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ENDOTHELIAL LIPASE AS NEW DIAGNOSTIC MARKER OF NON-ALCOHOLIC FATTY LIVER DISEASE IN HYPERTENSIVE SUBJECTS (REVIEW)

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Abstract. Non-alcoholic fatty liver disease (NAFLD) and hypertension are among the most common diseases in the world. One of the negative factors contributing to the formation of cardiovascular risk in patients with NAFLD affected with hypertension is the low level of HDL cholesterol in which metabolism endothelial lipase (EL) plays a leading role. Therefore, it is very relevant and expedient to study the various aspects of the use of EL to diagnose NAFLD and determe treatment strategy in patients with NAFLD and hypertension.
Key words: *non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, hypertension, endothelial lipase, lipid metabolism, overweight.*

1.1. Lipid metabolism disorders affected by hypertension

According to the majority of researchers, clinical significance of non-alcoholic fatty liver disease (NAFLD) is related with the genesis of atherosclerosis [1], which allows considering NAFLD as an independent risk factor of cardiovascular diseases (CVD) [2]. Triggering factors associated with the development of NAFLD and metabolic disorders include oxidation stress, inflammation, dyslipidaemia, insulin resistance (IR), abdominal obesity, low level of adiponectin, endothelium dysfunction, and postprandial dyslipidaemia [3].

The correlation between NAFLD and CVDs was established for patients with diabetes mellitus (DM) [4]. Significant evidence is provided by the work where patients with histologically confirmed NAFLD were observed for 21 years followed by an analysis of mortality causes. It was found that the primary causes were CVDs and malignant tumours [5]. There is also available data that histological severity of NAFLD and intensity of hepatic tissue inflammation significantly correlated with the increased CVD risk and atherogenicity of the lipid profile [6].

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The increased serum level of liver enzymes is an independent factor of hypertension and DM; these associations may be partly associated with NAFLD and insulin resistance. Several crossover studies found a correlation between the increased level of ALT and gamma glutamine transferase (GGT) and metabolic syndrome, DM and NAFLD on the other side. The association of GGT with the presence of atherosclerotic plaques is particularly significant for subjects with NAFLD [7]. Data is also available that NAFLD is associated with an increased risk of carotid artery atherosclerosis [8].

High blood pressure in metabolic disorders is a background for the development of ischemic heart disease (IHD), left ventricular (LV) hypertrophy, and, consequently, chronic heart failure (CHF), diseases of peripheral arteries, and strokes. The relevance of the issue of metabolic disorders draws attention to hypertension. Thus, the target blood pressure (BP) in case of NAFLD should not exceed 130/80 mmHg, while the target BP for other patient groups is 140/90 mmHg. [9].

Patients with hypertension in most cases have metabolic disorders: obesity in 74%, impaired carbohydrate metabolism in 26%, hypertriglyceridemia in 21%, and hypercholesteraemia in 18%. These statistical findings confirm complex pathophysiological links between IR, hypertension, NAFLD and obesity [10].

It has been proven that hypertension in metabolic disorders is developed when the renin-angiotensin-aldosterone system (RAAS) is

hyperactivated. Major adverse aspects of the RAAS are mediated by the main RAAS mediator angiotensin II (AT II): vasoconstriction, secretion of aldosterone, vasopressin, noradrenaline, fluid retention, proliferation of smooth muscle cells and cardiomyocytes, activation of the sympathoadrenal system, and glomerulosclerosis. RAAS is involved in the development and progression of atherosclerosis through the development of the endothelial dysfunction and inflammation in vascular walls. Development of hypertension in metabolic disorders can be explained by the following mechanisms:

• Retention of sodium ions in renal tubules;

• High concentration of calcium ions in vascular walls;

• Increased sensitivity of vascular walls to pressure due to the blockade of transmembrane ion exchange mechanisms (Na, K, Ca ATPase)

• Proliferation of smooth muscle cells and increased general peripheral resistance;

• Development of atherosclerosis due to the release of anti-inflammatory cytokines and dyslipidaemia;

• Impaired nitric oxide regulation;

• Impact of insulin on vascular receptors to angiotensin I, which increases vasoconstriction;

• Impact of insulin on the flexibility of large vessel walls and decreased ability of aorta to regenerate in response to pulse waves [11].

It is not proven that IR and endothelial dysfunction are links in a chain and play an important role in the development of metabolic disorders and, consequently, CVDs. It is endothelial dysfunction that causes atherosclerosis and predetermines the development of atherothrombosis [12].

Endothelial cells cover the vessels from inside and serve as a boundary between the blood and the tissues, which makes endothelium vulnerable to various factors such as hypercholesteremia, hyperglycemia, free radicals, high hydrostatic pressure, smoking, etc. Damage of the endothelium leads to a decrease in the release of endothelium-relaxing factors and an increase in the formation of vasoconstrictive factors, which causes endothelial dysfunction [13].

Recent epidemiological studies have shown that increased ALT is also associated with an increased risk of cardiovascular diseases [14] suggesting that NAFLD is associated with IHD irrespective of other features and manifestations of the metabolic syndrome (MS). It was established that patients with NAFLD symptoms have a positive correlation between the serum ALT level and the increased risk of carotid artery atherosclerosis [15]. One of the studies examined the correlation between the increased serum ALT and 10-year IHD risk assessed under the Framingham risk scale. It was found that the average ALT level in the group of males with a high risk of IHD was > 43 IU/l, while it was > 30 IU/l in females with a high risk [16].

The above findings and FIBAR study suggest a conclusion that increased GGT or ALT levels are an independent predictor of cardiovascular diseases. Besides, an increase in the GGT level above the normal range or around the upper normal limit is an independent predictor of new onset diabetes mellitus [17].

A prospective study by Lopez-Suarez A. et al. [18] found that the percentage of hypertension cases in subjects with NAFLD is 21.2% higher than in patients without clinical, laboratory and instrumental symptoms of NAFLD (95% CI, 11.8–30.6, P <0.0005). Therefore, NAFLD is an independent factor associated with hypertension prevalence; the adjusted odds ratio is 1.71 (95% CI, 1.10–2.65, P = 0.017). It was also established that, among the patients without critical arterial pressure (>140/90 mmHg), NAFLD is also independently associated with high normal systolic pressure (adjusted odds ratio is 2.13, 95% CI, 1.08–4.20, P = 0.029), but not with high normal diastolic pressure. The authors came to a conclusion that the detection of NAFLD, even with normal ALT, should be a reason for a comprehensive examination for the determination of metabolic parameters, exclusion of hypertension and intensification of efforts aimed at changing the lifestyle [18]. It should also be noted that the precise mechanism of NAFLD contributing to the development of cardiovascular diseases remains subject to investigation. In this aspect, it appears interesting that the age of onset of cardiovascular diseases in patients with NAFLD ranges between 45 and 65 years [19]. DeFilippis [20] showed that the diagnosis of NAFLD is associated with atherogenic dyslipidaemia. This correlation persisted after the correction of certain metabolic disorders and HOMA-IR, which points to a possible independent pathophysiological association between NAFLD and dyslipidemia.

Feitosa's studies [21] demonstrated that ALT ≥ 40 IU/l can be considered to be a predictor of high prevalence of coronary artery disease in males, whereas the specific weight of fat in the liver was insignificant according to CT findings. Akin L. Et al. [22] showed that even children

and adolescents with obesity in association with NAFLD are under risk of early atherosclerotic changes, which requires performing an additional liver ultrasound scan in this group of patients because hepatic tests alone may be insufficient for diagnosing NAFLD. Catena C. [23] found that in patients with hypertension without additional cardiovascular risks, NAFLD is associated with IR but not with increased artery rigidity. The so-called new cardiovascular risk factors including homocysteine, inflammation markers – C-reactive protein and lipoprotein A, and markers of the fibrinolytic and homeostatic function – fibrinogen, tissue plasminogen activator and plasminogen activator inhibitor-1 (PAI-1) are also of great potential importance. Recent findings indicate that all these markers are also associated with NAFLD. Latest studies point to a connection between NAFLD and increased intima media complex thickness. Fracanzani et al. (2008) concluded that fatty liver dystrophy is an independent risk factor predicting an increase in the intima media complex thickness with an odds ratio of 1.8, and an increase in the systolic pressure with an odds ratio of 2.3 [24].

Among the possible mechanisms associating NAFLD with cardiovascular pathology are oxidation stress and inflammation [25]. These data indicate that some components of the oxidation stress probably caused by direct hepatocyte damage in case of NAFLD may be involved in the pathogenesis of cardiovascular diseases; besides, oxidation stress plays an important role in the progression of fatty hepatosis towards non-alcoholic steatohepatitis (NASH) [26].

The link between oxidation stress and NAFLD in human was demonstrated by immunohistochemical detection of lipid peroxidation products and 8-hydroxy-deoxyguanosine in plasm and liver biopsy in patients with NAFLD. According to the current understanding, it is inflammation that is plays a decisive role in NAFLD pathogenesis because fatty tissue is considered a metabolically active endocrine organ capable of synthesizing a number of anti-inflammatory cytokines, including TNF-α, IL-6, C-reactive protein (CRP) and IL-8. There are studies indicating the activation of other inflammatory pathways and oxidation stress, and an increase in CRP over 1.48 mg/l is regarded as an independent NAFLD risk factor [27].

In case of obesity, hypertrophied and hyperplastic adipocytes produce TNF-α [28]. TNF-α activates the protein stimulating protective inflammatory reactions – inhibitor of kappa kinase beta (IKKβ) in adipocytes and hepatocytes, which leads to impaired bonding of insulin to the receptor. The impact of TNF-α on insulin receptor substrate 1 (IRS-1) is manifested in its phosphorylation resulting in a decrease in its affinity with insulin, a decrease in special transport protein GLUT4 ensuring glucose inflow into the cell – there is reduced glucose uptake and recycling and increased hyperglycaemia, which damages vascular endothelium and contributes to the development of DM [29].

The amount of fatty tissue in the body of a patient with NAFLD may also determine the CVD risk because visceral fatty tissue is a metabolically active endocrine organ capable of producing anti-inflammatory cytokines, adipokines and hormones that mediate inflammation and IR, which in turn influences the CVD risk profile [30].

However, mechanisms linking visceral fatty tissue or abdominal obesity (AO) with cardiovascular diseases are closely related to IR, which is itself related to CVD risk and atherosclerosis [31]. There is currently no consensus as to whether visceral fatty tissue contributes to a high cardiovascular risk through the secretion of factors or this process is realized through IR [32]. Dyslipidaemia that is also associated with NAFLD, activates transcription factor SREBP-1C (sterol regulatory element binding), which acts in synergy with insulin and stimulates genes involved in de-novo lipogenesis. SREBP-1C also inhibits synthetic fatty acids (SFA) oxidation, which leads to an increased concentration of lipids in the liver. In order to compensate for the increased concentration of TG in hepatocytes, the liver forms an atherogenic lipid profile consisting of high TG level, low High-density lipoproteins (HDLP) level, increased concentration of low-density lipoproteins (LDLP), very low density lipoprotein (VLDLP) and cholesterol, and increased concentration of apolipoprotein B. All these changes are closely associated with adverse cardiovascular events [33].

According to some findings, NAFLD can accelerate atherogenesis by changing lipoprotein metabolism in the postprandial period [21]; in its turn, postprandial hyperlipidaemia is a risk factor for both NAFLD and CVDs [26].

The results of recent studies indicate that such adipokines as leptin and adiponectin are actively involved in the development of endothelial dysfunction acting as antipodes and determining the cardiovascular risk in patients with obesity and MS; however, the role of these adipokines in

the development of CVDs in patients with NAFLD remains understudied [34].

In large concentrations, leptin increases the release of nitric oxide from endothelial cells, stimulates angiogenesis, natriuresis and diuresis. Based on this, it can be assumed that in addition to insulin resistance and hyperinsulinemia, hyperleptinemia is one of the factors of arterial hypertension development; besides, leptin causes endothelial dysfunction enhancing the effects of angiotensin II [35].

Based on the above evidence it can be stated that patients with NAFLD more frequently suffer from atherosclerotic changes, dyslipidaemia and ischemic heart disease, which requires timely diagnostics of NAFLD and standardization of various treatment methods. Answering the questions about the role of NAFLD in the development of cardiovascular complications is certainly of great interest in terms of developing new therapeutic strategies and is one of the goals of future research. Nevertheless, the currently available data suggest that the detection of NAFLD at the stage of ultrasound tests increases the CVD risk and requires screening and monitoring of the CVD risk in all patients with NAFLD. These patients are candidates not only for early treatment of liver diseases, but also related cardiovascular risk factors [36].

1.2. Clinical significance of endothelial lipase in the pathogenesis of the cardiometabolic risk

One of adverse factors contributing to the development of the cardiovascular risk in NAFLD affected by hypertension is low level of HDLP cholesterol, the metabolism of which largely relies on the activity of endothelial lipase [37] as controlled by micro-RNA [38]. Endothelial lipase (EL) is identified as a new member in the family of triglycerides and is very similar to lipoprotein lipase and hepatic lipase but is a more sensitive marker of phospholipid hydrolysis. EL is the only lipase that is synthesized by endothelial cells. Laboratory data has shown that EL can play a key role in the modulation of high-density lipoprotein metabolism and promotes the metabolism of atherogenic apo-B-containing lipoproteins. An increased plasma concentration of EL is associated with an increased triglyceride level and an increased concentration of apolipoprotein B in the blood plasma. These facts indicate that EL is one of a number of key regulatory enzymes of lipid metabolism [37].

Endothelial lipase is expressed by endothelial cells and is localized on these cells in many organs as well as on microphages. This lipase very poorly hydrolyses triacylglicerids, but it is affective as A1 phospholipase hydrolysing the bond between fatty acid and phospholipid glycerine in position 1. A distinctive feature of endothelial lipase regulation is the induction of its expression by anti-inflammatory cytokines such as IL-1β and TNF-α, and by the shear stress in the vessel [38].

It has been established that EL is identified as a new member of the triglyceride gene family. EL is very similar to lipoprotein lipase and hepatic lipase but is a more sensitive marker of phospholipid hydrolysis. EL is the only lipase that is synthesized by endothelial cells [37].

EL was studied in hemodialysis patients and it was found that it is the prevalent enzyme responsible for the lipolytical catabolism of HDLP and resolves the paradox observed between the low level of liver lipase and decreased HDLP cholesterol level in these patients. Besides, the ability to evaluate EL plasma concentration expands our knowledge about the mechanisms involved in overcoming HDLP and cardiovascular risk in patients with low HDLP value [39].

Also, the EL plasma concentration was increased in patient with diabetes mellitus. The impaired ability to induce cholesterol outflow in these patients is mainly associated with the low HDLP level and subclinical inflammation [40].

Endothelial lipase is the main factor determining HDLP metabolism and promoting the recruitment of monocytes. Local expression of EL can directly influence atherogenesis in addition to its systemic role in the HDLP metabolism. The EL gene has a common polymorphism 584C/T and is associated with the HDLP level and cardiovascular risk [41].

Karen O. Badellino et al.'s study provides evidence that plasm inflammatory markers directly correlate with EL plasma concentrations in humans, and experimental endotoxemia considerably increases the EL plasma concentration proving that EL is restored by inflammation in humans. This mechanism may partly account for the low HDLP cholesterol levels in obesity and metabolic syndrome. In a sample of 800 patients from the cohort of no-symptom subjects who have at least one family member experiencing an early onset of coronary artery disease, increased EL plasma concentration is negatively correlated with HDLP plasma concentrations [42]. In another sample of 80 overweight subjects, those with high EL plasma concentrations reduced HDL2-C, HDL-phospholipid and HDL2-phospholipids as compared to patients with a lower EL concentration [43].

Multiple linear regression analysis in Spanish-speaking subjects demonstrated an unexpected correlation between the T111I gene and increased HDLP and total cholesterol. The lipase activity of the selected missense mutants was investigated and different impacts on the EL function were established from normal to complete loss of activity. The results of this multidisciplinary approach determined the impact of EL and its variants on HDLP. Moreover, the results showed that EL is able to modulate vascular health due to its role in the signal pathways of fatty acids [44].

Inhibition or loss of EL function in mice leads to an increase in high-density lipoprotein cholesterol, which makes it a potential therapeutic target [45].

Conclusion

Therefore, the development of NAFLD is closely connected to metabolic disorders such as IR, overweight, and combination with hypertension, which causes not only progression of the pathological process in the liver, but also the development of CVDs. Taking into account that NAFLD is considered a cardiovascular risk predictor, its timely early diagnostics can improve the patients' life quality and prevent fatal complications. Thus, it can be pointed out that EL is a new marker of the cardiovascular risk that is closely associated with dyslipidaemia and insulin resistance and is poorly investigated in relation to NAFLD.

Conflict of interests

There is no conflict of interests.

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QUALITY OF LIFE IN PATIENTS WITH CHRONIC VENOUS DISEASES AND METHODS OF ITS IMPROVEMENT (REVIEW)

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Summary. Assessment of the quality of life is one of the leading directions in modern medicine and continues to develop intensively, remaining an integral part of comprehensive analysis of new methods of diagnosis, treatment and prevention. This article provides information about the history of the concept "quality of life" and the ambiguity of terminology. Particular attention is paid to the necessity of studying this indicator in patients with chronic veins diseases, the relevance of this direction in the early stages of the disease, as well as medicines able to solve the main tasks of drug therapy, to restore work capacity and, as a result improve the patient's life quality.
Key words: *quality of life, chronic venous diseases, diosmin.*

The learning of quality of life, that based on health assessment is one of the leading directions in modern medicine. It continues to develop intensively and remains as an integral part of the comprehensive analysis of new methods of diagnosis, treatment and prevention. This concept came to medicine from sociology and meant the totality of work and rest, quality of clothes, habitation, nutrition and environmental conditions.

The history of life quality research was started in 1949 after publication of the article "Clinical evaluation of chemotherapy in cancer" written by the professor D.A. Karnovsky from the Columbia University [1]. The necessity of studying psychological and social consequences of the disease together was identified as a result of prolonged observation of cancer patients. The term "quality of life" was used first by J.R. Elkington in 1966 in the "Medicine and quality of life" [2]. This term was recognized in medicine, using as a heading in "Cumulated Index Medicus" in 1977 [3]. The conception and development of the basic techniques for the studying of quality of life in various diseases was determined in the following decades [4–7]. MAPI Research Institute, which was not only the center for the study of quality of life but also for the coordinator of all researches about life quality in the world, has been functioning in France since 1995.

Up to now there are different definitions of quality of life. A.Novik, T.Ionova (1999) defined it as an inseparable relationship of the basic human states: emotional, physical, psychological and social [3], N. Senkevich, A.Belyavsky (2000) – as a comfort level of the individual within himself and the livability in the society where he lives [8]. The WHO defined the quality of life as a state of complete physical, mental and social well-being [9]. Nevertheless, it is generally accepted that this concept is multidimensional and reflects the impact of disease and treatment on the patient's state of health.

The study of quality of life is actively conducted in all fields of medicine [4–8], including phlebological practice, which is associated with high prevalence of chronic venous diseases. The studies on quality of life evaluated various treatment options of chronic venous diseases [10], adherence to systemic therapy of post-thrombotic disease [11], comparing conservative and surgical methods of treatment [12] allowing to evaluate the patient's perception of the outcome of any treatment.

To date, the prevalence of chronic venous insufficiency (CVI) according to various authors is 1–40% among women and 2–17% among men, the prevalence of varicose disease of the lower extremities is 1–73% among women and 2–56% among men [13]. Almost every 2nd inhabitant of the planet suffers from varicose veins already, 2 sick men account for 3–4 sick women, 62.3%

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of whom are women of reproductive age [14]. The number of schoolchildren who are found to have early signs of venous reflux is growing [15]. The highest prevalence of chronic venous diseases was observed at the age of 25–50 years – in the most socially active part of the population. According to the Edinburgh study (1999), chronic venous diseases were more common in men than in women, and their prevalence increased with age [16]. People over the age of 80 have a tendency to decrease the incidence of CVI, while the amount of complications increases [17].

High incidence allows to call CVI "a disease of civilization". The basis for this assessment of the disease was the fact that most people suffer from this disease, live in cities and in economically developed countries [18, 19]. Complicated forms of CVI are accompanied not only by cosmetic inconveniences, but also by the development of persistent and prolonged disability. About 1% of the population has acute or chronic ulcers, more than 50% of which require long-term therapy. The incidence of deep vein thrombosis is 100 per 100 000 population [20]. The development of chronic varicose diseases was shown to reduce quality of life [21, 22], while the improvement of the patient's condition after the treatment increases it [23–25].

Thus, increase in prevalence of CVI and its complications results in a disruption of the ability to engage in social and professional activities, a decrease in the quality of life and emergence of financial constraints, which is accompanied by an increase in economic costs in healthcare. For example, about 1 billion dollars a year are spent on the treatment of CVI and its complications in the United States, up to 2% of the total health budget – in all western countries, that raises the importance of this problem according to understanding of clinical manifestations, improving diagnostic methods and therapeutic possibilities [26].

There are many factors to formation of pathological ectasia, among which predisposing factors (genetic, mechanical) and realizing factors (lifestyle, reception of contraceptives, tight shoes, etc.) are distinguished. Their interaction helps to reduce the tone of the venous wall and leads to venous stasis which initiates a cascade of pathological changes on the molecular, cellular and tissue levels. As a result, it triggers conditions for increased thrombus formation.

Over the past 30 years a number of classifications of varicose veins, post-thrombotic syndrome and actual CVI of the lower extremities have been proposed. The best known classification of varicose disease was suggested by F. Martorell (1972), H.J. Leu (1979), CVI Widmer (1978), J. Porter (1988), V.S. Savel'eva (1972). The international classification of CEAP (1994), along with clinical manifestations of CVI, reflects the quality of life of the patient [27].

The initial degree of CVI is characterized by functional symptoms without special cosmetic effects. But such complaints as paresthesia, skin itching, night cramps can reduce the patient's QL. Progression of CVI manifested by persistent severe pain in the lower extremities and edema, increased after insignificant physical exertion, development of hyper- or hypopigmentation, trophic skin disorders and their complications sharply reduce patient's quality of life, lead to a decrease or loss of ability to work and permanent disability. Therefore, early symptoms should be regarded as a signal that the patient should see a doctor.

Subjective and objective methods of investigation are important to confirm a disorder of the venous system of the lower limbs and determine the kind of treatment. Thorough history taking is vital: characteristics of work and sport activity, characteristics of everyday clothes, past medical history, family history, etc. On examination it is necessary to inspect both lower extremities, inguinal areas, anterior and lateral walls of the abdomen, paying attention to the presence of dilated intradermal and subcutaneous veins, signs of varicose veins of large and small saphenous veins and presence of edema and trophic disorders on the skin of the legs. Dilation of veins on the legs can vary from small vascular "asterisks" and intradermal (reticular) nodules to large sinuous trunks, nodes, protruding plexuses that clearly appear in the vertical position of the patient.

Palpation allows to reveal the signs of thrombophlebitis and to determine the boundary zone of indurative cellulitis. Extended veins are elastic consistency, easily compressed with increased skin temperature above them. In recumbent position, the tension of the veins and the size of the varicose veins is decreased.

In all cases it is necessary to determine the pulsation of the arteries on feet. Instrumental diagnostic methods are used in cases when diagnosis and the nature of treatment are not clear, the scope of possible surgical manipulations is unclear.

Treatment of CVI should be complex and combine medical therapy, compression, sclerotherapy and surgical treatment. In recent

decades, the role of pharmacotherapy has significantly increased, the main goals of which are elimination / reduction of CVI, prevention of recurrence of the disease, postoperative rehabilitation, retention of work capacity, improvement of patient's quality of life, and prevention of CVI in risk groups. Oral venotropic drugs of plant or synthetic origin are able to solve the main tasks of drug therapy.

There are 4 groups of phlebotonics. So far drugs have been based on diosmin, which is considered to be the reference chemical compound for the production of various dosage forms [28]. This is natural isoflavonoid, obtained from plants of the Rutaceae family and it can be obtained by chemical synthesis [29]. Clinical efficacy and safety of diosmin have been widely studied. It has been shown to accumulate in venous vessels [30], to reduce norepinephrine metabolism in comparison with patients who did not take this drug [31], to improve microcirculation [32]. A clinical study with 16728 patients has convincingly demonstrated the ability of diosmin (600 mg) to effectively reduce the perimeter of the ankle independently from the age, gender and degree of CVI, good tolerance and low incidence of side effects [33], so it remains the drug of choice at all stages of the disease, including complicated forms [34]. Semisynthetic diosmin 600 mg was taken once a day and 300 mg was taken twice a day by 255 patients. It was compared in a double-blind, placebo-controlled therapeutic study. The obtained results were comparable, but clinical effect was more rapid with the 600 mg diosmin taken once a day [35]. In a prospective study with 80 patients, monotherapy with high diosmin dose showed reliable reduction of the severity of clinical symptoms of CVI, and changing the stage of the disease (according to the CEAP classification), and improvement of the quality of patient's life [36].

In addition, diosmin in the dose of 600 mg is successfully used in obstetrics and gynecology, it is not contraindicated to pregnant women [37, 38], has a positive effect onn glucose metabolism [39, 40], hepatoprotective effects [40] and is used in the treatment of cardiovascular diseases [41].

Thus, diosmin-containing venoprotectors are a bioavailable and biosafe group of drugs that are effective at all stages of chronic veins diseases, including complicated forms, and in patients with accompanying therapeutic pathology. Long-term administration of high doses of diosmin promotes regression of the disease, manifested by a decrease in the severity of clinical manifestations, improvement of venous and lymphatic outflow, correction of hemorheological disorders with minimal side effects. This leads to the restoration of work capacity and, as a result, to improving of the quality of the patient's life.

Conflict of interests

There is no conflict of interests.

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TIME COURSE OF SYMPTOMATIC MANIFESTATIONS IN CHILDREN WITH BRONCHIAL ASTHMA RESIDING IN KHARKIV REGION ACCORDING TO THE ISAAC STUDY

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Abstract. For the first time in Ukraine phase IV of the International ISAAC program was realized in Kharkiv Region in 2015–2017. 6330 of questionnaires were distributed. 6146 (97%) of schoolchildren took part in the program. 12.8% of them had respiratory complaints, 13.2% of children at the age from 6 to 7 years, 12.4% of children aged from 13 to 14 years old. A low level of asthma diagnosis in the region was observed. Only 0.5% of children in population were diagnosed with asthma. These results were compared with the data from phase I of ISAAC (V.A. Ognev, 1998) to determine the time course of respiratory symptoms incidence: over the last 19 years the prevalence of respiratory symptoms has decreased by 1.6 times in children of junior school age and by 2 times in adolescents. Significant fluctuations in wheezing prevalence in different districts of Kharkiv Region were revealed: from 5.5% (Barvinkivs'kyi District) to 14% (Derhachivs'kyi District). The study is aimed to improve early diagnosis of asthma in children.

Keywords: *children, bronchial asthma, prevalence, Kharkiv region, ISAAC.*

Introduction. Bronchial asthma (BA) is a chronic heterogeneous inflammatory disease manifesting by respiratory symptoms [1]. The problem of BA is important because of impossibility of complete cure. This significantly reduces the patients' quality of life and is followed by considerable economic costs both for family and society [2]. Despite significant progress in the disease treatment asthma is still one of the frequent reasons of invalidity in pediatrics [3].

According to official statistics BA is the most common chronic disease within pediatric population in different countries of the world [4] but even these high official data do not reflect the true scales of the problem. In order to improve the quality of epidemiological studies of allergic diseases and develop diagnosis on early stages of diseases the international ISAAC (International Study of Asthma and Allergy in Childhood) program, containing IV phases [5], has been realized since 1991 upon the recommendation of WHO.

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Thanks to international cooperation and accomplishing the tasks assigned for each stage, according to a standardized method the prevalence and severity of the respiratory symptoms of asthma in children in different regions of the world were determined and compared. During phase II of the program objective markers of allergy (IgE, skin-prisk test, bronchial hyperreactivity, etc.) were studied, their connection with leading clinical symptoms were set, risk factors were analyzed, algorithms of disease treatment in different regions of the world were compared. Phase III of ISAAC was objected to reveal dynamics of prevalence and severity of allergic diseases over long time periods (more than five years) and compare obtained data in research centers. Currently phase IV of ISAAC is being realized in many countries. It involves development and expansion of the ISAAC scope of application, the use of all resources to determine etiological and pathogenic mechanisms of BA in order to reduce the prevalence and severity of the disease [5].

The ISAAC program involves research centers in 105 countries of the world and approximately 2 millions of children have already taken part in it. In Ukraine for the first time in 1997 the research center of the international ISAAC program was founded under the guidance

Table 1

Results of Survey among Children Residing in Kharkiv Region Regarding Symptomatic Manifestations of Bronchial Asthma (the ISAAC program)

Questions about child's breathing pattern		6–7 y.o. n = 3421	13–14 y.o. n = 2725	Average value
1. Have you ever had wheezing previously?		10.3%(352/3421)	9.1%(249/2725)	9.7%(601/6146)
2. Did you have wheezing within the last 12 months?		4.5%(154/3421)	3.3%(91/2725)	4.0%(245/6146)
3. How many episodes of such type of breathing did you have within the last 12 months?	1 episode	2.0%(69/3421)	1.6%(44/2725)	1.8%(113/6146)
	from 2 to 3	1.7%(60/3421)	1.2%(33/2725)	1.5%(93/6146)
	from 4 to 12	0.4% (14/3421)	0.3%(9/2725)	0.4%(23/6146)
	more than 12	0.1% (4/3421)	0	0.1%(4/6146)
4. How many times (on average) did you have sleep disorder due to wheezing episode within the last 12 months?	never	2.9%(100/3421)	1.9%(52/2725)	2.4%(152/6146)
	less than once a week	1.1%(38/3421)	1.1%(31/2725)	1.1%(69/6146)
	1 time a week or more	0.2%(8/3421)	0.1%(3/2725)	0.2%(11/6146)
5. Did you have such a severe attack of wheezing, that the speech was complicated to pronouncing only 1–2 words between breaths within the last 12 months?		0.3%(11/3421)	0.2%(7/2725)	0.3%(18/6146)
6. Have you ever had asthma?		0.3%(11/3421)	0.7%(19/2725)	0.5%(30/6146)
7. Did you have wheezing in the chest during or after physical activity within the last 12 months?		1.3%(45/3421)	2.9%(79/2725)	2.0%(124/6146)
8. Did you have short cough at nights (not associated with cold or inflammatory diseases) within the last 12 months?		5.5%(190/3421)	4.7%(130/2725)	5.2%(320/6146)

of Professor Ognev V.A. at the premises of KhNMU. In 1997–2002 phases I, II and III were realized [7]. For our country implementation of phase IV is relevant.

2. PURPOSES, SUBJECTS and METHODS:

2.1. Purpose. Improvement of BA diagnosis in pediatric population of Kharkiv Region by means of phase IV of ISAAC implementation.

Tasks of study:

1. To estimate the current prevalence of BA respiratory symptoms in children of Kharkiv Region in accordance with standardized method of ISAAC.

2. To explore the time course of BA symptomatic manifestations in children of Kharkiv Region from 1998.

Drawing.1. Prevalence of Wheezing (in %) in Various Districts of Kharkiv Region

3. To analyze the prevalence of BA symptomatic manifestations in different districts of Kharkiv Region.

2.2. Subjects & Methods

In order to obtain accurate results on BA prevalence among children of Kharkiv Region the sampling amount was calculated by the formula of Lisitsin Y.P., 1987 [6] taking into account the number of pediatric population and BA prevalence.

After authorization from the official representative of Global Asthma Network organization, within the sphere of which the international ISAAC program is currently implemented, standardized questionnaires for children aged from 6 to 7 years old and from 13 to 14 years old were distributed. Schoolchildren and their parents had to fill in the questionnaire with passport data and answer 8 questions of a "closed" type about respiratory complaints.

To determine dynamics of prevalence of BA respiratory symptoms in children of Kharkiv Region, a comparison with the results of phase I of the ISAAC study implemented in 1998–1999 by Professor Ognev V.A. was made.

To estimate etiological and pathogenetic factors of BA prevalence of respiratory complaints frequency was compared in 8 districts of Kharkiv Region (Lozivs'kyi, Kupyans'kyi, Vovchans'kyi, Bohodukhivs'kyi, Sakhnovshchyns'kyi, Barvinkivs'kyi, Derhachivs'kyi, Novovodolaz'kyi), which differ both in geographic location and environmental characteristics.

The study was realized in compliance with human rights, corresponding to the current legislation of Ukraine. It meets the international ethical requirements and does not violate any ethical norms in science and standards of conducting biomedical research.

The obtained data were stored in the SQlite/MySql database, the calculation was conducted by variation statistics method.

Conflict of interests

There is no conflict of interests.

3. RESULTS AND DISCUSSION

By means of the sampling method 6330 pupils of schools in districts of Kharkiv Region were questioned using the standardized questionnaires of ISAAC in 2016–17 school years. 184 schoolchildren and their parents refused to take part in the questioning which amounted to 3% of respondents.

Among 6146 children of Kharkiv Region questioned respiratory complaints were revealed in 792 schoolchildren which amounted to 12.8%; in the age group of 6–7 years old positive answers were given by 13.2% of children, in adolescent group of 13–14 years old 12.4% of answers were positive. The answers to all 8 questions of the questionnaire are represented in *Table 1*.

Assessment of the answers for the ISAAC questionnaire received from the children residing in Kharkiv Region showed that almost every tenth child had a wheezing episode in past medical history. More often it happened at junior school age (10.3%), less often in pubertal period (9.7%). Most of the respiratory symptoms manifestations were not severe, as shown by the low percentage of patients with frequent awakenings at nights (question 4), absence of speech pathologies during BA exacerbations (question 5) and good physical activity tolerance in most patients (question 8).

What stands out is the extremely low percent of asthma diagnosis in the region (the average value is 0.5%, but among children of junior school age it equals to 0.3%). This fact is in contrary with the high prevalence of pathognomonic symptoms and epidemiological studies of Professor V.A. Ognev. This is another argument for intensifying efforts to improve the early diagnosis of BA in the region.

Comparison of the obtained results with the data of phase I of the ISAAC study (1998) has revealed the prevalence of BA symptomatic manifestations decrease in 1.6 times in children aged from 6 to 7 years old and in 2 times in adolescent group [5].

While comparing the prevalence of symptomatic manifestations of BA in Kharkiv Region and other regions of the world it should be mentioned that our data are higher than the ones in Africa and Indian Region, lower than in North and Latin America, Oceania and equal to the prevalence in Asia-Pacific Region and Western Europe [8].

The analysis of the ISAAC questionnaires of children living in various districts of Kharkov Region revealed significant differences in the prevalence of symptomatic manifestations of BA. Thus, the prevalence of wheezing among children was: 12.1% and 13.7% in Lozivs'kyi District, 13.2 and 7.7% in Kupyans'kyi District, 15.0% and 7.0% in Vovchans'kyi District, 12.0% and 4.0% in Bohodukhivs'kyi District, 11.7% and 9.4% in Sakhnovshchyns'kyi District, 2.8% and 10.6% in Barvinkivs'kyi District, 16.8% and 12.0% in Derhachivs'kyi District, 4.8% and 7.5% in Novovodolaz'kyi District for schoolchildren of 6–7 and 13–14 years old respectively. The average numbers of wheezing are represented in Drawing 1.

The revealed differences in prevalence of respiratory symptoms constituted the basis for planning of perspectives for future studies, in particular, the study of the role of environmental conditions, the search for other etiopathogenic factors affecting the development of BA.

3. Conclusions:

1. The current prevalence of bronchial asthma symptomatic manifestations among children of Kharkiv Region is 12.8%: at junior school age – 13.2%; in adolescence – 12.4%.

2. Over the last 19 years the prevalence of respiratory symptoms has decreased in 1.6 times in 6–7 years old children and in 2 times in adolescent age.

3. Significant differences in the prevalence of pathognomonic symptoms of BA in different districts of Kharkiv Region (from 5.5 to 14%) have been revealed, which makes it necessary to study the trigger factors of the region.

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FEATURES OF CYSTIC FIBROSIS COURSE IN CHILDREN DEPENDING ON INTERLEUKIN-4 GENE MUTATION

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Abstract. Cystic fibrosis (CF) course features depend not only on the difference in CF transmembrane conductance regulator gene mutations, but also on other gene modifiers. Interleukin-4 (IL-4) gene is a one of gene modifiers. The aim of the present study was to improve medical care for patients with CF by clarifying the pathogenic role of IL-4 gene polymorphism in the course of the disease. The study involved examination of 42 children with CF and 54 practically healthy children as control group. Patient examination was carried out by the standard methods in the remission period. Determination of C589T polymorphism of IL-4 gene was carried out using polymerase chain reaction in real time. DNA was isolated from buccal epithelium cells. Patients with IL-4 gene mutation (C589T) were characterized by more frequent primary manifestation of the respiratory signs, Staphylococcus aureus predominance within respiratory pathological microorganisms, the incidences of bronchiectasis and lung fibrosis, more severe liver lesions, elevated total serum immunoglobulin E level, elevated levels of the CD25 lymphocytes, circulating immune complex and reduced immunoglobulin A levels. The data demonstrate features of CF phenotype associated with IL-4 gene polymorphism.

Key words: *children, cystic fibrosis, clinical and paraclinical features, interleukin-4 gene mutation.*

Introduction. Cystic fibrosis (CF) is a hereditary disease characterized by variety of clinical manifestation depending not only on the difference in CF transmembrane conductance regulator gene mutations, but also on other gene modifiers [3, 13, 14, 22].

CF is characterized by lifelong inflammation [10]. The study of the influence of inflammatory factors on genetic defects is of great scientific interest. Scientists have identified a number of genes modifiers that influence CF severity (interleukin (IL)-1B, IL-4, IL-10 genes, tumor necrosis factor-α (TNF-α), transforming growth factor β1, mannose-binding lectin, α-1-antitrypsin etc.) [4, 5, 8, 13, 21, 24]. For example, IL-10 gene polymorphism (G1082A) is associated with *Aspergillus fumigatus* colonization, which has a significant role on the bronchopulmonary inflammation development [13]. Conversely, TNF-α gene polymorphism is associated with a milder course of CF and later colonization of *Pseudomonas aeruginosa (P. aeruginosa)* [13].

According to the scientists, C589T polymorphism of IL-4 gene is involved in the modification of various diseases. IL-4 is an anti-inflammatory cytokine synthesized by activated T-helper type 2, basophils, mast cells, switches B-lymphocytes to immunoglobulin (Ig) class E production [15]. Replacement of C allele with T allele leads to a significant increase of the IgE, which takes an important part not only in the development of allergic reactions, but also in protecting of the organism from infectious agents, which is very relevant for CF patients with the chronic bronchopulmonary inflammation [2, 9, 12].

The authors note to the significant influence of the cytokines polymorphism on the CF course, depending on the presence of which the disease acquires distinctive features with the same mutation CFTR [7].

Genetic defects that are harmless for general population and not accompanied by pathological manifestations can have a significant effect on CF course [1, 6, 13].

Determination of additional allelic genes that directly affect the CF phenotype provides an opportunity not only to expand scientific

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knowledge about the CF nature, but also to improve an individualized approach to compiling the patient's algorithm [16, 20].

2. PURPOSES, SUBJECTS and METHODS:

2.1 Purpose. To improve medical care for patients with CF by clarifying the pathogenic role of IL-4 gene polymorphism in the course of the disease.

Tasks of study:

1. To determine the clinical features of children with CF depending on IL-4 gene polymorphism.

2. To determine the features of the immune status of children with CF depending on IL-4 gene polymorphism.

2.2 Subjects & Methods

The research was conducted in the pulmonology department of Kharkiv Regional Clinical Children's Hospital No. 1 in 2015–2017. Clinical and paraclinical examination of patient with CF was carried out according to the Order of Ministry of Healthcare of Ukraine of 15 July 2016 No. 723 "On approval of the unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care "Cystic fibrosis", Order of Ministry of Healthcare of Ukraine of 29 January 2013 No. 59 "On approval of unified clinical protocols of medical care for children with diseases of the digestive system". Forty-two children with CF were observed. The control group (for assessment of immune analysis) consisted of 54 practically healthy children who had been randomized according to the age.

Determination of C589T polymorphism of IL-4 gene was carried out using polymerase chain reaction in real time. DNA was isolated from buccal epithelium cells using a special "DNA-express" kit ("Liteh" company).

Investigation of immune status was carried out by the standard methods in the remission period. Total immunoglobulin E (Ig E) in serum was determined by solid phase enzyme-linked immunosorbent assay (ELISA).

The study was conducted with respect to human rights in accordance with the current legislation in Ukraine, in compliance with international ethical requirements and did not violate ethical norms in science and standards for conducting biomedical research.

The results were processed by the IBM SPSS Statistics software according to the methods of variance statistics. Statistical significance was the difference between the indicators at $p < 0.05$.

Conflict of interests

There is no conflict of interests.

3. RESULTS AND DISCUSSION

The study involved examination of forty two children. CF was diagnosed by clinical and paraclinical characteristics and confirmed by the results of pilocarpine test. The examined patients were mainly boys (66.7 %). According to age, the majority of the children were of senior school age (*Table 1*).

Table 1

Distribution of children with CF by gender and age

Gender \ Age	1 year – 2 year 11 months 29 days		3 years – 6 years 11 months 29 days		7 years – 11 years 11 months 29 days		12 years – 17 years 11 months 29 days		Total	
	n	%	n	%	n	%	n	%	n	%
Boys	4	80	3	50	12	85,7	9	52,9	28	66,7
Girls	1	20	3	50	2	14,3	8	47,1	14	33,3
Total, n	5		6		14		17		42	

During the study of C589T polymorphism in IL-4 gene in children with CF allele T was determined in 15 cases. Homozygotes for allele T and heterozygotes among patients with CF were significantly more prevalent in comparison with the control group (*Table 2*).

The majority of patients were boys in all groups of children who were included in the study (*Fig. 1*).

Clinical features were studied in the group of children with IL-4 gene mutation (homozygous and heterozygous patients) compared to patients without IL-4 gene mutation because of children distribution and a small number of patients with TT phenotype.

Group with CT+TT genotype was characterized by a more frequent primary manifestation of the respiratory signs, but not gastrointestinal, unlike general population of patients (*Table 3*).

Assessment of CF severity showed that moderate course prevailed in all the groups. CC genotype frequency was significantly higher in

Table 2

Distribution of patients depending on C589T polymorphism of IL-4 gene

Genotype	CF patients group (n = 42)		Control group (n = 54)	
	n	%	n	%
CC	27	64.3*	45	83.3
CT	11	26.2*	8	14.8
TT	4	9.5*	1	1.9
Total, n	42	100	54	100

* compared with control group ($p<0.05$).

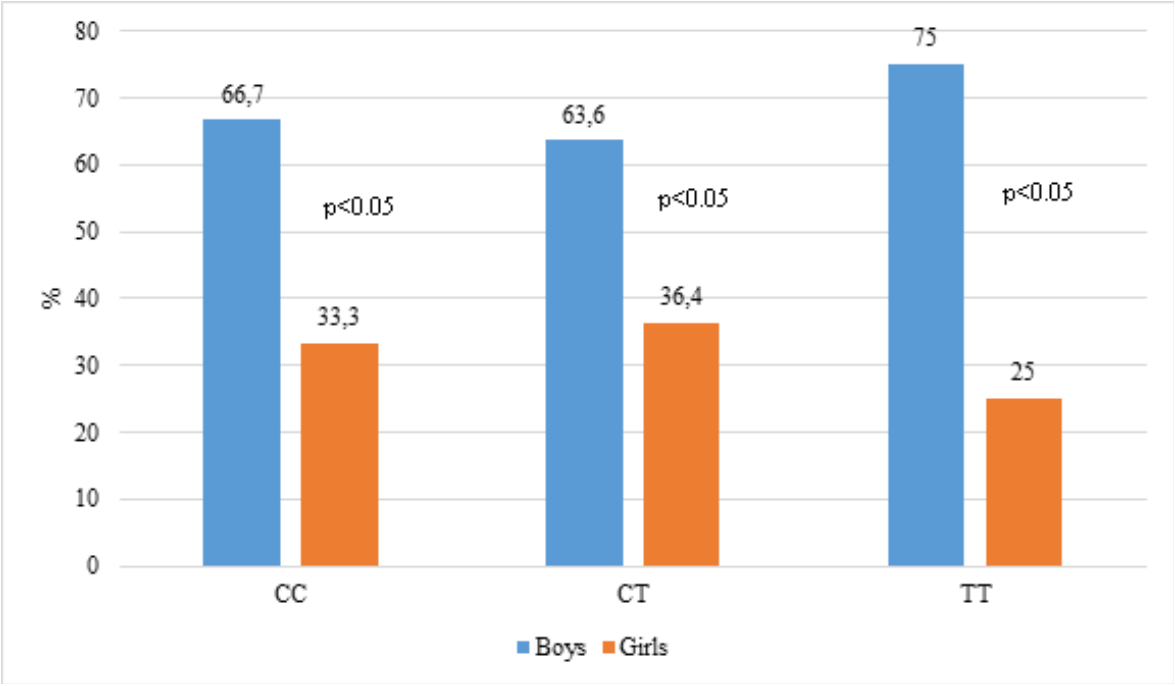

Fig. 1. Distribution of patients with CF by gender depending on C589T polymorphism of IL-4 gene

patients with mild course. CT+TT genotype group was characterized by significantly higher frequency in patients with severe course (*Fig. 2*).

The incidence of bronchiectasis and lung fibrosis was significantly higher in the CT+TT genotype group (66.7 % and 100 % vs 25.9 % and 65.9 % respectively).

The study of hepatic disorders showed that cirrhotic changes in liver parenchyma were more common in patients with IL-4 gene mutation (*Table 4*).

Bacteriological tests showed Staphylococcus aureus (S. aureus), P. aeruginosa, Candida albicans (C. albicans) were identified as predominant pathological microorganisms in the CT + TT genotype group (*Fig. 3*).

More frequent primary manifestation of the respiratory signs, S. aureus predominance within respiratory pathological microorganisms, more severe respiratory system and the liver lesions were found in the study of clinical features depending on C589T polymorphism of IL-4 gene.

Table 3

Manifestation of CF signs depending on C589T polymorphism of IL-4 gene

Genotype / Signs	CC (n=27)	CT+TT (n=15)
	%	%
gastrointestinal	74,07	53,4
respiratory	25,93	46,6*

* compared with CC genotype group ($p<0.05$).

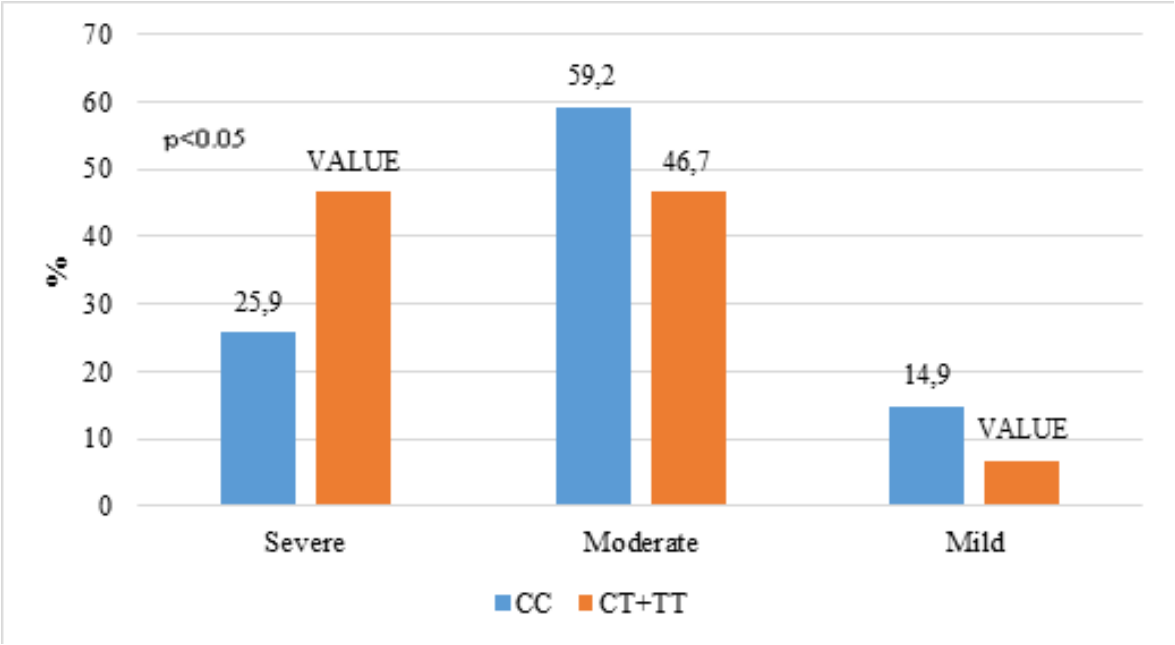

Fig. 2. The severity of CF course depending on C589T polymorphism of IL-4 gene

Elevated levels of CD25, circulating immune complex (CIC) and reduced IgA levels were found in patients of group with CT+TT genotype during the study of immune status (*Table 5*, *Fig. 4*).

The mean value of the total serum IgE was 344.6 (63.8; 670.3) IU / ml.

Elevated total serum IgE level frequency (80 %) was significantly higher in the CT + TT genotype group (446.9 (187.82; 884.72) IU/ml), when the CC genotype group was characterized by results within the age range (74%).

Discussion

C589T polymorphism of IL-4 gene affects the course of many diseases. For example, some authors described the negative effect of C589T polymorphism of IL-4 gene on the development of coronary artery disease [12].

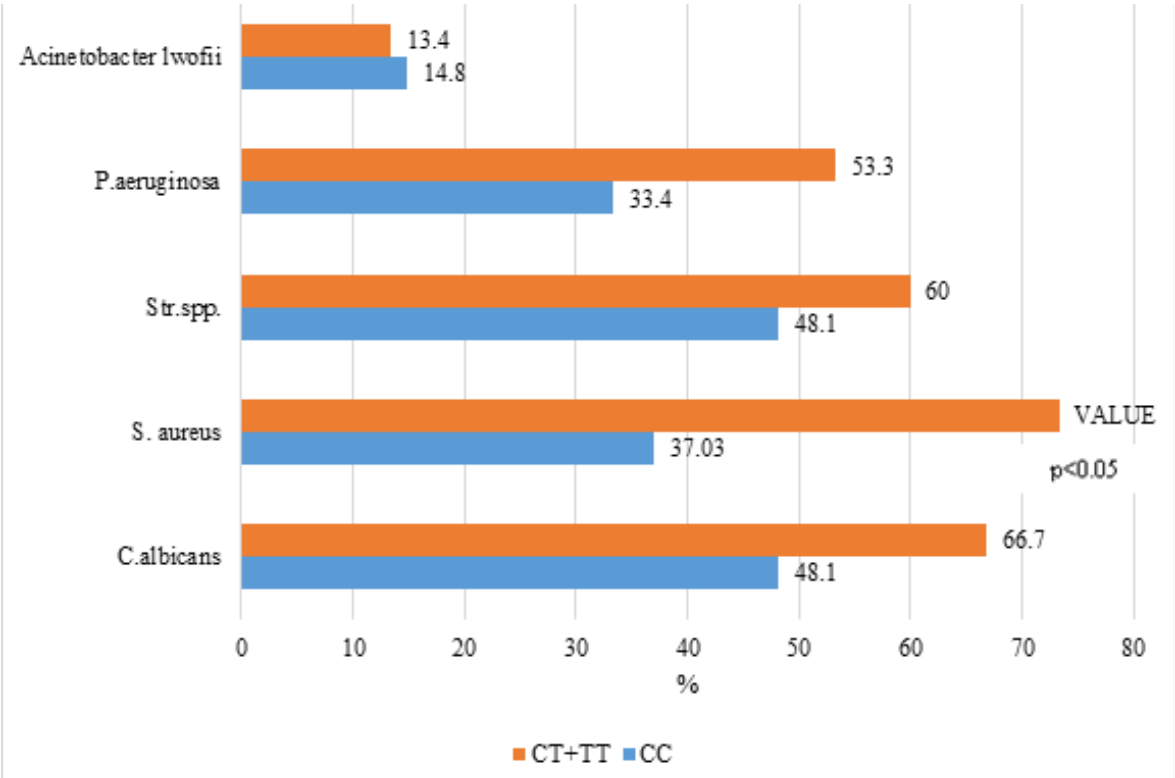

Fig 3. Indices of bacteriological tests depending on C589T polymorphism of IL-4 gene

Table 4

The degree of hepatic disorder depending on C589T polymorphism of IL-4 gene

Genotype / The degree of hepatic disorder	CC (n=27) %	CT+TT (n=15) %
Norm	29.6	6.6*
Moderate lesions	62.9	46.7*
Cirrhotic changes	7.5	46.7*

*compared with CC genotype group ($p<0.05$).

Table 5

Indices of immunological status of children with CF depending on C589T polymorphism of IL-4 gene

Indicator	IL-4 gene genotype			p_1	p_2	p_3
	CC (n=27)	CT+TT (n=15)	Control group (n=30)			
Leukocytes, $x10^9$/l	6.32 (5.5; 7.9)	6.5 (5.1; 7.5)	6.35 (5.47;7.0)	p >0.05	p >0.05	p >0.05
Neutrophils, %	49.0 (40.5; 61.0)	49.0 (42.0; 56.0)	51.0 (48.0;63.0)	p >0.05	p >0.05	p >0.05
Lymphocytes, %	50.0 (42.0; 61.0)	51.0 (44.0; 58.0)	43.0 (36.5;47.0)	p >0.05	p <0.05	p <0.05
CD 3, %	69.0 (65.5; 69.0)	66.0 (63.0; 70.0)	61.0 (58.7;69.0)	p >0.05	p >0.05	p >0.05
CD 4, %	40.0 (38.0; 40.0)	39.0 (37.0; 41.0)	44.0 (39.0;48.0)	p >0.05	p >0.05	p >0.05
CD 8, %	28.0 (27.0; 29.0)	27.0 (29.0; 29.0)	30.0 (29.0; 32.0)	p >0.05	p >0.05	p >0.05
CD 16, %	14.0 (10.0; 15.0)	12.0 (9.0; 16.0)	14.0 (13.75;15.0)	p >0.05	p >0.05	p >0.05
CD 22, %	19.0 (18.0; 20.5)	19.0 (17.0; 21.0)	18.0 (17.0; 20.0)	p >0.05	p >0.05	p >0.05
CD 25, %	21.0 (19.0; 37.0)	26.0 (17.0; 37.0)	17.0 (14.0;22.0)	p <0.05	p <0.05	p <0.05
Phagocytosis of latex, %	63.0 (59.0;68.0)	61.0 (54.0; 70.0)	60.0 (54.0; 65.0)	p >0.05	p >0.05	p >0.05
Phagocytic number	3.8 (3.7;4.1)	3.7 (3.54; 4.2)	3.5 (3.3;3.7)	p >0.05	p >0.05	p >0.05
Total complement (CH 50)	64.0 (61.0;65.0)	61.0 (62.0; 68.0)	48.0 (45.5; 52.0)	p >0.05	p >0.05	p >0.05
CIC with 3.5% PEG, units	7.6 (6.4;9.3)	8.3 (7.0; 9.9)	7.95 (6.8; 9.5)	p <0.05	p <0.05	p <0.05
Spontaneous nitroblue tetrazolium (NBT) tests, %	24.0 (18.0;42.0)	28.0 (17.0; 47.0)	30.0 (22.0; 32.0)	p >0.05	p >0.05	p >0.05
Spontaneous index of activated neutrophils (IAN) test, units	0.54 (0.26;0.81)	0.53 (0.27; 0.88)	0.58 (0.46; 0.8)	p >0.05	p >0.05	p >0.05
Stimulated NBT test, %	63.0 (52.0;68.0)	67.0 (62.0; 72.0)	55.0 (49.7; 70.0)	p >0.05	p >0.05	p >0.05
Stimulated IAN test, units	1.33 (1.12;1.49)	1.38 (1.22; 1.49)	1.18 (0.87; 1.29)	p >0.05	p >0.05	p >0.05
Lysosomal cationic proteins, units	1.18 (1.01;1.22)	1.19 (1.08; 1.27)	1.12 (0.93; 1.17)	p >0.05	p >0.05	p >0.05
Ig A, g/l	1.38 (1.02;1.54)	1.23 (0.99; 1.39)	1.18 (0.83; 1.33)	p <0.05	p <0.05	p <0.05
Ig M, g/l	1.02 (0.83;1.22)	0.98 (0.85; 1.08)	0.97 (0.64;1.2)	p >0.05	p >0.05	p >0.05
Ig G, g/l	10.38 (10.28;10.98)	10.29 (9.66; 10.64)	10.09 (8.53;10.9)	p >0.05	p >0.05	p >0.05

p_1 – CC genotype compared with the CT+TT genotype, p_2 – CC genotype compared with the control group, p_3 – CT+TT genotype compared with the control group.

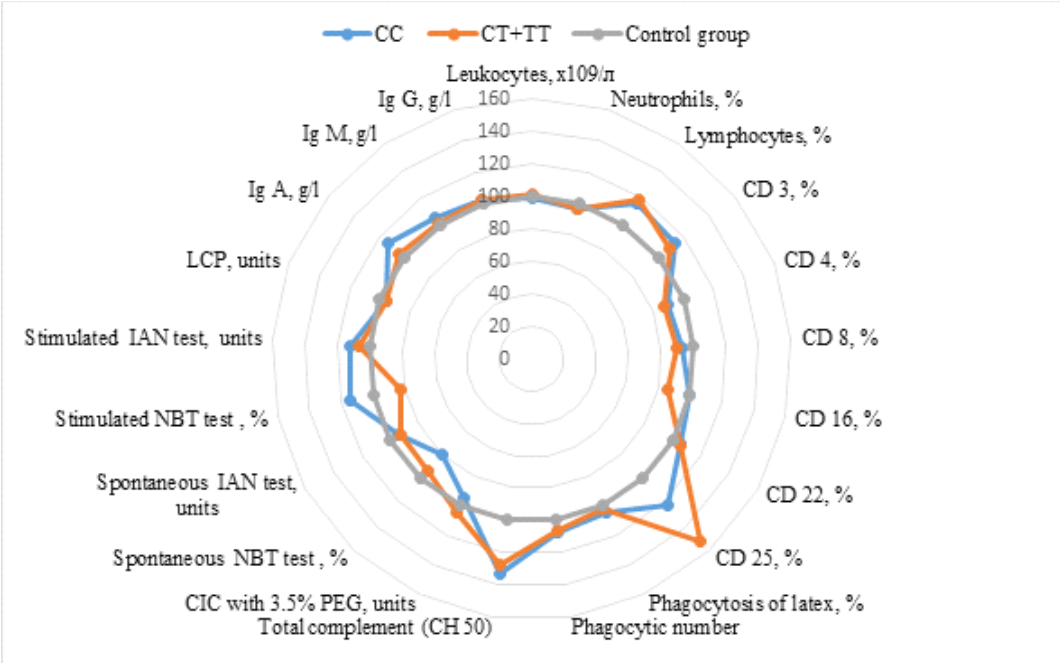

Fig. 4. Indices of immunological status of children with CF depending on C589T polymorphism of IL-4 gene

C589T polymorphism of IL-4 gene is associated with an elevated level of total IgE and bronchial hyperactivity in patients with bronchial asthma, which is an aggravating factor [17, 18].

There are not numerous studies regarding the influence of the IL-4 gene polymorphism the on CF. In this way, Sergienko DF and co-authors noted the relationship of 3'-UTR G/C mutation of IL-4 gene with the course severity of the bronchopulmonary inflammatory process [19].

Gembitskaya T.E. and co-authors studied the influence of IL-4 gene (C589T) mutation and its receptor (?-chain gene-IL-4R?) on the course severity of CF in the adult population (37 patients). Significant associations were not identified between polymorphic variants of IL-4 receptor gene and CF course, but the dependence of the clinical features on the IL-4 gene mutation was determined. It was found that homozygotes for T allele were only women [11].. According to our study, the influence of the C589T polymorphism of the IL-4 gene on the CF course severity was confirmed, but boys were dominated among patients with TT genotype.

Further research of the inflammatory genes modifiers will provide an opportunity to broaden knowledge about the peculiarities of the CF pathogenesis and mark new factors, which take part in the disease modification.

3. Conclusion.

Features of the CF phenotype associated with the polymorphism of the IL-4 gene were analyzed. More frequent primary manifestation of the respiratory signs, S. aureus predominance within respiratory pathological microorganisms, the incidence of bronchiectasis and lung fibrosis, more severe liver lesions, elevated total serum IgE level, elevated levels of the CD25 lymphocytes, CIC and reduced IgA levels were found in children with CF and C589T polymorphism of IL-4 gene.

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ERB-DUCHENNE PALSY (CASE REPORT)

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The frequency of damage to the brachial plexus is 0.5–2 per 1000 live births. Most of them (about 90 % cases) are Erb-Duchesnne palsy. Birth trauma of the brachial plexus occurs mainly in in full-term newborns. Correct diagnosis of Erb-Duchesnne palsy allows to avoid long-term complications as late treatment leads to disability. The article presents a clinical observation of Erb-Duchesnne palsy in a newborn patient, who was diagnosed on the first day of life. Conservative therapy was an effective strategy of baby's recovery.
Key words: *Erb-Duchenne palsy, birth injury, brachial plexus, newborn.*

The neonatal period of a child's life is the most important stage of human ontogeny, during which the formation and rapid development of all functional systems of the organism occur. The period of newborn is highlighted due to the special dynamism of the process of postnatal adaptation, and the greatest risk of disruption of this adaptation, much higher rates of morbidity and mortality. In our country in recent decades, research in neonatology has become importante due to the fact that at the present time the critical features of the neonatal ontogenesis are combined with extremely unfavorable social, biological and environmental factors, as well as with a severe demographic situation - the decline in fertility, short life expectancy and as a result a decrease in the population of Ukraine.

Erb-Duchenne palsy. ICD-10 / P00–P96 CLASS XVI Individual conditions originating in the perinatal period / P10–P15 Birth injury / P14 Birth injury of the peripheral nervous system.

P14.0 *Erb-Duchenne* palsy with birth injury

P14.1 Kliumpke palsy with birth injury

P14.2 Diaphragmatic nerve palsy with birth injury

P14.3 Other birth injuries of the brachial plexus

P14.8 Birth injuries of other parts of the peripheral nervous system

P14.9 Birth injury of peripheral nerves, "unspecified"

The proximal (upper) type, or *Erb-Duchenne* palsy (P14.0) (damage to rootlets from C5–C6 segments) is the most common type of palsy [1]. The following nerves and muscles are usually involved in the pathological process: n.axillaris (m.deltoideus), n.musculocutaneus (m.biceps et brachialis), n.radialis (m.brachioradialis et m.supinator brevis), n.suprascapularis (m. infraspinalis) [2]. This leads to atrophy of the shoulder muscles oand forearm and to impossibility of lifting the shoulder to the horizontal line, flexing the forearm, supination of the forearm and hand. The affected limb hangs drowsily along the torso and is rotated somewhat inward, as a result of which there is a Novik's symptom ("puppet hands"). The head is inclined to the lowered paretic shoulder, the hand is in the position of palmar flexion. Reflexes from the biceps are not caused. The paretic limb does not participate in the Moro reflex, grasping reflex is partially preserved. Muscle strength is reduced. There are no tendon reflexes with m. biceps, m. brachioradialis and m. triceps [3]. With a severe form of the paresis, a subluxation or dislocation of the head of the humerus can be observed due to a sharp decrease in muscle tone that fixes the shoulder joint. There is a symptom of Fink's "click". Sensitivity in the deltoid region is impaired. In 5% of cases, C3–C4 rootlets are involved in the pathological process, which is accompanied by damage of the diaphragmatic nerve. In such cases, in addition to limb palsy, respiratory

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disorders (rapid breathing, cyanosis, hiccough, dyspnea) are observed, especially with anxiety and screaming [4].

Along with Erb-Duchenne palsy, the distal lower Dejerine-Clumpke palsy, caused by the injury of the lower parts of the brachial plexus (C8-Th1) and total palsy of Kerer (C5-Th1 damage level) [5]. Duchesne-Erb palsy occurs more frequently in comparison with other diseases; in obstetrical practice its frequency is 1–2 cases per thousand newborns. Despite the developed methods of diagnosis and treatment, this pathology continues to be an urgent problem for a number of medical disciplines (neurology, orthopedics and traumatology, pediatrics, neonatology, obstetrics and gynecology).

The condition is mainly observed in full-term newborns. The frequency of damages of the brachial plexus is 0.5–2 per 1000 live births; among them, 90% of cases are Erb-Duchenne palsy [6].

The leading mechanism of the disease is stretching of the brachial plexus and neural roots, which form it and are fixed in the cervical spinal cord, due to excessive lateral (side) traction [7]. Thus, tractions and turn over the shoulder during the eruption of the head in case of breech presentation is a main cause of Erb-Duchenne palsy.

The upper roots of the plexus are most vulnerable, and as a result of excessive traction they are more often damaged. In severe cases of damage, detachment of the roots from the spinal cord, which can be accompanied by damage to the spinal cord itself, is present.

With less severe injury, hemorrhage and edema are observed in combination with rupture of the rootlets covers [8].

Important factors are maternal diabetes, excessive weight gain during pregnancy, which lead to embryonic macrosomia, which increases the risk of injury during childbirth.

It is not necessary to exclude the role of non-coordinated childbirth and rapid childbirth in the development of this pathology. It should be clarified that childbirth by caesarean section reduces, but does not completely eliminate the risk [9].

According to some sources, congenital varicella syndrome, as well as osteomyelitis of the head of the humerus or cervical vertebrae (due to plexus ischemia) can lead to complete palsy of the brachial plexus [10].

CLINICAL CASE

A child from the first pregnancy against a background of chronic tonsillopharyngitis in remission, anemia of mild degree from week 32. Baby from the first delivery at the gestational age of 39 weeks. The amniotic fluid was clear. Apgar score: at 1 minute – 6 points, at 5 min – 8 points.

At birth, the body weight was 3795 g, length 50 cm, head circumference 35 cm, chest circumference 37 cm.

Resuscitation measures were carried out in the hospital: sanation of the upper respiratory tract, artificial ventilation of the lungs with the Ambu bag. Cardiovascular system of the umbilical cord blood: pH-7,149, PCO2 – 50 mmHg.

At the initial examination, the limitation of mobility of the left upper limb was revealed (*Fig. 1*).

There was no signs of bone injury on X-ray examination.

Immobilization of the left arm by the outboard tire was made.

For further treatment, he was transferred to specialized department for thick neonates.

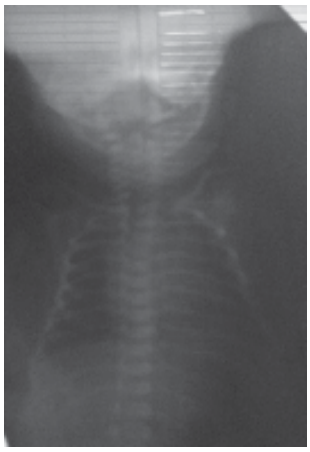

Fig. 2. X-ray, made just after the birth (no signs of injury)

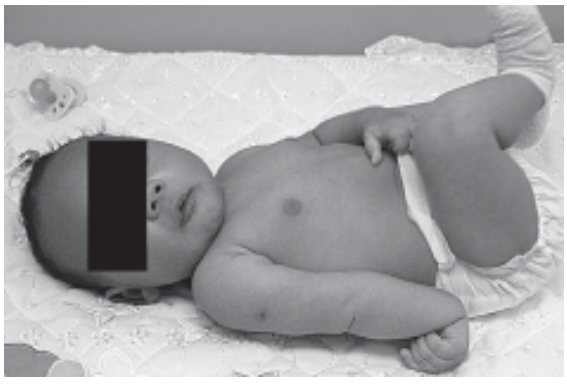

Fig. 1. Position of the right arm of newborn baby

Laboratory investigations showed the following:

Complete blood count:

Index	result
Hb	144 g/l
Erythrocytes	$4,08x10^{12}$/l
Ht	41%
Platelets	122 g/l
BCI	1,0
Leukocytes	$6,6x10^{9}$/l
Myelocytes	1%
Metamyelocytes	1%
Stabbed	5%
Segmented	27%
Eozinofiles	4%
Lymphocytes	55%
Monocytes	7%

Blood glucose-3,6 mmol / l

Clinical urinalysis:

Index	result
Color	yellow
Transparency	clear
Ph	acidic
Glucose	–
Protein	–
Leukocytes	–

Coprogram

Index	result
Color	Yellow
Neutral fat	Some
Leukocytes	–
Erythrocytes	–

Cranial ultrasound investigation: Echoes of edema of the brain, mainly periventricular zones.

Doppler-echocardioscopy: Patent foramen ovale, patent ductus arteriosus.

Orthopedic specialist diagnosed left-sided upper monoparesis, pronation-flexion system in the left elbow joint.

Neurologist confirmed the birth injury of the peripheral nervous system, left-sided Erb-Duchenne palsy.

Management. Immobilization of the left arm with an abducting splint, placement in the middle physiological position.

According to modern sources, the initial treatment is conservative. Physiotherapy and exercises with passive movements are indicated to prevent contractures (they can be started at the age of 7–10 days, after the extinction of post-injury neuritis). It is necessary to avoid the position of the "Statue of Liberty", as this leads to the development of contractures in the immobile shoulder. It can be helpful to overlay the longes on the wrist and fingers [6].

If the child does not noticeably improve the functionality of the affected arm in the first six months, surgical correction is usually recommended.

The prognosis of full recovery depends on the severity of the damages. If the roots of the nerves are not damaged and not broken, the prognosis is almost good (> 90%). If a significant improvement is observed during the first 2 weeks after birth, this indicates a complete or almost complete restoration of the plexus function. In most children, it is fully restored until the 3rd month of life. With a slow recovery, electromyography and investigation of the conductivity of the nerves make it possible to distinguish from avulsion (separation of the roots of the nerves from the spinal cord) from their stretching [6].

CONCLUSIONS

Erb-Duchenne palsy is a the condition that can be controlled. Its main symptoms in the form of restriction of movements in the shoulder and elbow joints can be minimized if medical aid is sought timely and drift.

Prophylaxis of the genital palsy of Erb is the adequate management of pregnancy and childbirth, the correct choice of the method of childbirth, which makes it possible to avoid the need for obstetric obstetrical manipulations.

Conflict of interests

There is no conflict of interests.

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TREATMENT OF COMMON BILE DUCT DISEASES COMPLICATED BY OBSTRUCTIVE JAUNDICE (REVIEW)

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Abstract. The article presents the up-to-date data concerning the treatment of common bile duct diseases complicated by obstructive jaundice. Nowadays, specialized clinics widely use mini-invasive interventions to treat this complicated pathology. Biliary tree decompression is the main objective of operative treatment. It is reasonable to perform antegrade and retrograde endobiliary interventions as preparatory and final stages of surgical treatment and in order to improve the patients' life quality and avoid hepatic impairment progression. Reconstructive-reparative operations following prior biliary decompression yield significantly better results as compared to surgical interventions without it.

Key words: *common bile duct diseases, obstructive jaundice, antegrade interventions, retrograde interventions, reconstructive-reparative operations.*

The issue of diagnosis and treatment of common bile duct diseases remains relevant due to the rapid growth of their prevalence among the population. In almost 95% of cases, they are accompanied by development of obstructive jaundice [1, p. 1004, 2, p. 68].

The causes of obstructive jaundice are benign and malignant diseases of hepato-pancreato-biliary organs [3, p. 757]. The literature points to the development of obstructive jaundice in 15–40% of patients with cholelithiasis and in the majority of patients with malignant bile duct neoplasms [4, p. 164].

Bile duct obstruction may be caused by choledocholithiasis as a complication of cholelithiasis and type I Mirizzi's syndrome – compression of the common bile duct lumen by a concrement located in the gallbladder duct. During biliary colic fits, concrements are likely to migrate from the gallbladder to the common bile duct through the gallbladder duct [5, p. 56].

The main causes of obstructive jaundice in case of malignant neoplasms of hepato-pancreato-biliary organs are as follows: pancreatic cancer – 47%, bile duct cancer – 20%, and major duodenal papilla and gallbladder cancer – around 15% [6, p. 5, 7, p. 6, 8, p. 118].

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Benign common bile duct neoplasms are rare, but they have a strong tendency to malignization. Literature describes their invasive growth and the tendency to local recurrence after isolated resections. As a rule, these diseases remain undiagnosed before the surgery or until the development of obstructive jaundice and cholangitis. Benign neoplasms mostly include granular cell tumors, adenomyomata, papillomata, and fibromata [9, p. 108].

Obstructive jaundice may not be accompanied by pain syndrome, but it may be manifested by the signs of cholangitis and hepatic impairment. It results in a large number of post-operative complications and the death rate reaches 15–30% [10, p. 172].

Dilation of bile ducts is an integral part of biliary hypertension. Hyperbilirubinemia develops as a consequence of increased serum bilirubin, which, in turn, is due to the penetration of bile components into blood. If serum bilirubin rises above 40 μmole/l, clinical signs of obstructive jaundice become grossly visible [11, p. 47].

The main cause of lethal outcomes in obstructive jaundice is hepatic impairment. Irrespective of obstructive jaundice etiology, the course of hepatic impairment is similar in all patients. Hepatic impairment is enhanced by the following factors: tumor intoxication, cholangitis, hemorrhage, general anesthesia, surgery trauma. The grade and duration of hyperbilirubinemia directly influence the frequency and severity of post-operative complications. Serum bilirubin

count above 200 μmole/l is considered hazardous, and the count of 400 μmole/l or more is critical for the development of hepatic impairment. Increased urea and serum creatinine is an unfavorable prognostic factor [12, p. 28].

Treatment outcomes depend directly on the severity of obstructive jaundice. Despite the rapid development of hepatobiliary surgery, there is no single classification of obstructive jaundice severity [13, p. 506].

Many researchers link the severity of obstructive jaundice to the baseline serum bilirubin. Thus, V. Fedorov et al. classify hyperbilirubinemia up to 100 μmole/l as mild jaundice, 100–200 μmole/l as moderate jaundice and above 200 μmole/l as severe obstructive jaundice [14, p. 19]. Other authors use several signs to determine the severity of obstructive jaundice. Pitt H. A. found that 10 signs identified by him reliably correlated with the number of post-operative complications, and 5 with lethality, multiple organ failure, and bacteremia [14, p. 20]. Dixon J. M. et al. distinguished three independent factors that correlate with post-operative complications and lethality: hematocrit below 30%, bilirubin over 200 μmole/l and malignant etiology of obstructive jaundice [15, p. 846].

The proposed classifications and assessment scales are quite laborious, detailed and based on complex etiopathogenetic and morphofunctional data, which is hardly applicable in the clinical practice. The process of obstructive jaundice severity assessment should be based on clinical signs and generally accepted laboratory data that are easily applied in everyday surgical practice.

Simplicity of the severity assessment concept is illustrated in the Child-Pugh score, which is widely used in patients with liver cirrhosis. It has been recognized in the whole world and is the commonly accepted severity scale. Unfortunately, this scale is not applicable to the assessment of obstructive jaundice severity [16, p. 53, 17, p. 646].

Most authors believe that operations at the bilirubin level below 50 μmole/l do not involve any complications [18, p. 3140, 19, p. 475].

Development of morphological and functional changes in the liver is due to lasting cholestasis and biliary hypertension. The latter results in the development of hepatic impairment, purulent cholangitis and disseminated intravascular coagulation. The majority of patients are aged 60 and above. At this age, the main disease in many patients is accompanied by grave co-morbidity dictating the necessity of choosing the least traumatic tactics of surgical treatment [20, p. 18, 21, p. 117, 22, p. 255, 23, p. 1170].

Due to the active clinical implementation of mini-invasive interventions – endoscopic, X-ray TV, laparoscopic, and their combinations, certain improvements have appeared in the treatment and diagnostic algorithm in patients with this grave pathology [24, p. 11, 25, p. 32].

In spite of the above, the issues of timely diagnosis and adequate treatment tactics in obstructive jaundice remain the most complicated ones in surgery of hepato-pancreato-biliary organs.

Endoscopic (retrograde) interventions remain the "golden standard" in the treatment of cholelithiasis complicated by choledocholithiasis. However, the question regarding the causes of endoscopic papillosphincterotomy failures remains unanswered. Such consequences of endoscopic papillosphincterotomy failures as reflux cholangitis and progressive hepatic impairment aggravate the patient's condition and necessitate reconstructive-reparative operations in the presence of obstructive jaundice and its direct complications [26, p. 59, 27, p. 26, 28, p. 49, 29, p. 77].

Endoscopic papillosphincterotomy involves a high surgical risk and a risk of such complications as acute pancreatitis, septic cholangitis, duodenal or common bile duct wall perforation. Literature indicates that complications following endoscopic papillosphincterotomy occur in 3–11% of cases, and death rates reach 0.8–15.5%. Anomalous position of bile ducts complicates the treatment and diagnostic measures. The final stage of retrograde endobiliary interventions is nasobiliary drainage with a thin catheter. Nasobiliary drainage significantly improves the effectiveness of endoscopic interventions and reduces the number of possible complications. Nasobiliary drainage is of great importance for such manipulations as stenting, treatment of external biliary fistula, cholangiogenic liver abscesses, bile aspiration for testing, and temporary bile duct drainage. Endoscopic papillosphincterotomy, and nasobiliary drainage up to separate bile duct stenting may be performed in patients with malignant bile duct pathology following endoscopic retrograde cholangiopancreatography [28, p. 50, 30, p. 70].

In addition to choledocholithiasis and common bile duct strictures, another grave disease of hepatobiliary organs is strictures of biliodigestive anastomoses of inflammatory origin. In nearly all cases, this pathology is a consequence of damaged bile ducts, their abnormal drainage, coarse surgical

manipulations on ducts and lasting tumor invasion [10, p. 172, 13, p. 508].

Direct mini-invasive access to bile ducts can be ensured through antegrade endobiliary interventions. A number of patients with known unsuccessful or impossible endoscopic papillosphincterotomy due to technical or anatomic reasons underwent percutaneous transhepatic cholangiodrainage under X-ray or ultrasound control with the aim of bile duct decompression [31, p. 39].

Percutaneous transhepatic cholangiodrainage can ensure both external and internal-external drainage of bile ducts. Cholangiodrainage beyond the stricture area is possible immediately after percutaneous transhepatic cholangiodrainage. If single-time external-internal percutaneous transhepatic cholangiodrainage is impossible, it can be performed 7–10 days after external percutaneous transhepatic cholangiodrainage. External-internal cholangiodrainage is more physiological because it ensures bile flow to the digestive tract. Cholangiodrainage ends with measured decompression of bile ducts with subsequent final restoration of bile passage to the digestive system by surgical means [32, p. 852].

However, questions of the duration of bile duct decompression and optimal terms of a radical or palliative operation remain disputable. According to different literature sources, operation terms vary from 1–2 weeks after drainage to 4–6 weeks after serum bilirubin normalization. Such different opinions can be explained by the variability of biochemical blood test results in the presence of obstructive jaundice, which makes it difficult to assess the functional liver status based on individual results [33, p. 480, 34, p. 443, 35, p. 134].

Measured bile duct decompression for 4–28 hours with pressure drops in biliary ducts not more than 10 mm H_2O should be performed to prevent the fast decompression syndrome. When the pressure in the bile ducts falls to 160 mm H_2O, it should be maintained at this level for another 24 hours. Measured bile duct decompression can be achieved by regulating the opening of the drainage catheter. External percutaneous transhepatic cholangiodrainage should be preferred in the presence of purulent cholangitis until full sanation of bile ducts and antibacterial therapy taking into account the associations of aerobic and anaerobic microflora. The following complications may develop following percutaneous transhepatic cholangiodrainage: migration of cholangiodrainage, bile outflow with the formation of bilomas, biliary peritonitis, hepatic impairment, etc. Complications were observed in 10–50% of patients with a lethality rate of 2.6–16.6% [35, p. 33].

Lethality rates associated directly with percutaneous transhepatic cholangiodrainage are low at less than 5%, and the prevailing number of lethal outcomes is due to general causes, especially hepatic impairment progression, and may reach 21.3%. Intra-abdominal hemorrhage and hepatic impairment remain fatal complications of percutaneous transhepatic cholangiodrainage [36, p. 55, 37, p. 48, 38, p. 447].

The following factors should be taken into account when choosing the type of drainage intervention: bile duct obstruction level (proximal or distal), propagation of the pathological process on the surrounding organs and tissues, patient's condition (whether a radical surgery is planned after bile duct drainage), patient's life expectancy after mini-invasive intervention if a radical surgery is not indicated; likelihood of possible complications, material and technical resources, and the quality of performance of a given mini-invasive intervention.

The operative interventions aimed at eliminating the cause of military obstruction is chosen after obstructive jaundice has been resolved.

According to the authors' data, in the case of benign common bile duct diseases, 15–25% of operations take the form of stenting biliodigestive anastomoses. In the case of malignant hepatobiliary diseases, the number of such operations increases to 50–84% [39, p. 39, 40, p. 97].

Cancer of hepato-pancreato-biliary organs is an umbrella term encompassing malignant neoplasms of pancreas, major duodenal papilla and bile ducts. Due to the anatomic and topographic proximity and direct interaction of these organs, there are no differences in the clinical pattern of tumors in this localization. In the recent decades, there has been a rapid growth in the prevalence of hepatobiliary cancer and, as a consequence, mortality due to it in the whole world [41, p. 25].

Malignant hepatobiliary neoplasms account for 10–20% of digestive organ tumors and 6–10% of all cancers. The median age of patients is 60 years. Pancreatic cancer accounts for more than 50% of all hepatobiliary tumors. Around 30% of malignant tumors are found in the liver, bile duct and gallbladder. Tumors of the major duodenal papilla are observed in 15% of cases [42, p. 458].

Among malignant neoplasms, pancreatic cancer, gallbladder cancer and cholangiocarcinomas are the most common causes of strictures and stenoses.

Cholangiocarcinomas prevail among malignant neoplasms and are among the most complicated ones; they are an unsolved and still relevant problem of hepatobiliary surgery; they are the second most common among primary malignant liver neoplasms. They can develop at any point of bile ducts – from minor intrahepatic to distal common bile duct regions. Cholangiocarcinomas develop from the bile duct epithelium and are characterized by infiltrative growth along bile ducts and through their walls [43, p. 170, 44, p. 860].

The disease was first described by the pathohistologist Gerald Klatskin in 1965 in the American Journal of Medicine. He described 13 observations of a special form of malignant bile duct tumor process localized in the region of hepatic duct confluence. The disease was then named after him [45, p. 244].

The classification of cholangiocarcinomas proposed by Bismuth-Corlette is currently the most frequently used. It takes into account pathomorphological features of cholangiocarcinomas and frequent combination of intra and extrahepatic localization [46, p. 172].

The risk of cholangiocarcinomas increases by 15% in the case of such congenital and chronic bile duct diseases as Caroli disease, cysts, adenomata, multiple papillomatosis of the common bile duct, and biliodigestive anastomoses [47, p. 375].

According to the findings, it has been established that cholelithiasis does not increase the risk of cholangiocarcinoma development, which is opposite to gallbladder cancer [48, p. 1034].

The only way to address cholangiocarcinomas is surgical treatment. Resectability of the tumor process is not more than 10% [49, p. 88].

The radicalism of the operative treatment can be achieved by extended resection of bile ducts and gallbladder, resection of the paracholedochal tissue and lymph nodes, and in some cases by extended liver and pancreato-duodenal resection [50, p. 107, 51, p. 68].

It should not be forgotten that radical operations in the presence of obstructive jaundice are associated with numerous post-operative complications, and the death rate reaches 15–30% [52, p. 160], which is 3–4 times higher as compared to operations following biliary decompression. Previously, the preparatory stage of radical treatment consisted in the deployment of biliodigestive anastomosis, whose type is determined by the level of bile duct blockage. Due to the implementation of mini-invasive interventions, such as percutaneous transhepatic cholangiodrainage and stenting, in the clinical practice, biliary decompression is not as traumatic as it used to be 20 years ago. However, the effectiveness of these two methods of biliary decompression prior to radical treatment remains an outstanding question. Also, the most disputable issues are the choice of the operation type depending on the localization and distribution of the tumor, as well as suitability of mini-invasive technologies as pre-operative preparation for a radical surgery [52, p. 160].

It is currently assumed that Bismuth-Corlette type III and type IV tumors are not a contraindication to radical operative treatment [22, p. 258].

Tumor invasion into hepatoduodenal ligament vessels is not a contraindication to resection. Portal vein resection ensures tumor-free resection and does not worsen the surgery outcome prognosis. On the contrary hepatic artery invasion worsens treatment results due to the perineural tumor extension [50, p. 112, 52, p. 20, 53, p. 37, 54, p. 38, 55, p. 12, 56, p. 812].

Liver resections combined with total caudal lobectomy and resection of extrahepatic bile ducts are performed at the majority of leading hepatobiliary surgical centers. This practice ensures 70% resectability in cholangiocarcinomas [57, p. 451, 58, p. 1494, 59, p. 331].

If cholangiocarcinoma is localized in distal regions of the common bile duct, an adequate extent of the operation was assumed to be pancreaticoduodenal resection. As a rule, radical operations involve more post-operative complications and higher lethality rates in spite of better direct outcomes of surgical treatment [60, p. 74].

According to the literature, lethality after such interventions is up to 13% and complications are reported in 2/3 of observations [56, p. 810, 61, p. 30].

Pre-operative preparation of patients for such major operative interventions is widely discusses in surgical communities. Murakami Y. et al. [62, p. 454] suggest performing biliary decompression on all patients with obstructive jaundice. This patient care tactics is followed by most Japanese hepatobiliary surgeons [61, p. 31].

The main reason for non-performance of radical surgical treatment is close proximity of

vital organs and great vessels that are quickly involved in the tumor infiltrate.

If non-resectable cholangiocarcinoma and non-operable condition are diagnosed, percutaneous transhepatic cholangiodrainage should be chosen as the treatment method. External-internal percutaneous transhepatic cholangiodrainage of bile duct stenting should be done if possible. According to the literature, 50–90% of patients require stenting [47, p. 372].

Antegrade endobiliary interventions are justified in patients with established non-operability of the tumor process as biliodigestive anastomoses in the presence of tumor infiltration of the common bile duct and obstructive jaundice are associated with the risk of an increased number of post-operative complications and, as a consequence, lethal outcomes. Most surgical clinics have now abandoned the practice of performing bile duct-stenting operations in patients with diagnosed cholangiocarcinoma. However, the problem of assessing the effectiveness of biliary decompression methods remains unsolved. The most disputable issues are selection of the operation type depending on the localization and extent of the tumor, suitability of antegrade endobiliary interventions for this pathology, and their effectiveness as palliative treatment [63, p. 157].

It is now recognized that external-internal percutaneous transhepatic cholangiodrainage and bile duct stenting are preferable to external cholangiodrainage as it is more physiological. In the case of external-internal drainage, constant access to the ducts is preserved with bile passage to the duodenum [64, p. 2424].

However, not all literature sources agree that external-internal cholangiodrainage should be preferred. These authors consider its main drawback to be lack of adequate sanation of bile ducts and estimate of the excreted bile volume. In their opinion, developing cholangitis is a consequence of the reflux of intestinal contents into biliary tracts [65, p. 255].

The main advantages of percutaneous transhepatic cholangiodrainage as compared to traditional bile removal interventions include mini-invasiveness that leads to fewer contraindications, which is especially important in the case of cholemia, and absence of any special pre-operative preparation.

Struggle against complications associated with external and external-internal percutaneous transhepatic cholangiodrainage, decreased life quality of patients and loss of bile urged the development of a mini-invasive method of internal drainage - the endobiliary stenting.

Nitinol shape-memory stents are widely used metal endoprostheses. These stents automatically adjust to the set diameter after opening [66, p. 180].

Stents without the self-expansion feature are opened by the in-built balloon catheter blowing up after introduction. The main advantages of self-expanding stents are their atraumaticity due to the small diameter of the delivery device and the stent's ability to assume the shape of the bile duct.

The emergence of nitinol stents with inner polyurethane or silicone coating increased its service life. Endoprostheses of this modification prevent the slotting or invasion of tumor or granular tissue into the stent cells. Comparative research of coated and uncoated stents in cholangiocarcinomas of distal bile duct sections demonstrated that the number of repeated procedures is lower in patients with coated stents [66, p. 181].

The most frequent complication following the deployment of coated stents is obturation of the cystic duct and the development of acute cholecystitis. The most severe complication associated with deployment of coated stents in the case of distal lesion of bile ducts is development of acute destructive pancreatitis due to the obturation of the pancreatic duct [67, p. 879].

The discussion related to the selection of methods for pancreatitis prophylaxis has been going on for a long time. It is assumed that prior endoscopic papillosphincterotomy is required for the prophylaxis of pancreatitis, but on the other hand it may result in the migration of the stent to the duodenal lumen [68, p. 449].

Conclusion

Antegrade endobiliary interventions in patients with benign common bile duct diseases, complicated by obstructive jaundice when it cannot be resolved by endoscopic means, had favorable effects on liver functioning, which is evidenced by clinical and laboratory data, in the first place by the total serum bilirubin count. Upon the analysis of treatment results, it can be noted that antegrade endobiliary interventions are not yet able to substitute endoscopic and traditional treatment of cholelithiasis complications, but they can be an alternative at the biliary decompression stage and can prepare the patient for a reconstructive-reparative operation and avoid the risk of post-operative complications.

Antegrade endobiliary interventions as a drainage treatment stage reduce the number of complications after the reconstructive-reparative treatment stage as compared to patients who

underwent surgeries without prior biliary decompression.

Antegrade endobiliary interventions are an alternative method of surgical treatment of cholangiocarcinomas. They cannot substitute radical surgical treatment and just improve patients' quality of life and life expectancy. Antegrade interventions are justified both at the stage of preparation for a radical surgery if the tumor is resectable and as a final treatment method.

Despite the advantages, antegrade interventions involve the risk of complications, which accounts for the need for up-to-date equipment and sufficient medical experience to perform such interventions.

When choosing the method of drainage and the extent of the reconstructive-reparative operation, the level of localization of cholangiocarcinoma, its extension on adjacent organs and tissues and the patient's condition should be taken into account.

Prevention of complications following antegrade interventions should be done at all stages of clinical care. The most important are preventive measures taken right during the intervention and aimed to minimize the operational trauma and the risk of complications.

Endobiliary stenting has become an effective method of internal bile removal in patients with cholangiocarcinomas as a palliative treatment method.

Conflict of interests

There is no conflict of interests.

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CYTOLOGICAL INDICES IN CHILDREN WITH GINGIVITIS

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Abstract. Development of gingivitis in children with fixed orthodontic appliances (FOA) is an urgent problem of today's periodontology, requiring elaboration of new methods that would give an opportunity not only to diagnose but also to predict the course of periodontitis in a given population. The investigation was conducted in patients with catarrhal and hypertrophic gingivitis during the treatment by FOA. It was established that cellular composition of gum mucosa undergoes cytosospecific alterations, which is manifested by qualitative changes of gingival epitheliocytes. In this case the indices of pathological shift point to the clinical and morphological form of the diagnosed inflammatory process in the gums. Conclusion. The maximal intensity of the inflammatory process in the gums takes 3 months of using FOA while the cytological criteria in this observation period are the functional state of segmental leukocytes and the alterative changes of intermediate cells in the form of foamy cytoplasm in children with catarrhal gingivitis. In children with hypertrophic gingivitis cytological adjustment indices are destructive changes in the epithelial cells, which manifests itself as the appearance of the naked core elements and signs of necrobiosis against the background of a large number of segmental leukocytes.
Keywords: *gingivitis, epithelial cells, fixed orthodontic appliances, cytological indicators, children.*

Introduction. Today, the intensity and prevalence of periodontal tissue diseases during the treatment with fixed orthodontic appliances increases, which is confirmed by a large number of studies [1–5].

The cytological method of research makes it possible noninvasively and in a short time to diagnose the presence and nature of pathological changes that occur in the gums, track the dynamics, objectivize the effectiveness of treatment and predict long-term results [6–8].

2. PURPOSES, SUBJECTS and METHODS:

2.1 Purpose: The aim of our research is to determine the cytological criteria for prognosis of clinical course of gingivitis in children with fixed orthodontic appliances and to examine the gums epithelium.

2.2. Subjects & Methods

The material was collected from the surface of the marginal part of the gums and cheeks at 1.5 cm below the teeth closure by scraping with a serpentine styler. Subsequently, the collected material was applied to a sterile objective glass. Drying of the material was carried out by dry fixation at room temperature, under the conditions of open access of air, with subsequent coloring. The principle of the combined coloring of the latch-dye of May-Grunwald and the dye of Himza-Romanovsky provides a coherent picture for the differentiation of the components of the epithelial cells. The pebbles were placed in a container and lowered into a dye-retaining cup [9–12].

It was fixed for 5 minutes, washed with water and stained with an aqueous solution of Romanovsky dye (10 ml of dye per 100 ml of distilled water), after which the glass was washed with water and spread out to a stand for drying. The analysis of the cytograms was carried out using Micros-50 microscope (Austria), using magnification of 1000. Planning and testing of cytological methods of the investigation and its implementation were carried out according to legal acts and ethical norms and requirements for scientific morphological research [13–15].

The study implied a detailed morphological analysis of the gum cell composition of 59 children with inflammatory diseases of periodontal tissues. The patients were divided into two groups depending on the diagnosed clinico-morphological

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form of gingivitis. The first group consisted of 33 children who had generalized catarrhal gingivitis with FOA (fixed on the lower jaw). The second group included 26 children with chronic generalized hypertrophic gingivitis (granulating form) in the treatment of FOA (fixed on the lower jaw). The control group comprised 28 persons of the corresponding age, without accompanying somatic pathology with an intact periodontal disease. In order to assess the pattern of cellular changes, the materials for cytological examination in Groups 1 and 2 were taken on the 3rd and 12th months of the FOA treatment.

We received written consent from patients to conduct research that met the ethical requirements [16].

Conflict of interests

There is no conflict of interests.

3. RESULTS AND DISCUSSION

The cell composition of the gums in the control group of the children at Himza-Romanovsky staining is represented by intermediate and superficial cells, as well as horny scales. The cytological organization of intermediate epithelial cells reflects the regional features of the anatomical site. The form of cells is mostly irregular, or elongated, the cytoplasm is weakly basophilic, less eosinophilic, with well-characterized nucleus of round or oval shape. Plasma cell has many wrapped edges. Surface epithelial cells are characterized by a hexagonal form and a decrease in the nuclear-cytoplasmic ratio toward the nucleus. The nuclei are mostly dense, with color sharply hyperchromic. It should be noted that the cells are located mainly in clusters (*Fig. 1*).

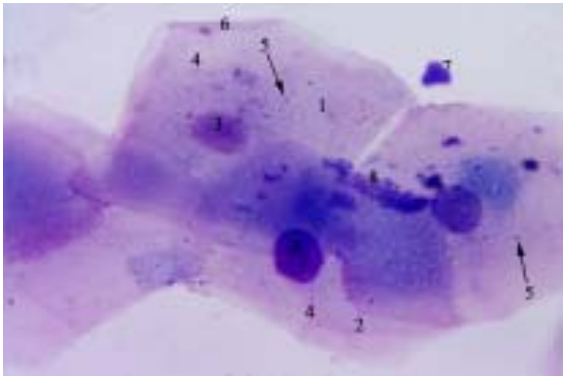

Fig. 1. Cellular composition of gum mucosa. Himza-Romanovsky staining. Magnification: ×100, approx. ×10: 1 – intermediate epithelial cell; 2 – superficial epitheliocytes; 3 – nucleus; 4 – cytoplasma; 5 – single azur-pozitive granules; 6– wrapped edge plasmolemma; 7 – segmental leukocyte; 8 – microflora

It is worth noting the presence of segmented leukocytes in the cellular composition. They are single, located mainly on the periphery of the epithelial cells. The presence of these type of cells provides the basis for protection of gums from the influence of microbial factor, which was visualized in insignificant quantities and contaminated the intermediate and superficial epithelial cells. Most of horn flakes have hexagonal shape, the cytoplasm is usually weakly basophilic, with a central location of the contours of the nucleus that was lost in the process of differentiation of the epithelial cell. Perinuclear space is surrounded by tonefilament inclusions, which form a mesh structure. Granules of keratogialin are stored, which confirms the phatism in the mechanisms of gingival germination, by orthoceratosis (*Fig. 2*).

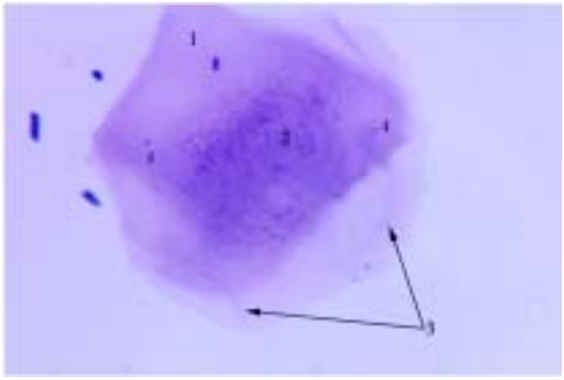

Fig. 2. Cellular composition of gum mucosa in control group children. Himza-Romanovsky staining. Magnification: ×100, approx. ×10: 1 – horny scales; 2 – nucleus shadow; 3 – inclusion of tonofilaments; 4 – granules of keratogialin

The peculiarity of the cellular composition of the gums in the control group of children was the absence of basal and parabasal epitheliocytes, as well as, in most, hematogenous cells. Only in isolated epithelial cells, the signs of destruction in the form of disturbances in the clarity of the plasmolemic contours were utilized. Consequently, the above-mentioned tinctorial characteristics of the gingival epitheliocytes characterize the functioning of the gum defense mechanisms in the normal manner, thereby providing homeostasis to the gum mucosa. In this case, the components that take an active part in phagocytosis and protect the tissues under conditions of microbial influence, however, play the role of the immune link in the cascade of pathogenetic mechanisms of damage to periodontal tissues. The cellular composition of

gums in the first group of children for 3 months of use of FOA was characterized by the presence of intermediate and superficial epitheliocytes and horny scales. Most of the intermediate cells had a stereotypical organization relative to this class of cells in the control group, but there were signs of cytological rebuilding in epitheliocyte section. They have become smaller in size by reducing the volume of the cytoplasm, the nucleus are partially optically light with scattered lumps of chromatin. The cytoplasm has a foamy organization. The peculiarity of the cellular composition of the gums for this observation period was the presence of hematogenous cells, in particular, a large number of neutrophilic granulocytes at different stages of phagocytosis, with clearly segmented nucleus, without junctions between segments. It should be noted that this type of cells was visualized regardless of the clinical-morphological form of gingivitis, but their functional status changed. In the conditions of chronic flow, segmental neutrophil granulocytes form cell clusters. In this case, the cell contours are clearly visualized and the nucleation segmentation is maintained. Intensive contamination, predominantly coca flora, has undergone interim epitheliocytes in the form of chain and semi-circular figures at this time of observation. Horny scales were visualized in a significantly smaller number, compared to their quantitative composition in the control group. They are mostly eosinophilic, polygonal, characterized by the absence of clear contours and obsession (*Fig. 3*).

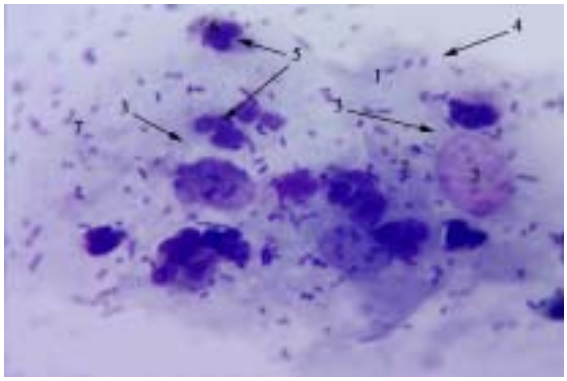

Fig. 3. Cellular composition of gum mucosa in Group 1 on the 3rd month of NOA administration. Himza-Romanovsky staining. Magnification: × 100, approx. ×10: 1 – intermediate epithelial cell; 2 – an optically light nucleus; 3 – foame cytoplasm; 4 – plasmolysis emulation; 5 – segmental leukocyte; 6 – segments of the the leucocyte; 7 – microflora

The analysis of the results of the research shows that for 3 months using FOA, the cellular composition of the gum undergoes a qualitative adjustment, with the cytomorphorphological pattern, due to the presence of segmental neutrophilic leukocytes, reflects catarrhal inflammation, against the background of abnormal erythema of the epithelial plate as a decrease in the activity of maturation processes and differentiation of epithelial cells to terminal stages. The appearance of cells with foamy cytoplasm is a consequence of the damaging effect of the gingival epithelium, which is accompanied by a pronounced cellular alteration and naturally accompanied by the presence of chronic inflammatory process in the gums. The cellular composition of the gums of the children of the first group for 12 months using FOA was characterized by the presence of intermediate, superficial epitheliocytes and horny scales. Intermediate cells had a stereotypical organization regarding this class of cells in control group of the children. However, it is quite interesting to note that, for the time of observation of qualitative rearrangement, superficial epitheliocytes have been exposed, in the form of elements of cytopathology. By evidence of varying frequency, depending on the intensity of the inflammatory process in the gums, there are dystrophic changes, namely the cytoplasmic vacuolation. It should be noted that the vacuolation has very hydrophilic character. Hydrophobic vacuoles are abundant, they are large in size and perinuclear. Small vacuoles are located mainly at the poles of superficial epitheliocytes. Cell nucleus of this class are hyperchromic and picnographic. It should be noted that the feature of the cellular composition of the gum at this time of observation is the presence of single macrophages that were in rest, had an elongated shape and an optically dense core. In the cytoplasm of the cell data, lysosomes are visualized. In addition to phagocytic function, this type of cells initiates the presentation of microbial agents to their lymphocytes. Also, it should be noted that along with the main function – phagocytosis and enzymatic cleavage of microbial factors, their availability is explained by the ability to secrete a number of biologically active substances and cytokines, and as a consequence, the proliferative and control function of cell data, which makes it possible to create a bar of the immune competent cell for further progression of the inflammatory process (*Fig. 4*).

Thus, changes in the cellular composition of the gum on the 12th months of using FOA is a

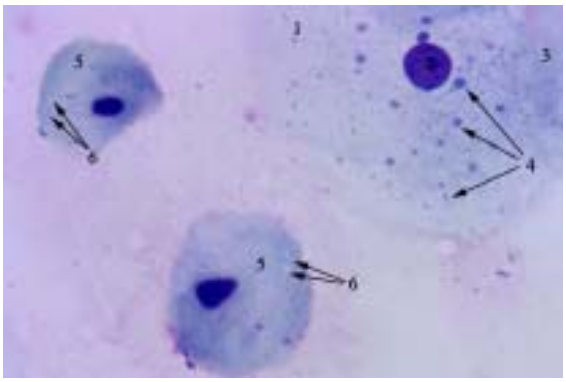

Fig. 4. Cellular composition of gum mucosa in Group 1 on the 12th month of NOA administration. Himza-Romanovsky staining. Magnification: ×100, approx. ×10: 1 – superficial epitheliocyte; 2 – nucleus; 3 – cytoplasm; 4 – vacuoles; 5 – macrophage; 6 – lysosomes

manifestation of the protective and adaptive reaction of the gum mucosa to the effect of FOA and the microbial factor, directed on delimitation and phagocytosis. And as an indicator of pathological shift in the characterization of the cellular composition of the gingival epithelium in children with chronic catarrhal gingivitis, cells with signs of vacuolic dystrophy stand against the background of the use of FOA. The cellular composition of the gums of Group 2 children for 3 months of FOA administration was characterized by the presence of intermediate, superficial epitheliocytes and horny scales. It should be noted that the number of cells and horny scales that are in the terminal stages of differentiation has decreased, compared with the control group. In our opinion, the shift of the cellular composition toward less differentiated forms of epithelial cells is associated with an increase in the proliferative activity of basal and parabasal cells, which is confirmed by the results of complex histological researches. The latter suggests that the use of FOA initiates the activation of mechanisms that prevent the maturation of epithelial cells gums until the terminal stages. Qualitative rearrangement has undergone a part of intermediate epitheliocytes, in the form of loss of clarity of plasmolars and urazation. Optical nucleus with diffused lumps of heterochromatin. The organization of most intermediate cells is also stereotyped. However, in the part of the intermediate epithelial cells, a cytospecific reorganization is determined. Among them, epithelial cells are visualized with signs of non-fibrotic changes. Quite often, the alkaline nucleus of intermediate epithelial cells were visualized. In our opinion, the bare nucleus of the cell in the form of chromatin breasts reflect the activity of the processes of phagocytosis of microorganisms that occur in cells and indicates the activity of phagocytic reaction, which includes the cytoplasmic enzymatic hydrolysis of bacteria. The peculiarity of the cellular composition of the gums in this observation period is the presence of a large number of segmental neutrophilic leukocytes, among which part the lysed and concentrated on the periphery of the epithelial clusters. Attention is drawn to intensive microbial population, among which the rods and cocci were dominated by representatives. Also, it stands to mention the presence of lymphocytes. The cytoplasm of the latter was characterized by basophilia, acquiring a light blue color and surrounding the nucleus in the form of a narrow border. The cytoplasm visualized the perinuclear zone. The presence of lymphocytes in our opinion, reflects the tension of the humoral chain of the immune system and confirms the results of complex histological studies of predecessors regarding the involvement of the immune system and the chronization of the process (*Fig.* 5).

By analyzing the cellular composition of gums in Group 2 children on the 3rd month of FOA administration, we can conclude that unlike control and Group 1 children, epitheliocytes of the gums are subject to a greater degree of destruction, which is manifested by the appearance of gloatuclear elements and signs of necrobiosis of epithelial cells. Cellular gums in Group 2 children

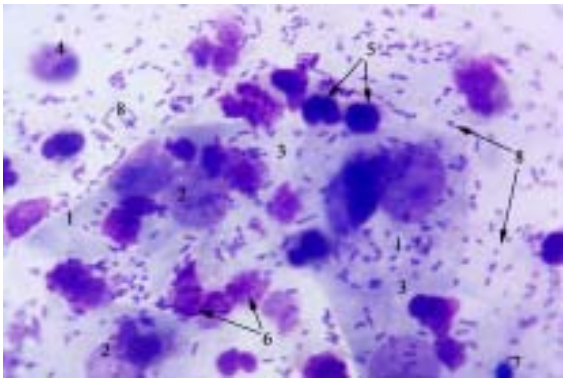

Fig. 5. Cellular composition of gum mucosa in Group 2 on the 3rd month of NOA administration. Himza-Romanovsky staining. Magnification: ×100, approx. ×10: 1 – intermediate cell with signs of necrobiosis; 2 – the nucleus of intermediate cell; 3 – cytoplasm; 4 – naked core; 5 – segmental neutrophilic leukocytes; 6 – neutrophilic leukocytes in the stage of lysis; 7 – lymphocyte; 8 – microflora

on the 12th month of FOA using was stereotyped and characterized by the presence of intermediate, superficial epitheliocytes and horny scales with a steady tendency to reduce the epithelial cells of terminal stages of diferon. The feature of the cellular composition of the gums at this time of observation was the presence of epithelial cells with signs of irritation. Visualized cells belong to superficial epitheliocytes and differ from the stereotypical class of these cells in smaller and sharply expressed basophilia of the cytoplasm. This makes it possible to suggest that in the case of hypertrophic gingivitis, mechanisms of violation of the desquamation processes of the epithelium, which provide the barrier function of the gums, due to the polymorphocyte infiltration of their own plate, are started in the background of the use of the FOA. The presence in the cellular composition of the lymphocytes confirms this assumption. The latter were characterized by basophilia of the cytoplasm, which surrounds the hyperchromatic nucleus in the form of a narrow border. The cytoplasm visualized the perinuclear zone (*Fig. 6*).

The indicated changes of cellular gum composition on the 12th month of FOA using are the result of violation of differentiation of different forms of epithelial cells, initiated by inflammatory infiltrates of own plate. Thus, it has been established that the main component of the cellular composition is gum in the control group of children, and the first and second groups of observations are cells of the multilayered flat epithelium. They are present in the cellular composition, both in normal state and in pathology. It should be noted

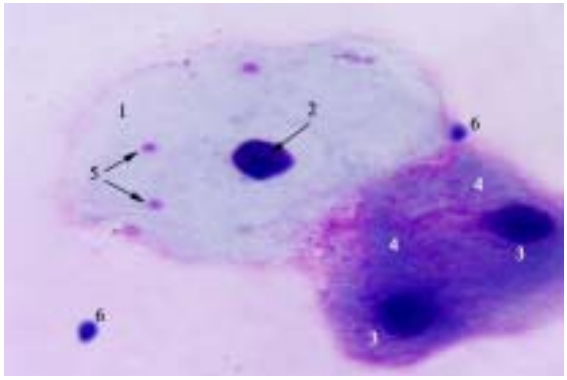

Fig. 6. Cellular composition of gum mucosa in Group 2 on the 12th month of NOA administration. Himza-Romanovsky staining. Magnification: ×100, approx. ×10: 1 – superficial cell; 2 – the pyknotic nucleus; 3 – epithelial cells with signs of irritation; 4 – sharply basophilic cytoplasm of superficial epitheliocutes; 5 – granules of keratogialin; 6 – lymphocyte

that the cells of the flat epithelium are heterogeneous, which reflects the heterogeneity of cells of the epithelial cover of the gums. On the background of the use of non-removable orthodontic appliances, the cellular composition of the gum undergoes a qualitative rearrangement, both in the epithelial and in the connective tissue component. The information above shows the violation of processes of differentiation of the gums epithelium as a result of the inflammatory process against the background of the use of FOA.

Discussion. The results obtained in this study are in agreement with previous studies and indicate that the above changes cause violation of differentiation processes epithelium gums in the result of the inflammatory process against the background of the use of FOA [17].

These provisions provide further development in the course and agree with the basic developments on the peculiarities of the cytological organization of gums in normal state and in inflammation [18–19]. Some differences are due to age-standardized aspect [20].

Conclusions

Cellular composition of the mucous membrane of the gums during the treatment by FOA that provide a cytosolic rebuilding, which manifests itself in qualitative changes of gingival epitheliocytes. In this case, indices of pathological shift justify the clinical and morphological form of the diagnosed inflammatory process in the gums. The maximal intensity of the inflammatory process in the gums takes 3 months of FOA using, while the cytological criteria in this observation period are the functional state of segmental leukocytes and the alterative changes of intermediate cells in the form of foamy cytoplasm in Group 1 children. In Group 2 children, in the given period of observations, cytological adjustment indices are destructive changes in the epithelial cells, which manifests itself as the appearance of the naked core elements and signs of necrobiosis against the background of a large number of segmental leukocytes. On the 12th month of FOA administration both groups of children were found to have reorganization of cellular composition characterized by signs of sustained dystrophic changes in epithelial cells, indicated by cells with signs of dystrophy and non-fibrotic changes. The above changes cause the violation of processes of differentiation of the gums epithelium as a result of the inflammatory process against the background of FOA administration.

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THE CRITERION "STRENGTH – WEAKNESS" OF THE NERVOUS VOCATIONAL SYSTEM IN APTITUDE OF WORKERS INVOLVED IN HAZARDOUS ACTIVITIES

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Summary. The principal aim of the paper is to make a physiological and hygienic assessment of the criterion "strength-weakness" of the nervous system in vocational aptitude of workers involved in hazardous activities. Interpretation of findings was carried out by means of generally recognized physiological consistency, where, according to Ya. Streliau, it was established that the optimal value of the criterion "strength-weakness" of the nervous system was 100%. In accordance with the study, the criteria for nosological diagnosis of people working under highly dangerous conditions were suggested. It was established that most people matched psychophysiological criteria. At the same time, the indeterminate number of people was considered as conditionally suitable for work (6%) and non-suitable (1%). The findings are considered as an experiment of confirmed principles of medicine as well as a ground for practical application of the criteria for nosological diagnosis under conditions of laboratory of clinical occupational pathology and psychophysiological expertise.
Key words: *strength of nervous system, highly dangerous occupations, job specification, chromoreflexometry, occupationally significant functions.*

Introduction

The strength of nervous processes is one of key basic features of the nervous system which provides stable functioning of the human body in achieving the goal of different types of activity, working practice, in particular [1]. A physiological sense of the strength of the nervous system consists in a specific peculiarity of the cerebral cortex cells which are characterized by ability to function consistently (non-stop) under conditions of extremely high or long-term excitation. This physiological phenomenon is closely associated with the integral indicator of functional status of the central nervous system, that is intellectual capacity which, in its turn, reflects a joint vector of changes of such psychophysiological functions as memory, attention and thinking [2].

Thus strength of the nervous system is of a great importance for workers, whose activities are connected with significant personal and collective hazards as well as it is used to estimate vocational aptitude.

2 PURPOSES, SUBJECTS and METHODS:

2.1. Purpose: To make a physiological and hygienic assessment of the criterion "strength – weakness" of the nervous system in vocational aptitude of workers involved in hazardous activities.

2.2. Subjects & Methods

The criterion "strength – weakness" of the nervous system was estimated according to results of nervous system index assessment in concordance with generally recognized L.O. Kopytova's method [2], whose principal is based on the ability of the nerve cells to stand long – term concentrated stress in multiple action of an irritant.

Interpretation of the findings was based on generally accepted physiological characteristic which, according to Ya. Streliau's formula, makes it possible to establish that the optimal value of the criterion "strength – weakness" of the nervous system is 100 %. This value means that the reverse reaction to external irritant in the initial series of signals was equal to the reaction of final series of signals, that was indicative of appropriate state ' of the nervous system of the patient under

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study. The value of the index of nervous system strength, which is lower than 100 %, suggests increased criterion "strength – weakness" of the nervous system in the involved patient resulting from development of inhibitory process. The value of the index which is higher than 100 % is considered as inability of the nervous system of an individual to react immediately to external irritant due to predominance of inhibitory process.

Individual assessment of findings as well as population one was made due to the criterion of "normal" Gaussian distribution, according to which the fitting criterion involved values of nervous system strength which were in the range from 60 to 140 %.

Statistical methods of processing the studies were carried out using parametric and nonparametric analysis

Conflict of interests

There is no conflict of interests.

3. RESULTS AND DISCUSSION

Highly dangerous occupations include the types of activities associated with individual and (or) collective risk of injuries, poisoning and other damages resulting in loss of health [3].

This group of occupations comprises those ones, which, according to the legislative records [4, 5] and findings of own job specific studies, include: highly explosive activities performed by locksmiths, electricians, electric welders; activities associated with nervous emotional tension which accompanies work of shift engineers, boiler house and steam turbine operators; activities associated with the use of fire – arms which are typical for "fighter" occupation; activities associated with petroleum pipe – line and gas pipeline servicing which are carried out by engineers and electric welders; fire hazardous work which squad fighters and commanders deal with; working at height, which according to employment duties are carried out by "shop – assistant", bricklayers, carpenters, elevator operators and others; activities at high voltage which are typical for electric generator repairmen, electromechanicians, electricians; activities associated with motor vehicle driving.

On the basis of specific significance of nervous system strength index, the quantitative analysis was carried out in accordance with the following criteria: type of activities, occupation, labor experience, age, sex.

As it was proved by observations, nervous system strength indices in representatives of different occupations of increased risk were different (*Table 1*). In workers dealing with highly explosive activities it was 94.54 ± 1.91 %, in people involved in nervous emotional tension it was 109.65 ± 8.30 %, in workers engaged into activities associated with fire – arms – 95.79 ± 1.33 %, in people whose work was associated with petroleum pipe – line and gas pipeline servicing – 92.72 ± 8.30 %, in workers dealing with fire hazardous work - 101.24 ± 4.90 %, in steeplejacks – 102.73 ± 1.26 %, in people working at high voltage – 104.46 ± 2.36 %, in drivers – 120.51 ± 10.83 %, in people working underground – 96.49 ± 5.35 %.

The analysis of the findings based on nervous system strength index has made it possible to establish that its most sustainable values are typical for workers who are engaged into the following safety criteria: fire hazardous, at height, at high voltage, underground. The average value of the criterion "strength – weakness" of the nervous system in representatives of these activity types was within the range from 96.49 ± 5.35 % to 104.46 ± 2.36 %.

According to individual features, this group of workers is able to react adequately in case of emergency situations and they can stand long – term intensive activities.

It was clarified that the upper deviation from sustainable value of the index of nervous processes strength (100 %) was observed in workers dealing with motor vehicle driving, nervous emotional tension activities, highly explosive activities, activities associated with fire – arms, petroleum pipe – line and gas pipeline servicing.

Herewith, the upper deviation ($p < 0.01$) in value of the index of nervous process strength from sustainable value was observed in workers involved into motor vehicle driving (120.51 ± 10.83 %) that is obviously indicative of predominant inhibitory process in this group of people which conclusively results in complicated activation and prompt response to change of circumstances. This phenomenon is focused to consider these specialists as representatives of increased attention group on the part of management team and psychophysiologists. Preventive measures aimed at training of psychophysiological functions directly associated with nervous system character, that is memory and attention, are useful. Based on the principal of reverse reaction, training will lead to improved functional condition of cortex cells and, consequently, will aid in optimization of important (central) element of providing of operational activity.

Significant deviation from optimal value, according to the criterion "strength – weakness"

Table 1

Value of nervous system strength index in workers involved in different activities associated with increased risk (M ± m %, n = 809)

Activity type	Indices	p
Highly explosive activities	94.54 ± 1.91	>0,05 – < 0,01
Nervous emotional tension activities	109.65 ± 8.30	
Activities associated with fire – arms	95.79 ± 1.33	
Pipeline servicing	92.72 ± 5.13	
Fire hazardous work	101.24 ± 4.90	
Working at height	102.73 ± 1.26	
Working at high voltage	104.46 ± 2.36	
Motor vehicle driving	120.51 ± 10.83	
Underground activities	96.49 ± 5.35	

of the nervous system, was observed in the group of workers dealing with petroleum pipe - line and gas pipeline servicing (92.72 ± 5.13 %, p < 0.05). Low values of the index of nervous processes strength are indicative of unstable nervous system in these workers, which is observed in the form of exhaustion associated with early development of inhibitory process in cortex cells. This group of workers is recommended to undergo preventive measures concerned with optimization of work – rest ratio as well as adaptogenic and sanogenic actions focused on improvement of body persistence to unfavorable workplace factors associated with pipeline servicing. Special attention should be paid to introduction of pshychohygienic measures directed to increase mental toughness of these workers, which, like back response principal, will contribute to optimization of functional condition of cortex cells.

Nine types of activities associated with increased hazards are carried out by representatives of 15 occupations. Thus, under conditions of physiological hygienic experiment, connection of the value of the criterion "strength – weakness" of the nervous system with specific occupational activity was studied. The control group enrolled workers, whose activity was not associated with hazards, accountants in particular.

As it had been proved by observations (the findings are presented in *Table 2*) the index of nervous processes strength characterizing the group of senior personnel involved into activities concerned with significant nervous emotional tension, was 102.40 ± 3.32 %. In other groups under study, where activity was associated with other risk factors in relation to individual and collective safety, the corresponding index of the criterion 'strength – weakness" of the nervous system was the following: in technicians – 106.00 ± 6.79 %, in locksmiths – 108.52 ± 4.12 %, in shop - assistants – 100.82 ± 3.86 %, in bricklayers – 101.51 ± 5.02 %, in engine drivers – 117.36 ± 11.43 %, in craftsmen – 103.97 ± 4.29 %, in engineers – 100.64 ± 2.19 %, in electric fitters – 104.58 ± 2.34, in electromechanicians –103.87 ± 2.04 %, in electric welders – 106.22 ± 7.36 %, in

Table 2

Value of the index of nervous system strength in representatives of different occupations, whose activity is associated with increased risk (M ± m %, n=716)

Occupations	Indices	p
Senior personnel	102.40 ± 3.32	>0,05 -<0,01
Technician	106.00 ± 6.79	
Locksmith	108.52 ± 4.12	
Shop – assistant	100.82 ± 3.86	
Bricklayer	101.51 ± 5.02	
Engine driver	117.36 ± 11.43	
Craftsman	103.97 ± 4.29	
Engineer	100.64 ± 2.19	
Electric fitter	104.58 ± 2.34	
Electromechanician	103.87 ± 2.04	
Electric welder	106.22 ± 7.36	
Electrician	94.27 ± 4.77	
Driver	120.03 ± 14.84	
Equipment operator	98.87 ± 2.43	
Fighter	99.58 ± 3.00	
Accountant and economist	94.84 ± 5.60	

electricians – 94.27 ± 4.77 %, in drivers – 120.03 ± 14.84 %, in equipment operators – 98.87 ± 2.43 %, in fighters – 99.58 ± 3.00 %. In the control group representatives, which included accountants and economists, the average index of nervous processes strength was 94.84 ± 5.60 %.

The comparative analysis of the findings is indicative of the fact that the upper deviation from average values is observed in the group of the drivers. The index value of 120.03 ± 14.84 % ($p < 0.05$) suggests some peculiarity of this psychophysiological function in these people which consists in their inability to be involved into activity immediately. In this case it is difficult for a worker to react rapidly to change of circumstances that is considered as a risk factor of individual and general safety.

As it has been proved by means of the study, the second risk group of relatively individual and group safety is represented by engine drivers, whose index of nervous processes strength is 117.36 ± 11.43 % ($p < 0.05$). This value is not significantly lower than that one of drivers that is indicative of inability of the representatives of this group to react rapidly to change of external circumstances. This fact makes it possible to consider engine drivers as risk group workers.

The opposite findings associated with low index of nervous processes strength were observed in electricians, where it was 94.27 ± 4.77 % ($p < 0.05$). This is an objective basis to regard instability of the nervous system in representatives of this group resulting in easy fatigability. The activities of electricians are connected with the risk of injury by high frequency current. Increased fatigability, in its turn, is a direct factor of impaired attention that increases injury risk. Therefore, in accordance with hygienic criteria, working conditions of electricians should be optimized; introduction of adequate mode- rest regime is particularly required.

The index of nervous processes strength in electricians is almost equal to the value of that one in the control group, that is 94.84 ± 5.60 ($p>0.05$), represented by accountants and economists.

In representatives of other groups under study the index of the criterion "strength – weakness" of the nervous system was higher, in the range from 98.87 ± 2.43 % (equipment operator) to 120.03 ± 14.84 % (driver). This consistency of formation of functional condition makes it possible to conclude that for the majority of people, working under conditions of increased danger, normal type of CNS reaction is typical (90 %) and for some workers – "backed - up" one (9 %, drivers and engine drivers predominantly). "Inhibitory" reaction type was observed in fewer people (1 %, electricians).

In the following the comparative analysis of dependence of value of the index of nervous processes strength on occupational experience, age and sex of workers was carried out (*Fig. 2–4*).

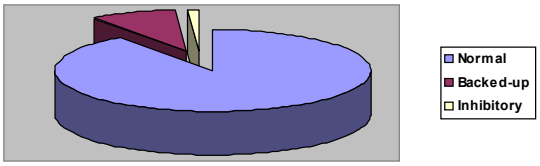

Fig. 1. Reaction type in workers dealing with hazardous activities (P ± p %, n=716)

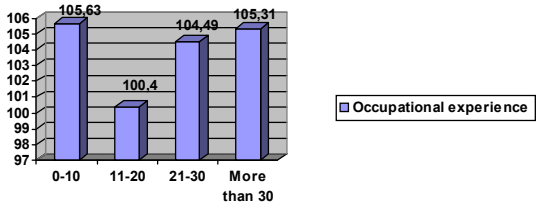

Fig. 2. Value of the index of nervous processes strength depending on occupational experience

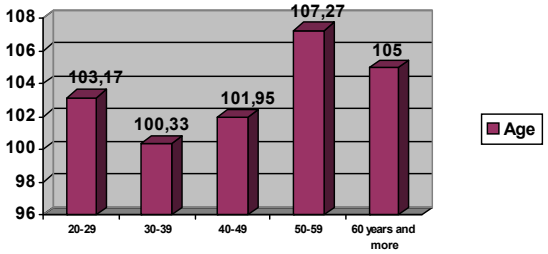

Fig. 3. Value of the index of nervous processes strength depending on age (M ± m %, n=800)

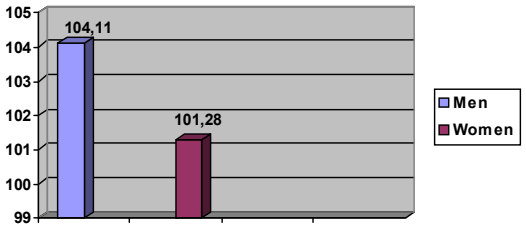

Fig. 4. Value of the index of nervous processes strength depending on sex (M ± m %, n=810)

It was established that value of the index of nervous processes strength in people with different occupational experience in hazardous activities was in the range from 100.40 ± 2.23 % to 105.63 ± 2.14 % ($p>0.05$).

The index of nervous processes strength depending on age of workers tended to be

increased: in workers aged from 20 to 29 this index was 103.17 ± 4.15 %, aged from 30 to 39 – 100.33 ± 1.81 %, aged from 40 to 49 - 101.95 ± 1.90, aged from 50 to 59 - 107.27 ± 3.23 %, aged 60 and older – 105.00 ± 3.16 %. These differences were not statistically significant (p>0.05).

The index of the criterion "strength – weakness" of the nervous system in men was somehow higher than that one in women (104.11 ± 1.36 % and 101.28 ± 2.61 %, respectively), but these differences were not statistically significant (p > 0.05).

Particularly, it should be noted that among all people under study dealing with highly hazardous activities, the average population values were within normal physiological range according to all criteria used. This fact is considered as background for qualitative carrying out of work activity along with health maintenance and prevention of workplace injuries and individual as well as group accidents.

Thus, there were no significant regularities in formation of the principal peculiarity of the nervous system, that is its strength, depending on occupational experience, age and sex.

In addition, significant impact on formation of the main psychophysiological function resulted from such criterion features as activity type and type of specific occupation associated with individual or collective danger.

Due to the final individual analysis of the role of nervous processes strength it was proved that among all workers dealing with different types of activities associated with high risk, 93 % of people under study met the requirements of vocational aptitude according to the criterion "strength – weakness" of the nervous system, 6 % of people were conditionally suitable that resulted in reduction of term to the next examination from two years (for suitable ones) to one (*Fig. 5*). Occupationally unsuitable people were represented by only 1 %.

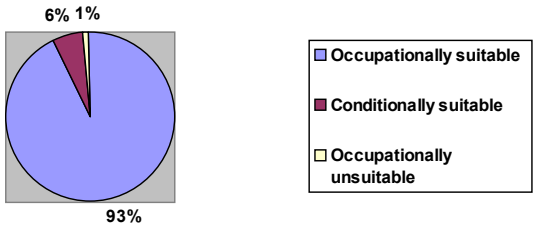

Fig. 5. Vocational aptitude of workers dealing with high risk activities (P ± p %, n=809)

The obtained results correspond to modern concepts of the role of the criterion "strength-weakness" of the nervous system in the formation of professional suitability. Substantially extends our scientific understanding of the role of psychophysiological functions in the success and safe production activities in the performance of hazardous work [3, 6].

Conclusions

1. The criterion "strength – weakness" of the nervous system is considered as a principal characteristic of vocational aptitude of workers involved in highly hazardous activities. It reflects qualitative and quantitative characteristics of neurodynamics.

2. Cortex neurodynamics, which is assessed by means of nervous system strength index, is closely associated with activity type and corresponding occupation of a worker and does not depend on his or her professional experience, age and sex.

3. The majority of the patients, who are engaged into highly hazardous activities, meet occupational requirements according to the criterion "strength - weakness" of the nervous system (93 %). The group of 'conditionally suitable' workers was represented by 6 % of people under study and the one of "occupationally unsuitable" workers – only by 1 %.

4. The upper deviations from population optimum were observed in people involved in occupations associated with motor vehicle driving, that is drivers and engine drivers, who are characterized by "backed – up" reaction type, when a person is unable to react immediately to change of circumstances.

5. The second group of workers with opposite character of reaction was represented by people dealing with petroleum pipe – line and gas pipeline servicing as well as electricians. These workers were characterized by inhibitory reaction type which was observed in the form of easy fatigability of cortex cells.

The set of corrective measures for representatives of these groups under study should include improvement of functional condition through training of occupationally significant psychophysiological functions as well as optimization of work – rest ratio focused on prevention of early fatigue.

In the article states the facts of the research and their results, which allows the use of physiological and hygienic assessment of the criterion "strength – weakness" of the nervous system in vocational aptitude of workers involved in hazardous activities.

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NONSPECIFIC IMMUNOLOGIC REACTIVITY IN RATS EXPOSED TO HYPOCALORIC DIET DURING PREGNANCY AND THEIR OFFSPRING

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Abstract. Inflammation as a manifestation of local tissue damage is a basis of a nonspecific component of the systemic immune response. Immune system mainly provides afferentation of information with cytokines which can be tracked to assess immune response. The study involved trials on 30 nonlinear pregnant rats (WAG/G Sto population) and their offspring. The levels of interleukin-4 (IL-4) and interleukin-12 (IL-12) in the blood serum were determined by immune-enzyme method using the sets of reactants of BEST Vector (Novosibirsk, the Russian Federation) and the sets of reactants of (Elisa Kit) Ani Biotech Oy, Orgenium laboratories Business Unit (Finland) according to the instructions attached.

Taking into consideration the disembodied data in the literature, dedicated to studying the issues, related to peculiarities of the immune system ontogenesis and orientation of immune responses, appearing secondary to pathological changes during perinatal and early periods of post-natal development, it is essential to clarify the role of the immune system in the mechanisms of damage of the pancreas structure and function. Assessment of the role of effector cytokines imbalance in immune reactions in rats exposed to hypocaloric diet during pregnancy and in their offspring, in comparison to the control, showed a significant imbalance of regulatory cytokines with a primary increase in IL-12 content, a decrease in IL-4 in rat mothers and 2-month-old infant rats, a decrease in both IL-12 content, and IL-4 in 1-month-old infant rats, demonstrating involvement in pathogenesis of damage of the pancreas and further development of chronic pancreatitis as both specific (Th-1) and nonspecific (macrophageal) cellular link of immunity. The latter is probably associated with an impairment of intercellular interaction, first of all, due to a decrease in functional activity of macrophages – cells of effectors, modulators of an immune response and sources of regulatory cytokines.

Keywords: *hypocaloric diet, cytokines, nonspecific immunologic reactivity, pancreas.*

Introduction. The complex of local and systemic protective responses is known to develop in response to disorders of different nature (stress, pregnancy, malnutrition). Inflammation as manifestation of the local tissue damage is a basis of a nonspecific component of the systemic immune response. Communicative interaction of the immune and neuroendocrine systems is provided with specific alarm mechanisms. Immune system provides afferentation of information mainly by cytokines which can be tracked to assess immune response [1, p. 86].

Taking into consideration the disembodied data in the literature, dedicated to the issues, related to peculiarities of the immune system ontogenesis and orientation of immune responses, appearing secondary to pathological changes during perinatal and early periods of post-natal development, it is essential to clarify the role of the immune system in the mechanisms of damage of the pancreas structure and function.

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2. PURPOSES, SUBJECTS and METHODS:

2.1. Purpose

The objective of the study is to determine the content of IL-12 and IL-4 cytokines and their ratio in the blood serum of the rat mothers that received a hypocaloric diet during their pregnancy and their offspring.

2.2. Subjects & Methods

The study involved trials on 30 nonlinear pregnant rats (WAG/G Sto population) and their offspring (120 specimen). The experimental animals were divided into the groups: the rats that during their pregnancy received a hypocaloric diet

at the expense of unbalanced nutrition with the reduced content of proteins and carbohydrates (10 specimen), 1-month-old rats (10 specimen), 2-month-old rats (10 specimen).

All the rats born to mothers of the above-mentioned group received a physiologic (balanced) nutrition after birth and were in usual conditions of a vivarium. The animals were decapitated within the terms according to the stages of the study; that is, females were removed from the study right after labor, infant rats were removed as soon as they reached the age of 1 and 2 months. All the procedures on the animals as well as the removal of the animals from the experiment by decapitation were made under anesthesia with the use of thiopental narcosis. The levels of interleukin-4 (IL-4) and interleukin-12 (IL-12) in the blood serum were determined by immune-enzyme method using the sets of reactants of BEST Vector (Novosibirsk, the Russian Federation) and the sets of reactants of (Elisa Kit) Ani Biotech Oy, Orgenium laboratories Business Unit (Finland) according to the instructions attached. The results of the study were processed by analysis package of Microsoft Excel-2003, Biostat.exe-2008 computer software [2].

Conflict of interests

There is no conflict of interests.

3. RESULTS AND DISCUSSION

The important regulatory role of cytokines is widely known. IL-4 induces proliferation of type 2 T-helpers (Th2) mediating the reactions of humoral immune response (stimulation of B-lymphocytes and production of antibodies) and is also an antagonist of gamma interferon inhibiting the proliferation of type 1 T-helpers (Th1) [1, P. 121] while IL-12 enhances the proliferation and differentiation of type 1 T-helpers (Th1) mediating the reactions of cellular immunity and at the same time inhibiting proliferation of type 2 T-helpers (Th2) [1, P. 122; 3, P. 312; 4, P. 435].

In rat mothers who were on a hypocaloric diet with the reduced content of proteins and carbohydrates during their pregnancy IL-12 content was found to be increased almost two-fold (*Table 1*), while the average level of IL-4 content in the animals of the studied group was significantly decreased with regard to the standard – by 2,3 times respectively.

The degree of proportionality of changes in IL-12 and IL-4 content was determined by IL-12/IL-4 ratio and an essential increase in IL-12/IL-4 ratio by 3,6 times in comparison with control which demonstrated cytokine imbalance in rats of the observation group.

Table 1

Contents of cytokines in the blood of rat mothers exposed to hypocaloric diet during their pregnancy (in % of the standard)

Indices	Rat Mothers
IL-12	186.6±9.1*** *(p_1<0.001)*
IL-4	45.4±6*** *(p_1<0.001)*
IL-12/IL-4	358±26.4*** *(p_1<0.001)*

Note. 1. ***p < 0.001, *p < 0.05 (comparison with the control group).

The obtained data indicate the tendency, by an increase in IL-12, first of all, to expansion of cellular type reactions through enhancement of proliferation and differentiation of Th1, secondary to inhibition of humoral response that is indicated by a decrease in IL-4 and, thus, confirming an important role of a specific cellular link of the immune system in the mechanisms of pancreas damage as a result of a prolonged hypocaloric diet during pregnancy [5, P. 41; 1, P. 122; 6, P. 63].

It is necessary to add to the information mentioned above that morphological study showed both signs of inflammation of pancreas in 40% of rats, and their absence in 60% of rats; however the degree of IL-4 decrease (by 2 times) in both groups was the same, but IL-12 level was increased significantly (195.3±17.2% of the standard, p<0.001) in the rats with inflammation in the pancreas tissue while in the animals without the signs of inflammation IL-12 level was within normal values (100.1±2.3%) [7, P. 208–211; 8, P. 12–20].

Next stage of the study involved an assessment of cytokine content in the blood of 1-month-old and 2-month-old infant rats born to mothers exposed to hypocaloric diet during pregnancy (*Table 2*).

Blood serum in 1-month-old infant rats was shown to have a decrease in the content of not only IL-4 but also IL-12 indicating an impairment of functional activity of macrophages – effectors and modulators of immune response, a source of regulatory cytokines (IL-12 is one of them), known to be in close cooperative interaction with Th potentiating the differentiation of Th 1 followed by Th1 and macrophage mutual activation of each other. Blood serum of 2-month-old infant rats was found to have an increase in IL-12 content and an essential (4-fold) decrease in the average level of IL-4 compared to the control which coincided with the indices in rat mothers, but had a little more expressive cytokine imbalance [9, P. 117–138, 10, P. 559–568].

Table 2

Content of cytokines in the blood serum of infant rats born to mothers exposed to hypocaloric diet during pregnancy (in % of standard)

Indices	Age (group) of infant rats	
	1 month old	2 months old
IL-12	55±1.5*** *(p_1<0.001)*	156 ±3.3*** *(p_1<0.001.p_Y<0.001)*
IL-4	25.6±3.4***	28.7±2.4***
IL-12 / IL-4	264.1±45.7*** *(p_1<0.001)*	575.7±42.8*** *(p_1=0.036.p_Y<0.001)*

Note. 1) ***p < 0.001, ** p < 0.01, *p < 0.05 (comparison with the group).

The obtained data are indicative of a more significant imbalance of regulatory cytokines in infant rats, as compared to rat mothers, and thus the prevalence of a nonspecific cellular link of immunologic reactivity increases the risk of developing chronic pancreatitis in infant rats in future.

The obtained experimental data are indicative of the fact that an unbalanced nutrition of pregnant rats is an essential risk factor of developing organic pathology of the pancreas with secretory failure not only in them, but also in their offspring, despite normal nutrition of the latter after birth, which proves the relevance of further research for clarification of means aimed at regeneration of the functional state of the pancreas after a long-term unbalanced nutrition of pregnant animals.

Conclusions

1. Rat mothers exposed to hypocaloric diet with the reduced content of proteins and carbohydrates during their pregnancy were found to have signs of disturbance of the immunologic reactivity in the form of imbalance of regulatory cytokines with prevalence of IL-12 content, reduced IL-4 level indicating a nonspecific cellular link of immunity in pathogenesis of the pancreas damage.

2. Infant rats born by to mothers exposed to hypocaloric diet during pregnancy despite their normal nutrition after birth were shown to have inhibition of immunologic reactivity in the blood serum after a month of life, demonstrated by a decrease in both IL-4 and IL-12 content.

3. In the blood serum of 2-month-old infant rats, cytokine content displayed unidirectional changes with the indices in rat mothers (increase in IL-12 content and decrease in IL-4 content), but the changes were more significant.

4. The imbalance of regulatory cytokines in rat mothers and their offspring indicated a specific (Th-1) and nonspecific (macrophageal) cellular link of immunity in the pathogenesis of the pancreas damage which is possibly bound to the disturbance of intercellular interaction due to a decrease in activity of effectors and modulators of an immune response – macrophages which are also a source of regulatory cytokines.

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