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An Integrated Approach to the Treatment of Ankylosing Spondylitis from the Position of the International Classification of Functioning

Abstract

Ankylosing spondylitis is a chronic, gradually progressive inflammatory disease characterized by damage of the sacroiliac joints and / or spine, with possible simultaneous damage of the enthesis and peripheral joints, leading to early disability and a decrease in the quality of life of patients, mainly of young age. The Assessment of SpondyloArthritis international Society (ASAS) recommends to combine non-pharmacological and pharmacological methods for treatment and rehabilitation of ankylosing spondylitis for the longest possible preservation of the quality of life of patients. This requires a multidisciplinary therapeutic approach.

Currently, in many European countries, the International Classification of Functioning, Disability and Health (ICF) is used as a universal approach to the assessment of human health. The ICF classifies the different areas of each patient's life that are health-related and affect health, thus describing changes in their physical functioning and psychological well-being. It helps to introduce multidisciplinary, patient-centered, problem-oriented rehabilitation care into real clinical practice.

The ICF shows a broader and more meaningful picture of the patient's health, which allows the multidisciplinary team to consider the patient from different perspectives — biological, personal and social. Using the ICF in the process of comprehensive treatment and rehabilitation of patients with ankylosing spondylitis, a multidisciplinary team can achieve a more complete agreement in the treatment of patients with ankylosing spondylitis, which is very important in achieving the success of therapy in this category of patients.

Key words: *ankylosing spondylitis, diagnosis, treatment, rehabilitation, international classification of functioning, disability and health*

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AS — ankylosing spondylitis, ICF — International Classification of Functioning, Disability and Health

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Ankylosing spondylitis (AS) is a chronic, gradually progressive inflammatory disease characterized by damage of the sacroiliac joints and/or the spine, which can occur with simultaneous damage of the enthesis and peripheral joints [1–3].

AS affects young people, more often men; leads to early disability, a decrease in the quality of life of patients due to the ankylosing of the spine and joints [4, 5].

The diagnosis of AS is established according to the modified New York criteria for diagnosis (1984) in the presence of X-ray criteria and at least one clinical criterion.

Clinical criteria:

1) pain and stiffness in the lower back (for at least 3 months), decreasing after exercise, but remaining at rest;
2) restrictions on movement in the lumbar spine in both the sagittal and frontal planes;
3) restriction of chest respiratory excursions in comparison with the parameters of healthy persons. X-ray criteria: bilateral sacroiliitis (stage II or higher according to the Kellgren classification) or unilateral (stage III–IV according to the Kellgren classification) [6].

The goal of treatment is to preserve the quality of life for as long as possible by managing the symptoms of inflammation, preventing the progression of structural damage, and maintaining/normalizing motor function and social status [3, 6].

Assessment of SpondyloArthritis international Society (ASAS) recommends combining non-pharmacological and pharmacological methods for the treatment and rehabilitation of patients with AS, which requires a multidisciplinary therapeutic approach [1–3, 6].

Modern patient rehabilitation requires introduction of multidisciplinary, patient-centered, problem-oriented rehabilitation into everyday clinical practice. To realize the transition to personalized, patient-centered care, when the patient is at the center of a multidisciplinary team and becomes a member of it, a tool that classifies the patient's health status from biological, personal, and social positions is necessary. Such an instrument is the International Classification of Functioning, Disability and Health (ICF) [7–9].

Currently, in many European countries (including Germany, France, Switzerland) ICF is used as a universal approach to the assessment of human health. ICF classifies the various spheres of life of each patient related to health and affecting health, which allows to describe the changes in the patient's physical functioning and psychological well-being [7, 10].

The use of ICF in rehabilitation practice in the Russian Federation was recommended by the I Russian Congress "Rehabilitation Treatment to the Population of Russia" in 2003. However, despite this, the main provisions of this classification remain little known to a wide range of medical professionals in the Russian Federation [11].

The ICF has two parts, each consisting of two components [10, 12]:

Part 1. Functioning and disability:
- a) body functions and structures;
- b) activities and participation.

Part 2. Contextual factors
- a) environmental factors;
- b) personal factors.

Diagnosis coded according to ICF is the alphabetic designation of an ICF component (b — functions, s — body structures, d — activities and participation, e — environmental factors), which is followed by a numeric code that starts with the chapter number (one digit), followed by the second level (next two digits), and the third and fourth level (one digit each), then, after a dividing point, an ICF qualifier follows, which denotes the magnitude of the level of health or severity of the problem at issue [10, 12, 13].

Body functions (b) are the physiological functions of body systems (including psychological functions). Body structures (s) are the anatomical parts of the body such as organs, limbs and their components. Activity (d) is the execution of a task or action by an individual. Participation is a person's involvement in a life situation. Environmental factors (e) make up the physical, social and attitudinal environment in which people live and spend their time. These factors are external in relation to an individual and can have both positive and negative effect on its realization in society, ~~its~~ potential ability, as well as on functions and structures of the organism. Personal factors are the particular background of an

individual's life and living, and comprise features of the individual that are not part of a health condition or health states. The qualifier is a numeric code that defines the degree or magnitude of functioning (restriction of life activity) in this category, or the extent to which the environmental factor acts as a relief factor or barrier [10, 12].

For example:

bxxx.0 — no impairment — extent of impairment 0–4%;

bxxx.1 — mild impairment — extent of impairment 5–24%;

bxxx.2 — moderate impairment — extent of impairment 25–49%;

bxxx.3 — severe impairment — extent of impairment 50–95%;

bxxx.4 — complete impairment — extent of impairment 96–100%.

Functional and instrumental methods of research confirm disturbances of the structures and functions of the body. Restrictions on activity and participation are assessed by the patient's subjective self-assessment of the ability to perform a particular type of activity specified under the ICF.

The basic set of the ICF has been used since 2001 in various fields of medicine in different countries of the world. Basic sets of the ICF for individual diseases have been developed: the main and brief ICF is a set of codes and categories for brain stroke, traumatic brain injury, back pain, multiple sclerosis, spinal cord injury, breast cancer, chronic obstructive pulmonary disease, coronary heart disease, diabetes, for professional rehabilitation and medical statistics [10, 12]. The use of the ICF provides a complete, complex, comprehensive description of the patient's functioning state, and allows an assessment of the rehabilitation potential [9, 14].

However, not all diseases have basic ICF sets [15], in particular, none has been developed for rheumatic diseases.

Considering the fact that in the absence of a necessary basic set, it is possible to use the Rehabilitation Set (or is possible to collect an arbitrary set of categories of the ICF [13]), the basic set of the ICF created for patients with back pain [10, 12] can become the theoretical basis for creating a basic set for patients with AS.

The works of foreign authors devoted to the use of ICF show the possibility to obtain an integrated assessment of the condition of patients with AS in the process of providing rehabilitation care as well as the possibility to analyze the effectiveness of care [16–21].

The diagnosis established from the position of the ICF in our patient with AS is given by the following example (Table 1).

Table 1. *Classification of pathological conditions according to ICD 10 and ICF*

Clinical diagnosis	ICD-10	ICF
Ankylosing spondylitis, HLA-B27-associated, bilateral grade 4 sacroiliitis, moderate activity (BASDAI 2). Functional class II.	M45	b280.2 — moderate intensity pain syndrome b710.2 — moderate mobility disorders in the spine b780.1 — morning stiffness up to 30 minutes b130.1 — mild (subclinical) depression b455.1 — slight fatigue in the last week s760.2 — moderate disorders in the structure of the thoracic spine s740.4 — pronounced deviation from the norm in the structure of the pelvic region (total ankylosis) d230.1 — minor difficulties in maintaining activity during the day d410.2 — moderate functional impairment d450.0 — there is no difficulty in walking d850.1 — small difficulties in performing paid work d760.1 — minor difficulties in spending time with family and friends

As can be seen from the table, ICF describes all the problems of the patient. To provide care to this patient, it is necessary to solve the list of their problems, which can be solved not only by medical methods (pharmacological and non-pharmacological therapy), but also by psychological correction, selection of activities for the patient and work with their environment (for example, working with the beliefs of relatives).

The information presented from the position of the ICF applies to both diagnosis and functioning, which shows a broader and more significant picture of the patient's health, which can be used to solve problems in the tactics of therapy and rehabilitation.

Thus, the ICF, which has been used worldwide since 2001, shows a broader and more significant picture of the patient's health, which makes it possible for a multidisciplinary team to examine the patient from different perspectives — biological, personal, and social. Using the ICF in the process of complex therapy and rehabilitation of patients with AS, a multidisciplinary team can achieve a higher consistency of views in the treatment of patients with AS, which is very important in achieving the success of therapy for this category of patients.

Author Contribution

R. R. Akhunova (ORCID ID: https://orcid.org/0000-0003-1917-9381): collection and analysis of manuscript materials, writing of the text, text editing, final manuscript approval.

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Diuretics in Chronic Kidney Disease

Abstract

The issues of diuretic therapy in patients with chronic kidney disease, pharmacokinetics of diuretics, the problem of diuretic resistance, the tactics of using thiazides and loop diuretics in patients with various stages of chronic kidney disease, according to the recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative are discussed in the article. Particular attention is paid to the prescription of this group of drugs to patients with end stage renal disease, as well as those undergoing renal replacement therapy (hemodialysis). Diuretics play an important role in the management of patients with chronic kidney disease with the development of hypertension and an increased extracellular fluid volume. In case of impaired renal function, the leading position in the treatment approach belongs to loop diuretics. Their combination with thiazide diuretics can increase the diuretic effect. The results of clinical trials assessing the effectiveness of the use of diuretics during decline of residual renal function are provided. It is reported about the effect of potassium-sparing diuretics on the incidence of cardiovascular complications, the development of hyperkalemia in patients undergoing dialysis treatment. The importance of continuation of intensive study about the possibility of antagonists of mineralocorticoid receptors usage, in particular the spironolactone, eplerenone, and finerenone in order to reduce cardiovascular complications and mortality, is indicated.

Key words: *chronic kidney disease, loop diuretics, potassium-sparing diuretics, thiazide diuretics, dialysis*

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ACE inhibitors — angiotensin-converting enzyme inhibitors, AMCRs — antimineralocorticoids, ARBs — angiotensin II receptor blockers, BP — blood pressure, CKD — chronic kidney disease, Cl^- — chlorine, EFV — extracellular fluid volume, GBM — glomerular basement membrane, GFR — glomerular filtration rate, HF — heart failure, K^+ — potassium, LDs — loop diuretics, LV — left ventricle, Na^+ — sodium, NS — nephrotic syndrome, RCT — randomized clinical trial, RRF — residual renal function, TDs — thiazide diuretics

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In memory of our teacher

Introduction

Diuretics are currently one of the common classes of drugs used in medical practice, including internal diseases, neurology, endocrinology, urology and other medical specialties [1-7]. Such a wide range of their use is explained by their different mechanisms of action and clinical effects.

Diuretics are widely used in the management of patients with various kidney diseases due to their main effects in controlling extracellular fluid volume (EFV) and hypertension, as well as their different effects on electrolyte levels due to the various pharmacodynamic characteristics of several groups of diuretics widely used in clinical nephrology [8-13]. At the same time, there are still many problems in treatment with diuretics which include the following: the lack of large-scale clinical studies on the impact of diuretics on the length of hospital stay and survival of patients with chronic kidney disease (CKD), including those receiving dialysis treatment. The aim of this review was to discuss the use of different groups of diuretics in patients with CKD, including patients undergoing dialysis treatment.

Chronic Kidney Disease: Definition

The term CKD means structural or functional kidney damage that affects the health state of the patient and persists for 3 months or longer [7]. CKD criteria are (one of the following, persisting for more than 3 months):

1. Markers of kidney damage (one or more): albuminuria (albumin excretion level ≥30 mg/24 h; albumin to creatinine ratio ≥30 mg/g (or ≥3 mg/mmol)); changes in urine sediment; electrolyte disorders due to tubular dysfunction; histological changes in kidneys; structural changes in kidneys revealed with imaging studies; history of kidney transplantation.
2. Decreased glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 [7].

CKD is a global medical and social problem. According to large population studies, approximately 10-13% [14] of the adult population have CKD, which can be explained by catastrophically increase of hypertension, type 2 diabetes mellitus, chronic obstructive pulmonary diseases, heart failure (HF), and obesity incidence, unreasonable and uncontrolled use of medications, tobacco smoking, alcohol abuse [2, 5-7, 15]. We should also note the high risk of cardiovascular complications related to CKD which progressively increases with renal function failure [10, 16]. Cardiovascular risk due to impaired renal function starts increasing in the earlier stages of renal pathology than it was previously assumed [16], which determines increased attention to the state of the cardiovascular system and has influence on the management of patients with CKD [17].

Possible development of cardiorenal syndrome in patients with cardiovascular diseases emphasizes the importance of the question about the optimal choice of diuretics, since symptomatic treatment for HF is limited by a progressive decrease in renal function [1, 6, 10].

Using Diuretics for Chronic Kidney Disease

Diuretics are successfully used in patients with CKD and [10, 12, 18, 19]. They have a hypotensive effect due to EFV decrease. The addition of diuretics to other classes of antihypertensive drugs (angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers) intensifies their hypotensive effect [6, 7, 18-21].

Potassium-sparing diuretics, primarily antimineralocorticoids (AMCRs) of aldosterone, are used for nephro- and cardioprotection (usually in combination with ACE inhibitors and ARBs), as well as for resistant hypertension, for hypokalemia which developed due to the use of loop (LD) and thiazide diuretics (TD) [8, 12, 18-20, 22]. Nephro- and cardioprotective effects of AMCRs are caused by the offsetting of the adverse effects of the activated renin-angiotensin-aldosterone system. Prescribing AMCRs is not recommended for hyperkalemia (potassium (K^+) > 5.5 mmol/L), for creatinine clearance less than 30 mL/min/1.73 m^2; it is prescribed with dose adjustment for patients with creatinine

clearance less than 60 mL/min/1.73 m² [23, 24]. Exceeding the recommended K^+ level is dangerous due to the increased risk of heart rhythm and conduction disorders, sudden cardiac death [25, 26] and mortality in patients receiving hemo- and peritoneal dialysis [27-29]. The combination of AMCRs with ACE inhibitors, non-steroidal anti-inflammatory drugs, cardiac glycosides, heparin, and β2-blockers sharply increases the possibility of developing hyperkalemia, increased creatinine and acute kidney damage [23, 30].

Data on the antihypertensive and antiproteinuric effects of AMCRs of aldosterone, spironolactone and eplerenone justify their use for CKD combined with hypertension and proteinuria (>1 g/day) under the strict control of K^+ and creatinine clearance [9, 31].

Pharmacokinetics of Diuretics, Resistance to Diuretic Treatment in Patients with Chronic Kidney Disease

The effect of diuretic drugs takes place after they enter the lumen of tubules. Specific gravity of glomerular filtration, which is responsible for the delivery of LDs and TDs in the lumen of tubules, is small, since the molecules of diuretics are closely connected to plasma proteins, and, therefore, their passage through glomerular filter is limited [32]. Acetazolamide, LDs and TDs are weak organic anions that are secreted into the lumen of the proximal tubule through the secretory pathway of organic acids [13, 33]. Amiloride and triamterene are secreted through the pathway of organic bases. As soon as diuretics reach the lumen of the proximal tubule, they go further down in the glomerular filtrate to the specific places of their action [13, 32]. Only a small quantity of albumin in physiological state is filtered and subsequently almost completely reabsorbed in proximal convoluted tubules [34]. LDs predominantly bind to plasma proteins (>90%) and, therefore, only a small fraction of drug is filtered in glomeruli. However, they are actively secreted into the lumen in proximal convoluted tubules through a transporter system.

LDs act at the level of the thick ascending loop of Henle. LDs combining with $Na^+/K^+/2Cl^-$ (NKCC2) by a co-transport protein localized in tubule membrane inhibit its effect while impairing the reabsorption of sodium (Na^+), K^+ and chlorine (Cl^-). The secretory ability of proximal renal tubules determines the quantity and, thus, the activity of diuretics, which then go to the distal nephron [1, 9, 35]. Both LDs and TDs reach the lumen of the proximal tubule by secretion by tubular cells with the help of transporters. However, the key mechanism of TDs action is inhibition of the Na^+/Cl^- co-transporter in the first segments of distal tubules. This protein regulates the reabsorption of Na^+ and Cl^- in distal tubular cells; therefore, its inhibition provides increased renal excretion of these electrolytes [36, 37].

Pharmacokinetic determinants that are responsible for LD and TD diuretic response include dose, route of administration, bioavailability, level of intestinal absorption, tubular secretory capacity, systemic blood pressure (BP) and renal blood flow [1, 9, 18, 37]. Some pharmacokinetic parameters of basic diuretics are shown in the table.

In the case of a drop in systemic blood pressure, decreased GFR, which is observed in relation to various kidney diseases and renovascular pathology, leads to a decrease in the filtered load of extracellular fluid and Na^+, limits the maximum achievable response to any diuretic, and is especially relevant for patients with renal failure [9]. However, although decreased GFR limits the effect of diuretics in patients with CKD, an adaptive increase in fluid delivery from the proximal tubule together with excessive expression of the transporter (both in the loop of Henle and in the distal tubule) retains a diuretic response even in patients with severe CKD [38]. In patients with GFR of about 15 mL/min/1.73 m², only 10-20% of the LD amount is secreted, which then goes into tubular fluid — in comparison with individuals with normal GFR and similar doses of diuretics [39]. Thus, in patients with severe CKD, the diuretic dose should be increased for its adequate delivery to the tubular fluid in order to induce diuretic response [9]. Even if TDs dosing corresponds well to the renal function, their use is limited in such patients since these drugs have low efficiency and a flat dose-response curve. Widely used TDs, even prescribed in large doses, can not help to achieve such a level of Na^+ reabsorption inhibition [9].

Table 1. *Pharmacokinetic parameters of basic diuretics*

Diuretic	Oral bioavailability, %	Elimination, $T_{1/2}$, h	
		Normal	CKD
Furosemide	50 (10-100)	1.5-2	2.8
Bumetanide	80-100	1	1.6
Torasemide	68-100	3-4	4-5
Hydrochlorothiazide	55-77	6-15	Prolonged
Indapamide	93	14	n/d
Chlorthalidone	64-72	40-60	Prolonged
Metolazone	70-90	14-20	Prolonged
Amiloride	About 50	6-26	100
Spironolactone	>90	1.5*	*
Eplerenone	50-69%	3-5	4-6

Notes: CKD — chronic kidney disease; n/d — no data; * — active metabolites of spironolactone have elimination $T_{1/2}$ more than 15 hours and accumulate in patients with CKD. Adapted from D. H. Ellison, 2019 [11]

Studies of patients with severe CKD revealed that maximum natriuretic response (approximately 20% of filtered Na^+ load) is achieved with intravenous administration of furosemide, bumetanide, and torasemide at doses of 160-200 mg, 6-8 mg, and 80-100 mg, respectively [40, 41]. Moreover, using dosages exceeding the indicated ones does not increase natriuretic response, which is rarely applicable in the course of clinical practice. LDs are suitable for patients with CKD at stages IV-V with hypertension. They can be taken per os 2-3 times a day [6, 21, 30, 42].

The normal dose-response ratio for LDs, which is observed in patients with CKD without edematous syndrome, can be distorted in a wide range of clinical conditions, ranging from decreased volume of intercellular fluid to HF or nephrotic syndrome (NS), as well as when taking various drugs, including non-steroidal anti-inflammatory drugs that can adversely change this relationship due to inhibition of prostaglandin synthesis, which significantly weakens the effect of LDs [43].

At the initial stages of treatment with PDs and TDs, increased natriuresis and diuresis are observed, which in most cases leads to a negative balance of Na^+, especially if its consumption is limited. Later, as diuretic treatment continues, a decrease in EFV and compensatory activation of neurohumoral mechanisms are present, which lead to increased Na^+ reabsorption in the proximal and distal tubule segments. These adaptive mechanisms that contribute to the development of diuretic resistance are called the "braking phenomenon" [5, 6, 21, 35].

Patients with NS often develop diuretic resistance even with normal GFR values [9]. Changes in both pharmacokinetic and pharmacodynamic properties of LDs cause a decrease in their efficacy. Patients with NS may also develop a less pronounced response to diuretic treatment due to orthostatic changes in hemodynamics. In addition, LD delivery in patients with hypoalbuminemia worsens due to the strong dependence of renal secretion of diuretics on plasma albumin concentration [39, 44, 45]. Decreased renal secretion of LDs in patients with NS is associated with the migration of these drugs from intravascular channel to interstitial space. For example, low serum albumin content can lead to a 10-fold increase in the distribution of furosemide. Finally, in addition to reducing LD secretion in patients with NS, the metabolism of diuretics increases along with an increase in the rate of conjugation with glucuronic acid in kidneys, which is applicable to furosemide [46].

According to KDIGO recommendations-2012, oral administration of LD once or twice a day is recommended for the patients with NS, taking into account that the effect of diuretics with this route of administration lasts longer in comparison with the parenteral one [47]. However, patients with severe NS may require intravenous (bolus or infusion) administration of diuretic drugs due to the development of edema of the intestinal wall and

impaired absorption. The combination of LDs with TDs can also be used for correction of diuretic resistance. A combination of diuretics with albumin infusion is also possible. However, the benefit of this approach has not yet been proven. Furthermore, it is believed that exogenously administered albumin can increase the severity of hypertension [47, 48]. Based on the results, the authors of Cochrane review 2019 argue that additional studies are necessary to define the role of albumin in the treatment of patients with NS [49].

LDs are the drugs of choice in patients with terminal stage of renal failure. They can produce a diuretic effect even in cases with GFR below 30 mL/min, which is particularly important in the presence of increased EFV, hypertension and HF often existing in such patients [50].

The change of one class of diuretics to another, as well as the replacement of drugs within one class, taking into account their bioavailability, can lead to increased diuretic response. So, if TDs take a certain place in diuretic treatment of patients with CKD stage I-III, then for more significant impairment of renal function (CKD stage IV-V) their diuretic effect is significantly reduced, and therefore, LDs should be preferred [30].

To achieve a diuretic effect in case of impaired renal function, high doses of TD are required: hydrochlorothiazide 50-100 mg/day for mild and moderate renal failure and 100-200 mg/day for severe one [9, 36, 51]. However, even at such dosages, the efficacy of TD in patients with severe renal impairment is negligible, and therefore, in the cases of severe renal failure (GFR <30 mL/min), a combination of TD with LD is recommended for achieving diuretic effect [30, 36]. This combination not only causes additional diuresis with underlying resistance to LDs but is also associated with a number of electrolyte disorders, including hypokalemia, hypomagnesemia, hypochloremia, leading to the development of metabolic alkalosis. In addition, adverse effects such as hyperuricemia, impaired glucose tolerance and hyperlipidemia may be observed [20, 30, 52].

This figure shows the tactics of using TDs and LDs in patients at different stages of CKD, which is recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) and summarized by D. Sica (2011) [9].

GFR (ml/min/1.73 m²)

Thiazide-like diuretics, metolazone and chlortalidone, are long-acting natriuretic agents due to their accumulation in red blood cells. Their pharmacokinetic characteristics cause a longer diuretic effect, as well as a more significant decrease in blood pressure in patients with CKD than TDs, both as a first-line drug and in combination with diuretics of other groups. In this connection, these drugs, and not TDs, should be preferred for the patients with I-III stages of CKD. However, for a more detailed study of the effects of thiazide-like diuretics, as well as for the assessment of their safety and effectiveness, randomized clinical trials (RCTs) are necessary [9, 20].

Potassium-sparing diuretics include drugs that block apical sodium channels (amiloride and triamterene) and do not interact with aldosterone receptors, and AMCRs (spironolactone and eplerenone).

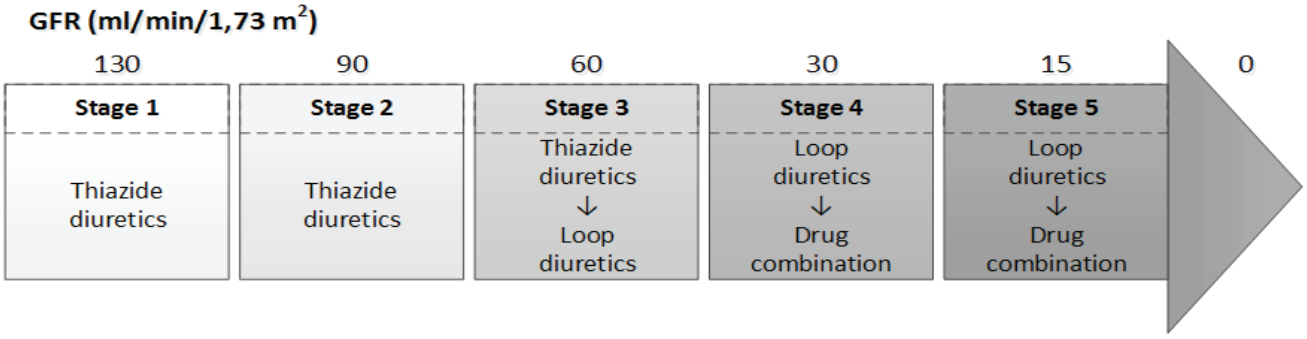

Figure 1. *Diuretic use at various stages of chronic kidney disease in accordance with the recommendations of NKF KDOQI*

Note: more intensive staining of the picture means an increased frequency of side effects observed in patients with GFR <60 ml/min/1.73 m². Adapted from D. Sica (2011) [9]

The mechanism of diuretic action of these classes of diuretics is similar and includes the inhibition of Na^+ absorption in the distal convoluted tubule and in the first part of the collecting tube, as well as a significant decrease in the secretion of K^+ and hydrogen cations [10, 53]. Although it was shown that mineralocorticoid receptor blockade has a positive effect on the condition of patients with CKD, the widespread use of common AMCRs with serious side effects is limited in clinical practice [54].

In a study by N. Tsuboi et al., it was demonstrated that the addition of eplerenone at the dose of 25-50 mg/day for 12 months to the treatment of patients with chronic renal failure and persistent proteinuria of non-diabetic origin, which persisted during use of ACE inhibitors, was associated with a decrease in protein excretion with urine by 38%. A decrease in the proteinuria level was more significant in patients with a moderately decreased renal function than in patients with intact renal function when the study began. Withdrawal criteria for this study were a decrease in GFR of less than 50 mL/min, as well as a level of K^+ >5 mmol/L. In the course of observation, a slight increase in K^+ level was registered [55].

The combination of AMCRs with ACE inhibitors leads to a decrease in the proteinuria level, as well as in markers of inflammation and renal tissue fibrosis [56]. However, the use of spironolactone and eplerenone in patients with CKD is limited due to the high risk of hyperkalemia. In contrast to abovementioned drugs, a non-steroid AMCR finerenone has greater selectivity and affinity for receptors and, therefore, a lower risk of hyperkalemia developing. The ARTS-HF study demonstrated the ability of finerenone to reduce albuminuria in patients with CKD and HF combined with better drug tolerance [57]. The ARTS-DN study showed that prescribing finerenone to patients with diabetic nephropathy (GFR ≤60 mL/min/m^2) resulted in a decrease in albuminuria level, while the risk of hyperkalemia was 2.1%, 3.2%, and 1.7% at finerenone doses of 7.5, 15 and 20 mg/day, respectively [58]. In 2020-2021, we expect the results of the phase III trial on evaluating the efficacy and safety of finerenone in patients with diabetic nephropathy, FIGARO-DKD, which includes 7,437 patients [59] and of the trial on evaluating the efficacy and safety in patients with type 2 diabetes mellitus and diabetic kidney disease, FIDELIO-DKD, which includes 5,734 patients [60].

In the CRIB-II study, spironolactone added to ACE inhibitors in 112 patients with CKD of stage 2-3 for 10 weeks led to a significant decrease in the prevalence of LV hypertrophy (50%), LV mass (11.8%) and myocardial mass index (11.4%) compared with the placebo group [61]. The results correlate with the level of aldosterone in non-diabetic patients with the terminal stage of renal failure undergoing hemodialysis [62, 63].

Complications of Diuretic Therapy

The main complications of therapy with LDs and TDs are metabolic disorders: hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, and metabolic alkalosis. Hypokalemia and metabolic alkalosis become less florid when using LDs and TDs in patients with reduced renal function [13, 64]. Using a combination of ACE inhibitors, or ARBs with AMCRs leads to hyperkalemia. Spironolactone may cause the development of metabolic acidosis [65]. In addition, due to its significant affinity for progesterone and androgen receptors, spironolactone induces adverse endocrine effects, including the development of gynecomastia, decreased libido, and menstrual disorder [13].

Hyponatremia is associated with negative prognosis in patients with CKD [66], as well as in the general population [67]. Hyponatremia is more commonly found during treatment with TDs that block Na^+ transport in the distal convoluted tubule. The genetic risk factor responsible for TD-induced hyponatremia and associated with impaired prostaglandin transport and decreased water excretion was found recently [68]. In any case, if diuretic therapy should be continued in patients with CKD and hyponatremia, TD should be discontinued and replaced with LD [13].

Hyperuricemia may be a relative contraindication for using diuretics. Gout combined with the inability to use non-steroidal anti-inflammatory drugs due to the high risk of renal function failure can also be a reason for not prescribing diuretics to patients with CKD.

Hypomagnesemia can be a special problem in patients with a transplanted kidney who are receiving tacrolimus along with diuretics. Physicians should pay attention to this complication, monitor the level of serum magnesium, if necessary, use magnesium supplements and not prescribe proton pump inhibitors simultaneously [13]. Finally, diuretics can aggravate urinary incontinence, especially in elderly patients, which can also be a reason for refusing to take these drugs. Thus, a decrease in adherence to diuretic therapy was reported, which was 3-4 times more frequent among patients with urinary incontinence [69].

Using Diuretics in Patients Under Dialysis

Using diuretics in dialysis patients requires a special discussion. Questionable approaches to prescribing diuretics for this category of patients are confirmed by the results of epidemiological studies that demonstrated high variability in their use in different dialysis departments — from 0 to 83.9% [18, 36, 70]. There is a number of clinical problems typical for dialysis patients with CKD that require appropriate treatment approaches; these problems include hypertension, volume overload, edemas, high risk of cardiovascular complications (acute coronary syndrome, HF, life-threatening rhythm disorders), high level of cardiovascular mortality [18, 36, 71, 72].

Hemodialysis has no significant effect on the pharmacokinetics of LDs. Dialysis eliminates <10% of diuretics due to the close connection with plasma proteins [9, 36].

During the inter-dialysis period, a significant increase in EFV, body weight, as well as congestion in pulmonary circulation with the development of cardiac asthma / pulmonary edema are often observed. In such cases, if there is residual renal function (RRF) established with excretion of more than 200-250 mL of urine per day without diuretics, LDs are indicated.

The role of RRF in treatment approaches was studied in several large trials, and the prognostic value for dialysis patients was demonstrated. Further analysis of the CANUSA PD study revealed that the risk of death in patients undergoing peritoneal dialysis was reduced if the daily amount of urine was more than 250 mL. The CHOICE study demonstrated decreased mortality, improved quality of life, and a lower need for erythropoietins in patients on hemodialysis in the presence of RRF [73, 74].

Unfortunately, dialysis patients have a progressive decrease in RRF level, which became the reason for searching for therapeutic approaches that could prevent such a decrease [36]. Using LDs is one of them. In the DOPPS prospective study, the effects of diuretic therapy on a number of clinical parameters in 16,420 hemodialysis patients were investigated. Using diuretics was associated with a decrease in weight gain between hemodialysis sessions, a decrease in hyperkalemia development, and a twofold increase in RRF level within one year in comparison with patients who did not receive LDs [70]. J. F. Medcalf et al. noted that there was no decrease of RRF in patients on peritoneal dialysis who received furosemide at the daily dosage of 250 mg [75].

The presence of RRF (or its retaining as an effect of LDs) contributes to the maintenance of the euvolemic state which plays an important role in preventing the development of volume overload and its adverse effects (left ventricular (LV) hypertrophy, congestive HF, uncontrolled hypertension). In addition, in the presence of RRF, the excretion of medium molecules increases, plasma levels of inflammatory markers decrease, blood pressure control improves, as well as hemoglobin and phosphorus levels, and all these changes potentially improve the quality of life and increase the survival of dialysis patients [50, 76].

Using LDs reduces the risk of hypertensive episodes during hemodialysis, the incidence and severity of hyperkalemia. Dialysis patients have to adhere to a strict diet with restriction of sodium chloride, potassium, phosphates and fluid. Using LDs allows them to make their diet more diversified and increase fluid intake, which improves their adherence to treatment [18, 70]. In addition, chronic LD administration in patients undergoing peritoneal dialysis demonstrated less frequent emergence of peritonitis [36].

In another major study, the effect of LDs on the frequency of hospitalizations, deaths, and intradialysis hypotension was evaluated. A monthly assessment of weight gain, predialysis systolic BP, and ultrafiltration levels was also performed. S. Sibbel

et al. reported that continued treatment with LDs during the intradialysis period was associated with a decreased frequency of hospitalizations, intradialysis hypotension, weight gain but there were no differences in mortality between groups of patients during 1 year of dialysis treatment [77].

Aldosterone levels increase as GFR decreases. In patients with CKD of stages 3-5, serum aldosterone levels increase, which allows characterizing CKD as a state of relative hyperaldosteronism [78]. The degree of its increase is most pronounced in patients with CKD of stage 5, which makes the prescribing of AMCRs one of the main tasks for this category of dialysis patients.

There is a high risk of developing cardiovascular complications and death in dialysis patients that exceeds that in the general population by 10 or more times. In this regard, the possibility of using AMCRs spironolactone and eplerenone for reducing cardiovascular complications and mortality is being intensively studied.

One of the serious complications of taking aldosterone antagonists is a high risk of developing hyperkalemia (especially with underlying renal failure). Analysis of literature performed by W. L. Baker et al. showed that using non-natriuretic dosages of aldosterone antagonists (spironolactone 25 mg/day and eplerenone 50 mg/day) in dialysis patients was characterized by a low incidence of severe hyperkalemia, and, therefore, their use is permissible but under strict control of K^+ in plasma [79]. In prospective, double-blind RCT, S. Taheri et al. studied the efficacy and safety of spironolactone (25 mg/day) in alternate day mode, in 18 dialysis patients with chronic HF of class III-IV according to NYHA. The authors of this study found no significant differences in plasma potassium levels between subjects who received spironolactone and those who did not receive it [80].

A number of RCTs demonstrated that when spironolactone (25 mg/day) was added to ACE inhibitor, or ARB, the increase of LV mass and the development of calcification of coronary arteries slowed down along with a low risk of severe hyperkalemia in dialysis patients [81, 82]. In this category of patients, P. Flevary et al. found that low doses of spironolactone (at a rate of 25 mg per day twice a week) caused a decrease in endothelial dysfunction and improved heart rate variability [72].

Results of a three-year DONAS RCT conducted by Y. Matsumoto et al. and published in 2014 deserve a special discussion [83]. This study included 309 dialysis patients, 157 of whom received spironolactone (25 mg/day) and 152 did not receive spironolactone (control group). In the spironolactone group, cardiovascular mortality and hospitalization rate for cardiovascular complications was 5.7% vs 12.5% in the control group ($p = 0.017$), and overall mortality rate was 6.4% vs 19.7% ($p = 0.002$). Hyperkalemia, which required the withdrawal of spironolactone, was registered only in 3 patients (1.9%).

High-potential RCTs are currently being performed on the study of the use of spironolactone in patients with the terminal stage of renal failure — ALCHEMIST (**AL**dosterone Antagonist Chronic **HEM**odialysis **I**nterventional **S**urvival **T**rial), which is planned to include 825 hemodialysis patients, and ACHIEVE trial (**A**ldosterone blo**C**kade for **H**ealth **I**mprovement **EV**aluation in **E**nd-stage Renal Disease) in 2,750 patients on hemodialysis or peritoneal dialysis [23].

Thus, the abovementioned results of the efficacy and safety of aldosterone antagonists in dialysis patients allow us to recommend their use for reducing cardiovascular and general mortality under the strict control of K^+ in plasma [9, 36, 83, 84].

Conclusion

Since CKD is associated with sodium retention, which causes edema syndrome and hypertension, diuretics take an important place among therapeutic approaches for the management of patients with kidney damage. Highly effective LDs remain the basic drugs used for diuretic therapy but their proper use requires deep understanding of the pharmacokinetics and pharmacodynamics of these drugs in the presence of CKD. LDs can be administered as monotherapy, or in combination with diuretics of other classes. In addition, diuretics are prescribed for the terminal stage of renal failure with RRF, thereby helping to reduce fluid retention during the inter-dialysis period. Despite a number of side effects of diuretics, these drugs remain important elements of treatment for the most part of patients with CKD.

Author Contribution

A. I. Dyadyk: principal creation of review idea (plan, structure, issues of discussing concerns)

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Yu. V. Suliman (ORCID ID: https://orcid.org/0000-0001-6538-9676): collection and analysis of literature data, writing of sections on pharmacokinetics and pharmacodynamics of diuretics

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V. I. Merkuriev: literature search and section writing about use of diuretics in patients on dialysis treatment

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

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Stroke in Children and Adolescents: Topical Problems of Pre-Hospital Diagnostics

Abstract

The article is devoted to the urgent problem of pediatrics and pediatric neurology: pre-hospital diagnosis of stroke in children. A review of domestic and foreign literature on the early diagnosis of stroke in children and adolescents, as well as epidemiological data on pediatric stroke, is presented. Particular attention is paid to the features of the symptoms of stroke and stroke-like conditions ("stroke masks") in the pediatric population, and the analysis of the main factors that influence errors in the early diagnosis of stroke in children and adolescents. Currently, in the diagnosis of ischemic stroke, its "masks" are found in 53.9% of cases, with hemorrhagic stroke, in 36.3%, and with transient ischemic attacks, in 9.8% of cases. One of the most common diseases that is necessary to differentiate with ischemic pediatric stroke is migraine. This problem is covered in academic writings that highlight the leading differential diagnostic criteria for migraine and stroke, and also represent a diagnostic algorithm. The clinical features of pediatric stroke, especially manifest symptoms, make it difficult to apply adult screening stroke scales in pediatrics. The article discusses the main scales for the early diagnosis of stroke in adults, and their potential application in pediatric practice. Currently accumulated experience in pre-hospital and early diagnosis of stroke in children determines the focus areas to reduce the time of diagnosis of acute cerebrovascular accidents in children, followed by the introduction of reperfusion therapy in pediatric practice.

Key words: *pediatric stroke, stroke risk scales, pre-hospital stage, emergency*

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ACVE — acute cerebrovascular event, EMC — emergency medical care, HA — headache, HS — hemorrhagic stroke, IS — ischemic stroke, VBS — vertebrobasilar system

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Introduction

Pediatric stroke is a disabling disease, which in 3-30% of cases leads to death, and 60-90% of children subsequently experience persistent neurological impairment in the form of motor and cognitive disorders, as well as neuropsychiatric disorders [1].

The first epidemiological studies of ischemic stroke (IS) in children date back to the 1970s. According to Schoenberg B. S. et al. (1978), the incidence of IS in children aged 1 month to 18 years was 0.63 cases per 100,000 children [2]. In this large-scale 10-year study, pediatric stroke was first defined as a separate issue requiring the special attention of clinicians.

Analysis of stroke incidence in children under 16 years in France for the period 1985-1993 performed by Giroud M. (1995) demonstrated a fairly high incidence of stroke — 13.02 per 100,000 children per year (95% CI 8.54-18.84), where the incidence of IS was 7.9 per 100,000 children per year (95% CI 2.56-14.57) [3].

According to the data from the Pediatric Stroke Register for the period 1992-2001 in Canada, the incidence of IS in children under the age of 18 was 1.72 per 100,000 children per year; 2.4 cases per 100,000 children per year were recorded for the same period (1993-2003) in Northern California [4, 5].

Results of the analysis of the Swiss Neuropaediatric Stroke Registry (SNPSR) for the period from January 2000 to December 2012 showed that the frequency of ischemic stroke and symptomatic cerebral sinus thrombosis in children under 16 years was 2.1 per 100,000 children per year [6].

In the later works by V. Ganesan (2011), the annual incidence rate of stroke in children over the age of one month was 0.6 per 100,000 [7]. In her work (2013), Lvova O. A. cited the following data on the incidence of stroke in children by age and country: among newborns, acute cerebrovascular event (ACVE) develops in 1 of 4,000 full-term ones, at an older age it barely reaches 0.2-0.3 per 100,000 children per year. The incidence of stroke among children under 1 year of age in the United States is 0.78 per 100,000, in France — about 1.3 per 100,000 children per year [8]. Results of the analysis on the incidence of pediatric stroke in different age groups published by Jeong G. and colleagues in 2015 amounted to 0.2-0.3 per 100,000 for children under 5 years, and 0.8-1.3 per 100,000 children per year for children aged from 5 to 14 years, which demonstrates no significant difference in comparison with previously published results [9].

Rivkin M. J. in his study (2016) reports about the incidence of pediatric stroke of 1.3 per 100,000, while for the adult population the figure is 175-200 per 100,000 [10]. In 2018, Yock-Corrales A. analyzed the accumulated information on pediatric strokes and showed that statistical data on the incidence of ACVE in children, as well as distribution by age and gender, do not differ significantly in developed and developing countries or in different climatic zones [11].

Data on the incidence of ischemic stroke in Russia are extremely scarce. In 2009, Zykov V. P. presented data on the incidence of IS in Moscow — 0.79 per 100,000 children per year [12]. According to Lvova O. A. et al. (2013), mortality in cases of IS in children ranges from 7 to 28%. For children aged under 5 years, IS mortality amounts to 15 cases per 1,000,000 annually; for children aged over 5 years — 7 deaths from cerebrovascular diseases, which is 10% of the total mortality in neurological departments. The death rate is higher among boys [8].

In more recent studies (2016-2018), there is a definite tendency for an increase in the incidence of pediatric stroke; it may be associated with better diagnostics of this pathology in the pediatric population (improved neuroimaging, concern of medical personnel about the problem of stroke in children).

Since stroke outcomes and mortality depend on timely diagnosis, the problem of early detection of ischemic and hemorrhagic brain damage in children and adolescents becomes very important. This problem was investigated in many articles, especially during the last two decades.

The objective of our work was to analyze the literature devoted to the problem of early (prehospital) diagnosis of pediatric stroke, to the features of differential diagnosis of stroke and stroke-like conditions ("stroke masks") in the pediatric population, and to analyze the use of screening scales for diagnosing stroke in children at the prehospital stage. The search for relevant scientific articles on the problem of early and pre-hospital

diagnosis of stroke in children was carried out using the pubmed.com medical scientific Internet portal. For the query with keywords "childhood stroke and stroke in children", 15,660 scientific papers were found, for the query "emergency and stroke in children" — 588 articles, "delay to diagnosis and stroke in children" — 274 articles, "differentiate in diagnostic stroke in children" — 56 articles.

The accumulated experience on the problem of stroke in children allowed specialists in different countries to formulate recommendations on the stages of providing medical care to children and adolescents with stroke: Federal Guide for Pediatric Neurology (2016, Russian Federation); The diagnosis and acute management of childhood stroke, Clinical guideline (2017, Australia); Stroke in children, clinical guideline for diagnosis, management and rehabilitation (2017, UK), and others [13-15].

The following stages of medical care for children with stroke were defined:

1) pre-hospital stage (ambulance teams, family physicians, pediatricians);
2) intensive care (centers of pediatric cerebrovascular pathology, intensive care units of pediatric departments, neurosurgical departments);
3) rehabilitation treatment (children's neurological department, rehabilitation departments and centers for children);
4) follow-up care (local pediatric neurologist, pediatrician, family physician) [16].

Children should receive high-quality qualified medical care at each stage.

Signs of pediatric stroke are to a large extent similar to those in adults: muscle weakness, impaired sensitivity and speech, facial asymmetry; but the diagnosis at the pre-hospital stage is often complicated due to the nonspecific, vague clinical pattern, which may include a variety of symptoms (headache, seizures, impaired consciousness, and others) typical for a wide range of diseases — not only of the central nervous system, but also of other organs and systems (Table 1) [17]. Other difficulties for the diagnosis of stroke in the pediatric population are associated with behavioral and age-related characteristics. For example, speech in newborns and children in their first years of life is not formed, and so they are not able to clearly define and describe their feelings. In addition, it is widely believed among practitioners that stroke is typical only for elderly patients, and IS is often not included on the list of diagnostic search performed in children for finding the possible etiological cause of present symptoms [7, 18, 19]. Many researchers have tried to describe the initial symptoms of stroke, as well as to perform a comparative analysis of the clinical manifestations of IS and hemorrhagic stroke (HS) in children (Table 1).

Table 1. *Symptoms of ischemic and hemorrhagic stroke in children according to various authors [20, 21]*

Symptoms	Earley C. J., 1998 n = 35	Mackay M. T., 2016 n = 92	Neville K., 2016 n = 53	Aroor S., 2017 n = 736	Meyer-Heim A. D., 2003 n = 35	
	IS n = 35	IS n = 55	IS n = 53	HS n = 37	IS n = 18	HS n = 17
Focal symptoms	+	+	+	-	+	+
Seizures	-	+	-	+	+	+
Cerebral symptoms	+	-	-	+	+	+
Hemiparesis	+	+	+	-	+	+
Speech impairment	+	+	+	-	+	-
Facial asymmetry	+	+	+	-	-	-
Inability to walk	+	+	+	+	+	+
Nausea, vomiting	-	-	-	+	-	+
Mental disorder	+	-	-	+	-	+
Impaired consciousness	-	-	-	+	+	+
Vision impairment	-	-	+	-	-	-
Headache	+	+	+	+	+	+

One of the main problems in pre-hospital diagnosis of stroke is the difficulty of differential diagnosis with "stroke masks" which can be found in 50-93% of all cases of primary suspicion of IS in children and adolescents [16, 21], while in adults, "stroke masks" are found in one third of patients with a sudden onset of focal neurological impairment [22].

A number of researchers analyzed the most frequent "stroke masks" that can be defined as pediatric stroke (Table 2).

Table 2. *The incidence of ACVE and "stroke masks" in pediatric population (Mackay & Yock-Corrales, 2016)*

Diagnosis	n = 102 (ACVE), n = 280 ("stroke masks")
ACVE	
Ischemic stroke	53.9%
Hemorrhagic stroke	36.3%
Transient ischemic attack	9.8%
"Stroke masks"	
Migraine	30%
Epilepsy	16.4%
Bell's palsy	10.4%
Conversion disorder	6.4%
Syncope	5%

Mackay M. T. and Yock-Corrales A. in 2016 analyzed not only "stroke masks" in children but also the frequency of different symptoms for each of them (Table 3). The authors studied case histories of 382 children with "stroke masks" and ACVEs for the period from January 2003 to December 2010. Data analysis showed no statistically significant difference between IS and HS. IS was the most common type of pediatric stroke and amounted to 55 (54%) cases; HS ranked second with 37 (36%) cases; transient ischemic attack (TIA) was found in 10 (9.8%) cases. The most frequent "stroke masks" in children with acute neurological deficit, or with symptoms of IS were the following: migraine in 84 (30%) cases, febrile or afebrile seizures in 46 (16.4%) cases, facial neuropathy (Bell's palsy) in 29 (10.4%) cases, conversion disorder in 18 (6.4%) cases, syncope in 14 (5%) cases [18, 22, 23].

In their paper, Mackay M. T. and Yock-Corrales A. defined 14 factors that increase the possibility of stroke diagnosis and 2 factors that reduce the possibility of stroke diagnosis. The sense of well-being during the week before hospitalization increased the possibility of making a final diagnosis of stroke while weakness in the arm, a neurological symptom that is considered one of the common signs of ACVE, was of low significance. Facial asymmetry

Table 3. *Symptoms of ACVE and "stroke masks" according to various authors*

Symptom	Mackay M. & Yock-Corrales A., 2016		Neville K. & Warren L., 2016	
	ACVE (n = 102)	"Stroke masks" (n = 280)	Ischemic stroke (n = 53)	"Stroke masks" (n = 53)
Headache	58/100 (58%)	161/280 (58%)	n. d.*	n. d.
Nausea, vomiting	32/100 (32%)	103/280 (37%)	n. d.	n. d.
Focal symptoms	58/102 (57%)	93/276 (34%)	35 (71%)	23 (44%)
Impaired sensitivity	17/102 (17%)	68/274 (25%)	n. d.	n. d.
Vision impairment	17/100 (17%)	66/276 (24%)	n. d.	n. d.
Seizures	21/102 (21%)	57/280 (20%)	n. d.	n. d.
Confusion	31/102 (30%)	53/278 (19%)	11 (21%)	8 (15%)
Dizziness	15/99 (15%)	58/276 (21%)	n. d.	n. d.
Speech impairment	37/102 (36%)	43/277 (16%)	9/33 (27%)	7 (17%)
Ataxia	18/101 (18%)	41/276 (15%)	n. d.	n. d.
Loss of consciousness	10/102 (10%)	35/278 (11%)	n. d.	n. d.
Disorientation	2/97 (2%)	10/274 (4%)	n. d.	n. d.
Facial asymmetry	n. d.	n. d.	21 (43%)	29 (55%)
Other symptoms	5/102 (5%)	59/279 (21%)	n. d.	n. d.

Note: *n. d. — there is no data

and inability to walk were also associated with an increased possibility of being diagnosed with stroke. In contrast, the presence of other symptoms (headache, nausea/vomiting, impaired sensitivity) was inversely related to the diagnosis of stroke. The following symptoms were also significant factors for the diagnosis of IS in the course of univariate analysis: hemiparesis, speech impairment, facial asymmetry, inability to walk. None of the children with IS had a loss of consciousness or was in coma (<9 points according to Glasgow Coma Scale). On the contrary, statistically significant factors for diagnosing a "stroke mask" included other, non-neurological (abdominal pain, dyspepsia, fever) symptoms and no neurological pathology during examination. Significant factors for the diagnosis of HS with univariate analysis were the following: sudden onset of symptoms, vomiting, borderline mental disorder, inability to walk, coma. All children with HS felt good for a week before admission, none had dizziness.

In literature, the discussion of "stroke masks" in children is often associated with the analysis of the frequency of occurrence of certain symptoms and with main directions of the diagnostic search for these signs.

Bhate S. and Ganesan V. in their work (2015) separately identified acute hemiparesis as the most common symptom of ACVE that requires differential diagnosis with a wide range of pathological conditions [24]. According to the authors, 20-30% of children with acute hemiparesis have a non-vascular diagnosis. In adults, the frequency of "stroke masks" is much lower, and acute hemiparesis is normally of vascular origin. Acute hemiparesis, except for vascular origin, can occur with underlying infection of the central nervous system (CNS), hemiplegic migraine, acute disseminated encephalomyelitis, reversible posterior leukoencephalopathy syndrome, and other conditions. Hypoglycemia in children with insulin-dependent diabetes mellitus can also be manifested by focal neurological deficit, including hemiplegia [24].

Another common symptom that requires the exclusion of pediatric stroke is seizures. In adults, seizures are more commonly related to HS; in children, the risk of their development is high in connection with both hemorrhage and ischemia. According to Fullerton H. J. et al. (2016), the seizure disorder occurs in 20-48% of cases of pediatric stroke regardless of age and type of stroke; Mackay M. T. (2018), based on his observations, reports a frequency of seizures related to IS of up to 58% [25]. The development of seizures during the first 24 hours from the onset of stroke increases the risk of epilepsy in the next 6 months [26]. Some researchers report seizures after migraine in 10% of adults, but Mackay M. T. notes that only 4% of children with migraines had seizures.

Vomiting, which is a common migraine symptom, especially in young children, is rare in connection with IS. The absence of focal neurological symptoms during examination in the emergency care department was more often associated with migraines, which is in accordance with the duration of migraine aura when focal neurological deficit usually disappears within 60 minutes, and in children often even in shorter periods of time. Therefore, an emergency medical care (EMC) physician may observe symptoms that may be a possible manifestation of ACVE but are completely resolved by the time of the patient's admission in intensive care unit [27].

Mackay M. T. [25] in his work devoted to migraine as the most frequent "stroke mask", refers to the data obtained by French researchers who examined 79,433 children with non-febrile, non-traumatic headache, which amounted to 2.6% of all calls in the emergency care department. Headache (HA) was associated with at least one neurological symptom in 102 (0.13%) cases. In the subgroup of children with HA and focal symptoms, migraine with aura was the most common diagnosis (62% of all cases); post-seizure HA related to epilepsy was diagnosed somewhat less (26% of cases). The patients were diagnosed with IS and TIA in only 6% of cases [25].

In 2016, Spalice A. et al. attempted to analyze the features of IS and migraine in children. However, their work was of rather descriptive nature with a discussion of the possible comorbidity of these diseases [27]. Other researchers, Gelfand A. A. et al. (2015), noted that migraine is not only similar to ischemic stroke in its symptoms but also increases the risk of IS development [28].

In 2018, continuing his work on diagnosing stroke and its "masks" at pre-hospital stage, Mackay M. T. emphasized the similarities and differences between IS and migraine attack (Table 4) [25]. The average

age of children included in this study was 13 years 5 months for children with migraine, and 5 years for patients with IS. All patients with ischemic stroke and one in three patients with migraine underwent neuroimaging study; 55% of patients had no neurological pathology upon admission at the hospital. Significant factors that reduce the probability of IS diagnosis were the following: older age, vomiting, impaired vision and sensitivity, cerebral symptoms and the absence of focal neurological symptoms during examination [25].

A comparative analysis of patients having migraine with aura or IS revealed that children with IS were younger (more than half of the children aged under 5 years); they had sudden onset of symptoms while migraine symptoms developed more gradually, with a predominance of vision and sensory disorders.

When discussing the results of this study, the authors emphasize that the EMC doctor plays a leading role in the diagnosis of stroke because he/she is the first to meet the patient. The correct assessment of manifest neurological symptoms has an influence on the algorithm for further diagnosis and treatment approach. Examination of patients with cerebral symptoms is always a challenge for pediatricians. According to Mackay M., the matching of the diagnosis of stroke at pre-hospital and hospital stages ranged from 51% to 81% [18].

Beslow L. A. and Lauren A. demonstrated, using the example of adult patients under the age of 50 (2017), that 21% of patients admitted at stroke departments had other, non-vascular diagnoses. At the same time, only 3% of patients aged over 50 years who were admitted at such departments with a suspected stroke were diagnosed with other diseases with clinical symptoms that are common for stroke. Speaking about the pediatric population, the authors noted that among 124 children with a referral diagnosis of "stroke", "stroke masks" were diagnosed in 76% of cases, which greatly complicates the work of EMC specialists [16].

Challenges facing EMC physicians lie in the differential diagnostics of different stroke-like conditions in children, which is necessary for the routing of patients' data to centers where round-the-clock radiation diagnostics can be performed, and, if necessary, emergency reperfusion therapy with consideration to a "therapeutic window". Screening scales can be an effective tool for early diagnostics of stroke in such cases.

Table 4. *Symptoms of ischemic stroke and migraine (Mackay M. T., 2018)*

Symptom	Ischemic stroke (n = 55)	Migraine (n = 84)
Acute onset	46 (84%)	54/83 (65%)
Headache	26/53 (49%)	83/83 (100%)
Nausea, vomiting	9/53 (17%)	39/83 (47%)
Limb weakness	40 (73%)	23/83 (28%)
Impaired sensitivity	9 (16%)	37/83 (45%)
Vision impairment	8/53 (15%)	35/82 (43%)
Seizures	12 (22%)	3/83 (4%)
Mental disorder	11 (20%)	11/83 (13%)
Dizziness	7/52 (13%)	19/83 (23%)
Speech impairment	28 (51%)	21/83 (25%)
Ataxia	13/54 (24%)	5/82 (6%)
Impaired consciousness	0 (0%)	4/83 (5%)

Early (pre-hospital) stroke scales

For the purpose of early detection of conditions suspected of ACVE at the pre-hospital stage, as well as for the purpose of differential diagnostics of ACVE and "stroke masks", special pre-hospital (or emergency, urgent, resuscitation) stroke scales are used. Currently, the most famous scales for pre-hospital diagnostics of stroke are FAST with BE-FAST modification, COTS, CPSS, ROSIER, and LAPS.

FAST — face, arm, speech, time. This scale was developed in the UK in 1998. The patient is asked to smile or to show teeth to assess facial symmetry; raise both hands up to an angle of 90° to assess muscle strength, or hemiparesis; the patient is asked to say a simple phrase to exclude speech impairment. If one of the above symptoms is found, the patient should be immediately hospitalized in a specialized hospital, which is relevant to the fourth element of the scale — time.

BE-FAST — balance, eyes, face, arm, speech, time — a modification of the FAST scale, which complements FAST with the assessment of coordination and vision impairments. FAST and BE-FAST scales were designed for use by paramedics for suspected stroke.

COTS (Central Ohio Trauma System) — includes 4 symptoms: decreased level (disorder) of consciousness, slurred speech, facial asymmetry and unilateral absence of active movements in extremities. Each item is rated as 0 (no signs), or 1 (signs are present), and so the total score ranges from 0 (no symptoms) to 4 (all symptoms). This scale is recommended for EMC specialists.

CPSS (Cincinnati Prehospital Stroke Scale) — Cincinnati scale — a scale for pre-hospital diagnostics of stroke including three positions: facial asymmetry, weakness in arm, speech impairment. Finding deviations in any of these items indicates the presence of a stroke in the patient with high sensitivity (66%) and specificity (87%) [18].

ROSIER (Recognition of stroke in the Emergency Room) — a scale for the early diagnostics of stroke in emergency care departments, in emergency rooms, or in intensive care units. In some countries, it is used by EMC physicians. According to this scale, the following symptoms are defined: impaired consciousness, seizures, asymmetric weakness of upper extremities, asymmetric weakness of lower extremities, facial asymmetry, speech impairment, vision impairment. Each symptom has its own score; the first two symptoms (impaired consciousness and seizures) have a score of "-1" as unlikely symptoms for stroke; other symptoms have a score of "+1" being typical for stroke. With a total of 1 or more points in the course of assessing patient's status, the physician suspects a stroke.

LAPS (Los Angeles Pre-hospital Stroke Screen) — a stroke scale for EMC based on the same criteria as the above scales: facial asymmetry, weakness in arm, speech impairment — but it also includes some additional items: age — more than 45 years, blood glucose, history/no history of seizures.

These scales are the main tool for EMC physicians in the quick differential diagnostics of stroke and stroke-like conditions ("masks"); they help to reduce the time between the onset of the first symptoms of stroke, hospitalization and neuroimaging confirming a stroke.

The above scales were developed and are successfully used in the pre-hospital diagnosis of stroke in adults but their use in pediatric practice has shown their low informative value [26, 29, 30].

In 2015, Bhate S. and Ganesan V. describing the differential diagnostics of acute hemiparesis in children in their work discussed the effectiveness of using the FAST scale in children. This scale can be used in older children but in younger ones, motor impairment may be less pronounced, and speech assessment is difficult [24]. In 2017, other researchers — Aroor S., Singh R. and Goldstein L. B. — compared the FAST scale with its BE-FAST modification [29]. Of the total of 736 patients included in this study, 104 (14.1%) patients had no FAST symptoms at the time of the examination. In most patients without FAST symptoms, gait disturbance (33%), decreased muscle strength in legs (10%), vision impairment (40%), and other non-FAST symptoms (8%) were observed. The use of the BE-FAST scale reduced the number of "undiagnosed" strokes from 14.1% to 4.4%, and it was also shown that patients for whom the BE-FAST scale was informative were younger and had more significant neurological deficit (according to Ped-NIHSS — Pediatric National Institutes of Health Stroke Scale — a scale for defining the severity of pediatric strokes) [30]. In addition, the authors, in the course of analyzing the data of magnetic resonance imaging (MRI) in the studied cohort of patients, found that 71% of strokes missed while using the FAST scale were limited to the vertebral-basilar arterial system; this fact was also mentioned by Beslow L. A. (2017) and Mármol-Szombathy I. (2018) [16, 31]. The proportion of missed strokes in the vertebrobasilar system (VBS) was reduced to 43% when using the BE-FAST scale.

Despite the fact that the BE-FAST scale is more effective for verification of pediatric stroke than the FAST scale, it disregards cerebral symptoms, decreased level of consciousness and seizures, which are typical for strokes in children.

When comparing the informative value of stroke diagnostic scales, Mackay M. and Churilov L. (2016) used CPSS and ROSIER scales. The authors conclude that adult stroke detection tools do not work well for the pediatric population and need to be modified because the use of CPSS and ROSIER scales by EMC physicians does not allow to accurately distinguish a stroke from its "masks" [18].

Another attempt to analyze the diagnostic value of pre-hospital scales was made in 2016 by Neville K., who retrospectively investigated sensitivity/error and features of stroke diagnostic scales, including cases with seizures as the first symptom of stroke. The author included in this analysis all children aged under 19 years who had a medical history of acute clinical symptoms and IS confirmed by MRI. The control group included patients with focal neurological symptoms brought to the emergency care department. Assessment according to COTS scale was performed, which was derived from CPSS and LAPS scales. The COTS score was calculated on the basis of neurological examination in the first record made by a neurologist, and for patients from the control group — in the first record made by a pediatrician. The median COTS score was 1.0 for both groups. However, the author concludes that despite the higher COTS score in children with stroke, these differences were statistically insignificant and using this scale in pediatrics does not improve the differential diagnostics of stroke with its "masks". Several elements — such as unilateral weakness of arm — can be used to develop a scale for pediatric strokes but it also requires some other parameters [32].

FAST, COTS and ROSIER scales in children were tested by Gorman K. M. and Wainwright M. S. (2017). The authors reported that in 54% of children who were assessed using these scales, different "stroke masks" were diagnosed. One of the important symptoms of stroke is speech impairment but there can be difficulties in its assessment in children. In said study, a full assessment using the scales (including speech assessment) was possible only in 61% of patients. Based on the results of this work, researchers concluded that these scales were less informative in pediatrics than in adult practice; this fact confirmed the need for the development of specific screening scales for diagnosing stroke in children, which will include the assessment of seizures [33].

Currently, due to vague clinical findings, the large number of "stroke masks", the lack of specific scales for pre-hospital diagnostics of stroke in children, both in developing and economically developed countries, there is a problem of delayed provision of pre-hospital care for children with suspected stroke and delayed hospitalization in a specialized hospital. There are only few publications in specialized literature on the timing of hospitalization and diagnosis from the onset of stroke symptoms in children. According to Rafay M. (2009), the average interval from the onset of symptoms to diagnosis is 22.7 hours (7.1-57.7 hours) [34]. It takes an EMC team an average of 1.7 hours (from 49 minutes to 8.1 hours) to deliver a patient to the hospital. Stojanovski B. et al. (2017) note that the immediate call for emergency medical care is a key factor in reducing the time of hospitalization for a stroke [35]. The authors point to limited public awareness of pediatric stroke (insufficiently clear description of symptoms when parents call an EMC operator) and the non-specificity of primary symptoms in children. Low diagnostic sensitivity (matching the diagnosis made by EMC specialist and the final diagnosis made in hospital) can be caused by the fact that the probability of stroke in children is not considered in the guidelines for paramedical clinical practice. In the study, only 68% of children with a referral diagnosis of ACVE were admitted to stroke centers [35]. The problem of delayed hospitalization and diagnosis in children with symptoms of stroke requires further study.

In 2014, when analyzing medical records of 287 children, Mackay M. noted that 21 of them were diagnosed with IS (7% of hospital admissions), while among 20 children who were suspected of having a stroke, the diagnosis was confirmed in 13 (65%) cases [36]. The sensitivity of stroke diagnostics among EMC physicians in this study was 62%. When comparing the sensitivity of emergency stroke diagnosis in children at the Australian Center (62%) with similar data in adults, it was found that in the latter it reaches 90% [35]. The biggest challenges in the diagnostics of ACVE are in younger children and when a stroke is localized in the vertebrobasilar system [36]. With this localization, the first symptoms of stroke may be dizziness and vomiting rather than focal neurological symptoms; this fact also complicates diagnostics at pre-hospital stage [32].

Thus, the analysis of literature data on pediatric stroke revealed that the main factors causing delay in its diagnosis in children at the pre-hospital stage are: underestimation of the severity of the child's condition by parents and guardians, and, as a result, late seeking of medical help; exclusion of the

Table 5. *Factors of the late diagnosis of stroke in children at the pre-hospital stage*

Modifiable factors	Unmodifiable factors
Delay in seeking medical advice	Features of the onset of stroke in children and adolescents
Lack of clinical suspicion in EMC doctors regarding pediatric stroke	Variety of "stroke masks" in children
Lack of valid screening scales for early diagnosis of pediatric stroke	

possibility of a child having a stroke by the EMC physician, EMC technician, paramedic; non-specific symptoms of a pediatric stroke with a large number of "stroke masks"; lack of proper screening scales for the early diagnostics of stroke in pediatrics. In order to determine the main directions in improving the quality of pre-hospital diagnostics of stroke in the pediatric population, all these factors can be divided into modifiable (factors that may be influenced) and unmodifiable factors (Table 5).

Conclusion

The increase in the number of diagnosed strokes in children and adolescents around the world makes the problem of early diagnosis and timely treatment relevant. In many countries, there were studies on the pre-hospital diagnosis of stroke in pediatrics, and, despite different healthcare systems and different organization of the emergency medical care, the same problems were defined for the early detection of stroke in children. According to foreign literature, the time interval from the symptoms onset to hospitalization in a specialized department is longer for children with stroke than for the adults; it averages 22 hours. This fact determines the need for work in this area, taking into account the large number of confirmed strokes in pediatric population. It is especially worth noting that the work of specialists in pediatric stroke should be carried out in several areas, including educational activities to inform pediatricians and parents about the problem of pediatric stroke; training activities — for physicians and EMC doctors about the signs of stroke and "stroke masks" in children; scientific activities — on the design and development of pre-hospital stroke scales in pediatrics.

Author Contribution:

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Yu. A. Khachaturov, I. O. Shchederkina, I. P. Vytkovskaya, A. M. Sidorov: material collection and processing

Yu. A. Khachaturov, I. O. Shchederkina, A. M. Sidorov, V. A. Kadyshev: text writing

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The Role of Intestinal Microflora in the Development of Cholelithiasis (Literature Review)

Abstract

Cholelithiasis is one of the most common diseases of the digestive system, which affects all segments of the population. Currently, cholelithiasis is considered as a long, multi-stage process in which the period of stone formation is preceded by changes in metabolism and physical and chemical properties of bile. However, among the many contributing factors, insufficient attention is paid to the role of the infectious factor in the development of cholelithiasis. The analysis of the literature data showed that today there are various mechanisms for promoting of development of cholelithiasis by enteric bacterial overgrowth. First, with bacterial overgrowth, duodeno-biliary reflux leads to infection of the biliary tract and the development of inflammation in the gallbladder. Substances that occur during the inflammatory process (proteins, mucus, exfoliated epithelium) are the matrix on which the gallstone is formed. Secondly, the role of dysbiosis in violation of enterohepatic circulation of bile acids is essential. The change in the ratio of conjugated and deconjugated bile acids contributes to the formation of lithogenic bile. Third, bacterial overgrowth leads to endotoxemia, which damages the metabolism of bile acids in the liver. Finally, the digestive and suction functions of the small intestine are in a certain dependence on the microbiota, but the participation of this channel in cholelithiasis requires further research.

Key words: *gallstone disease, enterohepatic circulation of bile acids, bacterial overgrowth, intestinal dysrhythmia, endotoxinemia*

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GSD — gallstone disease, BA — biliary acids, EH BAC — enterohepatic biliary acids circulation, BaO — bacterial overgrowth

Gallstone disease (GSD) is one of the most widespread diseases of the digestive organs, to which all segments of the population are exposed [1, 2]. The incidence of GSD in different countries (regions of the world) is 10-15%, while in Russia it ranges from 3 to 12% with a marked gender and age difference [3]. Nowadays, GSD is considered as a long, multistage process in which the period of stone formation is preceded by changes in metabolism and physical and chemical properties of bile. However,

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among many contributing factors, insufficient attention is paid to the role of the infectious agent in the development of cholelithiasis.

Data from studies of bacterial contamination of the biliary tract in GSD

Infection of the biliary tract most often occurs via intestines due to sphincter insufficiency on the one hand, and bacterial overgrowth in the small intestine on the other hand [4].

Excessive growth of opportunistic bacteria in the intestine, their dissemination in the body in presence of a decrease in barrier and other protective factors lead to the ingress of agents into the biliary tract and the development of the inflammatory process. Opportunistic Enterobacteriaceae colonize the bile ducts due to translocation from the large intestine in the setting of dysbiosis [5]. At the same time, bile-sensitive microorganisms die, and resistant ones acquire the ability to colonize the corresponding biotope with the development of an infectious and inflammatory process [6].

It has been established that in patients with various clinical forms of GSD, bile, gallbladder wall, and biliary concretions are predominantly infected by microflora that are characteristic of the intestine. Among the microorganisms isolated from the gall bladder of patients with cholecystitis and GSD, opportunistic Enterobacteriaceae, Escherichia coli, Streptococci, Staphylococci, Salmonella typhi, and protozoans (lamblia) rank high [7]. At the same time, there is a significant prevalence of aerobic flora over anaerobic flora. The antibacterial activity of bile and biliary acids against anaerobes (Bacteroides, Clostridium, Lactobacilli), as well as gram-positive cocci (Pneumococci, Staphylococci) is most pronounced. Gram-negative microorganisms are less susceptible to their action (Salmonella, Shigella, Escherichia coli) [6].

In patients with an increased risk of stone formation in the gall bladder and with GSD, studies of short-chain fatty acids in feces revealed a change in the qualitative composition of the microbiota, which is manifested by an increase in the activity of those genera of microorganisms that are involved in the 7-alpha dehydroxylation of biliary acids, namely aerobic microorganisms (in particular, Escherichia coli, etc.) and anaerobes (some strains of Bacteroides, Clostridia, Eubacteria).

V. A. Gritsenko at al. (2002) [8], after studying the problem of extra-intestinal escherichiosis, point out that in various variants of cholecystitis (phlegmonous, gangrenous, calculous), Escherichia coli is isolated from bile and the gall bladder in 30–60% of cases. Escherichia often provokes the development of purulent and inflammatory complications after cholecystectomy. The main mechanism of E. coli dissemination in the body and infection of the liver and gall bladder is translocation from the intestine to the lymphatic and blood circulatory system. There is evidence in the literature that a similar process of bacterial translocation is possible for other intestinal microorganisms — Enterobacteriaceae (Klebsiella, Serratia), Pseudomonas, Staphylococci, Enterococci, etc. [6].

Expressed resistance to bile of strains of E. coli isolated from cholecystitis is an adaptive reaction resulting from prolonged contact with bile. A relatively high level of resistance was shown by fecal E. coli strains obtained in cases of intestinal dysbiosis, which is due to the functioning of a "vicious circle", when bacteria from the intestine migrate to the portal veins, enter the liver, then into the bile ducts, interact with bile and re-enter the intestine [8].

The overwhelming majority of literature sources cite data suggesting that in cholecystitis, regardless of its nature, mainly Enterobacteriaceae represent bacteria in bile, among which E. coli accounts for 30–57%. In addition to Escherichia, other members of the Enterobacteriaceae family may represent bile culture: Klebsiella (1–10%), Proteus (7–8%), Enterobacter (9.2%) and others, up to 75% in total. Enterococci account for an average of 10 to 27%, Staphylococci — from 9.70 to 16.25%, and Streptococci — from 7.3 to 12.5%. Pseudomonas and yeast-like fungi are less common [9].

Data from literature sources [9, 10] indicate the prevalence of intestinal bacteria in bile of patients with hepatobiliary disease, although other results are available. For example, the study by K. I. Savitskaya et al. (2003) [11], where the data on isolation in 70% of cases of gram-positive cocci from the bile of patients with chronic pancreatitis are presented. According to the results of most bile cultures carried out in connection with GSD, Enterococci, which are representatives of the microbiota of the

human digestive tract, are ranked second after Enterobacteriaceae [9].

Among cultures of strict anaerobes obtained from bile, asporogenous species predominate (89%), and 11% of cases are represented by Clostridium [6]. Among anaerobic biliary cultures, representatives of the Bacteroidaceae family are most often identified, and 25% of cases are represented by Bacteroides fragilis (B. Fragilis). The proportion of anaerobic cocci (Peptococci, Peptostreptococci and anaerobic Streptococci) can be also significant in this disease and accounts for 21.4% of all anaerobic strains.

Bile can be one of the factors that regulate microbial composition in the gall bladder, ducts, and intestine, and thus form a certain microecology of the digestive tract [3]. A. V. Valyshev et al. (1996) [5] revealed the uniformity of pathogens isolated from feces and bile in 74% of cases, and the presence of persistence factors (anti-lysozyme, anti-interferon and anti-complementary activity) in isolated bacterial strains in cases of intestinal dysbiosis and biliary duct disorders. This confirms the leading role of intestinal microbiota in the occurrence of inflammatory processes in the hepatobiliary system and, as a result, the formation of lithogenic bile [12].

Microbiota in the impairment of enterohepatic circulation of biliary acids

The main component of bile is primary biliary acids (BA) (cholic and chenodeoxycholic) that are synthesized in hepatocytes from cholesterol with participation of cholesterol-7α-hydroxylase. Upon entering the ileum, about 85–90% of primary BA are deconjugated with participation of the intestinal microbiota, absorbed and transported through the portal vein to hepatocytes, where they are conjugated again and included into the bile [1, 13]. It was found that this process involves Bacteroides and Lactobacilli [14]. Approximately 5–10% of non-absorbed primary BA enters the large intestine, where under the action of 7α-dehydroxylase of gram-positive anaerobic bacteria (Eubacteria and Clostridia), secondary hydrophobic BA (deoxycholic and lithocholic) are formed, which are absorbed, enter the liver, and again undergo conjugation in hepatocytes. In patients with GSD, intestinal transit time is increased, which enhances formation of deoxycholic acid as a result of bacterial metabolism. Increased concentration of secondary BA in the gall bladder induces a lithogenic effect.

Disturbance of enterohepatic circulation of biliary acids (EH BAC) is believed to be of great importance for the development of cholelithiasis [15, 16]. A disorder of EH BAC, which is manifested by changes in the metabolism of cholic acid, cholesterol and phospholipids has been observed in patients with GSD and chronic stone-free cholecystitis. This is due to increased activity of anaerobic microorganisms involved in 7-alpha-dehydroxylation of BA [17]. More bacteria and increased 7-dehydroxylase activity in intestinal aspirate from the iliac combined with higher pH in the large intestine and longer transit time in the small and large intestine are detected in patients with GSD. A longer period of intestinal transit, which promotes an increase in the time of bacterial conjugation even with a constant quantitative and qualitative composition of microbiota, is identified among the known reasons for abnormal absorption of BA [18–20]. Great importance of EH BAC disorders relates to the acceleration of the intestinal passage, resulting in increased BA excretion with feces and reduction of their absorption [21].

At the same time, there is evidence that a decrease in the BA level reduces the antibacterial properties of the bile [22]. This contributes to the activation of opportunistic microorganisms and bacterial overgrowth (BaO) in the intestine. However, the incidence and peculiarities of the occurrence of BaO, as well as an intestinal dysbiosis in case of GSD remain insufficiently studied. To date, evidence has been accumulated, showing that intestinal microbiota is capable of performing biotransformation of BA, cholesterol and steroid hormones into various metabolites in the process of EH BAC [23].

Chronic biliary insufficiency has special influence on the course of the GSD, which results in bacterial overgrowth and premature deconjugation of BA that damage the mucosa of the small and even large intestine. Inflammatory process in the mucosa of small intestine results in EH BAC disorders accompanied by worsening of biliary insufficiency. In physiological conditions, the sterility of bile is ensured by the antibacterial effect of BA. With chronic biliary insufficiency, especially when combined with reduced concentration and evacuation

function of the gallbladder and sphincter of Oddi dysfunction, conditions for the reduction of antibacterial properties of bile are created. At the stage of biliary sludge formation, biliary insufficiency is detected in 91.7% of cases (of which 54.5% are mild and 45.5% — moderate) [19].

Reduced antibacterial properties of bile inevitably create favorable conditions for the development of BaO in the small intestine. More pronounced changes in small intestine microbiota occur in case of cholecystolithiasis. Due to a decrease of the protective function of the gallbladder in the intestine of a patient with GSD, which function is realized in the bactericidal action of the bile, bacterial overgrowth develop, while a number of representatives of obligate intestinal flora is reduced and replacement of this flora by opportunistic bacteria occurs. In the duodenum mucosa sample, the signs of activation of opportunistic microflora with the secretion of up to 28 different genera of microorganisms are found in patients with GSD. In such a case, hemolytic Staphylococci (53%), bacteria of the Enterobacteriaceae family (69%), fungi of the genus Candida (49%), and Bacteroides (47%) in the amount of 3.3–5.2 log CFU/g in combination of 2–7 cultures dominate [19].

As it was demonstrated by Vakhrushev Ya. M. et al. (2017) [24], the biochemical study of bile revealed a significant decrease in the concentration of BA in cystic and hepatic bile of patients with GSD in comparison with the control. There was also a tendency of an increase in the concentration of cholesterol and a significant decrease in the cholate-cholesterol rate in both cystic and hepatic portions of bile from patients with GSD. When studying individual fractions of BA in patients with GSD, there was a decrease in free (cholic, henodeoxycholic, deoxycholic) and an increase in conjugated (glycocholic, glycodeoxycholic, tauroholic, taurodeoxycholic, ursodeoxycholic) BA in the "B" and "C" portions of bile in comparison with the control. Disruption of the balance of free and conjugated BA leads to the development of colloidal instability of bile, which is a prerequisite for the development of cholelithiasis. In the same authors' study of the total content of BA in blood based on the results of mass spectrometry assay, its decrease in patients with GSD in comparison with the control was noted. Omnidirectional BA spectrum disorders were also noted. Thus, levels of chenodeoxycholic and deoxycholic acids were decreased, while those of ursodeoxycholic, glycocholic, glycodeoxycholic, tauronic and taurodeoxycholic acids were increased.

The synthesis of BA from cholesterol occurs in the hepatocyte and includes 17 different enzymes that are located in the cytosol, endoplasmic reticulum, mitochondria, and peroxisomes [25]. It is necessary to take into account that the synthesis of BA is influenced not only by the state of the liver and the BA itself, which can contribute to an increase or decrease in their content according to the principle of negative feedback, but also by cholesterol, thyroid hormones, glucocorticoids, insulin, and circadian rhythms [13, 25, 26]. The small intestine actively participates in maintaining the homeostasis of BA by synthesizing of the fibroblast growth factor-15 by enterocytes, which regulates a number of enzymes responsible for the synthesis of BA [13]. Changes in the composition of BA in the blood may be associated with increased absorption of BA in the proximal part of the small intestine. In patients with pre-stone stage of GSD, BaO leads to disorders in the normal absorption of BA in the distal ileum. This is characterized by premature deconjugation and absorption of BA [27, 28]. With underlying BaO, there is a decrease in free and an increase in conjugated BA in bile. In addition, BaO can serve as an initial link in the mechanism of bacterial translocation [29]. There are microorganisms that are more prone to translocation due to their better ability to adhere to the intestinal epithelium (Escherichia coli, Klebsiella, Enterococci). These bacteria are able of penetrating even through the histologically normal mucous membrane of the wall of intestine, then getting into the hepatobiliary system. It can be assumed that the detected BaO in most patients with pre-stone stage of GSD can be a cause of bile contamination, while bacterial colonization of extrahepatic bile ducts contributes to bile stone formation [30].

The process of deconjugation of BA in the distal part of the iliac and proximal part of the colon involves Lactobacillus and Bacteroid enzymes [31]. Intestinal dysbiosis is detected in fecal culture of 100% of patients with GSD, while in the majority of patients (91%) various versions of combined disorders in the colon microbiota were noted. A decrease in the number of Lactobacilli to less than 10^7 CFU/g in 40.9% of patients with pre-stone stage of GSD was

noted to a greater extent. There was also an increase in the proportion of lactose negative and hemolytic Escherichia coli (up to 28.6% and 18.2%, respectively) against the background of a decrease in full-functional Escherichia coli (in 31.8% of patients). Consequently, with underlying BaO and colonic dysbiosis, significant changes occur in the deconjugation of BA, which leads to a disorder in the ratio of conjugated and deconjugated BA in bile and blood. Disorder in the EH BAC leads to a decrease in the content of BA in the intestine. Malabsorption syndrome develops, the composition of the intestinal microbiota is disrupted, ethanol and organic acids are formed in excess, the pH of chyme decreases and the deconjugation of BA increases. The consequence is the progression of BaO, the formation of an increased number of endotoxins, their entry into the liver, and the development of systemic inflammation [32]. In this way, dysbiosis leads to a disruption of EH BAC, while a decrease in the intake of BA in the intestine exacerbates the dysbiosis.

Thus, the small intestine is an important link in the disruption of EH BAC. The increase in the absorption of prematurely deconjugated BA in the proximal part of the small intestine accelerates the time of return of BA to the liver, which reduces their synthesis in hepatocytes and excretion into bile. As a result of BaO in the distal ileum and colonic dysbiosis, significant changes in the deconjugation of BA occur, which leads to an impaired ratio of BA fractions in the blood and bile.

Influence of microbiota on the development of intestinal rhythm decrease

According to literature data, intestinal rhythm decrease is present in 90% of patients with GSD [31]. Frequently revealed cholecystolithiasis in intestinal disorder even allowed some authors to consider GSD as an "intestinal" disease. Studies have shown that patients with gastrointestinal disorders have impaired bowel emptying in the form of intestinal rhythm decrease, in contrast to the regular intestinal rhythm corresponding to 7 days a week with daily stools. Intestinal rhythm decrease occurs 2 times more often than obesity [27]. Intestinal rhythm decrease occurs in the setting of impaired colon microbiota in the form of the reduction of the content of the anaerobic component (Bifidobacteria, Lactobacilli), Escherichia coli with normal enzymatic properties, Enterococci, and an increase in the content of opportunistic microorganisms (Klebsiella, Enterobacter) [30].

In studies with the use of hydrogen breath tests with lactulose, most patients with GSD were found to have colon dysbiosis [24]. Dysbiosis contributes to the disruption of intestinal functions. With a decrease in the quantity of Bifidobacteria and Lactobicilli, a decrease in their enzymatic activity is noted, which leads to the disturbance of processes of utilization of biologically active compounds by the human organism, activation of putrefactive and fermentation processes. The increase in the number of representatives of opportunistic flora causes disruption of nutrient absorption processes, promotes competitive interaction with representatives of normal microbiota for participation in the processes of fermentation and assimilation of food nutrients. When the severity of dysbiosis increases, motor activity of the colon and the function of the ileocecal valve are more seriously damaged [10].

Changes in the composition and decrease in the amount of bile in the intestinal lumen in the setting of gall bladder dysfunction are accompanied by a decrease in the bactericidal activity of the duodenal content with excessive reproduction of bacteria in the duodenum and jejunum, followed by premature deconjugation of BA and formation of duodenal hypertension [33].

The disorder of intestinal microbiota is a cause of endotoxinemia, which contributes to a toxic effect on the liver [30, 34] and intestinal function, which is manifested by a disorder of BA synthesis and dystrophic changes in mucosa, leading to the disorder of the motor function and disruption of the hydrolysis-resorption process [35].

An important pathogenetic component in BaO is the premature deconjugation of primary BA, which is carried out by the small intestine microbiota, which determines its clinical signs. According to L. Bala et al. (2006), in patients with BaO, the average level of deconjugated BA was significantly higher compared to those who did not have it: 500 μmol/L (within the range of 40–600) and 10 μmol/L (within the range of 0–300), respectively [36]. Deconjugated BA have detergent properties and can damage the epithelium of the small intestine mucosa. Clinical

signs of these disorders are creatorrhea, amylorrhea, and steatorrhea [36]. In addition, deconjugated BA together with bacterial toxins disrupt water-salt metabolism. BA induce the disruption of sodium absorption [23], an increase secretion of chlorides and water into the intestinal lumen, accelerate peristalsis of the small intestine, which aggravates diarrhea in the setting of intestinal rhythm increase.

Conclusion

Based on the performed analysis of the literature data, various mechanisms for promoting the development of cholelithiasis by BaO are known today. First, in BaO the duodenal biliary reflux leads to infection of the biliary tract and the inflammation in the gall bladder. Substances that occur during the inflammatory process (proteins, mucus, sloughed epithelium) are the matrix on which the gallstone is formed. Secondly, dysbiosis plays an essential role of the disruption of EH BAC. Changes in the ratio of conjugated and deconjugated BA contribute to the formation of lithogenic bile. Third, BaO leads to endotoxinemia, which has a damaging effect on the metabolism of BA in the liver. Finally, the digestive and absorption functions of the small intestine depend on the microbiota, but the involvement of this component in cholelithiasis requires further investigation.

Contribution of Authors

N. A. Khokhlacheva: development of the concept and design of the article, responsible for all aspects of the work.
A. P. Lukashevich: data collection, analysis and interpretation, justification and writing of the manuscript.
N. N. Glazyrina: data collection, analysis and interpretation, justification and writing of the manuscript.
Ya. M. Vakhrushev: verification of critical intellectual content, final approval of the manuscript for publication.
T. S. Kosareva: data collection, analysis and interpretation.

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Focal Segmental Glomerulosclerosis: Current State of the Problem

Abstract

One of the most prognostically unfavorable variants of glomerulopathy is focal segmental glomerulosclerosis (FSGS), which is detected by nephrobiopsy in 5-20% of patients with nephrotic syndrome (NS) and in 15% of adult patients with chronic glomerulonephritis. FSGS recurs in a transplanted kidney in 30-50% of patients. Among adult patients with FSGS, men predominate. A poor prognosis of FSGS is explained by the heterogeneity of the disease and is exacerbated by a poor response to treatment. According to current data, FSGS is characterized by sclerosis of the mesangial matrix, hyalinosis, damage to capillaries, an increase in foam cells and their adhesion between the glomerular bundle and the Bowman capsule. In 2004, the following histological variants of FSGS were proposed: tip, perihilar, collapsing, cellular and classical. Each histological variant of FSGS differs in etiology, response to treatment, and prognosis. The clinical diagnosis of primary FSGS should be based on the exclusion of secondary causes of the disease. Focal sclerotic changes in the glomeruli can be caused by various factors and occur in various conditions, including the existing kidney pathology. According to international recommendations for the treatment of FSGS, one should focus on the amount of daily proteinuria. For patients with FSGS without pronounced proteinuria, the use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) is recommended. In FSGS and NS, immunosuppressive therapy is used along with ACE inhibitors or ARB. For adult patients, glucocorticoids (GC) are prescribed daily in a single dose at a dose of 1 mg/kg per day, the maximum dose is 80 mg with a daily intake and 120 mg with an alternating regimen. Resistance to GC is detected in the absence of effect after 16 weeks. In the presence of contraindications or intolerance to GC, calcineurin inhibitors are used. The recommended initial dose of cyclosporine is 2 mg/kg/day, taken twice a day with a gradual increase to 3.5-4 mg/kg/day. The duration of therapy with satisfactory tolerance to cyclosporine is more than six months. After achieving complete remission, the dose of cyclosporin is gradually reduced by 0.5 mg/kg/day to the minimum effective dose (1.5-2 mg/kg/day) and such maintenance therapy is carried out for 1-2 years. A treatment option is possible using lower doses of GC and cyclosporine, or a combination of mycophenolate mofetil with a high dose of dexamethasone.

Key words: *focal segmental glomerulosclerosis, glomerulonephritis, nephrotic syndrome, immunosuppressants, monoclonal antibodies*

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ACE inhibitors — angiotensin converting enzyme inhibitors, ARBs — angiotensin II receptor blockers, CI — calcineurin inhibitors, CPF — circulating permeability factors, FSGS — focal segmental glomerulosclerosis, GBM — glomerular basement membrane, GC — glucocorticoids, SSNR — Scientific Society of Nephrologists of Russia, RAAS — renin-angiotensin-aldosterone system, RF — renal failure, RRT — renal replacement therapy

Currently, significant progress has been made in understanding the complex molecular mechanisms and pathways responsible for maintaining the healthy state of podocytes with the structural and functional integrity of the glomerular filtration barrier. Structural abnormalities of podocytes, changes in actin cytoskeleton, smoothing of pedicles, and fusion of filtration gaps lead to the development of proteinuria, which is typical for most proteinuric forms of glomerulopathy [1, 2]. Proteinuria directly damages the tubule epithelium, which, in turn, stimulates the synthesis of vasoactive molecules, such as monocyte chemoattractant protein-1 (MCP-1), endothelin-1 and osteopontin [3]. The development of nephrosclerosis is based on the remodeling of tubulointerstitial tissue. Changes in the tubulointerstitial component of nephron are the most important element in the progression of chronic kidney disease. Excessive amounts of vasoactive molecules produced by renal tubules, MCP-1 and endothelin-1 are secreted through the basal parts of cells in the interstitium, which leads to the development of inflammatory reaction which, in most forms of nephritis, precedes the development of nephrosclerosis [3, 5]. In the structure of morphological variants of the glomerular lesion, focal segmental glomerulosclerosis (FSGS), which is based on podocytopathy [4, 5], plays a special role. According to current data, FSGS is characterized by sclerosis of the mesangial matrix, hyalinosis, capillary damage, enlargement of foam cells and their adhesion between the glomerular bundle and Bowman's capsule [6, 7]. According to the clinical recommendations of the Scientific Society of Nephrologists of Russia (SSNR), FSGS is characterized by sclerosis of separate segments (foci) in the part of glomeruli, with the remaining glomeruli having no changes at the start of this disease, i. e. only a part of a separate glomerulus is damaged [5]. FSGS is believed to be the most common type of glomerular lesion leading to terminal stage of renal failure (RF) when renal replacement therapy (RRT) is required.

It is important to note that the problem of FSGS involves the fact that it recurs in a transplanted kidney in 30-50% of patients. FSGS is found in 15% of adult patients with chronic glomerulonephritis; men dominate among adult patients with FSGS. FSGS is the most common cause of steroid-resistant nephrotic syndrome (NS) in children [5]. However, in previous analytical studies, it was noted that FSGS is also the most common cause of NS in adults [8]. Currently, FSGS is divided into primary (idiopathic) and secondary types [5]. Causes for primary FSGS are shown in Table No. 1; moreover, multiple factors play the etiological role in the formation of secondary FSGS.

Podocytes are highly differentiated, specialized cells with a complex structure. Podocytes wrap around glomerular capillaries and are the main component of glomerular filtration barrier. As stated above, the most important aspects of FSGS pathogenesis are structural and functional changes in podocytes [9, 10]. This fact is confirmed by the results of experimental studies where the severity of damage to podocytes and the grade of podocytopenia are closely correlated with the histological model of the damage [11]. Pathogenic mechanisms of FSGS are still not fully established. However, it was noted that gene mutations (ACTN4, INF2, COQ6, NPHS2, CD2AP, CD2AP, PDSS2, Glepp1, LMBX1, COL4A3/COL4A4, LAMB2, A3243G) that encode the state of the proteins of the podocyte gap membrane underlie the development of hereditary forms of this disease [12, 13]. In several families, different mutations of genetic factors related to FSGS were detected and described [14]. In the publication by A. A. Melnik (2019), the role of podocytic dysfunction in the formation of proteinuria during FSGS was definitely stated [8]. In particular, it was noted that the loss of less than 20% of podocytes can be regenerated by resident glomerular epithelial cells that migrate from a niche adjacent to Bowman's capsule to the glomerulus and replace podocytes damaged during necrosis or apoptosis [8]. As early

Table 1. *Factors for the secondary focal segmental glomerulosclerosis development*

1	**Genetically determined**
1.1.	Familial mutations (NPHS1, ACTN4, CD2AP, INF2, NPHS2, TRPC6, WT-1, LIMP2, mitochondrial cytopathies, etc.)
1.2.	Sporadic mutations (NPHS1-nephrine, NPHS2-podocin, ACTN4, CD2AP, etc.)
2	**Virus-induced**
	HIV, parvovirus B19, cytomegalovirus, Epstein-Barr virus, Coxsackievirus, etc.
3	**Drug-induced**
	Heroin, Interferon-α, adriamycin, doxorubicin, lithium, anabolic steroids, tacrolimus, pamidronate, valproic acid, etc.
4	**Structural and functional changes of glomeruli**
4.1.	With a decrease in the mass of renal tissue (oligomeganephronia, unilateral agenesis, renal dysplasia, cortical necrosis, reflux-nephropathy, nephrectomy, chronic transplant nephropathy, low birth weight, late stage of any kidney disease with a decrease in the mass of active nephrons, etc.)
4.2.	With initially normal number of nephrons (hypertension, diabetes, obesity, congenital cyanotic heart defects, sickle cell anemia, etc.)
5	**Malignant tumors (lymphoma, etc.)**
6	**Non-specific FSGS-like changes caused by nephrosclerosis in glomerular diseases**
	Focal proliferative GN, hereditary nephritis (Alport syndrome), membrane nephropathy, thrombotic microangiopathy, etc.

Note: HIV — human immunodeficiency virus; FSGS — focal segmental glomerulosclerosis; GN — glomerulonephritis

as 1974, R. J. Shalhoub suggested the existence of a "permeability factor" circulating in blood, produced by T cells and causing podocyte dysfunction with subsequent development of proteinuria, as well as having an effect on the glomerular basement membrane (GBM) or activated mesangial cells [15]. In FSGS, damage to podocytes also occurs with exposure to circulating permeability factors (CPFs) or external damaging agents. CPFs are a group of proteins that change glomerular permeability [15]. Cardiotrophin-like cytokine-1 (from interleukin-6 family) and a soluble urokinase receptor are considered as CPFs [5]. In FSGS and other non-proliferative glomerulopathies, the activity of CPFs depends on the balance between the production of these factors (as a result of T-cell dysregulation) and the loss of their inhibitors with urine (presumably, high density lipoproteins). Proteins of slit diaphragm of podocytes which are involved in maintaining the integrity of the structure and selectivity of the glomerular filter can be the target of CPFs [5]. So, with prolonged and/or significant effect of CPF, apoptosis mechanisms are activated, podocytes die, their connection with GBM is lost, and they are then desquamated in the urinary space, exposing areas of GBM in these parts [5]. As a rule, foci of fibrosis in glomeruli develop at the foci of podocyte fusion with GBM. In parts of segmental (focal) sclerosis, filtration changes its direction towards the interstitium that surrounds glomerulus [5]. As a result, global glomerular sclerosis and interstitial fibrosis are formed [16]. Subsequently, in the course of damage, podocytes undergo transdifferentiation, acquiring the properties of fibroblasts, and participate in the synthesis of the extracellular matrix, accelerating the formation of fibrosis foci [2, 5, 17]. According to D. Yu et al. (2005), podocytes can be found in the urine of patients with proteinuric types of glomerulopathy, which indicates the severity of glomerular damage [18]. It is possible that in the presence of primary FSGS, a special role at all stages of disease progression is played by pro-inflammatory cytokines; damaged podocytes are also the source of their production. When discussing details of the formation of secondary FSGS, it should be noted that the following hemodynamic mechanisms play an important role in the damage to podocytes: adaptive intraglomerular hypertension and hyperfiltration with increased glomerular volume, which leads to increased mechanical load on podocytes [19]. Hyperproduction of angiotensin II and increased synthesis of transforming growth factor beta-1 cause activation of apoptosis, reorganization of cytoskeleton and dedifferentiation of podocytes [5]. In cases of both primary and secondary FSGS, if the loss of podocytes is in the range

of 20-40%, then damage that is typical for FSGS appears, whereas loss of more than 40% of podocytes leads to global sclerosis [5, 8, 20]. Nevertheless, it was noted that the number of podocytes in the classic variant of FSGS was reduced and, on the contrary, increased in the case of a collapsing and cellular variant of this disease [21].

In 2004, five histological variants of FSGS were proposed, which are completely based on light microscopy [22]. Although this classification includes most of the primary and some secondary forms of FSGS [23], it will be appropriate to mention that histological variants of FSGS differ in etiology, response to treatment, and prognosis [5, 8]. As can be seen in Table No. 2, five-year renal survival with the tip variant is 76%, and three-year renal survival with the classic variant is 65% [5, 8]. Rare spontaneous remissions of primary FSGS justify the need to achieve drug remission, although spontaneous remissions are also possible with the tip variant of FSGS or with unexpressed proteinuria [5]. There is data that perihilar FSGS is often detected in patients with obesity, as well as with decreased proportion of functioning nephrons and hyperfiltration [24]. Clinically, the perihilar variant is most often manifested by incomplete NS [20]. In case of nephrobiopsy, perihilar FSGS requires preliminary exclusion of cellular, tip and collapsing variants [23]. According to several authors, one of the rare types (up to 5%) of primary FSGS is the cellular variant [25]. The cellular variant is diagnosed only when if tip and collapsing variants of FSGS are excluded [23]. With multiple glomerular damage, the process becomes similar to proliferative glomerulonephritis [26]. The cellular variant of FSGS is histologically characterized by the fusion of podocyte processes and is clinically manifested by nephrotic proteinuria [23].

M. A. Weiss et al. first described collapsing glomerulopathy in 1986, when they studied the clinical and morphological complex of severe NS and rapidly progressing RF in black patients [27]. The same researchers reported the detection of FSGS in some patients with viral infections, parvovirus B19, as well as in elderly subjects. Glomerular collapse is accompanied by severe hypertrophy and podocyte hyperplasia [23]. An important component of this histological subtype is tubulointerstitial damage, the development of which usually positively correlates with the grade of glomerular sclerosis. According to some authors, the concept of collapsing FSGS is used in cases where there is segmental or total obliteration of the lumen of glomerular capillaries, as well as GBM wrinkling and collapse, and these changes are associated with hypertrophy and hyperplasia of podocytes [28, 29]. It is worth noting that histological examination of collapsed lobes revealed wrinkling and a slight thickening of GBM, and underlying podocytes are characterized by noticeable hypertrophy and significant fusion of their processes. In addition, cells with empty cytoplasm were found during FSGS due to the disruption of actin cytoskeleton integrity. Significant fusion of the processes of podocytes was also found in intact capillaries. In other studies, it was reported that the collapsing variant of FSGS is rarely detected among the European population, whereas the incidence of collapsing FSGS among African Americans is quite high [23, 30].

Table 2. *Morphological classification of FSGS [5]*

Variant	Incidence	Description
Tip	17%	In most cases, serious proteinuria, NS, a positive response to GC therapy. Complete remissions of NS occur in 50% of patients. The prognosis is favorable; five-year renal survival is 76%.
Perihilar	26%	Rarely developed NS, mostly detected AH.
Collapsing	11%	High proteinuria, severe NS, rapid decline in renal function. Only 25% of patients have a positive response to GC.
Cellular	3%	Responding to therapy and the rate of progression of CKD occupies an intermediate position between tip variant and collapsing nephropathy.
Classic	42%	67% of patients develop NS, 80% — hypertension, complete remission is achieved in 13% of patients. The prognosis is favorable; three-year renal survival is 65%.

Note: FSGS — focal segmental glomerulosclerosis; GC — glucocorticoids; NS — nephrotic syndrome; CKD — chronic kidney disease

Diagnosis of FSGS

FSGS is a group of disorders united not by a specific etiological factor, but by the nature of histological changes. Clinical diagnostics of primary FSGS should be based on the exclusion of secondary causes of disease. Segmental (focal) sclerotic changes in glomeruli can be caused by various factors and occur with various underlying conditions, including an existing kidney pathology, in particular, semilunar glomerulonephritis, immunoglobulin-A nephropathy, Alport syndrome, etc. This fact reflects the endpoint in the histopathological evolution of different biological processes. Therefore, it is very important to exclude the secondary nature of FSGS development [5].

Drug Treatment of FSGS

The goal of pharmacological therapy of FSGS is to achieve complete or partial remission, and therefore, to prolong the pre-dialysis period of the disease. According to the recommendations of SSNR, during FSGS therapy, the daily proteinuria level should be considered [5].

In the case of FSGS without significant proteinuria (daily proteinuria below 500 mg), it is recommended to use angiotensin converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs). Prescribing statins, or the continuation of statin therapy (if previously prescribed) is also possible [5]. The antiproteinuric effect of ACE inhibitors / ARBs as the blockers of renin-angiotensin-aldosterone system (RAAS) can be explained by decreased apoptosis and hypertrophy, inhibition of podocyte actin cytoskeleton rearrangement, retained nephrin expression, decreased synthesis of IV type collagen a-3 chain, decreased endothelial permeability, and decreased synthesis of the extracellular matrix [31, 32].

In FSGS with severe proteinuria or NS, using RAAS blockers is indicated (when there are no contraindications for ACE inhibitors or ARBs). If daily proteinuria is more than 3.5 g or if it is not possible to reduce its level by the methods of maximum conservative therapy, then immunosuppressive therapy should be started [5]. High doses for at least 4 weeks are recommended as an initial therapy. If there is a tendency to a decrease in daily urinary protein excretion, high doses of GC should be continued, with satisfactory tolerance of up to maximum 16 weeks, or until complete remission if it develops earlier than 16 weeks [5]. Short-acting GC, i. e. prednisolone, is preferred. GCs stabilize cell membranes, reduce capillary permeability, inhibit the migration of monocytes, neutrophils, and macrophages to the inflammation focus and their phagocytic activity, and also restore the charge selectivity of podocytes. Long-term administration of GCs is accompanied by inhibition of the apoptosis process, increased stability of actin cytoskeleton, and decreased smoothing of podocyte pedicles [5]. Prednisolone for adult patients is prescribed once daily, at the dose of 1 mg/kg (maximum 80 mg/day), or in alternating mode, once every other day at the dose of 2 mg/kg (maximum 120 mg/day) [5, 33]. It is worth noting that refractoriness to GCs is detected if there is no decrease in proteinuria level after 16 weeks (4 months). In the cases of complete and incomplete remission, supporting therapy with GCs lasts about 24 months; it can be extended to 5 years, if necessary [5]. Patients with FSGS are considered steroid-dependent if they had two episodes of relapse within two weeks after completion of GC therapy [5]. The development of temporary resistance to GC with relapses of NS is often due to simultaneous viral, bacterial, or mycotic infections requiring targeted therapy [34]. In such cases, an examination is indicated to identify active infections and immunodeficiency [35]. Calcineurin inhibitors (CI) are proposed as first-line drugs in patients with relative contraindications or intolerance to high doses of GCs (gastric ulcer, steroid-induced osteoporosis, uncontrolled hyperglycemia, psychoses, cataract, hirsutism, etc.) [5, 33]. According to the recommendation of SSNR, the initial dose of cyclosporine is 2 mg/kg/day, in two intakes with a 12-hour break. Daily dosage should be gradually increased to 3.5-4 mg/kg/day for more than six months. It is important to note that the daily dose of cyclosporine should not exceed 5 mg/kg. During cyclosporine therapy, it is necessary to control hemodynamic parameters (with long-term intake), activity of hepatic transaminases and serum creatinine concentration. After achieving complete remission, the cyclosporine dose is gradually reduced by 0.5 mg/kg/day to the minimum effective dose (1.5-2 mg/kg/day),

and such supportive therapy should be carried out for 1-2 years [5].

After penetrating a cell, cyclosporin binds to cyclophillin protein, then the resulting complexes competitively inhibit phosphatase activity of calcineurin, which, in turn, inhibits dephosphorylation and nuclear translocation of the nuclear factor of activated T-lymphocytes [36]. This is accompanied by suppressed transcription of proinflammatory cytokine genes and disrupts the proliferation and differentiation of T-lymphocytes [36]. Therapy with cyclosporine provides remission of FSGS in a large portion of patients [5, 8, 37, 38]. Most of these patients are generally steroid-resistant; steroid-sensitive patients have better response to CI therapy. According to the recommendations, CI (cyclosporin A) is prescribed when daily proteinuria retains at the level of more than 3 g, in spite of GC therapy, as well as in cases where adult patients have not achieved at least partial remission after 8 weeks of daily use of prednisolone [5]. There are isolated reports where prescribing CI for patients with FSGS that are resistant to GCs reduced disease recurrence to 60-80%, [39, 40]. It should be remembered that KDIGO (Kidney Disease Improving Global Outcomes) recommends GC and immunosuppressive therapy for the initial treatment of FSGS only for the primary form of FSGS [41]. Recent molecular studies made it possible to better understand the nephroprotective potential of CIs. Cyclosporin has an effect on podocytes unrelated to T and B cells [42]. In particular, CI — cyclosporin inhibits calcineurin-mediated dephosphorylation of synaptopodin (protects it from hydrolysis) and thus stabilizes actin cytoskeleton of podocytes [43]. Accumulated results of numerous clinical studies have shown that using cyclosporine in patients with FSGS is currently considered fully justified [44, 45]. When partial or complete remission is achieved, it is proposed to continue treatment with CI (cyclosporine) for at least 12 months, followed by gradual dose tapering [5, 45]. Using cyclosporine is possible both in the form of monotherapy (when there are contraindications for GCs), and in combination with GCs (in small doses). If subjects taking cyclosporine for six months demonstrated no response to the therapy, then the question of replacing cyclosporin with another drug should be considered [5]. In particular, for patients who have resistance to GCs and cyclosporine intolerance, a combination of mycophenolate mofetil with a high dose of dexamethasone, or treatment only with mycophenolate mofetil can be proposed [5]. There are reports of the advisability of transferring patients with developed nephrotoxicity from CI (cyclosporine) to mycophenolate mofetil, which leads to the improvement of renal function [46]. According to M. S. Ignatova et al. (2017), simultaneous use of mycophenolate mofetil with cyclosporine for the treatment of NS is possible; it can apparently enhance the effect of both drugs and also reduce the nephrotoxic effect of CI [13]. Regarding the pathogenic therapy of primary FSGS, we should mention the possibility of using cytostatics. If patients with FSGS demonstrated resistance to GCs, treatment with cyclophosphamide is an optional variant [5, 8]. The recommended dose is 500 mg/m^2. The possibility of using azathioprine for primary FSGS is not considered, since it has a large number of undesirable effects. Although up to 2000, alkylating agents (cyclophosphamide and chlorobutine) were considered an alternative to cyclosporine; they caused long-term steady remission in patients with FSGS (30% steroid-resistant and 70% steroid-dependent). It should be remembered that patients with FSGS, as well as with membranous nephropathy, are at risk of systemic thromboembolic complications [5]. In this connection, it is preferable to use small doses of anticoagulants (rivaroxaban or warfarin), especially for severe proteinuria, hypoalbuminemia, hyperlipidemia, taking large doses of GCs and loop diuretics.

A controversial issue in the treatment of FSGS is the use of rituximab, which is a complex of chimeric monoclonal antibodies that act selectively on the B-lymphocyte surface antigen CD20. In addition, rituximab has a direct protective effect on podocytes [47]. Rituximab is administered in 2 or 4 injections at the dose of 375 mg/m^2 per week, or once every two weeks. T. Nakagawa et al. in their study (2016) demonstrated that using rituximab in three patients with steroid-resistant NS resulted in complete remission: in two patients after one treatment course; in one — after two courses [48]. Another study showed the effectiveness of treatment with rituximab in combination with pulse therapy with methylprednisolone and immunosuppressive drugs in eight out of ten patients with

steroid-resistant NS: complete long-term remission was achieved in seven patients, partial remission — in one [49]. In this study, there was no effect of therapy in two patients; they developed the terminal stage of chronic RF [49]. In a prospective study performed by C. S. Wang et al. (2017), a humanized anti-CD20 monoclonal antibody — ofatumumab — was used in five patients with steroid-resistant NS [50]. Ofatumumab was found to be effective in four patients; one patient could not complete the treatment course due to reactions that developed during drug infusion [50]. The possibility of achieving and maintaining the remission of NS with the help of ofatumumab was obtained in the course of a randomized controlled trial, where ofatumumab was compared with rituximab [51, 52]. It should be noted that the use of rituximab for primary FSGS is an additional method of therapy, and the question of the risk-benefit ratio concerning clinical nephrology is still open, although practical experience of using rituximab for membranous nephropathy is accumulating. A number of researchers report about the effectiveness of plasmapheresis for removing antibodies, immune complexes, cytokines, fibrinogen, and other biologically active substances [13]. This improves the function of the mononuclear phagocytic system, rheological properties of blood, and also increases sensitivity to immunosuppressive therapy. Usually, no more than 3-4 sessions of plasmapheresis are performed, with intervals of 1-2 days with the total volume of the removed plasma — 1 volume of circulating plasma with replacement of the removed volume with 10-20% albumin and rheopolyglukin [13]. Summarizing all these data, we would like to note that nephrologists and clinicians will have at their disposal such drugs as mizoribine, adalimumab, fresolimumab, etc. for the management of FSGS in the near future [8, 13].

Conclusion

Despite certain success achieved concerning diagnostics and management of FSGS, the prognosis for this type of glomerulopathy remains unfavorable. FSGS is the outcome of many glomerular pathological processes. In the routine clinical practice of nephrologists, the management of FSGS creates certain challenges, and the management of secondary forms of this disease of any origin requires establishing the nature of morphological changes in the kidneys, although it is not always possible to establish primary or secondary FSGS on the basis of the morphological form only. Studying genetic markers in patients with FSGS is impossible in real clinical practice. A more detailed analysis of the structural and functional conditions of podocytes and the results of controlled prospective studies in the near future will influence the outcomes of FSGS.

Author Contribution:

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I. S. Sabirov (ORCID ID: https://orcid.org/0000-0002-8387-5800): concept and design development
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Quality of Life and Physical Working Capacity in Pulmonary Sarcoidosis

Abstract

Objective To study the quality of life (QOL) and physical working capacity (PWC) in patients with pulmonary sarcoidosis. **Materials and methods.** Eighty patients with pulmonary sarcoidosis were examined (mean age 35 (39; 45) years), including 43 men (53.8 %) and 37 women (46.3 %). The duration of sarcoidosis was 3 (2; 4) years. Seventy-five percent of patients had pathologically proven sarcoidosis. All patients completed the SF-36 questionnaire; physical examination, chest computed tomography, spirometry and cardiopulmonary exercise testing (CPET) were conducted. PWC was determined according to the peak oxygen uptake (VO_2 peak) via CPET. **Results.** Thirty-six point three percent of patients had reduction of QOL (psychological and physical components of health). The most significant decrease of QOL was noted on the scale "general health" — 67 (47; 77) scores, "mental health" — 72 (54; 84) scores and "vitality" — 72.5 (50; 82.5) scores. Female patients (p=0.008) over 40 years of age (p=0.044) with clinically significant symptoms (p=0.012) and comorbidities (p=0.049) had a lower QOL. Patients with high or low QOL did not have differences in radiology stages, laboratory test results and lung function parameters. The female sex (OR 3.26, 95 % CI 1.15–9.23; p=0.026) and the clinical manifestations of sarcoidosis (OR 3.63, 95 % CI 1.06–15.47; p=0.041) were the independent factors of low QOL. Pulmonary sarcoidosis patients with exercise intolerance had the most significant reduction of the physical (p=0.037) and psychological components of health (p=0.033). **Conclusion.** Factors of QOL reduction in patients with sarcoidosis were female sex and clinically significant pulmonary sarcoidosis. In patients with low QOL, CPET can be used to determine the PWC and mechanisms of its reduction. The presented diagnostic algorithm will optimize the choice of therapy for patients with sarcoidosis.

Key words: *pulmonary sarcoidosis, quality of life, physical exercise, cardiopulmonary exercise testing*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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DV — due value, QOL — quality of life, CPET — cardiopulmonary exercise testing, FEV_1 — forced respiratory volume in 1 sec, sGCS — systemic glucocorticosteroids, FVC — forced vital capacity, PWC — physical working capacity, VO_2 peak — peak oxygen uptake, SF-36 — SF-36 Questionnaire (Short Form Medical Outcomes Study 36)

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Introduction

Sarcoidosis is a systemic inflammatory disease of unknown etiology, characterized by the formation of non-caseating granulomas with the activation of T-cells, excessive release of chemokines, proinflammatory cytokines, and damage to various organs [1].

Sarcoidosis more frequently affects respiratory organs (up to 95 %) and has diverse clinical manifestations. There is a high proportion of patients with an asymptomatic (up to 70 %) and/or benign course of sarcoidosis in which spontaneous remission is observed within 2 years from the onset of the disease. However, sarcoidosis can become chronic, and its progressive course may result in the development of permanent functional disorders that compromise the quality of life (QOL) and limit the physical working capacity (PWC) of patients [1].

Investigating the QOL is one of the essential tools to assess the subjective state of a patient. QOL is a multifaceted concept and covers the assessment of all areas of human activities. Modern medicine uses a narrower concept of "health-related quality of life", i. e., the assessment of parameters associated and not associated with the disease that make it possible to establish how the disease and treatment affect the patient's psychological and emotional state, and social status. QOL depends on the patient's ability to perform basic physiological functions, pain, and subjective perception of well-being, health or illness. QOL assessment tools include general and specific questionnaires [2]. It was shown that determining the patients' QOL in combination with other examination methods is of major clinical relevance and may be used to assess the treatment efficacy in different chronic diseases, including sarcoidosis [3].

Sarcoidosis affects the patients' psychophysiological state and self-perceived health status, irrespective of the severity of its symptoms. Studies on this issue show a reduction in the overall QOL level, as well as decreased physical and mental well-being, independence and social relationships scale scores [3, 4].

Currently, the study of physical working capacity (PWC) of sarcoidosis patients and the identification of its relationship with QOL is of particular interest. Marcellis R. G. et al. (2011) demonstrated that the QOL level in patients with sarcoidosis (assessed using the WHO questionnaire (WHOQOL-BREF)) varied depending on muscle strength (6-minute walk test, dynamometry of lower and upper extremity muscles) [5]. Pilzak K. et al. (2018) defined the relationship between the QOL in patients with sarcoidosis, as assessed using SF-36 Questionnaire (Short Form Medical Outcomes Study 36), and 6-minute walk test results [6]. The authors of the study noted that the PWC level was associated not only with QOL, but also with everyday physical activities [7].

Other studies used a more informative diagnostic technique to assess the PWC in patients with sarcoidosis, i. e., cardiopulmonary exercise testing with gas analysis (CPET). In particular, the PWC level determined by the peak oxygen uptake (VO_2 peak) dropped 20–30 % of the due values (DV) in patients with sarcoidosis, including those without pulmonary dysfunction. In addition, exercise tests reveal cardiac rhythm disorders, ventilation-perfusion ratio changes, enhanced alveolar-arterial oxygen pressure gradient and diminished breathing reserve in patients with sarcoidosis [1, 8, 9], which may affect the QOL as well.

Despite available literature data showing the reduced QOL and PWC in patients with sarcoidosis [7, 10], the relevance of these studies is limited. This is due to the small number of patients examined (30 to 200), non-homogeneous clinico-radiological phenotypes of sarcoidosis, use of different questionnaires for assessing the QOL and exercise tests for determining the PWC (6-minute walk test, treadmill test, isometric exercise testing, CPET) [2, 7, 10, 11]. Therefore, the objective of this study was to acquire additional knowledge and information about QOL and PWC characteristics in pulmonary sarcoidosis patients.

Materials and methods

The open-label, one-time, observational, comparative study was conducted at the City Clinical

Hospital No. 38 (Nizhny Novgorod). Eighty sarcoidosis patients aged 21 to 64 years (35 (29; 45) years) were examined. The male to female ratio was 1:0.9 (males — 43 (53.8 %); females — 37 (46.3 %)). The disease duration was 3 (2; 4) years. Sixty (75 %) patients had histologically confirmed diagnosis. The inclusion criteria were as follows: pulmonary sarcoidosis diagnosed in accordance with the Federal Guidelines of sarcoidosis diagnosis and treatment [1], age of 18–65 years, patient's consent to participate in the study. The exclusion criteria: PWC-limiting acute respiratory diseases and severe chronic non-contagious diseases at the time of examination (NYHA II–IV chronic heart failure, II–III degree chronic respiratory failure, decompensated forms of diabetes mellitus, cancer).

Clinical symptoms, potential risk factors, pulmonary sarcoidosis onset features (acute or chronic course), extrapulmonary sarcoidosis manifestations, comorbidities, administration of systemic glucocorticosteroids (sGCS) were assessed in all patients.

QOL was assessed using the non-specific SF-36 questionnaire, comprising of 36 questions and 8 scales. The scales in the questionnaire are combined into two cumulative measures of "Physical Health" and "Mental Health". Physical Health includes the following scales: Physical and Role-Physical Functioning, Pain Scale, General Health; and Mental Health includes the scales of Psychological Health, Role-Emotional Functioning, Social Functioning, and Vitality. The scores are assessed cumulatively from 0 to 100 points. The higher each score, the better the QOL according to that parameter.

The comprehensive study of pulmonary function parameters and CPET with gas analysis was conducted using Quark COSMED (Italy) in compliance with the American Thoracic Society (ATS) and European Respiratory Society (ERS) standards [12, 13]. Among spirometric parameters, forced vital capacity (FVC), forced respiratory volume in 1 sec (FEV1), modified FEV_1/FVC index, peak volumetric flow rate and mean forced expiratory flow rate from 25 to 75 % of FVC were assessed. The exercise testing used the incrementally increasing protocol, individually pre-adapted in such a way to ensure that the testing lasted 8 to 12 minutes [12]. The following CPET parameters were assessed: VO_2 peak and oxygen uptake at the anaerobic threshold (VO_2 AT, %), maximum exercise, respiratory rate, respiratory volume, minute ventilation, breathing reserve (BR), heart rate, oxygen pulse (VO_2 to heart rate ratio, ml/beats/min), expired CO_2 and O_2 left expiratory tension ($PetCO_2$ and $PetO_2$, mm Hg), ventilation equivalent for CO_2 (Ve/VCO_2). In addition, diagnostically significant electrocardiogram (ECG) changes were analyzed.

The study was conducted in accordance with the Good Clinical Practices and the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the Biology and Biomedicine Institute of the National Research State University of Nizhny Novgorod named after N. I. Lobachevsky (Protocol No. 33 dated 28.02.2019). All subjects signed the voluntary informed consent.

Statistical processing of the findings was performed using R 3.5.2 software. Quantitative data were presented as a median and interquartile interval: Me (Q_1 — 25th quartile; Q_3 — 75th quartile), and qualitative data — as absolute and percentage values. The Mann-Whitney U-test was used to compare the quantitative data; the Fisher exact test — for nominal variables with two categories; the likelihood-corrected Chi-Squared test ($\chi 2$) — for nominal variables with more than two categories. The variables were classified by the k-means cluster analysis. Multivariate analysis was carried out using binary logistic regression. Null hypothesis of no statistically significant differences was discarded at $p<0.05$.

Results

At the first stage, the comprehensive assessment of QOL was performed for all patients. Findings of the questionnaire (SF-36) survey in pulmonary sarcoidosis patients showed that the QOL parameters were different from 100 % "ideal" health: Physical Health scores — 79.1 (63.9; 90.3), and Mental Health scores — 76.2 (55.9; 87.8).

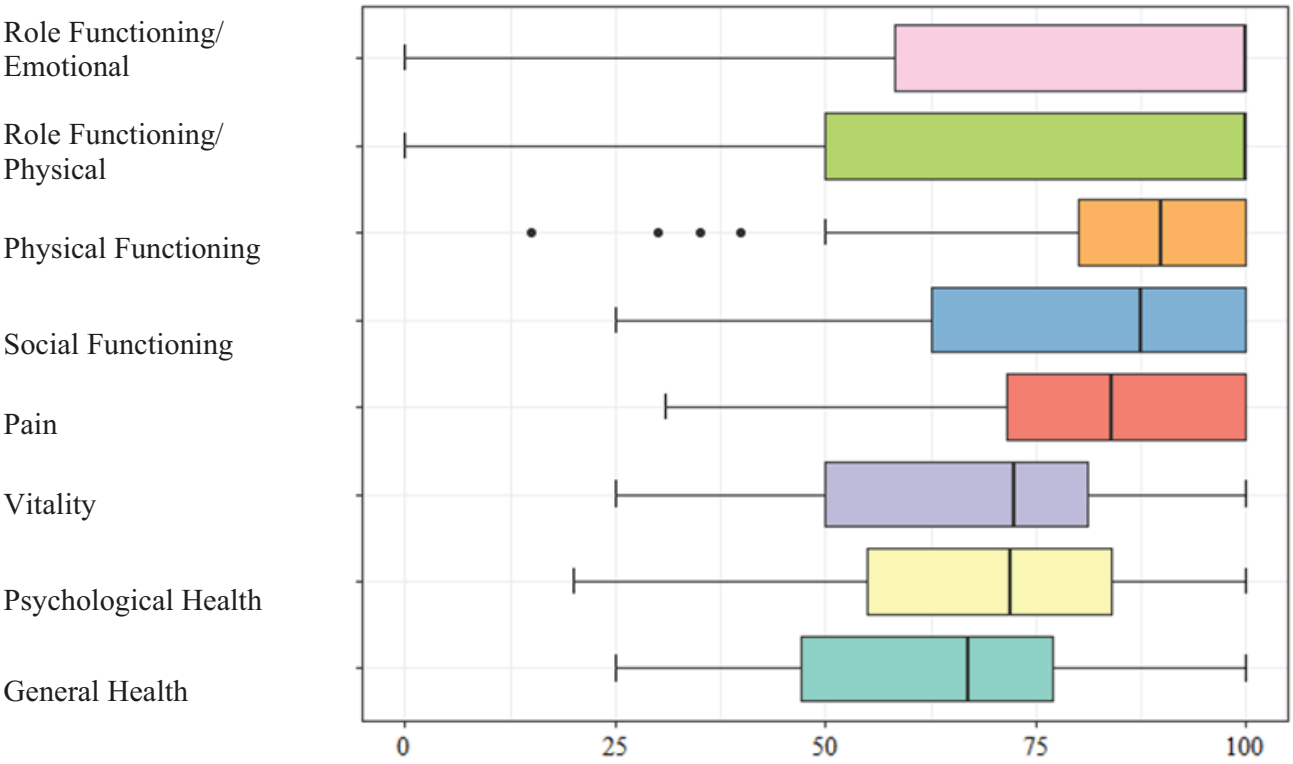

Figure 1. *QOL scores in patients with pulmonary sarcoidosis, taking into account the scales studied (SF-36 Questionnaire)*

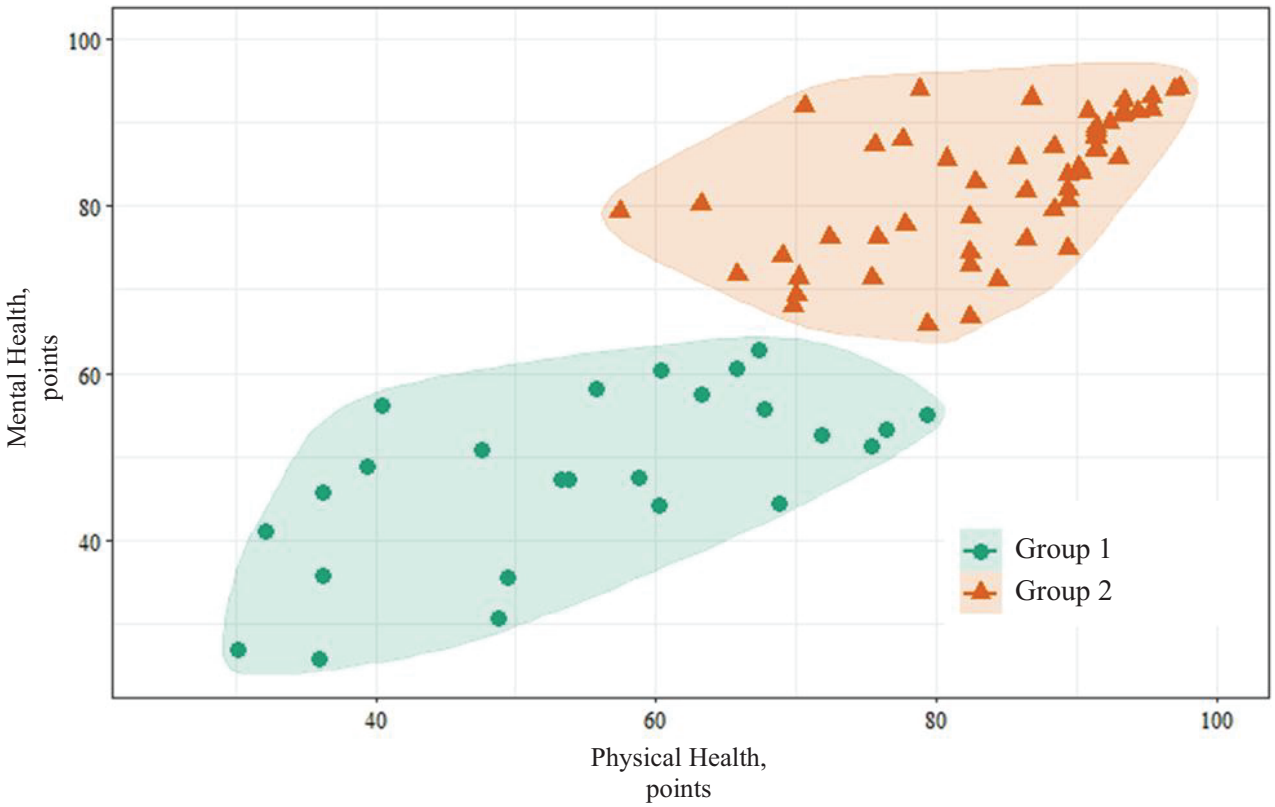

Figure 2. *Scatter diagram for health indicators that determine the QOL level in patients with sarcoidosis (k-means cluster analysis)*

There were no statistically significant differences between the health indicators analyzed (p=0.211). We noted the high QOL scores according to the Role Physical (100 (50; 100)) and Emotional Functioning scales (100 (50; 100)). The dramatic drop in QOL scores was observed on the General Health (67 (47; 77)), Psychological Health (72 (54; 84)) and Vitality scales (72.5 (50; 82.5)) (Figure 1).

To identify groups in the analyzed patient population based on the similarities and differences in the QOL parameters, the k-means cluster analysis was applied in the study. Two variables — Physical and Mental Health — were used as clustering criteria. Based on the clusters obtained, two groups of patients were identified on a provisional basis: Group 1 (n=26) — patients with reduced QOL, Group 2 (n=54) — patients with high QOL (Figure 2).

In Group 1, the median values for both health indicators did not exceed 60 points (Physical Health — 55.7 (40.2; 67.5) points, Mental Health — 48.1 (41; 55.9) points). Mental Health in this group of patients was significantly lower than Physical Health (p=0.039). In Group 2, the median values of Mental Health (85.1 (76.1; 93) points) and Physical Health (87.6 (77.8; 91.4) points) exceeded 80 points and have no differences between each other (p=0.224).

Patients with high QOL were younger (34.5 (29; 40) years) than those with low QOL (40.5 (32; 50) years) (p=0.044). Differences between the groups were determined by gender as well (Table 1).

Table 1. *Comparative characteristics of patients with pulmonary sarcoidosis depending on the QOL level*

Parameter		Group 1 (n=26)	Group 2 (n=54)	p
Age, years		40.5 (32; 50)	34.5 (29; 40)	0.044
Males/females		8 (30.8) / 18 (69.2)	35 (64.8) / 19 (35.2)	0.008
Disease duration, years		3 (2; 5)	3 (1; 4)	0.37
Radiographic stages	1	3 (11.5)	7 (13)	χ^2=0.566, df=2, p=0.754
	2	21 (80.8)	45 (83.3)	
	3	2 (7.7)	2 (3.7)	
Extrapulmonary manifestations		5 (19.2)	5 (9.3)	0.28
Acute and subacute onset		1 (3.8)	5 (9.3)	0.658
Asymptomatic course		4 (15.4)	25 (46.3)	0.012
Fatigue		19 (73.1)	10 (18.5)	<0.001
Cough		18 (69.2)	23 (42.6)	0.033
Dyspnea		10 (38.5)	4 (7.4)	0.001
Comorbidities		10 (38.5)	9 (16.7)	0.049
sGCS, including in past medical history		11 (42.3)	14 (25.9)	0.198
RBC, $*10^{12}$/l		4.5 (4.3; 4.87)	4.8 (4.5; 5.12)	0.099
WBC, $*10^{9}$/l		6.3 (6; 7.1)	6.4 (5.3; 7.3)	0.861
Hemoglobin, g/l		140 (133; 149)	145 (138; 157)	0.123
PLT, $*10^{9}$/l		217.5 (201; 241)	225 (204; 259)	0.622
Erythrocyte sedimentation rate, mm/hour		9 (4; 13)	5 (3; 13)	0.204

Note: data are presented as median and quartiles (Me (Q1; Q3)) or absolute and percentage values (n (%)), p — statistical significance of differences between the groups; χ^2 — chi-square; df — degree of freedom

Group 1 was dominated by females, while Group 2 had more males (p=0.008). Respondents with low QOL more frequently reported fatigue (p<0.001), cough (p=0.033) and dyspnea (p=0.001), and Group 2 was characterized by prevailing asymptomatic course of sarcoidosis (p=0.012). There were more comorbidities among the patients in Group 1 (p=0.049), of which 77.7 % were cardiovascular diseases. The analyzed groups of patients were comparable by the incidence of extrapulmonary manifestations, disease duration, radiographic stages of pulmonary sarcoidosis, and sGCS administration. Complete blood counts in patients with pulmonary sarcoidosis were normal and showed no differences between the groups.

In most cases, respiratory function parameters at rest in the examined patients were normal (>80 % DV) and comparable between the groups (Table 2).

Mild FVC reduction was diagnosed in three cases (1 patient in Group 1, and 2 patients in Group 2; p=1), mild obstructive disorders (FEV1 60–80 % DV) — in 7 patients (1 patient in Group 1, and 6 patients in Group 2; p=0.418).

To identify QOL-affecting factors, binary logistic regression analysis was performed using direct and reverse step-by-step inclusion of variables, for which the differences between the groups were revealed. Based on the analysis results, it was established that only the female sex (OR 3.26, 95 % CI 1.15–9.23; p=0.026) and clinically

Table 2. *Pre-test spirometry parameters in patients with pulmonary sarcoidosis depending on the QOL level*

Parameters	Group 1 (n=26)	Group 2 (n=54)	p
FVC, DV %	101.5 (98; 108)	103.5 (97; 114)	0.488
FEV_1, DV %	96.5 (92; 105)	99 (88; 107)	0.886
FEV_1/FVC	0.82 (0.77; 0.86)	0.79 (0.76; 0.84)	0.265
PEF, DV %	85.5 (77; 100)	94.5 (86; 106)	0.077
MEF25-75, DV %	88 (58; 98)	79 (64; 98)	0.7

Note: data are presented as median and quartiles (Me (Q1; Q3)); PEF — peak expiratory flow; MEF25-75 — mean forced expiratory flow rate from 25 to 75 % of FVC; p — statistical significance of differences between the groups

Table 3. *CPET parameters in patients with pulmonary sarcoidosis depending on the QOL level*

Parameters	Group 1 (n=26)	Group 2 (n=54)	p
Maximum exercise, W	122.5 (100; 125)	182.5 (130; 220)	<0.001
VO_2 peak, ml/min	1,632.9 (1,242.7; 1,943)	2,222.1 (1,692.8; 2,828.7)	<0.001
VO_2 peak, ml/min/kg	21.2 (18.1; 26.5)	29.2 (22.4; 33.3)	<0.001
VO_2 peak, DV %	82 (72.5; 93.5)	85 (77; 94)	0.494
Respiratory rate, movements/min	32.2 (27.9; 35.1)	33 (28.4; 39.5)	0.355
Respiratory volume, l	1.6 (1.3; 2.5)	2.2 (1.8; 2.7)	0.002
Minute ventilation, l/min	49.8 (43.6; 66.2)	77.5 (61.2; 93.6)	<0.001
CO_2 left expiratory tension, mm Hg	38 (34; 40)	39 (35; 42)	0.506
Oxygen pulse, ml/beats/min	10.4 (8.6; 11.6)	12.7 (10.1; 16.5)	0.012
Breathing reserve, %	49 (44; 64)	49 (37; 57)	0.149

Note: data are presented as median and quartiles (Me (Q1; Q3)); p — statistical significance of differences between the groups

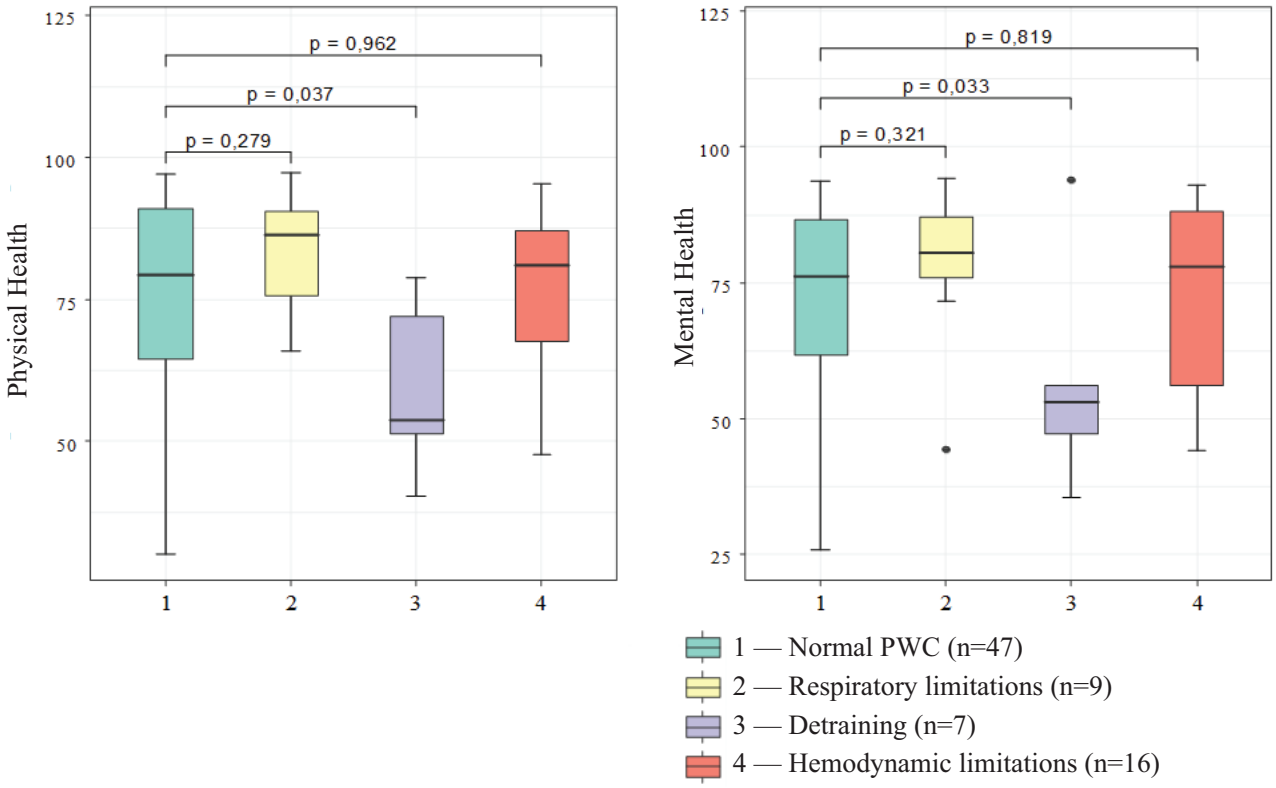

Figure 3. *Quality of life parameters in patients with pulmonary sarcoidosis depending on types of functional limitations (n=79)*

significant manifestations of sarcoidosis (OR 3.63, 95 % CI 1.06–15.47; p=0.041) were independent factors for higher probability of QOL reduction. In other cases, no statistically significant impact of the variables was identified (p>0.05).

At the second stage, the comparative analysis of CPET parameters was performed. Patients in Group 1 showed a statistically significant reduction in maximum exercise (p<0.001), VO_2 peak (ml/min and ml/min/kg) (p<0.001), respiratory volume (p=0.002), minute ventilation (p<0.001) and oxygen pulse (p=0.012) as compared to Group 2. VO_2 peak reflected in DV % was comparable in both groups (p=0.494) (Table 3).

In order to clarify the impact of the reasons for PWC reduction on the QOL in pulmonary sarcoidosis patients, the exercise testing results were analyzed in accordance with the American Thoracic Society recommendations [12] with the aim to identify leading limiting pathophysiological mechanisms.

Depending on functional limitation types, the following groups were formed: patients with normal PWC (n=47), detrained patients (n=7), persons with hemodynamic (n=16) and respiratory abnormalities (n=9). In one patient, PWC reduction was related to obesity (this patient was disregarded in the analysis).

Figure 3 shows the QOL comparison results (Physical and Mental Health) for sarcoidosis patients with normal PWC and various functional limitations based on the exercise testing. It should be noted that the lowest Physical and Mental Health was reported in detrained persons versus other analyzed groups (p<0.05). Moreover, detrained patients with pulmonary sarcoidosis had lower QOL scores according to the Physical (p=0.009) and Social (p=0.025) Functioning scales, Role-Physical (p=0.03) and Emotional (p=0.011) Functioning scales as compared to patients with normal PWC.

Discussion

The QOL of a patient assessed by the questionnaire survey is a subjective diagnostic tool, but is still important for a doctor. This is mainly because not only laboratory and instrumental health indicators are important for every patient, but also the sense of well-being in respect of the physical, mental and social aspects. In this study, 63.7 % of respondents with pulmonary sarcoidosis had a high QOL score according to the key parameters of the SF-36 Questionnaire. This score was probably related to specific features of the enrolled patients (more frequently — with asymptomatic course (36.3 %) or minimum clinical manifestations, rarely — with extrapulmonary damages (12.5 %) and impaired pulmonary ventilation at rest (8.7 %), lack of "honeycomb" changes in lung parenchyma according to the high-resolution computer tomography).

This study found no significant differences in the QOL depending on the incidence of extrapulmonary manifestations of sarcoidosis, while there were opposite results in the available literature [14]. This is probably related to the localization and severity of extrapulmonary damages. It is known that the QOL is significantly compromised by cardiac sarcoidosis due to the high risk of life-threatening complications and side effects of high doses of sGCS [15], as well as visual organ and nervous system damages that may lead to permanent functional impairments. Only mild systemic manifestation of skin changes (non-granulomatous erythema nodosum) was observed in the study population of pulmonary sarcoidosis patients.

The reduction of QOL in patients with sarcoidosis may be considerably due to comorbidities and concomitant conditions, the number of which increases with age. According to A. A. Vizel et al. (2018), the incidence of comorbidities in sarcoidosis patients over 55 years old is higher than 70 % [16]. In this study, a comorbid condition was reported in every fifth patient and was associated with low QOL.

The study findings made it possible to identify relevant factors affecting the reduction of QOL in patients with sarcoidosis: female sex and clinically significant symptoms, which in some cases is consistent with findings of foreign authors [17, 18].

The maximum exercise and VO_2 peak (ml/min/kg) based on the exercise testing in patients with low QOL were substantially lower than in the group with retained QOL. The results may be related to the prevailing number of female patients in Group 1, in whom VO_2 peak (ml/min/kg) is consistently lower than in males. This fact has been confirmed by the lack of significant differences in VO_2 peak (DV %) between the groups, when the patient's sex, age, height and weight were taken into account, and this demonstrates that the PWC was comparable between the groups. Similar results and their justification are provided by Pilzak K. et al. (2018) [6].

The ability to do physical exercise depends not only on the somatic musculature status, but also on the coherence of the cardiorespiratory system, which supplies oxygen to tissues [12, 13]. In this paper, the comparative appraisal of QOL in patients with sarcoidosis was performed for the first time, taking into account PWC, as assessed in the standardized exercise testing, as well as depending on the limiting mechanism. This approach to the QOL analysis in pulmonary sarcoidosis patients with reduced PWC and various functional limitations revealed that subjective health assessment is least in detrained patients. These data suggest that active physical exercise in patients with sarcoidosis may positively affect the QOL. Some evidence of the positive impact of respiratory muscle exercise using respiratory exercisers with inspiratory pressure increase for 30 minutes twice a day for 6 weeks, including on the QOL in patients with sarcoidosis, was provided in the study conducted by Karadallı M. N. et al. (2016) [19].

Conclusion

The study results for the QOL in patients with pulmonary sarcoidosis demonstrated the reduction in this health indicator in 32.5 % of cases. The deterioration of QOL was related to reductions

in both mental and physical health. The QOL-decreasing factors for sarcoidosis patients were the female sex and clinically significant progress of the disease.

The CPET with gas analysis in sarcoidosis patients revealed that the PWC decreased in patients with pulmonary sarcoidosis due to various reasons: cardiorespiratory system disorders, weak peripheral musculature, ventilation limitations. At the same time, it was shown that the subjective QOL assessment by patients with sarcoidosis was primarily affected by detraining.

Thus, the QOL investigation and monitoring in patients with sarcoidosis is a valuable cost-effective tool to identify groups of patients, including those with paucisymptomatic progress and retained functional capacity of lungs at rest, for whom it is appropriate to perform CPET with gas analysis in order to diagnose latent PWC limitations and determine its reduction mechanisms. Such a diagnostic algorithm can optimize the selection of therapy for patients with sarcoidosis.

Author Contribution

A. L. Gudim (ORCID ID: https://orcid.org/0000-0002-8509-7133): collection of clinical materials, collection and processing of materials, analysis and interpretation of study results, writing

L. B. Postnikova (ORCID ID: https://orcid.org/0000-0002-8509-7133): article concept and design, text editing, final manuscript approval

V. A. Kostrov: collection of clinical materials

A. A. Mironov (ORCID ID: https://orcid.org/0000-0001-7387-286): collection of clinical materials

N. I. Kubysheva: text writing and editing

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

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Selection of Medications in Comorbidity

Abstract

New classification divides medications on five classes by influence on comorbid diseases and conditions and rates drug's effects as favorable (A), possible (B), neutral (C), undesirable (D), and unfavorable (X). Class A includes drugs used in treatment of comorbid disease, class B embraced drugs with positive influence, class C includes drugs without significant influence or contradictory influence, class D consist of drugs with possible non-severe adverse effects, and class X includes drugs with severe adverse effects. The more universal drug classification according to influence on comorbid diseases can include and unite other classifications. Classification may help unify marks of positive and negative influences drugs on comorbidity and help practitioners in selection of effective and safe treatment.

Key words: *comorbidity, treatment, classification of medicines*

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In clinical settings, the choice of medication for patients with comorbid diseases and conditions often presents challenges, since it is necessary to take into account the scattered and often contradictory information provided in the instructions for use, clinical guidelines and articles. Few works systematize information on the treatment of diseases in comorbid conditions.

Instructions for use in the sections of side effects, contraindications, special instructions, and use in cases of renal and hepatic dysfunction are not sufficiently adapted for making clinical decisions and are often outdated. Sections of comorbidity in different guidelines are concise, not always informative enough, or may not be available at all. Specialized articles describe the problem in more detail, but the probability of inaccurate statements is higher.

For convenient information handling, classifications that group objects with similar characteristics are widely used. The study of the problem of choosing medications for the treatment of diseases in the conditions of comorbidity allowed us to propose a classification that includes five classes with a favorable, possible, neutral, undesirable and unfavorable effect on comorbid diseases and conditions [1].

In order to improve and make it easier to use, this paper proposes to supplement the classification with letters that are used in many international classifications and are familiar to medical practitioners (Table 1). A similar approach is used in the classifications of the safety of medication in pregnancy, first proposed by the United States Food and Drug Administration (FDA), and the FORTA classification (Fit fOR The Aged), which separates

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Table 1. *Classification of medicines by their effect on comorbid diseases and states*

Class	Effect of the medicine	Effect on comorbid diseases and conditions
A	FAVORABLE	The medicine can be used as a monotherapy
B	POSSIBLE	Moderate therapeutic effect
C	NEUTRAL	The medicine does not have a significant effect or there are not enough data to assess the effect
D	UNDESIRABLE	Rare risk of deterioration
X	UNFAVORABLE	High incidence of life-threatening complications

medicines according to their effectiveness and safety in elderly and senile patients [2].

The proposed classification of medicines by their effect on comorbid diseases and conditions is more versatile and allows us to include well-known specialized classifications.

The main problem with correct ranking of medicines is the lack of more reliable randomized controlled trials in patients with severe comorbid diseases. The latter are usually excluded from clinical trials in order to more objectively assess the effect of the medicine and reduce the number of adverse side effects [3]. Therefore, the main source of information is the findings of less accurate observational studies and registers. In recent years, mathematical techniques have been used more often to improve the accuracy of observational research results by leveling differences in patient groups [4]. The opinion of expert groups is widely used, which prevails in modern guidelines. For example, in influential American and European cardiac guidelines, only 8–14% of the statements confirmed in a large randomized study or meta-analysis of the latter can be considered reliable, while 41–55% are based only on the opinion of experts.

Practitioners often experience difficulties when choosing medications to treat diseases in patients with concomitant liver disease. Information on such clinical situations is more difficult to find than in such combinations as hypertension and renal dysfunction or atrial fibrillation in patients with coronary syndromes.

Table 2. *Classification of medicines for the treatment of chronic coronary syndrome according to the effect on liver cirrhosis*

Class	Medicines
A	Non-selective beta blockers
B	$Beta_1$-blockers, isosorbide mononitrate, statins
C	Calcium antagonists, molsidomine, nitrates, nicorandil, trimetazidine
D	Antiaggregants
X	Ranolazine, rivaroxaban

Here we consider the use of classification when choosing treatment for patients with various types of chronic coronary syndrome, heart failure, and mental disorders in combination with severe chronic liver disease at the stage of cirrhosis. The urgency of the problem relates to the fact that cardiovascular diseases significantly increase mortality, and mental disorders reduce the quality of life of patients with liver cirrhosis and persist in a significant part of patients after liver transplantation [5–8].

The paper does not set a task to justify in detail and strictly justify the assignment of medicine in different categories, which may be the subject of discussion due to the lack of reliable research, but to demonstrate the practical feasibility, principles of development and the possibility of applying the classification.

Classification of the medicines for the treatment of coronary heart disease in combination with liver cirrhosis is presented in Table 2.

Class A includes non-selective beta-blockers that reduce portal venous pressure by narrowing the vessels and reducing cardiac output. These medicines are essential for primary and secondary prevention of bleeding from enlarged esophageal veins, and can reduce mortality and the risk of hepatocellular carcinoma [9, 10].

Among nitrates, it is preferable to use isosorbide mononitrate, since isosorbide dinitrate is converted to active mononitrate in the liver and has variable bioavailability (10–90%). The effect of isosorbide mononitrate on portal pressure is lower than non-selective beta-blockers, and so the medicine is used in combination with beta-blockers [11].

There is a very common wariness among patients and doctors about possible liver damage when using statins. At the same time, many studies show a positive effect of statins on the course of even very severe liver diseases, which allowed the medicines to be classified in class B. Statins have been shown to reduce the severity of liver fibrosis, the frequency of decompensation of liver cirrhosis, and even mortality [12, 13]. Statins can also slightly reduce portal hypertension by reducing intrahepatic vascular resistance [14]. According to a meta-analysis of observational studies, treatment with statins was associated with a 37% reduction in the risk of developing hepatocellular carcinoma [15]. A change in the stance on statins has been noted in the latest recommendations on liver cirrhosis [16].

Antiaggregants that are assigned to class D may increase the risk of bleeding in case of vitamin K-dependent coagulopathy, thrombocytopenia, esophageal varices, erosive ulcerative lesions of the stomach, which are usually found in the setting of severe liver cirrhosis.

Ranolazine, which has antiarrhythmic properties along with antiischemic effect, is contraindicated in case of liver cirrhosis, because the concentration of medicine increases by 80% already in moderate liver dysfunction with a 3-fold increase in QT prolongation frequency. The latter is especially dangerous in the presence of heart diseases.

A recently completed COMPASS study raised a question regarding the possibility of applying rivaroxaban in small doses in patients with stable atherosclerosis. In this case, it should be taken into account that rivaroxaban is not recommended in patients with liver cirrhosis, even in Child-Pugh class B, because the exposure of medicine increases more than twice and the risk of large bleeding increases [17, 18].

Table 3 presents a classification of medicines for the treatment of chronic heart failure with concomitant liver cirrhosis. Along with cardiogenic heart failure, cirrhotic cardiomyopathy should be noted [19].

One of the frequent life-threatening complications of liver cirrhosis is bleeding from the esophageal varices. Non-selective beta-blockers are recommended for primary and secondary prevention of varicose bleeding and mortality reduction, of which only carvedilol is approved for treatment of systolic heart failure. The latter reduces portal pressure, also due to the alpha-blocking effect. Diuretics and spironolactone are used to correct ascites caused mainly by portal hypertension and hypoalbuminemia. Eplerenone can be prescribed during development of painful gynecomastia in patients taking spironolactone [20].

Table 3. *Classification of medicines for the treatment of chronic heart failure according to their effect on liver cirrhosis*

Class	Medicines
A	Diuretics, carvedilol, spironolactone
B	Beta$_1$-adgeneric blockers, eplerenone
C	Digoxin, ivabradine
D	Angiotensin converting enzyme inhibitors, angiotensin II receptor blockers

Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers can reduce portal pressure and fibrosis development, but there is an increased risk of hypotension and renal dysfunction with decompensation of liver disease [21–23].

It is obvious that the proposed classification is not without shortcomings, and as a result of consideration and discussion can be significantly improved, including clarification of the criteria for assigning a medicine to a particular class, as well as verification of systematically collected evidence-based medicine data. It was important to show the principles and approaches to the development and use of the original classification.

The proposed classification of medicines by their effect on comorbid diseases and conditions allows us to unify the assessment of the positive and negative impact of treatment of the main disease, can significantly facilitate the work of the doctor and optimize the treatment of patients, taking into account the principles of individual approach.

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Status of Cardiovascular System in Patients with Chronic Obstructive Pulmonary Disease According to the Results of a Pulse Wave Contour Analysis

Abstract

The combination of chronic obstructive pulmonary disease and cardiovascular disease is an urgent public health problem that determines more severe disease course and poor prognosis for the patient. **The objective of the study** was to evaluate the cardiovascular system state using applanation tonometry in patients with chronic obstructive pulmonary disease depending on the severity of bronchial obstruction. **Material and methods.** Applanation tonometry was performed in 60 patients (56 men, age 63.5 [IQR 59; 70] years) with chronic obstructive pulmonary disease to assess central hemodynamic parameters. The severity of obstructive disorders was determined by spirometry after bronchodilator use. **Results.** In case of progression of bronchial obstruction, a decrease in parameters characterizing coronary blood flow was detected, mainly determined by an increase in heart rate and by a decrease in the duration of diastole. In addition, higher values of augmentation pressure corrected to heart rate of 75 bpm, pulse pressure, central pulse height at the point of maximum rise of direct pulse wave were determined in patients with more severe bronchial obstruction. These parameters indicate higher values of arterial stiffness in this group of patients. **Conclusion.** In patients with chronic obstructive pulmonary disease and high values of bronchial obstruction, there is an imbalance of myocardial load and actual blood supply, and increased arterial stiffness with impaired aortic damping function, which contributes to the development of cardiovascular disease in this group of patients.

Key words: *chronic obstructive pulmonary disease, spirometry, pulse waveform contour analysis, applanation tonometry, central hemodynamics, subendocardial viability ratio*

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Aix_{75} — augmentation index corrected to HR of 75 beats per minute; C_AP_{75} — augmentation pressure corrected to HR of 75 beats per minute; C_DPTI — central diastolic pressure time index; C_MPD — central mean pressure in diastole; C_MPS — central mean pressure in systole; C_P_{T1h} — central pulse height at the point of maximum rise of direct pulse wave;

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C_SEVR — central subendocardial viability ratio; C_TTI — central tension time index; COPD — chronic obstructive pulmonary disease; CVD — cardiovascular disease; DBP — diastolic blood pressure; DBP_c — central diastolic blood pressure; DD — duration of diastole; $DD_{\%}$ — duration of diastole relative to the period of cardiac cycle; ED — duration of systole; FEV1 — forced expiratory volume in the first second; HR — heart rate; PBP — pulse blood pressure; PBPc — central pulse blood pressure; P_MAX_DPDT — maximum rise rate of peripheral pulse wave; $SatO_2$ — blood saturation; SBP — systolic blood pressure; SBPc — central systolic blood pressure; VC — vital capacity of lungs

Introduction

Today, much attention is paid to the comorbidity of chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVD). This combination of nosologies is an urgent public health problem due to the high prevalence of CVD among patients with COPD, its complex therapy and the high mortality rate of such patients. According to the World Health Organization (WHO), mortality from COPD is ranked 3rd, and according to the TORCH (2007) study, CVD is the cause of death in one in four patients suffering from COPD [1]. A retrospective study of a large group of patients (more than 900 thousand people), conducted by Cazzola M., et al. (2012), showed higher risks of CVD in patients with obstructive diseases such as bronchial asthma and COPD [2]. In addition, a twice as high risk of CVD was proven for patients with COPD in the presence of severe bronchial obstruction [3].

Assessment of the state of the cardiovascular system in patients with COPD is relevant for the detection of CVD and assignment of adequate treatment. One of the state-of-the-art methods of cardiovascular system examination is pulse waveform contour analysis, which allows assessing the levels of central blood pressure and arterial stiffness parameters and revealing an imbalance between the myocardial load and coronary perfusion — parameters that have an effect on the prognosis for the health and life of a comorbid patient [4].

Objective: to assess the state of the cardiovascular system in patients with COPD based on the results of a pulse waveform contour analysis depending on the severity of bronchial obstruction.

Materials and Methods

We examined 60 patients (56 men and 4 women, 63.5 [IQR 59; 70] years) who had been diagnosed with COPD in the pulmonology departments of the Regional State Budgetary Healthcare Institution «Smolensk Regional Clinical Hospital» and the Regional State Budgetary Healthcare Institution «Clinical hospital № 1».

Criteria for the inclusion of patients in this study were the following: confirmed diagnosis of COPD, forced expiratory volume in the first second less than 70%, modified Tiffeneau index less than 0.7.

Exclusion criteria were as follows: heart failure of functional class II-IV, permanent atrial fibrillation, lack of patient cooperation during spirometry.

To evaluate pulmonary function, all patients underwent spirometry 20 minutes after taking salbutamol at the dose of 400 μg. Forced expiratory volume in the first second (FEV_1), vital lung capacity (VC) and modified Tiffeneau index (FEV_1/FVC) were assessed.

Parameters of central hemodynamics were found using applanation tonometry (SphygmoCor). The following parameters were assessed: heart rate (HR), levels of peripheral and central systolic, diastolic and pulse blood pressure (SBP, DBP, PBP, SBPc, DBPc, PBPc), central mean pressure in systole and diastole (C_MPS, C_MPD), maximum rise rate of peripheral pulse wave (P_MAX_DPDT), central pulse height at the point of maximum rise of direct (antegrade) pulse wave (C_P_{T1h}), pressure and aortic augmentation index corrected to the heart rate 75 beats per minute (C_AP_{75}, Aix_{75}), diastole duration (DD), systole duration (ED, ejection duration), ratio of diastole duration to cardiac cycle duration, as a percentage ($DD_{\%}$). The P_MAX_DPDT parameter, according to the literature, reflects myocardial contractility [5]. C_AP_{75} and Aix_{75} were used as parameters of the stiffness of the arterial bed [6]. To assess the load on the myocardium, we used the Central Tension Time Index (C_TTI), which was defined as the area under the systolic part of the pulse curve [7]. The area under the diastolic part of the pulse curve, or Central Diastolic Pressure Time Index

(C_DPTI), was used as a parameter for subendocardial perfusion. The ratio of C_DPTI to C_TTI expressed as a percentage and referred to as the Central Subendocardial Viability Ratio (C_SEVR) characterized the ratio of coronary blood flow to the load on the myocardium (myocardial oxygen demand) [8]. Applanation tonometry was performed in the morning before taking antihypertensive drugs and after the time of action of taken bronchodilators.

Patients were divided into 3 equal groups of 20 people relative to FEV_1 tertiles. Group 1 included patients with FEV_1 less than the first tertile, which amounted to 43.10%; group 3 included patients with FEV_1 more than the second tertile, which equals 56.37%; group 2 included patients with FEV_1 between the first and second tertile.

Data are presented as Me (IQR), where Me is the median, and IQR is the interquartile range: 25th percentile — 75th percentile. To compare hemodynamic parameters in the studied groups, the Kruskal-Wallis test was used. For posteriori pairwise comparisons, Dunn's test was used. For correlation analysis, the Spearman rank correlation coefficient was used. Statistical hypotheses were checked at a significance level of $p<0.05$. Statistical processing was carried out using MS Office Excel 2007 and Statistica 10 software packages.

Results

Characteristics of study group: 56 men and 4 women aged 63.5 [59; 70] years; height — 172 [167; 175.3] cm; body weight — 69.5 [60; 83.3] kg; body mass index (BMI) — 24.4 [21.3; 26.1] kg/m^2; tobacco exposure — 50 [35; 60] packs/years; severity of dyspnea according to mMRC — 2 [1; 2]; severity of symptoms according to the results of COPD Assessment Test (COPD Assessment Test, CAT test) — 19.5 [14; 26] points. Blood saturation ($SatO_2$) at rest was 95 [93; 96] %. According to the history and examination results, hypertension was revealed in 43 patients (71.7%). Parameters of pulmonary function and applanation tonometry are shown in Tables 1 and 2.

Groups of patients with bronchial obstruction of different severity did not differ in age, anthropometric parameters, and tobacco exposure. Groups were comparable in the number of patients with hypertension (15 (75%) patients in group 1, 14 (70%) — in groups 2 and 3). Characteristics of groups of patients with COPD and different severity of bronchial obstruction are shown in Table 3. Hemodynamic parameters in three groups of patients obtained by dividing patients by the level of FEV_1 are presented in Table 4.

Table 1. *Spirometry parameters in patients with chronic obstructive pulmonary disease (n = 60) after the use of bronchodilator*

Parameter	Value, Me (IQR)
FEV_1, L	1.5 [1.1; 1.8]
FEV_1, %	53.1 [38.5; 58.5]
FEV_1/FVC, %	46 [37.3; 52.7]
VC, L	3.5 [3; 4.4]
VC, %	90.3 [80.9; 107.1]

Table 2. *Hemodynamic parameters in patients with chronic obstructive pulmonary disease (n = 60)*

Parameter	Value, Me (IQR)
Peripheral hemodynamic parameters	
SBP, mm Hg	132 [120,8; 145]
DBP, mm Hg	83,5 [75; 90]
PBP, mm Hg	47 [41; 60]
HR, bpm	75 [69; 85]
P_MAX_DPDT, mm Hg/s	729 [610; 978.3]
Central hemodynamic parameters	
SBP_c, mm Hg	121 [110; 130.3]
DBP_c, mm Hg	85 [76; 91]
PBP_c, mm Hg	35.5 [31; 45.3]
C_MPS, mm Hg	112.5 [100.8; 120]
C_MPD, mm Hg	95.5 [85; 102.3]
C_P_{T1h}, mm Hg	26 [23; 34]
C_AP_{75}, mm Hg	9.5 [6; 12]
Aix_{75}, %	25 [19; 30.3]
ED, ms	278 [258.8; 299]
DD, ms	522.5 [454.8; 587.3]
$DD_{\%}$, %	64 [62; 67]
C_TTI, mm Hg*s/min	2,361 [2,054; 2,660]
C_DPTI, mm Hg*s/min	3,701 [3,328; 4,035]
C_SEVR, %	156 [138.8; 179]

Table 3. *Characteristics of groups of patients with chronic obstructive pulmonary disease and different severity of bronchial obstruction*

Parameter	Group 1 (FEV_1<43.10%) n = 20	Group 2 (FEV_1 = 43.10-56.37%) n = 20	Group 3 (FEV_1>56.37%) n = 20	H	p-value
Age, years	69 [62.3; 71]	61.5 [58; 67.3]	63.5 [61; 70]	5.11	0.0777
Height, cm	170.5 [168.8; 175]	170.5 [165.5; 178]	172 [169.3; 175]	0.21	0.8994
Weight, kg	62 [57.8; 76]	72 [66.5; 92.3]	75 [63; 84.3]	4.41	0.1105
BMI, kg/m²	21.8 [20.3; 24.5]	24.6 [21.7; 30]	25.1 [21.9; 26.1]	4.77	0.0922
Tobacco exposure, packs/years	54 [33.8; 67.1]	47.5 [33.8; 51.3]	45 [41.5; 55.3]	1.75	0.4167
$SatO_2$, %	93 [92; 94.3]	95 [94.8; 96.3]	95 [95; 96]	9.71*	0.0078

***** — difference is significant between groups 1 and 2, 1 and 3 at p<0.05

Table 4. *Applanation tonometry parameters in patients with chronic obstructive pulmonary disease and different severity of bronchial obstruction*

Parameter	Group 1 (FEV_1<43.10%) n = 20	Group 2 (FEV_1 = 43.10-56.37%) n = 20	Group 3 (FEV_1>56.37%) n = 20	H	p-value
Peripheral hemodynamic parameters					
SBP, mm Hg	138 [120; 147.8]	135 [120.8; 145.5]	132 [121.8; 137.8]	0.70	0.7032
DBP, mm Hg	79 [70; 85.8]	86 [80; 91.8]	85 [77.3; 92.3]	5.04	0.0804
PBP, mm Hg	60 [47.5; 70.5]	44.5 [40.8; 54.3]	44.5 [40; 51.8]	7.37	0.0251
HR, bpm	90 [76; 95.3]	71 [68.3; 78]	70 [67.8; 76.8]	19.69*	0.0001
P_MAX_DPDT, mm Hg/s	996 [674.8; 1,188]	641 [578.5; 769.5]	702.5 [620.3; 837.5]	8.73**	0.0127
Central hemodynamic parameters					
SBP_c, mm Hg	118.5 [108; 132]	123.5 [114.8; 137.5]	120 [112.8; 126.3]	0.67	0.7168
DBP_c, mm Hg	80 [71; 87.3]	87.5 [81; 92.8]	86 [78.3; 93.3]	4.19	0.1232
PBP_c, mm Hg	42 [34.8; 50]	33.5 [30.8; 42.3]	33.5 [29.5; 40]	4.84	0.0890
C_MPS, mm Hg	108 [97.5; 120.5]	114.5 [106; 124.3]	111.5 [102.8; 116.3]	0.99	0.6098
C_MPD, mm Hg	92 [82.3; 99.3]	97.5 [89.8; 103.5]	96.5 [86.5; 102.5]	2.56	0.2787
C_P_{T1h}, mm Hg	33.5 [25.5; 37.8]	25 [22.8; 31.3]	25.5 [22; 29.5]	6.41	0.0406
C_AP_{75}, mm Hg	11.5 [9.8; 16]	8 [6; 11]	8.5 [4.8; 11]	7.90***	0.0193
Aix_{75}, %	28 [23.8; 32]	22 [19; 29.3]	24 [17; 30.3]	2.31	0.3143
ED, ms	273.5 [250.8; 291.8]	290.5 [277.5; 304.3]	272 [259.5; 287]	3.36	0.1865
DD, ms	392.5 [371.5; 502.5]	554 [482; 593.3]	571 [514.8; 609]	21.95*	<0.0001
$DD_{\%}$, %	60 [57; 63.3]	65.5 [63.8; 67.3]	67 [64; 69.3]	26.65*	<0.0001
C_TTI, mm Hg*s/min	2,472 [2,272; 2,934]	2,372 [2,005; 2,660]	2,168 [1,976; 2,428]	7.54***	0.0231
C_DPTI, mm Hg*s/min	3,267 [3,020; 3,726]	3,793 [3,625; 4,063]	3,778 [3,494; 4,130]	11.16*	0.0038
C_SEVR, %	135 [111.5; 142.8]	165 [147; 180.5]	175 [162.3; 190.5]	29.71*	<0.0001

Note: * — difference is significant between groups 1 and 2, 1 and 3 at p<0.05; ** — difference is significant between groups 1 and 2 at p<0.05; *** — difference is significant between groups 1 and 3 at p<0.05

Patients with the most severe bronchial obstruction (group 1) showed the lowest coronary blood flow efficiency value (C_SEVR) among all three groups due to both a decreased parameter (C_DPTI) characterizing the level of pressure in coronary arteries throughout the diastole and the duration of coronary blood flow, and an increased myocardial load (C_TTI). Decrease in coronary blood flow in group 1 was determined mainly by absolute (DD) and relative ($DD_{\%}$) decrease in diastole duration due to increased HR. In addition, the decreased area of the diastolic part of the central pulse wave and an increased area of the systolic part of the pulse wave occurred due to the earlier return of reflected waves generated at the periphery to the heart, as a result of increased rigidity of main arteries. This is evidenced by an increase in augmentation pressure of central systolic pressure corrected to HR of 75 beats per minute in patients with a more significant impairment of bronchial obstruction. However, no statistically significant differences in the levels of central blood pressure were found. In case of more severe bronchial obstruction, an increased rate of maximum rise of the peripheral pulse wave (P_MAX_DPDT) and of the pressure at the point of maximum rise of the central pulse wave (C_P_{T1h}) was observed. An increase in these parameters and in the peripheral pulse pressure indicates the impaired damping function of the aorta as a result of its increased stiffness in the group of patients with the most severe bronchial obstruction.

Moderate correlation was found between FEV_1 and C_SEVR, FEV_1 and diastole duration, between FEV_1 and HR, between FEV_1 and saturation, between saturation and HR.

Graphical representation of the relationships found is shown in Figures 1-5.

Discussion

Analysis of the relationship between parameters of applanation tonometry and severity of obstructive ventilation disorders indicates increasing discrepancy between actual myocardial blood supply and myocardial load in patients with COPD with disease progression. Pathophysiological processes that develop in the presence of bronchial obstruction can explain deterioration of myocardial blood supply as FEV1 decreases. There is evidence of decreased myocardial contractility in patients with severe and extremely severe COPD, as well as the negative effect of hypoxia and persistent inflammation on myocardial contractility [9]. Decrease in myocardial blood supply seems to be based on HR increase, which rises with the decrease in FEV_1; it is indirectly confirmed by finding correlation between these parameters. On the one hand, HR increase is a compensatory mechanism for supporting tissue perfusion, and is adaptive and protective in case of systolic myocardial dysfunction. On the other hand, specific myocardial blood supply in diastole leads to the fact that, as HR increases, the time for blood perfusion through the coronary arteries is reduced, thereby negatively affecting blood supply to myocardium [10, 11]. However, other mechanisms of the mutual influence of these parameters on the reduction of coronary blood flow cannot be excluded. For example, M. A. Makarova, et al. (2013) demonstrated the effect of hypoxia on the development of endothelial dysfunction in patients with COPD [12]. Impaired endothelial function leads to an increased risk of blood clots in the arterial bed, and to an imbalance of vasoconstrictor and vasodilation mechanisms [13]. In addition, there is evidence of a relationship between persistent inflammation and increased heart rate [14]. Taking into account the age of patients, we can assume an increase in the frequency of cardiac catastrophes in patients with COPD as the ventilation function of lungs decreases; it compares favorably to the results obtained by Canadian researchers (Sin D., et al., 2005), which showed a higher risk of coronary events in patients with COPD with underlying progression of bronchial obstruction [15].

Higher values of C_AP_{75} and pulse pressure in the group of patients with significant bronchial obstruction indicate a higher degree of arterial stiffness. High values of P_MAX_DPDT in this group of patients are probably determined not by increased cardiac output, but by the impaired damping function of rigid aortic wall. In this case, there is no decrease in cardiac output due to the expansion of the aorta in systole; all energy reaches the periphery and leads to a rapid rise of the pulse wave. Impaired damping of the pulse wave is also confirmed by the increased height of the central pulse at the point of maximum rise of the direct pulse wave (C_P_{T1h}).

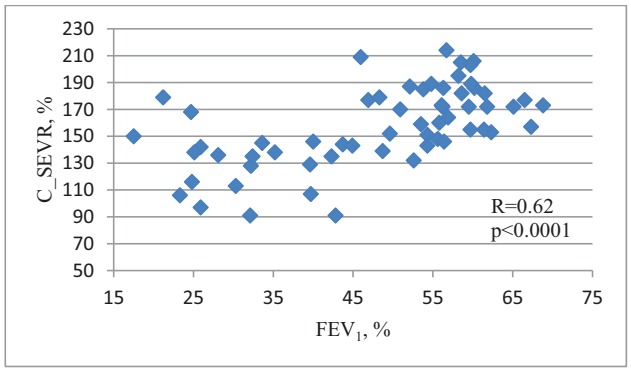

Figure 1. *Scatter plot of C_SEVR relative to FEV_1*

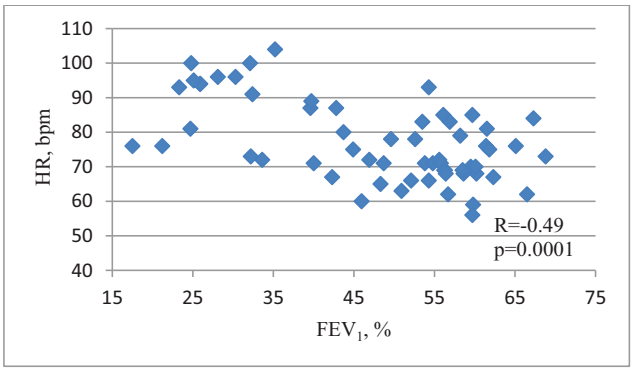

Figure 2. *Scatter plot of HR relative to FEV_1*

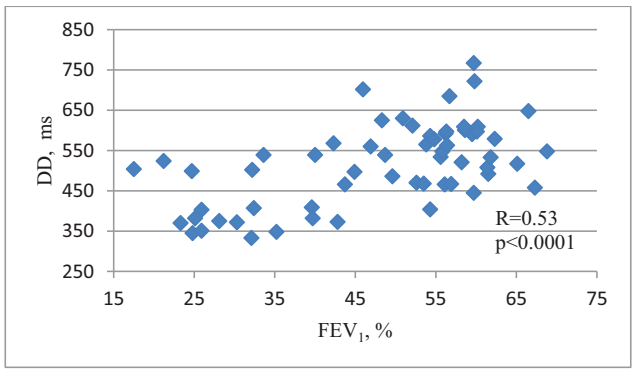

Figure 3. *Scatter plot of DD relative to FEV_1*

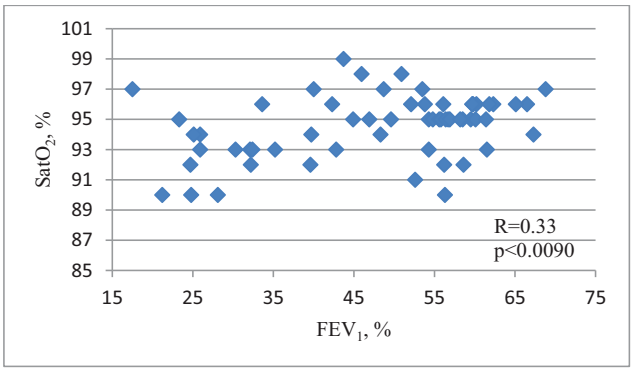

Figure 4. *Scatter plot of $SatO_2$ relative to FEV_1*

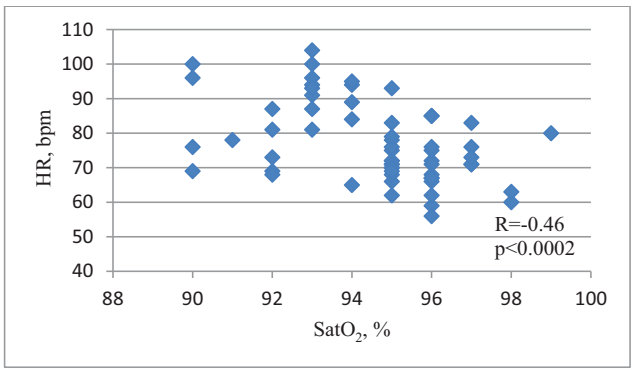

Figure 5. *Scatter plot of HR relative to $SatO_2$*

It was proven that increased vascular rigidity that led to an increase in cardiac output energy has a damaging effect on target organs and is a recognized risk factor for the development of cardiovascular events [4]; it can partly explain the high prevalence of cardiovascular diseases in patients with COPD.

Conclusions

In patients with severe obstruction, increased arterial stiffness with impaired aortic damping function is observed; it results in impaired transfer of systole energy to diastole, which leads to an increase in the pressure of augmentation of the central pulse

wave (C_AP_{75}), the height of central pulse at the point of maximum rise of the antegrade pulse wave (C_P_{T1h}), the maximum rise rate of the peripheral pulse wave (P_MAX_DPDT).

In patients with COPD, as bronchial obstruction increases, an imbalance in the ratio between myocardial load and actual blood supply increases, which can also contribute to the development of cardiovascular pathology in patients with COPD.

Author Contribution

D. A. Punin (ORCID ID: https://orcid.org/0000-0003-3424-4540): study design development, conducting research (spirometry, applanation tonometry), statistical processing, analysis and interpretation of the data, making up the conclusions, manuscript preparation

V. A. Milyagin (ORCID ID: https://orcid.org/0000-0003-0383-1072): a systematic review of the problem and the choice of research direction, study design development, data analysis, making up the conclusions

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Ankylosing Spinal Hyperostosis or Forestier Disease: Difficulty in Diagnosing or Lack of Knowledge?

Abstract

The article demonstrates a clinical case of a disease that occurs mainly in older age groups — ankylosing spinal hyperostosis (ASH), or Forestier disease. The rarity and lack of knowledge of ASH and the associated lack of alertness in relation to this disease makes its diagnosis a challenge. The disease is more common in older people, which requires differential diagnosis with degenerative changes of the vertebrae. ASH is an oligosymptomatic disease. Clinical symptoms are determined not by hyperostosis of the ligaments and tendons by themselves, but by the development of reactive inflammation of these structures during the process of ossification, overloading of still moving segments of the spine adjacent to ankylosed vertebrae. The damage of the anterior longitudinal ligament, the continuity of its ossification for at least four vertebrae (in contrast to trauma, tumors) is of particular importance for this disease. The absence or low severity of ankylosis of the facet joints, sacroiliitis, paravertebral ossification symmetry, characteristic of ankylosing spondylitis, is also important. The absence or mild severity of degenerative changes in the intervertebral discs detected in osteochondrosis matters. The presence of laboratory and clinical signs of inflammation, damage to other organs and systems is not typical to this pathology. At present, we have no treatment standards for ASH, which also makes the choice of patient management approach complicated.

The insufficient amount of information about this disease makes wider coverage of the pathology necessary in order to improve diagnostic skills, timely and complete treatment.

Key words: *ankylosing spinal hyperostosis, Forestier disease, ossification of the anterior longitudinal ligament*

Conflict of Interests

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ASH — ankylosing spinal hyperostosis

Ankylosing spinal hyperostosis (ASH), or Forestier disease, is a rare non-inflammatory disease, with ossification of the anterior longitudinal ligament of the spine. It is part of diffuse idiopathic skeletal hyperostosis, which is characterized by multiple ossification of the tendons, ligaments, aponeuroses,

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capsules of joints. ASH is more common in the elderly (94.5% of patients older than 60 years). The reference value specified is not true (source of information checked), and has been corrected to the true value [1]. The disease occurs without any external cause, and is therefore referred to as idiopathic. Rare occurrence makes it difficult to study the causal factors of ASH. Late onset is a reason to believe that ASH is caused by the aging processes occurring in the connective tissue. Much less often, similar changes occur in young or middle age, and in this case, this is a manifestation of some endocrine or metabolic disease.

The corresponding pattern, named "ankylosing senile hyperostosis" of the spine, was first described by J. Forestier and J. Rots-Querol in 1950. Subsequently, this pathological process was designated as "Forestier disease".

In most cases, the disease is manifested by a lesion in the thoracic spine, often capturing its central part, then the lumbar and cervical sections become involved in the process [2–4]. Ossification starts mainly on the right side, which is presumably due to the absence of aortic pulsation, which prevents calcification of the spine tissues on the left.

Diagnosis of ASH is based mainly on the analysis of X-ray changes [5]. A lateral view is crucial to get an image of the spine and anterior longitudinal ligament. Distinctive features of the disease are: ossification with a sharp thickening of the anterior longitudinal ligament along the entire anterior surface of the vertebrae from the occipital bone to the sacrum, the continuity and extent of ossification at the level of several vertebral segments, the absence of significant changes in the vertebral bodies and intervertebral spaces, and the symmetry of paravertebral ossifications. Less typical for ASH is the formation of osteophytes, ossifications of the posterior longitudinal ligament, and capsules of the facet joints.

ASH is an oligosymptomatic disease. However, debilitating daily pain in many parts of the spine that do not respond to standard therapy may be encountered.

Clinical symptoms: pain, discomfort, stiffness in different parts of the spine are determined not so much by hyperostosis of the ligaments and tendons themselves, but by the development of reactive inflammation of these structures in the process of ossification, overloading of still-mobile segments of the spine adjacent to ankylosed vertebrae. If the thoracic spine is affected, there may be a restriction of the respiratory excursion of the chest; if the cervical spine is involved in the process, dysphagia, dysarthria occur due to compression of the esophagus, larynx, and trachea. In the case of hypertrophy of the posterior longitudinal ligament, there is a threat of compression of the spinal cord with the development of myelopathy, paresis and paralysis [6]. Markers of inflammation do not exceed the norm.

Since there is no clear understanding of the factors that cause ASH, its specific treatment is the subject of exploration and research. To alleviate the condition of patients, symptomatic therapy is used, including the prescription of anti-inflammatory drugs (meloxicam, celecoxib, ibuprofen), magnetic therapy, laser therapy, hydrotherapy (hydrogen sulfide and radon general health baths), massage, exercise therapy (remedial gymnastics). Radiating pain is relieved by local administration of glucocorticosteroids and anesthetics, application of anti-inflammatory medicines, and the prescription of phonophoresis of hydrocortisone ointment. In case of an adverse course of the disease, especially accompanied by compression of internal organs, surgical treatment is possible: using the Cloward technique, the enlarged ossified anterior longitudinal ligament is removed and a fixing plate is implanted on the anterior surface of the vertebral bodies.

The rarity of this pathology makes it preferable to cover individual clinical cases of the disease in order to improve its diagnosis and find the optimal treatment approach.

Here we present a clinical case that demonstrates the peculiarities of the symptoms and diagnosis of ASH.

Patient P., 58, salesperson, was admitted to Rheumatology Department of SHCI "Regional clinical hospital" with complaints of constant pain at the front of the neck, not connected with movements and not increasing at rest, "girdle sensation" around the neck, difficulty in swallowing, especially solid food, dysfunction of phonation of the voice, hoarseness, difficulty of movement in the cervical spine when bending forward and to the side.

From the history of the disease, it is known that in 2016 (at the age of 56 years), she was observed by

a neurologist with complaints of neck pain and related difficulties in spine movements. The diagnosis of osteochondrosis of the cervical spine was established, and drug and physical therapy was carried out with a positive effect. The changes detected during magnetic resonance imaging (MRI) in the cervical spine — ossification of the anterior longitudinal ligament with a length of 35 mm — were not properly evaluated (Figure 1).

In the summer of 2018 (at the age of 58), she suffered acute respiratory infection complicated with purulent otitis. The patient was successfully treated by an ENT specialist, but soon began to notice the above complaints. Outpatient fibrolaryngoscopy was performed, which revealed the mobility of the vocal and scapular ligaments, their symmetry during phonation, a wide glottis, free sinuses, and the absence of changes in the epiglottis and subglottic space. Along the posterior wall of the oropharynx (at the level of the upper edge of the epiglottis), a submucosal formation up to 2 cm in diameter with mucosa that was unchanged and displaced above it was visualized.

To clarify the diagnosis, standard computed tomography (CT) of the larynx, pharynx and cervical spine was performed. There were pronounced structural changes in the cervical spine with the straightening of the cervical lordosis, fragmentary ossification of the posterior longitudinal ligament that protrudes into the vertebral canal. On the ventral surface of the vertebral bodies, massive bony growths of the ossified anterior longitudinal ligament were determined with thickness of up to 9 mm on the right and 11 mm on the left, with the axial size up to 14 26 mm, merging with each other in the vertical direction, forming a bony array up to 77 mm long (increased more than 2-fold in comparison with the year 2016). The dorsal sections of the oropharynx and esophagus wall were pushed back by bone growths ventrally, and had an asymmetric localization. The left sections of the upper and middle constrictors of the pharynx, the palatopharyngeal tonsil, the aryepiglottic fold, the vestibular fold and the posterior wall of the pharynx are thickened relative to the right sections by 0.3–2.6 mm. The oropharyngeal lumen is asymmetric due to the reduction of the size on the left. The epiglottis is located slightly obliquely with ventral displacement of the left sections. Its caudal section on the left was twice as wide as the right half. As a conclusion of the study it was noted that the deformation of the oropharynx and asymmetry of the dorsal structures forming the rear wall with thickening and an increase in the volume on the left are due to the effect of disfiguring ossifying ligamentosis of the anterior longitudinal ligament of the cervical spine. Incomplete closure of the vocal cords during phonation with diastasis between false folds of 0.2 mm and between true folds of 1.3 mm was revealed (Figures 2, 3).

When examined in hospital, the patient's appearance is unremarkable. There is a slight smoothing of the physiological curves of the spine. Movement in the thoracic and lumbar spine without restriction: Thomayer test is 3 cm, Schober and Ott test are 5 cm, chest excursion is 5 cm. Certain deviations were detected from the side of cervical region: distance between the chin and the sternum is 3 cm, the angle of lateral inclination of the cervical spine in both directions is less than 45 degrees. There is no pain in the spinous processes throughout the spine. The joints are not changed, movements there are not restricted. There was no abnormalities on the part of internal organs.

In order to exclude the disease from the group of seronegative spondyloarthritis, laboratory parameters were studied: complete blood count (CBC) and urinalysis (UA) — no pathological changes; C-reactive protein, glucose, cholesterol, alkaline phosphatase, rheumatoid factor within normal limits, HLA-B27 antigen was not detected.

No abnormalities were observed in the MRI examination of the sacroiliac joints. Repeated CT scans further revealed ossification of the anterior longitudinal ligament along the anterior border of the vertebral bodies throughout the thoracic and lumbar spine, most pronounced at the level of Th5–Th10, Th12–L3 vertebrae, no changes in the shape of the vertebral bodies were observed.

The examination of the patient made it possible to establish the following diagnosis: *Ankylosing hyperostosis of the spine (Forestier disease).*

The patient was treated with etoricoxib 60–90 mg/day, magnetic therapy, which led to the complete disappearance of neck pain and difficulties in swallowing. The patient was further advised follow up by a rheumatologist and, if necessary, drug or surgical treatment.

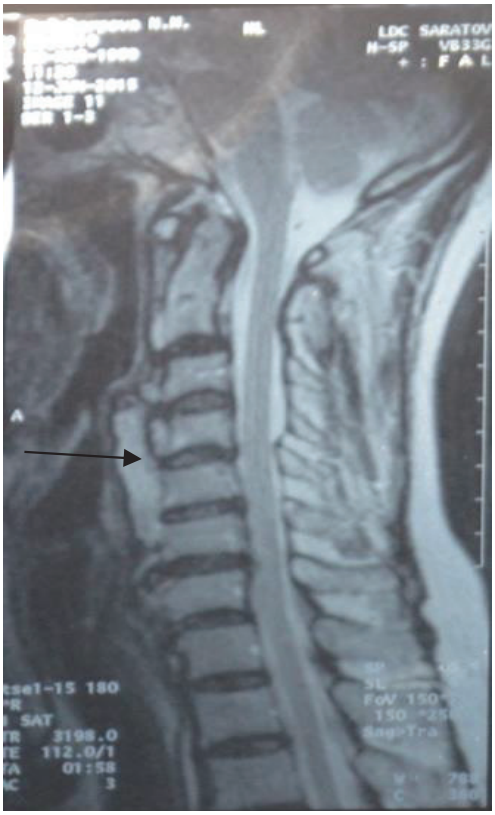

Figure 1. *Magnetic resonance imaging of the cervical spine. Ossification of the anterior longitudinal ligament over 35 mm*

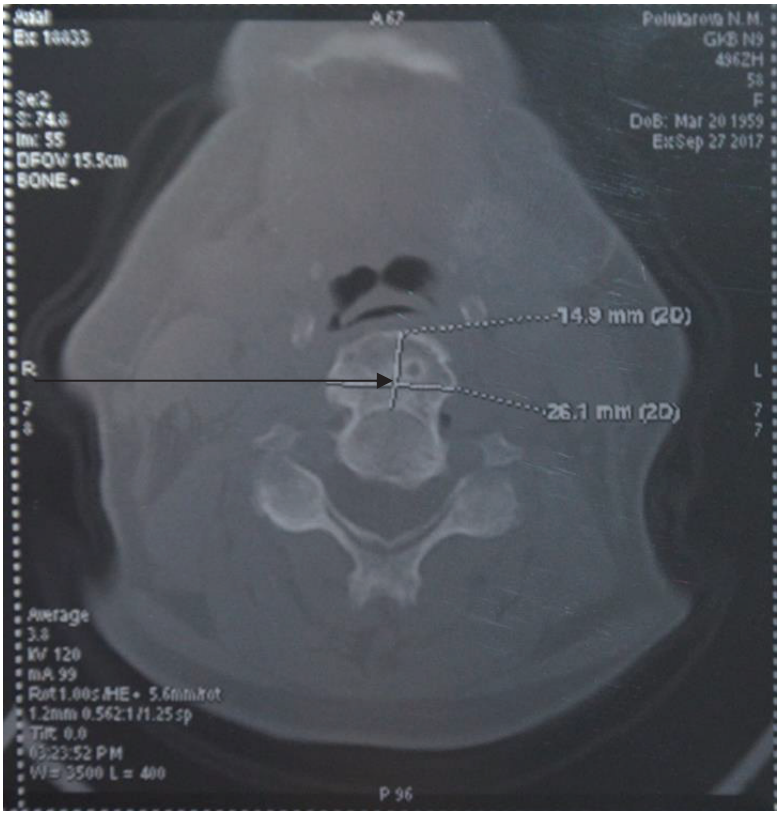

Figure 2. *Computed tomography of the cervical spine, axial view. The arrow indicates the ossification of the anterior longitudinal ligament on the anterior surface of the vertebral body measuring 14.9 × 26.1 mm*

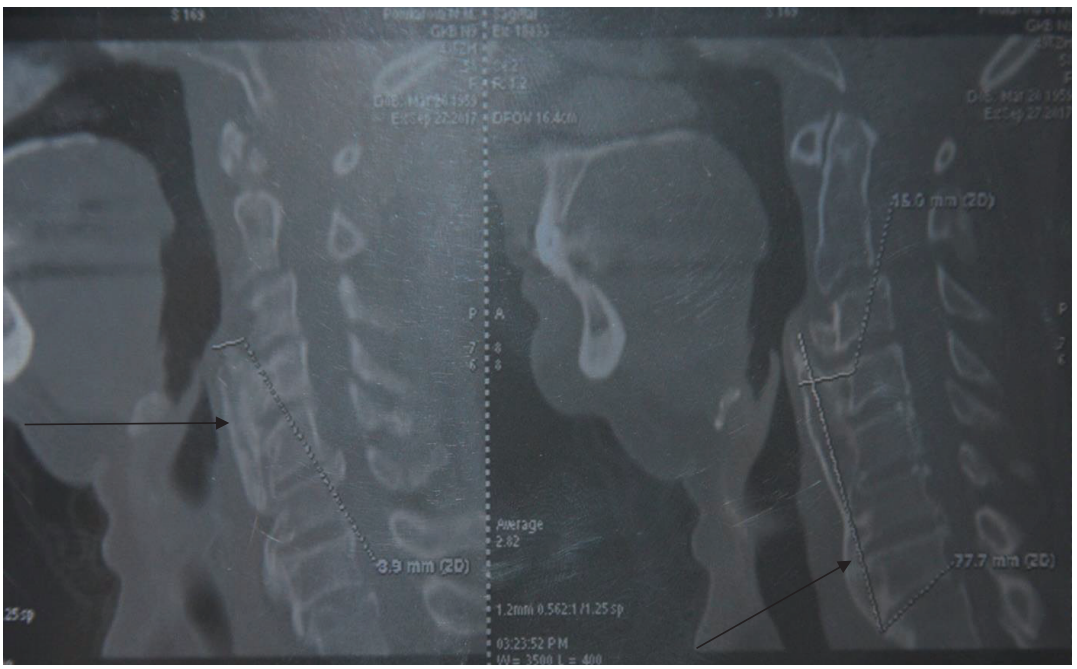

Figure 3. *Computed tomography of the cervical spine, lateral view. Arrows indicate osteophytes of the anterior longitudinal ligament, merging with each other in the vertical direction, forming a mass 77.7 mm long, up to 16.0 mm wide*

Discussion

Nowadays, more and more attention is paid to the changes occurring in the body of elderly people, including the presence of chronic inflammation, pain syndrome, selection of adequate, safe therapy. Back pain occurs in almost every person during life, but most often in older people. The pain syndrome can be associated with different pathological processes. However, physicians, especially at the primary level, when dealing with back pain in older patients, do not always pay sufficient attention to diagnostics, linking the symptoms to the most common degenerative-dystrophic diseases. Awareness and a broad-minded approach of doctors will not only contribute to early diagnosis, but will also increase patient adherence to treatment, reduce polypragmasia, which is especially important in elderly patients. In our work, we demonstrated a clinical case of a disease that occurs mainly in elder patients.

The rarity and insufficient knowledge of ASH, and the associated lack of alertness in relation to this disease, make the diagnostic search extremely difficult for the doctor and, sometimes, severe for the patient [7]. The resemblance of ASH in many aspects to some diseases accompanied by spinal cord affection (tumors, injuries, osteochondrosis, ankylosing spondylitis, etc.) complicates diagnosis. In this regard, it is necessary to use the most informative methods of research, CT and MRI, taking into account diagnostic signs (D. Resnica and Y. Niwayama, 1988), which helps to better understand features of symptoms and differential diagnosis of ASH [6]. Noting the predominant lesion of the anterior longitudinal ligament in ASH, the authors consider the first sign of the disease to be the continuity of its ossification for at least four vertebrae. This condition makes it possible to distinguish ASH from such pathological conditions as infections, tumors, and injuries characterized by local processes in the spine. The second feature, according to the authors, is the absence of ankylosis of the facet joints and sacroiliitis, which are characteristic of ankylosing spondylitis. The lack of symmetry of paravertebral ossification, clinical and laboratory signs of inflammation in ASH can be added to that. The third sign of ASH from the point of view of said authors is the absence (or mildness) of degenerative changes in the intervertebral discs (decrease in their height, marginal sclerosis of the vertebral bodies), which are detected in osteochondrosis.

In addition to these signs, it is also possible to note the absence of damage to other organs and systems characteristic of ASH, with the exception of ectopic ossification of the enthesis, ligaments and tendons.

All specific features of ASH, including age, correspond to the signs that were noted in our patient, which suggests the validity of the diagnosis of ASH.

Conclusions

The rarity and insufficient knowledge of ASH makes it necessary to discuss this disease more widely in order to develop diagnostic skills and provide timely and proper care to patients.

Distinctive features of ASH are: the elderly age of patients, the continuity of ossification of the anterior longitudinal ligament of at least four vertebrae, the absence or weak severity of degenerative changes in intervertebral discs, X-ray signs of ankylosis of facet joints, and the symmetry of paravertebral ossifications of other organs and systems.

In our case, the diagnosis was made one year after the MRI scan, where the ossification of the anterior longitudinal ligament was not properly assessed. According to the literature, the path to establishing the diagnosis of ASH is complicated and long: osteochondrosis, expansive processes of the esophagus and larynx are detected during repeated CT scans, in some cases tracheostomy is performed and biopsy of the formation is recommended before the diagnosis of ASH is verified [1, 5–6].

Contribution of Authors

E. N. Skryabina: the concept of the article, analysis, interpretation of data, writing of the manuscript, verification of intellectual content, approval of the manuscript for publication.

N. A. Magdeeva: analysis, interpretation of data, writing of the manuscript, verification of intellectual content.

Yu. M. Korneva: data collection, analysis, and interpretation of results.

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Fisher-Evans Syndrome. Casereport in Physician's Practice

Abstract

This article presents the clinical features and treatment options for autoimmune thrombocytopenic purpura associated with autoimmune hemolytic anemia — Fisher-Evans syndrome. Patient P., aged 68 years, was admitted to the hospital by an ambulance team with a referral diagnosis of acute pancreatitis. Hemorrhagic and anemic syndromes were the main clinical signs. Physical examination revealed a strip-formed hemorrhagic rash in the area of inguinal folds, the anterior surface of thighs and lower legs. In the course of differential diagnostics, Fisher-Evans syndrome was diagnosed. Initial oral and pulse therapy with prednisolone was not effective. The patient received platelet transfusions regularly. When eltrombopag was included in therapy, there was an improvement in the patient's condition, as well as a tendency to a rising level of platelets. On the 35th day, the patient was discharged from the hospital.

We examined various clinical variants of thrombocytopenia common in real clinical practice.

Keywords: *Fisher-Evans syndrome, clinical features of thrombocytopenia, prednisolone, eltrombopag*

Conflict of interests

The authors declare no conflict of interests.

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BP — blood pressure, CBC — complete blood count, CT — computed tomography, UA — urinalysis, EGD — esophagogastroduodenoscopy, FCS — fibrocolonoscopy, FES — Fisher-Evans syndrome, GC — glucocorticoids, GED — gastroenterological department, HELLP syndrome –hemolysis, elevated liver enzymes, low platelet count (thrombocytopenia) in the third trimester of pregnancy, ITP — idiopathic thrombocytopenic purpura, NSAIDs — non-steroidal anti-inflammatory drugs, US — ultrasound

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Introduction

Idiopathic thrombocytopenic purpura, or primary immune thrombocytopenia (ITP), is a disease that is an isolated immune-mediated thrombocytopenia (the number of platelets in peripheral blood is less than 100×10^9/L) that occurs and/or persists without any clear reasons, with or without hemorrhagic syndrome of different severity [1]. Typical manifestation of ITP is the development of petechiae or purpura with an underlying health condition a few days or weeks after past infectious diseases.

ITP combined with autoimmune hemolytic anemia is called Fisher-Evans syndrome (FES). The disease was first described in 1947 by J.A. Fisher who suggested the immune genesis of anemia and thrombocytopenia. In 1951, R. Evans examined 24 patients aged 3 to 78 years with isolated AIHA, isolated thrombocytopenia (in some cases neutropenia was also registered) and different variants of their combinations [2].

The incidence of ITP in the world is 1.6-3.9 cases per 100,000 people per year; the prevalence ranges from 4.5 to 20 cases per 100,000 people.. Children are sick more often than adults are, and peak incidence occurs in five years.

Despite the fact that the first cases of the development of FES were described in pediatrics, its manifestation can be observed at any age. According to one study performed in Denmark from 1977 to 2017, the median incidence of FES was 58.5 years [3].

FES is a diagnosis of exclusion because it can be both primary and secondary in relation to other diseases. Its association with the following pathological conditions was described: systemic lupus erythematosus, antiphospholipid syndrome, HIV infection, viral hepatitis, lymphoproliferative diseases, etc. Association of FES with Helicobacter pylori contamination can not be excluded.

The following is a description of the clinical case of patient P., aged 69 years, with primary FES.

Case report

Patient P., until 2018, had a satisfactory state of health. There was a history of compensated hypertensive disease with maximum blood pressure (BP) of 150 and 90 mm Hg, without cardiovascular events; as well as general osteochondritis with back pain; for it, the patient took non-steroidal anti-inflammatory drugs (NSAIDs) systematically for six months. In addition, since 2017 there was noticeable weight loss by 20 kg (from 73 kg to 53 kg).

No significant hereditary or medication history: the patient and her relatives had no allergic or autoimmune diseases, no malignant neoplasms.

In the spring of 2018, patient P. noted the appearance of weakness and shortness of breath with slight physical exertion; as a result, she consulted a therapist at the place of residence.

CBC in the course of outpatient examination revealed decreased hemoglobin to 95 g/L, white blood cells amounted to $5.8*10^9$/L), platelets were not determined. Without testing for serum iron level, an iron supplement was prescribed; the patient took it for 2 months with no effect. Two weeks before hospitalization, dull pains emerged in the epigastric area and left hypochondrium with no definite connection with food intake or physical activity, as well as temperature periodically raising up to 38 °C without chills, which lasted up to 1-2 hours, twice a week, and normalized without any interventions. There were no dyspeptic or dysuric signs. Stool was formed, with no blood admixtures.

P. visited the local clinic at the place of residence wherefrom she was transported by an ambulance team to Buyanov City Clinical Hospital with a referral diagnosis of acute pancreatitis (?). During examination in the emergency room, no data for acute surgical pathology was obtained (the following was performed: plain radiography and ultrasound examination (US) of abdominal organs, complete blood count (CBC) and urinalysis (UA), consultation by surgeon). Due to the unclear cause of abdominal pain, the patient was hospitalized in the Gastroenterological Department (GED).

In the GED, the patient had the same complaints of weakness, fatigue, discomfort in the epigastric area. Her condition was considered as of moderate severity. Body temperature was 36.8 °C. Body mass index — 18.75 kg/m^2. Skin and visible mucosae were pale, with no icteric discolor. Lymph nodes were not enlarged. On the skin, in the area of inguinal folds and on the anterior surface of both thighs, there was a hemorrhagic rash in the form of a strip

4 cm wide; a similar but less intense rash was in the area of the lower legs (Figure 1).

In lungs — vesicular breathing, tachypnea — up to 24 respiratory movements per minute. Heart sounds were weakened, rhythm was regular, tachycardia — heart rate of 100 bpm, hypotension (BP — 90 and 60 mm Hg). The tongue was moist. The abdomen was of normal size, soft, not sharply tender on palpation in the upper part, in the right hypochondrium. The liver and spleen on percussion and palpation are not enlarged.

CBC revealed mild normochromic microcytic anemia (hemoglobin — 94 g/L), leukopenia — 3.3×10^9/L with no WBC differential shift, and severe thrombocytopenia — 14×10^9/L. Blood test showed reticulocytosis (25%); as a result, the hemolytic nature of anemia was suspected and subsequently confirmed with Coombs test.

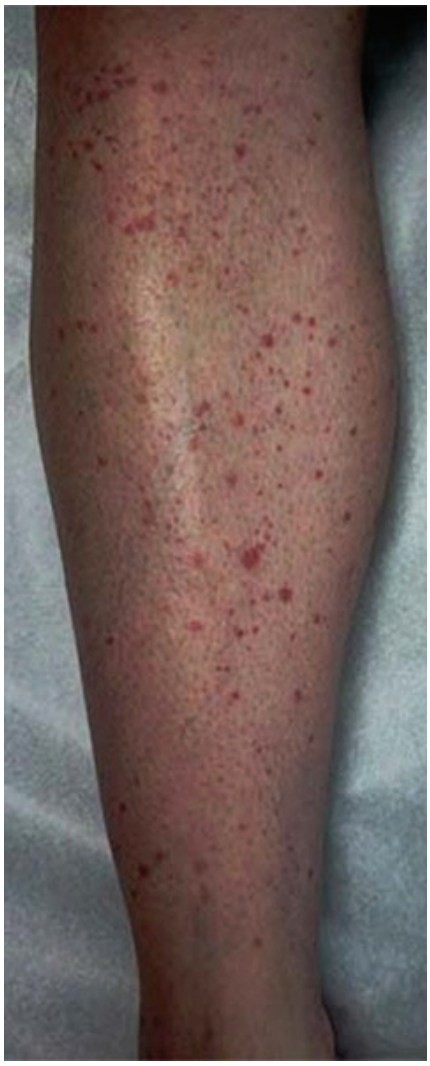

Figure 1. *Petechial rash on the lower extremity of patient P.*

UA results revealed urobilinogen (3.2 μmol/L); qualitative bilirubin determination was negative; protein, glucose — not found.

Blood biochemistry results were the following: alanine (9 IU/L) and aspartate (27 IU/L) aminotransferases, total bilirubin (15 μmol/L), conjugated bilirubin (2 μmol/L), unconjugated bilirubin (13 μmol/L), alkaline phosphatase (108 IU/L), lactate dehydrogenase (230 IU/L), total protein (66 g/L), urea (7 mmol/L), creatinine (92 μmol/L), serum iron (11 μmol/L), glucose (5.2 mmol/L), a-amylase (108 IU/L) — nothing abnormal detected. Coagulogram revealed a more than five-fold increase in D-dimers (3,020 μg/L), other parameters (prothrombin index (100%), thrombin time (17.4 s), fibrinogen (2.2 g/L), international normalized relation (1)) were within the reference range.

During bacteriological tests of body fluids (blood, urine), no microflora growth was obtained.

ECG: normal position of QRS axis, signs of left ventricular hypertrophy, tachycardia — 98 bpm.

Ultrasound of abdominal organs and kidneys revealed no pathological changes in the liver, biliary system, spleen, and kidneys; there was only increased echogenicity of pancreas.

Taking into account the long-term use of NSAIDs and anemia, endoscopic studies were performed.

Results of esophagogastroduodenoscopy (EGD) showed the following: cardiac rosette closes incompletely, superficial gastritis (gastric mucosa is diffusely moderately hyperemic, thinned, vascular pattern is accentuated); no visible changes of esophageal and duodenal mucosa. During fibrocolonoscopy (FCS), all parts of the colon were examined, an endoscope was introduced in the cecum. Mucosa of the colon was pale pink, smooth, vascular pattern without changes, mucosa was segmentally hyperemic only in certain parts of the sigmoid colon, with superficial, contact-bleeding, single erosions of up to 2-3 mm with clearly visible vasculature. No biopsy of intestinal mucosa was performed due to the high risk of bleeding.

The patient was also comprehensively examined in connection with oncologic alarm: computer tomography (CT) of thorax, abdomen and small pelvis revealed no pathological changes.

Sternal puncture was performed to exclude an oncohematological disease. The bone marrow

biopsy specimen was rich in cell elements, there were no blasts, the amount of plasmatic cells was 2%. Megakaryocytes were present in sufficient quantity (0.5%). Impaired platelet release deserved special attention.

Tests for antiphospholipid and lupus antibodies were also performed in order to exclude systemic lupus erythematosus in a patient with fever, hemorrhagic rash and thrombocytopenia; negative results were obtained.

Taking into account severe thrombocytopenia, hemorrhagic presentation and required invasive examination methods (sternal puncture, endoscopy, FCS, blood tests), multiple platelet transfusions were performed (in the amount of 1 dose, daily, during 20 days). The control test 2 hours after transfusion showed that the platelet level increased to $80x10^9$/L, however, the next day it returned to baseline. Changes in blood test parameters are presented in Table 1.

Based on examination results, patient P. was diagnosed with primary FES, glucocorticoid (GC) therapy was started — Metypred 44 mg.

However, on the 14th day of treatment with GC, the aggravation of hemorrhagic syndrome was observed, which was manifested by confluent ecchymoses on the right upper extremity and the abdomen, and hemorrhage in the conjunctiva of the right eye. The patient's condition was considered unstable, in light of which platelet mass transfusion in the same dose was continued, and GC pulse therapy was performed — for three days with intravenous prednisolone at the dose of 300 mg/day.

Due to the lack of positive changes in the patient's condition on the 25th day of hospitalization, a stimulator of thrombocytopoiesis, eltromboрag, was added once to the treatment of P. — at the dose of 50 mg per os (for the period of 25th — 35th day of hospitalization). Gradual dose tapering of GC was started.

The patient was discharged on the 35th day with the final diagnosis of primary, rapidly developed FES (extremely severe thrombocytopenia, mild anemia, minimal leukopenia). Complications: erosive sigmoiditis. Concomitant pathology: hypertensive disease stage 2, grade 2, risk 3 (medical history data). Chronic kidney disease 3a (glomerular filtration rate according to CKD-EPI — 54.73 mL/min/1.73 m^2). Chronic gastritis, cardia insufficiency. General osteochondritis with back pain.

In the course of treatment, P.'s condition stabilized (body temperature remained normal, the area and intensity of hemorrhagic rash decreased, the severity of weakness also decreased), platelets, hemoglobin, WBC with a tendency to increase (Table 1).

Table 1. *Changes in basic laboratory parameters in patient P.*

Parameters, reference range /	23.06.18	25.06.18	26.06.18	09.07.2018	21.07.2018	25.07.18
Hemoglobin (112-153 g/L)	94	93	87	93	105	106
RBC (3.8-5.15*10^{12}/L)	3.60	3.31	3.13	3.39	3.68	3.54
Hematocrit (34.9-45.6%)	28.6	26.9	26.0	28.6	31.4	30.4
Mean Cell Volume (82-98 fL)	79.4	81.0	83.1	84.0	85.3	86.0
Mean Cell Hemoglobin (26.7-33 pg)	26.1	28.2	27.2	27.4	28.5	30.0
Platelets (150-375*10^9/L)	14	10	11	9	16	81
WBC (3.4-10.8*10^9/L)	3.3	3.10	1.90	6.80	4.50	5.40
Iron (9.0-30.4 μmol/L)	-	-	10.5	-	10.4	-
Procalcitonin (0.05-0.50 ng/mL)	-	0.11	-	-	-	-
C-reactive protein (0.1~7.0)	-	17.9	17.7	3.9	1.6	-

The patient was recommended to continue taking eltrombopag at the dose of 50 mg per day with food; Metypred 16 mg (8 mg at 07:00 a.m. and 8 mg at 10:00 a.m.); Omeprazole 20 mg in the evening; Rebamipide 100 mg three times a day; Enalapril 10 mg twice daily. The patent was referred to a hematologist at the place of residence for further management and therapy correction. If any invasive methods of examination and treatment are required, in order to prevent hemorrhagic complications, it will be preferable to perform platelet transfusions for patient P. It is recommended to avoid insolation and taking drugs that block platelet function; to exclude NSAIDs; to avoid contact with patients with viral infections. The decision to conduct vaccine prophylaxis should be made strictly on an individual basis.

Discussion

At the stage of the initial examination of patient P., clinical signs were caused by anemic syndrome. Difficulties in establishing primary diagnosis involved the need for making differential diagnosis between a stable existing chronic disease and a subacute life-threatening pathology. Tachypnea, hypotension, tachycardia with fever required the exclusion of organ dysfunction syndrome. In this regard, the question of the patient's location — in the general ward or in intensive care unit — was solved.

In clinical practice, the SOFA scale is used to assess organ dysfunction syndrome. According to literature, the most important aspect in the treatment of multiple organ failure, including sepsis, is its timely diagnosis. In order to screen for organ dysfunction at the patient's side, Quick SOFA criteria were developed. Our patient had 2 points (systolic BP at admission — 90 mm Hg, RR — 24/min), which also indicated a high probability (80%) of sepsis.

Changes in laboratory parameters (cytopenia and high D-dimers) did not exclude the possibility of generalized response to an unspecified infectious agent. However, the patient had no classic symptoms of inflammation. Instrumental diagnostic methods revealed no infectious focus.

An important aspect in the diagnosis of sepsis is finding biomarkers. The procalcitonin level in P. was 0.11 ng/mL, which, with a high degree of accuracy, indicates the absence of sepsis. Negative results of biological fluids culture were a significant confirmation of this suggestion. Thus, the patient's severe condition was most likely due to a chronic disease.

The differential diagnosis included the following: hemoblastoses, myelodysplastic paraneoplastic syndromes, aplastic anemia. Absence of splenomegaly, normal level of lactate dehydroginase activity made it possible to exclude myelofibrosis, acute leukemia, etc.

No signs of disseminated intravascular coagulation in the presence of hemolytic anemia brought into question such a rare pathology as paroxysmal nocturnal hemoglobinuria in this patient. Taking into account the prevailing hemorrhagic syndrome, we could not exclude platelet pathology as the main factor determining the clinical picture.

Hemorrhagic syndrome can be of various etiology. There can be vasculitis, thrombocytopathy, coagulopathy. The type of bleeding in these cases has a microcirculatory character and occurs with thrombocytopenias and thrombocytopathies, von Willebrand disease, deficiency of prothrombin complex factors (VII, X, V and II), some variants of hypo- and dysfibrinogenemias, moderate overdose of anticoagulants.

It should also be emphasized that thrombocytopenia can both be a primary pathology and proceed with an underlying oncological process. According to the results of thorough instrumental examination (CT of thoracic and abdominal organs, ultrasound of abdomen, kidneys, small pelvis, thyroid gland, EGD, FCS), no signs of tumor process were found.

In the analyzed case, the leading pathological symptom in the clinical picture of patient P. was pancytopenia in combination with hemorrhagic and anemic syndromes. Hyperthermia was apparently non-specific. Taking into account the clinical picture and results of examination in patient P., we diagnosed her with FES.

Thus, differential diagnostics of thrombocytopenia is a very difficult task. Figure 2 shows the most common diseases associated with thrombocytopenia.

We suppose that, first of all, urgent pathology requiring urgent hospitalization should be excluded. Patients with infectious pathology belong to a special category. Burdened epidemiological history, prodromal period, and fever are reliable markers

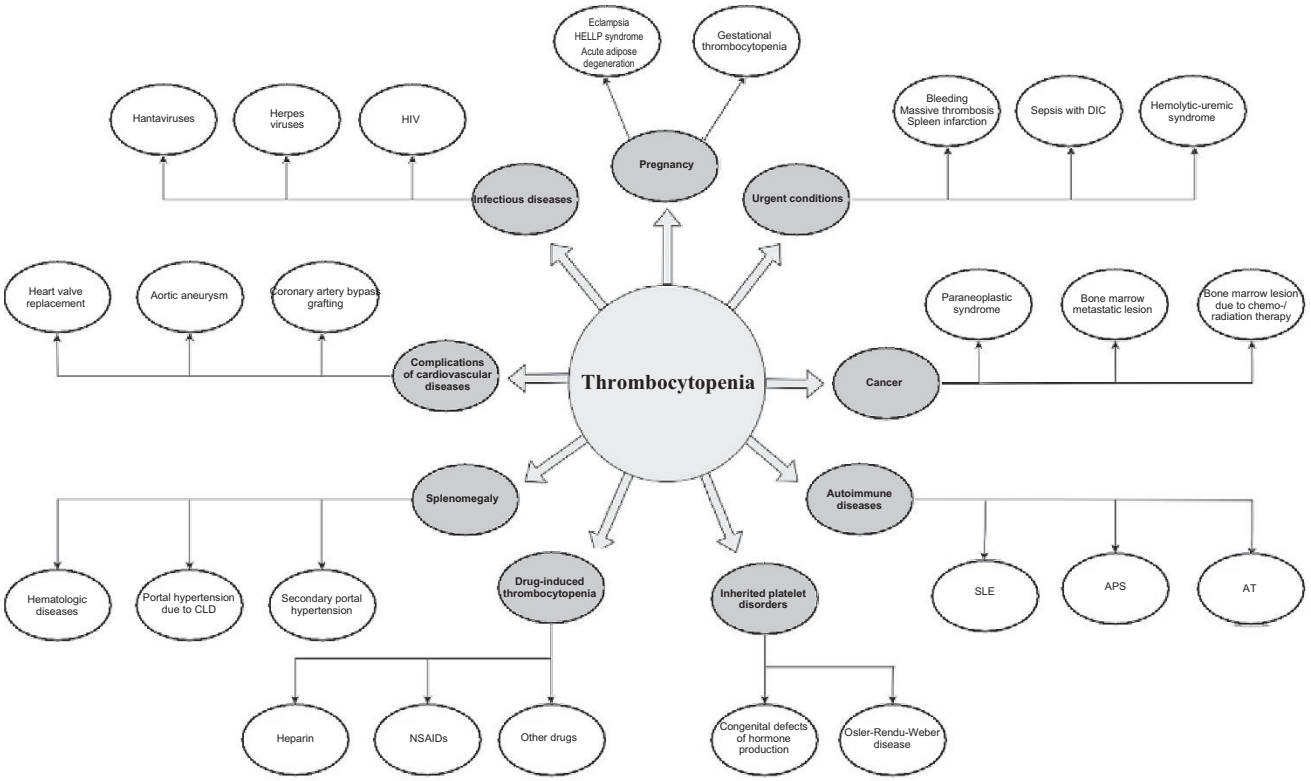

Figure 2. *Thrombocytopenia-associated conditions*

Note: AT — autoimmune thyroiditis, APS — antiphospholipid syndrome, HIV — human immunodeficiency virus, HUS — hemolytic-uremic syndrome, DIC — disseminated intravascular coagulation, NSAIDs — non-steroidal anti-inflammatory drugs, SLE — systemic lupus erythematosus, CLD — chronic liver disease, HELLP syndrome — hemolysis, elevated liver enzymes, low platelet count in the third trimester of pregnancy

for diagnosing this condition. The main cause of thrombocytopenia in the intensive care unit is sepsis complicated by disseminated intravascular coagulation syndrome, most often caused by pneumonia, urosepsis, or soft tissue infection.

Considering special medical and social significance, attention should be paid to women of childbearing age. Gestational thrombocytopenia is the most common cause; it is characterized by spontaneous regression after childbirth and is not associated with adverse outcomes for mother and child. However, we should not forget about such serious conditions as eclampsia/preeclampsia and HELLP syndrome.

In addition to thrombocytopenias typical for gestation, hematological pathology, including ITP, can not be excluded in women.

The exclusion of any technical error in laboratory tests should be considered the second step in the diagnostics of thrombocytopenia; it requires the assessment of morphological characteristics and platelet count according to the Fonio method.

Splenomegaly is typical for the pathology of both the hepatobiliary area due to portal hypertension and hematological pathology. Differential diagnosis is performed taking into account hepatic cell function (prothrombin, total protein and fractions, activity of cytolysis and cholestasis enzymes), the exclusion of secondary portal hypertension. In difficult cases, sternal puncture is performed.

The diagnosis of drug-induced thrombocytopenia is complex. According to some authors, the presence of antiplatelet antibodies is not a reliable marker of this pathology. Only an increase in platelet count after drug withdrawal allows its diagnosis. In addition to common heparin-induced thrombocytopenia, there are many descriptions of cases with decreased platelet count while taking NSAIDs, antiarrhythmic, or antibacterial agents. Drug-induced thrombocytopenia develops more often within 1-5 days of drug administration.

In addition, there are secondary thrombocytopenias in patients with rheumatological and oncological diseases.

It is also not always possible to correct thrombocytopenia in patients with severe cardiovascular diseases, especially after surgical interventions.

Conclusion

FES is a diagnosis of exclusion. However, in addition to difficulties in diagnosing this syndrome, it should be emphasized that in the case of our patient there was resistance to treatment.

According to Russian and foreign publications, GCs (in particular, prednisolone) are the first-line FES therapy, at the dose of 1-2 mg/kg of body weight.

In patient P., 44 mg of Metypred per os and pulse therapy had no expected effect. In more than 70% of adult patients with FES, this tactic is also not effective [1, 5].

Due to the small number of patients, no randomized studies of other therapeutic options for FES were performed, and no therapy algorithm was developed.

Second-line therapy includes rituximab, cyclosporin A, mycophenolate mofetil, vincristine; splenectomy and transplantation of stem hematopoietic cells can be performed [4, 5].

We effectively used a thrombopoietin receptor agonist eltrombopag. This approach was successfully used in patients of different age groups, and it was first used in children with FES.

Using blood components is discussed as a separate issue in the treatment of FES. According to the recommendations of the Russian Society of Hematologists, transfusion of platelet concentrate is not effective. However, with a decrease in platelet count to $50x10^9$ L, the risks of hemorrhagic events appear [1, 5]; in this regard, transfusion of a platelet concentrate in such conditions is necessary, and with the appearance of small-point hemorrhages on the upper part of the body, hemorrhages in conjunctiva and fundus, local bleedings (gastrointestinal tract, uterus, kidneys, bladder), transfusion of platelet concentrate is an urgent, vitally indicated procedure.

Thus, FES is one of the complex diagnostic and therapeutic problems, the awareness of which will allow physicians to help their patients more effectively and in a timely manner. However, in general, the prognosis of FES remains serious due to the recurrent nature of this disease, as well as the development of infectious and hemorrhagic complications during ongoing GC therapy.

Contribution of the authors:

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

A.A. Yakushev: writing, creating figures
L.Yu. Ilchenko: writing and editing the article
I.G. Fedorov: analysis of obtained data
S.S. Shmykova: search for literature
N.V. Ilyin: search for literature
G.G. Totolyan: analysis of obtained data
I.O. Sirenova: editing of the article
I.G. Nikitin: design and approval of the final version of article

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