of severe sepsis and septic shock. The CLIF-C scale is a more accurate tool for dynamically

assessing the degree of organ dysfunction, as well as the estimated survival rate in patients with liver disease [16].

An extremely important role in the management of patient D. was played by GCS administration under the cover of antibacterial drugs. Only on Day 22 of staying in the intensive care unit GCS allowed to achieve stabilization of the patient.

According to international recommendations for the treatment of patients with sepsis, GCS may be used in cases of absence of stabilization of the disease, but with adequate water load and vasopressor therapy (the third-line therapy) [17]. The authors of the recommendations refer to publications with proposals to consider GCS, in particular hydrocortisone, in moderate doses (200 mg/day) in patients with refractory septic shock [18].

In the present clinical observation, endotoxemia in patient D. was primarily due to the activity of UC — increased permeability of the intestinal wall. However, despite adequate antibiotic therapy, the symptoms of BT persisted. We do not exclude that due to the etiological therapy in combination with GCS, it was possible to reduce SIRS and suppress the growth of bacterial flora.

The difficulties in management of patient D. lay not only in the features of long-term therapy of critical conditions, but also in the need to continue treatment in gastroenterological department, as well as in the choice of further tactics after discharge.

According to clinical guidelines for the management of patients with PSC, UDCA (at a dose of 15-20 mg/day) plays a major role. However, its use does not have a proven effect on the life expectancy of patients, but only improves the results of surrogate prognostic markers [13].

The second important aspect is the use of glucocorticosteroids, recommended for patients with UC/PSC and AIH signs. During GCS therapy at a dose of 40 mg/day with subsequent replacement with 5-ASA (mesalazine) at a dose of 2.4 g/day, the patient showed significant positive changes. An important role was played by spasmolytic therapy, correction of trophic insufficiency, as well as long-term psychological support with an explanation of the principles of diet therapy and the promotion of a positive attitude towards such a serious disease.

It is also necessary to mention the problem of compliance of patients with UC/PSC. Their average life expectancy is 25 years from the time of diagnosis, provided there is compliance with all the doctor's recommendations [19], and in the absence of treatment, the UC acquires an uncontrolled course with frequent exacerbations or attacks of the disease.

Some authors believe that a lack of adherence to treatment regimens is a major problem in patients with any chronic disease, and about half of them do not follow the prescribed regimen to such an extent that they do not receive optimal clinical benefit [20]. The most effective strategy for increasing patient adherence today is the so-called compliance therapy based on a motivational interview [20].

Today, the problem of UC/PSC and their combination with other autoimmune conditions remains insufficiently studied. Etiological treatment does not exist; however, the use of pathogenetic therapy, UDCA, GCS, 5-ASA, in adequate doses can help to achieve longer and improved quality of life of patients.

Conflict of interests

The authors declare no conflict of interests.

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PANHYPOPITUITARISM IN ADULTS: MODERN VIEWS AND CASE ANALYSIS

Abstract

The article is devoted to the problem of panhypopituitarism, the diagnosis of which presents certain difficulties in connection with the combined lesion of several peripheral endocrine glands. Modern classification, etiopathogenesis, diagnosis and treatment of the disease are presented. Acquired hypopituitarism in adults develops, as a rule, at the age of 30–60 years, mostly women are affected. Panhypopituitarism is diagnosed when pituitary production of all tropic hormones is affected, which is observed in case of damage to 90 % of the adenohypophysis cells. The variety of clinical signs of the disease is determined by the different effects of pituitary hormones and the degree of their deficiency. The diagnosis is based on a history of etiological factors causing damage to the pituitary gland, and clinical signs of insufficiency of peripheral endocrine organs, which is confirmed by the results of laboratory studies. In hypopituitarism due to, for example, the growth of pituitary adenoma, the clinical picture develops gradually, and the disorder of the secretion of the pituitary tropic hormones usually occurs in the following sequence: growth hormone, gonadotropins, then thyrotropic and adrenocorticotropic hormones, and, the last one, prolactin. Neurosurgery or hemorrhage in the pituitary gland causes a rapid manifestation of the disease, and the severity of the condition is associated mainly with adrenal insufficiency. In the case of surgery for pituitary adenoma, there is a recommendation to determine morning blood cortisol on the 3rd day after the intervention. Conservative treatment is aimed at compensating for hormone deficiency. According to the clinical significance of endocrine disorders, their correction is carried out in the following sequence — first, compensation for adrenal insufficiency, then thyroid, sex glands and growth hormone. In case of damage to the posterior lobe of the pituitary gland with the development of diabetes insipidus, replacement therapy for vasopressin deficiency is also required. The clinical case presented in the article reflects the difficulty of diagnosis and interpreting the data of hormonal analysis in panhypopituitarism. An analysis of the described clinical case shows the importance of understanding the pathogenesis of the disease when conducting a diagnostic search. Adequate replacement therapy can restore normal well-being in patients with hypopituitarism.

Key words: *hypopituitarism, adenohypophysis, hypocorticism, hypothyroidism, hypogonadism*

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ACTH — adrenocorticotropic hormone, IGF-1 — insulin-like growth factor, LH — luteinizing hormone, MRI — magnetic resonance imaging, FT4 — free thyroxine, GH — growth hormone, TSH — thyroid-stimulating hormone, USS — ultrasound scanning, FSH — follicle-stimulating hormone

Good judgment comes from experience,
and experience comes from bad judgment.
Hodja Nasreddin

Diagnosis and treatment of hypopituitarism, or pituitary insufficiency, often present challenges. This is due to the combined affection of several endocrine glands, where symptoms and interpretation of the results of hormonal analysis have a number of peculiarities if compared with isolated damage to a particular organ of internal secretion. Insufficient awareness of the problem of hypopituitarism

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is also important. The author hopes that the presented article with information about the diagnosis and treatment of this disease and the analysis of the clinical case will be of help to practitioners.

Hypopituitarism is caused by a decrease in the secretion of tropic hormones of the adenohypophysis, which is manifested by the functional insufficiency of the corresponding peripheral endocrine organs.

Acquired hypopituitarism in adults is observed usually at the age of 30–60 years; mostly women suffer, due to the higher frequency of diseases that cause this pathology.

Etiopathogenesis

The causes of the syndrome of acquired hypopituitarism include tumors of the pituitary gland and the hypothalamic region, vascular pathology (ischemic or hemorrhagic damage to the pituitary, cavernous sinus thrombosis, etc.), empty sella syndrome, brain injuries, neurosurgical interventions, irradiation of the hypothalamic-pituitary region, as also damage of inflammatory, infectious, infiltrative, and toxic genesis.

The condition for the progression of disease is a direct damage to the pituitary gland or weakening of the stimulating effect of the hypothalamus, releasing hormones of which regulate both functional and proliferative activities of the adenohypophysis being subjected to atrophy when hypothalamic control is reduced. Hypopituitarism is observed when 70–75 % of cells of adenohypophysis are destroyed, panhypopituitarism — in case of damage to 90 % of cells.

Classification

Based on the localization of the pathological process. In case of direct damage to the pituitary gland, primary hypopituitarism is diagnosed, while in case of disorder of the regulatory function of hypothalamus, it is diagnosed as secondary.

Depending on the clinical manifestations, the following forms of the disease are distinguished: isolated hypopituitarism (with loss of one tropic function), partial (in case of disorder of two tropic functions or more, but not all), and also panhypopituitarism (with affection of all tropic functions) [3, 5, 6, 10].

Clinical Course

With hypopituitarism caused by, for example, the growth of pituitary adenoma, the clinical picture develops gradually and it can take several years from the beginning of the disease to diagnosis. Disorder of secretion of tropic hormones of the pituitary gland occurs, as a rule, in the following sequence: first, a decrease in production of growth hormone (GH), gonadotropins (luteinizing hormone, LH, and follicle-stimulating hormone, FSH), then thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH) and, last of all, prolactin, occurs. In this regard, the earliest signs of hypopituitarism are sexual disorders, while the partial lesion of the pituitary gland in most cases is characterized by somato- and gonadotropic insufficiency.

Neurosurgical intervention or hemorrhage in the pituitary gland causes rapid manifestation of the disease, often within a few hours, and the severity of the condition is mainly associated with adrenal insufficiency, requiring immediate replacement therapy.

The variety of clinical manifestations of hypopituitarism is determined by various effects of tropic hormones and the degree of their deficiency.

Hypoproduction of GH leads to a decrease in the intensity of metabolic processes. As a result, the amount of visceral fat and blood cholesterol increases, while muscle mass and bone mineral density decreases; the skin becomes dry and thinned. Tendency to apathy, depression, low self-esteem and ability for social adaptation are typical.

In women, gonadotropin deficiency or hypogonadotropic hypogonadism is manifested by menstrual irregularities (oligo-, opsomenorrhea), infertility, atrophic changes in the vaginal mucosa and urogenital disorders up to urinary incontinence, reduction of pubic hair, hypoplasia of mammary glands, and decrease of libido. Deficiency of gonadotropins in men also causes a decrease in sexual function, gonad atrophy, a reduction in hair on the face and body; gynecomastia is possible. In addition, hypoandrogenism in males leads to development of anemia. Regardless of gender, hypogonadism contributes to the formation of osteoporosis and early atherosclerosis, accompanied by a loss of interest in the world and to oneself.

Characteristic symptoms of thyrotropic insufficiency, causing secondary hypothyroidism, are

drowsiness, lethargy, retardation, cold intolerance, reduced intellectual and physical activity, dry and pale skin, puffy tissue, hair loss on the head, a tendency to bradycardia, and constipation.

Signs of a decrease in ACTH production with the development of secondary hypocorticism include general weakness, fatigue, loss of appetite up to nausea and vomiting, weight loss, decreased blood pressure, especially in orthostasis, a tendency to hypoglycemia manifested by intolerance to hunger, attacks of dizziness on an empty stomach; reduced heart rate is also possible. Patients' well-being worsens in the evening, with emotional and physical stress.

It is also necessary to bear in mind that in case of diseases of the pituitary gland there is a possibility of damage of its posterior lobe — the neurohypophysis. Unlike the anterior lobe, the adenohypophysis, the posterior pituitary is not a hormone-producing gland. Hormones of the posterior lobe (vasopressin and oxytocin) are synthesized in the bodies of the hypothalamic neurons, and then transported along axons and accumulate in their terminal extensions, forming the neurohypophysis. Vasopressin, or an antidiuretic hormone, possesses the main clinical importance providing reabsorption of water in the kidney and increasing the peripheral vascular tone. Deficiency of this hormone causes the development of diabetes insipidus, manifested by polyuria and polydipsia [1, 2, 4, 7, 8].

Diagnosis

First of all, diagnosis is based on the detection of a history of the above etiological factors — trauma, neurosurgery, radiation, disease of the hypothalamic-pituitary area of inflammatory, infiltrative nature, etc. Progressive decrease in visual acuity and/or narrowing of the visual fields may be a symptom of a pituitary tumor. Ischemia of the pituitary, as the cause of pituitary insufficiency, may be indicated by massive bleeding during childbirth. Hemorrhage in the pituitary gland, or apoplexy, is characterized by an episode of sudden severe headache with marked well-being impairment.

Attention should be paid to such complaints as menstrual disorders in women and sexual dysfunction in men, as well as general weakness, decreased muscle strength, drowsiness, memory disorders, poor appetite, and increased fatigue, the severity of which increases by the end of the day and during exercise.

On examination, dryness and pallor of skin, bradycardia, orthostatic hypotension, increase in visceral fat and decrease in muscle mass, reduction of pubic hair, atrophic changes in the genital organs, breast hypoplasia in women and gynecomastia in men are diagnostically significant.

It must be emphasized that adrenal insufficiency poses the greatest threat to a patient who may need urgent therapy. In severe cases, the diagnosis of hypocorticism is primarily based on clinical manifestations, among which the most typical are poor appetite, weight loss and a decrease in blood pressure.

The main manifestations of diabetes insipidus are thirst and polyuria from 3 to 18 l/day. For brain injuries and surgeries, diabetes insipidus may be transient and can be resolved within 3–6 months. Concomitant adrenal insufficiency masks the symptoms of diabetes insipidus, since glucocorticoids contribute to water excretion by the kidney, while compensation for hypocorticism in such cases leads to increased polyuria.

The insufficiency of the tropic hormones of the pituitary gland is confirmed during laboratory studies. Considering the previously noted sequence in the damage of tropic functions, assay of the blood levels of insulin-like growth factor (IGF-1), LH, FSH, free thyroxine (FT4), TSH, and testosterone in men is recommended as disease screening.

The extent of laboratory studies necessary to confirm GH deficiency depends on the level of IGF-1 and the severity of damage to the hypothalamic-pituitary region. Detection of low levels of IGF-1 against the background of irreversible organic hypothalamic-pituitary damage with a decrease in the secretion of three other tropic hormones is a sufficient basis for the diagnosis of growth hormone insufficiency. It should be taken into account that the normal concentration of IGF-1 does not exclude the deficiency of GH (in 20–30 % of adults this figure may be within the reference range). In these cases, it is necessary to study the blood level of GH during a stimulation test, since the secretion of somatotropin has an impulsive nature and the assay of its basal level is not informative.

In patients with irreversible organic damage to the hypothalamic-pituitary region and a decrease in secretion of two other tropic hormones, the

secretion of GH is analyzed using one stimulation test. For suspected isolated GH deficiency, or combined with one or other tropic hormone deficiency, two stimulation tests are required.

For this purpose, insulin is most often used; the development of hypoglycemia during its administration provokes secretion of hypothalamic GH-releasing hormone, as well as clonidine, a centrally acting adrenergic agonist. The insulin hypoglycemia test is considered to be the "gold standard", but it is dangerous for patients with cardiovascular disease and with a tendency to convulsions. Tests with arginine, glucagon and somatoliberin may be an alternative. Arginine suppresses secretion of somatostatin, the mechanism of action of glucagon is determined by development of late hypoglycemia, and somatoliberin is a hypothalamic releasing factor, and unlike other tests, the use of the latter is not accompanied by side effects.

The most physiological assessment of somatotropic function is daily monitoring of GH secretion and determination of its nocturnal production, but due to the high cost, such studies are carried out in research centers.

GH-insufficiency requires confirmation both in adult patients with hypothalamic-pituitary diseases and in case of growth hormone deficiency from childhood or adolescence. Integrity of GH production should be assessed after compensation of the thyroid state. In the case of brain injuries and subarachnoid hemorrhage, a transient disorder of somatotropic function is possible. Therefore, its study is conducted one year after these events.

To assess the gonadotropic function, the levels of LH, FSH, as well as estradiol in women and testosterone in men are analyzed. Hypopituitarism is characterized by a decrease in the concentration of peripheral sex hormones in combination with a low or normal content of gonadotropins. In women of reproductive age, changes in the level of these hormones can be poorly manifested. In these cases the diagnosis of a deficiency of sex hormones is based on data from a gynecological examination.

Thyroid deficiency is confirmed by TSH and FT4 reduced blood concentration. In some cases, the level of TSH may be within the normal range and even slightly higher, but attention should be paid to its inadequacy to the low content of FT4.

To detect ACTH deficiency, it is recommended to evaluate the blood cortisol content during stimulation tests, since the assay of the basal cortisol level is not always informative. Insulin, Metopirone and tetracosactide (1–24 ACTH) are used as stimulants. The stimulating effect of insulin is determined by the development of hypoglycemia (2.2 mmol/l), on the background of which cortisol content should exceed 500–550 mmol/l. Metopirone blocks the enzyme of steroidogenesis (11-beta-hydroxylase), which causes a decrease in cortisol production to 140 nmol/l or less, and as a result, an increase in ACTH secretion of more than 150 pg/ml. Tetracosactide is a synthetic analogue of natural corticotropin, consisting of the first 24 amino acids of its molecule. After its administration the level of cortisol must be above 750 nmol/l. The advantages of the latter test include the absence of side effects, while conducting an insulin test may be complicated by the development of severe hypoglycemia, seizure syndrome, and acute adrenal insufficiency. Side effects of Metopirone test include nausea.

In the case of surgery for pituitary adenoma, there is a recommendation to determine morning blood cortisol on the 3rd day after surgery. It is shown that cortisol level above 15 μg/dl allows to exclude adrenal insufficiency.

Diabetes insipidus is characterized by hypernatremia, increased blood osmolarity, as well as by low relative density of urine (less than 1,005 g/l) and urine osmolarity (less than 300 mOsm/kg).

Laboratory research in hypopituitarism also includes clinical and biochemical blood tests, in which attention should be paid to the parameters of red blood cells, lipid profile, glucose, electrolytes, liver enzymes and nitrogenous waste. In addition, the analysis of daily fluctuations in blood glucose, which, in case of hypocorticism, is characterized by monotonic low or low-normal values, the so-called "flat sugar curve", is diagnostically valuable.

It should be emphasized that the clinical symptoms of the disease are of paramount importance for the diagnosis, which is either confirmed or rejected on the basis of hormonal studies.

The main method of instrumental diagnosis of hypopituitarism is magnetic resonance imaging (MRI) of the brain. With a disease duration of more than a year, osteodensitometry is recommended.

In the course of diagnosis of the disease, consultation of an ophthalmologist in case of visual impairment, as well as a gynecologist for women and an andrologist for men, is necessary.

When describing the diagnosis, the damage to peripheral endocrine glands is listed in the order of clinical significance: hypocorticism, hypothyroidism, and hypogonadism [5, 7, 9, 11].

Treatment

If in patients with hypopituitarism a space-occupying lesion in the chiasmatic-sellar region is detected, surgery may be necessary.

Conservative treatment is aimed at compensation for hormonal deficiency. Taking into account the clinical significance of endocrine disorders, their correction is carried out in the following sequence — first, compensation of adrenal insufficiency, then thyroid, gonads and GH insufficiency. For replacement therapy of adrenal insufficiency, natural glucocorticoids — hydrocortisone and cortisone acetate, as well as a semi-synthetic analogue, prednisolone, are used. The drug of choice is hydrocortisone, which is an analogue of the cortisol molecule, the main endogenous glucocorticoid. Cortisone acetate is a precursor of hydrocortisone and its activity is somewhat lower, since the action is manifested after a number of transformations in the liver. The need for glucocorticoids in secondary genesis of adrenal insufficiency is somewhat lower than in primary hypocorticism. Thus, in the onset of the disease, it can be 5–10 mg of hydrocortisone or 6.25–12.5 mg of cortisone acetate in single daily dose taken in the morning. If necessary, the dosage is increased and prescribed in 2–3 doses, taking into account the daily rhythm of cortisol, according to which 2/3 of the daily dose is recommended to be taken in the morning, from 8 am to 12 pm. The daily dose of hydrocortisone usually does not exceed 20 mg, which corresponds to the amount of cortisol produced in healthy people. In stressful situations, the dose of glucocorticoids is increased by 1.5–2 times and, if necessary, administered parenterally. In case of secondary hypocorticism, mineralocorticoids, as a rule, are not required, since the secretion of aldosterone largely depends on renin.

The effectiveness of treatment is evaluated clinically — by the absence of symptoms of hypocorticism, while the study of the level of cortisol and ACTH is not advisable.

Treatment of secondary hypothyroidism is carried out after compensation of adrenal insufficiency. For this purpose levothyroxine sodium preparations are used. The initial dose is usually 25 μg, which is gradually increased under the control of the blood level of FT4 until its normalization, which is a criterion for the effectiveness of treatment. TSH assay is not diagnostically informative. In the future, an annual blood test for the content of FT4 is recommended.

Replacement therapy with sex hormones is indicated in most cases of hypopituitarism. It is carried out after the compensation of adrenal and thyroid insufficiency. For women, the use of analogues of natural estrogens (estradiol) and progestogens (progesterone, dydrogesterone) is recommended, and the regimen of administration and dosage depend on age. Up to the age of 45 years, the drugs are prescribed in a cyclic mode: in the first two weeks of the menstrual cycle, estrogen 1–3 mg/day (per estradiol), and in the second two weeks — in combination with gestagen. For over 45–50 years of age, a monophasic treatment regimen is recommended: daily estrogen 1–2 mg/day in combination with a gestagen, the dose of which also decreases about 2 times.

Estrogen-containing medicines available exist in the form of oral preparations and transdermal gels. The advantage of the latter is the possibility of use in cases of pathology of liver, disorders of lipid and carbohydrate metabolism. In addition, the transdermal route of administration provides a more constant blood level of estrogen compared with oral forms. Gestagens may be prescribed for oral and intravaginal administration.

In cases where a woman has no uterus, only estrogen preparations (0.5–1.5 mg of estradiol) are prescribed, transdermal administration is preferred. In postmenopausal women, when relatively low doses of estrogens are required for replacement therapy, it is recommended to use oral medications, the bioavailability of which is relatively low due to rapid destruction in liver.

Treatment continues until the age of natural menopause, the average age for which is 51 years. In some cases, therapy may last up to 55–65 years, since postmenopause ends at 65–68 years.

Androgenic deficiency in men is eliminated by testosterone preparations for enteral, parenteral and transdermal administration. Testosterone undecanoate is taken orally, 40–80 mg 3 times a day, a mixture of testosterone esters — 1 ml IM every 2–4 weeks, a prolonged testosterone preparation,

the advantage of which is the absence of supraphysiological peaks of the blood hormone concentration — 1,000 mg IM every 3 months, a hydroalcoholic testosterone gel is applied to the skin at a dose of 50 mg daily. The advantage of short-term medicines is the possibility of their cancellation in case contraindications to androgen therapy is identified. Treatment of androgen deficiency in men is usually carried out for life.

The goal of sex hormone replacement therapy is to restore urinary functions, correct metabolic disorders, and maintain normal bone mineral density. When the recovery of fertility is required, treatment includes gonadotropin preparations that stimulate ovulation in women and spermatogenesis in men.

Unlike replacement therapy with glucocorticoids and thyroid preparations, treatment with sex hormones has contraindications. These are malignant neoplasms of the sexual sphere (uterus, ovaries, mammary glands in women; prostate and mammary glands in men), decompensation of liver and kidney function. In addition, contraindications to the use of sex hormone preparations in women are thrombotic diseases and the presence of a hormonally active pituitary tumor, and in men — benign prostatic hyperplasia with marked urethral obstruction.

Replacement therapy with sex hormones requires dynamic monitoring of the reproductive system status. For this purpose, women are subjected to ultrasound scanning of the pelvic organs (USS) every 6–12 months, as well as an examination of the mammary glands: at the age below 45, an ultrasound scan every 12 months, over 45 — mammography 1 time in 12–24 months.

In men, the first follow-up examination is recommended 1–3 months from the beginning of therapy to assess its adequacy and safety. The following assays are performed: blood testosterone levels (for parenteral administration — before the next injection), hematocrit and hemoglobin levels (hematocrit is above 55 %, and/or hemoglobin levels higher than 180 g/l are indications to reduce testosterone dosage), and a prostate-specific antigen concentration (more than 4 ng/ml requires cancellation of treatment and the patient should be examined by an urologist). The condition of the prostate gland is assessed by an urologist or andrologist according to the outcome of rectal examination and/or ultrasound. In future, such assessment is recommended every 6–12 months.

In some cases of hypopituitarism, replacement therapy with growth hormone is recommended, which is carried out after compensation of all other types of pituitary insufficiency. The indications are the clinical symptoms of GH deficiency and low levels of IGF-1 in the blood. An analogue of human growth hormone is used, its initial dose is 0.03–0.04 IU/kg body weight per week (0.4-0.5 IU/day), which, if necessary, is increased monthly by 0.2–0.5 IU. The average maintenance dose of growth hormone is about 0.125–0.25 IU/kg body weight per week (0.8–2.4 IU/day). With age, the need for growth hormone decreases, and elderly patients need more careful monitoring of treatment.

The main criterion of effectiveness is the level of IGF-1. It is assayed one month after each increase in the dose of the medicine, and with the achievement of the physiological values of this parameter, its monitoring is carried out once in 6–12 months. Against the background of therapy, a gradual, within 3–6 months, decrease in fat mass, an increase in muscle mass, an improvement in psychological status are observed; in some cases, such changes develop at a slower pace.

Contraindications for growth hormone replacement therapy include cancer, severe intracranial hypertension and proliferative diabetic retinopathy.

For replacement therapy in vasopressin deficiency, a synthetic analogue of its molecule with a less pronounced vasospastic effect, as well as greater antidiuretic activity and resistance to enzymatic destruction — desmopressin, is used in sublingual, oral and intranasal dosage forms. Adjustment of dosage is carried out clinically — based on the absence of symptoms of hormone deficiency (excessive thirst, polyuria) or overdose (edema, high blood pressure, reduced diuresis). The drug is administered 2–3 times a day, starting with minimal doses — 0.1 mg for oral tablets, 60 μg for sublingual tablets, 10 μg (1 dose) for intranasal spray or 5–10 μg (1–2 drops) for intranasal drops. Preference is given to sublingual tablets, which, unlike the oral form of the medicine, enter the bloodstream bypassing the liver, thus being effective at a lower dose, and unlike intranasal agents, their effectiveness does not change in case of catarrhal signs and chronic rhinitis.

Further monitoring of patients with hypopituitarism involves examination every 6–12 months, which includes an assessment of the clinical status of the above laboratory and instrumental data.

If space-occupying lesion of the hypothalamic-pituitary region is present, MRI of the brain is performed once in 6–18 months to exclude the growth of the pathological focus. Hypopituitarism due to the empty sella syndrome, irradiation of the hypothalamic-pituitary region, brain injury, pituitary infarction or lymphocytic hypophysitis does not require dynamic MRI monitoring of the brain [3, 6, 9, 12].

Prognosis

Adequate replacement therapy can restore normal health in patients with hypopituitarism. However, there is evidence of a twofold increase in mortality compared with the general population, the main causes of which are respiratory, cerebrovascular and cardiovascular pathology. The unfavorable factors of prognosis include female gender, the development of the disease due to craniopharyngioma and radiation therapy, a young age at the disease onset, and inadequate treatment.

Clinical Case

A 33-year-old female patient in July 2017 came with complains of headaches and reduced visual acuity. The examination revealed a hormonally inactive macroadenoma of the pituitary gland, based on which transsphenoidal adenomectomy was performed on 02.08.2017. Almost immediately after the operation, the headaches stopped, eyesight was restored, but appetite was lost; nausea and vomiting, thirst and polyuria, weakness appeared; the patient began to lose weight, which was regarded as a condition after surgery. Examination of the patient for adrenal insufficiency (blood cortisol level, endocrinologist consultation) was not carried out at that stage, apparently due to an underestimation of symptoms such as loss of appetite, dyspepsia, and fatigue. After discharge from the hospital, nausea and vomiting became more frequent, pains in the stomach appeared, the patient continued to produce large amounts of urine and drink a lot of water, weakness and weight loss increased, a deterioration of mood was observed, amenorrhea developed. Three weeks after the operation, the patient fell unconscious, and was taken by ambulance to the palliative care unit of the central regional hospital, where she stayed from 22.08. to 04.09.2017.

The examination showed a low specific gravity of urine (1,005 g/l, (1,009–1,025)), hypoproteinemia (58 g/l, (65–85)), and low-normal fasting glucose (3.87 mmol/l (3.3–5.5). Analysis of the blood electrolytes levels did not detect abnormalities: potassium — 3.8 mmol/l (3.5–5.5), sodium — 140 mmol/l (135–155). The study of the hormonal status revealed a decrease in the blood content of gonadotropins (FSH — 1.02 mIU/ml (2.8–11.3); LH — 0.92 mIU/ml (1.1-8.7)), TSH — 0.041 μIU/ml (0.23–3.5) along with a slight increase in the level of free thyroxine (FT4 — 2.01 ng/dl (0.8–1.9)). Prolactin concentration was 151 μIU/ml (40.3–530), and the growth hormone level was 0.4 ng/ml (0.06–5.0). On ECG — sinus bradycardia 40 in 1 minute.

The diagnosis was established: "Condition after removal of the pituitary macroadenoma. Alimentary exhaustion. Diffuse toxic goiter. Adrenal insufficiency?". Despite the suspected hypocorticism, cortisol levels were not examined.

Symptomatic (infusion of 10 % glucose solution, salt solutions, protein preparations, proton pump inhibitor, probiotic), as well as thyrostatic therapy — thiamazole 10 mg 2 times a day was prescribed with subsequent control of blood levels of TSH and FT4 in 2 months.

According to the patient, during two weeks of inpatient treatment, the state of health improved somewhat, but after discharge it began to deteriorate progressively again — there was a constant noise in the head, shortness of breath, she had to lie down almost all the time because of weakness, had no appetite, and continued to lose weight: 14 kg in 4 months after surgery.

On November 24, 2017, the patient was hospitalized to the Endocrinology Department of the G. G. Kuvatov RCH. According to the examination, there was a pronounced deficit of body weight (weight 41 kg with height 164 cm, body mass index — 15.5 kg/m^2), pallor and increased dryness of the skin, hypotension — 70 and 50 mm Hg, bradycardia of 45 beats per 1 min. According to the results of laboratory analyses iron deficiency anemia was revealed (red blood cells — 2.62*10^{12}/l (4.04–5.9), hemoglobin — 69.5 g/l (120–170), iron — 5.1 μmol/l (12.5–32.2)); hypoproteinemia (58 g/l (65–85)), hyperenzymemia (aspartate aminotransferase — 199.3 U/l (5.0-38.0), alanine aminotransferase — 128.8 U/l (5.0–42.0)), lack

of an adequate increase in the blood glucose level after a meal (daily glycemic fluctuations were 5.1–5.2–5.7 mmol/l). Blood electrolytes content was within the range of reference values (potassium — 3.7 mmol/l, sodium — 142 mmol/l). Urinalysis showed a low specific gravity — 1,005 g/l, Zimnitsky Urine Test did not exceed 1,000–1,002 g/l (1,009–1,025). According to hormonal analysis data, cortisol was 515.8 nmol/l (101.2–835.7), FT4 — 7.66 pmol/l (9.0–19.5). It should be noted that thyrostatic therapy was completed a month before this study, therefore its effect on the result was excluded. Repeated studies of the TSH level were not conducted, since the secondary genesis of hypothyroidism was obvious. Electrocardiography detected bradycardia (48 bpm) and significant diffuse disturbances of repolarization processes.

Considering the history of adenomectomy for pituitary macroadenoma, the development of typical clinical signs of adrenal and thyroid insufficiency (significant weight loss, lack of appetite, nausea, vomiting, pain in the epigastrium, severe hypotension and weakness, pallor and dry skin, bradycardia) and diabetes insipidus (thirst and polyuria), appeared after the surgery, data of hormonal blood tests (decrease of gonadotropins, TSH and FT4 levels), biochemical blood test (flat blood sugar curve, low levels of hemoglobin and iron, hyperenzymemia), urinalysis (low specific gravity), the following diagnosis was established: Postoperative hypopituitarism: secondary hypocorticism, hypothyroidism, hypogonadism. Diabetes insipidus. Complications: Iron deficiency anemia of moderate severity.

The severity of the patient's condition required the immediate prescription of glucocorticoids, in connection with which a decision was made on replacement glucocorticoid therapy, the positive effect of which from the first days of treatment convincingly confirmed the diagnosis established. During the first 5 days prednisolone was administered parenterally: for 3 days, 90 mg intravenously in the morning, 60 mg intravenously in the afternoon and 30 mg intramuscularly in the evening; the next 2 days the doses decreased to 60 mg intravenously in the morning and 30 mg intramuscularly in the afternoon and evening, and then 30 mg twice a day: intravenously in the morning and intramuscularly in the afternoon. Infusion therapy (5 % glucose solution, 0.9 % sodium chloride solution) volume was 2 liters per day. The patient was then switched to oral hydrocortisone — 10 mg in the morning and 5 mg after lunch with blood pressure monitoring. For the purpose of replacement therapy of vasopressin deficiency, desmopressin sublingual 60 μg was prescribed 2 times a day under the control of the fluid intake and output. On the seventh day of treatment with glucocorticoids, therapy was supplemented with levothyroxine at a dose of 25 μg in the morning. In addition, as an antianemic drug, the patient received iron (III) hydroxide polymaltose complex 100 mg 2 times a day.

During treatment, pain in the stomach, nausea and vomiting stopped, appetite was restored, weakness decreased, the patient began to gain weight, blood pressure and heart rate were normalized. According to the results of repeated laboratory analyses, normalization of protein levels in blood, transferases, positive changes in hemoglobin and iron content, as well as the achievement of reference urine specific gravity values were observed.

The patient was discharged home in a satisfactory condition with a recommendation to continue taking hydrocortisone at a dose of 10 mg in the morning and 5 mg after lunch under control of blood pressure, body weight and general well-being, levothyroxine at a dose of 25 μg in the morning, followed by determination of the blood level of FT4 after 1 month for dose adjustment if necessary, as well as desmopressin 60 μg 2 times a day under the control of urine output.

After compensation of thyroid status, consultations with a gynecologist and endocrinologist are recommended to decide on the prescription of sex hormone replacement therapy.

Commenting on the presented case, it would be desirable, first of all, to pay attention to the fact that after surgery the patient developed typical symptoms of pituitary insufficiency, of which the most pronounced were symptoms of adrenal hormone deficiency. And although this diagnosis was assumed, since it is indicated under the question mark in the discharge note from the hospital at the place of residence, the patient's condition and the results of the studies were regarded as a result of diffuse toxic goiter (DTG). Such a judgment seems to be related to the patient's complaint about losing weight and hormonal analysis data that revealed a decrease in TSH and an increase in FT4, which is characteristic of thyrotoxicosis. However, the

interpretation of the results of a hormonal study without a comprehensive analysis of the clinical picture caused an erroneous diagnosis and, accordingly, inadequate treatment, which led to further deterioration and re-hospitalization.

As regards DTG, its clinical manifestations are due to thyrotoxic hypersympathicotonia; therefore weight loss occurs due to increased metabolism, while a decrease in appetite is not characteristic. The clinical picture of DTG unfolds gradually; first neurological symptoms of hyperthyroxinemia prevail: anxiety, sweating, sleep disturbance, and tachycardia. In the described case, a decrease in strength and mood, lack of appetite and a decrease in body weight, bradycardia were observed, with the listed symptoms developing almost immediately after neurosurgical operation.

It should be noted that a reduced level of TSH was combined with a decrease in gonadotropins and signs of diabetes insipidus — polyuria, thirst and low urine density, which indicates the need to search for a single genesis of the identified changes. In this case, it is surgery on the pituitary gland with the development of hypopituitarism. As for the slightly increased level of FT4, detected 3 weeks after adenomectomy, this is apparently due to the body's response to a stressful situation.

Manifestations of glucocorticoid insufficiency are primarily explained by their influence on carbohydrate metabolism, namely, a decrease in glucose production, which causes the most characteristic symptoms of the disease, such as lack of appetite, weight loss, asthenization, tendency to hypoglycemia, which was the case in our patient.

The effectiveness of glucocorticoid replacement therapy convincingly confirmed the diagnosis of hypocorticism "ex juvantibus".

Thus, the priority of the clinical picture in the interpretation of the results of the examination of the patient is a fundamental principle, the use of which makes it possible to clarify many diagnostic situations which, at first glance, appear complicated. At the same time, the wide availability of various diagnostic manipulations in this day and age has the other side of the coin; their results may not only not solve the problem of diagnosis, but on the contrary, raise even more questions. In this regard, the words of the founder of clinical medicine in Russia Matvey Yakovlevich Mudrov "*Knowledge of the disease is half of the treatment*" become even more relevant.

Conflict of interests

The authors declare no conflict of interests.

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