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THE GENETIC SUSCEPTIBILITY TO ATHEROSCLEROSIS

Abstract

Atherosclerosis is a complex multifactorial disease of medium and major arteries which involves multiple genetic and environmental factors. Atherosclerosis is the main cause of death and disability in developed countries, while in developing countries the incidence of this disease is growing rapidly. Advances in techniques of molecular genetics have revealed that genetic polymorphisms significantly influence susceptibility to atherosclerotic vascular diseases. A large number of candidate genes, genetic polymorphisms and susceptibility loci associated with atherosclerosis have been identified in recent years and their number is rapidly increasing. In recent years, there is significant interest in identifying additional factors of genetic risk for atherosclerosis. In recent years, a large number of genetic studies have been carried out to prove the genetic effect on the atherosclerotic process. Rapid progress in the sequencing of the human genome and molecular genetic methods have helped in the definition of susceptibility loci and associated candidate genes with atherosclerosis and concomitant diseases. The association of a large number of susceptibility genes with atherosclerosis reflects the enormous complexity of the disease. Multiple factors, including endothelial dysfunction, lipid metabolism defects, inflammation and immune responses, oxidative stress, cell proliferation, tissue remodeling, and hemostatic defects are involved in the pathogenesis of atherosclerosis. In this review we focus on and discuss some of the major candidate genes and genetic polymorphisms associated with human atherosclerotic vascular diseases.

Key words: *atherosclerosis, gene, polymorphisms, genetic testing*

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ABC — ATP-binding cassette transporters, apoB — apolipoprotein B, apoE — apolipoprotein E, CRP — C-reactive protein, eNOS — endothelial NO-synthase, MMP — matrix metalloproteinases, NO — nitric oxide, MI — myocardial infarction, HDL — high density lipoproteins, LDL — low density lipoproteins, VLDL — very low density lipoproteins, NADH — nicotinamide adenine dinucleotide, NADPH — nicotinamide adenine dinucleotide phosphate, FHC — familial hypercholesterolemia, FCH — familial combined hyperlipidemia, CVD — cardiovascular disease, TG — triglycerides, CL — cholesterol

Introduction

Atherosclerosis is a complex multifactorial disease of medium and major arteries which involves multiple genetic and environmental factors. Atherosclerosis is the main cause of death and disability in developed countries, while in developing countries the incidence of this disease is growing rapidly [1, 2]. Atherosclerosis can cause stenosis or occlusion of the arteries and is the main pathology in coronary arteries, peripheral arteries and carotid artery disease. Similarly, atherosclerosis in the mesenteric and renal arteries can lead to mesenteric and renal ischemia, respectively. In addition, atherosclerosis can also lead to aneurysms in the arteries.

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Taking into account the fact that clinical manifestations of cardiovascular diseases (CVD), such as myocardial infarction (MI), stroke and peripheral vascular disease, are manifested in middle age, the process of atherogenesis can begin in early childhood. The results of numerous epidemiological studies show that the main constitutional risk factors of cardiovascular diseases such as atherogenic dyslipidemia, hypertension, overweight, diabetes, positive family history exist or are formed in childhood and have a genetic basis [2]. External, or environmental, CVD risk factors, such as smoking, hypodynamia, stressful situations, also begin to act from childhood, and are closely related to constitutional factors, and their role is no less important than the role of constitutional factors [3].

Endothelial dysfunction, inflammation, impaired metabolism of lipoprotein and homocysteine, as well as dysfunctional coagulation and fibrinolysis (Fig. 1), as is known, play an important role in the development of atherosclerotic lesions (Fig. 1) [4]. The relationship between genes and atherosclerosis is complex with the hereditary component of cardiovascular diseases in most populations ranging from 40 to 60%, and most cardiovascular disorders are affected by interactions between multiple genes and environmental factors [5].

Advances in laboratory genetics have shown that genetic disorders significantly affect susceptibility to atherosclerotic vascular lesions. In recent years, a large number of candidate genes, genetic polymorphisms and susceptibility loci associated with atherosclerosis have been identified, and their number is growing rapidly, which in turn leads to a significant increase in interest in identifying additional genetic risk factors for atherosclerosis, and in initiating a large number of genetic studies to prove the genetic impact on the atherosclerotic process [6].

Hereditary disorders of lipid metabolism are dominant and significantly contribute to the development of atherosclerosis being the pathological basis of CVD [7]. Although subclinical atherosclerosis can be detected at a very early age, CVD-related events such as heart attack and stroke are rare in children and adolescents. Published studies have convincingly shown that: (1) atherogenesis begins in childhood; (2) risk factors, including elevated cholesterol levels, in childhood, persist in adults and are associated with moderate and high risk of CVD; and (3) in individuals with genetic dyslipidemia, risk factors

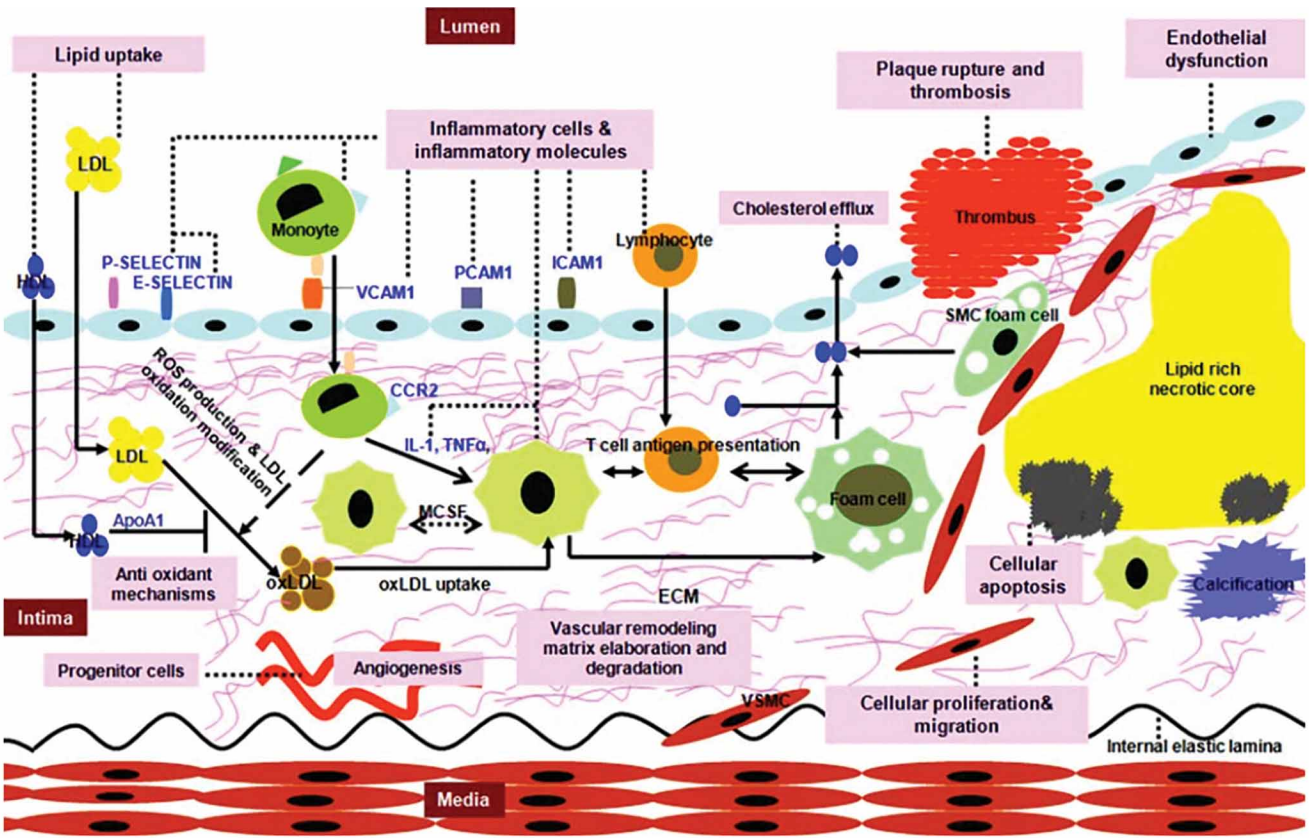

Figure 1. *Key molecular and cellular mechanisms involved in atherogenesis [9]*

accelerate CVD development. The formation of such a vulnerable group of children at risk of atherosclerotic vascular damage will create an opportunity to prevent the development of premature conditions associated with CVD through effective management of genetic and acquired risk factors [8].

This review examines the main susceptibility genes and genetic polymorphisms associated with atherosclerotic vascular disorders.

Genes Associated with Lipid Metabolism

The risk group for the development of atherosclerosis is children who have an increase in cholesterol (CL), low density lipoproteins (LDL), its apoprotein B, as well as a combined increase in triglyceride (TG) levels and a decrease in the level of high-density lipoproteins (HDL).

Blood lipoprotein levels and diseases associated with disorders of lipid metabolism are closely associated with onset and progression of atherosclerosis. Among the various hereditary genetic causes of atherosclerosis there are monogenic forms of hereditary hyperlipidemia (family hyperlipidemia, OMIM #143890) [10], which are characterized by earlier development of CVD. In monogenic forms of lipid metabolism disorders, a correlation between polymorphisms in several groups of genes involved in lipid metabolism and atherosclerosis was established [11].

LDL Metabolism

High LDL levels are associated with an increased risk of atherosclerosis and, consequently, genes that affect lipoprotein metabolism and LDL levels are involved in the pathogenesis of atherosclerosis [12]. The low density lipoprotein receptor gene (*LDLR*) family consists of the *LDLR* gene, a very low density lipoprotein receptor gene (*VLDLR*); a protein associated with the lipoprotein receptor (*LRP*), *LRP1b*, megalin/*LRP2*, multiple epidermal growth factor containing protein 7 *(MEGF7)*/*LRP4*, *LRP5*, *LRP6*, and apolipoprotein E-receptor 2 (*apoER2)*/*LRP8* [13]. Familial hypercholesterolemia (FHC) is an autosomal dominant disease characterized by the absence or impaired function of the LDL gene ***LDLR***. FHC affects about 1 in 500 people worldwide. Mutations in the *LDLR* gene lead to impaired LDL metabolism, which leads to high LDL levels and increased predisposition to atherosclerosis. More than a thousand variants in the *LDLR* gene have been described in patients with FHC, and these mutations are localized in all functional regions of LDL protein [13].

Autosomal recessive type of hypercholesterolemia is described in a small number of families with severe hypercholesterolemia [14]. Mutations in the *LDLRAP1* gene, also known as *ARH*, were identified in these patients [14]. LDLRAP1 is an adapter protein that interacts with the lipoprotein receptor, and is involved in its endocytosis. The prevalence of coronary artery disease is relatively lower in patients with autosomal recessive FHC compared to the autosomal dominant form [15].

LRP is a multifunctional receptor that is involved in several biological processes related to the development of atherosclerosis (Schulz et al., 2003). Polymorphisms in the *LRP* gene, in particular, C200T, are probably associated with the risk of premature CAD [16].

Apolipoprotein B (apoB) is a key glycoprotein in lipoprotein metabolism. The *apoB* gene is characterized by multiple polymorphic sites. Missense mutations in the LDL receptor-binding domain of the *apoB* gene lead to the formation of a family of ligand-defective apoB-100, which is characterized by hypercholesterolemia and early development of CAD. Other mutations in the *apoB* gene cause familial hypobetalipoproteinemia characterized by hypocholesterolemia and atherosclerosis resistance [17]. Three polymorphisms in the *apoB* gene including two due to the presence/absence of a restriction site for restriction enzymes (XbaI and EcoRI) and one insert/deletion polymorphism (SpIns/Del) of size 9-bp, which lead to the appearance or deletion of three amino acids in the signal peptide apoprotein, are often associated with CAD and/or myocardial infarction (MI). Meta-analysis of published studies suggested that EcoRI allele polymorphism, D-allele SpIns/Del polymorphism, and homozygous TT genotype of XbaI polymorphism in the *apoB* gene are associated with increased risk of CAD/MI [18].

Apolipoprotein E (apoE) is a major component of VLDL. apoE4 allele is associated with elevated levels of CL, LDL and increased risk of coronary atherosclerosis. apoE2 and apoE4 alleles in men are associated with a significant increased risk of CAD (Lahoz et al. 2001). Heterozygous carriers of apoE2/E3 alleles have lower LDL levels and lower

risk of atherosclerosis [19]. Based on epidemiological data on the prevalence of *apoE* gene polymorphisms and CVD, it is concluded that they are poor prognostic markers during screening for clinically manifested atherosclerosis [20].

Mutations in the gene that encodes the proprotein convertase subtilisin/kexin type 9 (***PCSK9***) are associated with a rare severe form of autosomal dominant FHC. *PCSK9* gene encodes the regulation of convertase, which is expressed in the liver and is involved in the metabolism of cholesterol. The E670G polymorphism in the *PCSK9* gene have been identified as important determinants of LDL level in plasma and is associated with the severity of coronary atherosclerosis (Chen et al. 2005) and the risk of stroke [21].

Cholesterol 7α-hydroxylase catalyzes the initial stage of cholesterol catabolism and synthesis of bile acids. Deletion in the ***CYP7A1*** gene, which encodes the enzyme cholesterol 7α-hydroxylase, causes a rare form of hyperlipidemia in homozygous and heterozygous individuals. Genotype CC of A278C polymorphism in *CYP7A1* gene increases the progression of atherosclerosis [22].

Familial combined hyperlipidemia (FCH) is a disease characterized by elevated levels of TG and CL, and early development of CAD. This pathology affects about 2% of the population, and about 20% of patients with middle age MI have FCH. FCH is associated with a gene encoding transcription factor (*USF1*), which is known to regulate several genes for glucose and lipid metabolism [23]. Alleles of the *USF1* gene have been recently found to be associated with coronary atherosclerosis.

HDL Metabolism

Feedback between HDL and atherosclerosis has been established, but not all people with low HDL are necessarily at risk of premature CAD. **Lecithin-cholesterol acyltransferase (LCAT)** is a key enzyme in reverse cholesterol transport and HDL metabolism. Mutations in the *LCAT* gene in familial LCAT deficiency are associated with low levels of HDL. Polymorphism of P143L in exon 4 of LCAT gene is associated with reduced HDL level and increased risk of dyslipidemia and CAD [24].

Apolipoprotein A-I (apoA-I) is a key component of HDL and the anti-atherogenic properties of HDL are mainly derived from apoA-I. G75GA polymorphism in *apoA-1* gene is associated with coronary atherosclerosis [25].

The family of ATP-binding cassette (ABC) transporters is a family that includes 48 genes. About 50 mutations and a number of polymorphisms were identified in the *ABCA1* gene [26]. ABCA1 plays an important role in HDL metabolism. Mutations in the *ABCA1* gene cause Tangier disease (Tangier disease, OMIM# 205400) which is characterized by the absence of HDL and premature atherosclerosis [10]. Polymorphisms of G3456C, C477T and C565T in the *ABCA1* gene are associated with the risk of coronary atherosclerosis. Mutations in the genes encoding *ABCG5* and *ABCG8* transporters cause the rare autosomal recessive disease, sitosterolemia [27]. Patients with sitosterolemia often have hypercholesterolemia, xanthomas and premature atherosclerosis [26].

Paraoxonase has antioxidant properties and the ability to hydrolyze oxidized lipids in LDL. The paraoxonase family (PON) consists of three members, *PON1*, *PON2* and *PON3*. *PON1* and *PON3* are HDL-associated proteins mainly expressed in the liver and contributing to the anti-atherogenic effects of HDL [28]. In contrast to *PON1*, *PON3* expression is not regulated by oxidized lipids. *PON2*, although not associated with HDL, is universally expressed and exhibits its antioxidant function at the cellular level. M55L and Q192R polymorphisms in the *PON1* gene have been shown to be associated with CAD and increased risk of carotid atherosclerosis. Polymorphisms of C107T and Q192R in *PON1* gene were associated with the risk of stroke [28].

Hepatic lipase catalyzes the hydrolysis of lipoprotein triacylglycerols and phospholipids. It participates with surface proteoglycans as a ligand in the activation of lipoprotein uptake by the liver including triglyceride-rich lipoprotein residues, LDL and HDL particles. Although the role of hepatic lipase in lipoprotein catabolism is well established, its role as an anti- or pro-atherogenic factor is still debatable. Probably, the anti- or proatherogenic role is mediated with the simultaneous presence of other abnormal lipids. Four polymorphisms of G250A, C514T, T710C, and A763G in the promoter region of the hepatic lipase gene (*LIPC*) have been described and associated with elevated HDL levels and CAD risk [29].

Triglyceride Metabolism

Serum triglyceride levels are an important independent risk factor for atherosclerosis. **Lipoprotein lipase (LPL)** is a key enzyme for the catabolism of triglyceride-rich lipoprotein particles using apoC-II as a cofactor. Reduced LPL activity leads to elevated triglyceride levels. More than 60 mutations of the *LPL* gene have been identified. D9N and N291S variants in the *LPL* gene are associated with an increased risk of coronary atherosclerosis [30].

Genetic risk factors for CVD that are not related to lipid metabolism attract attention as markers of predisposition to atherosclerosis.

Genes Associated with Endothelial Function

Endothelial dysfunction plays a key role in the development and progression of atherosclerosis. Reduced bioavailability of nitric oxide (NO) derived from endothelial **NO synthase (eNOS**) leads to deterioration of endothelial relaxation in arteries. NO also inhibits the aggregation of platelets, adhesion of leukocytes to the endothelium and the growth of vascular smooth muscle cells. eNOS is encoded by the *NOS3* gene, which is localized in chromosome 7q35/q36. Polymorphisms in the *NOS3* gene are associated with atherosclerosis. Polymorphisms of G894T and T786C in the promoter region of *NOS3* gene are associated with MI [31].

Manganese superoxide dismutase (MnSOD) is an antioxidant enzyme. MnSOD deficiency increases endothelial dysfunction. A16V polymorphism in the *MnSOD* gene is associated with the risk of carotid artery atherosclerosis and CAD [32].

Vascular endothelial growth factor (VEGF) receptor-2 (KDR) is the primary receptor for VEGF signals in endothelial cells. T604C polymorphisms in the promoter region of *KDR* G1192A and A1719T genes are associated with increased risk of CAD [33].

Genes Associated with Oxidative Stress

Reactive oxygen species (ROS) are also involved in the development of atherosclerosis. The system of nicotinamide adenine dinucleotide (NADH) / nicotinamide adenine dinucleotide phosphate (NADPH) oxidase which is a key source of superoxide anions in blood vessels affects lipid peroxidation and atherosclerosis [34].

CYBA gene encodes p22phox, a component of NADPH oxidase. C242T polymorphism of *CYBA* gene is associated with reduced oxidase activity of NADPH, reduced ROS production and increased risk of early CAD [35].

Myeloperoxidase (MPO) is an enzyme that is mainly produced by activated neutrophils and monocytes. MPO generates several ROS and is an active mediator of atherogenesis. G463A polymorphism in the promoter region of the MPO gene regulates MPO expression. A/A and A/G alleles are associated with reduced risk of coronary atherosclerosis [36].

Extracellular superoxide dismutase (EC-SOD) is an antioxidant enzyme found in high concentrations in blood vessels. R213G polymorphism of *EC-SOD* gene has been shown to be associated with increased risk of CAD in Danish population [36].

Glutathione peroxidase 1 (GPX1) is involved in limiting cellular damage caused by oxidation, and its deficiency leads to endothelial dysfunction. Reduced GPX-1 activity is associated with an increased risk of atherosclerosis. *GPX* gene polymorphisms are associated with increased risk of atherosclerosis [37].

Glutathione-s-transferase (GST) is an enzyme that plays a key role in cellular antioxidant defense mechanisms. In a recent study, the authors suggested that variants in GST gene may alter susceptibility to atherosclerosis [38].

Unbound protein 2 (UCP2) regulates ROS production in macrophages. G866A polymorphism in *UCP2* gene is associated with the risk of carotid artery atherosclerosis and CAD [39].

Hemoxygenase (HO) is the enzyme that is rate-limiting in the degradation of heme. *HO-1* gene is mapped to 22q12 chromosome. Short (GT)n repeats in *HO-1* gene increase transcription activity in response to oxidative stress and reduce the risk of CAD, while long (GT)n repeats in the promoter region of the *HO-1* gene increase the risk of CAD [40].

Genes Associated with Inflammation

Atherosclerosis is considered as chronic inflammatory disease, and inflammatory processes are crucial for the development of atherosclerotic plaques. The interaction between cellular and molecular immune/inflammatory components occurs at different stages of atherosclerosis. The relationship between immune/inflammatory genes and atherosclerosis is complex,

but recent genetic studies have given significant insight into the role of immune/inflammatory molecules in the pathogenesis of atherosclerosis [9].

Local and systemic inflammation is a key feature of atherogenesis, and increased levels of inflammatory biomarkers such as C-reactive protein (CRP) and fibrinogen are associated with increased risk of CVD. CRP is an acute phase marker and has prognostic value in atherosclerotic diseases. Polymorphisms in *CRP* gene, which are associated with a marked increase in CRP levels, may be predictors of increased risk of CAD [41].

Fibrinogen concentrations in plasma are considered as an independent predictor of MI. In addition to its role as a nonspecific marker of inflammation, fibrinogen may also play a direct role in atherogenesis and thrombogenesis, acting as a bridging molecule for many types of cell adhesion critical to atherogenesis [42]. Gene polymorphisms of fibrinogen are significantly associated with levels of fibrinogen in patients after MI, with the risk of MI, regardless of the plasma fibrinogen concentration [42].

Interleukins are a large group of cytokines with a wide range of inflammatory and immune functions. Genetic variations within *IL-1* gene cluster have been highlighted in the pathogenesis and progression of atherosclerotic diseases. Variants of the gene encoding *IL-1* receptor antagonist (*IL-1Ra*) promote susceptibility to carotid atherosclerosis and MI [43]. *IL-6* gene polymorphisms are associated with atherosclerosis of peripheral arteries and carotid arteries. IL-18 is a pro-inflammatory cytokine, and increased concentration of IL-18 increases the risk of CAD. Variants in *IL-18* gene affect IL-18 concentration and, therefore, can participate in the development of atherosclerosis. IL-10 has an anti-inflammatory effect, and the association of A4259G, G1082A, C592A and G2849A polymorphisms in *IL-10* gene with atherosclerosis of coronary and cerebrovascular arteries was established [43].

Proinflammatory cytokine TNF-α affects endothelial function, coagulation, insulin resistance and lipid metabolism. Lymphotoxin-alpha (LTα, also known as TNF-β) is a cytokine with multiple functions in the regulation of the immune system and in inflammatory reactions. The role of *TNF-α, TNF-β* and *TNF* receptor gene polymorphisms in atherosclerotic diseases is disputable [43].

Toll-like receptors (TLR) are immune receptors that recognize the difference between different pathogens and activate an innate immune response. TLR can also be activated by host-derived molecules. It has been suggested that TLR may be a key link between the development of cardiovascular disease and the immune system. *TLR* expression is regulated in endothelial cells and macrophages of atherosclerotic lesions. A299G polymorphism in *TLR* gene is associated with a reduced risk of atherosclerosis in the carotid artery, acute coronary syndrome, and MI [44].

Genes Associated with Vascular Modeling

In atherosclerosis there are changes in the structure and composition of the extracellular matrix. Matrix metalloproteinases (MMP) and transforming growth factor (TGF)β1 are crucial determinants of vascular remodeling and are involved in the pathogenesis of atherosclerosis. TGF-β1, which is involved in various processes including tissue remodeling, angiogenesis, immune response and inflammation, has been extensively studied in its role in atherosclerosis. Polymorphisms in the *TGF-β1* gene are described as risk factors for genetic susceptibility to MI, ischemic stroke, and carotid atherosclerosis [45].

Several studies on the relationship between polymorphisms in different MMP genes and atherosclerosis have been carried out. A common polymorphism in the promoter region of stromelysin-1 gene (*MMP-3*), in which one allele has a plot of six adenosines (6A) and the other one has five adenosines (5A) has been described. 6A/6A genotype was significantly associated with greater progression of coronary artery atherosclerosis and atherosclerosis of the carotid artery. It was also suggested that allele 5A which has high activity may predispose to plaque rupture and MI [46]. 1G/2G polymorphism in *MMP-1* gene can affect the risk of coronary artery disease, and *MMP-1 2G/2G* genotype in combination with 6A/6A genotype of stromelysin-1 significantly increases the risk of atherosclerosis in carotid artery. C1562T polymorphism in *MMP9* gene is also associated with the risk of CAD. A181G and C153T polymorphisms in *MMP-7* gene and A82G polymorphism in *MMP-12* gene affects the size of the coronary artery

lumen. Thus, polymorphisms in *MMP-1, MMP-3, MMP-7, MMP-9,* and *MMP-12* genes are possible risk factors for early atherosclerosis [46].

Genes Associated with Arterial Thrombosis

The formation of a blood clot in atherosclerotic lesions causes acute cardiovascular conditions, such as acute coronary syndrome and acute peripheral artery occlusion syndrome. Inflammation and extracellular proteases play an important role in plaque rupture, attract thrombogenic blood components in the subendothelial layer of the artery and result in thrombus formation [9]. The interaction between the cellular and molecular components of the coagulation and fibrinolysis pathways is essential for the formation of blood clots. Numerous studies have established the relationship of polymorphisms in genes encoding various coagulation factors, fibrinolysis factors and platelet surface receptors with atherosclerosis [47]. G1691A polymorphism of factor V gene and G20210A gene of prothrombin is associated with the risk of CAD [47]. Thrombomodulin is an endothelial glycoprotein that reduces thrombin activity. G33a polymorphism in the thrombomodulin gene reduces promoter activity and is significantly associated with MI, coronary artery disease, and carotid atherosclerosis [47]. Genetic variants in hemostatic genes are likely to have a moderate effect on the risk of atherosclerosis, but can modulate the balance between coagulation and fibrinolysis, thereby affecting vulnerability to thrombus blockage in atherosclerotic arteries.

Other Genes that Modulate Susceptibility to Atherosclerosis

Peroxisome proliferator-activated receptor (**PPAR**)γ is a member of the nuclear receptor family that helps in regulating fatty acid metabolism and differentiation of adipocytes. PPARγ plays a critical role in the pathogenesis of insulin resistance in type 2 diabetes mellitus and metabolic syndrome. The role of PPARγ in inflammation and atherosclerosis has recently been described [48]. P12A polymorphism in *PPARγ* gene is usually associated with atherosclerotic lesions. The protective role of 12A allele in carotid atherosclerosis and MI was established [48]. *PPARα* regulates genes involved in lipoprotein metabolism, inflammation and apparently also plays a role in the pathogenesis of atherosclerosis. L162V polymorphism in *PPARα* gene may have a protective role against atherosclerosis and CAD in patients with type 2 diabetes [48].

Thrombospondins consist of five extracellular multifunctional matrix glycoproteins. They play an important role in cell adhesion, coagulation and angiogenesis and serve as ligands for CD36 and integrins. In a study conducted in predominantly Caucasian populations, A387P polymorphism in thrombospondin-4 gene and N700S polymorphism in the gene of thrombospondin-1 were associated with early MI and CAD, whereas T > G substitution in the 3` nontranslated region of thrombospondin-2 had a protective effect against MI [49].

Elevated plasma homocysteine levels are a risk factor for atherosclerosis. Increasing the fasting homocysteine level by every 5 μmol/l increases the risk of CAD by 1.6–1.8 times. **Methyltetrahydrofolate reductase (MTHFR)** is a key enzyme in homocysteine metabolism, and polymorphism in *MTHFR* gene is a possible genetic risk factor for atherosclerosis. Associations of C677T polymorphism in *MTHFR* gene and atherosclerosis have been comprehensively investigated. Meta-analysis showed that all three C677T genotypes were associated with different degrees of risk for atherosclerosis. Szamosi et al., 2004, revealed hyperhomocystinemia in 32 children and adolescents among 15 examined persons at the age of 4–18 years, whose parents had signs of atherosclerosis at the age of up to 45 years (the frequency was 30.5%, in the control group — 5.4%); and an increase in homocysteine level was found in almost all homozytic carriers of C677T mutation [50].

Phosphodiesterase 4D (PDE4D) selectively degrades the second cAMP messenger, which plays a central role in the signal transduction and regulation of physiological reactions. Polymorphisms in *PDE4D* gene predispose to the development of carotid and cardioembolic stroke, regardless of the usual risk factors. Association between *PDE4D* gene polymorphisms and cardioembolic stroke was observed in some studies [51]. *PDE4D* gene polymorphisms are believed to affect the risk of ischemic stroke, but association with atherosclerosis remains controversial.

Recent Discoveries in the Molecular Genetics of Atherosclerosis

Several genomic studies have shown that the locus on 9p21 chromosome is significantly associated with the risk of CAD and MI. The genes of cyclin-dependent kinase inhibitor *CDKN2A* (encodes INK4 p16INK4a protein) and *CDKN2B* (encodes p15INK4b protein), *PSRC1* gene (encoding a proline-rich protein) on 1p13.3 chromosome, the gene of melanoma activity inhibition 3 (*MIA3*) on 1q41 chromosome, *SMAD3* gene on 15q22,33 chromosome, gene of methylenetetrahydrofolate dehydrogenase-like protein (*MTHFD1L*) on 6q25.1 chromosome and *CXCL12* gene on 10q11.21 chromosome, new genes in which polymorphisms may contribute to risk of developing early atherosclerosis, are associated with the development of CAD and MI. These findings strictly imply the role of cell cycle regulation in atherosclerosis pathogenesis [52].

In a recent study, the authors showed that a new locus near *PSRC1* and *CELSR2* genes on chromosome 1 probably increases the risk of coronary atherosclerosis by affecting LDL levels in plasma [53]. A recent meta-analysis of three genomes identified several polymorphisms associated with increased LDL concentrations that were present with increased frequency in CAD cases [54]. These results suggest that polymorphisms in new genes are involved in the regulation of LDL metabolism and the pathogenesis of atherosclerosis.

CXCL12 gene, which is associated with CAD, plays a role in mobilizing, differentiating vascular progenitor cells in response to vascular damage. Moreover, polymorphisms in *GATA2* gene are associated with coronary atherosclerosis [55]. GATA2 transcription factor is necessary for the development and differentiation of hematopoietic stem cells and progenitor cells. These observations show that genes and transcription factors that regulate hematopoietic stem cells and progenitor cells play a role in atherosclerosis / CAD pathogenesis. *GATA2* gene is expressed in both endothelial cells and vascular smooth muscle cells and is known to regulate several other endothelial-specific genes that are associated with CAD [55]. Polymorphisms in the *KALRN* gene located next to *GATA2* gene on chromosome 3 were also associated with CAD.

The long antisense non-coding RNA (*ANRIL*) gene was identified as the primary candidate gene for CAD susceptibility on 9p21 chromosome. The biological functions of *ANRIL* are largely unknown, but it is expressed in tissues and cell types that are involved in atherosclerosis [56]. Variants in 2 genes: *VAMP8*, which participates in platelet degranulation, and *HNRPUL1*, which encodes ribonuclear protein, are associated with early MI development [57]. The 719R allele in the gene which is a member of the kinesin 6 family (KIF6) was associated with an increased risk of CAD/MI. Kinesins are a large family of proteins involved in intracellular transport [58]. The identification of new genes, their exact functions and genetic polymorphisms will improve our understanding of the molecular mechanisms in atherosclerosis.

Promising Areas for Further Research

The development of atherosclerosis genetics is based on combined approaches. The availability of powerful molecular genetic research methods is likely to facilitate the identification of new genes and genetic polymorphisms associated with atherosclerosis and enhance our understanding of the pathophysiology of atherosclerotic vascular diseases. New-generation high-density matrices for genotyping provide improved resolution for genomic evaluation of common polymorphisms associated with atherosclerosis.

The study of gene expression profile by the microchip method was originally used to investigate transcriptional changes in human and animal atherosclerotic tissues. New-generation DNA microchips allow simultaneous analysis of thousands of transcripts in a single analysis. Interpretation of results with these high-performance technologies is often difficult and requires careful analysis. However, these studies can provide a wealth of information and sometimes unexpected results. Microchips can also be used to study the effects of treatment at molecular levels. Gene expression studies are likely to play an important role in the design of future diagnostic, prognostic, and therapeutic strategies for atherosclerotic vascular diseases. In recent years, there has also been a growing interest in systemic biology research, which focuses not on molecular components, but on interactions within gene networks. Using computerized

algorithms, it is possible to identify gene networks of atherosclerosis development. It is likely that in the long term, systemic biological approaches will increasingly be used to investigate the molecular mechanisms underlying the complex and heterogeneous phenotypes of human atherosclerosis.

The role of genetic variants in modulating therapeutic responses to drugs is also growing, which is likely to lead to the discovery of new approaches for individual treatment for patients suffering from atherosclerotic vascular diseases. However, the role of genetic testing in predicting atherosclerosis is controversial. Genetic screening tests for some monogenic diseases, such as FHC, have been successfully used to detect presymptomatic signs and have been found to be cost-effective. Genetic testing in screening for monogenic atherosclerotic disorders is likely to become more popular in the coming years. In non-monogenic atherosclerosis, the effect of any single gene variant on the clinical outcome of atherosclerosis is relatively modest. But the use of a panel of appropriate genetic tests in combination with risk factors for complex non-monogenic atherosclerosis can significantly improve the ability to predict the risk of atherosclerosis.

Conclusions

Rapid progress in human genome sequencing and molecular genetic techniques have helped in identifying susceptibility loci and associated candidate genes with atherosclerosis and comorbidities. Association of a large number of susceptibility genes with atherosclerosis reflects the enormous complexity of the disease. Multiple factors including endothelial dysfunction, defects in lipid metabolism, inflammation and immune responses, oxidative stress, cell proliferation, tissue remodeling and hemostatic defects are involved in the pathogenesis of atherosclerosis. Other genetic and environmental factors such as diabetes, hypertension, smoking, diet, exercise and stress further complicate the scenario.

The lack of consistent results from different studies and populations tends to create ambiguity in terms of the role of genetic variants in the pathogenesis of atherosclerosis. The probable reason is that many of the individual genetic variants have only a moderate impact on the risk of atherosclerosis, but their effects are enhanced in synergy with other genetic and environmental factors. In addition, variations in population groups, including differences in age, gender, ethnicity, and sample size, as well as differences in clinical outcomes, can significantly influence research results.

Conflict of Interests

The authors declare no conflict of interests

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STRATIFICATION OF NEPHROCEREBRAL AND CARDIOVASCULAR RISK IN CHRONIC GLOMERULONEPHRITIS (LITERATURE REVIEW)

Abstract

This article analyzes the literature data concerning the origin and progression of cerebrovascular and cardiac diseases in renal dysfunction. Cardiovascular diseases and chronic kidney disease have common "traditional" risk factors, while the growth of patients with renal impairment population currently occurs mainly due to secondary renal damage on the background of socially important diseases such as obesity, hypertension, atherosclerosis, type 2 diabetes mellitus, ischemic heart disease, and chronic heart failure. The presented data of scientific researches show the direct correlation between the decrease of the renal function and the increased risk of cardio- and cerebrovascular diseases and death, irrespective of other risk factors. Obesity and associated biological substrates are independent risk factors for persistent impairment of renal function. An increase in the body mass index causes both direct damage to the kidneys due to the disrupted synthesis of cytokines with nephrotoxic action by adipose tissue, and indirect damage by inducing the development of type 2 diabetes mellitus and hypertension, which are the most frequent risk factors for chronic kidney disease and cardiovascular diseases. The data are presented on the role of endothelial dysfunction in impaired renal function, which contributes to the formation of atherosclerosis, and the increase in the severity of the atherosclerotic process contributes to an increase in the severity of renal failure. Literature data on the place of the heart rate are also presented. The increase in the heart rate can lead to atherosclerotic induration of the arteries, which is associated increase in pulse wave velocity a violation of the mechanisms of autoregulation of the blood flow in the brain and kidneys.

Key words: *chronic kidney disease, glomerular filtration rate, risk factors, cardiovascular risk, cerebrovascular diseases*

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AP — atheromatous plaque; LVH — left ventricular hypertrophy; IHD — ischemic heart disease; MI — myocardial infarction; BMI — body mass index; LA — left atrium; CS — cerebral stroke; MRI — magnetic resonance imaging; DM —

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diabetes mellitus; GFR — glomerular filtration rate; CVD — cardiovascular diseases; CVC — cardiovascular complications; CIMT — carotid intima-media thickness; LVEF — left ventricular ejection fraction; AF — atrial fibrillation; RF — risk factors; CKD — chronic kidney disease; CG — chronic glomerulonephritis; HECGM — Holter ECG monitoring; Ch — cholesterol; CeVD — cerebrovascular diseases; HR — heart rate

The onset and progression of cerebrovascular and cardiac diseases in renal dysfunction are becoming relevant due to the widespread prevalence of chronic kidney disease (CKD), in particular chronic glomerulonephritis (CG). Recent studies have found that even a mild decrease in renal function is associated with an increase in the risk of cardio- and cerebrovascular diseases (CeVD) and death, regardless of other risk factors (RF) [1, 2]. Cardiovascular diseases (CVD) and CKD have common "traditional" RF, while the growth of the population of patients with renal impairment currently occurs mainly due to secondary kidney damage in the context of socially significant diseases: obesity [3, 4], hypertension [5, 6], atherosclerosis [7, 8], type 2 diabetes mellitus (DM) [9, 10], ischemic heart disease (IHD) [11, 12], and chronic heart failure [13, 14]. CVD prevalence in a population of patients with renal dysfunction is 64% higher than in individuals with normal renal function [15]. An independent inverse relationship was shown between glomerular filtration rate (GFR) < 60 ml/min / 1.73 m^2 and increased risk of death, cardiovascular complications (CVC), and hospitalization. The overall prevalence of CKD among obese people is 3.94% (3.62% among men and 4.25% among women), with a tendency to increase with age [16]. At the same time, the researchers confirmed that a history of hypertension, DM, myocardial infarction (MI) and cerebral stroke (CS) among the participants was associated with a higher risk of developing renal dysfunction, regardless of gender. Obesity and the associated biological substrates are independent RF of persistent deterioration of renal function: a 10% increase in body mass index (BMI) leads to an increase in the probability of 1.27-fold GFR decline [17]. In recent years, the incidence of glomerulopathy associated with obesity has practically increased 10-fold [18]. M. C. Foster et al. (2011) showed an association of albuminuria among men with an increase in visceral adipose tissue measured by computed tomography [19]. Most researchers agree that an increase in BMI causes direct kidney injury due to impaired synthesis of various nephrotoxic cytokines by adipose tissue, and also causes indirect kidney injury due to the induction of the development of type 2 DM and hypertension, which are the most frequent RF of CKD and CVD [18, 20]. Potential mechanisms of damage to both cardiovascular and renal systems in obesity are also realized through the effects of adipokines, primarily leptin, on the myocardium, the vessel wall and kidney tissue, with the development of generalized endothelial dysfunction [21, 22].

Due to the low resistance of the cerebral and renal arterial blood vessels, these organs in hypertension are subjected to hemodynamic stress due to a deeper penetration of the accelerated pulse wave. Therefore, hypertension contributes to a significant acceleration of the development and progression of atherosclerotic lesions of the main arteries of the brain and kidneys [23, 24]. In turn, a tense hemodynamic situation in case of elevated BP leads to the fact that the formation of atherosclerotic plaque (AP) can be complicated by its destabilization due to the loss of integrity of the plaque cap and the appearance of ulcerations of the plaque surface with parietal thrombus formation, as well as the development of hemorrhage into the plaque with an increase in its volume and obstruction of the lumen of the vessel that feeds the brain and kidneys [25]. Unstable AP can cause the development of cardiocerebral events and the progression of ischemic CKD, especially in elderly persons [26, 27].

An increase in BMI can often be accompanied by an increase in BP associated with the activation of sympathetic tone caused by the development of insulin resistance and atherogenic dyslipidemia [28]. Absolutely, these changes lead to progression of renal dysfunction and CVD. The presence of white matter hyperintensities and silent cerebral infarction is accompanied by an elevated risk of CS, cognitive impairment and dementia [29, 30-32]. Magnetic resonance imaging (MRI) performed on patients with hypertension and without obvious CVDs showed that silent cerebrovascular lesions are even more common (44%) than subclinical

cardiac and kidney damage (21% and 26%, respectively), and are often found in the absence of signs of damage to other organs [33]. In addition, typical for hypertension asymptomatic small deep brain infarcts, leukoaraiosis, atrophic changes in the form of dilation of the subarachnoid spaces and the brain ventricular system, are also a morphological substrate of vascular cognitive impairment.

The role of hypertension in the prognosis of cerebrovascular and cardiac complications in patients with CKD can hardly be overestimated. Timely and adequate correction of hypertension reliably postpones the onset of dialysis-dependent stage of renal dysfunction. According to some researchers, the frequency of hypertension is up to 40% at stage 1-2 of CKD, that is close to the frequency of hypertension in the general population [34, 35]. Diastolic dysfunction and/or left ventricular hypertrophy (LVH) developing in hypertension causes overload and dilation of the left atrium (LA), distension of ostia of pulmonary veins, which is a morphological prerequisite for the onset of cardiac arrhythmias, in particular, atrial fibrillation (AF) [36, 37]. On the one hand, high group ectopic electrical activity of the myocardium is a predictor of AF, and on the other hand, it is a predictor of the development of the LV geometry impairment [37, 38]. According to P. Kirchhof et al. (2016), in CKD, the risk of AF development is 2.5% at the 1st and 2nd stages of the disease, and the probability of AF is increased to 68% if GFR is ≤ 60 ml/min [38]. In another study by J. P. Piccini et al. (2013), a further decline in GFR (≤ 58 ml/min) by 5 ml/min was found to be accompanied by an increase in the development of CS by 9% [39]. It has been established that an increase in the risk of CS in AF is inversely related to the rate of decline in GFR [40], the progression of the disease, the development of the dialysis-dependent stage of CKD in the presence of AF [41], and an increased risk of MI [42]. It is important to note that timely, rational antihypertensive therapy reduces the relative risk of recurrent CS by 19% and coronary events by 20–25% [43, 44]. An ultrasound examination of the carotid arteries with measurement of carotid intima-media thickness (CIMT) and the assessment of the presence of plaques allows us to predict both cerebrovascular diseases (CeVD) and IHD, regardless of traditional cardiovascular RF [45, 46].

Endothelial dysfunction is already present in the early stages of CKD [47]. As CKD and endothelial dysfunction progress renal impairment contribute to the formation of atherosclerosis, an increase in the severity of the atherosclerotic process contributes to an increase in the severity of renal failure. At the same time, activation of inflammation processes and endothelial dysfunction occur concurrently with a decrease in GFR, an additional laboratory manifestation of which can be an increased CRP level in plasma. Higher concentrations of CRP are associated with accelerated loss of renal function on the one hand, and progression of endothelial dysfunction on the other hand [48]. Activation of inflammation occurs in parallel with the enhancement of the mechanisms of apoptosis with the underlying CKD [49]. APs are often detected in the carotid arteries when CIMT value is normal [50, 51]. The appearance of APs and an increase in CIMT were obtained in the study by O. V. Piyankina et al. among the patients with CKD at the predialysis stage of the disease [52]. Moreover, an *in vivo* study of the APs structure revealed its increased vulnerability in case of renal dysfunction [53].

Heart rate (HR) is a specific marker of life expectancy, reflecting the state of metabolism in the body [54]. Slowing the heart rate improves the balance between myocardial oxygen supply and demand in patients with IHD and significantly reduces the risk of cardiovascular complications and death. Increased HR is one of the predictors of hypertension and kidney hemodynamic stress development [55]. In the Framingham Heart Study, the overall mortality and mortality from CVD in people with hypertension almost doubled with an increase in HR for every 40 beats per min, regardless of additional RF [56]. At the same time, an increase in heart rate at rest can be a marker of imbalance of the autonomic nervous system, i.e. suppression of vagal activity or increasing sympathetic activity [57]. High HR increases the risk of AP damage due to hydrodynamic disorders, which underlies the development of acute cardiovascular and nephrocerebral events [58]. The mechanism of anti-atherosclerotic action of low HR is probably due to a positive effect on arterial stiffness. In contrast, the increase in HR can lead to atherosclerotic induration of the arteries, which is associated with

an increase in pulse wave velocity. Certainly, autoregulation of blood flow in the brain and kidneys is disturbed due to non-uniform elasticity, the presence of multiple arterial branches and low resistance of blood vessels.

The negative effect of an increase in HR is realized by several mechanisms, including an increase in myocardial oxygen consumption, a decrease in coronary blood flow during the diastole, an increased fibrillation threshold, stimulation of atherogenesis and AP ruptures, and possibly a reduction in renal blood flow (especially in the elderly patients). Conversely, HR reduction in myocardial ischemia reduces myocardial oxygen demand, prolongs the diastole, increases the blood supply to the damaged myocardial areas (in particular, the subendocardium), prevents AP rupture, has a beneficial effect on the ischemic myocardium and supports the contractile function of the heart, thereby inhibiting GFR decline. According to Copie et al. [59], HR assessed during Holter ECG monitoring (HECGM) has a prognostic value even higher than LVEF, which is usually used as a prognostic index. K. H. Bonaa et al. (1992) studied the relationship between HR and levels of cholesterol (Ch) and its fractions in plasma in more than 19,000 women and men of young and middle age [60]. Correlation of heart rate with the severity of coronary atherosclerosis was found in people who had myocardial infarction at a young age [61]. In this study, the increase in HR at rest by 5 beats per min corresponded to the progression of the lesion from 0.21 to 0.27 points [62]. Thus, summing up the data of literature analysis, we note that a comprehensive clinical and instrumental examination is necessary in case of renal dysfunction in order to identify potential RF of nephrocerebral and cardiovascular disorders to prevent serious cardiovascular and renal complications.

Conclusion

The complex integrative relationship of RF of nephrocerebral and cardiovascular disorders in renal dysfunction gives us grounds for further scientific research, which is of undoubted importance for improving the effectiveness of preventive measures, as well as improving the prognosis of disease and life in this category of patients.

Conflict of Interests

The authors declare no conflict of interests.

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ANTIBIOTIC-ASSOCIATED DIARRHEA: PATHOGENESIS, ACTUAL ASPECTS OF PREVENTION AND TREATMENT

Abstract

The article provides an overview of current Russian and foreign literature on the problem of pathogenesis, treatment and prevention of antibiotic-associated diarrhea. Antibiotic-associated diarrhea is one of the most relevant aspects of modern drug therapy due to the frequent prescription of antibacterial agents. Antibiotic-associated diarrhea (according to WHO) is defined as the presence of three or more episodes of an unformed stool for two or more consecutive days that occurred during or after the end of antibiotic therapy. The risk of this disorder development is high when using aminopenicillins, as well as their combinations with clavulanic acid, cephalosporins, or clindamycin. Despite the presence of a common etiologic factor — the intake of antibacterial agents, the immediate causes and mechanisms of antibiotic-associated diarrhea development in patients may be different. The article describes the main issues of the etiology and pathogenesis of this pathology, the risk factors for the development of antibiotic-associated diarrhea are named, which allows predicting this complication in certain categories of patients. The virulence factors of Clostridium difficile, Klebsiella oxytoca, Candida spp. and the clinical manifestations associated with their effects are highlighted. The clinical variants of this disease are described: 1) pseudomembranous colitis; 2) segmental hemorrhagic colitis; and 3) "mild illness". Contemporary literature data on the possibilities of prevention, as well as effective methods of treatment of antibiotic-associated diarrhea, are presented. For the treatment and prevention of all clinical forms of antibiotic-associated diarrhea, most authors suggest the use of drugs that make up the deficiency of normal intestinal microbiota — probiotics and prebiotics. The problem of the benefits of adjuvant therapy with probiotics during the course of antibiotics for the prevention of antibiotic-associated diarrhea remains controversial, the effectiveness and safety of the use of various probiotic cultures for this purpose is being studied. The information presented in this review is intended to target physicians to the rational use of antibacterial agents, and to early diagnosis of their most frequent side effect, antibiotic-associated diarrhea.

Key words: *antibiotic-associated diarrhea, pseudomembranous colitis, segmental hemorrhagic colitis, intestinal candidiasis, probiotics*

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AAD — antibiotic-associated diarrhea

The history of the existence and use of antibiotics as pharmaceuticals is less than a century, since the discovery of penicillin in 1928 by Alexander Fleming. However, it is impossible to imagine modern medicine without this group of drugs. Doctors of almost all medical specialties in their daily practice are faced with diseases and conditions that require the administration of antibiotic therapy. However,

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in addition to the undoubted benefits for humanity in terms of combating infectious agents, antibiotics have brought new problems and challenges to medical science, namely, a variety of pathologies associated with the violation of the qualitative and quantitative composition of human symbiotic microflora. One of the most common of these problems is antibiotic-associated diarrhea.

Antibiotic-associated diarrhea (AAD) occurs in 5–30% of patients, early — directly during antibiotic therapy, delayed — within two months after its completion.

Antibiotic-associated diarrhea (according to WHO) refers to the presence of three or more episodes of loose stools for two or more consecutive days that occurred during or after antibiotic therapy.

Almost all antibiotics can cause diarrhea, but the risk is highest when using aminopenicillins, as well as their combinations with clavulanic acid, cephalosporins, clindamycin [1, 2, 3]. According to the literature, the following incidence of AAD with administration of antibacterial agents was found: clindamycin — 20–30%, amoxicillin/clavulanate — 10–25%, cefixime — 15–20%, ampicillin — 5–10%, macrolides — 5%, fluoroquinolones — 2% [4] (Figure 1).

Experts from the Russian Gastroenterological Association in the guidelines for the diagnosis and treatment of Clostridium difficile-associated disease (2016) [5] identify the main risk factors for this infection, which include the fact of antibiotic therapy, as well as being treated in a hospital, and proven risk factors: age over 65 years, presence of concurrent diseases, recent surgery on the digestive tract, enteral nutrition, reduced acid production in the stomach, including, as a result of antisecretory therapy, and immunosuppressive therapy. A significant number of studies described in foreign literature are devoted to the study of risk factors for the development of AAD, and in particular AAD caused by Clostridium difficile infection [6–9, 10]. According to the results of meta-analyses of these numerous works, the importance of the following factors is also proven: simultaneous administration of several antibiotics, prior therapy with fluoroquinolones [8], administration of non-steroidal anti-inflammatory drugs, prolonged hospitalizations. Vitamin D deficiency [9] and high level of fecal interleukin-8 [10] were identified as possible risk factors for Clostridium difficile infection. The authors note the need for further research in this area, as the more significant factors of Clostridium difficile infection development will be determined, the more successful its prevention can become.

Despite the presence of a common etiological factor — treatment with antibacterial agents — direct causes and mechanisms of AAD in patients may be different. Different variants of AAD classifications based on AAD etiology and pathogenesis can be found in the literature. The division of AAD into diarrhea caused by Clostridium difficile infection and idiopathic form is most widely used [11]. Idiopathic AAD, in turn, is divided into infectious and non-infectious variants. Infectious idiopathic AAD is a diarrhea developed as a result of excessive growth of opportunistic intestinal flora due to suppression of normal microbiota. The most common etiological factor of this AAD variant is Clostridium difficile (16–20% of cases), as well as Clostridium perfringens, Staphylococcus aureus, Klebsiella oxytoca, and Candida spp. [2, 3]. Non-infectious idiopathic AAD may be due to the chemical effect of the antibiotic itself and/or is a consequence of its side effects on the

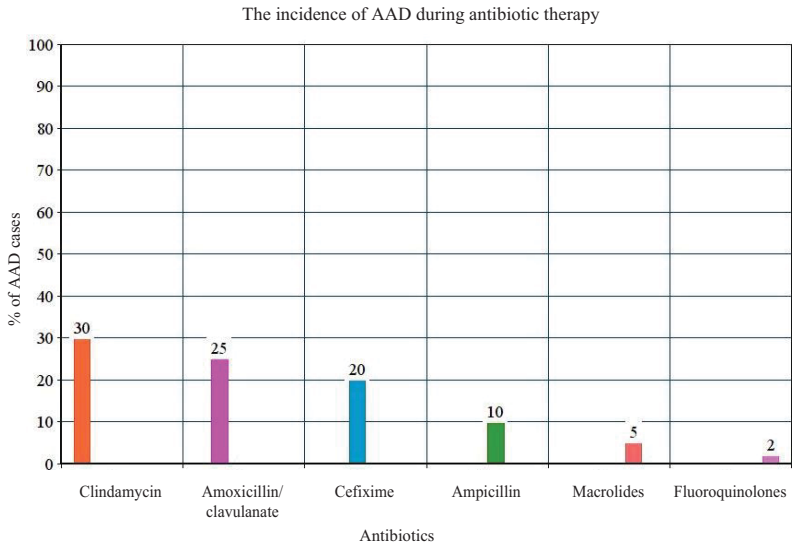

Figure 1. *The incidence of AAD during treatment with various antibiotics*

intestinal wall: for example, macrolides have the ability to stimulate the motilin receptors of the digestive tract and accelerate gastric evacuation and intestinal transit [12]; clavulanic acid enhances the motility of the small intestine; cephalosporin antibiotics stimulate postsynaptic receptors of gamma-aminobutyric acid in the mesenteric plexus and thus stimulate intestinal motility. Non-infectious AAD can also be osmotic or secretory in nature and occur due to impaired metabolism of bile acids and decomposition of carbohydrates in obligate anaerobic microflora [12]. In addition, osmotic pressure in the lumen of the intestine may increase due to incomplete decomposition and absorption of antibiotics themselves (cefixime). Intensification and acceleration of deconjugation and dehydroxylation processes of bile acids disrupts the absorption of fats, resulting in steatorrhea [13]. On the other hand, the suppression of lactobacilli increases the content of non-metabolized bile acids, which provoke the secretion of water and chloride ions in the lumen of the large intestine, which causes the secretory component of diarrhea.

Excessive growth and colonization of the large intestine with Clostridium difficile, an endospore-forming Gram-negative bacterium, causes the development of the most severe type of AAD — pseudomembranous colitis. Clostridium difficile is an obligate anaerobe; its endospores are found in large amounts in soil and water. It is known that up to 6% of healthy individuals have this bacterium in a very small amount in their intestinal microbiota. Due to the fact that Clostridium difficile is resistant to most antibiotics, during antibiotic therapy in the suppression of obligate intestinal flora, it is able to multiply excessively. Clostridium difficile is considered the cause of AAD in 10–25% of cases [3].

Clostridium difficile does not have the ability to invade. Pathological processes in the mucous membrane of the large intestine in pseudomembranous colitis develop under the action of bacterial exotoxins — enterotoxin A and enterotoxin B.

Enterotoxin A has a direct cytotoxic effect on the epithelial cells of the colon, binding to receptors on the apical surface of epithelial cells and reducing the density of the cell connection with each other, which leads to increased fluid secretion in the lumen of the intestine and enterotoxin B penetration into the intestinal wall. Enterotoxin B increases vascular permeability and stimulates the release of proinflammatory cytokines. Along with cytotoxic and cytopathic effects, it also contributes to the development of pronounced general intoxication and, in some cases, encephalopathy [14].

One of the waste products of Clostridium difficile, p-cresol, inhibits beta-dopamine-hydroxylase resulting in impaired formation of norepinephrine from dopamine. Thus, in the human body there is an imbalance of neurotransmitters, which explains the phenomenon of encephalopathy in patients with pseudomembranous colitis. In severe cases, a significant deficiency of norepinephrine and related phenomena of neurogenic orthostatic hypotension are possible [15].

The clinical manifestations of AAD vary from mild spontaneously stopped diarrhea to fulminant pseudomembranous colitis. There are three variants of AAD depending on the etiological agent, symptoms and features of intestinal mucosa lesion [17]: 1) pseudomembranous colitis; 2) segmental hemorrhagic colitis; 3) mild illness.

Pseudomembranous colitisis (AAD, the etiological agent of which is Clostridium difficile) is characterized by a watery stool with possible impurities of blood and mucus with a frequency of defecation from 5 to 30, presence of fever, leukocytosis. In severe pseudomembranous colitis fluid and electrolyte disorders, cardiovascular disorders, possible complications (toxic megacolon, toxic shock syndrome, intestinal perforation) develop.

Segmental hemorrhagic colitis is a variant of AAD, the etiological agent of which is Klebsiella oxytoca, a Gram-negative facultative aerobic bacterium, a representative of human opportunistic microflora. It is known that there is a toxigenic strain of Klebsiella oxytoca that can actively reproduce in the intestine when suppressing a normal microbiota and produces a toxin that has a direct cytotoxic effect on intestinal epithelial cells. As a result, hemorrhagic inflammation develops, which is manifested by diarrhea with blood admixture [16].

Mild illness is the mildest form of AAD, including any symptoms from the intestines occurring due to antibiotic therapy unrelated to any of the above variants of AAD. Thus, this definition includes dysbiosis that occurs when antibiotics are used, including that which is associated with excessive growth of Candida fungi in the intestine [17]. Colonization of

both the large and small intestine by Candida spp. becomes possible due to the suppression of normal intestinal microbiota by broad-spectrum antibiotics with anti-anaerobic activity and/or antibiotics creating a high concentration in the wall of the digestive tract, such as cephalosporins of the third and fourth generations. The presence of risk factors such as hypochlorhydria or achlorhydria, reduced motility, prior mucosal damage as a result of any chronic pathology, nutrient deficiency, chemotherapy or radiation therapy is also significant.

Virulence factors of Candida spp.: capacity for adhesion in almost all human tissues; mycogenic sensitization of the patient's body due to the action of Candida-produced alcohol dehydrogenase and acid P2-protein; ability to synthesize aspartic protease and phospholipase, as well as hemolysin, the presence of various endotoxins that damage human tissues; capacity for rapid adaptive phenotypic variability; immunomodulatory effects that reduce the effectiveness of human antifungal resistance; capacity for suppression of normal human flora.

The growth of Candida fungi in the human digestive tract can have three forms:

1) Silent fungal carriage.
2) Non-invasive enterocolitis (luminal mycopathy) is an inflammation of the mucosa not penetrating beyond the lamina propria of the mucosa; occurs without transformation of fungus in filamentous form; the pathogenesis of this form of intestinal candidiasis is associated with the development and extension of dysbiosis with intoxication due to the products of abnormal fermentation of nutrients and metabolites of fungi, with the development of secondary immunodeficiency and fungal allergy.
3) Invasive damage to the intestinal wall due to the penetration of the filamentous form into the mucous membrane. Most often, these forms of intestinal candidiasis are stages of the pathological process [17].

Treatment of AAD depends on the specific etiological agent. General measures are discontinuation of antibiotic treatment causing AAD, correction of fluid and electrolyte disorders, malabsorption syndrome, correction of immunodeficiency. The use of antidiarrheal agents that reduce motility is absolutely unacceptable, as it increases the time of contact of bacterial or fungal toxins with the intestinal wall.

Vancomycin and/or metronidazole are used for the treatment of pseudomembranous colitis caused by Clostridium difficile. An important condition is the oral administration of vancomycin and metronidazole, intravenous administration of these drugs is much less effective, since this method of administration does not create sufficient concentrations in the intestinal wall [4, 20]. Segmental hemorrhagic colitis caused by Klebsiella oxytoca usually does not require antibiotics, but in some severe cases it is possible to use fluoroquinolones or metronidazole [16].

In the treatment of intestinal candidiasis when choosing antifungal agents, it is important to correctly assess the form of candidiasis: invasive or non-invasive.

Non-invasive candidiasis (luminal mycopathy) does not require the administration of resorbable antifungal agents, and it is enough to use slightly resorbable polyenes: nystatin, natamycin. In invasive candidiasis administration of resorbable azole antifungals in mean therapeutic doses is mandatory [17].

For the treatment and prevention of all clinical AAD forms, most authors suggest the use of drugs that compensate for the deficiency of the normal intestinal microbiota — probiotics and prebiotics [19, 21, 22]. The question of the benefits of concomitant probiotic therapy during the course of antibacterial agents for the prevention of AAD remains debatable to some extent, and efficacy and safety of various probiotic cultures used for this purpose are being studied. It is believed that probiotics restore the resistance of the intestinal mucosa to colonization by pathogenic and opportunistic bacteria, which is reduced due to the suppression of normal intestinal microbiota, and increase local immunity. Also, the contribution of prebiotic strains to the process of intestinal digestion, which also becomes defective secondary to antibiotic therapy due to changes in the composition of the intestinal microflora, is important to prevent the development of diarrhea. It should be taken into account that the efficacy of various probiotics for the treatment and prevention of AAD varies and depends on the resistance of the culture to the action of gastric acid and bile, the ability to colonize the mucous membrane of the colon and sensitivity to antibiotics [22].

Experts from the Global Gastroenterological Association agree that, to date, convincing evidence of the efficacy of therapy with probiotics in the prevention of Clostridium difficile infection has been accumulated. However, they agree with the opinion of USA Food and Drug Administration (FDA) that more information is required which is based on randomized placebo-controlled blind studies in order to be able to name specific probiotics with proven efficacy [23]. On the other hand, in foreign literature in recent years there are more reviews on this issue, as well as meta-analyses of data on the efficacy and safety of probiotics for the prevention of Clostridium difficile infection designed to help the practitioner to form an opinion on this problem [24, 25, 26, 27]. The data presented in these works convincingly show a positive result of early and rational use of probiotics with antibiotic therapy to prevent the development of AAD.

A systematic review and regression meta-analysis conducted by scientists at Cornell University (New York) include 19 published studies with a total of 6,261 patients. The incidence of manifest Clostridium difficile infection was shown to be 1.6% in patients receiving probiotics during antibiotic therapy compared with 3.9% in the control cohort, and this difference was statistically significant ($P < 0.001$). Meta-analysis showed that the efficacy of probiotic therapy for the prevention of AAD was the higher, the faster it was started after the first dose of the antibiotic. There was no increase in the frequency of any side effects in combined therapy with antibiotics and probiotics. The authors concluded that early administration of probiotics reduces the risk of Clostridium difficile infection by more than 50% in inpatients receiving antibiotics [27].

Other meta-analyses have also shown that polycomponent probiotics including up to 16 different strains, as well as monocomponent ones containing Saccharomyces boulardii and Lactobacillus rhamnosus GG have the highest preventive efficacy [28]. For the treatment of severe and recurrent forms of pseudomembranous colitis that are resistant to vancomycin and/or metronidazole, some authors suggest using the method of fecal microbiota transplantation. In Western literature in recent years, a number of studies have been published that report the successful use of this method, including in patients with immunodeficiency [29, 30, 31, 32].

Despite gradually accumulating experience of a successful fight against AAD, many authors recognize that the best way of preventing this condition is a carefully weighed approach to antibiotic therapy in each case.

Based on the given literature data, it can be concluded that antibiotic-associated diarrhea is one of the important problems in modern medicine attracting the attention of scientists and doctors around the world. Risk factors and pathogenetic mechanisms of development of this pathology, as well as the potential of probiotic therapy in terms of preventing the occurrence of AAD require further study.

Conflict of Interests

The authors declare no conflict of interests.

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DENGUE FEVER IN EMERGENCY MEDICINE PRACTICE

Abstract

Due to the increasing number of Russian citizen's visits to the tropics, the number of cases of imported endemic infectious diseases, mostly dengue fever (DF), also has increased. Dengue fever is an acute viral vector transmitted disease characterized by fever and intoxication, with the possible development of hemorrhagic syndrome and shock, in which survival depends on the time of the onset of intensive care. The greatest incidence of DF in Moscow is associated with travelling to the tropics during the Christmas holidays, which coincides with the seasonal rise in the incidence of influenza and other ARVIs. However, emergency medical technicians mostly (except for cases of calling the ambulance to the medical institution during the working hours of the laboratory) are not able to carry out and assess even minimal hematological parameters. Therefore, when diagnosis and determining the phase of the disease and its severity, the emergency medical technician can rely only on epidemiological and clinical data. In this regard, a group of authors proposed an algorithm for early diagnosis and treatment of patients with suspected dengue fever at the prehospital stage, taking into account clinical symptoms and standard tourniquet test.

Key words: *dengue fever, emergency medicine, tourniquet test, dengue shock syndrome, classification*

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DF — dengue fever, CDF — classical dengue fever, DHF — dengue hemorrhagic fever

Fever is one of the most common causes of seeking emergency medical care. It is also the most common reason for calling an ambulance in up to 30% of cases, and a house-call pediatrician in 8 of 10 calls [1]. The number of calls for ambulance and emergency medical care due to high body temperature has a pronounced seasonality with a maximum in March (up to 600 calls every day) and a minimum in June (up to 150).

Dengue fever (DF) is an acute viral vector transmitted zooanthroponosis characterized by fever, severe myalgia and arthralgia, exanthema, lymphadenopathy, and leukopenia [2]. According to the World Health Organization (WHO), there are now more than 2.5 billion people living in areas where DF is spread, which makes DF the second most common transmissible infection in the world after malaria.

The DF pathogen is the dengue virus belonging to the Flaviviridae family, which has 4 genotypes, and the immune response is type-specific and life-long, which allows for recurrent disease when infected with heterologous genotype. At the same time, it is

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believed that re-infection can lead to the development of more severe forms of the disease due to the phenomenon of antibody-dependent enhancement of the infection [3, 4].

The spread of DF is closely related to natural area of vectors — mosquitoes of Aedes genus, primarily, Ae. aegypti. The disease is common in both hemispheres throughout the tropical and partly subtropical zone limited to the winter isotherm equal to 10 °C, which prevents the reproduction of mosquitoes [4]. Cases of local transmission in Southern Europe associated with an alternative, more cold-resistant vector, Ae. albopictus, are reported regularly. On the territory of the Krasnodar Krai there are stable populations of Ae. aegypti, which may predetermine local transmission within the Russian Federation.

On the basis of sanitary rules, DF is included in the list of diseases requiring measures for sanitary control of Moscow [1, 2, 5, 6]. Official registration of DF in the Russian Federation began in 2012. During this time more than 800 cases of the disease were registered [7], while after the recession associated with the economic crisis in 2013–2014, the number of DF cases has continued to grow in recent years (Figure 1). An increase in the number of DF cases inevitably leads to severe forms of the disease. A case of hemorrhagic DF with severe liver damage secondary to Wilson's disease was described in 2013 [8]. A case of acute myocardial infarction secondary to severe DF was described in 2018 [9], and in 2014 the first case of fatal dengue shock syndrome was registered in Russia, in a woman who had visited an endemic region for the first time [10]. Currently, the International Classification of Diseases, X revision (ICD-10) has been adopted as a single classifier in Russia [11]. In this classification, dengue fever has two codes: A90 is dengue fever or classical dengue fever (CDF), and A91 is hemorrhagic fever caused by dengue virus (HDF) [12].

According to the 10-year observation conducted at the State Budgetary Healthcare Institution of Infectious Clinical Hospital No. 1 of the Department of Health of Moscow, more than 90% of cases of DF are imported from the Asian region, with more than 50% from Thailand.

In the analysis of referral diagnoses in patients with DF hospitalized in 2009–2018, diagnosis of fever of unknown etiology was the most commonly reported for referral (Table 1).

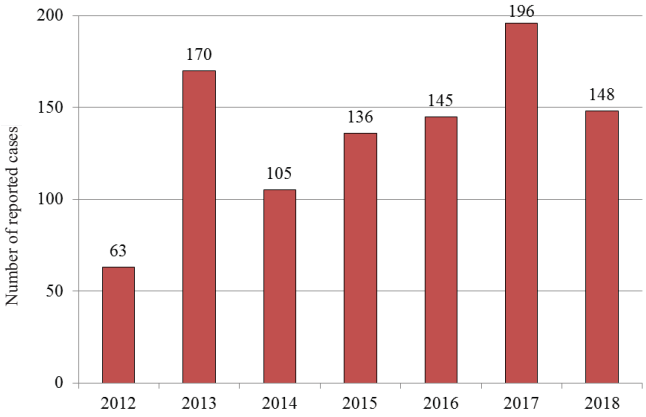

Figure 1. *Incidence of dengue fever in the Russian Federation from 2012 till June 2018 (according to the data of the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, Rospotrebnadzor)*

Table 1. *Referral diagnoses of patients with dengue fever (n = 257)*

Referral diagnosis	Number of cases	%
Fever of unknown etiology	168	65.4
Dengue fever	40	15.6
ARVI	36	14.0
Influenza	8	3.1
Rubella	2	0.8
Meningitis	1	0.4
Paratonsillar abscess	1	0.4
Hepatitis A	1	0.4

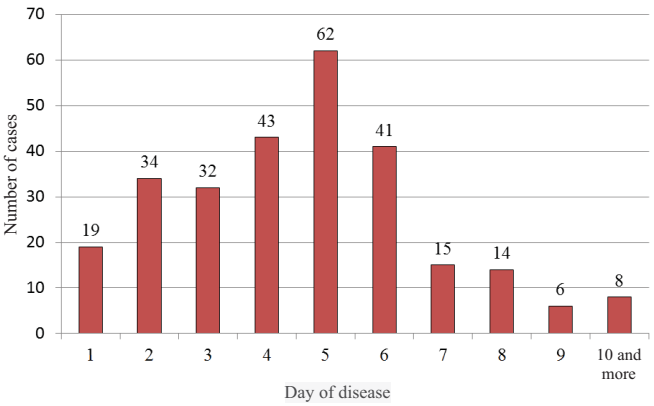

Figure 2. *Days from disease onset to admittance (according to data of Infectious Clinical Hospital No. 1, Moscow)*

Among hospitalized patients, 31% was hospitalized during the first 3 days of the disease, 58% — in 4 to 7 days, and 11% — during the second week of the disease (Figure 2), which was associated with both late seeking of medical care and incorrect interpretation of the fever by primary care physicians, which in turn led to delayed laboratory examination and unjustified prescription of treatment. Among the interviewed patients, 17.8% received antibiotics, and no tests for malaria were performed in an outpatient setting in any case, which is mandatory in febrile patients arriving from endemic regions.

Classification and Diagnosis of Dengue Fever

Currently, two classifications of DF are used in the world. The WHO classification dated 1997 provides for the division of dengue fever into classical and hemorrhagic (Table 2), with differentiation of HDF by 4 degrees of severity, of which 3 and 4 were attributed to shock syndrome [13].

Experience has shown that, in practice, this grading did not always correspond to the severity of the disease, and in 2009, WHO experts proposed a new interpretation (Table 3), which includes the following categories: probable dengue fever, dengue fever with severe signs and severe dengue fever [4]. In examination of patients admitted to intensive care units (ICUs), it was found that the 2009 classification has the advantage that it includes the definition of dysfunction of any system as a criterion of severe dengue fever, while the 1997 WHO classification takes into account only hemodynamic disorders as a criterion for hemorrhagic fever of III and IV degrees [14, 15]. However, according to Brazilian researchers, APACHE II scale was more sensitive than both WHO classifications of patient survival at ICU admission [15]. In addition, the study conducted in 2018 showed that mortality in patients with DF who were in ICU correlated with a low score on the Glasgow coma scale, platelet count, and multiple organ dysfunction syndrome severity [16].

It should be noted that all three classifications provide for the assessment of laboratory parameters (hematocrit, platelet count, electrolyte composition), which can be done only when calling an

Table 2. *Grading the severity of dengue fever (WHO, 1997)*

Form	Severity	Clinical symptoms	Laboratory criteria
CDF		Fever and 2 or more symptoms: headache, retroorbital pain, myalgia, arthralgia	Leukopenia (not in all cases). Thrombocytopenia may exist. No signs of plasma loss
HDF	I	The same symptoms + positive tourniquet test	The same parameters + thrombocytopenia less than 100,000/μl Hematocrit ≥ 20% of normal range
HDF	II	The same symptoms and occurrence of spontaneous bleeding	
HDF	III	The same symptoms with hemodynamic disorders	
HDF	IV	Shock with undetectable pulse and blood pressure	

Table 3. *Suggested dengue fever classification and levels of severity (WHO, 2009)*

Probable dengue fever	Dengue fever with severe signs	Severe dengue fever
Accommodation or travel to an endemic area, fever, and two or more of the following symptoms: - nausea, vomiting; - exanthema; - retroorbital pain; - positive tourniquet test; - leucopenia; - any grave symptom.	Abdominal pain Repeated vomiting Signs of fluid accumulation (swelling, ascites, etc.) Bleeding of mucous membranes Lethargy or anxiety Hepatomegaly > 2 cm Increased hematocrit Rapid reduction of platelet count	Signs of plasma loss (shock, fluid accumulation in the cavities, respiratory distress syndrome) Acute bleeding Multiple organ dysfunction syndrome Increased AST or ALT ≥ 1000 Impairment of consciousness

ambulance to a medical institution during laboratory working hours. In this regard, for assessment of the severity of the disease and choice of strategy of therapy and medical evacuation, the medical worker can only rely on clinical symptoms.

According to the general opinion of leading specialists in infectious diseases, due to pronounced clinical polymorphism, the final diagnosis of dengue fever should be confirmed by specific laboratory methods [3]. In this regard, there is a controversial question on the possibility of dengue fever diagnosis at the pre-hospital stage. The WHO classification makes it possible to establish the diagnosis of probable dengue fever (see Table 2) [4]. A similar recommendation for diagnosis is presented in the clinical guidelines on dengue fever in adults of the National society of infectious diseases [3]. Such a diagnostic approach has been approved by the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing for a number of infectious diseases [17, 18]. Thus, the presence of fever that has developed after a visit to countries in South and South-East Asia, combined with two or more symptoms from the following: nausea, vomiting, exanthema, eye pain, positive tourniquet test, abdominal pain, bleeding of mucous membranes, lethargy or anxiety, hepatomegaly more than 2 cm from the costal margin, gives reason to diagnose suspicion of dengue fever by an emergency medical technician.

Therapeutic Strategy in Different Timing of the Disease

When examining a patient with fever, it is especially necessary to pay attention to their social history. When gathering anamnestic data, the fact of the patient staying in an endemic area (risk area) during the seasonal rise of morbidity (risk time) within the incubation period of the disease, the presence of contact with a patient suffering from a similar disease, or contact with infectious material, the patient having mosquito, lice, fleas, tick bites (risk factors), as well as for other possible risks of infection, including the patient's attitude to the contingents at risk, are clarified [19]. At the same time, as shown by our observations, severe forms of DF can develop in primary infection, and therefore the lack of data on previous DF does not allow excluding the development of hemorrhagic or shocking syndrome.

Currently, during DF it is customary to distinguish three phases of the disease: febrile phase, critical phase, and recovery or convalescence phase. The division of the disease by stages is determined not only by the clinical symptoms typical for each of them, but also directly reflects the pathogenetic chain, and allows to choose the necessary therapeutic strategy based on the timing of the disease (Figure 3).

The febrile phase lasts up to 3–4 days from the moment of the sudden onset of the disease and is accompanied by high fever with chills, headache, eye pain, and myalgia of varying intensity. During physical examination of the patient, moderate skin hyperemia can be detected; although, with underlying sunburn obtained in the endemic region, the skin color can be difficult to assess. Oropharyngeal mucosal hyperemia quite often occurs in patients, which can lead to an erroneous diagnosis of ARVI. But the absence of sore throat, rhinitis, cough, and, first of all, patient's social history, do not give grounds to diagnose respiratory infection. It should be noted that in the first 3 days in patients with dengue fever, complications do not develop, and in this regard, oral hydration, paracetamol (drugs containing acetylsalicylic acid are excluded) and control of platelet and hematocrit parameters are recommended. In addition, based on SanPiN 3.2.3215-14, all patients with high body temperature, who came from tropical regions, should be examined for malaria [20]. In this regard, if it is impossible to perform examination on an outpatient basis, hospitalization in an infectious disease hospital is indicated.

The critical phase (4 to 7 days of the disease) is caused by damage to the capillary vessel wall with the development of endothelial dysfunction syndrome common to all hemorrhagic fevers. In these terms, hemorrhagic syndrome and/or plasma leakage from the blood stream to the interstitial space may develop. Typical complaints: occurrence of pruritus or paresthesia of the hands and feet, petechial rash (most often on the shins), dizziness, dry mouth, reduced diuresis, the occurrence of previously unusual bleeding of the mucous membranes,

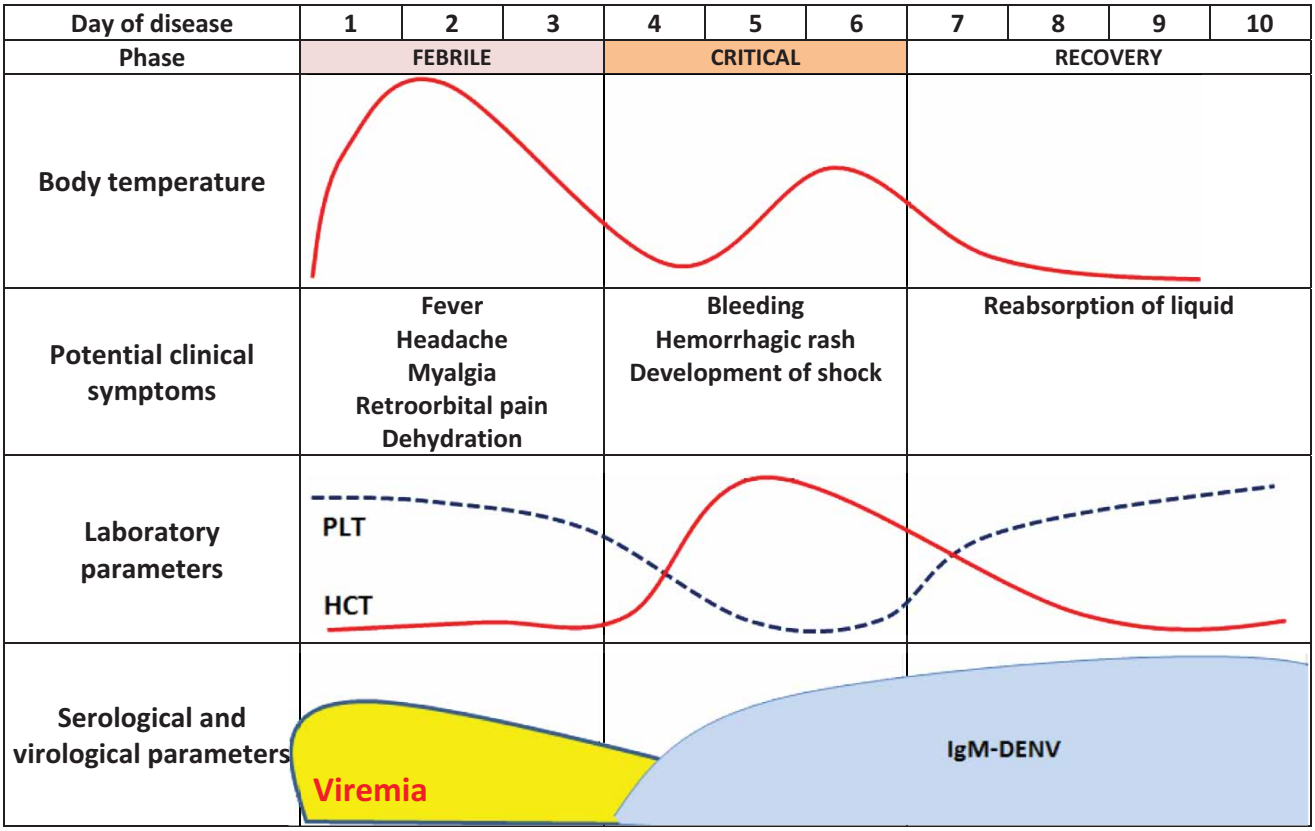

Figure 3. *Dengue fever phases (scheme)*

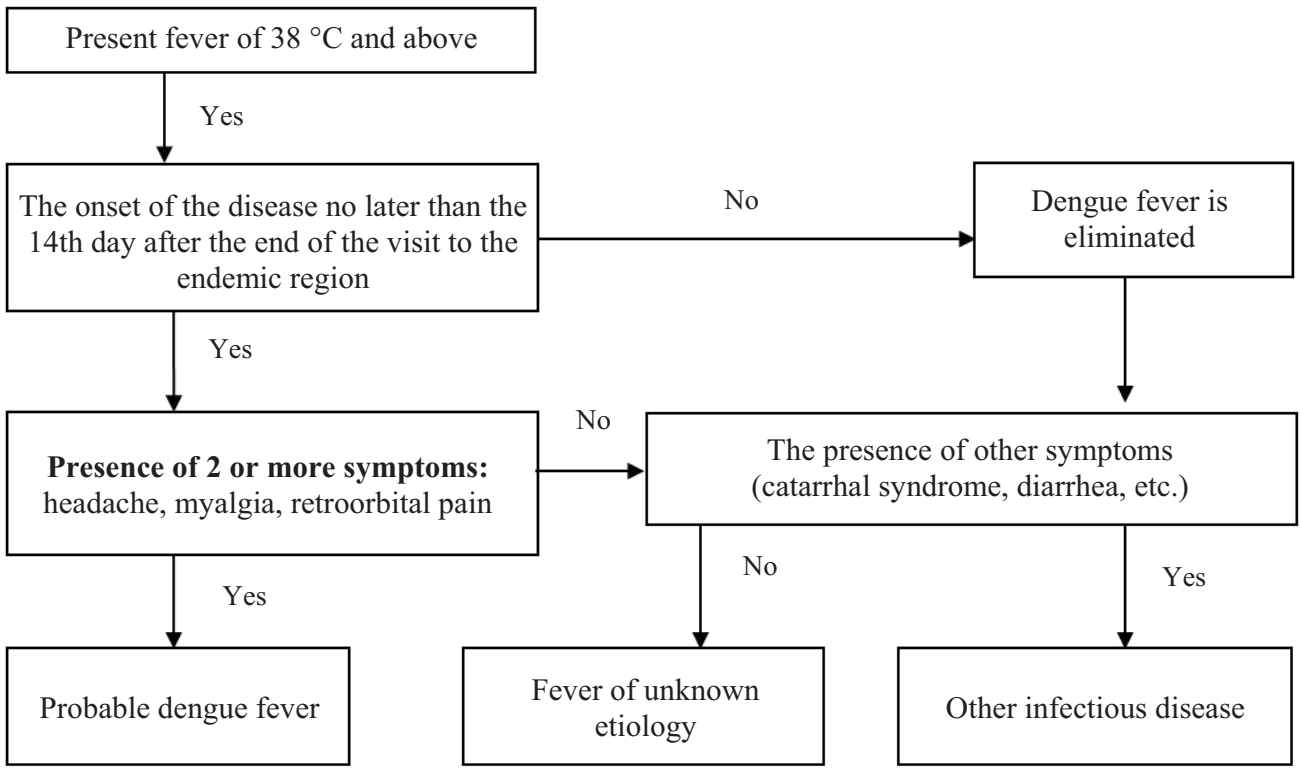

Figure 4. *Dengue fever diagnosis algorithm*

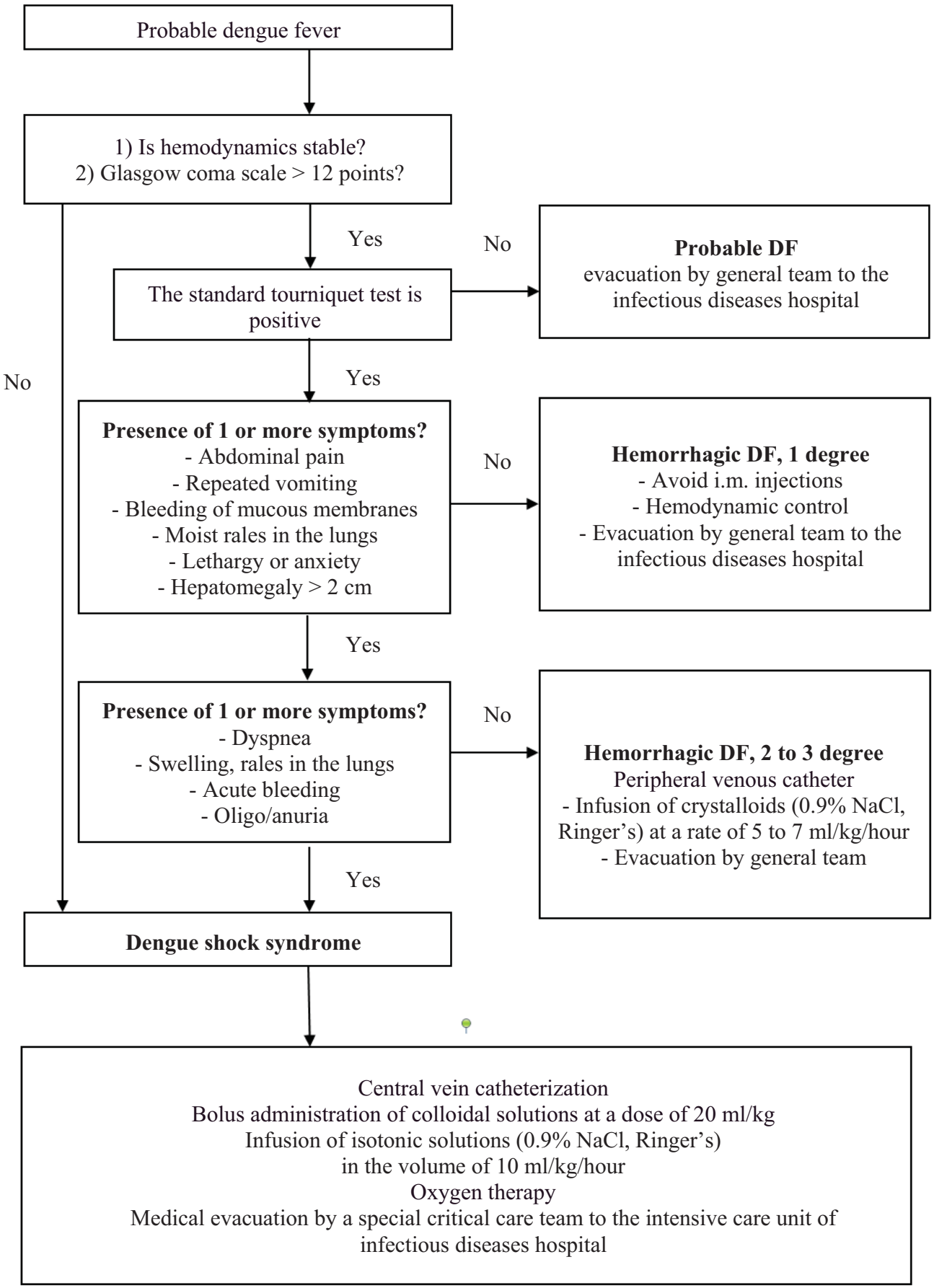

Figure 5. *Algorithm of therapy and medical evacuation of a patient with probable dengue fever*

premature and/or more abundant vaginal discharge. Assessment of hemorrhagic syndrome is carried out on the basis of the patient's complaints (the presence of nasal bleeding, bleeding gums, bleeding from the genital tract, not peculiar to the patient). Even in the absence of such complaints, the patient on Day 4 to 7 of the disease is required to take a standard tourniquet test, with a positive result of which it is necessary to diagnose hemorrhagic dengue fever. With stable hemodynamics and no signs of internal bleeding, the patient is hospitalized in the isolation unit of the infectious disease hospital.

With the development of dengue fever with emergency signs, the administration of isotonic saline solutions (0.9% sodium chloride, Ringer's, Hartmann's solutions) in an amount of 5 to 7 ml/kg per hour for 1–2 hours, and then 3 to 5 ml/kg for 2–4 hours is indicated, after which the volume of infusion is reduced to 2–3 ml/kg per hour. In the absence of improvement and increase in hematocrit, the infusion rate is increased to 10 ml/kg per hour.

The problem of the use of crystalloid solutions is associated with a rapid redistribution of the injected volume from the bloodstream to the interstitial fluid. The existing experience of therapeutic use of colloidal solutions indicates the advisability of their administration in the case of development of hemodynamic disorders associated with endothelial dysfunction [21]. With the development of hypotension and shock syndrome, WHO recommends bolus administration of colloidal solutions in the volume of 20 ml/kg followed by administration of crystalloids at a rate of 10 ml/kg per hour [4].

The recovery phase (the second week of the disease) is accompanied by stabilization of body temperature, blood pressure, resorption of fluid from tissues into the bloodstream. Within 1–2 months, patients may complain of weakness, sweating, hair loss, and work decrement. These symptoms are not specific to DF, but are inherent in all viral fevers accompanied by damage to the endothelium. At this stage of the disease, hospitalization is not required; outpatient follow-up with hematological control and serological examination for mosquito fevers is indicated taking into account the region of stay.

Standard Tourniquet Test

The procedure for carrying out a standard tourniquet test (for its conduction it is necessary to have a mechanical tonometer and a stopwatch, a ruler or a sheet of paper with a cut circle with a diameter of 3 cm)

1. Measure blood pressure.
2. Create a compression of shoulder using tonometer cuff at the level of pulse pressure for 5 minutes.
3. Release air and remove the cuff.
4. Estimate the number of petechial elements appearing on the forearm. Make a calculation in the area of the maximum number of elements.

If there are 20 or more elements per square inch, the tourniquet test is considered as positive.

Thus, the diagnosis, as well as the first aid and medical evacuation strategy can be represented as the following algorithm (Figure 4, 5):

Conflict of Interests

The authors declare no conflict of interests.

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THE MEDIC-STATISTICAL CHARACTERISTIC INCIDENCE OF PNEUMONIA IN THE UDMURT REPUBLIC

Abstract

Community-acquired pneumonia (CAP) is an urgent problem of modern medicine due to its high prevalence, severe course, the increasing resistance to antibacterial therapy, a large number of complications, and high mortality. Udmurt Republic is one of the leaders in respiratory diseases incidence, including CAP, among other regions of the Russian Federation. It is therefore necessary to analyse and predict CAP incidence for further improving the health care. **The objective** of the study was to analyse respiratory disease incidence and mortality in the Udmurt Republic over a period of 2009-2016. **Materials and methods**. A retrospective and prospective clinical and epidemiological study on the prevalence and primary incidence of respiratory diseases among the adult population of the Udmurt Republic (UR) living in 4 cities (Izhevsk, Sarapul, Glazov, Votkinsk) and 25 rural areas for the 8-year period (2009–2016) was conducted. The analysis is carried out based on the data from state statistical accounts and records of the Budgetary Healthcare Institution of the Udmurt Republic Republican Medical Information and Analytical Center of the Ministry of Health of the Udmurt Republic. **The results of the study**. The prevalence of respiratory diseases in the Udmurt Republic was 49,871.39 ± 1.33 per 100,000 people. Mean growth rate was 2.3%, and mean increment rate was 0.25%. Compared to the data for the same period in Russia, mean growth rate was 1.7%, and mean increment rate was 5.48%, which indicates a slight decrease in the incidence. In the analysis of the structure of respiratory diseases incidence in the population of the Udmurt Republic it was found that this rate has not changed significantly throughout the follow-up period. At the same time, pneumonia and chronic obstructive pulmonary disease (COPD) dominate every year. Assessing the rate of the primary respiratory diseases incidence, it is noted that mean growth rate in the UR is 105.42%, the mean increment rate is 5.42%, compared to the mean growth rate (87.07%) and mean increment rate (12.93%) in the Russian Federation. **The conclusion**. Thus, in the UR, as in the entire Russian Federation, there is a consistently high pneumonia incidence. At the same time, there is a tendency to higher incidence and mortality caused by this pathology. This circumstance requires further study of the problem of pneumonia, including the improvement of methods for its medical treatment.

Key words: *respiratory diseases, community-acquired pneumonia, the Udmurt Republic, medic-statistical characteristic of incidence rate*

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CAP — community-acquired pneumonia, UR — the Udmurt Republic, COPD — chronic obstructive pulmonary disease

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Respiratory diseases dominate in the structure of the overall incidence and mortality worldwide [1, 4, 5, 11]. Among them, community-acquired pneumonia (CAP) is an urgent problem of modern pulmonology. Despite the great progress made in understanding the etiology, pathogenesis and treatment of this pathology, there is an increase in the number of patients worldwide, and, consequently, mortality [4, 6]. Thus, the average annual incidence of community-acquired pneumonia among adults in recent years in Europe was 1.07–1.2 per 1,000 inhabitants per year, and in older age groups it was 14 per 1,000 person-years [10]. Primary incidence rates in the CIS generally indicate a significant increase in the incidence of respiratory diseases [8]. In 2015, the primary incidence of respiratory diseases in Russia increased by 1.3%, amounting to 338 cases per 1,000 people [7]. Thus, the level of incidence and mortality from CAP remains at a consistently high level, thereby giving the prerequisites for development and methods of improving the treatment of this disease.

Study Objective

Analysis of incidence and mortality rate from respiratory diseases in the Udmurt Republic over a period of 2009–2016.

Materials and Methods

A retrospective and prospective clinical and epidemiological study on the prevalence and primary incidence of respiratory diseases among the adult population of the Udmurt Republic (UR) living in 4 cities (Izhevsk, Sarapul, Glazov, Votkinsk) and 25 rural areas for the 8-year period (2009–2016) was conducted. The analysis is carried out based on the data from state statistical accounts and records of the Budgetary Healthcare Institution of the Udmurt Republic Republican Medical Information and Analytical Center of the Ministry of Health of the Udmurt Republic.

A special epidemiological map was developed on paper to collect information. The source of information was in-patient medical records (003/y form), the register of patients and refusals for hospitalization (001/y form). The following nosological forms of pneumonia in accordance with ICD-10 were taken into account: J12.0 — Viral pneumonia; J-18.0 — Bronchopneumonia, unspecified organism; J18.1 — Lobar pneumonia, unspecified; J18.2 — Hypostatic pneumonia, unspecified organism; J18.8 — Other pneumonia, unspecified organism; J18.9 — Pneumonia, unspecified organism.

After collecting the actual material, the incidence and prevalence of respiratory diseases, including pneumonia, were calculated. The incidence rates were calculated for 100,000 people per year.

The calculation of the incidence rate was carried out according to the formula:

$$Y = n \times 105 / N, \text{ where}$$

Y is incidence or prevalence (per 100,000 people of the corresponding age) per year;
n is the number of detected cases per year;
N is the mean annual population of the study age group.

The prognosis of the incidence for the next five years using the method of exponential smoothing was carried out by the following formula to identify patterns of respiratory diseases at the present stage and to identify risk factors:

$$U_{t+1} = \alpha \times y_t + (1 - \alpha) \times U_t, \text{ where}$$

U_{t+1} is the incidence rate in the prognosis period;
α is the smoothing parameter;
y_t is the incidence rate preceding the projected parameter;
U_t is the incidence rate calculated as an exponentially weighted mean (for the period preceding the predicted one).

Statistical analysis was performed according to the methods used in biomedical statistics [2, 3]. Study results are presented in international SI units and subjected to statistical processing using STATISTICA 6.0 and BioStat 2008 software packages.

Results

The prevalence of respiratory diseases in the Udmurt Republic was 49,871.39 ± 1.33 per 100,000 people. At the same time, these parameters tended to

decrease from 2009 to 2014 and increased from 2015 compared to 2009 by 1.01%. Mean growth rate was 2.3%, and mean increment rate was 0.25%. Compared to the data for the same period in Russia, mean growth rate was 1.7%, and mean increment rate was 5.48%, which indicates a slight decrease in the incidence (Figure 1).

A comparative analysis of the overall respiratory diseases incidence between cities and districts of the UR showed that the incidence in urban population was significantly higher ($p > 0.05$) compared to the same parameter in rural areas, which may be due to higher contagiousness within this group (Figure 2).

In the analysis of the structure of respiratory diseases incidence in the population of the Udmurt Republic it was found that this rate has not changed significantly throughout the follow-up period. At the same time, pneumonia and chronic obstructive pulmonary disease (COPD) dominate every year. In 2015 pneumonia (47.43%) was ranked first among respiratory diseases, followed by chronic bronchitis (17.73%), and COPD (15.2%) (Figure 3).

Among patients diagnosed with moderate CAP, chest X-ray examination revealed predominantly bisegmented nature of lung tissue lesions in 45.3%, segmented nature of the lesion was observed

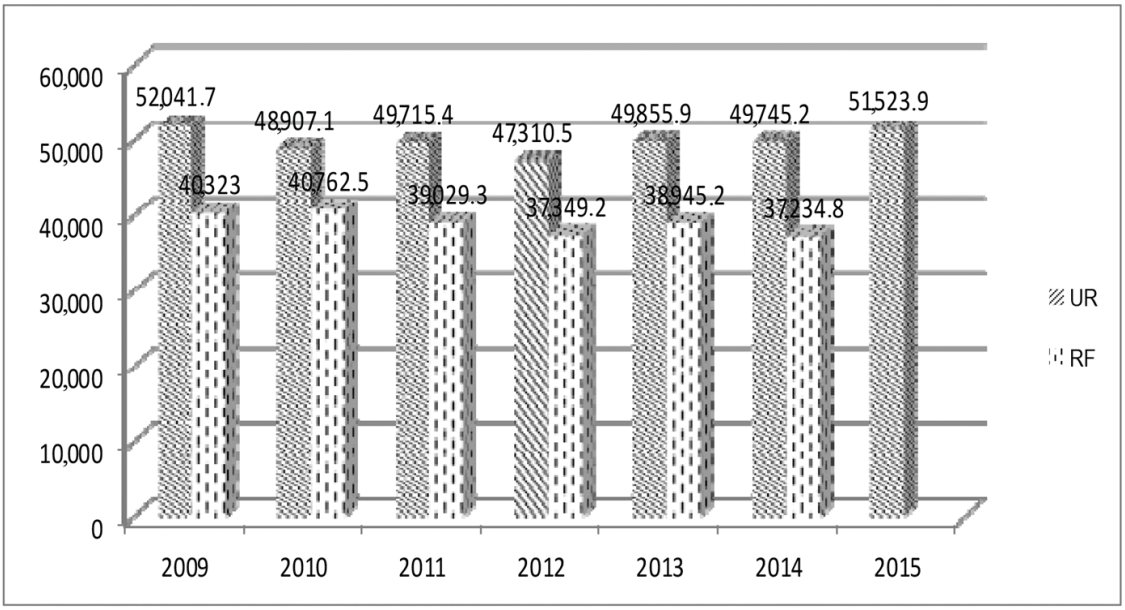

Figure 1. *Dynamics of the general respiratory disease incidence level in the Udmurt Republic and the Russian Federation over a period of 2009–2015 (per 100,000 people)*

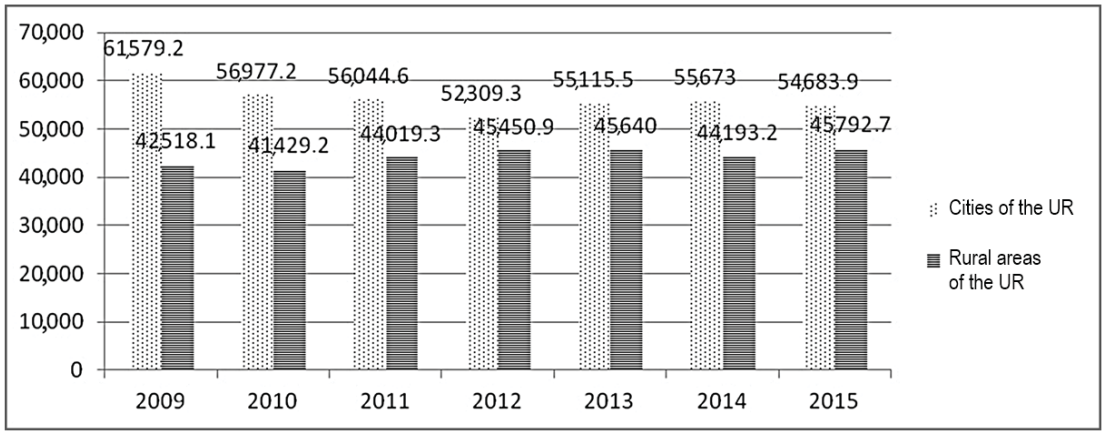

Figure 2. *Dynamics of the general respiratory disease incidence level in urban and rural population of the UR over a period of 2009–2015 (per 100,000 people)*

in 28.2%, and multisegmented — in 26.5%. In patients with severe CAP, multisegmented nature of the lesion was revealed in 100%.

All patients received antibiotic therapy for CAP mainly with cephalosporins in combination with respiratory fluoroquinolones or macrolides. Patients in intensive care rooms or ICU received mainly carbapenems and detoxification therapy.

According to the literature, detection of pathogens in CAP is possible only in 30–50% [9].

However, studying the pathogens by ELISA, it was found that in the UR in 30% of cases of CAP in patients not from ICU the causative agent of pneumonia was S. pneumoniae, and atypical bacteria accounts for 11 to 28%, namely Chlamydophila pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, and in 2.9% of patients diagnosed with severe CAP Staphylococcus aureus was revealed as the causative agent.

At the same time, in our opinion, the effective detection of pathogens in CAP in the UR requires further improvement.

The criteria of public health also include parameters of primary respiratory diseases (Figure 4). During the analyzed period, it was noted that the UR had a consistently high level of the primary incidence compared to the Russian Federation, compared to federal values (Figure 4).

Assessing the rate of the primary respiratory diseases incidence, it is noted that mean growth rate in the UR is 105.42%, the mean increment rate is 5.42%, compared to the mean growth rate (87.07%)

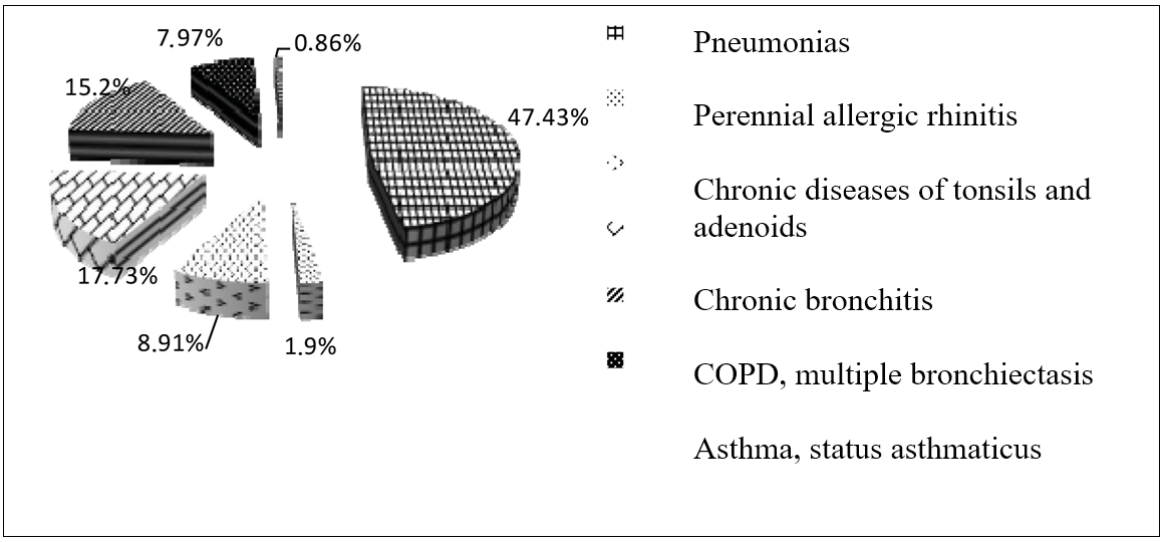

Figure 3. *Structure of respiratory diseases in the UR in 2015*

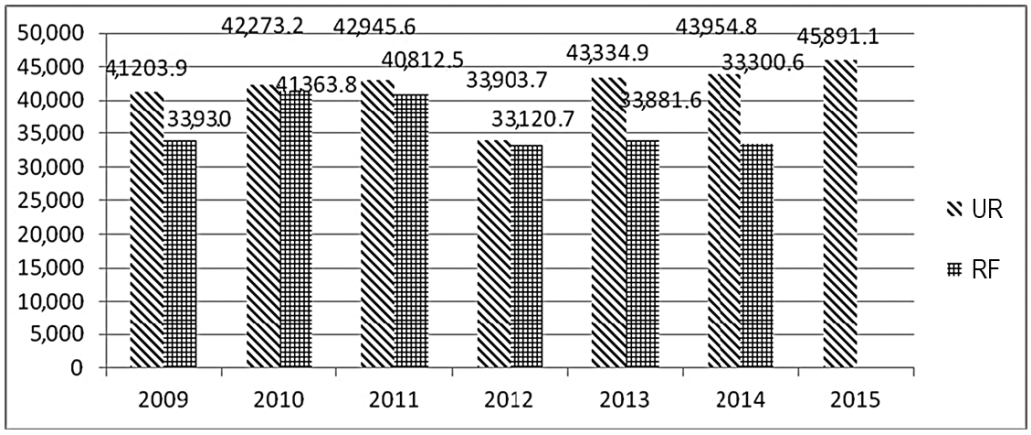

Figure 4. *Dynamics of primary respiratory disease incidence level in the UR and the RF over a period of 2009–2015 (per 100,000 people)*

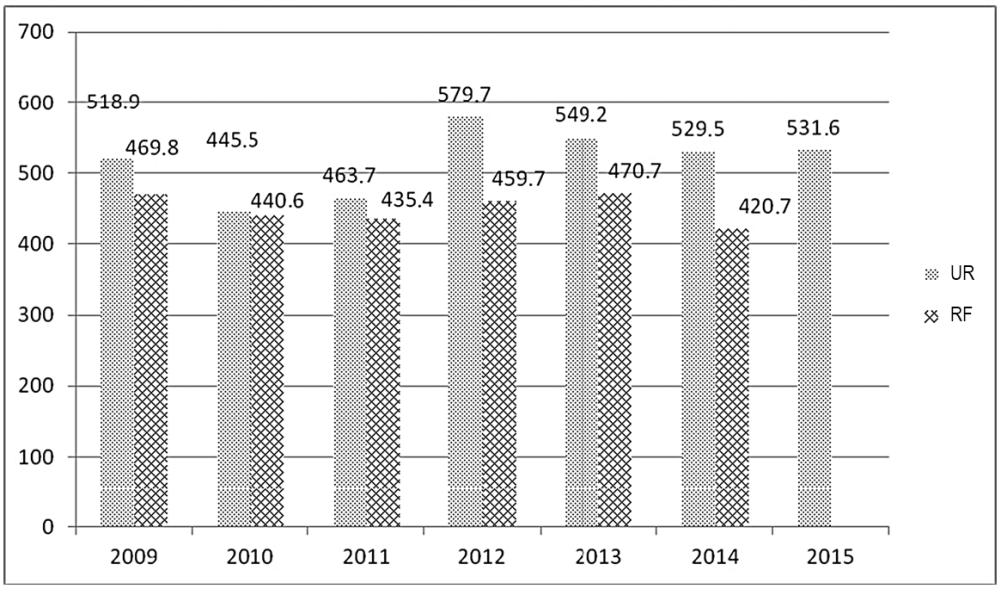

Figure 5. *Dynamics of the pneumonia incidence in the UR and the RF over a period of 2009–2015*

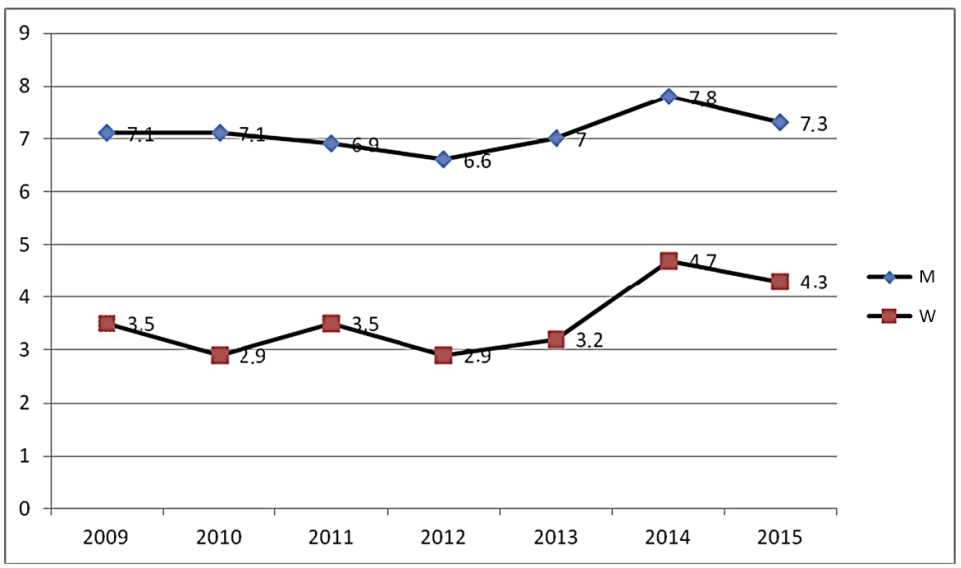

Figure 6. *Dynamics of respiratory disease mortality structure in the UR over a period of 2009–2015 (%)*

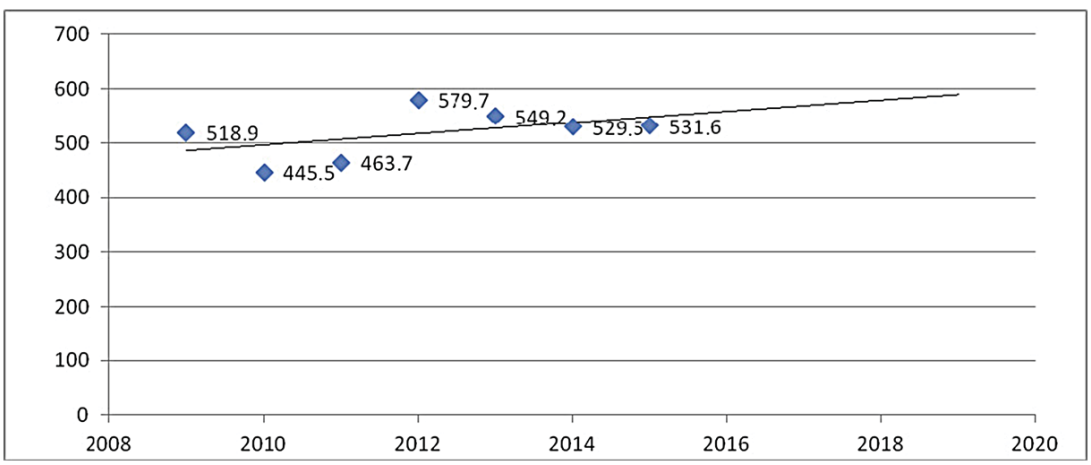

Figure 7. *The pneumonia incidence prediction for 2019*

and mean increment rate (12.93%) in the Russian Federation.

Data on the total pneumonia incidence in the UR: mean growth rate was 102.41%, and mean increment rate was 2.41%.

The study revealed significant differences in the overall pneumonia incidence on average for the analyzed period that allowed to divide the districts of the UR into 3 groups.

Group 1 included districts where the mean rate of the general incidence was 1.5 to 2.0 times higher than the same parameter for the UR. These districts included Grakhovsky, Vavozhsky, Yarsky, Yukamensky, Kezsky, and Balezinsky districts (2,527 ± 217.8).

Group 2 included districts where the mean level of the total pneumonias incidence was consistent with that of the UR: Yakshur-Bodinsky, Glazovsky, and Mozhginsky districts (1,559.5 ± 249.6).

In group 3, the overall pneumonia incidence was 1.2–1.4 times lower than in the UR. These districts included Alnashsky, Votkinsky, Debessky, Zavyalovsky, Kambarsky, Sharkansky, Karakulinsky, Kiznersky, Kiyasovsky, Malopurginsky, Sarapulsky, Syumsinsky, Seltinsky, and Uvinski districts (1,139.7 ± 130.4).

The mapping carried out allowed to plan further treatment and diagnostic and preventive actions differentially, depending on incidence rate.

In analysis of the pneumonia incidence rate over the time, it is observed that the incidence rate in the UR is significantly ($\rho \leq 0.05$) higher compared to the Russian Federation (Figure 5).

When analyzing the mortality rate for pneumonia, there is a consistently high mortality rate in men compared to women (Figure 6).

During the prognosis of the incidence rate in the UR up to 2019, we predicted a further increase in the pneumonia incidence, which reflects the need for further development of methods for prevention and treatment of this pathology (Figure 7).

Conclusion

Thus, in the UR, as in the entire Russian Federation, there is a consistently high pneumonia incidence. At the same time, there is a tendency to higher incidence and mortality caused by this pathology. This circumstance requires further study of the problem of pneumonia, including the improvement of methods for its medical treatment.

Conflict of interests

The authors declare no conflict of interests.

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RESULTS OF THE INTEGRATED ASSESSMENT OF THE POTENTIAL OF LIFESTYLE OF PATIENTS WITH ARTERIAL HYPERTENSION WITH DIFFERENT LEVEL OF TREATMENT PERFORMANCE

Abstract

Introduction. Hypertension is one of the most serious problems of the modern health care. Within the qualimetric approach the quantification of "lifestyle potential" is also provided. However, there are not enough studies examining the relationship between the cardiac health care effectiveness and the lifestyle of patients with hypertension. **The objective** was to study the lifestyle potential of patients with hypertension and its role in the ensuring the treatment effectiveness. **Materials and methods**. The study was conducted on the basis of the medical institutions of the Kostroma region. Research methods were: expert, sociological, analytical, and statistical. Data on 400 cardiac patients, lifestyle parameters monitoring using the original automated program Management of Performance Factors for Cardiac Medical Care data, expert evaluation of patient's lifestyle and the sociological survey data according to the questionnaire, consisting of 8 questions, were analyzed. **Results and discussion**. Patients with hypertension has reduced lifestyle potential in all its components, including the low medical activity, low medical awareness, insufficient level of recreational activity, disregard for the principles of rational nutrition, and the prevalence of bad habits. There are significant differences in the lifestyle potential of patients with low and high levels of treatment success proving the importance of modifying the lifestyle of patients and its improvement in the practice of primary care physicians. **Conclusions and proposals**. It is recommended to monitor the lifestyle potential of patients with hypertension in conditions of district out-patient departments.

Key words: *hypertension, lifestyle, effectiveness of treatment*

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Introduction

Hypertension is one of the major problems of modern health care due to the high prevalence of the disease and the development of its complications [1]. According to experts, elevated blood pressure is recorded in one in four adults in developed countries [2, 9, 10, 11]. In Russia, direct and indirect financial losses due to the treatment of complications of hypertension amount to 30 billion rubles per year and are constantly increasing [3].

In the well-known model of factor dependence for public health developed by academician Yu. P. Lisitsyn, 50% accounts for human lifestyle [4]. Studies confirm this theory with respect to patients with hypertension [5]. However, there are not enough studies examining the lifestyle of patients with hypertension.

Using the potential of health care without the active participation of the patient, and changing their behavior towards health care does not allow to provide the desired result in the treatment of the disease [6]. In health care, in recent years, qualimetric approach is increasingly used to characterize patients, and it provides a quantitative assessment of their qualitative characteristics, such as quality of life, and others. Under this approach, quantitative assessment of the "lifestyle potential" is carried out, which means quantitative assessment of whether the patient's actual activity matches the optimum level which, in its turn, matches tasks of preserving, improving, and restoring health and quitting bad habits [7]. The use of quantitative assessment of patients' lifestyle potential allows to store and process information in electronic form, conduct comparative analysis, and identify priority parameters of reduction that require targeted correction and recovery [7]. However, there is a dearth of research on the relationship between the effectiveness of cardiac medical care and completeness of realization of the lifestyle potential in patients. In light of the above, a medical and social study was conducted to investigate the lifestyle potential of patients with hypertension and its role in ensuring the effectiveness of treatment.

Materials and Methods

The study was conducted at medical institutions in the Kostroma Region. Study methods were: expert, sociological, analytical, and statistical. Data on 400 patients of cardiac profile were analyzed: data on lifestyle and data on the effectiveness of treatment. The information base for gathering material was data on social monitoring of patients' lifestyle parameters using the original automated program Management of Performance Factors for Cardiac Medical Care [8] which was introduced in the medical institutions of the Kostroma Region and consisted of data on expert assessment by the doctor of patient's lifestyle, as well as data on a sociological survey of these patients using Medical and Social Characteristics of Cardiac Patients questionnaire, including a block of patient demographics (age, gender, social status) and a block of 8 closed-ended questions on lifestyle. Characterization of lifestyle (activity) was given based on the following main parameters:

I. Physical activity level:
1. Low (do not do sports, do not do morning exercises, motor activity: less than 2 hours a day)
2. Closer to low, not optimal (do not do sports, do morning exercises, motor activity: 2–5 hours a day)
3. High (do sports, do morning exercises, motor activity: more than 5 hours a day)

II. Hygiene activity level:
1. Low (do not follow rules of personal hygiene, do not brush their teeth, take a shower irregularly, do not carry out cold training)
2. Closer to low, not optimal (carry out all the above activities, but not in full)
3. High (carry out all these activities completely)

III. Recreational activity level:
1. Low (sleep less than 6 hours, mostly passive recreation (watching TV, lying, sitting), no walks, no established system of work and rest cycles, no positive emotions, do not attend cultural and sporting events)
2. Closer to low, not optimal (sleep lasting for 6 to 7 hours, passive-active recreation, rare walks, no established system of work and rest

cycles, rare positive emotions, rarely attend cultural and sports events)
3. High (carry out all these activities completely)

IV. Household activity level:
1. Low (do not clean rooms, do not ventilate rooms, do not monitor temperature and humidity level in their home)
2. Closer to low, not optimal (carry out the above activities, but not regularly)
3. High (carry out above activities completely)

V. Medical activity level:
1. Low (do not seek timely medical advice, do not perform doctor's recommendations, do not comply with the regimen that contributes to health preservation, not interested in information about health preservation)
2. Closer to low, not optimal (carry out all the above activities, but not in full)
3. High (carry out above mentioned activities completely)

VI. Bad habits:
1. overeating (1. constantly; 2. rarely)
2. combining eating and reading (1. constantly; 2. rarely)
3. adding salt to food (1. constantly; 2. rarely)
4. adding spices to food (1. constantly; 2. rarely)
5. increased consumption of sweets (1. constantly; 2. rarely)
6. smoking (1. constantly; 2. rarely)
7. alcohol intake (1. constantly; 2. rarely)

Each parameter was evaluated by the doctor taking into account the survey of patients according to a three-point system (3 points corresponded to the optimal level, 2 points — intermediate, 1 point — low level of the parameter). Based on integrated assessment of patients' lifestyle (Mushnikov D. L., 2017, [7]), the automated program calculated the index of realization of the lifestyle potential, i.e. the correspondence of the patients' lifestyle characteristics to their optimal level according to the formula:

$$I_{pog} = (SP_f / SP_{max}) \times 100\%$$

The level of the lifestyle potential assessment in the range of 95–100% was considered as high, in the range of 75–94% as sub-optimal, and in the range of 1–74% as low. In addition, the following questions were reflected in the questionnaire: according to recreational activity (compliance with sleep and rest regimen, duration of the working day, sleep duration, duration of out-of-doors period), characteristics of nutrition status (balanced diet, tendency to overeat, frequency of eating, abuse of food which is undesirable with hypertension, frequency of consumption of fruits and vegetables, body mass index level), characteristics of physical activity (frequency, volume, swimming pool), attitude towards bad habits (presence of bad habits, volume and type of smoking and consumption of alcoholic beverages), medical activity level in patients (the implementation of doctor's recommendations, timely visit to the doctor for preventive purposes, timely visit in case of acute illness, timely attendance for medical examination, complete implementation of doctor's recommendations, the reasons of failure to follow recommendations, self-monitoring of blood pressure, the rejection of self-medication, trust in physician, reasons for visits to the doctor and refusal from visits, reasons for refused admission, which was indicated, the presence of a blood pressure monitor at home and the skill of its usage), information activity (reading, medical newspapers and magazines, use of advertising brochures and stands as a source of information).

The effectiveness of medical care for patients with stage II to III hypertension was evaluated by experts according to the following criteria: low efficacy of secondary and tertiary prevention (frequent emergency calls more than 8 times a year and the presence of complications); high efficacy of secondary and tertiary prevention (with the frequency of emergency calls from 4 to 8 times a year and the absence of complications).

A comparative analysis of the data of assessing the lifestyle potential in patients with low (the first group — 155 patients) and high (the second group — 245 patients) effectiveness of care was carried out.

Statistica 10.0 (StatSoft, Inc) was used for statistical processing of data (mean and relative values, their errors, reliability of their difference according to the Student's test). The critical value of statistical significance level was equal to 5%.

Results and Discussion

The composition of the groups was as follows: 69% of patients in the first group (155 people) were women, 31% — men, and in the second group (245 people) — 65.7% and 34.3%, respectively. The mean age of patients in the first group was (58.7 ± 0.3) years compared to (52.3 ± 0.1) years in the second group. Individuals aged over 60 years dominated among patients of the first group (87.25%), whereas in the second group, the proportion was significantly lower (61.2%) ($p < 0.05$). In the distribution by level of education, it was found that the majority of respondents (45.0%) of the first group had higher education, 34.5% had secondary special education, 18.0% secondary education, and 2.5% incomplete secondary and primary education, and in the second group this distribution was as follows: 23.3%, 56.3%, 20.0%, 0.4%. As can be seen from the data presented, in the first group the proportion of persons with higher education (45.0% vs. 23.3%) and low level of education (2.5% vs. 0.4%) is significantly higher than in the second group.

Among the interviewed individuals workers accounted for 21.3% (group I) vs. 45.3% (group II), office workers — 9.0% and 3.2%, managers — 7.1% and 4.5%, entrepreneurs — 2.6% and 1.6%, teachers — 9.7% and 2.5%, health care professionals — 1.9% and 0.0%, pensioners — 18.7% and 17.6%, persons with disabilities — 29.7% and 25.3%, respectively ($p < 0.05$).

All respondents, without exception, have chronic diseases other than hypertension, and they are aware of this. The incidence of comorbidity in the first group was 234.5 per 100 patients compared to 121.5 per 100 patients in the second group ($p < 0.05$). And the first group had a significantly higher frequency of such a pathology as chronic kidney disease, diabetes, thyroid disease, and degenerative spine disease.

According to the results of the integral assessment of the lifestyle potential of cardiac patients with hypertension, it was found that the overall index of potential realization was 72.5%, including in the first group — 60.5%, in the second group — 79.5%, indicating the presence of a deviation of this parameter from the optimal value (100%) by 27.5%, 39.5% and 20.5%, respectively ($p < 0.05$) (Table 1).

As can be seen from Table 1, the first ranking place in terms of the lifestyle potential belongs to the "Hygiene activity" component (in the first group I_{pog} index was (89.0 ± 1.4)%, in the second group — (94.5 ± 1.6)%, and the overall index was (92.5 ± 1.5)%) ($p < 0.05$); the second ranking place belongs to "Household activity" (in the first group I_{pog} index was (86.5 ± 1.5)%, in the second group — (93.5 ± 1.8)%, and overall index was (88.5 ± 1.6)%) ($p < 0.05$); the third ranking place belongs to "Bad habits" (in the first group I_{pog} index was (70.5 ± 1.6)%, in the second group — (79.5 ± 1.5)%, and the overall index was (75.0 ± 1.7)%) ($p < 0.05$); the fourth ranking

Table 1. *Summary of the lifestyle potential assessment of patients with hypertension (%)*

Lifestyle potential components	Level of implementation			Rank of potential realization
	The first group (low effectiveness of treatment)	The second group (high effectiveness of treatment)	In both groups	
Physical activity	70.5 ± 1.5	79.5 ± 1.8*	74.5±1.6	4
Hygiene activity	89.0 ± 1.4	94.5 ± 1.6*	92.5±1.5	1
Recreational activity	68.5 ± 1.7	75.5 ± 1.5*	73.2±1.3	5
Household activity	86.5 ± 1.5	93.5 ± 1.8*	88.5±1.6	2
Medical activity	64.5 ± 1.4	72.0 ± 1.9*	68.5±1.6	6
Bad habits	70.5 ± 1.6	79.5 ± 1.5*	75.0±1.7	3
Potential fulfillment	60.5 ± 1.4	79.5 ± 1.5*	72.5±1.6	
Potential fulfillment margin	39.5 ± 1.4	20.5 ± 1.5*	27.5±1.6	

Note. * There is a significant difference in parameters ($p < 0.05$)

place belongs to "Physical activity" (in the first group I_{pog} index was (70.5 ± 1.5)%, in the second group — (79.5 ± 1.8)%, and the overall index was (74.5 ± 1.6)%) (p < 0.05); the fifth ranking place belongs to "Recreational activity" (in the first group I_{pog} index was (68.5 ± 1.7)%, in the second group — (75.5 ± 1.5)%, and overall index was (73.2 ± 1.3)%) (p < 0.05); and the sixth ranking place belongs to "Medical activity" (in the first group I_{pog} index was (64.5 ± 1.4)%, in the second group — (72.0 ± 1.9)%, and overall index was (68.5 ± 1.6)%) (p < 0.05). Thus, the priority components of improving the lifestyle of patients with hypertension are: medical activity (margin for improvement: 31.5%), recreational activity (margin for improvement: 26.8%) and physical activity of patients (margin for improvement: 25.5%), which should be taken into account in the formation of "School for Patients with Hypertension" programs.

Let us discuss the results of the sociological survey among patients based on the individual lifestyle components in detail.

Recreational activity is one of the important components of a healthy lifestyle and a condition of active longevity. However, as the survey showed, a significant part of patients do not get enough rest. Thus, 17.3% of respondents of the first and 34.7% of the second group (p < 0.05) pay attention to the observance of sleep and rest regimen. The duration of the working day in 53.3% of the respondents of the first group was 8 hours, in 11.0% — 12 hours, in 2.8% — 24 hours (daily duty), vs. 78.9%, 14.5%, and 6.6% in the second group (p < 0.05), respectively. In the first group, 35.5% of respondents complain of regular fatigue at work, vs. 12.5% in the second group (p < 0.05). Sleep duration in 86% of respondents of the first group is 8 hours a day, in 12.0% — 9 to 12 hours, in 2.0% — less than 8 hours, vs. 83.4%, 16.0% and 0.6% in the second group (p < 0.05), respectively. Daily outdoor activity is typical only for 19.75% of respondents of the first group and 29.8% of the second group (p < 0.05).

Proper, rational diet is one of the elements of hypertension treatment. However, as the survey showed, a significant proportion of patients do not adhere to the principles of rational nutrition. Only 24.75% of respondents of the first group follow a balanced and regular diet, and irregular and unbalanced nutrition is typical for 57.75%, of them overeating is noted by 22.25%; 17.5% of people found it difficult to answer; and in the second group this distribution looked as follows: 55.4%, 34.5%, 10.1% (p < 0.05). Most respondents of the first group eat 3 times a day (59.5%), 27.25% eat 4 or more times a day, and 13.25% eat 1 to 2 times a day. And in the second group the distribution is as follows: 67.8%, 30.2%, 2% (p < 0.05), respectively. It was noted that the abuse of food undesirable for hypertension (fatty, salty, spicy, high carbohydrate foods) is typical for 57.25% of respondents of the first group and 23.1% of the second group (p < 0.05). Fruits and vegetables are in the daily diet of 53.5% of the respondents of the first group, and 20.25% of people consume fruits and vegetables more than 2 times a week; fruits and vegetables in the diet are found only 2 times a week in 23.5%, less than 2 times a week — in 2.75%; the distribution in the second group is as follows: 69.5%, 24.5%, 6%, 3% (p < 0.05), respectively. When calculating the Quetelet index (body mass index) by the formula weight/height (kg/m^2), only 14.8% of patients of the first group had normal weight, 56.0% of patients were overweight, 26.8% have 1st degree obesity, 2.5% of patients have 2nd degree obesity; in the second group the distribution is as follows: 53.2%, 34.5%, 18.3%, 4% (p < 0.05), respectively.

Only 13.3% of respondents of the first group and 34.5% of the second group (p < 0.05) pay attention to improving their health (they are physically active, visit swimming pool).

Attitude towards bad habits is reflected by the following survey results: about a third of patients with hypertension of the first group smoke (29%), 65.5% of patients do not smoke, and of them 5.5% were former smokers, but had quit; in the second group the distribution is as follows: 17.6%, 69.4%, 13% (p < 0.05), respectively. In the first group, 9.2% smoke more than 1 pack of cigarettes per day, vs. 1.4% in the second group. Alcohol abuse is typical for 52% of men and 1.7% of women in the first group and for 21.3% and 0.3% in the second group, respectively (p < 0.05). Among all of them, 12.5% prefer dry wine, 21.5% — stiff wine, 64.5% — vodka, 1.2% — cognac, and 0.3% — moonshine (p < 0.05).

Medical activity level of patients with hypertension was studied. It was found that in the first group, almost half of the patients (46.0%) follow doctor's recommendations clearly, 35.8% — partially, 18.3% — scarcely follow vs. 89.0%, 10.0%, 1% in the second group, respectively ($p < 0.05$). In the first group only 13.5% of patients visit the primary care physician for preventive purposes, 72.0% — when feeling unwell, 5.5% — do not visit at all vs. 44.5%, 52.3%, 3.2% in the second group, respectively ($p < 0.05$). In the case of disease exacerbation among patients of the first group, 19.3% of patients visit the out-patient department at the place of residence, 2.0% go to private clinics, 9.7% — to familiar doctors, 63.3% — to emergency doctors, and 5.7% — to another out-patient department or hospital; in the second group, the distribution is as follows: 44.5%, 3.4%, 10.2%, 35.4%, 6.5% ($p < 0.05$), respectively. Among patients of the first group, only 21.0% go for medical examination on their own at the appointed time, 12.3% go only after repeated call, and 66.8% of the respondents do not go at all vs. 45.6%, 49.0%, 5.4% in the second group, respectively ($p < 0.05$). Prescriptions and recommendations of the primary care physician were followed and performed in full by 52.5% of patients of the first group, partially — by 40.0%, and were not followed by 7.5%; in the second group the distribution is as follows: 79.8%, 20.0%, 0.2% ($p < 0.05$), respectively. The reasons for non-compliance with the prescriptions and recommendations of the primary care physician in patients of the first group was the lack of financial capacity to buy drugs (9.0%), ineffectiveness of recommended treatment (29.3%), and personal irresponsibility (22.0%) vs. 17.5%, 24.3%, 10.9% in the second group, respectively ($p < 0.05$). Regular monitoring of blood pressure is performed by 20.0% of respondents in the first group, only when feeling unwell — by 40.5%, and 29.5% do not monitor their pressure; in the second group, the distribution is as follows: 44.5%, 50.5%, 5% ($p < 0.05$), respectively. Self-treatment of hypertension was performed by 26.5% of patients of the first group, and by 10.2% of the second group. The main reason for seeking medical advice is to obtain a temporary disability certificate (34.5% of respondents). Only 15.0% of respondents in the first group and 34.5% in the second group ($p < 0.05$) fully trust their doctor as a specialist. Patients reported unfriendly, inattentive attitude and dishonesty of the doctor (52.5% of patients), long queues at the primary care physician and other specialists (43%), misunderstanding of the patient's problems by the doctor (4.5%) ($p < 0.05$) among the reasons for not visiting the outpatient department. Among patients of the first group, 7.8% of patients agree to inpatient treatment (if necessary), 22.8% agree in some cases, and 20.8% categorically refuse, 48.8% of patients do not want to be treated in hospital at the place of residence, and the figures in the second group were 44.5%, 30.5%, 12.3%, 12.7% ($p < 0.05$), respectively. Among the reasons for refusal of inpatient treatment, patients noted: poor attitude of medical staff (64.0%) and the lack of effect from treatment provided by the doctors of the hospital (42.5%).

Raising patients' awareness of the disease, methods of prevention of its worsening and risk factors is one of the important aspects of successful treatment of hypertension as a chronic disease which the patient will have to cope with all their life. However, according to the survey, among patients of the first group, 26.8% of respondents read medical literature on hypertension, 2.5% of respondents subscribed to newspapers and medical journals, 21.3% of respondents used advertising brochures and stands as a source of information, only 3.0% of patients bought literature on the treatment and prevention of hypertension; in the second group, this distribution is as follows: 45.6%, 3.9%, 34.5%, 7.8% ($p < 0.05$), respectively. These data suggest that patients of the second group had significantly higher information activity than patients of the first group.

Monitoring of blood pressure in hypertension is the main and universally accessible method of disease diagnosis. Hence, this issue has been studied among patients of comparison groups. It is established that 57.0% of patients have a blood pressure monitor at home and measure blood pressure, 0.3% of patients use the device of neighbors; 9.2% of respondents call an ambulance for this purpose; 10.5% call the primary care physician; 20% of patients visit the out-patient department for measurement of pressure; in the second group,

the figures are as follows: 76.5%, 0.2%, 3.2%, 8.7%, 11.4% ($p < 0.05$), respectively. From these data it follows that in the first group, patients are 2 times more likely than in the second group to seek assistance from doctors in out-patient departments and emergency medical care only to measure the pressure.

Conclusions

Thus, in patients with hypertension, there is a decrease in lifestyle potential, in all its components, including low medical activity, low medical awareness, insufficient level of recreational activity, disregard for the principles of rational nutrition, and the prevalence of bad habits.

There are significant differences in the lifestyle potential of patients with low and high levels of treatment success proving the importance of modifying the lifestyle of patients and its improvement in the practice of primary care physicians.

It is recommended to monitor the lifestyle potential of patients with hypertension in conditions of district out-patient departments with the determination of priority medical and social problems of patients, opportunities and margins for improving lifestyle. The heads of primary health care institutions should pay attention to the availability and quality of activities to form the basis of healthy lifestyle in patients with hypertension by health professionals.

Conflict of interests

The authors declare no conflict of interests.

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THE RELATIONSHIP OF THIOL STATUS, AND COMPONENTS OF SIGNALING PATHWAYS THAT REGULATE INFLAMMATION IN CONVALESCENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

Abstract

The study discusses the relationship of thiol concentrations in intercellular fluid with the level of peripheral blood mononuclear cells (MNCs) components of mitogen-activated (MAPK) / stress-activated (SAPK) and JAK/STAT signaling pathways, and nuclear transcription factor NF-κB in community-acquired pneumonia (CAP) convalescents. The content and level of phosphorylation of JAK2 protein kinase, signal transducers and transcription activators STAT3, STAT5A, STAT6, NF-κB nuclear transcription factor inhibitor (IκBα), JNK, ERK stress-activated protein kinases, and the level of nuclear transcription factor NF-κB p50 subunit were determined by ELISA in MNCs. The results of the study indicate that the stage of CAP convalescence is characterized by a lack of antioxidant protection manifested by a decrease in the concentration of thiol-containing compounds in cell culture supernatants, on the background of which there is a decrease in the level of phosphorylation of JAK2 protein kinase, factors STAT3, STAT5, STAT6, JNK, which is also associated with an increase in the level of phosphorylation of ERK protein kinase. The analysis showed that the thiol status is characterized by a positive relationship with the activity of STAT5A, JNK, p50. The thiol level and ERK, as well as STAT3, was characterized by a negative relationship. Thus, the increase in the thiol level contributes to an increase in the activity of the transcription factor STAT5A and a decrease in the activity of the transcription factor STAT3 with a corresponding change in cell reactivity with respect to specific cytokines, as well as a specific effect on the differentiation of individual populations of immunocompetent cells.

Key words: *thiol status, STAT5A, pneumonia, NF-κB*

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ERK — extracellular signal-regulated protein kinase, IκBα — nuclear transcription factor inhibitor κB, NF-κB — nuclear transcription factor κB, JAK — Janus kinases, JNK — c-jun-N-terminal protein kinase, MAPK — mitogen-activated protein kinase, p50 — nuclear κB transcription factor p50 subunit, SAPK — stress-activated protein kinases, STAT — signal transducers and transcription activators, AOP — antioxidant protection, CAP — community-acquired pneumonia, ICC — immunocompetent cells, MNC — mononuclear cells, LPO — lipid peroxidation, TC — thiol-containing compounds

As is well known, antioxidant protection (AOP) determines the activity of sanogenesis processes in various pathological conditions. Antioxidant deficiency or low AOP enzyme activity leads to an increase in lipid peroxidation (LPO), which is accompanied by membrane structure and function disruption, molecule enzymatic activity disorder, activation of apoptosis processes and pro-inflammatory activation preservation of immunocompetent cells [1]. At the same time, LPO plays an important physiological role by regulating prostaglandin, leukotriene and thromboxane biosynthesis, which determines the importance for the normal sanogenesis processes of maintaining LPO/AOP at the optimal level, avoiding a significant deficit of antioxidants [2, 3]. The balance of AOP/LPO is maintained due to the functioning of specific enzymes that catalyze the splitting of reactive oxygen species, including superoxide dismutase, catalase, thioredoxin reductase, etc. The deficiency of antioxidants, including thiol-containing compounds (TC), is associated with increased viral infections, including those caused by respiratory syncytial virus and metapneumovirus. In this case, AOP suppression is accompanied by an excessive pro-inflammatory activation of immunocompetent cells, a decrease in the efficiency of phagocytosis, increased cytokine production and prolonged resolution of the pathological process, which is associated with various complications in such patients [4]. It has also been shown that many intracellular molecular regulators, such as protein kinases that are part of the intracellular signaling pathways, are redox-sensitive molecules that respond to antioxidant deficiency by activating and stimulating metabolic processes leading to immunocompetent cell apoptosis or differentiation, in particular, macrophage polarization, T-helper differentiation, etc. [2]. In addition, intracellular signaling pathway activation, in particular MAPK/SAPK and JAK/STAT in response to cell stimulation with bacterial components and cytokines leads to antioxidant pool depletion due to their increased expenditure while forming a systemic inflammatory reaction occurring amid increasing production of reactive oxygen species [2, 3]. Convalescence of an acute infectious-inflammatory process, often accompanied by dysregulation of intracellular signaling mechanisms, also takes place with AOP deficiency, which is determined by decreased antioxidant production [4–6].

At the same time, antioxidant deficiency contributes to the progression of such chronic non-infectious diseases as coronary artery disease, atherosclerosis, diabetes mellitus, also contributing to premature body aging and suppression of reparative processes in tissues [1, 3]. Despite the importance of this issue, the relationship between intracellular molecular regulators that determine cellular reactivity with respect to external signals and the LPO/AOP state at the final stage of the inflammatory process has not been fully investigated. In this regard, the aim of this study was to investigate the relationship of MAPK/SAPK components and JAK/STAT signaling pathways with thiol-containing compound concentration in cell culture supernatants in community-acquired pneumonia (CAP) convalescents.

Materials and Methods

The material of this study was venous blood from the cubital vein taken in the morning (from 7:00 to 7:30 AM). Thirty male patients (mean age: (26 ± 5.2) years) with bacterial mild CAP (60–65 points of the PORT score) on 15–17 days of disease (just before discharging from the hospital) were included in the main (study) group. The control group consisted of 15 healthy male blood donors, aged 20–37 years (mean age: (27 ± 6) years).

The diagnosis of pneumonia was verified in accordance with national clinical guidelines (2013). Criteria for the inclusion of patients in

the study were: X-ray verification of infiltrative lung changes, unilateral segmental nature of infiltrative changes; bacteriological verification of gram-positive microorganisms that are typical pneumonia etiological agents (S. pneumoniae, S. aureus), as well as M. pneumoniae; uncomplicated disease course; positive therapy effect (reduction of infiltrative changes volume no less than 2/3 from the initial level by the time of discharge from the hospital). All patients received parenteral antibiotic therapy with third-generation cephalosporins (cefotaxime) at an average daily dose of 2 g, or clarithromycin at an average daily dose of 1 g, nonsteroidal anti-inflammatory drugs and physiotherapy.

The clinical study was approved by the Academic Council and the Local Ethics Committee of the Medical Institute of the Federal State Budgetary Educational Institution of Higher Education Tula State University (Protocol No. 2, September 1, 2014). All patients and donors signed an informed consent form.

In this work, we used kits for whole blood cell cultivation and mitogenic stimulation Cytokine-Stimul-Best (ZAO Vector-Best, Novosibirsk). In aseptic conditions, 1 ml of whole blood was introduced into a vial containing 4 ml of supporting medium DMEM, heparin (2.5 U/ml), gentamicin (100 μg/ml) and L-glutamine (0.6 mg/ml). All blood samples were placed in a thermostat (37 °C) and incubated for 24 hours. After incubation, 1 ml of the supernatant was taken from blood sample vials to determine the concentration of thiol-containing compounds by ELISA.

To obtain the MNC fraction, 4 ml of the cell suspension was layered on a ficoll-verografin solution (ρ = 1.077, MedBioSpectr, Russia), followed by centrifugation at 5,000 rpm for 30 minutes. The isolated MNCs were washed twice in phosphate-saline buffer and 1 ml of cell suspension containing 5×10^6 cells, lysed using a following composition solution (Sigma-Aldrich, USA): 10 mM Tris, pH 7.4; 100 mM NaCl, 1 mM EDTA, 1 mM EGTA, 1 mM NaF, 20 mM $Na_4P_2O_7$, 2 mM Na_3VO_4, 1% Triton X-100, 10% glycerol, 0.1% SDS, 0.5% deoxycholate, 1 mM PMSF (matrix 0.3 M solution in DMSO). A 1% protease inhibitor (Sigma-Aldrich, USA) was added to the lysing solution (ex tempore) and kept on ice (at t = +4–5 °C) for 15 minutes, aliquoted and frozen at –76 °C.

In the lysates, we evaluated the content (in relative units per ng of protein — U/ng) of twice tyrosine 1007/1008 phosphorylation of JAK2 receptor protein kinase, tyrosine 705 phosphorylation of the signal transducer form and transcription activator STAT3, 694 phosphorylation of STAT5A form, and 641 phosphorylation of STAT6 form, using the ELISA. We also determined the level of tyrosine 202/204 phosphorylation of ERK protein kinase (isoforms 1 and 2), as well as the tryptophan and tyrosine 183 phosphorylation level and tyrosine 185 phosphorylation level of JNK protein kinase (isoforms 1 and 2). In addition, the concentration of the nuclear transcription factor NF-κB p50 subunit was determined.

The studies were carried out using Cusabio Biotech (China), Panomix (USA), Cloud-Clone (USA), IBL (Germany), and Bender Medsystems (Austria) kits. The enzyme immunoassay was performed on a Personal LAB analyzer (Adaltis Italia S.p.A., Italy) in accordance with the protocol recommended by the reagent kit manufacturer.

Cell counting and their viability analysis were performed on the TC20 cell counter (Bio-Rad, USA). The viability of isolated MNCs exceeded 90%.

Statistic processing was carried out using Statistica 7.0 software. The study results are presented in the following form: mean value (x), sample median (Me); 25th and 75th percentiles (25%, 75%). The statistical significance (p) for intergroup differences was assessed using the Mann-Whitney U-test. The relationship between the studied factors was assessed by linear regression analysis with step-wise variable inclusion in the mathematical model.

Results and Discussion

The results of the study are presented in Table 1.

The conducted analysis showed that for CAP convalescents, against the background of thiol-containing compound deficiency, there is a decrease in the phosphorylation level of JAK2 and JNK protein kinases, as well as STAT factors. These changes were associated with increased activity in the MNC of ERK protein kinase.

The statistical significance of the identified differences is presented in Table 2.

Table 1. *The level of the studied parameters in groups*

Factors	Control group				Main group			
	x	25%	Me	75%	*x*	25%	Me	75%
JAK2, U/ng	0.82	0.71	0.82	0.94	0.6	0.42	0.59	0.73
STAT3, U/ng	0.99	0.82	0.99	1.17	0.91	0.67	1.0	1.11
STAT5A, U/ng	0.81	0.78	0.81	0.84	0.65	0.56	0.66	0.72
STAT6, U/ng	2.29	2.29	2.30	2.3	1.82	1.34	1.68	2.02
JNK, U/ng	1.03	1.03	1.03	1.03	0.9	0.67	0.83	1.13
ERK, U/ng	3.17	3.08	3.17	3.26	3.32	2.67	3.25	3.6
ρ50, ng/ml	1.38	1.36	1.39	1.41	1.35	1.11	1.34	1.56
TC, μmol/ml	2.46	2.17	2.46	2.75	2.12	1.65	2.21	2.66

Table 2. *Statistical significance of the identified differences*

Factors	Intergroup difference value	Level of difference significance (ρ)
JAK2	–26.8	0.007
STAT3	–8.1	0.007
STAT5	–19.8	0.007
STAT6	–20.5	0.00001
JNK1/2	–12.6	0.00001
ERK1/2	4.7	0.007
ρ50	–2.2	0.35
TC	–13.8	0.007

Table 3. *Results of linear regression analysis*

Factor	β	$m_β$	B	m_B	t	ρ
STAT3	–0.41	0.2	–0.95	0.45	–2.1	0.046
STAT5	0.7	0.23	2.26	0.73	3.09	0.005
JNK1/2	0.67	0.22	0.76	0.25	3.01	0.006
ERK1/2	–0.57	0.27	–0.88	0.41	–2.11	0.045
ρ50	0.64	0.22	1.03	0.36	2.9	0.008

Note: B — regression coefficient; β — standardized regression coefficient; m_B — standard error of regression coefficient estimation; $m_β$ — standard error of standardized regression coefficient estimation; t — T-test value for the factor included in the model; ρ — significance level of the T-test.

Table 4. *The results of the evaluation of partial correlations*

Factor	Partial correlation (r)	Semi-partial correlation (r)	Coefficient of determination (R^2)
STAT3	–0.31	–0.04	0.96
SATA5A	0.39	0.07	0.98
JNK1/2	0.37	0.09	0.95
ERK1/2	–0.09	–0.02	0.96
ρ50	0.38	0.06	0.96

The analysis of the statistical significance of the identified intergroup differences indicates that the convalescence phase is accompanied by the normalization of the level in the MNC of MAPK/SAPK signaling pathway, in particular ERK and JNK. However, against this background, there is an increase in the ERK protein kinase activity, as well as a decrease in JNK activity, which is seen in the corresponding change of their phosphorylation status.

The study of the relationship between the signaling pathway components and the concentration of thiol-containing compounds was carried out by linear regression analysis with inclusion of step-by-step variables in the regression model, the results of which are presented in Table 3.

The results of the regression analysis show that the correlation coefficient of the regression equation (R) reflecting the connection strength between thiol concentration and the combination of factors included in the model, was 0.98. The coefficient of determination was 0.96 (adjusted coefficient of determination was 0.94); it determines the variation proportion in the concentration of thiol-containing compounds explained by the resulting mathematical model (R^2), indicating a high influence of the studied parameters on the TC.

The model is characterized by statistical significance, as indicated by the F value (F = 266.5; $\rho < 0.0000$) and low residuals correlation (Durbin-Watson coefficient = 1.7; linear residuals correlation coefficient = 0.15). The standard absolute error in model estimating is 0.54 units, which is 25.5% of the mean estimated thiol concentration. In this model, the STAT5A factor state, the JNK protein kinase content and the nuclear transcription factor NF-κB p50 subunit have the most significant positive effect on the thiol status, while the ERK factor concentration and the STAT3 phosphorylation level have a negative effect on thiol-containing compound concentration.

The statistical analysis shows that the dependence of thiol concentration on the signaling pathway component level and activity that we identified may be shown as follows:

$$TS = 2.26 \times STAT5A + 0.76 \times JNK + \\ + 1.03 \times p50 - 0.88 \times ERK - 0.95 \times STAT3$$

Table 4 shows the partial and semi-partial component correlation values, which show the nature of the relationship between each specific signaling pathway component included in the model and the thiol-containing compound concentration, while excluding the influence of other factors.

Partial correlation analysis indicates that the studied factors, in general, are characterized by a moderate connection with thiol concentration, while the connection between thiol-containing compounds and ERK level is weak. At the same time, a high determination coefficient identifies the relevant significance level in the revealed correlations reflecting the existing indirect relationships.

Discussion

The postclinical CAP phase proceeds with a decrease in JAK/STAT signaling pathway components, as well as JNK protein kinase, with an increase in the ERK protein kinase activity accompanied by a decrease in the thiol-containing compound concentration. This circumstance indicates the dysregulatory changes and AOP deficiency in the examined patients [5, 6]. The statistical analysis allowed us to assess the nature of the relationship between the investigated regulatory components and the thiol status representing the AOP state in the whole blood cell intercellular medium. At the same time, a significant association of thiol concentration in the extracellular medium was revealed with STAT5A and p50 factors in the MNC, as well as JNK and ERK protein kinases. Taking into account the moderate nature of the relationship between thiol status and the signaling pathway components and their stochastic nature, it is obvious that the mechanism of the revealed relationship is the indirect influence of thiol on the redox-sensitive component status of the molecular mechanism regulators, including phosphatases such as PTP1B, PP2CA, MCP-1 directly governing the activity of MAPK/SAPK and JAK/STAT signaling pathways [2, 7].

The described mathematical model linking the thiol level and the signaling molecular cell reactivity mechanisms can also be considered as predictive. It can be assumed that an increase in the blood thiol level will be accompanied by an

increase in the STAT5A transcription factor activity, which, in turn, suggests an increase in cell sensitivity to cytokines such as IL-2, IL-3, as well as erythropoetin and thrombopoetin, stimulating hematopoiesis [8, 9]. At the same time, a decrease in STAT3 activity accompanied by a reduction in cell sensitivity to pro-inflammatory cytokines, including IL-6 and IL-5, as well as T-helper 17 differentiation inhibition, suggests the formation of pro-inflammatory effect from an increase in thiol concentration in the blood. In addition, the JNK protein kinase content stimulation in convalescents under thiol influence can stimulate the repair of the double-stranded DNA breaks due to sirtuin phosphorylation [10]. Moreover, an increase in the STAT5A level determines the activation of sanogenesis mechanism identifying the restoration of the normal AOP level [11, 12]. Taking into account the obtained results, it can be assumed that the dynamics of the thiol-containing compound level in the body can be considered as one of the goals for lower respiratory tract infection treatment, as well as immune rehabilitation of such patients, characterized by preserving the proinflammatory activation of immunocompetent cells (ICC) in the convalescence CAP phase reflecting incomplete pathological process by the time of clinical recovery [13]. Under these conditions, stimulation of restored thiol-containing compounds accumulation in the extracellular fluid, while increasing the antioxidant status, will accelerate the recovery from an infectious-inflammatory process, including the normalization of ICC reactivity [14].

The study results suggest that ICC stimulation by pathogen components, as well as by cytokines with intracellular molecular pathway activation for the receptor information transmission plays an important role in maintaining the LPO/AOP balance and it is necessary to maintain the antioxidant level in the intercellular medium. At the same time, excessive suppression of the key signaling pathway components studied during this research can negatively affect AOP, in particular, can result in the decrease of the TC level in patients coming through CAP. So, it is advisable to avoid over-suppressing immune response when providing medical care to such patients, including by limiting the adrenal gland hormone use without absolute indications and unreasonably long-term antibacterial drug therapy. Considering the revealed dependence of the effect of thiol-containing compounds on the activation of the terminal signaling pathway components, it is reasonable to prescribe water-soluble antioxidants, in particular taurine, cysteine or lipoic acid along with the main therapy to such patients in order to maintain optimal biochemical process activation in ICC [1, 3, 14].

Conclusions

1. Among CAP convalescents with thiol-containing compound deficiency, there is a statistically significant decrease in the JAK2 protein kinase phosphorylation level by 26.8%, STAT3 factors by 8.1%, STAT5 by 19.8%, STAT6 by 20.5%, JNK by 12.6%, while a slight increase was observed in the ERK protein kinase phosphorylation level by 4.7%. These changes indicate a close relationship between the activity of the studied signaling pathways and the LPO/AOP state.

2. Regression analysis showed that the thiol status is characterized by a positive relationship with the STAT5A factor activity in the MNC, the JNK protein kinase content in the cell, the nuclear transcription factor NF-κB p50 subunit, while the negative relationship is characterized by the ERK factor content and the STAT3 phosphorylation level. The mathematical model linking the thiol level and ICC reactivity molecular mechanisms allows to judge the potential antioxidant effect, as well as possible pathophysiological AOP manifestations in the CAP convalescence phase. It can facilitate the prediction of the effectiveness of immune rehabilitation in these patients.

3. Taking into account the nature of the identified relationships, it is possible to formulate a hypothesis that an increase in the thiol level contributes to an increase in the activity of the transcription factor STAT5A and a decrease in STAT3 activity with increased cell sensitivity to IL-2, IL-3, erythropoetin and thrombopoetin while reducing ICC sensitivity to pro-inflammatory cytokines, including IL-6 and IL-5, as well as T-helper 17 differentiation inhibition. So, water-soluble antioxidant

therapy in CAP convalescents may promote the correction of the state of intracellular signal transduction mechanisms and accelerate recovery after CAP.

Conflict of interests

The authors declare no conflict of interests.

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BILE MORPHOMETRIC ANALYSIS IN EARLY DIAGNOSIS OF GALLSTONE FORMATION

Abstract

Study objective. To study the changes in the morphological pattern of bile depending on the age of patients and the possibility of using the information obtained in the early diagnosis of gallstone formation. **Material and methods.** The study enrolled 396 patients with stage I cholelithiasis, group 1 consisted of 125 patients of young adult age (30–44 years), group 2 — 164 patients of middle adult age (45–59 years), and group 3 — 107 patients of late adult age (60–74 years). The studied groups were gender-balanced. In the verification of the diagnosis, in addition to general clinical data, results of the gallbladder ultrasound were used. Multifractional duodenal drainage with the subsequent macroscopic, microscopic, morphometric, biochemical, and physical bile tests was carried out. To assess the morphological pattern and features of the microstructure of bile, crystallogram analysis was carried out. **Results.** According to gallbladder ultrasound, signs of biliary sludge were determined in all patients. The destabilization of bile is evidenced by an increase in cholesterol, a decrease in bile acids, cholesterol-to-bile acid ratio, an increase in its viscosity and surface tension. A morphometric study of bile at the early stage of gallstone disease showed a decrease in the angle of slope of liquid crystal lines, as well as the appearance of optically active inclusions, such as branched dendrites with lamellar branches, tangled fibrous aggregates, shield-shaped aggregates and short branched dendrites. With an increase in the tendency of gallstone formation, the optical activity of microcrystals increases, lamellar druses and branched plateau-like aggregates are determined. **Conclusion.** The crystal-optical method of bile analysis is highly sensitive, but at the same time it is easy to perform and can be widely used in the early diagnosis of CLT. The degree of impairment in the bile microstructure increases with increasing age of patients.

Key words: *early diagnosis of gallstones, lithogenic bile, bile morphometry*

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BV — bile viscosity, CLT — cholelithiasis, BA_B — bile acids, GB — gallbladder, LCL — liquid-crystalline line, ST_B — surface tension of bile, CL_B — cholesterol of bile, CBR_B — biliary cholesterol-to-bile acid ratio

Introduction

Cholelithiasis (CLT) can be attributed to the category of socially significant pathology and, of course, be considered as one of the urgent issues of clinical gastroenterology due to the increase in morbidity with coverage of the most able-bodied part of the population, a pronounced negative impact on social activity and quality of life [1, 2, 3]. Great difficulties in early clinical diagnosis and timely use of preventive measures are caused by nonspecific clinical signs and "silent" course of the disease.

In recent years, the study of the phase composition of various biological media in the body based on the idea of liquid crystals involved in the pathogenesis of a number of diseases has become increasingly

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common [4, 5]. According to few literature data, some biological fluids, in particular, bile, under certain conditions, are able to crystallize with the formation of patterns. The change in morphology of the latter depends significantly on the nature of the pathological process, which allows them to be used for diagnostic purposes [6, 7, 8, 9].

Study Objective

To study the changes in the morphological pattern of bile depending on the age of patients and the possibility of using the information obtained in the early diagnosis of gallstone formation.

Materials and Methods

Three hundred and ninety-six patients with stage I CLT (classification of Central Research Institute of Gastroenterology (CRIG), 2001), secondary to hepatobiliary diseases (functional disorders of the biliary system, chronic non-calculous cholecystitis, non-alcoholic fatty liver and non-alcoholic steatohepatitis) were examined. According to the WHO classification (2012), the 1st group consisted of 125 patients of young adult age (30 to 44 years), 2nd group — of 164 patients of middle adult age (45 to 59 years), and 3rd group — of 107 patients of late adult age (60 to 74 years). Examination of patients was carried out on the basis of informed voluntary consent according to the order No. 390n of the Ministry of Health of the Russian Federation dated April 23, 2012 (registered by the Ministry of Justice on May 5, 2012 under No. 24082), in compliance with ethical principles.

The scope of the study was justified statistically by the sampling frequency using the following formula

$$n=t^2\rho q/\Delta^2,$$

where n is the number of observations in the sample study, ρ is the frequency of the studied event, q is the difference between the conditional number based on which the frequency of the studied event is calculated and the value of this parameter, t is the confidence coefficient, and Δ is the maximum error.

Group formation was carried out using random and stratified sampling procedure among patients who were hospitalized in the internal medicine and gastroenterology departments of hospital No. 8 of Izhevsk.

In the verification of the diagnosis, along with anamnestic and general clinical data, the results of ultrasound examination of the gallbladder were taken into account. All patients underwent multifractional duodenal drainage followed by macroscopic, microscopic, morphometric, biochemical, and physical examination of bile.

To identify signs of bile destabilization in bile portions B and C, the total concentration of bile acids (BA_B) and cholesterol (CL_B) was determined [10], the biliary cholesterol-to-bile acid ratio (CBR_B), which is an index of bile lithogenicity, was calculated. The study of the surface tension of bile (ST_B) and bile viscosity (BV) was carried out using the method developed by T. L. Redinova for saliva [11] and adapted by us for bile.

The method of wedge-shaped dehydration was used to study the morphological pattern of gallbladder bile. Three μl of bile portion B was applied in the form of droplet on the surface of ungreased polished quartz glass, was dried in a desiccator with desiccant, placed in a dry-air cabinet at 35 °C for 2–2.5 hours. The formation of structures occurred due to evaporation from the edges of the sample and primarily appeared in the peripheral areas. Sample review (crystallograms) was made by simple polarization in transmitted light using a Leica DM 2500 (lens × 3.5) microscope with a Leica DFC 420 digital camera and Leica applications software. The main morphokinetic changes in the sample begin in the first hours and occur by the end of the first day [12], so the sample was studied 3 hours and 24 hours after its preparation. Using ImageJ (Free Ware) program, the features of bile microstructure were determined, and the images were input into a computer, analyzed and processed using the original computer program VIDEO test.

The results of laboratory and instrumental examination of patients were compared with the data in the control group, which consisted of 50 healthy individuals aged 20 to 50 years who had no complaints about the gastrointestinal tract.

The obtained data were analyzed using SPSS statistical processing program. The data are presented as mean values (MV) with the determination of their errors (±m). P-value was assessed by Student's t-test in the normal distribution of the sample.

Results and Discussion

In all patients, ultrasound examination of the gallbladder revealed signs of biliary sludge (microlithiasis, putty bile), bile microscopy in 72.6% revealed crystals of cholesterol and calcium bilirubinate which is evidence of the I (precalculous) stage of CLT.

The results of the biochemical analysis of bile in observed patients are especially noteworthy (*Table)*. One hundred percent showed signs of destabilization of bile portions B and C. The decrease in BAs_B concentration, which are stabilizers of the colloidal state of bile, subsequently leads to precipitation of CL_B, supersaturation of bile, bile propensity to gallstone formation, as evidenced by a significant decrease in the biliary cholesterol-to-bile acid ratio (CBR_B), which is an index of bile lithogenicity. Obviously, with age, changes in all of the above parameters progress, which means that the risk of gallstone formation also increases.

Of particular interest is the fact that in young adulthood (group 1), lithogenic properties of bile are mainly associated with elevated cholesterol levels, in late adulthood (group 3) — with a reduced level of bile acid pool, and in middle adulthood (group 2) these changes are approximately balanced. Our results are consistent with the literature data indicating that in case of the propensity to cholelithiasis in young people the metabolism of exogenous cholesterol significantly slows down, in the elderly, the activity of 7-alpha-hydroxylase involved in the synthesis of bile acids from cholesterol decreases [12, 13].

Test of the physical properties of bile revealed elevated BV and ST_B levels in both portions, which is in agreement with few literature data [15, 16, 17]. The inspissation of bile and increase in its viscosity reduces the solubility of various components including the deposition of cholesterol crystals, agglomeration and nucleation of bile. Bile lithogenicity determined by its physical characteristics increases in older age groups.

It is known that the process of lithogenesis occurs in three stages: saturation, crystallization, and growth [13, 15, 18]. The decisive factor is the stage of bile supersaturation with cholesterol, which commences when solubilization of all cholesterol by vesicles becomes impossible. Supersaturated vesicle is very unstable, and it aggregates forming liquid crystals (liposomes). After that, the nucleation of cholesterol crystals occurs with the deposition of cholesterol monohydrate crystals (solid crystals) which are the center of crystallization [8, 19], a key link and the basis for the formation of gallstones [20].

Bile crystallography is a research method based on the ability of some crystal-forming substances to

Table. *Physical and chemical properties of bile tested*

Parameter	control (n = 50)	group 1 (n = 125)	group 2 (n = 164)	group 3 (n = 107)
CL_B (mmol/l):				
Portion B	7.56 ± 0.07	27.76 ± 2.14*	29.96 ± 2.45*	19.96 ± 2.15*
Portion C	3.63 ± 0.06	14.99 ± 2.16*	14.87 ± 1.33*	8.41 ± 1.54*
BA_B (mmol/l):				
Portion B	54.33 ± 0.14	49.35 ± 2.17*	48.93 ± 2.67*	26.02 ± 1.34*
Portion C	20.76 ± 0.20	18.01 ± 2.23	17.37 ± 2.31	10.43 ± 2.01*
CBR_B (U):				
Portion B	7.15 ± 0.07	2.77 ± 0.04*	1.63 ± 0.07*	1.3 ± 0.07*
Portion C	6.14 ± 0.10	1.45 ± 0.04*	1.16 ± 0.07*	1.2 ± 0.07*
BV (U):				
Portion B	2.74 ± 0.20	3.78 ± 0.29*	4.15 ± 0.3*	4.41 ± 0.56*
Portion C	2.52 ± 0.02	3.22 ± 0.03*	3.81 ± 0.19*	4.23 ± 0.8*
ST_B:				
Portion B	22.31 ± 0.15	22.95 ± 2.15	24.16 ± 2.03	28.34 ± 1.16*
Portion C	22.05 ± 0.14	24.99 ± 1.19*	25.96 ± 1.19*	28.04 ± 2.41*

Note: n is the number of observations; * P < 0.05, compared to control

form different structures. The shape of the crystal is a natural system of indication for the chemical composition of the biological fluid [4].

In the control group the morphometric study of gallbladder bile microstructure revealed the presence of widely branched crystals which were analyzed on the basis of liquid crystal lines (LCL) (Figure 1A). The angle of slope for LCL was (98.97 ± 2.92)°.

The morphological pattern of bile in patients with stage I of CLT was dependent on age. The group 1 of patients (Figure 1B) also was characterized by the presence of widely branched crystals, but there were a decrease in the slope angle of LCL down to (46.16 ± 3.67)° (p in relation to the control was < 0.01) and a fuzzy structure.

In addition, optically active inclusions reacting to polarized light appear in the initial stage of CLT. A lower degree of destabilization of bile colloidal structure (group 1) is characterized by the appearance of crystals with low optical activity (Figure 2: A, B), the so-called cholesterol monohydrate crystals. The most typical were branched dendrites with lamellar branches (in 49 patients — 39.2%) and tangled fibrous aggregates (in 62 patients — 49.6%).

The increase in biochemical signs of bile instability (group 2) led to the formation of crystals with high optical activity (Figure 3: A, B), the so-called large spherolites. Such characteristic structures as shield-shaped aggregates (in 52 patients — 31.7%) and short branched dendrites (in 96 patients — 58.5%) were shown.

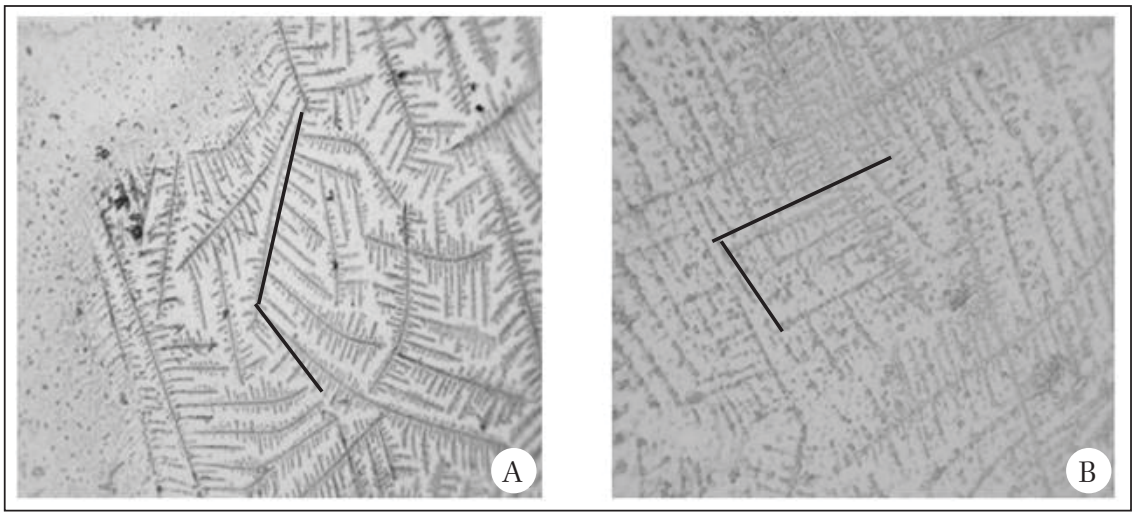

Figure 1. *Bile crystallograms: A – bile of healthy individuals; B – bile of the group 1 patients*

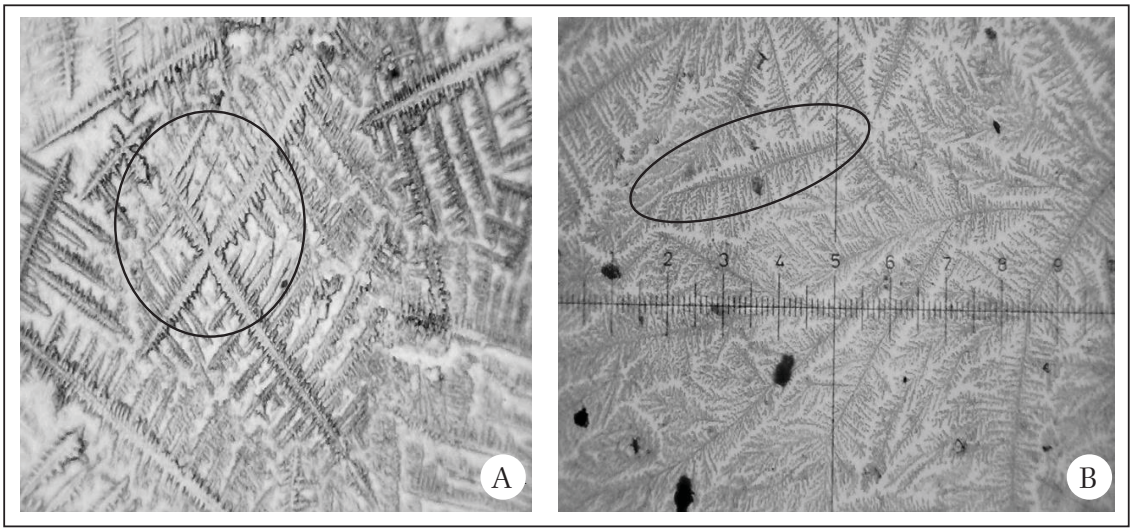

Figure 2. *Bile crystallograms (group 1): A – branched dendrites with lamellar branches; B – tangled fibrous aggregates*

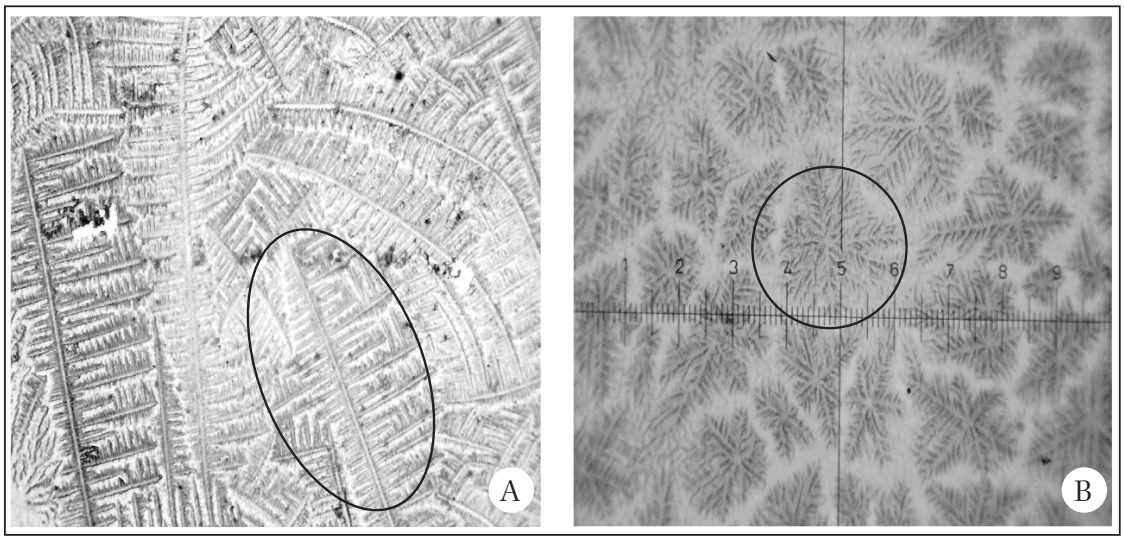

Figure 3. *Bile crystallograms (group 2): A – shield-shaped aggregates; B – short branched dendrites*

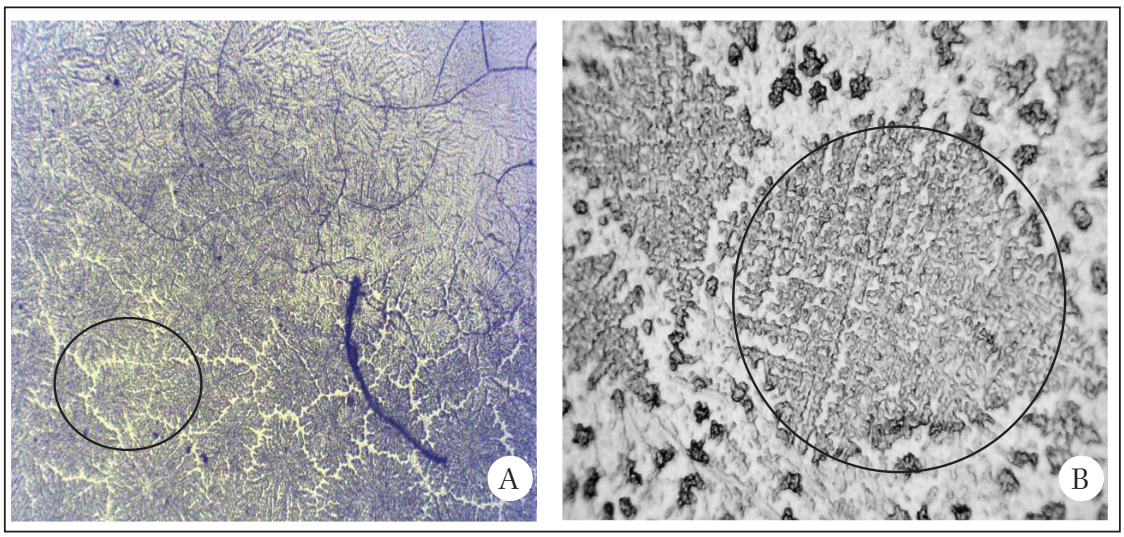

Figure 4. *Bile crystallograms (group 3): A – lamellar druses, B – branched plateau-like aggregates*

The morphological pattern of bile in group 3 patients is characterized by the presence of microcrystals (Figure 4: A, B): lamellar druses and branched plateau-like aggregates (in 42 patients — 39.2% and 51 patients — 47.6%, respectively) (Figure 4) were found approximately with the same frequency.

Our crystal-optical studies indicate that the found crystal-optical morphotypes have a selective morphology in accordance with the age and the degree of bile lithogenicity. With an increase in bile lithogenicity, there is an increase in optical activity of crystals [21, 22], its tendency to precipitate cholesterol with the formation of liquid crystal structures [6, 7, 8].

Thus, polarization microscopy reflecting the spatial supramolecular structures of the biological fluid [4] reveals deeper changes in bile structure in contrast to the biochemical method, which determines only the quantitative content of the main bile components.

Conclusion

1. The crystal-optical method of bile examination is highly sensitive, but at the same time it is easy to perform and can be widely used in the early diagnosis of CLT.

2. Branched dendrites with lamellar branches and short branched dendrites in bile are transitional

forms (promicrolites) and precede the formation of microlites — microcrystals in the form of lamellar druses and branched plateau-like aggregates.
3. The degree of impairment in the bile microstructure increases with increasing age of patients.

Conflict of Interests

The authors declare no conflict of interests.

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RISK FACTORS OF DAMAGE OF THE CARDIOVASCULAR SYSTEM IN PATIENTS WITH PRIMARY OSTEOARTHRITIS WITH IDENTIFIED CORONARY ATHEROSCLEROSIS

Abstract

The objective of the study was to assess risk factors of the cardiovascular system damage in patients with primary osteoarthrosis and diagnosed coronary atherosclerosis. **Materials and methods.** Fifty-two patients at the mean age of 41 [34; 52] years were involved in the study. There were 37 women and 15 men among them. Elective coronary angiography using the ALLURA Xper FD20 Philips 2012 device was provided to all patients. As a result, hemodynamically insignificant (less than 50%) atherosclerotic stenosis of the heart vessels was verified in this group. The height, weight, and waist circumference with the calculation of body mass index by the Kettle method were determined in patients. Evaluation of cardiovascular risk factors, such as smoking, family history of CVD, and hypodynamia, was performed using questionnaires. The daily monitoring of blood pressure (BP) was carried out with the Cardiotechnika-07-AD-3 device; complete blood count and biochemical analysis were performed, and the systemic coronary risk was evaluated. **Results.** Each patient had from 1 to 6 risk factors of cardiovascular diseases, the median [25th; 75th percentiles] was 3 [2; 5]. In women, family history of cardiovascular diseases, hypodynamia and hypertension were significantly more common than in men (p=0,002). The presence of bad habits (smoking), high levels of triglycerides and low density lipoproteins (p = 0.0001) occurred with higher frequency in men. The correlation analysis revealed that the incidence of hypertension, hypodynamia and dyslipidemia was associated with the duration of osteoarthrosis, the intensity of pain according to visual analog scale and the number of affected joints. **Conclusion.** The presence of generalized subclinical inflammation in patients with osteoarthrosis together with the classic risk factors of cardiovascular diseases, probably mediates the early onset of atherosclerosis in this category of patients.

Key words: *osteoarthrosis, atherosclerosis, inflammation, risk factors, cardiovascular diseases*

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BP — blood pressure; VAS — visual analogue scale; BMI — body mass index; NSAIDs — nonsteroidal anti-inflammatory drugs; OA — osteoarthrosis; CVD — cardiovascular diseases; RF — risk factors

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According to the Federal Rheumatology Center, the incidence of osteoarthrosis (OA) is 11.4 per 1,000 people aged over 18, and the increase in the incidence is 20% annually. The frequent combination of OA with cardiovascular diseases (CVD) is one of the urgent problems facing modern medicine, since the death rate from vascular accidents in this category of patients is much higher than in the general population [6, 7, 13, 15, 18]. At the same time, there is a significant reduction in the age of patients with both OA and atherosclerosis [1, 23].

Study objective: to assess the cardiovascular risk factors in patients with primary osteoarthrosis in whom coronary atherosclerosis was diagnosed.

Materials and Methods

The study was conducted at the State Healthcare Institution Krai Clinical Hospital and Federal State Budgetary Educational Institution of Higher Education Chita State Medical Academy. The study enrolled 52 patients with primary osteoarthrosis (37 women, 15 men). Median [25th; 75th percentiles] of age was 41 [34; 52] years. The OA duration in the study group was 7 [5; 8] years, the diagnosis was made on the basis of the ACR classification criteria with regard of the radiological Kellgren and Lawrence classification. All patients underwent elective coronary angiography using the ALLURA Xper FD20 Philips 2012 device during the period from September 2017 to June 2018, and hemodynamically insignificant (up to 50%) atherosclerotic coronary stenoses were verified. The individuals enrolled in the study gave their consent to undergo the manipulations. The Ethics Committee has approved study protocol.

The height, weight, and waist circumference with the calculation of body mass index (BMI) by the Kettle method were determined in patients. Obesity was diagnosed with an index value of 30 or more. Evaluation of cardiovascular risk factors (RF), such as smoking, family history of CVD, and hypodynamia, was performed using questionnaires. The questionnaire also included questions regarding the intensity of pain syndrome according to the visual analogue scale (VAS), the need for analgesia, the frequency of nonsteroidal anti-inflammatory drug (NSAIDs) use. In women, the state of reproductive function was further specified. The daily monitoring of blood pressure (BP) was carried out with the Cardiotechnika-07-AD-3 device; complete blood count and biochemical analysis were performed, and the systemic coronary risk was evaluated.

The data were processed using the Statistica 10.0 (StatSoft, USA) software package, nonparametric methods were used. Comparison of two independent groups was carried out using the Mann-Whitney test. For the correlation analysis, the Spearman method was used. The comparison of frequencies of qualitative variables between independent groups was performed using the χ^2 test. Significance of differences was determined at $p < 0.05$.

Results

In patients of the examined group, polyosteoarthrosis was most often identified with a predominant lesion of the knee, hip, shoulder and small joints of the hands and feet, at the radiographic stage 2–3. Clinical and laboratory characteristics of patients with OA are shown in Table 1.

Almost all respondents (92%) had their onset of OA with mechanical arthralgias, 8% noted a feeling of stiffness in the joints after a long rest in the early period of the disease. In terms of the disease duration and the onset age of OA, gender differences were not determined; in the general group, the medians were 7 years and 34 years, respectively. 10% of patients received regular course treatment with long-acting disease-modifying agents (glucosamine sulfate, chondroitin hydrochloride); the remaining 90% of patients did not comply with the prescribed dosage regimen or completely ignored medical prescriptions. It should be noted that chondroprotective agents were prescribed in 100% of cases. 64% of patients experienced the need for analgesia (NSAID group use) 3–4 times a week for the last 3 months. Aceclofenac, Nise and Movalis were the most frequently used selective NSAIDs. More than half of the respondents reported strong intensity of arthralgia, the median pain index according to the VAS was 60 mm. All respondents with hypertension received antihypertensive therapy: 36 persons (70%) received

Table 1. *Clinical and laboratory characteristics of patients with osteoarthrosis*

Parameters	Median [25th; 75th percentiles]
OA duration	7 [5; 8]
Number of affected joints	5 [3; 12]
OA onset age	34 [30; 42]
Radiographic stage	2 [2; 3]
Pain intensity according to VAS, mm (within 3 months)	60 [40; 90]
Need for NSAIDs (number of tablets per week for the last 3 months)	3 [1; 7]
Average daily BP score Systolic BP (mm Hg) Diastolic BP (mm Hg)	 135 ± 5 75 ± 12
CRP, mg/L, ρ = 0.002	0.5 [0.2; 4]
ESR, mm/hour	12 [6; 22]

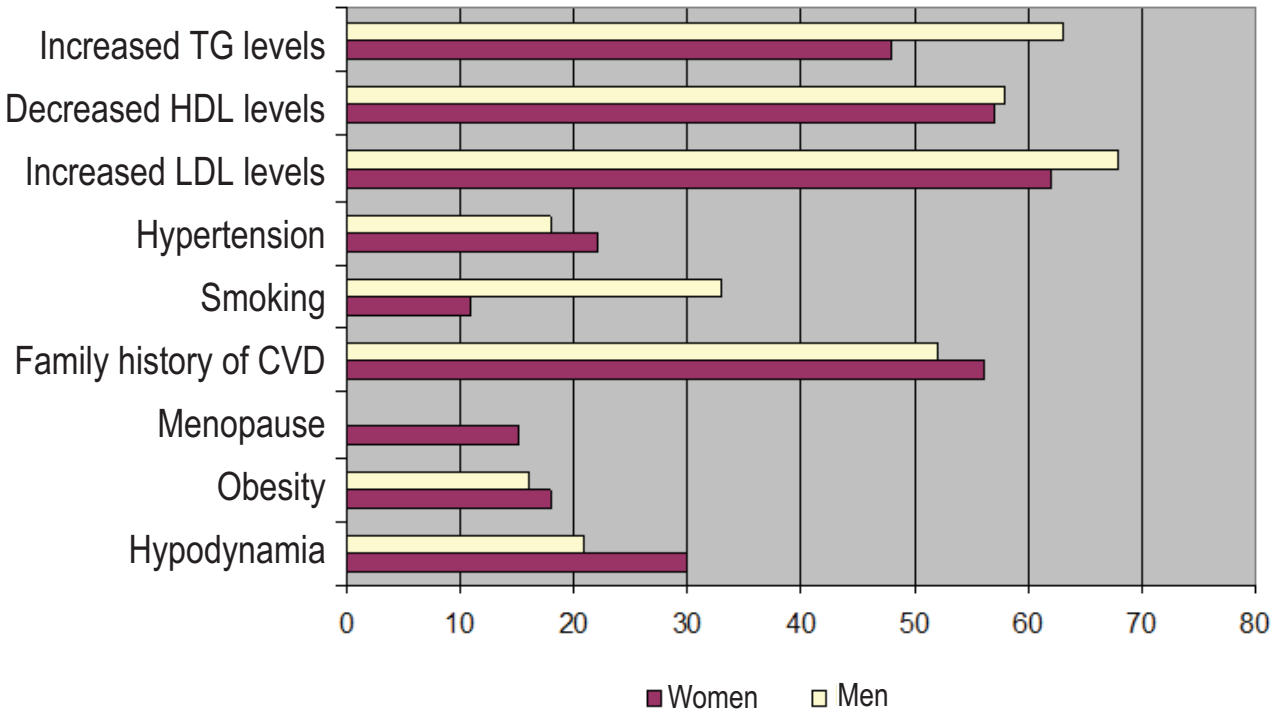

Figure 1. *Frequency of cardiovascular disease risk factors in patients with osteoarthrosis*

Table 2. *Indicators of correlation analysis of cardiovascular disease risk factors with clinical characteristics of osteoarthrosis*

	OA duration	Number of affected joints	Pain intensity according to VAS	Dosage frequency of NSAIDs
Hypertension	r = 0.63*	r = 0.72	r = 0.85*	r = 0.74*
Hypodynamia	r = 0.62*	r = 0.61*	r = 0.82*	-
Dyslipidemia	r = 0.71*	r = 0.58*	r = 0.66*	r = 0.56*

Note. * ρ < 0.05

monotherapy, and 16 persons (30%) received two-component therapy with angiotensin II receptor blockers and thiazide diuretics predominantly. Treatment of dyslipidemia before coronary angiography was provided only for 12% of patients, who were indicated for its use; atorvastatin was prescribed in the vast majority of cases (94%).

The results of the assessment of the frequency of CVD RF are presented in Figure 1.

Each patient had 1 to 6 CVD RF, median [25th; 75th percentile] was 3 [2; 5]. In the women group, hypodynamia, hypertension and a family history of CVD ($p = 0.002$) were significantly more common than in men. In 6 female patients (15%) menopause occurred as a result of surgery. The presence of bad habits (smoking), high levels of triglycerides and low density lipoproteins ($p = 0.0001$) occurred with higher frequency in men. High-density lipoprotein and BMI values did not differ in the compared groups. The presence of verified coronary atherosclerosis makes it possible to classify all individuals enrolled in the study as a group of very high systemic coronary risk, regardless of other factors.

Correlation analysis revealed that the frequency of hypertension, hypodynamia and dyslipidemia was associated with the OA duration, the pain intensity according to the VAS and the number of joints affected (Table 2). At the same time, hypertension and the high level of triglycerides were more frequent, the more the respondent took NSAIDs.

Discussion

According to standard scoring systems, age and hypertension grade are the main factors of high cardiovascular risk. Our study represents young people with medically achieved target blood pressure levels, and all of them have atherosclerotic lesions of the coronary arteries and belong to a group with very high systemic coronary risk.

The role of the immune and inflammatory process in the development and progression of atherosclerosis is illustrated by a number of rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus [7, 9, 12, 22]. In the OA pathogenesis, persistent inflammation also plays a key role, and causes the progression of cartilage destruction with the development of secondary chondritis, synovitis, osteitis and periarthritis [2, 8, 11, 19]. Destructive cytokines activate and regulate a cascade of pathophysiological reactions, which leads to a change in the functional activity of chondrocytes [11, 17, 24]. Hyperplasia and mononuclear infiltration of synovia in OA is indistinguishable from that in rheumatoid arthritis [16, 18, 23]. Along with inflammation and accumulation of classical CVD RF, adverse effects of the drug therapy also contribute to atherogenesis in OA. Inhibitors of the proinflammatory cyclooxygenase are prescribed to almost all patients for the treatment of pain and inflammation in OA [4, 10, 20, 21]. It is known that increasing the risk of myocardial infarction and sudden coronary death is one of the most common cardiovascular complications associated with taking NSAIDs [3, 5, 14, 25].

Conclusions

Thus, the presence of generalized subclinical inflammation in patients with OA, along with classical CVD RF, probably mediates the early development of atherosclerosis in this category of patients. In addition, OA patients use NSAIDs with certain frequency, which also adversely affects the state of the vessel wall. There is need to continue and deepen the study of the role of inflammation in primary OA in the development and progression of atherosclerosis. It is reasonable to develop specialized models for assessing the risk of damage to the cardiovascular system for patients with primary OA.

Conflict of Interests

The authors declare no conflict of interests.

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THE ASSESSMENT OF EFFICACY AND OF SAFETY USING SELF-MONITORING OF DISEASE ACTIVITY VIA INTERNET PORTAL IN THE MANAGEMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS

Abstract

The objective was to identify the exacerbation of the disease as quickly as possible and timely enhance the treatment to achieve remission or low disease activity more rapidly. **Methods:** The authors created an interactive web portal for self-monitoring of RA activity. The patient management model using this method is that a patient conducts a monthly self-assessment of the disease activity and transfers this information to his/her attending physician in a remote manner via the web portal. In case of state worsening and in the absence of any change, according to the patient, he/she is invited to the center, where this information is verified by the doctor. If case of state improvement, according to the patient, he/she does not come to the clinic and continues the treatment. Currently, 30 women with RA, mean age is 57 years old (38; 71), who completed the 6-month treatment, are enrolled in the study. Twenty women are enrolled in the control group, mean age is 60.5 (40; 77). **Results:** During 6 months, there was a positive dynamic of the course of the disease, the activity of RA, according to DAS 28 score, decreased. Initially, 5 patients (16.7%) showed high DAS activity, 24 moderate DAS activity (80%), and 1- low DAS activity (3.3%). After 6 months of treatment, 8 patients (26.7%) showed low activity and 22 (73.3%) achieved remission. The mean value of the DAS 28 score at the time of inclusion was 3.99 (2.46; 5.78), and after 6 months of management it was 2.175 (0.79; 4.31), which is a statistically significant decrease (Wilcoxon T-test = 5). The DAS 28 score in the control group was 4.1 (2.46; 5.78), and after 6 months of management it was 3.9 (0.79; 4.31), which is a statistically significant decrease (Wilcoxon T-test = 5). Analysis of clinical and laboratory parameters did not reveal statistically significant deviations. **Conclusions:** The 6-month period of patient management via the web portal for self-monitoring of rheumatoid arthritis activity proved the possibility of achieving remission and low disease activity in all patients.

Key words: *web portal, rheumatoid arthritis, self-monitoring of disease activity*

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RA — rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is an autoimmune rheumatic disease of unknown etiology characterized by chronic erosive arthritis (synovitis) and systemic damage to internal organs [1]. RA incidence occupies a leading position among the inflammatory diseases of the musculoskeletal system. More than 20 million people worldwide suffer from RA [2]. In 2013, the number of RA patients in the Russian Federation was 286,005 people [3].

RA often leads to both temporary and persistent disability of patients. The Russian epidemiological study RAISER conducted in 2010 showed that among 1,500 RA patients, 68% of patients had disabilities, and 2/3 of them were completely disabled. In 83.4% of cases, the causes of disability were the relapsing course of RA and the ineffectiveness of treatment. The mean age of RA patients with disability was (47.5 ± 12.3) years, permanent total disability was observed at the age of (54.6 ± 12.0) years. Moreover, 22.7% of RA patients applied for social benefits due to financial problems [4].

At some later time, I. Yu. Zinchuk and V. N. Amirdjanova in their work showed slightly smaller but nevertheless quite significant indicators of permanent disability detected in 17.9% of RA patients in the Russian Federation. The total number of patients with grade 3 disability, working patients with grade 2 disability, and patients who had to change their jobs due to RA, was 18.1% [5].

At the present time, the achievement of the main goal of RA treatment is theoretically possible, since there is a sufficient range of disease-modifying anti-rheumatic drugs, which are expected to be prescribed in the early stages of the disease [24]. The concept of monitoring has also changed, it is now stricter. The disease activity indicators should be determined by a rheumatologist every month in the case of a high/moderate degree of RA activity, and every 3–6 months in the case of a stable activity. Monitoring of the disease activity in routine practice is performed using standardized international disease activity indices [6, 8, 23].

However, only 5–6% of RA patients can achieve remission in actual practice [7]. There are a number of reasons, both on the part of the patient (difficulty of visiting the hospital due to restricted mobility, low compliance, low efficacy of drugs due to the pathogenetic features of the disease, intolerance of drugs), and on the part of doctors (insufficient number of rheumatologists) [9, 10].

Self-assessment of health status is actively used worldwide in such diseases as chronic heart failure, essential hypertension, and diabetes mellitus. There are various methods of self-assessment of RA activity [12–22]. In 2014, we created a structured training program for training of RA patients in self-monitoring of disease activity, which allows patients to self-assess painful and swollen joints. The study evaluating the effectiveness of this program showed that 68% of patients can properly assess swollen joints, and 60% of patients can properly assess painful joints [11].

In 2015, we created a web portal for the self-monitoring of rheumatoid arthritis activity. The structure of the web portal includes three sections: 1) photo- and video materials with information about RA; 2) teaching photo- and video materials on the method of self-assessment of RA activity; 3) personal account for the patient and the doctor. This electronic resource uses a personalized approach to the patient. A patient's electronic medical record is provided in the doctor's personal account (Fig. 1a), which contains clinical, demographic, laboratory and instrumental data; treatment information; data from questionnaires that are filled in by both the patient and the doctor (Fig. 1b). Many parameters are also presented graphically, their time course is shown. Patients are pre-trained according to the methodology "Structured Training Program for Patients with Rheumatoid Arthritis to Self-Monitor Disease Activity". The patient performs the self-assessment of disease activity on a monthly basis. The patient enters the results of the self-assessment of painful and swollen joints into the chart in their account, assesses various parameters according to the VAS, and fills out HAQ and EQ-5 D questionnaires.

The data received from the patient are remotely transferred via the web portal to the attending physician. The doctor receives information about the state of health of the patient in a processed form by email in as short a time as possible. If the course of the disease worsens or in the absence of

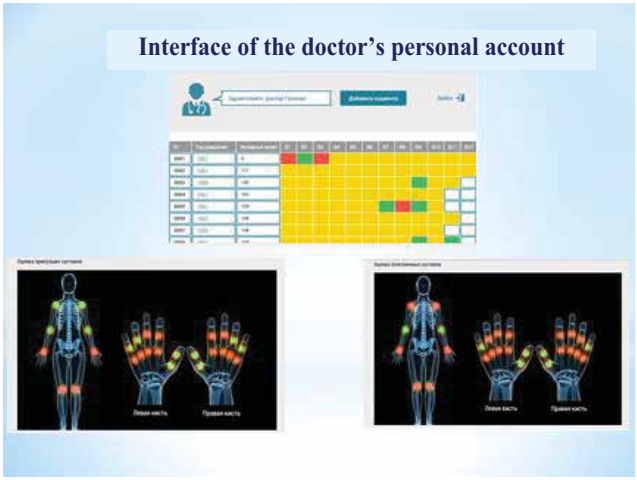

Figure 1a. *The interface of the doctor's personal account. Electronic medical record of the patient*

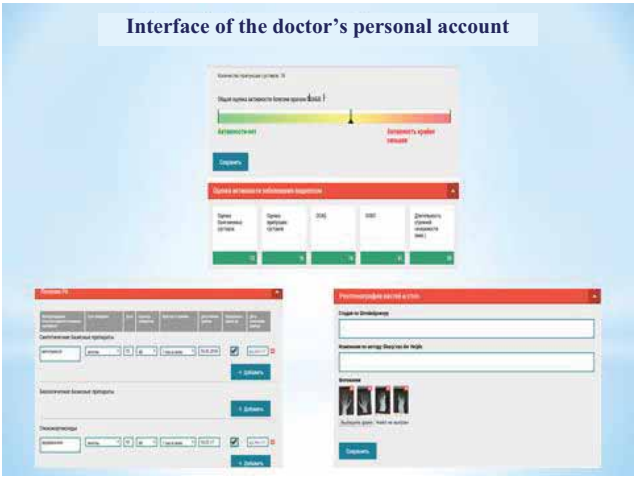

Figure 1b. *The interface of the doctor's personal account. Time course of treatment and disease activity*

any changes, according to the patient, the patient is asked to come to the Center, where the obtained information is verified by the doctor and, if necessary, the treatment is corrected. If an improvement is observed, according to the patient, then the patient does not come to the doctor for a visit, but continues the treatment (Fig. 2).

The web portal, similar to that proposed by us, was developed by the French Society of Rheumatology (SFR) in 2013. This web portal is anonymous and involves an active patient-doctor dialogue through electronic technologies, but without using a personalized approach and long-term dynamic observation. However, there is no scientific evidence of the effectiveness of the portal in the available literature (Sanoia. www.sanoia.com/e-sante/Polyarthrite-Rhumatoide.php).

Therefore, **the objective of our study** was to assess the effectiveness of management of patients with rheumatoid arthritis using the web portal of self-monitoring of rheumatoid arthritis activity.

Study design: during the study, the patient was assumed to perform a monthly self-assessment of RA activity and an unscheduled self-assessment in case of deterioration of the RA course. Mandatory in-person meeting with the doctor at the clinic and laboratory monitoring were carried out once in 3 months, as well as during deterioration of health, according to the patient. All patients underwent radiography of the hands and feet twice a year (Fig. 3).

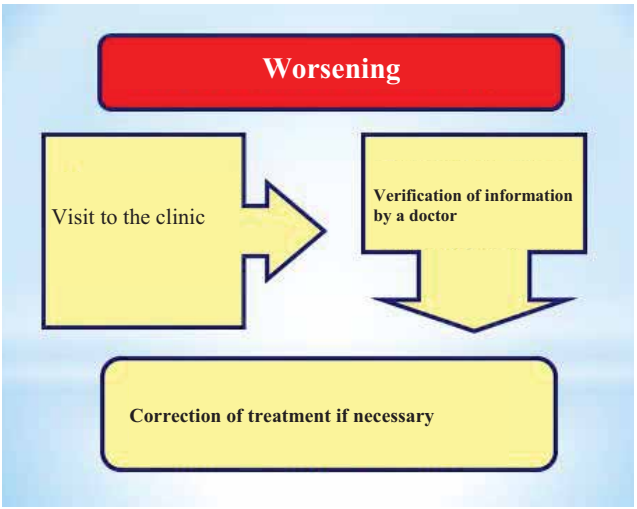

Figure 2. *The procedure in case of worsening*

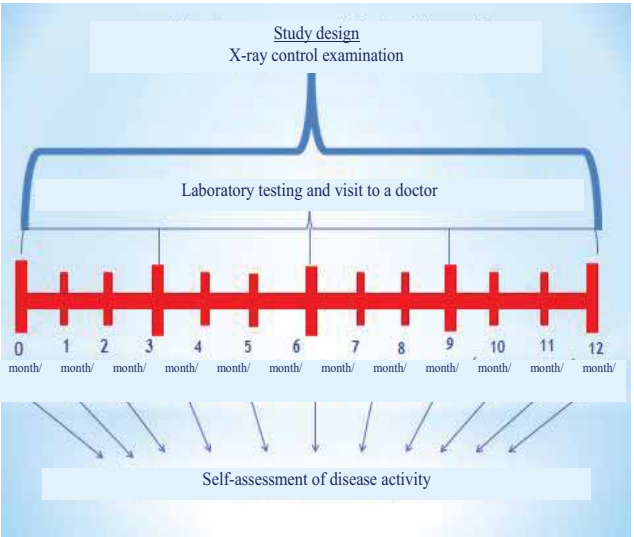

Figure 3. *Study design*

Materials and Methods

The study enrolled 30 women diagnosed with RA, the mean age was 57 years (32; 78). The control group consisted of 20 RA patients comparable in age, gender, and the degree of disease activity with the study group, treated in actual clinical practice settings.

Results

Within 6 months, all 30 patients of the study group were examined and received treatment recommendations. In the study group, there was a statistically significant decrease in the mean value of the DAS 28 score after 6 months of observation (Table 1).

By the 6th month of observation, all patients achieved remission and the degree of disease activity was low (Table. 2).

There was no positive change of the disease course in the control group (Table 3).

On average, patients in the control group visited the doctor 3.89 times (1; 11) per year, while patients from the study group – at least 12 times per year. Remote monitoring enabled to identify the deterioration of the patient's health / exacerbation of the disease in 36.7% (11 of 30) of patients in the study group.

Initially, patients in the study group received the following treatment: methotrexate: 16 (53.3%) patients, methotrexate + glucocorticosteroids: 11 (36.7%) patients, sulfasalazine: 1 (3.3%) patient, sulfasalazine + methotrexate: 1 (3.3%) patient, sulfasalazine + methotrexate + glucocorticosteroids: 1 (3, 3%) patient. By the 6th month, the average dose of methotrexate was increased by 2.5 mg in 2 (18.2%) patients, by 5 mg in 7 (63.6%) patients, and by 10 mg in 2 (18.2%) patients.

The majority of patients in the control group received methotrexate as a basic treatment; the treatment was adjusted only in 47% of cases, but the adjustment was not effective enough; none of the patients achieved remission. 10.5% (2 of 20) patients did not receive disease-modifying antirheumatic drugs; they received non-steroidal anti-inflammatory drugs (Table 4).

Table 1. *Mean DAS 28 score in study and control groups*

	DAS 28 at the time of inclusion	**DAS 28 after 6 months**
Study group	3.99 (2.46; 5.78)	2.175 (0.79; 4.31)
Control group	4.1 (3.3; 4.9)	3.9 (2.39; 4.8)

Note. * Reliable Wilcoxon T-test was 5 ($p < 0.05$) when comparing DAS 28 score in the study group; ** Wilcoxon T-test was 8 when comparing DAS 28 score in the control group; *** Reliable Mann-Whitney T-test was 57 ($p < 0.05$) when comparing DAS 28 score in the control and study groups

Table 2. *The degrees of RA activity in the study group*

	Number of patients at the time of inclusion	**Number of patients after 6 months**
Remission		73.3% (22 of 30)
First degree of activity	3.3% (1 of 30)	26.7% (8 of 30)
Second degree of activity	80% (24 of 30)	0
Third degree of activity	16.7% (5 of 30)	0

Table 3. *The degrees of RA activity in the control group*

	Number of patients at the time of inclusion	**Number of patients after 6 months**
Remission		0
First degree of activity	5% (1 of 20)	10% (2 of 20)
Second degree of activity	90% (18 of 20)	90% (18 of 20)
Third degree of activity	5% (1 of 20)	0

Table 4. *The average doses of methotrexate in study and control groups*

	At the time of inclusion	After 6 months
The average dose of methotrexate in study group, mg	12.9 (10; 30)	14.6 (10; 25)
The average dose of methotrexate in control group, mg	10.8 (0; 20)	13.5 (0; 20)

Discussion

The patients in the study group achieved remission/reduction in the level of RA activity faster than the patients in the control group, as they were under close medical supervision via the web portal and more often contacted the doctor in accordance with the method of the study.

The emission in the study group was achieved by the 3rd month of the study in 33.3% of cases; 10% of patients achieved remission by 4–5th months, and another 16.7% – by the 6th month of the study. In 13.3% of patients in the study group, decrease in the degree of disease activity was achieved only by the 6th month of observation. At visit 1, the dose of methotrexate in the study group was increased in 14.2% of cases (2 of 14), at visit 3 — in 42.9% of cases (6 of 14), and at visit 6 – in 42.9% of cases (6 of 14). Unfortunately, 6% of patients (2 of 30) had adverse reactions to methotrexate (increased liver enzymes levels) and therefore it was necessary to reduce the dose. In the control group, no patient achieved remission in 6 months of observation and treatment in actual clinical practice settings. There was a slight decrease in the DAS 28 score: 4.1 and 3.9 at the time of enrollment and after 6 months, respectively.

Conclusions

1. Management of patients using the web portal of self-monitoring of rheumatoid arthritis activity allows achieving the main goal of treatment: remission in 73.3% of cases and low RA activity in 26.7% of cases in a short time (from 3 to 6 months) in most patients.

2. Enhanced self-monitoring of the disease activity by the patient and remote monitoring by the physician made it possible to quickly identify the exacerbation of RA in 36.7% of patients and to adjust the treatment.

Conflict of Interests

The authors declare no conflict of interests.

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CASE REPORT: OBESITY AND MALNUTRITION IN A PATIENT WITH CHRONIC ALCOHOLIC PANCREATITIS

Abstract

The article represents a case report of such two opposite conditions as obesity and malnutrition in a patient with chronic pancreatitis. The patient was admitted with exacerbation of chronic pancreatitis associated with alcohol abuse. The examination revealed exocrine pancreatic insufficiency and mild malnutrition. The patient was prescribed with enzyme replacement therapy and supplemental sip feeding with following improvement. Exocrine pancreatic insufficiency was managed in 10 weeks, but malnutrition remained and required a longer course of treatment. The relevance of this problem, the main difficulties of diagnosis are presented in the article. To assess the nutritional status, anthropometric measurements, BMI, lymphocytes, total protein, and albumin level tests should be provided. Using BMI alone leads to underdiagnosis of nutritional status in patients with chronic pancreatitis.

Key words: *chronic pancreatitis, obesity, malnutrition, BMI, lymphocytes, albumin*

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WHO — World Health Organization, CLT — cholelithiasis, BMI — body mass index, TSFT — triceps skin-fold thickness, CT — computed tomography, AP — acute pancreatitis, UAC — upper arm circumference, UAMC — upper arm muscle circumference, PC — pancreas, CP — chronic pancreatitis, EI — exocrine insufficiency

Currently, much attention is paid to the problem of obesity in the population. The number of people with obesity is steadily increasing every year both in Russia and abroad. According to the World Health Organization (WHO), 1.9 billion people aged over 18 years were overweight in 2016, of whom more than 650 million were obese. The number of people with obesity worldwide tripled from 1975 to 2016. High prevalence of overweight and obesity is common not only in high-income countries, but also in low- and middle-income countries, especially in urban areas [1]. According to the ESSE-RF (Epidemiology of cardiovascular diseases and risk factors in regions of Russian Federation) study, 26 to 41% of men and 24 to 52% of women in the Russian population aged 35 to 64 years are obese, and obesity was twice as common in older people [2].

The problem of eating disorders can be represented by two edge conditions: obesity and malnutrition. Based on the above statistics, the problem of malnutrition seems insignificant. However, since

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2014, this problem has attracted the attention of WHO experts. According to WHO, in 2014 about 462 million people among the adult population worldwide suffered from underweight [3].

In 2018, the results of a study conducted in China were published: body mass index (BMI) was measured in 737 adult patients; of them: malnutrition was determined in 83 (11%), and obesity — in 118 (16%) [4]. From the presented analysis it follows that the number of patients with malnutrition slightly differs in comparison with the prevalence of obesity among outpatients.

Obesity and malnutrition have been shown to be risk factors for acute pancreatitis (AP) and chronic pancreatitis (CP) [5, 6, 7].

However, malnutrition is more common in patients with CP and has a multifactorial nature (limiting the amount of food taken, malabsorption, diabetes and chronic alcoholism) [8].

The severity of malnutrition correlates with two main factors: with nutrient depletion (alcoholism and pain) and malabsorption, causing a change in nutritional status and an increase in metabolic activity due to the inflammatory component of CP, depending on the severity of the disease. Patients with food risk have an increased number of complications and a poor prognosis, but no specific studies on this problem in patients with CP have been conducted [9].

The main cause of weight loss is associated with impaired digestion of fats [9, 10, 11]. Exacerbation of CP is accompanied by hypermetabolism (total metabolic response of the body to generalized inflammatory response) [12], as a result of which there is a proteolysis of skeletal muscle tissue, a decrease in the level of amino acids by 40% of normal values and a loss of total muscle mass by 15%, i.e. sarcopenia [13].

Currently, there are no generally accepted criteria for diagnosis of malnutrition. The anthropometric method based on the measurement of height and weight of the patient, calculation method including determining BMI and other formulas (the fat content in the body), circumference method (determination of the upper arm circumference at the level of the middle third), and calipometry (determination of triceps skin fold thickness) remain the most common in routine practice.

Among laboratory methods of malnutrition diagnosis the most common method in clinical practice is the calculation of lymphocyte count and the determination of albumin level.

Table 1. *Criteria for diagnosis of nutritional status (adapted according to V. M. Luft) [14]*

Criteria	Reference range	Malnutrition		
		Mild	Moderate	Severe
Points	3	2	1	0
BMI, kg/m²:				
– 18–25 years	23–18.5	18.5–17	16.9–15	< 15
– > 25 years	26–19	19–17.5	17.5–15.5	< 15.5
UAC, cm:				
– women	29–26	26–23	23–20	< 20
– men	28–25	25–22.5	22.5–19.5	< 19.5
TSFT, mm				
– men	10.5–9.5	9.5–8.4	8.4–7.4	< 7.4
– women	14.5–13	13–11.6	11.6–10.1	< 10.1
UAMC, cm				
– men	25.7–23	23–20.4	20.4–17.5	< 17.5
– women	23–21	21–18.5	18.5–16.5	< 16.5
Total protein, g/L	≤ 65	64.9–55	54.9–45	≤ 44
Albumin, g/L	> 35	34.9–30	29.9–25	≤ 24
Lymphocytes, 10^3/uL	> 1.8	1.8-1.5	1.4-0.9	< 0.9
Total points	21	20–15	14–9	< 9

In Russia, the malnutrition classification most widely used in clinical practice is the one based on severity proposed by V. M. Luft and A. L. Kostyuchenko (Table 1) [14].

To use this classification, one must perform calculations using the following formulas:

1. BMI = weight / (height)^2

2. Upper arm muscle circumference (UAMC) = upper arm circumference (UAC) – (0.314 × triceps skin-fold thickness (TSFT).

In addition, the greatest attention is paid to laboratory methods — bioelectrical impedance analysis, computed tomography (CT), dual X-ray energy absorptiometry, and magnetic resonance imaging. Thus, malnutrition verification is difficult in patients with CP due to the lack of unified guidelines on diagnosis. Below is a clinical case of a combination of malnutrition and obesity in a patient with chronic pancreatitis.

Case Report

Patient P., 28 years old, was admitted to a hospital with complaints of dull girdle pain in the upper abdomen occurring after meals and alcoholic beverages, nausea, and weakness.

According to the patient, he had been ill for the last 5 years. He had been abusing alcohol for 5 years, prefers beer in the amount of 6,000 ml 1–2 times a week.

He had been smoking for 10 years, more than 20 cigarettes per day, smoking index– 10 pack-years. He worked as a mechanic, had secondary vocational education. He was single, lived with his parents in an apartment.

Examination results: BMI was 33 kg/m^2 (the 1st degree of obesity). UAC was 29 cm, TSFT was 12 mm, and UAMC was 25.2 cm. The patient's state was of moderate severity. No swelling was detected. Respiratory and cardiovascular systems were without abnormalities.

By palpation of the abdomen, pain in the epigastrium and the right hypochondrium was determined. Mendel symptom was positive. Liver sizes by Kurlov's percussion were 9 × 8 × 7 cm. The lower spleen pole was not palpable.

Urination was without abnormalities. Costovertebral angle tenderness was absent on both sides.

During clinical and laboratory examination in complete blood count lymphopenia was revealed as abnormal sign (1.7 × 10^3/μl). No abnormalities were revealed in the urinalysis.

Blood chemistry revealed only amylasemia (266 mmol/l, N — 25–220 U/l), lipasemia (101 U/l, N — 13–45 U/l), total protein of 64 g/l (N — 65–85 g/l), albumin of 34 g/l (N — 33.3–57.1 g/l). Diastasuria (urine amylase — 1,230 U/l (N — 0–1,000 U/l) was revealed.

Coprological examination revealed semi-liquid feces, creatorrhoea, neutral fat, salts of fatty acids, amylorrhea, and bacteriological study has shown the overgrowth of Proteus mirabilis.

Fecal elastase was 1–125 μg/g (N — 200–500 μg/g). Hydrogen breath test result was 15 ppm (N — 0–10 ppm).

Abdominal ultrasound: diffuse changes in the liver and pancreas.

Esophagogastroduodenoscopy results: superficial duodenitis.

Based on the patient's complaints, physical examination data, laboratory and instrumental examination, the patient was diagnosed with: chronic toxic and metabolic pancreatitis, stage C2 by Buchler, the exacerbation phase. Malnutrition of mild severity (18 points). Syndrome of small intestinal bacterial overgrowth. The 1st degree of obesity

The patient received combined therapy (Creon 30,000 U, Ensure TwoCal), proton-pump inhibitors. On treatment, the pain syndrome was managed on Day 6, and dyspepsia on Day 1.

By the end of the inpatient treatment in the control amylase and lipase levels corresponded to the reference values. After 10 weeks of treatment, normalization of fecal elastase-1 level was noted. In addition, PC EI regressed, but mild malnutrition persisted, indicating the need for a longer course of combination therapy.

Discussion

Currently, new definitions such as sarcopenia, presacropenia, sarcopenic obesity, and osteosarcopenia have replaced the old concepts of marasmus and kwashiorkor. In our opinion, the introduction of these clinical terms into medical practice is more appropriate, since it would allow characterizing malnutrition in detail, taking into account the

fat and muscle composition and the definition of muscle function.

Depending on the etiology, primary (associated with aging) and secondary sarcopenia are isolated [15].

Secondary sarcopenia can be caused by low physical activity, malnutrition and chronic diseases. Data on the prevalence of sarcopenia vary: sarcopenia is observed in 15 to 50% of patients with cancer, in 30 to 45% of patients with hepatic failure, and in 60 to 70% of critically ill patients [16, 17].

Sarcopenia is often combined with other changes in body composition — reduced bone mass (sarcoosteoporosis or osteosarcopenia), increased fat mass (sarcopenic obesity) or a combination of these changes (osteosarcopenic obesity).

According to N. Kawao, musculoskeletal interaction is regulated by biologically active substances synthesized by bone and muscle tissue [18]. This substance is myostatin, which production is enhanced during immobilization, infections, injury, etc. [19]. Myostatin inhibits the growth and differentiation of muscle tissue, and has an antiosteogenic effect.

In addition, each attack of CP is accompanied by a reaction of hypermetabolism (the total metabolic response of the body to a systemic inflammatory response) [12], leading to proteolysis of skeletal muscle tissue and a decrease in the level of amino acids by 40% of normal values. As a result, there is a decrease in total muscle mass by 15% [13], which is the cause of sarcopenia in patients with CP.

Sarcopenia and osteosarcopenic obesity are the most unfavorable of complex metabolic disorders, the development of which correlates with a high level of comorbidity, cardiovascular risk and mortality [20].

Sarcopenia and obesity have a mutually reinforcing effect: sarcopenia leads to a decrease in physical activity and, as a consequence, to an increase in fat mass, while the development of obesity is accompanied by an increase in the production of pro-inflammatory cytokines, impaired regulation of leptin and adiponectin secretion, a decrease in muscle sensitivity to insulin, which further exacerbates sarcopenia.

Currently, there are no statistics on the presence of a combination of obesity and malnutrition in patients with CP. In our study, 15 (10%) of 148 patients had a combination of obesity and malnutrition. Both Russian and foreign medical resources (Pubmed, eLibrary, Encyclomedia) were analyzed. However, publications devoted to this problem are few.

Three hundred and forty-four outpatient records for patients with obesity were analyzed retrospectively in the work of Moskaleva A. B., among them 232 patients were diagnosed with different degrees of malnutrition [21].

In the study by Lyadov V. K. et al., the musculoskeletal index L_3 was evaluated by CT in 22 patients with chronic calcific and/or pseudotumorous pancreatitis (16 men and 6 women aged 29 to 63 years). Sarcopenia was detected in 15 (68%) patients: in 13 men and 2 women. In one patient, body weight was reduced (BMI was 15.9 kg/m^2), in 5 patients — excessive (BMI was 25.0–29.9 kg/m^2). Only one patient out of 5 patients with increased body weight was diagnosed with sarcopenia. [22].

In our patient, malnutrition is primarily due to PC EI, however, an important role is played by a sedentary lifestyle, unbalanced diet and addiction to alcohol (6 liters of beer 2–3 times per week). The administration of enzyme replacement therapy allowed in a short time to normalize the function of pancreas. Patient P. should be attributed to the risk group for the development of sarcopenia and even more severe condition — sarcopenic obesity. Such patients require an individual approach in the diagnosis and treatment of such conditions, and algorithms should be created for their management. Anthropometric criteria should be revised, as their use is uninformative. The use of BMI alone is controversial due to the lack of a true standard for the diagnosis of malnutrition, and there is no assessment of the reduction in muscle tissue volume [23]. In addition, the patient may have malnutrition with normal and even with elevated BMI [24, 25].

Optimization and implementation in real clinical practice of biochemical and instrumental estimation methods for TS is necessary.

Conflict of Interests

The authors declare no conflict of interests.

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CASE OF ACQUIRED COAGULOPATHY

Abstract

In recent years, the number of patients receiving anticoagulant therapy is growing rapidly worldwide. This is due to the rapidly expanding scope of their application: an increasing number of patients with non-valvular heart disease, including atrial fibrillation, the risk of thromboembolic events, an increase in the number of surgical interventions, especially in cardiac surgery (in the treatment of valvular heart disease, cardiac anomalies, infective endocarditis, inserting of cardiac pacemakers, and conducting electrical cardioversion), the use of anticoagulants in the treatment of other organs and systems (in neurology, vascular surgery, obstetrics and gynecology). Despite the wide range of anticoagulants for a modern physician, one of the most studied and often prescribed one is warfarin. Warfarin is a coumarin anticoagulant of the indirect action, a competitive antagonist of vitamin K. However, along with high availability and efficiency of its use, it has a large number of possible contraindications and use patterns, such as: a lot of drug-drug and other interactions, the need for careful control of the dosage and the regimen of the drug use, strict control of the international normalized ratio throughout therapy. This drug should be used in patients who use alcohol and have cognitive impairment with caution. In this group of patients, in addition to personal awareness of patients, it is necessary to conduct explanatory conversations with relatives/caregivers about all possible side effects and measures for their prevention. Non-observance of precautionary measures at therapy by warfarin can lead to severe consequences, and in rare instances even death. Among such consequences is warfarin-induced coagulopathy. We present a clinical case of the development of severe acquired (warfarin-induced) coagulopathy in a patient with cognitive dysfunction.

Key words: *warfarin, acquired coagulopathy, cognitive impairment*

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ICU — intensive care unit; INR — international normalized ratio; AF — atrial fibrillation

Acquired coagulopathies are one of the most common syndromes of critical conditions. According to the literature, clinical signs of coagulopathy (bleeding) are observed in 16%, and laboratory signs — in 66% of patients in the intensive care units (ICU) [5]. One of the reasons for the development of acquired coagulopathy is an overdose of anticoagulant agents, in particular warfarin.

Warfarin is an indirect anticoagulant, one of the substances that inhibit coagulant element of hemostasis. Their administration prevents the formation of blood clots and stops the growth of blood clots already formed. This property of indirect anticoagulant agents is actively used in cardiology, neurology and surgery [2].

The mechanism of warfarin action is an impairment of the metabolism of vitamin K, which is a cofactor for synthesis of II, VII, IX and X coagulation factors [4]. When taking warfarin it is mandatory to perform regular laboratory monitoring of INR (International Normalized Ratio) throughout the course of therapy. INR is a laboratory test recommended by WHO, which reflects the state of the blood coagulation system. The optimal INR

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value in patients receiving warfarin is determined individually for a particular clinical situation and is usually in the range of 2–3 [1].

Warfarin poisoning is rarely intentional; usually it is the result of an accidental overdose. It should be remembered that the effect of warfarin is influenced by many factors: food, drinks, taking related drugs. Therefore, during its administration, the diet should not be changed dramatically, and when changing concomitant drug therapy, its effect on the warfarin effectiveness should be carefully studied. Clinical signs of warfarin overdose (the appearance of hematomas, hematuria, blood in the stool, menorrhagia) are not specific. The most severe complications are intracranial hemorrhages, which develop in 2% of patients.

The bleeding risk index for patients using warfarin takes into account four independent factors: age of 65 years and over; previous stroke; a history of gastrointestinal bleeding; recent myocardial infarction, and hematocrit below 30% [6]. Elderly patients taking this anticoagulant agent should be carefully monitored because they have a high risk of adverse effects. This is evidenced by our observation.

The female patient M., 77 years old, was delivered by an ambulance crew to the sanitary inspection room of the hospital on 15.03.2018 with complaints of dyspnea, weakness, palpitations, coughing and hemoptysis for two weeks.

In her youth, she often had tonsillitis and underwent tonsillectomy. During two pregnancies and childbirth, a cardiac malformation was suspected, but the patient was not examined. In 2009, she had ischemic stroke, at the same time atrial fibrillation (AF) and concomitant mitral defect was detected. In 2010, she underwent mitral valve replacement (bicuspid mechanical prosthesis) with the subsequent prescription of warfarin. INR was maintained at 2–3 and was monitored regularly.

In 2017, her memory deteriorated sharply after a "transient ischemic attack". The patient monitored INR rarely, adjusting the dose of warfarin by herself from 2.5 to 5 mg/day. (INR dated 13.03.2018: 15.58).

Physical examination data: the condition of the patient was severe, the patient was inhibited, answered questions with difficulty, she confused events and dates. The skin was pale, multiple hemorrhagic rashes (petechiae, ecchymoses) on the skin of the body, upper and lower extremities were observed. The largest (Figure 1) ones were on the left side of the abdomen spreading to the lower back (up to 20 cm in diameter), the inner surface of the left thigh (up to 15 cm) and the left forearm (up to 8 cm). There was a purple color hematoma on the tongue up to 1.5 cm in diameter, towering above the surface.

The breath sounds were vesicular, diminished, with respiration rate 30 per minute, there were fine crackles in the lower lung fields on both sides and dry rales in the interscapular region. The heart sounds were arrhythmic, mechanical valve clicking was detected, the heart rate was 120 beats per minute, pulse deficiency was up to 40 per minute, and the blood pressure was 140/80 mm Hg. The abdomen was soft, tender in the right subcostal space. The inferior margin of the liver (at percussion) was at the site of umbilicus. Feet and shins were swollen. The patient was admitted to the ICU.

Laboratory tests data: complete blood count: anemia (RBC — 2.08 T/l, Hb — 76 g/l, Ht — 21%), leukocytosis (15.9 g/l), thrombocytosis (748 g/l), INR — 12.4.

Warfarin-induced coagulopathy was diagnosed. The treatment included warfarin discontinuation, transfusion of fresh frozen plasma, packed RBCs, administration of Vicasol, Ferrum Lek, treatment of

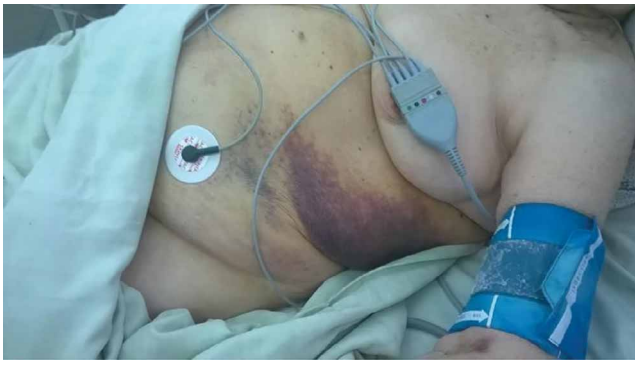

Figure 1. *Extensive hematoma in the left subcostal space with spreading to the lower back*

respiratory (oxygen) and heart (furosemide, bisoprolol, lisinopril, digoxin) failure. INR was monitored daily.

On treatment, the patient's condition improved, hemoptysis and hematuria disappeared, congestion in the systemic and pulmonary circulation decreased, and normal sinus rhythm was achieved. The complete blood count of 20.03.2018 showed: RBC — 3.0 T/l, Hb — 96 g/l, Ht - 30%, INR - 1.92. The patient was transferred to the rehabilitation department, where warfarin administration was resumed under the control of the INR (within 2–3), first at a dose of 2.5 mg/day and then 5 mg/day.

The patient was examined by a neurologist in the department, the following diagnosis was made: "Multifocal brain damage due to repeated cardiogenic embolism with silent lacunar infarctions, mild cognitive impairment". The patient was discharged on the 12th day of hospital stay for outpatient treatment. The INR value was 2.6.

Before discharge, the conversation was held with the patient's relatives about the importance of adhering to a selected dose of warfarin, regular monitoring of INR, taking related drugs (bisoprolol, digoxin, lisinopril, Ferrum Lek) and regular monitoring by community-based medical staff.

Thus, we observed an elderly patient who developed a severe hypocoagulation syndrome associated with an overdose of warfarin. A prerequisite for warfarin therapy is strict patient compliance with the prescribed dose of the drug under regular monitoring of INR [7]. In the case of an incorrect dose regimen or if the patient does not adhere to the regimen, an overdose may develop with potential serious and even life-threatening complications, as happened in our patient.

In addition, the treatment of elderly patients should be carried out with special precautions, since the synthesis of coagulation factors and hepatic metabolism are reduced, which can result in an excessive anticoagulant effect of warfarin [3]. Furthermore, the risk of cognitive impairment increases, as a person ages, especially in people with AF. This arrhythmia can lead to a decline in cognitive abilities or even dementia through various mechanisms, most often as a result of a stroke. In addition to clinical strokes, "silent" strokes, which are often seen in AF, can also lead to the development of cognitive impairment [8]. This is confirmed by this case: based on the results of the examination of our patient, "Multi-focal brain damage due to repeated cardiogenic embolism with silent lacunar infarctions, mild cognitive disorders" was diagnosed by a neurologist.

Considering all of the above factors, warfarin therapy should be strictly controlled by the patient personally, or if it is impossible (alcoholism, cognitive disorders, dementia), by the relatives or relevant medical staff.

Conflict of Interests

The authors declare no conflict of interests.

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