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E.Y. Arkhiy, L.B. Prylypko, O.M. Horlenko, O.M. Moskal
HSEE "Uzhhorod National University", Medical faculty, Uzhhorod

THE ROLE OF INFLAMMATORY RESPONSE AND ANTIOXIDANT PROTECTION MARKERS IN THE PATHOGENESIS OF ABDOMENALGIA IN PATIENTS WITH CHRONIC PANCREATITIS COMORBID WITH HYPERTENSIVE DISEASE

e-mail: name.lyubka@gmail.com

Modern medicine is gradually losing the mononosological nature of the disease course, and the trend towards polymorbidity is becoming more and more noticeable. The combination of multi-organ changes has a negative effect on the clinical course of all diseases. A frequent common combination in clinical practice is a combination of chronic pancreatitis and hypertension. The purpose of our study was to determine the effect of laboratory parameters of the antioxidant defense system and markers of inflammatory response on the intensity of abdominal pain in patients with chronic pancreatitis comorbid with hypertension disease. The results of our study are complementary to the fundamental knowledge on the pathogenesis of combined pathology, namely the element of a subjective parameter formation - abdominal pain. It has been proven that leukocytes, ESR, α 1-antitrypsin, glutathione peroxidase, selenium and zinc are key parameters in the formation of abdominal pain. Based on these laboratory parameters activity level, it is recommended to expand the basic set of medical measures in order to accelerate removing of abdominal pain.

Key words: chronic pancreatitis, hypertension, abdominal pain, markers of inflammation, antioxidants.

The work is a fragment of the research project "Polymorbid pathology in diseases of the digestive system, features of pathogenesis, possibility of correction", state registration No. 0118U004365.

One of the major problems in modern medicine is comorbid (multimorbid) conditions, which occupy a leading place in the daily practice of clinicians. This is due to many reasons, because the combination of two or more diseases mutually complicate the course of each other, significantly impair the quality of patients' life, complicate the diagnostic process and require using a whole arsenal of drugs, which are often incompatible with each other [1].

Therapeutic nosologies, which can often be combined, include chronic pancreatitis (CP) and hypertension disease (HD) [2]. At first sight, these diseases are pathogenetically difficult to associate with each other. However, a number of researchers point out to the presence of common etiopathogenetic links in the formation of combined pathology [2, 6, 7]. One of them is the presence of a systemic inflammatory response that causes the continuity of pathological changes and promotes disease progression [9]. Equally important is the role of oxidative stress, which, according to current scientific claims, is considered a significant pathophysiological mechanism for many diseases formation. Intensification of lipid peroxidation processes under the conditions of imbalance or insufficiency of the antioxidant system is the basis for excess free radicals accumulation with subsequent damage to the vascular wall and deepening ischemic changes in organs and tissues [3].

In our opinion, a detailed study of the abdominal pain syndrome in patients with a combination of CP and HD is interesting. This is primarily due to the fact that abdominal pain is a leading complaint in almost all patients with chronic pancreatic disease (CP). The mechanisms of the abdominal pain syndrome formation are diverse, however, the main role belongs to the focus of inflammation present in the parenchyma of the pancreas gland [4]. Activation and persistence of the inflammatory response certainly disrupts the equilibrium in the pro- and antioxidant (AO) system. With the imbalance of the antioxidant system, the most favorable conditions for triggering oxidative stress are formed, which in the long run significantly worsens the course of the disease and determines the severity of the clinical picture.

The purpose of the study was to identify key indices of inflammatory response and antioxidant defense system that are leading in the abdominal pain onset in patients with comorbid pathology (chronic pancreatitis and hypertension disease).

Materials and methods. In order to achieve this purpose, we have performed a comprehensive general clinical and laboratory examination of 102 patients with stage II CP and HD who were hospitalized at Khust Central District Hospital within 2017-2018. The diagnosis of CP was based on the positions of "Unified Clinical Protocol of Primary, Secondary (Specialized) Medical Assistance and Medical Rehabilitation. Chronic pancreatitis", approved by the MOH of Ukraine's order No. 638 of 10.09.2014;

HD – on the requirements of the “Unified Clinical Protocol for Primary, Emergency and Secondary (Specialized) Medical Care. Hypertension”, approved by the MOH of Ukraine’s order No. 384 of 24.05.2012, clinical recommendations for hypertension by the European Society of Hypertension (ESH) and the European Society of Cardiologists (ESC) (2013 and 2018).

We divided all patients into two groups. The basis for the division was the assessment of abdominal pain on a ten-point visual-analogue scale of pain (J. J. Bonica, 1990). Group I (n = 17) included patients who indicated pain intensity of five or less points; group II (n = 85) included patients with pain intensity of six or more points. Duration of CP in patients of group I was 5.71 ± 2.37 years, HD - 5.24 ± 2.01 years, in group II - 6.14 ± 3.04 years and 5.95 ± 2.79 years, respectively. The gender distribution of the study groups indicated a predominance of males in group I (n = 10 vs. n = 7) and female dominance in group II (n = 50 versus n = 35).

For the study of the pancreas exocrine secretion function, determination of the fecal elastase-1 (FE-1) level was performed by ELISA test (Pancreatic Elastase 1 Stool Test).

In order to diagnose the activity of inflammatory response markers in the examined patients, we measured the content of the following parameters in the patients’ blood: leukocytes, erythrocyte sedimentation rate (ESR), albumin, interleukin-4 (IL-4) and interleukin-6 (IL-6) (by means of enzyme-linked immunosorbent assay), fibrinogen (R.A. Rutberg's gravimetric method), α 1-antitrypsin (α 1-AT) (immunoturbidimetric method), and cortisol (enzyme immunoassay).

Out of a wide arsenal of known representatives of the antioxidant system, we determined the levels of such antioxidants (AO) in the blood of our patients with CP in combination with HD: glutathione peroxidase (GPO) by enzyme immunoassay, transferrin by immunoturbidimetric method, selenium (Se) by spectrofluorometry and zinc (Zn) by means of atomic absorption spectroscopy.

All studies were carried out in compliance with the main provisions of the World Health Association Declaration on Ethical Principles for Human Research (1964-2000), GCP (1996), the Council of Europe Convention on Human Rights and Biomedicine of 04.04.1997.

Data Processing. Statistical analysis of the study results was performed with a personal computer using Microsoft Office Excel and Statistica for Windows 10.0 software packages. The difference between the data was considered significant at $p < 0.05$. The statistical significance (p) of the mean values in the studied samples with normal distribution was assessed using the Student's test and, in the absence of signs of normal distribution, the Wilcoxon test.

Results of the study and their discussion. In all of our patients, the syndrome of abdominal pain was dominant, but not the only one in the clinical course. Thus, in addition to abdominalgia, dyspeptic syndrome, exocrine secretion failure syndrome, asthenovegetative and hypertension syndromes were recorded.

Concerning the level of blood pressure, it met the criteria of 1-2 degree arterial hypertension (in group I – $153.98 \pm 10.18 / 95.27 \pm 9.25$ mm Hg, in group II of patients – $155.35 \pm 9.49 / 93.53 \pm 9.17$ mm Hg) and did not differ significantly between groups (p (SAT) = 0.59; p (DAT) = 0.48).

It is well known that in the presence of chronic pancreatitis, special attention of clinicians is focused on the detection of exocrine hypofunction of the pancreas and the possibilities of its correction. In patients of our study groups, the exocrine secretion failure of the pancreas fluctuated on the border of moderate and mild degree according to the results of the analysis on the elastase-1 content in feces without statistically significant difference between the groups (in patients of group I - 158.94 ± 21.86 mcg / g, in the surveyed of group II - 157.60 ± 16.37 μ g / g (p = 0.77), fig. 1).

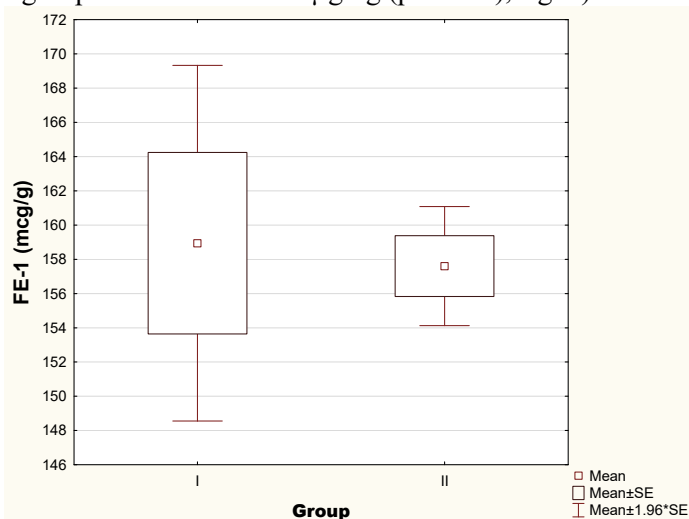


Fig. 1. Elastase-1 content in feces

Despite the lack of a significant difference between the results obtained, it is important to analyze the range of FE-1 content variations in patients of group I, whose subjective sensation of pain in the abdomen was less intense. In our opinion, this is primarily due to the fact that in patients with mild exocrine secretion failure, the focus of inflammatory acinocytes is lower, therefore, the intensity of abdominalgia is lower. In addition, in patients with more pronounced exocrine secretion failure, a lower intensity of abdominalgia is caused by more widespread fibrosis of the parenchymal organ tissue than in patients with mild exocrine dysfunction.

The next step in our study was to determine the levels of the laboratory parameters in the inflammatory response. In general, pain is one of the five classic signs of inflammation and its occurrence is the result of the direct or indirect action of activators, mediators of the inflammatory process on the sensitive nerve endings. The assessment of indices that reproduce the of the inflammatory response activity in the groups of patients examined by us represents the following features (table 1).

Table 1

Activity of inflammatory markers in the blood of patients with CP combined with HD

Indices	Group I (n=17)	Group II (n=85)	Difference reliability (p)
Leukocytes 4.0-9.0, g/L	6.10±1.91	9.36±2.69	0.7*10 ⁻⁵
ESR 2-15, mm/hour	6.06±2.79	10.53±5.54	0.002
Albumin 38-51, g/L	40.29±3.41	39.25±2.71	0.17
Fibrinogen 1.8-3.5, g/L	2.83±0.43	2.95±0.56	0.39
IL-4 0-4, pg/ml	2.01±0.16	1.91±0.22	0.11
IL-6 0-10, pg/ml	11.71±1.50	11.99±1.62	0.52
α1- antitrypsin 0.9-2.0, g/L	1.41±0.16	1.54±0.25	0.04
Cortisol in the morning 190-690, nmol/L	898.82±250.34	975.48±222.65	0.21

Visual data indicate a pronounced activity of inflammatory response in patients of group II, whose intensity of abdominal pain was higher than in patients of group I. This was confirmed by the presence of statistically significant differences between the groups in terms of: ESR ($p = 0.002$), leukocyte level ($p = 0.7 * 10^{-5}$) and α1-AT ($p = 0.04$). Therefore, we can assume that these laboratory markers of inflammation are active participants in the formation of pain. Increased leukocyte levels and acceleration of ESR are a direct consequence of the activation and synthesis of a number of inflammatory mediators. As for the involvement of α1-AT in the cascade of the inflammatory response, its role is also unambiguous, as it is one of the most active inhibitors of lysosomal proteases released from granules of activated and damaged polymorphonuclear leukocytes, as well as a regulator of leukocyte migration and leukocyte balance. Although the levels of the interleukins under study did not manage to achieve cross-group differences, however, in Group I, there was a tendency for more active involvement of anti-inflammatory IL-4 and lower concentration of pro-inflammatory IL-6, which also explains the lower severity of abdominal pain.

Harmony and consistency in the system of prooxidants and AO provides homeostasis of the body. In the presence of chronic inflammation and in conditions of comorbidity, the balance of this system is broken. This may be due to both the excessive amount of oxidants and the insufficient capacity of the AO. In our study, we tried to determine the activity of the antioxidant system in patients with CP associated with HD, depending on the severity of abdominal pain. The results obtained are summarized in table 2.

Table 2

Level of antioxidants in the blood of patients with a combination of CP and HD

Indices	Group I (n=17)	Group II (n=85)	Difference reliability (p)
Glutathione peroxidase 12.5-200, ng/ml	51.46±10.84	43.97±10.58	0.009
Selenium 23-190, μg/L	72.53±15.59	61.91±18.58	0.03
Zinc 543-1130, μg/L	874.18±222.06	714.42±188.67	0.003
Transferrin 2.0-3.6, g/L	2.34±0.29	2.33±0.24	0.89

The results indicate statistically significant higher glutathione peroxidase activity in patients of group I. The involvement of transferrin in the elimination of abusive stress in patients of the both groups was almost the same, so we cannot speak about the true significance of this AO in the development of pain syndrom. Let us dwell on the analysis of the Se and Zn effect on the severity of abdominal pain. One of the properties of selenium, as AO, is its ability to accumulate in the focus of ischemia, which necessarily arises under the conditions of oxidative stress, and to produce active membranous resistance. The antioxidant property of zinc is related to its ability to inhibit the formation of H₂O₂ and hydroxyl radicals.

Naturally, the most informative way is to determine the concentration of trace elements in the tissue of the pancreas, but such research is invasive, which limits the possibility of its use in daily practice. Instead, determining the level of essential trace elements studied in the blood is a direct reproducing the mean value of their recent entry into the human body with food. In addition, the pancreas belongs to a

group of parenchymal organs that have the ability to deposit both Se and Zn. Both microelements under study are structural components of potent AO of enzymatic origin (Se - glutathione peroxidase, Zn - superoxide dismutase). Due to the higher content of Se in the blood of group I patients in comparison with the results obtained in patients of group II, the level of GPO is also naturally higher. This is due to the fact that four Se atoms are required for the synthesis of one GPO molecule. The role of GPO in multifactor protection of the whole body from the products of free radical peroxidation is leading. And this is confirmed by a number of scientific studies.

In our opinion, the lower concentration of Se, Zn, GPO in the blood of patients of group II, unlike the examined group I, causes insufficient ability of the antioxidant protection system to suppress oxidative stress. Therefore, due to insufficient intensity regulation of radical formation, patients will subjectively have a more pronounced level of abdominalgia, which will significantly impair the quality of their life and contribute to the deepening of pathological changes.

Our statements clearly correlate with the scientific view of prof. L.S. Babinets, who also indicates the dominance of deep deficiency of antioxidant system in patients with comorbid pathology (CP and osteoarthritis) [1]. A study by K. Venardos et al, performed in rats, demonstrated that Se deficiency contributes to damage of the endothelium of the vascular wall and myocardium by enhancing protein and lipid peroxidation [8]. B. N. Girish et al assessed the content of zinc in patients with CP and studied their relationship with exocrine and endocrine failure of pancreas. The study involved 101 patients with CP and 113 healthy controls. The mean Zn level was significantly lower in patients with CP compared to the group of healthy persons [5]. According to prof. T.M. Khristich for the treatment of abdominal pain in CP it is promising to use antioxidants that are able to actively inhibit oxidation, block catalysts of free radical oxidation, activate antiradical enzymes of the protection system [4].

Thus, as a result of the study, we have managed to determine which indices of inflammatory response and AO system most actively affect the pain intensity in patients with a combination of CP and HD, which will permit to apply comprehensive pathogenetically justified therapy with the possibility of reducing the abdominal pain intensity in clinical practice.

Conclusions

1. Subjective perception of abdominalgia in chronic pancreatic injury depends on the features of the inflammatory response course and homeostasis of the antioxidant system.
2. Among laboratory parameters that identify the of the inflammatory response activity, leukocytes, erythrocyte sedimentation rate, and α 1-antitrypsin play a leading role in the severity of pain.
3. Glutathione peroxidase, selenium and zinc are the key laboratory parameters of the antioxidant group that significantly affect the abdominal pain intensity in patients with chronic pancreatitis and hypertension disease.

Prospects of further research are as follows. In order to deepen and improve the knowledge gained during this study, we consider it necessary to further increase the number of patients with comorbid pathology in the study groups and to expand the spectrum of diagnostic search with involvement of more laboratory parameters.

References

1. Babinets LS, Halabitska IM, Maievska TH. Zovnishnyosekretorna nedostatnist pidshlunkovoyi zalozy ta dysbalans systemy prooksydanty-antyoksydanty pry pervynnomu osteoartrozi z komorbidnymy stanamy. 2017; (3):22-25. doi: 10.11603/1811-2471.2017.v1.i3.8099 [In Ukrainian]
2. Vyun TI. Mekhanizmy realizatsii osteopenichnykh staniv u patsientiv iz sukupnym perebihom khronichnoho pankreatytu ta hipertoničnoyi khvoroby. Visnyk klubu pankreatolohiv. 2018; 4(41):36-41. [In Ukrainian]
3. Sulejmanova AD, Ljubina EN. Rol mineralnykh veshchestv v regulyatsii processov svobodnoradikalnogo oksileniya v organizme. Actual science. 2016; 2(1):7-8. [In Russian]
4. Khrystych TN, Hontsariuk DO. Dyferentsiyna diahnostyka abdominalnogo bolyovoho syndromu pry khronichnomu pankreatyti. Zdorovya Ukrayiny. 2018; 1(47):57-9. [In Ukrainian]
5. Girish BN, Rajesh G, Vaidyanathan K, Balakrishnan V. Zinc/copper ratio: a predictor of pancreatic function in chronic pancreatitis? Trop Gastroenterol. 2016 Jan-Mar; 37(1):19-26.
6. De la Iglesia D, Vallejo-Senra N, López-López A, Iglesias-García J, Lariño-Noia J, Nieto-García L, et al. Pancreatic exocrine insufficiency and cardiovascular risk in patients with chronic pancreatitis: A prospective, longitudinal cohort study. J Gastroenterol Hepatol. 2019 Jan;34(1):277-83. doi: 10.1111/jgh.14460.
7. Nowińska P, Kasacka I. Changes in the pancreas caused by different types of hypertension. Acta Biochim Pol. 2017; 64(4):591-5. doi: 10.18388/abp.2017_1504.
8. Venardos KM, Kaye DM. Myocardial Ischemia-Reperfusion Injury, Antioxidant Enzyme Systems, and Selenium: A Review. Current Medical Chemistry. 2016; 42(23):1025-32.
9. Watanabe T, Kudo M, Strober W. Immunopathogenesis of pancreatitis. Mucosal Immunol. 2017 Mar; 10(2):283-98. doi: 10.1038/mi.2016.101.

Реферати

**РОЛЬ МАРКЕРІВ ЗАПАЛЬНОЇ ВІДПОВІДІ
ТА АНТИОКСИДАНТНОГО ЗАХИСТУ
У ПАТОГЕНЕЗІ АБДОМЕНАЛГІЇ У ПАЦІЄНТІВ
ІЗ ХРОНІЧНИМ ПАНКРЕАТИТОМ,
КОМОРБІДНИМ ІЗ ГІПЕРТОНІЧНОЮ
ХВОРОБОЮ**

Архій Е.Й., Прилипко Л.Б., Горленко О.М.
Москаль О.М.

Сучасна медицина поступово втрачає мононозологічний характер перебігу захворювань, і все помітніше стає тенденція до поліморбідності. Поєднання мультиорганичних змін негативно відбивається на клінічному перебігу всіх захворювань. Досить частим поєднанням в практиці клініцистів є поєднання хронічного панкреатита і гіпертонічної хвороби. Мета нашого дослідження полягала у визначенні впливу лабораторних параметрів системи антиоксидантного захисту та маркерів запальної реакції на інтенсивність абдоменалгії у хворих на хронічний панкреатит в поєднанні з гіпертонічною хворобою. Результати нашого дослідження є доповненням фундаментальних знань патогенезу поєднаної патології, а саме елементу формування суб'єктивного параметра - абдоменалгії. Доведено, що лейкоцити, ШОЕ, α 1-антитрипсин, глутатионпероксидаза, селен і цинк є ключовими параметрами формування болю в животі. На основі рівня активності зазначених лабораторних параметрів рекомендовано розширювати базовий комплекс медикаментозних заходів з метою прискорення нівелювання абдоменалгії.

Ключові слова: хронічний панкреатит, гіпертонічна хвороба, абдоменалгія, маркери запалення, антиоксиданти.

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**РОЛЬ МАРКЕРОВ ВОСПАЛИТЕЛЬНОГО
ОТВЕТА И АНТИОКСИДАНТНОЙ ЗАЩИТЫ
В ПАТОГЕНЕЗЕ АБДОМЕНАЛГИИ
В ПАЦИЕНТОВ С ХРОНИЧЕСКИМ ПАНКРЕАТИТОМ,
КОМОРБИДНЫМ С ГИПЕРТОНИЧЕСКОЙ
БОЛЕЗНЬЮ**

Архий Э. Й., Прилипко Л. Б., Горленко О. М.
Москаль О. Н.

Современная медицина постепенно теряет мононозологический характер течения заболеваний, и все заметнее становится тенденция к полиморбидности. Сочетание мультиорганных изменений негативно отражается на клиническом течении всех заболеваний. Достаточно частым сочетанием в практике клиницистов является сочетание хронического панкреатита и гипертонической болезни. Цель нашего исследования состояла в определении влияния лабораторных параметров системы антиоксидантной защиты и маркеров воспалительной реакции на интенсивность абдоменалгии у больных хроническим панкреатитом в сочетании с гипертонической болезнью. Результаты нашего исследования являются дополнением фундаментальных знаний патогенеза сочетанной патологии, а именно элемента формирования субъективного параметра – абдоменалгии. Доказано, что лейкоциты, СОЭ, α 1-антитрипсин, глутатионпероксидаза, селен и цинк являются ключевыми параметрами формирования боли в животе. На основе уровня активности указанных лабораторных параметров рекомендовано расширять базовый комплекс медикаментозных мероприятий с целью ускорения нивелирования абдоменалгии.

Ключевые слова: хронический панкреатит, гипертоническая болезнь, абдоменалгия, маркеры воспаления, антиоксиданты.

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O.M. Bilovol, I.I. Kniazkova, M.V. Bogun, N.V. Kuzminova¹, V.I. Korneichuk, A.O. Gavrylyuk¹

Kharkiv National Medical University, Kharkiv

¹National Pirogov Memorial Medical University, Vinnytsya

**EFFICACY OF PHARMACOLOGICAL CORRECTION OF MAGNESIUM DEFICIENCY
IN PATIENTS WITH ARTERIAL HYPERTENSION AND TYPE 2 DIABETES**

e-mail: sskripka72@gmail.com

The purpose of the study was to assess the efficacy of therapy with addition of magnesium orotate (MO) in patients (pts) with AH and type 2 DM with hypomagnesemia. The total of 62 pts with AH and DM with hypomagnesemia were examined. After registration of the baseline data, baseline therapy was prescribed to all pts, 32 of them (group 1) obtained an additional MO for 8 weeks and 28 pts were included in the comparison group. It was found that antihypertensive efficacy had been more significant in group 1. In group 1 showed significant positive changes in lipid and carbohydrate metabolism and along with an improvement in the quality of life. Thus, an addition of MO in the complex therapy of pts with AH and DM with hypomagnesemia increases the efficacy of antihypertensive therapy, positively affects glucometabolic parameters and the quality of life in this category of patients.

Keywords: magnesium deficiency, arterial hypertension, type 2 diabetes mellitus, daily blood pressure monitoring, treatment.

The work is a fragment of the research project "Development of methods for early diagnosis and drug prevention of fibrosis processes in patients with comorbid pathology (hypertension and type 2 diabetes mellitus) based on the assessment of cardiohemodynamics and renal function", state registration No. 0120U102062.

Significant data have been collected on high prevalence of arterial hypertension (AH) in patients with type 2 diabetes mellitus (type 2 DM) [2]. The combination of hypertension and type 2 DM leads to the mutual influence on the course of the diseases, nature and severity of complications, often aggravates diagnosis, determines a specific choice of drug therapy. It has been demonstrated that the combination of AH and type 2 DM is associated with earlier disability of this cohort of patients, increased risk of development of cardiovascular complications and higher mortality rate compared to the whole population [6].

In conditions of high comorbidity, researchers have been recently focused on studying the role of magnesium deficiency in the development and progression of AH in patients with type 2 DM. It has been demonstrated that magnesium dyshomeostasis can affect vascular tone, endothelial function, lipid metabolism, platelet aggregation, coagulation system and cardiac conduction system, what makes this problem topical for practical public health. It is especially important at the initial stages of the disease, as it helps to prevent or slow down the appearance of vascular complications. It has been established that organic magnesium salts are more effective in correction of magnesium deficiency, especially in combination with orotic acid [1]. One of the widely used in clinical practice drugs for the correction of magnesium deficiency is magnesium orotate, which has a long history of use in cardiology [7]. Thus, it is necessary to study the influence of magnesium deficiency on the pathogenetic mechanisms of the disease progression with a combination of AH and type 2 DM. There is very little data on the advisability of administration of magnesium preparations as a part of combination AH therapy in patients with type 2 DM.

The purpose of the study was to evaluate the influence of magnesium deficiency pharmacological correction on the efficacy of antihypertensive therapy, glucometabolic parameters and quality of life in patients with AH and type 2 DM with hypomagnesemia.

Materials and methods. The total of 60 patients were examined (17 females and 43 males, mean age 52.3 ± 2.7 years) with stage II, grade 2 AH and concomitant type 2 DM (moderate severity, subcompensation stage) with hypomagnesemia. The diagnosis of AH was made in accordance with the recommendations of the European Society of Hypertension and the European Society of Cardiology (ESH / ESC, 2018). Diagnosis of type 2 DM was made according to the general recommendations of the European Association for the Study of Diabetes (EASD, 2018). The study included patients with serum magnesium levels <0.7 mmol/l.

The control group included 20 practically healthy volunteers with an average age 52.7 ± 2.5 years. All examined persons signed an informed consent to participate in the study.

All examined persons underwent general clinical examination, physical examination, office BP, heart rate (HR) were measured, clinical analyses of blood and urine were made, fasting blood serum (FBS), levels of glycosylated hemoglobin (HbA1c) in whole blood, insulin, lipid profile indices (total cholesterol - TC, low density lipoprotein cholesterol - LDL-C, high density lipoprotein cholesterol - HDL-C, triglycerides - TGs) were determined, insulin resistance was evaluated by the HOMA-IR index.

Daily blood pressure monitoring (DBPM) was performed using "ABPM-02" equipment (Meditech, Hungary). The following indicators were determined: daytime, nighttime, daily average (24 hours) of systolic (SBP) and diastolic (DBP), HR.

For the preliminary diagnosis of magnesium deficiency, the questionnaire of Trace Element Institute for UNESCO was used. The test results were interpreted as follows: 0-9 points - no magnesium deficiency, 10-19 - risk group for magnesium deficiency, 20-29 - moderate magnesium deficiency, 30-39 - magnesium deficiency, 40-56 - severe magnesium deficiency. The concentration of magnesium in blood serum was determined with the automatic biochemical analyzer "Humalyzer 2000" (Germany, the limits of normal fluctuations - 0.85-1.2 mmol/l).

The questionnaire SF-36 was used to assess the quality of life (QL). The questionnaire includes physical and mental health. The parameters of physical health (FH) include: physical activity, role-physical functioning, pain and general health. The parameters of mental health (MH) were also taken into account: vitality, social activity, role emotional functioning, as well as the comparison of patients' health (CH). All answers are standardized so that 1 corresponds to the best QL and 5 to the worst one. The total number of points was calculated by summing up all the answers followed by the transformation to a scale from 0 to 100, where a higher score indicates lower QL.

After registration of the initial data, the patients were randomly divided into 2 groups. Basic therapy and magnesium orotate (32.8 mg of magnesium) were administered to 32 patients of the main group (group 1) - Magnerot (Verwag Pharma, Germany) 500 mg 3 times a day for 8 weeks. The comparison group (group 2) included 28 people receiving basic therapy, which included antihypertensive therapy (combination of lisinopril, carvedilol in individually selected doses), antihypertensive therapy (metformin + gliclazide), statins, antiplatelet therapy. These groups of patients were comparable by age, sex, AH duration and type 2 DM, office BP, state of carbohydrate metabolism and presence of magnesium metabolism disorders.

All patients successfully completed the study according to the protocol. The follow up study was performed after 8 weeks of treatment. Side and undesirable effects during this period are not reported.

Mathematical computer processing of the results of the study was carried out using the software package "Statistica 9.0" (Statsoft Inc, USA). Mean value (M), variance, standard deviation, median (m), probability and significance level (p) were calculated. The differences were considered significant at the

level of statistical significance $p < 0.05$. To evaluate the correlation between the indicators, the method of correlation analysis with the calculation of Pearson correlation coefficients (at normal distribution) and Spearman correlation coefficients (at distribution different from normal) was used.

Results of the study and their discussion. During testing for identification of clinical signs of magnesium deficiency at baseline in patients of the main group and the comparison group, moderate magnesium deficiency was found in 84.4% (27 people) and 85.7% (24 people); signs of magnesium deficiency - in 15.6% (5 people) and 14.3% (4 people) of patients, respectively. The differences were statistically significant compared with the control group - $p < 0.05$. At baseline, a decrease in serum magnesium levels to 0.64 ± 0.06 mmol/l in patients of the 1st group and to 0.65 ± 0.05 mmol/l in the 2nd group (versus 0.95 ± 0.03 mmol/l in the control group) was found. An inverse correlation was established between the serum magnesium concentration and the number of test points for clinical signs of magnesium deficiency ($r = -0.45$; $p < 0.05$).

After the course of therapy, an increase of serum magnesium concentration to 0.98 ± 0.05 mmol/l was observed in patients of group 1. In addition, by comparison of the values of this indicator with the data from a group of healthy individuals, no significant differences were found, what, apparently, shows the compensation of magnesium deficiency in this patient population. Moreover, in patients of group 2, the magnesium content in the blood serum was 0.67 ± 0.03 mmol/l, i.e. it did not change significantly. The results are consistent with the previous studies [3], which showed that administration of magnesium preparations significantly affects the magnesium content in the blood and allows to maintain its normal concentration for a long time.

On the background of the therapy, a positive time change of the main indicators of lipid metabolism in patients with AH and type 2 DM of both groups (Table 1) was observed. A significant decrease of the level of TC, triglycerides and LDL-C was observed with a statistically significant increase in the level of HDL-C.

Table 1

Changes in glucometabolic parameters in patients with AH and type 2 DM in the therapy time course (M \pm m)

Indicators	Group 1 (n=32)		Group 2 (n=28)	
	Before treatment	After treatment	Before treatment	After treatment
TC, mmol/l	5.64 \pm 0.16	5.0 \pm 0.08**	5.63 \pm 0.18	5.2 \pm 0.08*
LDL-C, mmol/l	3.4 \pm 0.18	2.4 \pm 0.12**	3.5 \pm 0.17	2.8 \pm 0.11**
HDL-C, mmol/l	1.08 \pm 0.06	1.23 \pm 0.03*	1.09 \pm 0.05	1.11 \pm 0.03*
TG, mmol/l	1.98 \pm 0.07	1.74 \pm 0.06**	1.97 \pm 0.07	1.78 \pm 0.05**
FBS, mmol/l	6.2 \pm 0.13	5.2 \pm 0.07***	6.2 \pm 0.12	5.4 \pm 0.07***
HbA1c, %	6.1 \pm 0.12	5.1 \pm 0.10***	6.2 \pm 0.13	5.4 \pm 0.11***
Insulin, mcU/ml	17.1 \pm 0.43	14.3 \pm 0.41**	17.3 \pm 0.45	15.5 \pm 0.40**
HOMA-IR, mcU/ml	4.9 \pm 0.19	3.5 \pm 0.16**	4.9 \pm 0.20	3.9 \pm 0.15**

Notes: 1. * – significance of differences compared to the original data; 2. * – $p < 0.05$; 3. ** – $p < 0.01$; 4. *** – $p < 0.001$.

At the same time, the patients in the main group had a more pronounced decrease in TC ($p < 0.01$), LDL-C ($p < 0.05$), as well as a significant increase in the antiatherogenic fraction of HDL-C ($p < 0.05$) compared to the patients of the comparison group. These time change appears to be the result of a direct action of magnesium on the process of atherogenesis, which helps to reduce the risk of micro- and macroangiopathies [5].

On the background of the conducted therapy, a significant improvement of the parameters of the carbohydrate profile was observed in patients of both groups compared to the baseline data (Table 1). At the same time, more significant changes in FBS, HbA1c, fasting insulin level, HOMA-IR index ($p < 0.05$) were observed in patients of the main group. The data obtained confirm the effect of magnesium on various units of a single pathological mechanism – insulin resistance [4]. Following the correction of magnesium levels in patients with AH and type 2 DM, there was an increase of insulin sensitivity (a significant decrease in the HOMA-IR index) and an improvement in metabolic control (a significant decrease in FBS, HbA1c) in contrast to group 2.

On the background of treatment in patients of group 1 a greater reduction of office BP was observed: SBP by 28.9 ± 3.6 mm Hg ($p < 0.001$) and DBP by 16.4 mm Hg. ($p < 0.001$) compared with group 2 by 18.5 mm Hg ($p < 0.01$) and 9.1 mm Hg ($p < 0.05$) respectively (Table 2). At the same time, the target BP level was reached by 93.8% of patients in group 1 and 89.3% of patients in the comparison group.

According to DMBP after 8 weeks of treatment, the patients in the main group showed a significantly more pronounced decrease of maximal SBP at day and maximal SBP and DBP at night than in the comparison group (table 2).

Change of the indicators of office BP and DBPM under the therapy (M±m)

Indicator	Group 1 (n=32)		Group 2 (n=28)	
	Before treatment	After treatment	Before treatment	After treatment
1	2	3	4	5
Sphygmomanometry:				
SBP, mm Hg	156.5±4.5	127.6±3.4***	157.2±4.6	138.7±3.1**
DBP, mm Hg	95.7±3.6	79.3±2.6***	96.1±3.2	87.0±2.5*
DBPM				
SBP (24), mm Hg	148.5±3.3	130.6±2.4*	149.3±3.5	138.1±2.3*
DBP (24), mm Hg	94.5±2.3	80.9±2.1*	93.9±2.3	85.5±2.1*
TISBP (24), %	69.5±7.9	15.9±5.9**	69.3±7.2	22.3±6.5**
TIDBP(24), %	59.7±7.1	12.1±5.8**	59.5±7.2	16.3±5.1**
SBP (D), mm Hg	148.3±3.3	126.7±2.9*	140.8±3.3	131.8±2.4*
DBP(D), mm Hg	95.9±2.5	80.3±2.3*	96.4±2.3	85.9±3.5*
TISBP(D), %	62.5±6.6	19.4±5.7**	63.3±7.1	23.3±5.2**
TIDBP(D), %	57.2±8.8	15.1±7.1*	58.1±8.5	19.8±7.1**
SBP(N), mm Hg	140.7±3.3	122.9±3.1*	141.5±3.5	129.3±3.3*
DBP(N), mm Hg	89.9±2.3	78.3±2.1*	85.1±3.6	83.3±2.3*
TISBP (N), %	71.3±9.8	11.9±7.8*	71.6±9.7	15.7±9.3*
TIDBP (N), %	52.4±8.3	10.1±8.1*	52.5±8.5	12.3±8.6*

Notes: 1. * – significance of differences compared to the original data; 2. * – p<0.05; 3. ** – p<0.01; 4. *** – p<0.001.

After treatment, an improvement in the indicators characterizing QL in both groups of patients with AH and type 2 DM (Table 3) was observed.

Table 3

Time change of life quality parameters for patients with AH and type 2 DM in the course of treatment (M±m)

SF-36 questionnaire scales, points	Observation period	Control group	Group 1 (n=32)	Group 2 (n=28)
Physical activity	At baseline	86.9±2.6	63.4±2.9	66.2±2.8
	After treatment		84.6±2.4*	75.5±2.5*
The role of physical problems in disability	At baseline	73.6±2.5	48.3±2.5	47.9±2.7
	After treatment		72.0±2.3*	62.1±2.5*
Body pain	At baseline	76.9±3.8	36.9±3.6	37.1±3.5
	After treatment		75.4±3.3*	58.7±3.3*
General health perception	At baseline	82.1±3.7	55.3±3.8	55.8±3.7
	After treatment		76.8±3.6*	66.9±3.3*
Vitality	At baseline	69.1±2.1	60.5±2.5	60.1±2.6
	After treatment		67.3±2.1*	64.7±2.5*
Social activity	At baseline	82.3±3.3	66.8±3.5	66.9±3.6
	After treatment		81.1±3.3*	76.7±3.5*
The role of emotional problems in disabilities	At baseline	69.5±3.1	42.4±2.9	43.5±2.7
	After treatment		69.5±2.5*	65.7±2.3*
Mental health	At baseline	73.7±3.1	57.1±3.3	57.5±3.4
	After treatment		71.3±2.8*	61.9±2.9*
The health compared with the previous year	At baseline	61.3±3.3	60.8±3.5	60.4±3.6
	After treatment		63.3±3.0	62.7±3.1

Notes: 1. * – significance of differences compared to the original data; 2. * – p<0.05.

Analysis of the obtained data showed that in patients of group 1, on the background of basic therapy with addition of magnesium orotate, a significant increase in QL was observed on almost all scales characterizing physical (physical activity, role of physical problems in disabilities, body pain, general perception of health) and mental health (vitality, social activity, mental health). In patients of group 2, a significant improvement was observed only on the scales of physical health (physical activity, role of physical problems in disability, body pain, general perception of health). Moreover, on the scales characterizing mental health (vitality, social activity, mental health) an observed positive time change was unreliable.

It has been demonstrated that magnesium deficiency can play an important role in the development of both AH [1] and DM 2 [5]. It was shown that the elimination of magnesium deficiency in the blood of patients with AH is accompanied by an increase of the efficacy of antihypertensive therapy [7]. However,

the effect of the pharmacological correction of magnesium deficiency with comorbidity of AH and type 2 DM on the progression of both diseases and the efficacy of the therapy remains poorly studied. The data obtained indicate that an inclusion of magnesium orotate in the complex therapy of patients with AH and type 2 DM with hypomagnesemia is accompanied by a significantly larger decrease in maximum values of SBP and DBP within 24 hours, a decrease in the variability of BP, which, apparently, is associated with a stimulating effect of magnesium orotate on the endogenous synthesis of nitric oxide and endothelial function [7]. On the background of hypomagnesemia correction, a significant improvement of indices of carbohydrate metabolism, an additional more pronounced decrease of atherogenic lipoprotein fractions in patients taking magnesium orotate, as well as a significant increase of antiatherogenic fraction of HDL, what reflects a direct effect of magnesium on the process of atherogenesis and indirect effect by a decrease of the degree of insulin resistance, have been noted. It allowed to achieve more significant results in the improvement of the quality of life of patients of the main group. The results of the study demonstrated perspectiveness of further clinical trials, in which attention would be paid to the shown changes in central hemodynamics, indices of lipid metabolism and carbohydrate blood profile in patients with comorbidity of AH and type 2 DM.

Thus, an inclusion of magnesium orotate in the therapeutic complex in patients with AH and type 2 DM with hypomagnesemia increases the efficacy of antihypertensive therapy, improves BP daily profiles, positively affects glucometabolic parameters and quality of life in this category of patients.

Conclusions

1. Addition of magnesium orotate to the combination therapy of patients with AH and type 2 DM with hypomagnesemia allows to achieve the target levels of magnesium in the blood serum, increase efficacy of lipid-lowering therapy and hypoglycemic drugs.

2. On the background of the combination therapy for patients with AH, type 2 DM and hypomagnesemia, it was found that antihypertensive efficacy had been more significant in the group receiving additional magnesium orotate.

3. The inclusion of magnesium orotate in the complex treatment of patients with AH and type 2 DM with hypomagnesemia for 8 weeks allows to improve the quality of life of patients on all scales of the questionnaire. In patients of the comparison group, a significant improvement was observed only on the physical health scales, while on the scales of mental health, the observed positive time change was unreliable.

References

- Eremenko NN, Shikh EV, Serebrova SY, Sizova ZM. Comparative study of the bioavailability of magnesium salts. *Drug Metab Pers Ther.* 2019; 34(3). pii: /j/dmdi.2019.34.issue-3/dmpt-2019-0004/dmpt-2019-0004.xml. doi: 10.1515/dmpt-2019-0004.
- Gosmanov AR, Lu JL, Sumida K. Synergistic association of combined glycemic and blood pressure level with risk of complications in US veterans with diabetes. *J Hypertens.* 2016; 34:907–913.
- Gromova OA, Torshin IY, Kobalava ZD, Nazarenko AG. Systematic Analysis of the Roles of Trace Elements in the Prevention and Treatment of Chronic Heart Failure. *Kardiologija.* 2019; 59(6):26–34. doi: 10.18087/cardio.2019.6.n683.
- Kostov K. Effects of Magnesium Deficiency on Mechanisms of Insulin Resistance in Type 2 Diabetes: Focusing on the Processes of Insulin Secretion and Signaling. *Int J Mol Sci.* 2019; 20(6). pii: E1351. doi: 10.3390/ijms20061351.
- Severino P, Netti L, Mariani MV, Maraone A, D'Amato A, Scarpati R, Infusino F, Pucci M, Lavalle C, Maestrini V, Mancone M, Fedele F. Prevention of Cardiovascular Disease: Screening for Magnesium Deficiency. *Cardiol Res Pract.* 2019; 2019:4874921. doi: 10.1155/2019/4874921.
- Song J, Sheng CS, Huang QF, Li LH, Ma CS, Guo XH, Ji LN, Wang JG. Management of hypertension and diabetes mellitus by cardiovascular and endocrine physicians: a China registry. *J Hypertens.* 2016; 34:1648–53.
- Torshin IY, Gromova OA, Kalacheva AG, Oshchepkova EV, Martynov AI. Meta-analysis of clinical trials of cardiovascular effects of magnesium orotate. *Ter Arkh.* 2015; 87(6):88–97. doi: 10.17116/terarkh201587688–97.

Реферати

ЕФЕКТИВНІСТЬ ФАРМАКОЛОГІЧНОЇ КОРЕКЦІЇ ДЕФИЦИТУ МАГНІЮ У ХВОРИХ НА АРТЕРІАЛЬНУ ГІПЕРТЕНЗІЮ ТА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ

Біловол О.М., Князькова І.І., Богун М.В.,
Кузьміна Н.В., Корнійчук В.І., Гаврилюк А.О.

Метою дослідження було оцінити ефективність терапії з додаванням оротату магнію у пацієнтів з АГ і ЦД 2 типу з гіпомagneмією. Обстежено 60 хворих з АГ та ЦД 2 типу з гіпомagneмією. Після реєстрації вихідних даних усім пацієнтам призначалась базисна терапія, з яких 32 пацієнтам (1 група) додатково – оротат магнію протягом 8 тижнів і 28 пацієнтів склали

ЭФФЕКТИВНОСТЬ ФАРМАКОЛОГИЧЕСКОЙ КОРРЕКЦИИ ДЕФИЦИТА МАГНИЯ У БОЛЬНЫХ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ И САХАРНЫМ ДИАБЕТОМ 2 ТИПА

Беловол А.Н., Князькова И.И., Богун М.В., Кузьмина
Н.В., Корнейчук В.И., Гаврилюк А.А.

Целью исследования было оценить эффективность оротата магния у пациентов с артериальной гипертензией (АГ) и сахарным диабетом (СД) 2 типа с гипомagneмией. Исследовано 60 больных с АГ и СД 2 типа с гипомagneмией. После регистрации исходных данных всем больным назначалась базисная терапия, из которых 32 пациентам (1 группа) дополнительно назначали оротат магния на протяжении 8 недель

групу порівняння. Встановлено, що антигіпертензивна ефективність терапії була більшою в 1 групі. Визначено більш виражену позитивну динаміку показників ліпідного обміну та вуглеводного профілю, показників якості життя у пацієнтів 1 групи. Таким чином, включення в терапевтичний комплекс оротату магнію пацієнтам з АГ і ЦД з гіпомагніємією підвищує ефективність гіпотензивної терапії, позитивно впливає на глюкометаболічні параметри та якість життя у цієї категорії хворих.

Ключові слова: дефіцит магнію, артеріальна гіпертензія, цукровий діабет 2 типу, добовий моніторинг артеріального тиску, лікування

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и 28 пациента составили группу сравнения. После лечения отмечено, что у пациентов 1 группы антигипертензивная эффективность оказалась более выраженной; наблюдались более значимые положительные изменения показателей липидного и углеводного обмена и улучшением показателей качества жизни. Таким образом, включение оротата магния к базисной терапии у пациентов с АГ и СД 2 типа с гипомagneмией повышает эффективность гипотензивной терапии, положительно влияет на глюкометаболические параметры и качество жизни у этой категории больных.

Ключевые слова: дефицит магния, артериальная гипертензия, сахарный диабет 2 типа, суточный мониторинг артериального давления, лечение

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K.M. Vergeles, L.V. Horokhova¹, M.A. Kozlovets¹, I.A. Holovanova¹, O.L. Sokolovsky¹,
A.O. Gavrilyuk, R.G. Zharlinska, T.M. Vergeles
National Pirogov Memorial Medical University, Vinnytsia, ¹Zhytomyr Ivan Franko State
University, Zhytomyr, ²Ukrainian Medical Stomatological Academy, Poltava

HEALTHCARE SYSTEM REFORMING IN UKRAINE IN THE CONTEXT OF PRIVATE HEALTH CARE SYSTEM EXPANSION

e-mail: allahavryliuk25@gmail.com

The analysis and assessment of the peculiarities of practical implementation of the health care system reform in the context of private health care system expansion in the political decentralization processes and the local self-government reform in Ukraine was performed in the article. The conditions and features of the implementation of the National Health Reform Strategy for Ukraine 2015-2025 in terms of ensuring the effective organization of the health care system, in particular in the context of private health care system expansion have been studied. Prospects for further research on the conditions and ways to improve the system of medical care in Ukraine were proposed.

Key words: political decentralization, medical reform, health care system, private health care system, health expenditures.

The study is a fragment of the research project "Early diagnosis of dysplastic, metaplastic and neoplastic changes in the pathology of the gastrointestinal tract, respiratory, urogenital and neuroendocrine system", state registration No. 0117U000001.

Ukrainian society has once again found itself at the epicenter of modern reforms in various fields. The relevance of the studied problem is that every citizen, as well as the state as a whole, became participants in reforms at different levels. In August 2014, the processes of political decentralization led to the initiation by the Ministry of Health to develop the National Health Reform Strategy for Ukraine 2015-2025 [9]. The strategy outlined the main directions of reform in the field of health care and service provision, financing of the health care system, management and pharmaceuticals. Decentralization and grassroots initiatives, according to strategic plans, should become a new reality in the branch, and the Ministry of Health of Ukraine should not solve all the problems of the medical sphere alone [8]. In addition, public and professional medical organizations must be aware of their responsibility for the future of the field in which they are engaged or where they have experience. The importance of the study is evidenced by its relevance, which confirms the significant number of available publications [1, 4, 5, 9, 11], as well as the hope of Ukrainian citizens that we have every chance to become a country without broken roads, abandoned villages and destroyed houses. It is possible to achieve these results, but to do this, not only communities need to believe in reform, gain power, resources and join responsible self-government, and the state must not only "de jure" prescribe all the processes, but also try to implement them "de facto" as much as possible.

The purpose of the study was to study and analyze the specifics of the health care system reforming and its implementation in the context of private health care system expansion under the conditions of political decentralization in Ukraine.

Materials and methods. In the course of the study, the authors used the materials and methodology of the World Bank to determine the advantages and disadvantages in the public services provision, adapted to the conditions of the Ukrainian health care system, which is based on a survey on health issues in different regions of Ukraine. In addition, on the basis of statistical data of decentralization monitoring in

the health care field, the analysis and comparison of the health care budget of Ukraine was carried out, and the implementation of the National Health Reform Strategy for Ukraine at the present stage was studied.

Results of the study and their discussion. In the current context of local self-government reform, the state is increasingly delegating powers to local authorities, including the issue of improving the efficiency of health care and public health. The National Health Reform Strategy for Ukraine 2015-2025 was a component of the Decree of the President of Ukraine of January 12, 2015 No. 5/2015 "Sustainable Development Strategy for Ukraine – 2020" and the Government of Ukraine (program of activities of the Cabinet of Ministers of Ukraine, approved by the resolution of the Verkhovna Rada of Ukraine of December 11, 2014 No. 26-VIII) National Action Plan of Reforms [2]. As practical experience showed, the reform of secondary medical institutions without the successful implementation of changes at the primary level is impossible, and sometimes hinders it. In our opinion, the researchers are right that the problem of medical infrastructure optimizing is important in the process of the health care system reforming in Ukraine, since in accordance with the reform of budget decentralization, the maintenance of medical institutions is now directly subordinate to local authorities [1, p. 33]. As a result, local self-government bodies (LSGB) will have the funds and the opportunity to independently determine the priorities for the health care facilities development, to create competitive conditions for their optimization, maintenance and development, and improve the quality of medical services. Accordingly, the capacity and quality of such services will again depend to a greater extent on funding. However, if we compare that the largest hospital in London (England) has an annual budget of about 1.5 billion pounds (45 billion UAH), and the budget of specialized medical care in Ukraine in 2019 – 55.5 billion UAH [7], then we can draw the appropriate conclusions and fully agree with the opinion of Ye. Meshko, coordinator for support of health care reform that it will not be easier for us, but we will hope for positive changes.

The strategy is a document that defines the priorities and main steps for reforming the Ukrainian healthcare system. The real obstacles to its implementation are the inefficient work and shortcomings of the domestic health care system, accumulated due to the lack of modernization, ignoring current global

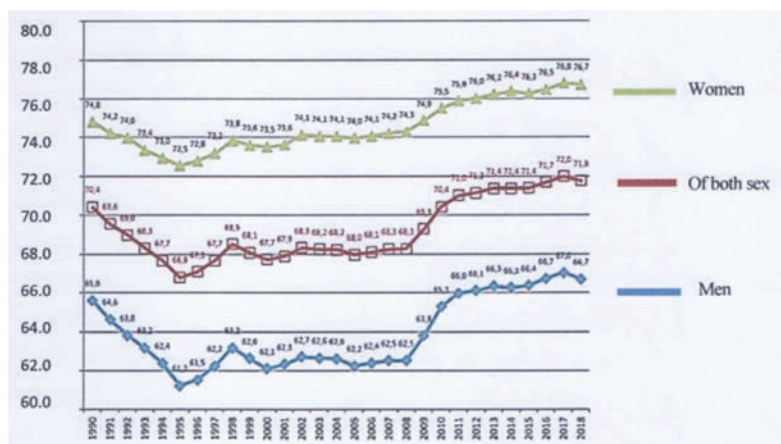


Fig. 1. Average life expectancy at birth in Ukraine in 1990-2018

Singapore and Japan it was even lower, and among the countries of the former USSR, the highest birth rate – 26, had the poorest country Tajikistan. In the world as a whole, according to the World Bank [10], the birth rate increased from 36 in 1963 to 19 in 2017.

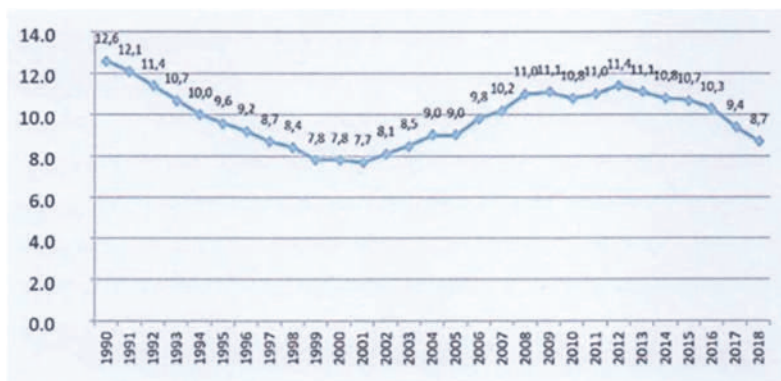


Fig. 2. Birth rate in Ukraine in 1990-2018

At the same time, as a result of the introduction of financial fertility incentive programs, the total birth rate has not changed in a few years, only children have been born a few years earlier.

trends and needs of the population and high levels of corruption. In addition, according to statistics, Ukraine differs radically from European countries in terms of fertility, life expectancy and mortality, which factors are insufficient physical activity, overweight and alcohol and tobacco abuse, as well as the spread of infectious diseases and a high level of injuries (fig. 1, 2) [10, 12].

In 2018, the birth rate in Ukraine was 8.7, but in Germany,

However, it should be noted that the birth rate depends on many social factors, and its reduction is an inevitable consequence of economic and social progress, and the birth rate is not an indicator of public health or the health care system effectiveness.

As early as the 19th century, J. Bertillon, studying the birth rate in Vienna, Berlin, and Paris, found that "the lowest birth rates were observed in the wealthiest families" [3].

Analysis of World Bank statistics [12] also revealed that despite the fact that in Ukraine a significant part of GDP (about 7%) is committed to health services, the level of GDP per capita is lower than in most European countries (fig. 3). In terms of absolute health care costs per capita, Ukraine lags behind, so insufficient funding is usually considered to be the cause of health problems. For example, in 2015, there were 5 times more tuberculosis cases in Ukraine than in Poland and Turkey, and 14 times more than in Slovakia, but these figures are lower than ten years ago.

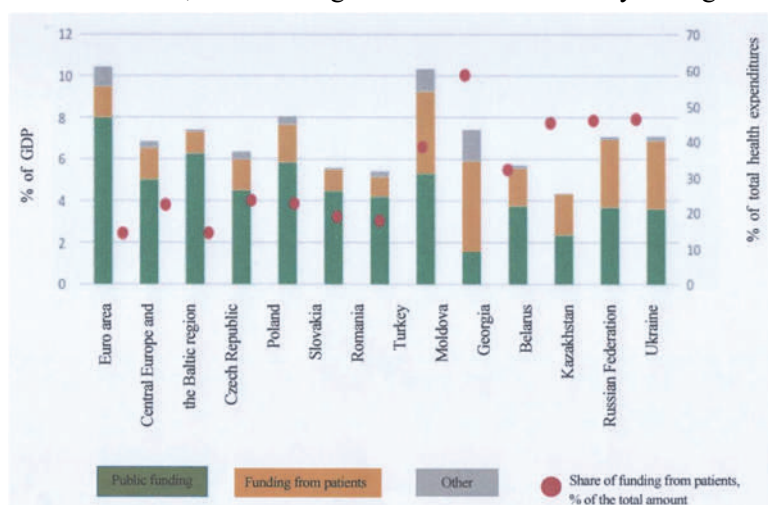


Fig. 3. Structure of health care expenditures by source and share of patient funding (in %)

of the private health care system expansion in the political decentralization processes and the local self-government reform.

It should be noted that to date, the domestic medical industry has an excessive number of highly specialized doctors (about 100 medical specialties). In addition, there are a significant number of city and regional medical institutions that accept citizens (more than 8,300 clinics, hospitals and specialized early treatment centers for one disease) (HIV/AIDS, tuberculosis, oncology, etc.). A serious problem is the limited services in primary care facilities, as a result of which patients try to seek medical help directly from specialists, who usually provide care for a semi-formal or informal fee. The analysis of the situation shows that the state of the domestic health care system is complicated not only by the reduction in the number of doctors, nurses and other qualified medical staff, but also by other factors, such as: rapid aging of the population of Ukraine, low wages, regardless of the volume and quality of work, low living standards, etc. Despite the fact that as of January 1, 2020, in the process of the primary level reforming, more than 29 million citizens chose their doctor, and 1,464 medical institutions and private individuals signed an agreement with the National Health Service of Ukraine and switched to a new funding model, the issues and problems are not fully resolved.

International experience allows us to see that effective health care based on solidarity, justice and public participation can be provided by a system that is able to use available resources in a socially responsible manner, promptly respond to the needs and expectations of the population and guarantee them transparency and responsibility for the measures taken or not taken. An important point in this process is to ensure a close link between the health of the population and the development of the national economy and the well-being of citizens. According to the survey, two thirds of citizens are satisfied with their choice, and the rest do not want to use services that do not meet their needs and aspirations for health care. Deteriorating health of the population can also lead to problems of increasing inequality for certain groups in access to health care, inefficient use of financial resources and further dissatisfaction of people with public policy in general and health care in particular. Regardless of age, social status or place of actual residence, people understand that they are entitled to significantly better health care. Society is extremely dissatisfied with excessive bureaucratization and corruption in the system, which hinders the timely satisfaction of needs, does not take into account health risks and does not use all possible resources for sustainable financing of the industry.

It is also interesting to note that the predictions and views on the prospects of private health care system in the context of health care reform are not unambiguous, nor are the reasons why private entities sign cooperation agreements with the NHSU. There are various assumptions about private health care system: some explain this cooperation by the desire to increase the influx of potential customers for more expensive services, others – believe that the concept of private medical institutions contradicts the recommended solution, mainly in the family doctor's office. At the same time, the tariff set for the year

Although insignificant, but positive dynamics, we have in other indices: "in 2016, the total health care expenditures in Ukraine amounted to 7.8% of gross domestic product, while the share of total expenditures in nominal GDP in the world as a whole is 8.6%, and in the European region – 8.9%, which is almost at the level or above the EU member states after 2004 (on average about 7.0%)" [1, p. 31].

Therefore, we can talk about certain changes in the domestic health care system, which we will consider in more detail in the context

according to the existing prices will be able to cover the costs of individual consultations, not including transport costs for home examinations, necessary laboratory diagnostics, operation and depreciation of medical equipment, maintenance and care of premises, wages, staff training. In addition, health care reform defines as a "chargeable unit" in both public and private institutions the medical service provided to a particular patient, regardless of which doctor or institution the patient sought help from. Accordingly, this has led to serious competition in regions and cities with a large number of private health care institutions for public service agreements with the state. At the same time, patients were given the opportunity to choose a family doctor in both private and public facilities, which also led to competition in the modern market of medical services.

After analyzing these facts, we can note that the initiated reform aims not only to improve the competitive environment of the health care system, but also to attract significant investment in the health sector. A study of statistical data from sociological surveys carried out by the Razumkov Centre on the reform situation in Ukraine, revealed that 65.2% of respondents expressed a negative attitude to health care reform, while only 18.6% expressed positive views on the situation, noting that they support radical changes in the health care system and believe that private health care system can become a model for the state (municipal) in the process of implementing reforms [11]. At the same time, representatives of the medical sector note that private medical institutions should be not only a "driving force" in the process of the health care system reforming, but also a partner of the state in raising the standards of medical services. Today, the share of private medical institutions in Ukraine is more than 20%, they are specialized in dentistry, ultrasound diagnostics, obstetrics and gynecology, neurology, therapy, etc.

Joint events, in particular the All-Ukrainian Medical Summit held in February 2020 in Kyiv, confirm the cooperation between the private and public medical sectors. The reason for such an event was that the National Health Service of Ukraine published not entirely positive statistics that only 21% of medical institutions are ready for the second stage of medical reform [2]. The relevance of the summit was confirmed not only by its scale and "famous" speakers (the leadership of the Ministry of Education and Science, heads of health care institutions, business representatives, doctors, lawyers, etc.), but also the opportunity to learn about the latest medical developments.

An important component of the processes of political decentralization and the medical sector reforming is the division of functions between buyers and service providers. Given that the state will retire from direct management of the financing of health care facilities, which will provide services on a contractual basis and agreed reimbursement schemes in the short term, this will increase the efficiency of the use of funds. In Ukraine, corruption is a painful issue during tenders, which affects the reputation of the health care system and the government as a whole. In practice, one of the best-known and fastest ways to address corruption in the procurement of medicines is to outsource international organizations that perform such tasks on behalf of the government.

An important task in the near future is to focus on reforming the principles and mechanisms of resource allocation and payments without significantly changing the sources of funding and the calculation of service packages that can be financed by the state. Analysis and comparison of statistical data on monitoring the process of political decentralization and local self-government reforming revealed that improving the availability and quality of health care, especially in rural areas, is one of the tasks of political decentralization. This is confirmed by real figures, including state financial support for local and regional development in Ukraine in comparison with 2014 increased 41.5 times and amounted to 20.75 billion UAH, of which – 5 billion UAH is a subvention for the development of medicine in rural areas. A certain disadvantage of this achievement can be considered only that UAH 4 billion out of 5 is a transitional balance from 2018. However, there are more positive changes – as of January 2020, 2,023 cars were purchased, of which 190 – in January (with funding of 0.99 billion UAH) and 3,969 medical kits, of which 122 – in January (with funding of 0.413 billion UAH). In addition, in January 2020, 1 new outpatient clinic was opened and 67 existing outpatient clinics were overhauled or reconstructed [8]. The development of partnerships with the private sector in the field of high-tech services is also envisaged. According to the Strategy, the development of public and private partnership involves a pragmatic approach based on evidence-based medicine, without confrontation between the public and private sectors.

As the experience of developed countries shows, the responsibility for spending public money should remain with hospitals and medical professionals, who will have the administrative and fiscal authority to reinvest in infrastructural or technological change. In most countries, the financing and income of service providers depend on their volume and quality, not on bureaucratic preferences, but on the free choice of the consumer. It is also important to be able to diversify sources of income in addition to

government benefits, in particular through new medical services such as plastic surgery or through the involvement of private insurance companies.

The reform also provides for the introduction of the autonomy of health care facilities, in particular in such key areas as financial management, delegation of management powers and service development planning, which has been taking place since 2020. Successful implementation of planned activities requires a team approach involving all possible partners and beneficiaries. It is also necessary to determine the degree of delegated authority, develop legislation, improve the financial management system, create a system of contracting and evaluation of results, determine personnel policy, and so on.

In our opinion, domestic experts and participants in the reform process should use foreign experience, at least in order to avoid mistakes and achieve positive results. For their part, the state and the government, taking into account the European aspirations of the country, maintain the current regulatory requirements and recognize the requirements of all EU member states for health care facilities. Accordingly, domestic and European standards must be equally recognized for the authorization of medical practice. Reforming the branch will help restructure the health care system on the basis of three fundamental principles:

- people-centered, which means that the health care system takes into account the needs (both of patients and employees) and ensures the safety of services;
- result-oriented approach, which requires the effectiveness of care and/or prevention programs, financial protection of patients and efficient use of funds, based on the wishes of patients;
- focus on implementation, which promotes great ideas and new models to open access to relevant services (including funding for health services, which should be effective, reduce financial risks, etc.) [9, p. 6].

Notwithstanding a number of adopted regulations aimed at implementing the second stage of medical reform from April 1, 2020, the issue of structural changes in primary and emergency medical care, which provided for the creation of new financing mechanisms (including the conclusion of contracts with health care providers), stimulation and implementation of the referral mechanism to secondary and tertiary institutions still need to be finalized. In particular, for more than two years, in accordance with the innovations of the reform, money "goes" for primary care patients, and the reform of secondary and tertiary care has only been announced. It is not clear how the COVID-19 pandemic and its consequences in the world in general and in Ukraine in particular will affect its beginning and implementation. Therefore, in our opinion, it is too early to draw conclusions about the results of the implementation of the medical system reform, introduced with the adoption of the Law of Ukraine "On State Financial Guarantees for Medical Care of the Population" [3]. The reform process began after the adoption of regulations, and the initial moment was a revolutionary change in the organization and financing of the primary health care system. According to the law, budgetary institutions were subject to reorganization, which provided for the creation of municipal non-profit enterprises, the founders of which were local self-government bodies. Therefore, the provision of medical care to citizens and the responsibility for its organization and the quality of services provided is assigned to LSGBs and united territorial communities. Given the significant changes in the forecasts of Ukraine's economic development in the near future due to the pandemic and the challenges facing domestic medicine, we will hope that health care will become a priority area of funding in the country. The results of these processes will be the tasks of our further research.

It should be noted that both in the scientific discourse and among the public, there is still a discussion about the expediency and effectiveness of the planned reforms, including medical ones [1, 2, 3, 6, 11]. The study found that not only society but also the authorities are not always ready for challenges and force majeure, as was the case with the COVID-19 pandemic. Our results indicate that it was not possible to implement and execute all the steps planned by the government to decentralize power within the framework of reforming the medical system in a timely manner. Therefore, it is hoped that at least partially (at the level of united territorial communities and LSGBs, as well as private health facilities), the planned stages of reform will be implemented. However, it should be emphasized that an important point in the process of local self-government reforming is the material side of the issue and as evidenced by statistics [6, 8, 11] the issue of medical financing remains open. This is confirmed by real figures, which showed that despite the fact that the amount of total health expenditures in the draft budget for 2020 increased by 9.8 billion UAH, compared to 2019, and amounted to 108 billion UAH, and the revised draft amendments to the state budget for 2020 provided for an increase in funding from the Ministry of Health by 16.7%, or from 16.367 billion to 114.55 billion UAH, there is still no final decision. In addition, despite the fact that state financial support for local and regional development in Ukraine in 2019 increased

compared to 2014 and amounted to 20.75 billion UAH, of which – from the 5 billion UAH subvention for the development of medicine in rural areas, 4 billion UAH was the transitional balance of the previous year [8]. The urgency of the issue is also confirmed by events and discussions, which seek opportunities for the implementation of the National Strategy [2, 3, 4, 7, 9], so we believe that some issues raised in our study will open new opportunities for implementation.

Conclusion

The current decentralization reform is not fully operational, as health facilities in some regions, districts/cities are better funded, as they receive additional allocations from local budgets. At the same time, this creates unequal access to medical services for residents of different regions, and the medical subventions are sometimes even lacking for the payment of salaries, coverage of utilities and the purchase of essential medicines. Capital expenditures (repair and purchase of equipment) are financed from local budgets or by donor companies or international organizations. A significant change in the reform process was the separation of primary care. The state has introduced programs to reimburse the cost of certain drugs, but their practical implementation is not perfect. One of the important stages of the reform was the autonomy and transformation of institutions into communal non-profit enterprises. In addition, public health facilities have been able to provide paid services and compete in this market with private clinics. However, a certain obstacle to this is the outdated material and technical base in most institutions, in particular, the lack of necessary modernized equipment and facilities. The reformatting of hospitals at the enterprises allowed them to be financed by receiving payments from the NHSU, which will help to speed up logistic processes and improve the quality of medical services.

Prospects for further research are as follows. The authors plan to study the practical execution and implementation of specific plans for the health care system reform in the context of private health care system expansion in the political decentralization processes and the local self-government reform in Ukraine at the present stage. It is also planned to cover current problems and issues of analysis and comparison not only of domestic and world experience, but also to study the situations of specific regions or united territorial communities, which will be reflected in further scientific research.

References

1. Verheles K., Horokhova L., Havryliuk A., Zharlinska R., Babiichuk O., Mishchuk A. Doslidzhennia praktychnoy realizatsiyi systemy medychnoho obsluhovuvannia v Ukraini v umovakh detsentralizatsiyi. Svit Medytsyny ta Biolohiyi. 2019; 4 (70): 30–4. [in Ukrainian]
2. Vseukrayinskyi medychnyi samit: TOP 5 prychn, chomu vy povynni buty tam. #Bukvy. [Internet] 2020. Dostupno: <https://bykvu.com/ua/bukvy/vseukrainskij-medicinskij-sammit-top-5-prichin-pochemu-vy-dolznyi-byt-tam/> [in Ukrainian]
3. Zakon Ukrainy «Pro derzhavni finansovi harantii medychnoho obsluhovuvannia naselennia» [Internet] 2019. Dostupno: <https://zakon.rada.gov.ua/laws/show/2168-194>. Kostyuk B. Medychna reforma: yak spivisnuvatymut derzhavna i pryvatna medytsyna? Radio svoboda [Internet]. 2018. Dostupno na: <https://www.radiosvoboda.org/a/29035683.html> [in Ukrainian]
5. Krasovskyi K. Narodzhuvanist v Ukraini – chy mozhna yiyi zbilshyty i chy treba tse robyty? Ukrayinska pravda [Internet]. 2019. Dostupno na: <https://life.prawda.com.ua/columns/2019/09/5/238117/> [in Ukrainian]
6. Kupliu zdorovia: TOP pryvatnykh medychnykh zakladiv Ukrainy. You Control [Internet]. 2018. Dostupno na: <https://youcontrol.com.ua/data-research/kupliu-zdorovia-top-pryvatnykh-medychnykh-zakladiv-ukrayiny/> [in Ukrainian]
7. Meshko Ye. Medychna reforma: yak zminytsia «vtorynka» Detsentralizatsiya daye mozhlyvosti [Internet]. 2019. Dostupno na: <https://decentralization.gov.ua/news/11880?page=7> [in Ukrainian]
8. Monitorynh protsesu detsentralizatsiyi ta reformuvannia mistsevoho samovriaduvannia. Detsentralizatsiya daye mozhlyvosti. [Internet] 2020. Dostupno: https://decentralization.gov.ua/mainmonitoring#main_info [in Ukrainian]
9. Natsionalna stratehiya reformuvannia systemy okhorony zdorovya v Ukraini na 2015–2025 roky [Internet]. 2015; 41 s. Dostupno: <https://moz.gov.ua/strategija> [in Ukrainian]
10. Svitovyi bank v Ukraini. Ohliad diyalnosti (zhovten 2019 r.) [Internet] 2019. Dostupno: <http://pubdocs.worldbank.org/en/620911573198550753/Ukraine-Snapshot-Oct2019-uk.pdf> [in Ukrainian]
11. Stavlennia hromadian do reform v Ukraini. [Internet]. Kyiv: Razumkov tsentr: sotsiolohichni doslidzhennia; 04 bereznia 2019. Dostupno: <http://razumkov.org.ua/napriamky/sotsiologichni-doslidzhennia/stavlennya-gromadyan-do-reform-v-ukrayini> [in Ukrainian]
12. The world bank. 2019. [Internet]. Dostupno: <https://data.worldbank.org/country/ukraine?locale=uk>

Реферати

РЕФОРМУВАННЯ СИСТЕМИ ОХОРОНИ ЗДОРОВ'Я В УКРАЇНІ В КОНТЕКСТІ РОЗШИРЕННЯ ПРИВАТНОЇ МЕДИЦИНИ

Вергелес К.М., Горохова Л.В., Козловець М.А., Голованова І.А., Соколовський О.Л., Гаврилюк А.О., Жарлінська Р.Г., Вергелес Т.М.

У статті здійснено аналіз та оцінку особливостей практичної реалізації реформи системи медичного обслуговування в контексті розширення приватної медицини в умовах процесів децентралізації влади та реформування місцевого самоврядування в Україні.

РЕФОРМИРОВАНИЕ СИСТЕМЫ ЗДРАВООХРАНЕНИЯ В УКРАИНЕ В КОНТЕКСТЕ РАСШИРЕНИЯ ЧАСТНОЙ МЕДИЦИНЫ

Вергелес К.Н., Горохова Л.В., Козловец Н.А., Голованова И.А., Соколовский О.Л., Гаврилюк А.А., Жарлинская Р.Г., Вергелес Т.Н.

В статье осуществлен анализ и оценка особенностей практической реализации реформы системы медицинского обслуживания в контексте расширения частной медицины в условиях децентрализации власти и реформирования местного самоуправления в Украине. Исследованы условия

Досліджено умови та особливості реалізації Національної стратегії реформи системи охорони здоров'я України на 2015–2025 роки з точки зору забезпечення ефективної організації системи охорони здоров'я, зокрема в контексті розширення приватної медицини. Запропоновано перспективи подальших досліджень умов та шляхів удосконалення системи надання медичної допомоги в Україні.

Ключові слова: децентралізація влади, медична реформа, система медичного обслуговування, приватна медицина, видатки на охорону здоров'я.

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и особенности реализации Национальной стратегии реформы системы здравоохранения Украины на 2015–2025 годы с точки зрения обеспечения эффективной организации системы здравоохранения, в частности в контексте расширения частной медицины. Предложено перспективы дальнейших исследований условий и путей совершенствования системы оказания медицинской помощи в Украине.

Ключевые слова: децентрализация власти, медицинская реформа, система медицинского обслуживания, частная медицина, расходы на здравоохранение.

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O.O. Viltaniuk, L.D. Kotsur, A.G. Stepaniuk, O.Y. Tkachenko, A.O. Gavriluk
National Pirogov Memorial Medical University, Vinnytsya

CLINICAL FEATURES OF THE COURSE AND RESULTS OF TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA IN PATIENTS WITH OPIOID ADDICTION

e-mail: viokol1983@gmail.com

The article describes the study results of the clinic features and effectiveness of traditional treatment methods of the community-acquired pneumonia with severe course in opioid addicted patients and non-drug users. It was found that the severity of the disease in this category of patients was caused by latent polyorgan pathology, association of antibiotic-resistant bacteria and fungi of the genus *Candida*, as well as the development of systemic inflammatory response. In addition, traditional approaches to the treatment of severe community-acquired pneumonia in this category of patients were found to be accompanied by longer ($p < 0.05$) hospitalization and significantly ($p < 0.05$) higher mortality.

Key words: community-acquired pneumonia, opioid addiction, latent polyorgan pathology, results of treatment of non-hospital pneumonia in drug-addicted patients.

The work is a fragment of the research project "Features of diagnosis and treatment of internal organs diseases in the case of their combination: pharmacoepidemiological, pharmaco-economic aspects, life quality indices", state registration № 0115U006745.

Despite advances in the management of severe infectious diseases, community-acquired pneumonia (CAP) remains the major cause of mortality in developed countries. Approximately 10% of hospitalized patients with CAP require admission to an intensive care unit (ICU), where 20–50% of them will ultimately die. [1, 4, 6, 7].

The issue of timely diagnosis and treatment of drug-addicts with CAP has long been medicinally and socially essential. However, it still remains understudied in terms of morphological changes and in the sphere of clinical manifestations. The patients of the group demonstrate strong risk factors as they are prone to a high level of complications, which reaches 100 cases per 1000 patients, whereas in the group of drug-free patients complications occur in only 10 to 40 cases per 1000 patients [8, 9, 12]. The features of causative agents of CAP in drug-dependent patients need further high-quality research studies that will address the impact of antimicrobial susceptibility and virulence on treatment decisions and patient outcomes [12, 13].

The analysis of literature has shown that the management of CAP treatment of patients with opium addiction holds no clear justification of the reasons for unsatisfactory results of fighting this pathology. The informative value of clinical and laboratory markers, as well as indicators of endogenous intoxication in the dynamics of the treatment of CAP, needs to be enriched with more evidence and treatment strategies. The species composition, biological properties and sensitivity of microorganisms to antimicrobial agents, which cause CAP in drug-dependent patients, also require further studies. Finally, there seems to be a lack of research on morphological changes in the lungs and other organs caused by the use of drugs. All of the above mentioned factors demonstrate the urgent need for in-depth analysis of treatment strategies for drug-dependent patients with CAP, the evidence of which will help develop new pathogenetically substantiated approaches to the treatment of this pathology and improve the results of CAP treatment in drug-dependent patients.

The purpose of the study was to define the treatment course and estimate the effectiveness of community-acquired pneumonia treatment by traditional methods in patients with opium addiction.

Materials and methods. The study has been done within the frame of integrated approach that combined the use of experimental, clinical, laboratory, microbiological and morphological methods. The study objects were 89 patients with severe CAP. The patients were divided into two groups. The main group consisted of 42 CAP patients with opioid addiction, including 25 males (59.5%) and 17 females (40.5%). The comparison group (47 patients) comprised 28 men (59.6%) and 19 women (40.4%) accordingly. The average age of the main group patients was 27.5 ± 5.5 years, their history of drug abuse varied from 1 to 13 years.

Patients in both groups received treatment according to existing standards which included antimicrobial, detoxicational and symptomatic therapy.

The estimation of the overall condition of patients was carried out by standard laboratory and biochemical tests and the indicators of endogenous intoxication (EI) were determined: leukocyte index of intoxication (LII), hematological indicator of intoxication (HII) and the levels of metabolites in the average weight (MAM) in blood [3, 5]. Besides, the determination of biochemical parameters of systemic inflammatory response (SIR): C-reactive protein (CRP) and Pro-inflammatory cytokines: the tumor necrosis factor - α (TNF- α) and interleukin-6 (IL-6) was performed [9, 11]. Microbiological studies have included determining the nature of CAP and their sensitivity to antibiotics and antiseptics [10].

The influence of antibiotics and antiseptics on the adhesive properties of microorganisms was studied according to the method of Bryliss et al. [2].

The study of morphological changes in internal organs under the influence of the use of opium drugs was performed in 32 opium addicted patients. The causes of death were drug overdose - 29 patients (90.6%), 3 suffered a violent death (9.4%).

Statistical processing of the obtained data was performed to determine the significance of differences in both groups of patients in the integrated system STATISTICA® 5.5 (STAT + SOFT® Snc, USA) using a licensed program (A XX 910A374605FA).

The results of the study and their discussion. The course of CAP in patients of the main group was significantly different from the course of CAP in patients of the comparison group.

The number of red blood cells in patients in the comparison group averaged $4.2 \pm 0.18 \times 10^{12}/l$, whilst in the main group their number was $3.0 \pm 0.09 \times 10^{12}/l$ and significantly ($p < 0.01$) differed from the indicators in the comparison group. Hemoglobin was 97.4 ± 5.2 g/l, while in the comparison group this indicator was at the level of 137.3 ± 4.2 g/l ($p < 0.01$). The leukocyte count was $6.76 \pm 1.91 \times 10^9/l$ in the main group versus $17.6 \pm 2.31 \times 10^9/l$ to the comparison group ($p < 0.01$).

Information on the dynamics of laboratory parameters is presented in tables 1, 2. In the group of drug-dependent patients on the third day of CAP treatment there was a decrease in the counts of red blood cells and hemoglobin. In the comparison group anemia was also on the increase up to the 7th day of treatment. On the 9th day of observation and before the patient discharge the average counts of hemoglobin and red blood cells were at the lower limit of the norm. In the main group of patients during the treatment period the red blood cells and hemoglobin counts remained low and the downward trend was observed up to 9 days, and was significantly lower ($p < 0.05$) from that of the hospitalization, and only since the 15th day of observation, the indicators of hemoglobin and erythrocytes began to rise, but were still significantly lower ($p < 0.05$) than in the comparison group. All drug addicted patients had anemia before discharge, red blood cell counts made up $2.87 \pm 0.14 \times 10^{12}/l$, hemoglobin – 87.35 ± 4.36 g/l. Leukocytes counts were also significantly ($p < 0.05$) lower during the entire observation period, although the treatment resulted in a significant increase in the number of leukocytes from $6.75 \pm 1.91 \times 10^9/l$ at admission to $10.3 \pm 4.12 \times 10^{12}/l$ on day 7 of observation ($p < 0.05$) and then decreased to $5.77 \pm 1.71 \times 10^{12}/l$ before discharge. The erythrocyte sedimentation rate (ESR) in contrast to the performance of ESR in patients in the comparison group showed a decreasing tendency.

If in the comparison group this figure gradually decreased to 19.6 ± 1.8 mm/h before discharge, than in the main group ESR before discharge was 63.41 ± 8.84 mm/h ($p > 0.05$).

In both groups, a significant decrease in total protein was observed, but in the comparison group a decrease was observed at day 7, and since day 15, the total protein increased and reached 70.0 ± 0.9 g/l, approaching normal levels. Whereas, the total protein score in the main group of patients at the third day from the start of treatment was 65.4 ± 1.8 g/l, what was significantly lower ($p < 0.05$) than in the comparison group patients.

Despite albumin transfusions, this index remained significantly lower ($p < 0.01$) than in the comparison group. Urea and creatinine levels in the main group patients were also significantly higher ($p < 0.05$) than in the comparison group patients.

Dynamics of laboratory blood indicators changes in patients with severe flow of CAP at drug users and patients of the comparison group

No	Index Term	Erythrocytes, $\times 10^{12}/l$		Hemoglobin, g/l		Leukocytes, $\times 10^9/l$		ESR, mm/hour	
		Comparison group (n=47)	Main group (n=42)	Comparison group (n=47)	Main group (n=42)	Comparison group (n=47)	Main group (n=42)	Comparison group (n=47)	Main group (n=42)
1.	Hospitalization	4.20 ± 0.18	3.0 $\pm 0.09^{**}$	137.3 ± 4.2	97.4 $\pm 5.2^{**}$	17.6 ± 2.31	6.76 $\pm 1.9^{**}$	65.3 ± 7.2	53.3 $\pm 3.5^*$
2.	3rd day	3.77 ± 0.13	2.86 $\pm 0.53^*$	128.1 ± 2.7	94.8 $\pm 4.8^{**}$	16.1 ± 1.62	7.27 $\pm 3.7^{**}$	64.7 ± 6.3	54.8 $\pm 4.1^*$
3.	5th day	3.56 ± 0.17	2.54 $\pm 0.71^*$	125.0 ± 3.8	96.4 $\pm 2.9^{**}$	14.2 ± 1.87	8.1 $\pm 2.9^{**}$	49.8 ± 5.4	48.6 ± 4.5
4.	7th day	3.38 ± 0.12	2.31 $\pm 0.09^{**}$	107.2 ± 5.1	100.0 $\pm 4.5^{**}$	13.8 ± 1.32	10.3 $\pm 4.1^{**}$	44.3 ± 4.6	50.1 $\pm 3.1^{**}$
5.	9th day	3.49 ± 0.14	2.38 $\pm 0.11^{**}$	110.3 ± 3.9	88.7 $\pm 1.3^{**}$	12.3 ± 1.52	8.24 $\pm 2.1^{**}$	32.2 ± 4.5	50.7 $\pm 5.4^{**}$
6.	15th day	3.55 ± 0.10	2.62 $\pm 0.42^{**}$	118.4 ± 2.9	83.7 $\pm 1.5^{**}$	9.4 ± 2.10	5.84 $\pm 2.3^{**}$	28.4 ± 3.7	62.7 $\pm 5.9^{**}$
7.	Before discharge	3.86 ± 0.21	2.87 $\pm 0.14^*$	129.2 ± 3.1	87.3 $\pm 4.3^{**}$	7.6 ± 0.53	5.77 $\pm 1.7^*$	19.6 ± 1.8	63.4 $\pm 8.8^{**}$

Note. 1. * - $p < 0.05$ the difference is significant in comparison with the data of the group of patients, who did not use drugs. 2. ** - $p < 0.01$ difference is significant in comparison with the data of the group of patients, who did not use drugs.

Table 2

Dynamics of biochemical parameters in blood at drug addicts and patients from the control group with severe CAP

No	Index Term	Total protein, g/l		Urea, $\mu\text{mol}/l$		Creatinine, $\mu\text{mol}/l$	
		Comparison group (n=47)	Main group (n=42)	Comparison group (n=47)	Main group (n=42)	Comparison group (n=47)	Main group (n=42)
1.	Hospitalization	73.9 \pm 3.89	68.9 \pm 2.04	8.87 \pm 0.64	9.11 \pm 0.77*	118.6 \pm 11.43	6 \pm 11.27*
2.	3rd day	71.1 \pm 2.63	65.4 \pm 1.8	8.64 \pm 0.72	9.06 \pm 0.84*	116.4 \pm 9.8	120.8 \pm 9.92*
3.	5th day	70.9 \pm 1.81	62.3 \pm 0.7**	8.81 \pm 0.65	8.93 \pm 0.57	117.2 \pm 10.71	120.1 \pm 11.4*
4.	7th day	64.2 \pm 1.73	58.6 \pm 7.1*	8.29 \pm 0.31	8.69 \pm 0.64	114.6 \pm 8.36	117.5 \pm 8.36*
5.	9th day	63.6 \pm 0.86	59.2 \pm 1.3*	7.94 \pm 0.42	8.38 \pm 0.76**	109.5 \pm 5.3	115.8 \pm 9.56*
6.	15th day	68.7 \pm 0.92	63.6 \pm 0.9*	7.80 \pm 0.81	8.11 \pm 0.41*	100.2 \pm 4.3	109.8 \pm 5.32**
7.	Before discharge	69.8 \pm 0.88	66.5 \pm 1.78*	7.23 \pm 0.02	7.42 \pm 0.24	76.8 \pm 2.76	100.7 \pm 3.43**

Note. 1. * - $p < 0.05$ the difference is significant in comparison with the data of the group of patients, who did not use drugs. 2. ** - $p < 0.01$ difference is significant in comparison with the data of the group of patients, who did not use drugs.

Determination of EI indicators showed that no significant increase in LII in drug users was observed at hospitalization. LII was 2.07 ± 0.4 CONV.U., which was only 4 times higher than normal, whereas patients in the comparison group during the time of hospitalization demonstrated LII of 7.82 ± 0.8 CONV.U., which exceeded the normal rate by 15 times. In the dynamics LII in drug-users had a tendency to increase on day 3 to 3.76 ± 0.51 CONV.U. Gradually up to the 5th day of observation LII figure reduced to 1.36 ± 0.2 CONV.U., and before discharge exceeded normal levels by almost 3 times and did not differ significantly from LII at admission. At the same time, patients in the comparison group demonstrated a decrease in LII, which before discharge significantly ($p < 0.05$) did not differ from the norm. The HII also did not fully illustrate the severity of the patients' conditions, which was associated with the discrepancy between LII and ESR. The treatment led to the growth of HII on the 3rd day of observation followed by the decrease on day 5 to 4.66 ± 1.4 CONV.U., which was significantly lower ($p < 0.05$) than the previous observation period. On the 7th day there was an increase of HII up to 12.23 ± 2.7 CONV.U. followed by its further drop to 3.36 ± 1.06 CONV.U. On the 15th day, a slight increase in the HII was recorded at 5.43 ± 0.52 CONV.U., which remained 3.5 times higher than normal before discharge, whereas in the comparison group before discharge, patients' HII was within the normal range. The level of MAM in drug-dependent patients was consistently high, exceeding the normal markers almost twice, and had no tendency to decrease, remaining high even before discharge (0.415 ± 0.24 CONV.U.). In patients from the comparison group, the level of MAM for the 5th day of observation decreased to 0.396 ± 0.11 CONV.U., and before discharge was within the normal range (0.248 ± 0.15 CONV.U.)

Laboratory indicators of SEI also differed in both groups of patients. Information on the dynamics of laboratory indicators is presented in tables 3. In the course of disease treatment there was a significant ($p < 0.05$) growth of all indicators. Since the 9th day of observation in the comparison group there observed a decrease of these parameters (CRP – 24.3 ± 1.76 mg/l, IL-6 and 15.1 ± 0.86 pg/l, TNF- α – 198.0 ± 16.3 pg/l), which were significantly ($p < 0.05$) lower than during hospitalization.

studies, the etiology of CAP has not been identified as a risk factor for mortality. These questions have important implications for clinical care as well as risk adjustment [7, 8, 10, 12].

The obtained data allow us to explain the severity of CAP in these patients. Severity of the disease was caused by the presence of hidden polyorgan pathology in patients with opioid addiction, which is superimposed by intoxication syndrome due to the development of the inflammatory process in the lungs. CAP in this group of patients is caused by highly virulent antibiotic-resistant bacteria and fungi which were sensitive to antiseptics. Therefore, the treatment of community-acquired pneumonia using conventional methods has low efficiency, the CAP progresses rapidly, leads to the development of destructive changes in the lungs and is accompanied by high level of mortality.

Conclusions

1. CAP in drug addicted patients has a severe complicated course and is accompanied by severe endogenous intoxication and development of systemic inflammatory response syndrome, as evidenced by the high level of MAW, CRP, IL-6 and TNF- α that are significantly ($p < 0.05$) higher than those in the comparison group.

2. CAP in drug-dependent patients is caused by high virulent antibiotic-resistant strains: *S. aureus* – 19 (37.3%), *Kl. pneumonia* – 7 (13.7%), *S. pneumonia* – (11.7%), *S. epidermidis* – 3 (5.9%). and *Candida* - 16 (31.4 %). At the same time as monoculture bacteria were selected in 15 cases (48.4%), and in 16 (51.6%) of cases as an association of microorganisms or associations of microorganisms and fungi. Antiseptics (etonium, miramistin and decamethoxin) have a high antimicrobial activity against selected causative agents of CAP.

3. The severity of CAP in patients with opioid addiction was caused by the presence of hidden polyorgan pathology.

4. The use of traditional approaches to the treatment of CAP in drug addicted patients need significantly ($p < 0.05$) prolonged hospitalisation and is accompanied by a significantly ($p < 0.05$) higher development of destructive changes in the lungs (35.7% vs. 17.0% of patients who do not use drugs) and by significantly ($p < 0.05$) higher mortality (23.8% versus 4.3% accordingly).

Reference

1. Brilis VI, Brilene TA, Levkov LA. Metodicheskie vozmozhnosti izucheniya roli adgezii v koloniziruyushey sposobnosti mikroorganizmov. Moskva: 1986. 206-211 s. [in Russian]
2. Gabrielyan NI, Lipatova VI. Opyt ispolzovaniya pokazateley srednikh molekul v krovi dlya diagnostiki nefrologicheskikh zabolevaniy u detey. Laboratornoye delo: 1984; 3: 138-140. [in Russian]
3. Golubev AM, Smelaya TV, Moroz VV, Popov AA, Tolbatov AA, Medunetskaya SV. Negospitalnaya i nozokomialnaya pnevmoniya: kliniko-morfologicheskie osobennosti. Obshchaya reanimatologiya. 2010; 6(3):5. [in Russian]
4. Karpischenko AI. Meditsinskie laboratornyye tehnologii. Geotar-Media: 1part : 2012; 480 s. [in Russian]
5. Mostovoy YuM. Suchasni klasyfikatsiyi ta standarty likuvannya rozpovsyudzhennykh zakhvoryuvan vnutrishnikh orhaniv. Nevidkladni stany v terapiyi. Analizy: normativni pokazachnyky, traktuvannya zmin. Kyiv : Tsentri DZK; 2018, 792 s. [in Ukrainian]
6. Angus DC, van der Poll T. Severe Sepsis and Septic Shock. N.Engl.J.Med. 2013; 369:840 -885.
7. Ayatollahi-Mousavi SA, Asadikaram G, Nakhaee N. The effects of opium addiction on the immune system function in patients with fungal infection. Addict Health. 2016; 8(4): 218-26.
8. Azdaki N., Zardast M., Anani-Sarab G. Comparison between homocysteine, fibrinogen, PT, PTT, INR and CRP in male smokers with / without addiction to opium. Addict Health. 2017; 9(1): 17-23.
9. Vacci MR, Leme RC, Zing NP. IL-6 and TNF- α serum levels are associated with early death in community-acquired pneumonia Braz J Med Biol Res. 2015; 48(5): 427-432.
10. Barnett K, Mercer SW, Norbury. Epidemiology of multimorbidity and implications for health care, research and medical education: A cross-sectional study. Lancet Lond. Engl. 2012, 7, 37-43.
11. Edelman JE, Kirsha SG, Crothers K. Association of prescribed opioids with increased risk of community-acquired pneumonia among patients with and without HIV. JAMA Int. Med. 2019; 179(3):297-304.
12. Florence CS, Zhou C, Luo F. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care. 2016; 54(10):901-906.
13. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death 2013 a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 385:117-171.

Реферати

**КЛІНІЧНІ ОСОБЛИВОСТІ ПЕРЕБІГУ
ТА РЕЗУЛЬТАТИ ЛІКУВАННЯ
НЕГОСПІТАЛЬНОЇ ПНЕВМОНІЇ У ХВОРИХ
ІЗ ОПОЇДНОЮ НАРКОМАНІЄЮ**

**Вільцанюк О.О., Коцур Л.Д., Степанюк. А.Г.,
Ткаченко О.В., Гаврилюк А.О.**

У статті описані результати дослідження особливостей клініки та ефективності традиційних

**КЛИНИЧЕСКИЕ ОСОБЕННОСТИ ТЕЧЕНИЯ
И РЕЗУЛЬТАТЫ ЛЕЧЕНИЯ НЕГОСПИТАЛЬНОЙ
ПНЕВМОНИИ У БОЛЬНЫХ С ОПИОИДНОЙ
НАРКОМАНИЕЙ**

**Вильцанюк О.А., Коцур Л.Д., Степанюк. А.Г.,
Ткаченко Е.В., Гаврилюк А.А.**

В статье описаны результаты исследования особенностей клиники и эффективности традиционных

методів лікування не госпітальної пневмонії з важким перебігом у наркозалежних пацієнтів та осіб, які не вживають наркотики. Було встановлено, що тяжкість захворювання у цієї категорії хворих спричинялася латентною поліорганною патологією, асоціацією антибіотикорезистентних бактерій та грибків роду *Candida*, а також розвитком системної запальної реакції організму. Крім того, було виявлено, що традиційні підходи до лікування важкої пневмонії в цій категорії пацієнтів супроводжуються більш тривалою ($p < 0,05$) госпіталізацією та значно ($p < 0,05$) більш високою смертністю.

Ключові слова: негоспітальна пневмонія, опіоїдна наркоманія, прихована поліорганна патологія, результати лікування негоспітальної пневмонії у наркозалежних хворих.

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методов лечения негоспитальной пневмонии, с тяжелым течением у наркозависимых пациентов и лиц, не употребляющих наркотики. Было установлено, что тяжесть заболевания у этой категории больных была обусловлена латентной полиорганной патологией, ассоциацией антибиотико резистентных бактерий и грибков рода *Candida*, а также развитием системной воспалительной реакции организма. Кроме того, было установлено, что традиционные подходы к лечению тяжелой пневмонии, у этой категории пациентов, сопровождались более длительной ($p < 0,05$) госпитализацией и достоверно ($p < 0,05$) более высокой смертностью.

Ключевые слова: внебольничная пневмония, опиоидная наркомания, скрытая полиорганная патология, результаты лечения внебольничной пневмонии у наркозависимых больных.

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A.O. Gavrylyuk, R.G. Zharlinska¹, A.A. Mishchuk, K.M. Vergeles, A.M. Berezovskyi,
Ya.M. Pashynskiy², I.I. Iakovtsova
Vinnytsia Pirogov National Memorial Medical University, Vinnytsia
¹Vasyl Stus Donetsk National University, Vinnytsia
²Kharkiv Medical Academy of Postgraduate Education, Kharkiv

IMPROVEMENT OF THE PATIENT CARE PROCESS BASED ON THE PRINCIPLES OF CLINICAL AUDIT

e-mail: allahavryliuk25@gmail.com

The purpose of the study was to analyse the possibilities of implementing a clinical audit in the activities of the health care institutions (HCI) and to summarize the steps taken during the audit. The article analyses modern approaches to clinical auditing and existing models based on the principles of the Deming - Shewhart cycle (PDCA). A standardized model of the patient's clinical route based on the principles of clinical audit has been developed. The clinical route of the patient is differentiated into blocks that reflect the principle of optimal distribution of responsibilities among staff, which will improve the quality of patient care.

Key words: clinical audit, quality of medical care, Deming - Shewhart cycle, patient-oriented approach, clinical route of the patient.

The work is a fragment of the research project "Early diagnosis of dysplastic, metaplastic and neoplastic changes in the pathology of the gastrointestinal tract, respiratory, urogenital and neuroendocrine systems", state registration No. 0117U000001.

At the present stage of important scientific and practical significance and relevance are studies aimed at developing special assessment methods, new approaches to the organization, planning and management of clinical and economic activities of HCIs, aimed at providing quality and safe health care services. The introduction of the concept of health care quality management in the health care practice requires the organization of clinical audit as a tool for assessing the quality of health care services, a mechanism for improving health care, a means of stimulating the professional activities of medical staff. Problems of clinical audit as one of the means of quality control of health care services were considered in the works of domestic researchers, including: Zimenkovskiy A.B., Bagdatsaryan V.E., Biriukov V., Bohomaz V.M., Smiianov V.A., Stepanenko A.V., as well as foreign authors Barry K., Kumar S., Linke R., Dawes E., Miettunen K., Metsala E., Imoh L.C., Mutale M., Parker C.T., Mangla G., Arora V.K., Singh N. and others. Analysis of the literature shows that the term "clinical audit" is interpreted differently by experts [1,2,4,7], which indicates the incompleteness of the process of identification properties of this concept. As for the practical aspects of the functioning of clinical audit in domestic HCI, we can note their insufficient coverage by domestic experts, which indicates, in our opinion, either the limited use of clinical audit in hospitals for various reasons (consequently, little experience and low efficiency), or imperfect legal regulations and undeveloped methodological aspects of audit in the current conditions of reforming the medical sector in Ukraine (the main legal act dates back to 2012 - Order of the Ministry of Health of 28.09.2012 No 752 "On the quality control of health care", recommendations for improving the quality management system of health care in Ukraine - 2009). The lack of compulsory health insurance slows down the process of active introduction of clinical audit in the HCIs.

The purpose of the study was to analyse the possibilities of implementing clinical audit in the activities of the HCIs; development of a standardized patient-oriented model of the clinical route based on the principles of clinical audit.

Materials and methods. The materials of the research are normative-legal acts regulating the health care quality control in the field of health care in Ukraine, and international standards in the field of health care. The general scientific research methods are used in the work: system, process and conceptual approaches.

Results of the study and their discussion. Administrative team approach to provision of quality in health care system, based on principles of control that was valid in Ukraine till the last time did not correspond to organizational, legal and economic conditions of this branch functioning and must be changed by another approach, based on principles of process management. Continuously rising quality provides complex, integrated and dynamical approach through the prism of quality enhancement, forwarded to improvement of work results of the system in common, constant modification and improvement of the system by its own, not just detection and punishment related to co-workers, whose practice or results don't correspond to the established standard.

Clinical audit is an integral part of the quality improvement process. Some researchers understand clinical audit as a review of the effectiveness of treatment of a pathology, others - inspection or critical analysis of established, obsolete schemes of diagnosis, treatment or prevention [1, 2, 7, 8].

To explain the essence of clinical audit, it is necessary to proceed from its target function, aimed at improving medical practice in a particular HCI. The subject of research of this type of audit is the existing practice in the institution. This means that the clinical audit is aimed at improving the process of providing health care services. According to Stepanenko A.V., Smiyanov V.A. [8], clinical audit aims to improve the processes and outcomes of care to patients through its systematic review against detailed criteria and the implementation of changes where care or its results do not reach the expected level.

The main goal of clinical audit is to improve existing clinical practice and provide leadership in the provision of health care services based on constant choice to address the most pressing challenges facing the HCI or its structural unit. Other objectives of the clinical audit include ensuring the protection of citizens' rights in the field of health care and providing the population with quality services under guaranteed state or insurance programs of healthcare; improving the diagnosis, treatment and rehabilitation of socially significant and other diseases treated by the population [3].

Bohomaz V.M. notes that the use of audit is a form of feedback that indirectly contributes to the professional development of staff. To achieve these goals and ensure such communication, the leadership of the HCI must successfully address a few issues:

- to form a quality control service in the HCI
- to optimize the management of personnel activities (standardize processes, develop algorithms)
- based on evidence-based medicine to conduct a revision of treatment regimens adopted in this for the most important and socially significant diseases [2].

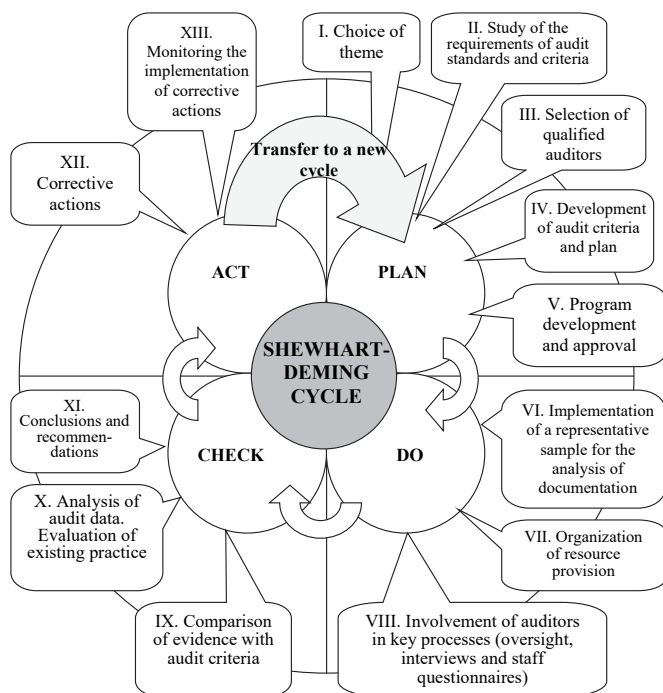


Fig. 1. Cycle of clinical audit [1].

The most common model of health care audit provided to patients is the basic model of quality measurement, developed by Donabedian A. and distributed in industries. It contains the following components:

- internal resources - in medicine, in addition to material resources, they also include the structure that provides resources (for example, equipment and tools of doctors, HCI and a combination of human resources and skill level)
- process - is a way to use resources, such as the style of relationships with patients
- result - the price consequence of the intervention, measured by both medical and functional indicators.

Unlike classical quality control, clinical audit is based on the principle of continuous quality improvement, which is reflected in the cycle Deming - Shewhart, or spiral PDCA (Plan-Do-Check-Act), which

clearly demonstrates the cyclical nature of work (fig. 1), i. e. not only conducting evaluation activities directly, but also further changes in work practice, as well as further control in the dynamics.

The main principle of the whole process of clinical audit is that it should lead to further improvement of clinical practice to improve the results of treatment of patients [4]. It carries out a systematic critical review of the multidisciplinary command as a clinical practice. With the help of clinical audit, it is possible to monitor the processes of diagnosis, treatment and care of patients, the resources used and the impact of health care on life.

In addition, the following principles of clinical audit are distinguished: it begins within the boundaries of the HCI; already available data are used; confidentiality; no one will be punished or accused of conducting a clinical audit.

Two fundamental principles of clinical audit in HCI differ it from the expert assessment approach: confidentiality (research results neither divulged nor used for chastisement) and free cooperation between medical and non-medical professionals [1].

Control and audit can combine the retrospective nature of the activity. Some differences between these concepts are given below.

Table

Comparison of control and audit processes [1]

Control	Audit
Evaluation of compliance with one or more parameters, "the senior controls the junior"	Collection and analysis of complete information on a certain type of activity by a specially created working group
Formalized process	Formalized criteria are complemented by an informal creative approach
Establishing compliance with a previously established level	Determining the required level with the approval of the action plan

The audit compares the current practice with the standards of medical practice. As a result of the comparison, any shortcomings in the current practice can be identified and eliminated.

There are currently several models of clinical audit. All of them are based on the principles of PDCA but have significant differences. The clinical audit systems of the National Health Service of the United Kingdom (NHS) and the United States function primarily as accreditation mechanisms.

These systems are particularly promising, but it should be noted that the practice of standardization and clinical audits in the UK and US was introduced more than 30 years ago and now such audit methodologies are used there to further improve national health systems, but they are not applicable to those countries where medical practice is insufficiently systematized.

Over the past 20 years, the world has undergone qualitative changes in the health care system, including the development of the so-called patient-centred approach based on the principles of respect for the patient and focus on his individual interests, needs and values, as well as involvement it to the decision-making process for the provision of health care. This is confirmed by Zimenkovskiy A.B., Stepanenko A.V., Ieremeeva T.V., Shibinskyi V.Y. noting that "the evolution of clinical audit interpretations reflects its gradual transformation from a professional-oriented approach to a patient-oriented one. Thus, it should be noted that in modern conditions, the "focus on the patient" has significantly influenced the methodology of clinical audit. No wonder there was even a statement that the clinical audit is conducted "by people, not people and, in our deep conviction - for people" [4, p. 9]. This approach has become the main basis for managing a modern health care organization, as practice confirms the optimality of management decisions made on its basis.

On the example of the analysis of different approaches to monitoring the quality of diagnostics, we have formed a methodology of clinical audit, focused on assessing the organization of logistics. A key component of the methodology is a standardized patient-centred model of the clinical route when performing diagnostic studies. The main idea of the audit is to compare the actual state of the patient's logistics and a standardized model of the clinical route with the subsequent formulation of individualized recommendations aimed at improving the quality of the diagnostic department (considering local characteristics). In general, the audit methodology is developed considering international recommendations and is a system that improves the quality of both patient admission and work organization within the department.

In developing the standardized model, we were guided by the Law of Ukraine "Fundamentals of the legislation of Ukraine on health care", Art. 4 which defines in particular such principles of health care as: observance of human and civil rights and freedoms in the field of health care and provision of related state guarantees; focus on modern standards of health and medical care, a combination of national traditions and achievements with world experience in the field of health care [5]. In addition, the development of the clinical route of the patient is regulated by the norm of the Ministry of Health of Ukraine from 29.12.2016 No 1422, as well as the need for interaction between the HCI in the provision of health care in order to meet the requirements of the standard, a unified clinical protocol of health care and a new clinical protocol of health care. The clinical route of the patient is developed in any form, considering the characteristics of

the relevant HCI [6]. Given the above rules, the patient's route was differentiated into blocks, which primarily reflect the principle of optimal distribution of responsibilities between staff (fig. 2).

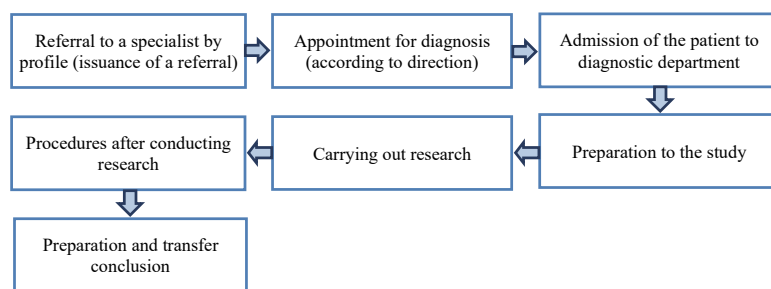


Fig. 2. Standardized patient-oriented model of clinical route

needs to obtain timely and reliable diagnostic information that affects the subsequent tactics of treatment of the patient.

The attending physician refers the patient for research, establishes the nature of the clinical problem to be solved and realistically evaluates the possibility of obtaining useful diagnostic information as a result of the study, and selects the most informative study based on approved recommendations of the HCI or national standards. The attending physician is obliged to inform the patient about possible complications of the diagnostic procedure and make sure that there are no contraindications to its implementation, as well as to enter the relevant information (both in the presence of contraindications and in their absence) in the patient's medical records.

2. Appointment for diagnosis. Registration for research in health care organizations can be implemented in different ways depending on the availability of electronic system-health or the use of patient information protection systems based on block chain technology, but the priority is to preserve patient data and the ability to obtain complete information about the status of the study. Registration for the diagnostic examination should be carried out with the involvement of a minimum number of persons. It is advisable to establish direct routing between the person who refers the patient (doctor) and the doctor who receives (a specialist in an area of diagnosis), without the participation of the medical commission. Registration for the study can be done both electronically and in documentary form, provided that the information is stored by the attending physician and the transfer of this information to the patient, as well as the person recording the study (administrator), laboratory assistant and specialist.

3. Admission of the patient to the diagnostic department. To avoid unintentional harm to the patient and staff, any admission of the patient to the ward / office should be expected and provided for in the organization of the ward. The staff of the department should make sure that the planned examination of a patient is necessary and safe, as well as the preservation of this information, as it may be required in controversial cases.

4. Preparation for the study. In preparation for any diagnostic test, it is necessary to provide the patient with maximum privacy and comfort, as well as to comply with sanitary and hygienic standards when working with medicines and medical equipment, including when working with blood.

5. Conducting research. The performance of diagnostic tests should be regulated as much as possible to ensure not only the high quality of the diagnostic procedure, but also the safety of the test for both the patient and the staff.

6. Procedures after the study. Upon completion of the study, the medical staff of the department should make sure that:

-the patient received adequate medical care, he was informed about the progress of the study and the procedure for obtaining results,

-the patient's doctor will receive a detailed description of the results of the required study in a certain direction.

7. Preparation and transmission of the conclusion. The results of the study should be promptly analysed and described by a specialist, and then passed on to all parties - both the patient and the doctor - while maintaining the confidentiality of data.

It should be noted that in countries with developed health care, clinical audit is usually used to assess the success of the implementation of a method or clinical guidelines [1,2,4]. There are also frequent cases of using audits to conduct a large-scale inspection of the health care quality in individual hospitals, in the field of general practitioners, in outpatient facilities and even in the field of medicine. Often in foreign practice, audits are conducted to study the economic efficiency of the use of certain methods [4]. Sometimes the audit reveals the facts of significant systemic excess of the cost of health care services, but most publications confirm their economic effectiveness. Clinical audit is widely used both in treatment and in assessing the correctness of various diagnostic procedures: for example, when performing radiological

examinations, express-tests, aspiration biopsies [9-12]. Our standardized patient-oriented model of the clinical route reflects the most important factors that may affect the quality of care in planning and conducting diagnostic tests. This gives reason to agree that clinical audit can be effectively used to optimize diagnostic procedures as well as treatment.

Conclusion

The concept of clinical audit has gone through a few evolutionary stages, which resulted in methodologies that have found wide global application in the health systems of developed countries. Clinical audit is a mandatory component of quality work of the HCI and its structural clinical units. The method of choice for conducting a clinical audit is to compare the performance of the structural unit of the HCI with a standardized patient-oriented model of the clinical route in the study. The result of the audit in this case is a reasonable (due to the standardized model), individualized (due to local characteristics) recommendations for optimizing and improving the quality of the structural unit of the HCI.

Prospects for further research are to validate and analyse the results of the proposed standardized patient-oriented model of the clinical route.

References

1. Byriukov VS. Systemy menedzhmenta kachestva i audyt v uchrezhdeniyakh zdorookhraneniya (teoriya y praktyka yndustryalizatsyy medytynskoi deiatelnosti). Kyev: Osvyta Ukrainy. 2016. 334 s. [in Russian]
2. Bohomaz VM. Vprovadzhennia klinichnoho audytu v zakladakh okhorony zdorovia. Ukraina. Zdorovia natsii. 2010; 2(14): 108-115. [in Ukrainian]
3. Zharlinska RG, Mishchuk AA. Rol klinichnoho audytu u formuvanni marketynhovo konkurentnoi stratehii zakladu okhorony zdorovia. Ekonomika, biznes-administruvannia, pravo. 2017; 2(2): 265-278. [in Ukrainian]
4. Zimenkovskiy AB, Stepanenko AV, Yereimeieva TV, Shybinskiy VYa. Suchasnyi mizhnarodnyi dosvid klinichnoho audytu (na prykladi universytetskoho shpytaliu St. George, Universytet Londona, Velyka Brytaniia). Klinichna farmatsiia, farmakoterapiia ta medychna standartyzatsiia. 2012; 1-2: 7-13 [in Ukrainian]
5. Osnovy zakonodavstva Ukrainy pro okhoronu zdorovia: Zakon Ukrainy vid 19.11.1992 r. No 2801-XII.- Vidomosti Verkhovnoi Rady Ukrainy. 1993; 4:19. [in Ukrainian]
6. Pro vnesennia zmin do nakazu Ministerstva okhorony zdorovia Ukrainy vid 28 veresnia 2012 roku No 75: Nakaz MOZ Ukrainy vid 29.12.2016 No 1422. [Internet]. Dostupno na: <https://zakon.rada.gov.ua/laws/show/z0530-17>. [in Ukrainian]
7. Smiianov VA, Stepanenko AV, Petrenko VYu, Tarasenko SV. Orhanizatsiino-metodolohichni pidkhdid do upravlinnia yakistiu medychnoi dopomohy u zakladi okhorony zdorovia. Visnyk sotsialnoi hihiieny ta orhanizatsii okhorony zdorovia Ukrainy. 2013; 3:11-18. [in Ukrainian]
8. Stepanenko AV, Smiianov VA. Mistse klinichnoho audytu v systemi upravlinnia yakistiu medychnoi dopomohy. Klinichna farmatsiia, farmakoterapiia ta medychna standartyzatsiia. 2011; 1-2:97-104. [in Ukrainian]
9. Barry K, Kumar S, Linke R, Dawes E. A clinical audit of anatomical side marker uses in a pediatric medical imaging department. J Med Radiat Sci. 2016; 63(3):148-154.
10. Imoh LC, Mutale M, Parker CT. Laboratory — based clinical audit as a tool for continual improvement: an example from CSF chemistry turnaround time audit in a South-African teaching hospital. Biochemia Medical. 2016; 26(2):194-201.
11. Mangla G, Arora R, Singh N. Clinical audit of ultrasound guided fine needle aspiration in a general cytopathology service. J Cytol. 2015; 32(1):6-11.
12. Miettunen K, Metsala E. Auditor recommendations resulting from three clinical audit rounds in Finnish radiology units. Acta Radiol. 2017;58(6):692-697.

Реферати

ВДОСКОНАЛЕННЯ ПРОЦЕСУ ОБСЛУГОВУВАННЯ ПАЦІЄНТІВ НА ПРИНЦИПАХ КЛІНІЧНОГО АУДИТУ

Гаврилюк А.О., Жарлінська Р.Г.,
Мишук А.А., Вергелес К.М., Березовський А.М.,
Пашинський Я.М., Яковцова І.І.

Метою дослідження був аналіз можливостей впровадження в діяльність ЗОЗ клінічного аудиту та узагальнення кроків, які здійснюються під час аудиту. У статті проаналізовано сучасні підходи до клінічного аудиту та існуючі моделі на принципах циклу Deming - Shewhart (PDCA). Розроблено стандартизовану модель клінічного маршруту пацієнта на принципах клінічного аудиту. Клінічний маршрут пацієнта диференційовано на блоки, які відображають принцип оптимального розподілу відповідальності між персоналом, що дозволить покращити якість медичного обслуговування пацієнтів.

Ключові слова: клінічний аудит, якість медичної допомоги, цикл Deming - Shewhart, пацієнт-орієнтований підхід, клінічний маршрут пацієнта.

Стаття надійшла 24.07.2019 р.

УСОВЕРШЕНСТВОВАНИЕ ПРОЦЕССА ОБСЛУЖИВАНИЯ ПАЦИЕНТОВ НА ПРИНЦИПАХ КЛИНИЧЕСКОГО АУДИТА

Гаврилюк А.А., Жарлинская Р.Г.,
Мишук А.А., Вергелес К.М., Березовский А.М.,
Пашинский Я.М., Яковцова И.И.

Целью исследования был анализ возможностей внедрения в деятельность учреждений здравоохранения клинического аудита и обобщения этапов, которые осуществляют в ходе аудита. В статье проанализированы современные подходы к клиническому аудиту и существующие модели на принципах цикла Deming - Shewhart (PDCA). Разработана стандартизованная модель клинического маршрута пациента на принципах клинического аудита. Клинический маршрут пациента дифференцирован на блоки, отражающие принцип оптимального распределения ответственности между персоналом, что позволит улучшить качество медицинского обслуживания пациентов.

Ключевые слова: клинический аудит, качество медицинской помощи, цикл Deming - Shewhart, пациент-ориентированный подход, клинический маршрут пациента.

Рецензент Голованова І.А.

V.M. Hladka, T.Y. Purdenko, K.A. Taryanyk
Ukrainian Medical Stomatological Academy, Poltava

PARRY-ROMBERG SYNDROME: DIFFICULTIES OF DIAGNOSIS AND IMPROVEMENT OF TREATMENT

e-mail: gladkaja@meta.ua

The article described a case of a rare disease – progressive facial hemiatrophy in a patient of the Neurological Department of Poltava Regional Clinical Hospital. We reviewed a literature on the problem, analyzed the etiological factors, pathogenesis and clinical characteristics of the disease. There was defined a range of necessary examination methods of patients, which included examination by a neurologist, rheumatologist, endocrinologist, as well as the use of additional instrumental and laboratory research methods. Comprehensive treatment tactics include the use of trophotropic, vascular drugs, anabolic hormones, potassium supplements, massage, physical therapy.

Key words: facial hemiatrophy, Parry-Romberg syndrome, neurodental syndrome.

The work is a fragment of the research project “Clinical and pathogenetic optimization of diagnosis, prognosis, treatment and prevention of complicated disorders of the central nervous system, as well as neurological disorders in somatic pathology”, state registration No. 0116U004190.

Parry-Romberg syndrome is a progressive facial hemiatrophy, neurodental syndrome. The disease incidence is 1 case per 2,000 people [1, 4]. According to the information provided by the National Organization for Rare Diseases (NORD), Parry-Romberg syndrome affects about 1,000,000 people worldwide [5]. The first mention of this disease is found in the study of English physician Caleb Hillier Parry, published in 1825. The disease was later described in detail by the German neurologist Moritz Heinrich Romberg, who included this syndrome in the category of trophoneurosis [4].

Most often, Parry-Romberg syndrome occurs at the age of 10-20 years and very rarely in people over 30 years. The prevalence is higher in women than in men in a ratio of approximately 3:0.2 [3]. The left side is affected more often than the right. Most cases are considered sporadic. At the same time, familial cases are described, presumably with autosomal recessive and autosomal dominant types of inheritance and incomplete penetrance. The etiology and pathogenesis of the disease are still unknown, there is suspicion about the multifactorial genesis. A number of authors [3] consider progressive facial hemiatrophy as a variant of scleroderma, but in contrast to systemic sclerosis, the process of atrophy is limited to unilateral skin lesions, subcutaneous tissue and is not accompanied by other manifestations of collagenosis.

In the occurrence of Parry-Romberg syndrome are important lesions of the hypothalamus, pathology of the sympathetic division of the autonomic nervous system, lesions of the superior sympathetic ganglion, trigeminal nerve system, focal lesions of the cerebral cortex. The connection of facial hemiatrophy with cerebrovascular disease in the brain stem is described [4]. The onset of the disease is sometimes preceded by injuries to the face and skull, infectious diseases. In some cases, Parry-Romberg syndrome is manifested as a syndrome of syringomyelia, syphilis, brain tumors, cerebral echinococcosis. There is an assumption that patients have congenital functional changes of the autonomic nervous system at the level of suprasegmental stem–diencephalic divisions, and these factors play the role of a “trigger” mechanism [3].

The purpose of the study was to highlight the current view of a rare disease – Parry-Romberg syndrome, the diagnosis of which presents significant difficulties, and to present our own observations with atypical clinical symptoms, as well as determining the range of necessary examination methods in such patients and improving the treatment of this disease. The relevance of this study is determined by the unexplored pathogenesis and etiology of the disease, the occurrence of a serious cosmetic defect, the lack of differential diagnostic criteria and adequate treatment regimens.

Materials and methods. The following examination methods were used to diagnose the Parry-Romberg syndrome: clinical (objective and neurological examination of the patient, consultation with a rheumatologist). Laboratory methods: complete blood count, clinical urine test, biochemical blood test (including creatine phosphokinase), electrolytes (to exclude the acute infectious process, metabolic disorders), thyroid hormones (to exclude thyroid gland disorders), rheumatoid factor tests – to clarify the presence of systemic dysplasia of connective tissue. Instrumental examinations: ECG, REG (to determine cerebrovascular disorders), electroneuromyography (ENMG) – to assess the primary lesion of a muscle or nerve structure. Neuroimaging methods (MRI of the brain – to exclude the expansive intracranial process, acute cerebrovascular accident, neurosyphilis, post-traumatic or parasitic lesions).

Results of the study and their discussion. Patient K., 59 years old, was hospitalized in the Neurological Department of Poltava Regional Clinical Hospital. Was admitted with the next complaints: facial asymmetry (left side deformity). History of the present illness: facial asymmetry occurred 2 years ago for no apparent reason. First patient noticed a thinning of the left cheek muscles, then – the forehead and later – the neck. Past medical history: grew and developed according to gender and age. Patient denied any previously suffered diseases, injuries, operations, infections. Heredity was not burdened. There was no bad habits. Clinician-observed: the patient's condition was satisfactory, the skin was normal color, vesicular respiration in the lungs, without wheezing, rhythmic heart sounds, heart rate – 74 per minute, blood pressure – 140/80 mm Hg. Body temperature was 36.6 °C. The abdomen was soft, with painless palpation. Healthy bladder and bowel habits.

Neurological status: consciousness was clear, oriented to person, place and time. There were no meningeal signs. Cranial nerves: pupils D=S, palpebral fissure – mild ptosis of the upper eyelid on the left, without nystagmus, smoothed left nasolabial fold, atrophy of the left buccinator muscle, masticatory muscles, frontalis muscles on the left, subcutaneous tissue on the left (Fig. 1a, c). The motor function of the facial muscles was preserved. There was mild hypotrophy of the left sternocleidomastoid muscle (Fig. 1b). The skin of the face and neck on the affected side was without foci of depigmentation. Deviation of the tongue to the left, mild atrophy of the muscles of the left side of the tongue, twitching of the tongue. The tone of the limb muscles was normal, the strength is sufficient, there were no pathological reflexes. Reflexes of the upper and lower extremities were of medium vivacity, without asymmetry. There was no atrophy of the limb muscles. Coordination tests were performed satisfactorily. In Romberg's standing position was stable. Violations of superficial and deep sensitivity were not detected. Pelvic functions were not impaired.



Fig. 1a. Patient K., anterior view



Fig. 1b. Patient K., lateral view



Fig. 1c. Patient K., frontalis muscles atrophy

Examination results: complete blood count, clinical urine test, biochemical blood test, electrolytes, thyroid hormones, rheumatoid factor tests – within normal limits. ECG – without pathology. The rheumatologist excluded connective tissue pathology.

REG: pulse blood volume in the left carotid system was increased, in the vertebrobasilar arterial system – reduced, in the right carotid system – normal. In all arteries there were signs of increased arterial tone. In the vertebrobasilar system there were signs of complications in venous outflow, in the carotid system venous outflow was normal.

MRI of the brain (December 22, 2017): In the left frontal lobe near the anterior horn of the left lateral ventricle, in the left side of thalamus and in the left parietal lobe area near the posterior horn of the left lateral ventricle, the foci of MRI signal hyperintensities on T2WI, FLAIR, iso-/low signal intensity on T1WI, irregularly shaped, with clear uneven contours up to 5-6 mm in diameter were determined, the MRI signal on diffusion was not changed (probably, foci of dyscirculation). Conclusion: foci of altered MRI signal of the left hemisphere of the brain (probably of vascular origin). (Fig. 2, 3).

On MRI of the cervical spine (December 14, 2017): Common degenerative disc disease of the cervical spine, stage I-II of osteochondrosis, posterior central protrusion C3-C4 of the intervertebral disc up to 2 mm. Osteophytes were up to 4 mm of C6 and C7 vertebral bodies.

ENMG: the obtained data corresponded to the primary myopathy of the facial muscles and the muscles of the left side of shoulder girdle.

Based on the history of the present illness, clinical evidence and examination results, the diagnosis was made: progressive left-sided hemifacial atrophy.

The patient was prescribed treatment: actovegin, tocopheryl acetate, piracetam, neurotrophin, neuromidin, darsonvalization of the head and neck area. It was recommended to take outpatient courses of vascular and metabolic therapy, neuroprotective agents, vitamins, physiotherapy, and massage 1-2 times a year.

Usually first develops atrophy of a particular facial area (orbital cavity, cheeks, lower jaw), atrophy of the skin and its depigmentation or hyperpigmentation, then atrophy of the subcutaneous tissue, muscles, bones. Muscle motor function was usually little disturbed. There were no objective sensitivity disorders, Horner-Bernard syndrome can be observed. Sometimes atrophy affected the neck, arm and even half of the body on the same and opposite sides. Parry-Romberg syndrome could be accompanied by alopecia, atrophy of the tongue, various occlusal disorders, refractive pathology, heterochromia of the iris.

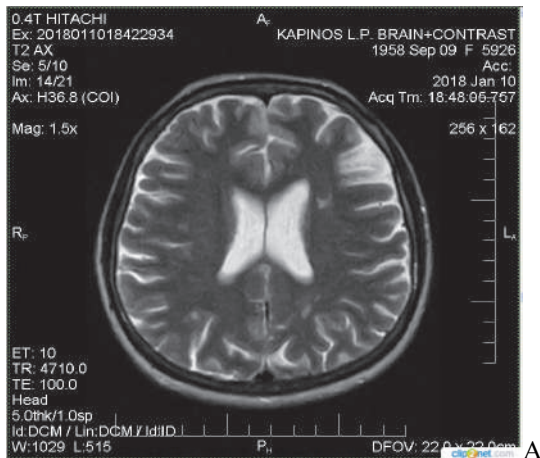


Fig. 2. T2WI MRI of the brain of patient K. (January 10, 2018)

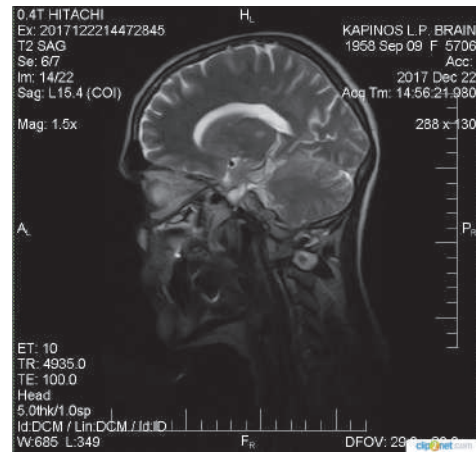


Fig. 3. T2WI MRI of the brain of patient K.. (December 22, 2017)

Facial hemiatrophy syndrome in lesions of the segmental autonomic system most often occurred due to pathology of the superior sympathetic ganglion or lateral horns of the spinal cord CVII-DII or white ramus communicans of this level. It was characterized by minor soft tissues atrophy of half side of the face, mainly cheeks, hyperpigmentation, very slow progression, frequent combination with sympathetic pain, changes in the intensity of the iris color, moderate dilation of the pupil [1].

In Parry-Romberg syndrome of the stem level, the causes were usually syringomyelia, stem encephalitis, brain tumor and other pathological processes. In syringomyelia, autonomic dysfunction in the affected side of the face was manifested by complete or incomplete Horner-Bernard syndrome, cyanosis or skin paleness, the presence of wrinkles and uneven distribution of hair, as well as pain on palpation of the neurovascular bundle running along the anterior surface of the neck. Often patients had diffuse hypotrophy of the soft tissues of the cheek, dissociated sensitivity in the arm and torso, mild bulbar disorders, horizontal nystagmus. It was characterized by the absence of a gross cosmetic defect [1].

Peripheral Parry-Romberg syndrome could be of iatrogenic origin and occurred, in particular, due to procaine-alcohol blockade in patients with trigeminal neuralgia. In these cases, trophic disorders occurred in the area of innervation of the affected communicans. They were manifested by moderate soft tissue atrophy in the area of the cheek, eyelid, lower jaw, the tip of the nose and its alae, as well as the masticatory and temporal muscles. There also were swelling of the cheeks, hair loss, focal hyperpigmentation in the fronto-temporal lobe or abundant moles on the cheek. The disease can begin with trigeminal neuralgia, then there is atrophy in any limited area. The atrophic process can spread to the corresponding side of the neck and torso, affecting the vocal cords and half of the larynx. In severe forms of the disease there is a thinning and sagging of the chin bone, jaw reduction, tooth loss. Ophthalmic symptoms occur in 15% of patients. Typical: loss of eyelashes, eyebrows, enophthalmos, ophthalmoparesis (due to atrophy of orbital tissue and extraocular muscles on the affected side), narrowing of the eyelid, keratitis [3]. The disease progresses slowly over 3-5 years, after which, as a rule, the condition stabilizes.

At affection of a cerebral cortex besides a facial hemiatrophy, neurologic symptoms of lesions of brain structures were defined (focal Jackson's and generalized epileptic seizures, upper motor neuron lesion, cerebellar disorders). At carrying out EEG, the focal epileptic activity in a homolateral hemisphere could be found. On the affected areas, there may be graying and loss of hair on the head, eyebrows and eyelashes, there is no sweating. Muscle motor function was little disturbed.

The diagnosis is based on the progressive development of tissue atrophy of one side of the body or only the face with the presence of autonomic and trophic disorders [4]. There is no radical treatment for Parry-Romberg syndrome. Therapeutic tactics include the use of trophotropic drugs, anabolic hormones, potassium supplements, anticonvulsants and dehydrators, massage, physical therapy.

In case of irreversible paralysis of the facial muscles, surgical treatment is indicated: static and kinetic suspension of the lowered tissues, musculoplasty, canthoplasty – plastic surgery for the case of the eyelid narrowing, that is, its elongation and expansion [1]. In our clinical case, there were found dyscirculatory foci in the left and left frontal and parietal lobes due to hemodynamic disturbances in the vertebrobasilar arterial system, which were the probable cause of Parry-Romberg syndrome in the patient. Thus, the above-described case of progressive facial atrophy is characterized by a typical for this disease gradual onset, slow progress with the development of facial asymmetry, atrophy of facial muscles, tongue, subcutaneous fat on the left with preserved motor muscle function.

Conclusion

Facial hemiatrophy or Parry-Romberg syndrome can be either an independent disease or a syndrome of the prior disease (scleroderma, syringomyelia, encephalitis, lesions of the sympathetic ganglion, etc.). It is advisable to comprehensively examine patients, which includes examination by a neurologist, rheumatologist, endocrinologist, as well as the use of additional instrumental and laboratory diagnostic methods (electroneuromyography, rheoencephalography, electroencephalography, MRI of the brain and cervical spinal cord). The disease requires the application of non-specific therapy, including vasoactive, metabolic drugs, antihypoxants, neuroprotectors, anticholinesterase drugs. With regard to the patient's life, the prognosis is favorable, with regard to recovery – unfavorable, but early diagnosis, regular combined treatment is necessary to achieve a positive effect.

Prospects for further research are: it is planned to continue monitoring the course of the disease in the patient, re-examination and additional courses of maintenance therapy.

References

1. Stolbova YeA, Kislitsina YeN, Epshteyn AM. Redkiy sluchay bolezni Parri-Romberga v klinicheskoy praktike. Vyatskiy meditsinskiy vestnik. 2013; 7:13-18. [in Russian]
2. Kuzina ZA, Fomina-Chertousova NA, Slatina YaV, Kovalova IP. Sindrom gemiatrofii litsa Parri-Romberga kak mezhdistsiplinarnaya problema (dermatologicheskiye, nevrologicheskiye, kosmetologicheskiye voprosy). Zhurnal fundamentalnoy meditsiny i biologii. 2012; 4:22-27. [in Russian]
3. Ivolgina IV. Sindrom Parri-Romberga. Klinicheskoy sluchay. Vestnik Tambovskogo universiteta. Seriya Yestestvennyye i tekhnicheskoye nauki. 2016; 21(2):566-569. [in Russian]
4. Mukvich AN, Belskaya YeA, Petrenko LB, Goncharenko NI, Matskevich AN. Progressiruyushchaya gemiatrofiya litsa Parri-Romberga. Sovremennaya pediatriya. 2016; 3(75):121-125 [in Russian]
5. Lobzin SV, Kula II, Raznatovskiy KI. Gemiatrofiya litsa, sindrom Parri-Romberga: klinika, diagnostika i lecheniye. Vestnik Dalnevostochnogo gosudarstvennogo meditsinskogo universiteta. 2012; 3: 108-111. [in Russian]

Реферати

СИНДРОМ ПАРРИ-РОМБЕРГА: СКЛАДНОСТІ ДІАГНОСТИКИ ТА ВДОСКОНАЛЕННЯ МЕТОДИКИ ЛІКУВАННЯ

Гладка В.М., Пурденко Т.Й., Таряник К.А.

Представлений опис випадку рідкісного захворювання – прогресуючої атрофії обличчя у пацієнтки неврологічного відділення Полтавської обласної клінічної лікарні. Проведений огляд літератури щодо проблеми, проаналізовані етіологічні чинники, патогенез та клінічні характеристики захворювання. Визначене коло необхідних методів обстеження хворих, яке включає огляд невролога, ревматолога, ендокринолога, а також використання додаткових інструментальних і лабораторних методів дослідження. Комплексна лікувальна тактика передбачає використання трофотропних, судинних засобів, анаболічних гормонів, препаратів калію, масаж, ЛФК.

Ключові слова: геміатрофія обличчя, синдром Паррі-Ромберга, нейростоматологічний синдром.

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СИНДРОМ ПАРРИ-РОМБЕРГА: СЛОЖНОСТИ ДІАГНОСТИКИ И УСОВЕРШЕНСТВОВАНИЕ МЕТОДИКИ ЛЕЧЕНИЯ

Гладка В.М., Пурденко Т.И., Таряник К.А.

Представлено описание случая редкого заболевания – прогрессирующей атрофии лица у пациентки неврологического отделения Полтавской областной клинической больницы. Проведен обзор литературы по проблеме, проанализированы этиологические факторы, патогенез и клинические характеристики заболевания. Определен круг необходимых методов обследования больных, включая осмотр невролога, ревматолога, эндокринолога, а также использование дополнительных инструментальных и лабораторных методов исследования. Комплексная лечебная тактика предполагает использование трофотропных, сосудистых средств, анаболических гормонов, препаратов калия, массаж, ЛФК.

Ключевые слова: геміатрофія лица, синдром Паррі-Ромберга, нейростоматологический синдром.

Рецензент Дельва М.Ю.

O.Y. Horodynska, L.E. Bobryyova
Ukrainian Medical Stomatological Academy, Poltava

IODINE DEFICIENCY AS A FACTOR OF THE THYROID PATHOLOGY DEVELOPMENT IN THE POLTAVA REGION

e-mail: lena.gorodinskaya@gmail.com

Iodine deficiency – a problem for the entire territory of Ukraine. It varies only in severity – from mild on the East, South and centre of the country, to moderate and severe in the mountainous areas of the Carpathians. The purpose of the work was to analyze the thyroid pathology in the Poltava region in the conditions of iodine deficiency. Assessment of the ecological situation in the Poltava region shows that this region is the zone of moderate iodine deficiency because a decline in the iodine content is observed in all aquifers of Poltava region. The preventive measures must be permanent, because iodine deficiency is impossible to eliminate, as the environmental problem. The world and domestic experience shows that the cessation of prevention leads to a rapid increase of the frequency of iodine deficiency diseases in the population. Prevention of iodine deficiency diseases is much more effective than the treatment of the iodine deficiency effects, especially since some of them (mental retardation, cretinism) are almost irreversible. Thus in the development of endemic goiter the environmental conditions of a region play a big role. The inducer of thyroid pathology in general is iodine deficiency, both direct and relative, the main cause of which is anthropogenic pollution (fluoride, of radionuclide, etc.). That is endemic goiter or iodine deficiency has regional differences related to the environmental conditions of that particular region.

Key words: thyroid gland, thyroid pathology, iodine deficiency disease, iodine, fluorine, radionuclide contamination.

The work is a fragment of the research project "Development of a strategy for the use of epigenetic mechanisms for prevention and treatment of diseases associated with systemic inflammation", № 0114U000784.

The term "iodine-deficient diseases" (IDD) is used for all unfavorable influences of iodine deficient (direct or indirect) on the growth and the development of organism and for the forming of infant brain first of all. The prevalence of regions with iodine deficiency in the biosphere is large. According to the data of WHO and UNISEPH, approximately 1.5 billion persons with high risk of IDD development live in these regions. In 200 million (from the total number of such persons) the goiter is diagnosed. About 3 million persons have endemic cretinism. Millions of persons suffer from more mild form of psychomotor disorders. As the iodine resorption by the thyroid gland in endemic regions is increased, the gland is more sensitive to radioactive effect. These cases were registered after the accident at the Chernobyl Nuclear Power Plant. The most fatal consequences of iodine deficiency are the birth of defective intellect babies. Ukraine (the third part of it is iodine deficient) inaugurates one school every year for defective intellect children. In some generations it can lead to intellectual degeneration of nation [1-3, 9, 10].

The purpose of work was to analyze the thyroid pathology in the Poltava region in the conditions of iodine deficiency.

Materials and methods. The study of iodine, fluorine and radionuclides containing in drinking water, what Poltava region residents use, was held and analyzed morbidity of thyroid disease in Ukraine and Poltava region. Comparative characteristics of thyroid pathology in the last 20 years have been carried out with the assistance of the annual review of the Ministry of Health of Ukraine and the Institute of Endocrinology and Metabolism "Main indicators of activity of the endocrinological service of Ukraine". Statistical processing of the data was carried out using the standard package of statistical calculations of Microsoft Excel.

Results of the study and their discussion. It should be noted that the water supply districts of Poltava region is provided by three basic water-bearing stratum: the Senoman-lower-cretaceous, Buchatsky and Alluvial. Evaluating the ecological situation in the Poltava region, we note that this region is the zone of moderate iodine deficiency because a decline in the iodine content in all aquifers of Poltava region. Increases insufficiency of iodine the increased level of fluoride in Buchach water-bearing stratum, which provides water to 42.3% of districts of Poltava region. Fluorine is more active halogen, entering the tissue of the thyroid gland, inhibits of the thyroid peroxidase and organification iodides in the thyroid gland, which leads to the decrease in the synthesis of thyroid hormones [1].

The analysis of the prevalence of disease of the thyroid gland in Ukraine and in Poltava region indicates that beginning with 1980 to 2003 has increased not only the amount of thyroid pathology in general, but also changed its structure. This period of time is taken not by chance – at the Chernobyl nuclear power plant occurred the accident in April 1986. In the environment has been thrown a huge number of short - and long-lived radionuclides, which played a role in the development of thyroid pathology. So, only since 1989 have started to be recorded in the reports of diseases such as nodular goiter, thyroiditis, cancer

of thyroid gland, simple and inadjusted goiter of 1-2 degrees (up to that point had recorded only its 3-5 degree increase).

It should be noted that for the last 20 years in the Poltava region thyroiditis increased proportion of 54.5 times, while in Ukraine - in 31.7, 18.3 times increased volume of nodular goiter, in Ukraine it rise to 12, 7 times, thyroid cancer increased up to 0.6 times, in Ukraine – up to 0,4 times; hypothyroidism – up to 3.6 times, this pathology has grown up to 4.2 times in Ukraine in general and the proportion of diffuse toxic goiter - a total of 1.3 times, in Ukraine - 3.1 times [1].

According Yarmonenko S. [7] glands of internal secretion is radioresistant, including the thyroid gland. The radiosensitivity of the thyroid gland increases sharply in a state of hyperplasia. The hyperplasia or goiter of I-II degree is dominant of all the pathology of the thyroid gland, in the period after the Chernobyl accident. Thus, we can assume, that radionuclides with short half - life - Ra224, J131 - are bombarding tissue, depriving them of "radioprotection" and then on "unprotected" tissue affect radionuclides with a long half-life (U234, U235, U238, Ra226, Sr89, Sr90, etc.), that is, in the development of hyperplasia of the thyroid gland play a big role radionuclides with short half-life, and in the development of thyroid cancer - radionuclides with long half-life.

Thus, the group of patients with hyperplasia of the thyroid gland should be considered as "the risk group" for thyroid cancer and, of course, from this group should start preventive measures (fig. 1).

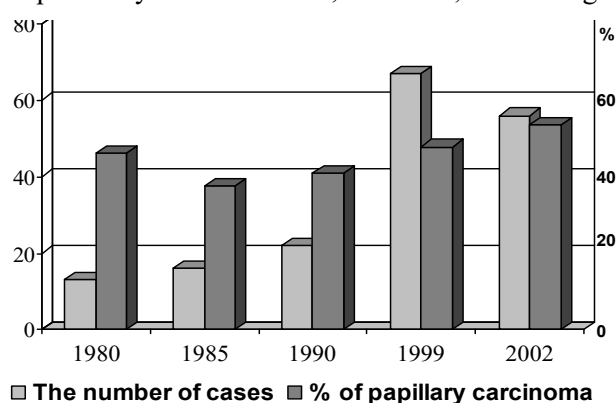


Fig. 1. Number of cases and percentage of papillary carcinoma in patients with hyperplasia of the thyroid gland.

Radiation induced thyroid cancer is papillary cancer. We studied the data of histological examination of remote tumors of the thyroid gland - with malignant neoplasms, there were papillary, follicular, medullary, and undifferentiated carcinoma and others [1, 6, 8].

It should be noted that patients who were born in 1968 and later operated on for thyroid cancer, the papillary cancer is dominated, in 1999 of 6 cases of thyroid cancer in 33.3% is papillary cancer, in 2000 of 5 cases – in 100% is papillary cancer, in 2001 of 9 cases – in 77,8% is papillary cancer and in 2002 of 6 cases – in 66,7% is also papillary cancer.

One of the most significant indicators of the prevalence of severity of iodine deficiency diseases is the frequency of goiter in children of primary school age. Nowadays, the term "goiter" refers to any increase in thyroid in excess of the physiological norm. The size of the thyroid gland is determined by palpation or with the help of ultrasonography. Modern classification of goitre has been adapted by experts for mass screening of thyroid disease and takes into account the growth of the child. The volume of one lobe of the thyroid gland in norm does not exceed the size of the distal phalanx of the thumb of the examinee [1, 3, 4].

As the critical point of the prevalence of thyroid disease in the population of children of primary school age selected the threshold of 5%, which allows to take into account the fact, that the goitre may develop and in the population with normal iodine content due to other causes (autoimmune thyroiditis, the effect of goitrogenic, etc.). If the frequency of the goiter at carrying out of screening studies exceeds 5%, problems with provision of iodine of the population proved. In regions with iodine deficiency of medium severity and subject to the effects of other goitrogenic (industrial pollutant, poor nutrition of the population, of excess pesticides and herbicides in the soil, water chlorination, etc.) frequency of the goiter may exceed 20%, and in severe iodine deficiency – 40% [3, 5, 11].

Since 2007, an additional criterion of the severity of IDD in the population recognized the frequency of newborns with hyperthyrotropinemia – levels of TSH above 5 mu/l according to the data of neonatal screening for congenital hypothyroidism. Numerous studies have shown that in regions with adequate iodine provision of the population, including pregnant women, those children are born down to 3%. The higher the degree of iodine deficiency, the more disturbed hormonogenesis of the thyroid of mother and fetus, the higher the frequency of neonatal hyperthyrotropinemia [1, 2, 5].

Implementation of prevention of IDD considering regional features of iodine deficiency more efficiently, than treating the consequences of iodine deficiency, especially as some of them (mental retardation, cretinism) is practically irreversible. Daily need for iodine is extremely small is 3-5 g of iodine. The norm of iodine should receive daily, year after year. It's enough to forget about it, as iodine deficiency reminds of itself. Real consumption of iodine in Ukraine is only 40-60 mg a day that two to three times

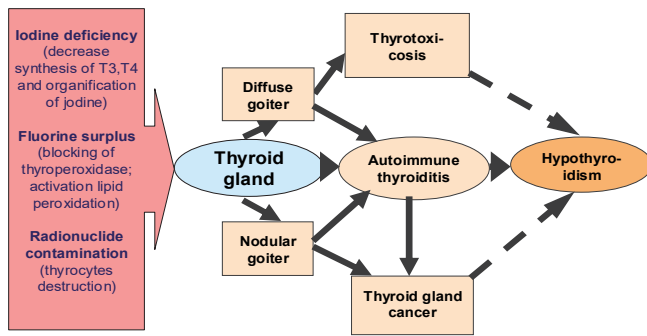


Fig. 2. Scheme of the thyroid pathology occurrence resulting from the iodine deficiency.

lower than the recommended level, which requires the implementation of measures for the prevention of mass and group, taking into account regional differences in iodine deficiency (fig. 2).

For optimal realization of this program it is essential to implement educational activities among all groups of population (the organization of endocrinology clinics at schools and to highlight this problem in the media) [1, 8, 10].

Conclusions

Thus in the development of endemic goiter the environmental conditions of a region play a big role. The inductor of thyroid pathology in general is iodine deficiency, both direct and relative, the main cause of which is anthropogenic pollution (fluoride, of radionuclide, etc.). That is endemic goiter or iodine deficiency has regional differences related to the environmental conditions of that particular region. In this case, environmental conditions are such that the primary pathology is nodular goiter, thyroiditis autoimmune etc. More than half of autoimmune thyroiditis ends the development of hypothyroidism. On this basis, treatment and prevention of endemic goiter should be carried out taking into account the environmental conditions of the region concerned.

References

1. Bobryyova LYe, Dvornyk IL, Muravlyova OV, Gorodynska OYu. Diagnostyka ta likuvannya yododefitsytnykh zakhvoryuvan: navchalnyi posibnyk. Poltava; 2016. 142 s. [in Ukrainian]
2. Botsyrko VI. Endemichnyy zob. Zdorovya Ukrainy. 2011; 2:50-51. [in Ukrainian]
3. De Benua B, Shvets OV. Ustraneniye defitsita yoda — odna iz klyuchevykh zadach zdavookhraneniya. Mezhdunarodnyi endokrinologicheskii zhurnal. 2011; 6(38):9-17. [in Russian]
4. Karachentseva YuI, Kazakova AV. 100 izbrannykh lektsiy po endokrinologii (vtoroy vypusk). Kharkov: "S.A.M."; 2014. 1000 s. [in Russian]
5. Pankiv BI. Praktychna tyreoyidolohiya. Donetsk: Vydavets Zaslavskiy OYu; 2011. 223 s. [in Ukrainian]
6. Tronko MD, Polumbryk MO, Kravchenko VI, Balyon YaH. Naukovi aspekty vyrishennya problemy yododefitsytu u naseleण्या Ukrainy. Endokrynolohiya. 2011; 16(2):189-199. [in Ukrainian]
7. Yarmonenko SP. Radiobiologiya cheloveka i zhivotnykh. Moskva: Vyssh.shk.; 1988: 424 s. [in Russian]
8. Jochner S, Thamm M, Schmits R. Is measurement of iodine concentration consistently reliable to assess iodine status. Eur. Thyroid J. 2014; 3(1):115-123.
9. Leung AM, Braverman LE. Consequences of excess iodine 2013. Nat. Rev. Endocrinol. 2013; 10:P. 251-259.
10. Pearce EN, Andersson M, Zimmermann MB. Globalnaya situatsiya s obespecheniem yodom v 2013 godu. Gazeta "Zdorovya Ukrainy". Tematychnyi nomer "Endokry`nologiya". 2013 Jan; 34-35.
11. Vanderpump MPJ. The epidemiology of thyroid disease. Br. Med. Bull. 2011; 99(1): 39-51.

Реферати

ЙОДДЕФИЦИТ ЯК ФАКТОР РОЗВИТКУ ТИРЕОЇДНОЇ ПАТОЛОГІЇ В ПОЛТАВСЬКІЙ ОБЛАСТІ

Городинська О.Ю., Бобирьова Л.С.

Йодний дефіцит - проблема актуальна для всієї території України. Різниця полягає тільки в його тяжкості - від легкого на сході, півдні та в центрі країни до середньотяжкого і важкого в гірських районах Карпат. Метою дослідження було провести аналіз патології щитовидної залози в Полтавській області за умов йоддефіциту. Оцінюючи екологічну ситуацію в Полтавській області, можна відзначити, що дана область відноситься до зони помірного йодного дефіциту, оскільки відзначається зниження вмісту йоду по всім водоносним горизонтам Полтавської області. Профілактичні заходи повинні бути постійними, оскільки йодний дефіцит як екологічну проблему ліквідувати неможливо. Світовий і вітчизняний досвід показують, що припинення профілактики призводить до швидкого зростання частоти йоддефіцитних захворювань в популяції. Здійснення профілактики йоддефіцитних захворювань набагато ефективніше, ніж лікування наслідків йодного дефіциту,

ЙОДДЕФИЦИТ КАК ФАКТОР РАЗВИТИЯ ТИРЕОИДНОЙ ПАТОЛОГИИ В ПОЛТАВСКОЙ ОБЛАСТИ

Городинская Е.Ю., Бобирева Л.Е.

Йодный дефицит – проблема актуальная для всей территории Украины. Разнится только в его тяжести – от легкого на востоке, юге и в центре страны до среднетяжелого и тяжелого в горных районах Карпат. Целью исследования было проведение анализа патологии щитовидной железы в условиях йоддефицита. Оценивая экологическую ситуацию в Полтавской области, можно отметить, что данная область относится к зоне умеренного йодного дефицита, поскольку отмечается снижение содержания йода по всем водоносным горизонтам Полтавской области. Профилактические меры должны быть постоянными, поскольку йодный дефицит как экологическую проблему ликвидировать невозможно. Мировой и отечественный опыт показывают, что прекращение профилактики приводит к быстрому росту частоты йоддефицитных заболеваний в популяции. Осуществление профилактики йоддефицитных заболеваний гораздо эффективнее, чем лечение последствий йодного дефицита, тем более, что некоторые из них (умственная

тим більше, що деякі з них (розумова відсталість, кретинизм) практично незворотні. Таким чином, у розвитку зобної ендемії велику роль відіграють екологічні умови відповідного регіону. Індуктором тиреоїдної патології в цілому є йододефіцит, як прямий, так і відносний, основною причиною якого є техногенне забруднення навколишнього середовища (фтористі з'єднання, радіонукліди і ін.). Тобто зобна ендемія або йододефіцит має регіональні відмінності, які пов'язані з екологічними умовами цього чи іншого регіону.

Ключові слова: щитовидна залоза, патологія щитовидної залози, йододефіцитні захворювання, йод, фтор, забруднення радіонуклідами.

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отсталость, кретинизм) практически необратимы. Таким образом, в развитии зобной эндемии большую роль играют экологические условия соответствующего региона. Индуктором тиреоидной патологии в целом является йододефицит, как прямой, так и относительный, основной причиной которого является техногенное загрязнение окружающей среды (фтористые соединения, радионуклиды и др.). То есть зобная эндемия или йододефицит имеет региональные различия, связанные с экологическими условиями этого или иного региона.

Ключевые слова: щитовидная железа, патология щитовидной железы, йододефицитные заболевания, йод, фтор, загрязнение радионуклидами.

Рецензент Костенко В.О.

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S.O. Guryev¹, N.I. Iskra, V.Y. Kuzmin, P.V. Tanasienko¹
P.L. Shupik National Medical Academy of Postgraduate Education, Kyiv
¹SI "Ukrainian Scientific and Practical Center of Emergency Medical Care
and Disaster Medicine MOH of Ukraine", Kyiv

COMMON LABORATORY DIAGNOSTIC DATA ANALYSIS OF PATIENTS WITH DUPUYTREN'S CONTRACTURE AT THE STAGES OF PATHOLOGICAL PROCESSES IN PALM APONEUROSIS

e-mail: radix.vn@ukr.net

The study of the characteristic features of laboratory data in patients with Dupuytren's contracture, which in the past was verified as having been exposed to ionizing radiation, showed that in the examined patients with Dupuytren's contracture there is a concordance of the fibrous process in the palmar aponeurosis and liver, and the pathological process in the liver is one of the primary pathogenetic links in the formation of contracture. It was revealed that there is a relationship between the degree of fibrous liver damage and the biochemical blood parameters of patients with Dupuytren's contracture.

Key words: Dupuytren's contracture, liver fibrosis, connective tissue, ionizing radiation.

The work is a fragment of the research project "Determination of the connective tissue pathology etiopathogenesis in victims after radiation accidents based on which the pathogenetic justification for the victims treatment will be developed", state registration No. 0118U002106.

Frequent connective tissue pathology symptoms regularity is diagnosed as neuromuscular affect and lesions of the joint, which may be characterized by muscle weakness, myalgia, arthralgia, arthritis (mostly observed symmetrical joint damage). This fact is proved by the logical progress of symptoms of various extrahepatic manifestations, among which the DC often comes to the fore in the clinical picture and a significant number of experts consider DC as a typical stigma for patients with chronic alcoholic hepatitis [3, 4, 5].

The worldwide studies of the impact of ionizing radiation on the connection tissue were carried out, but those studies were carried out in experiments at significant irradiation doses for a very short time without regard to radionuclide incorporation.

Statistics points out the increase in the prevalence of clinically manifested pathology of connection tissue in individuals exposed to ionizing radiation and scientists describe such phenomena [2, 4, 6].

The purpose of the study was to identify the typical peculiarities of common laboratory data of patients with Dupuytren's contracture who had been exposed to ionizing radiation (this fact was verified and confirmed by state register records) at different stages of the pathological process in the liver with determination of typical morphological changes till pathological changes in the tissues of the palm aponeurosis.

Materials and methods. The results of our work are based on the integrated dynamic supervision data of the individuals (accident liquidators of the Chernobyl nuclear power plant (ChNPP)) with Dupuytren's contracture (DC) performed on the basis of the clinic of radiation registry of the National Academy of medical Sciences (NAMS) of Ukraine in 2002 through 2012. The study used case follow-up cards and patient's chart stored in the archive of the National Research Center for Radiation Medicine (NRCRM) of NAMS of Ukraine, military hospital in Irpin and surgical departments of the Kyiv City Emergency Care Hospital (KCECH).

To achieve the purpose, we examined 188 patients (male, aged 41-71 years) with DC, which were treated in the hospital of NRCRM of NAMS of Ukraine, the military hospital in Irpin and surgical departments of the KCECH. All patients were operated because of calculous cholecystitis.

The duration of the pathological process in the liver and palmar aponeurosis for all the patients was as follows: up to 5 years; 5 to 10 years; 10 and more years. Depending on the liver fibrosis stage (F) the patients were divided into 3 groups. The first group included 110 patients who had the I-st stage of liver fibrosis (F1); the second group – included 59 patients with II-nd stage of liver fibrosis (F2); the third group included 19 patients who had III-rd stage of liver fibrosis (F3).

All the patients passed through laboratory blood analysis, fiber test using BioPredictive method (France), elastometry and liver biopsy.

All calculations were carried out according to the requirements and criteria of the evidence-based medicine, and the results are within the range of probability.

Mathematical methods of parametric statistics were applied to estimate the statistical probability of materials obtained during the study. The study was performed in the circumference of the necessary and sufficient, selection of each trait was by performed by the method of irreversible randomization and the formation of controlled randomized groups (clusters) applied parametric statistics methods using the Student's coefficient and determining the mean errors in each cluster.

Results of the study and their discussion. The analysis of DC degree variation with liver fibrosis stage showed that the inspected patients with liver fibrosis stage F1 were dispersed among DC degrees I, II and III in about the same quantity. Among patients with stage of liver fibrosis F2 the DC degree II was found in almost half of cases (49.2%). At the same time among patients with liver fibrosis stage F3 the majority of individuals (57.9%) had DC degrees III. The mean age of patients with DC and liver fibrosis stage F1 was 47 ± 0.7 years old. 47% of the inspected patients were in the age cohort of 41-50 years, 29% – 51-60 years; the rest – 61-70 years (table. 1).

The mean age of patients with second stage of liver fibrosis (F2) was 49 ± 0.8 years: 30% of the studied patients were within the age cohort of 41-50 years, 39% – 51-60 years; the rest – 61-70 years. The mean age of patients with DC and third stage of liver fibrosis (F3) was 49 ± 0.9 years. Among patients of this group 37% were in the age of 41-50 years, 29% – 51-60 years, and the rest – within the age of 61-70 years.

Table 1

Variation of Dupuytren's contracture degree with liver fibrosis stage

DC degree	Liver fibrosis stage		
	F1 (n=110)	F2 (n=59)	F3 (n=19)
I (n=62)	42 (38.2%)	18 (30.5%)	2 (10.5%)
II (n=65)	30 (27.3%)	29 (49.2%)	6 (31.6%)
III (n=61)	38 (34.5%)	12 (20.3%)	11 (57.9%)
Total	110 (100%)	59 (100%)	19 (100%)

All the inspected were passing through blood tests until the appearance of clinical symptoms and during the treatment. Till clinical manifestations the inspected patients' leucogram was characterized by a tendency to increase the total number of white blood cells, increase in blood relative of band, segmented neutrophils and the percentage decreasing of lymphocytes. ESR was 1.8 times higher than the reference.

At the same time for patients with DC moderate activity of chronic hepatitis the deviations of blood values received from the clinical blood analysis were often observed: reducing the number of red blood cells in 41.3% of cases, hemoglobin – 36.9%, leukocytes – 41.3%, neutrophils – 58.7%. The eosinophilia was found in 65.2% of patients, relative lymphocytosis (absolute lymphocyte content was maintained at a physiological level) – in 6.5% and acceleration of erythrocyte sedimentation – in 50%.

When biochemical indices were studied the raised index of gamma glutamine transferase (GGT) was registered in all the patients, and high levels of alkaline phosphatase (ALP) – in 58 (44.6%) patients. 88 (66.6%) patients had a protein synthesis dysfunction in liver as hypo-, dysproteinemia, reduction of prothrombin.

Comparison of the mean values of basic hematological parameters appointed by analysis procedure for patients suffering from DC with liver fibrosis revealed slight deviations from the control group (table 2.).

An increased number of leukocytes, lymphocytes, eosinophiles, monocytes and decreased content of segmented and stab neutrophils was detected in patients with DC with liver fibrosis stage F1. However, none of the mean values of the aforementioned parameters have exceeded significantly the accepted standards. The analysis of the frequency of clinical blood test parameters deviations from the reference

demonstrated that the platelet count was reduced in 9 (8%) patients, neutrophils – in 26 (24%). 13 (12%) patients had a slight eosinophilia. Other indices of peripheral blood deviated from the reference occasionally.

Table 2

Peripheral blood hematological indicators for patients with Dupuytren's contracture depending on liver fibrosis degree

Indices	Study groups				Reference range
	F1 (n=110)	F2 (n=59)	F3 (n=19)	Control (n=45)	
leukocytes, $\times 10^9/l$	6.2 \pm 0.16 p<0.05	5.9 \pm 0.18	6.4 \pm 0.44 p<0.05	5.63 \pm 0.17	4.0-8.8
lymphocytes, %	38.03 \pm 0.76	39.5 \pm 1.37	37.2 \pm 1.56	37.23 \pm 0.57	19-37
lymphocytes, $\times 10^9/l$	2.34 \pm 0.07 p<0.05	2.3 \pm 0.1 p<0.05	2.35 \pm 0.17 p<0.05	1.31 \pm 0.23	1.5-2.4
erythrocytes, $\times 10^9/l$	4.9 \pm 0.04	4.8 \pm 0.05	4.9 \pm 0.08	4.73 \pm 0.05	4.0-5.5
hematoglobulins, g/l	150.2 \pm 0.99	148.3 \pm 1.53	151.7 \pm 3.19	146.40 \pm 1.58	130-160
platelets, $\times 10^9/l$	255.6 \pm 4.79	242.6 \pm 4.77	258.9 \pm 6.98	251.80 \pm 5.24	180-320
segmented neutrophils, %	51.2 \pm 0.83 p<0.05	49.5 \pm 1.31 p<0.05	53.7 \pm 1.65	56.17 \pm 0.65	47-72
stab neutrophils, %	0.8 \pm 0.09 p<0.05	0.8 \pm 0.14 p<0.05	0.47 \pm 0.16 p<0.05	1.60 \pm 0.16	1-6
eosinophiles, %	3.1 \pm 0.25 p<0.05	2.98 \pm 0.28	2.21 \pm 0.44	2.31 \pm 0.27	0.5-5
basophils, %	0.24 \pm 0.05	0.34 \pm 0.08	0	0.31 \pm 0.09	0-1
monocytes, %	6.3 \pm 0.25 p<0.05	6.7 \pm 0.36 p<0.05	6.3 \pm 0.47 p<0.05	2.37 \pm 0.35	3-11

Note. p – is the probability of a difference compared to the control group.

Similar, but less numerous changes (compared with control group), namely an increased number of lymphocytes, monocytes and decreased content of segmented and stab neutrophils were detected in patients with DC with liver fibrosis stage F2. Just as in the group of F1, the mean values of changed indices didn't significantly differ from the reference ones. Indices of the deviation frequency analysis based on clinical blood test showed that platelet count was reduced in 8 (13%) patients and neutrophils count - in 22 (38%).

7 (12%) patients had a slight eosinophilia. Other indices of deviations from the reference were fixed occasionally.

Patients with liver fibrosis stage F3 who suffered from DC had the indices main value that differed from the reference ones in the following: the increased number of leukocytes, lymphocytes, monocytes; the decreased number of stab neutrophils. However, the only index, namely, the content of stab neutrophils was significantly reduced compared to the lower limit of reference. The analysis of the frequency of deviations of the clinical blood test parameters from the reference ones demonstrated that the neutrophils number was reduced in 3 (15.8%) patients. 2 (10.5%) patients had slight eosinophilia. Other indices of clinical blood test deviated from the reference occasionally.

Since in the vast majority of patients with DC the key indices of peripheral blood were within the reference, it is possible to summarize that the found tendency to change notably the tendency to leuko-, lympho-, eozyno- and monocytosis and neutropenia is not clinically significant. The only notable and the most probabilistic breach which should be admitted is moderate stab neutropenia in patients with DC and with the liver fibrosis stage F3, but in our opinion, such an infringement is directly associated neither with any pathological process in the liver nor with the development of contractures.

The study of the biochemical blood tests results of the affected by DC revealed the presence of moderate cytologic and dysproteinemic syndromes (table. 3).

For the patients with DC and liver fibrosis stage F1 a significant increase of alanine aminotransferase ALT, aspartate aminotransferase AST and ALP was revealed when the average values were compared with reference group indicators.

It should be noted that this increase was significant not only in comparison with the reference group, but also in comparison with the upper limit of the admitted standards.

The fact that a significant increase in serum iron and γ -globulin content of protein fractions and reduction of albumin by comparison with the control and reference limits was fixed for patients with DC and fibrosis stage F1. In addition, the thymol test indicator tended to grow but it didn't exceed the upper limit, so this trend cannot be considered as clinically significant.

Frequency analysis of biochemical blood parameters deviation from the reference values showed that 89 (81%) patients with DC and first degree of fibrosis had the raised level of ALT, 68 (62%) patients had the raised level of AST, 77 (70%) – of ALP, 88 (80%) – of serum iron, 63 (57%) of β -globulins and

63 (57%) of γ -globulins relative content. 34 (31%) patients had the increased thymol level. The reduced content of albumin in the group of first degree of liver fibrosis (F1) was observed in 62% of cases.

Table 3

Biochemical blood indicators variations with liver fibrosis degree for patients with Dupuytren's contracture

Indices	Study groups				Reference range
	F1 (n=110)	F2 (n=59)	F3 (n=19)	Control (n=65)	
ALT, units/l	157.2±12.9 p<0.001	130.9±16.3 p<0.001	168.9±27.4 p<0.001	29.4±2.4	8-54
AST, units/l	73.1±6.3 p<0.01	71.4±9.7 p<0.01	70.7±11.4 p<0.01	25.3±2.2	16-40
ALP, units/l	131.3±5.7 p<0.01	124.3±8.8 p<0.01	119.5±13.6 p<0.01	52.7±3.9	36-92
PTI, %	88.5±1.1	88.7±2.2	89.8±2.9	92.5±6.3	80-105
Total protein, g/l	75.25±0.9	76.3±0.9	75.9±1.2	72.3±3.8	63-87
Thymol test, units	3.6±0.3 p<0.05	3.2±0.4	4.7±0.8 p<0.05	2.0±1.0	0-4
Serum iron, μ M /l	37.8±4.4 p<0.001	24.3±3.2	25.7±2.1 p<0.05	17.8±3.6	10.5-25.0
Globulins, g/l	30.5±0.7	30.8±1.2	33.2±1.2	26.0±4.5	17-35
Albumins, g/l	44.9±0.5	44.9±0.6	42.7±0.6	42.5±6.3	30-55
Albumins, %	48.6±0.7 p<0.05	51.3±1.2	53.4±1.9	55.9±1.8	52.0-65.0
α_1 - globulins, %	3.9±0.14	4.4±0.3	3.6±0.3	3.5±0.6	2.5-5.0
α_2 - globulins, %	10.6±0.3	9.75±0.3	9.6±0.7	9.4±0.8	7.0-13.0
β - globulins, %	15.0±0.4	13.3±0.4	13.5±0.9	12.0±1.1	8.0-14.0
γ - globulins, %	22.4±0.5 p<0.05	21.7±0.8	20.4±1.0	18.7±1.7	12.0-18.0

Note. p – the probability of a difference compared to the control group.

A significant increase of ALT, AST and ALP was revealed in patients with DC and liver fibrosis stage F2 like the group of patients with F1. There weren't other changes in the indices according to the mean values comparison results.

Frequency analysis data of biochemical parameters deviation from the reference values showed that 46 (78%) patients with DC and second stage of fibrosis (F2) had the raised value of ALT, 29 (49%) patients had the raised value of AST, 37 (63.5%) – of ALP, 29 (50%) – of serum iron, 19 (33%) of β -globulins and 29 (50%) – of γ -globulins relative content.

Thymol exceeded the reference values in 14 (23%) cases. As well as in the case of the patients with F1, 62% of the patients with the liver fibrosis stage F2 had the decreased albumin relative content.

Like patients with fibrosis stage F1 and F2, patients with DC and liver fibrosis of the third stage (F3) had a significant increase of ALT, AST and ALP, and of the thymol test index. It was revealed by biochemical blood analysis. These changes were found significant when they were compared to the control and the upper limit of the reference. At the same time the raised level of serum iron was found only after the main values had been compared, but it was inconspicuous compared to reference limits.

Patients with liver fibrosis of the third stage (F3) had the increased ALT in 17 (88.9%) cases, AST – in 12 (63.1%), ALP – in 13 (68.7)%, serum iron – in 9 (50%) cases, the relative content of β - and γ -globulins – in 5 (28.6%) and 8 (42.9%) cases, respectively. Thymol exceeded the reference values in 60% of cases. The albumin relative content was reduced in 4 (21.4%) cases of the group with the third stage fibrosis.

The data of our study correlated to some extent with the data of on the pathogenetic features of fibrosis development, but the development rates were 30% less than our findings which can be explained by the impact of ionizing radiation [2, 7]. The role of liver and hepatogenic fibrosis in the development of DC is indicated also in the study [5], however, the correlation between liver disease and fibrosis was significantly lower (6.8%) in these studies. The role of fibro genes has also been thoroughly examined in [8], whose data on fibrogenesis correlated with our results but did not take into account the ionizing factor. The relationship of DC and factors of liver injury were pointed out, but there was no verification of the fibrosis itself in his work indicating correlation of liver fibrosis and DC, but this was not proven at a probable level [9]. Similar opinion was stated in the works by some researchers, however, all indices were 29-50% lower due to the fact that the studied contingent was not exposed to ionizing radiation [1]. Data analysis indicates that there is some correlation of liver pathology and palm aponeurosis, but there is no data on patients with irradiation, so the correlation of indices is not correct [9]. Thus our studies have almost no analogues at present.

Conclusions

1. Based on the study results one can say with high probability that there is a coherence between two processes: palmar aponeurosis and liver fibrosis process on the one hand and the pathological process in the liver on the other hand. It is one of the primary pathogenetic elements which form the Dupuytren's contracture.

2. The examined patients having Dupuytren's contracture had an association between the stage of liver injury and fibrous blood biochemical indicators. The patients with Dupuytren's contracture and the liver fibrosis stage F1 had the most notable changes in biochemical blood parameters. These changes demonstrate the active development of the pathological process in the liver. Patients from group F1 should be classified as "prospectively dangerous", and palm deformity should not be considered as completed.

3. According to the results of biochemical examination, patients with the liver fibrosis stage F2 have stabilization of the pathological process in the liver, which is often accompanied by the formation of the second degree of Dupuytren's contracture. Such patients may be considered as the most "biochemically stable".

4. For patients with the liver fibrosis stage F3 pathological processes in the liver are less active than in those with F1, but deeper than in F2 patients, and they are mostly associated with the formation of Dupuytren's contracture of stage III.

References

1. Shchudlo NA, Shchudlo MM, Stupina TA. Patomorfologicheskie osobennosti kontraktury Dyupuytrena u patsienta s boleznju pecheni. Geniy ortopedii. 2019; 4(25):576-579. doi:10.18019/1028-4427-2019-25-4-576-579. [in Russian]
2. Bogdanov I, Rowland Payne C. Dupuytren's contracture as a sign of systemic disease. Clin. Dermatol. 2019; 37(6):675-678. doi: 10.1016/j.clindermatol.2019.07.027
3. Butaev CZ, Kuklin IA. Treatment of Dupuytren's Contracture at the Present Stage. Acta Biomedica Scientifica. 2019; 4(6):72-76. doi:10.29413/ABS.2019-4.6.11
4. Hoang D, Steven P, Chen VW, Stasiak A, Cohen M. Use of Acellular Dermal Matrix Following Fasciectomy for the Treatment of Dupuytren's Disease. Plast Reconstr Surg Glob Open. 2019 May 23; 7(5):2263. doi: 10.1097/GOX.0000000000002263
5. Nanchahal J, Ball C, Davidson D, Sones W. Anti-Tumour Necrosis Factor Therapy for Dupuytren's Disease: A Randomised Dose Response Proof of Concept Phase 2a Clinical Trial. EBioMedicine. 2018 Jul; 33:282-288. doi:10.1016/j.ebiom.2018.06.022
6. Okano J, Arakawa A, Ogino S, Suzuki Y. Bilateral plantar fibromatosis complicated by Dupuytren's contracture. J Surg Case Rep. 2020 Feb 28; 2020(2):rjz402. doi: 10.1093/jscr/rjz402
7. Orenstein JM. An ultrastructural pathologist's views on fibroblasts, modified smooth muscle cells, wound healing, stenosing arteriopathies, Kawasaki disease, Dupuytren's contracture, and the stroma of carcinomas. Ultrastruct Pathol. 2020 Jan 2; 44(1):2-14. doi: 10.1080/01913123.2019.1704332
8. Shchudlo N, Varsegova T, Stupina. Assessment of palmar subcutaneous tissue vascularization in patients with Dupuytren's contracture. World J Orthop. 2018 Sep 18; 9(9): 130-137. doi: 10.5312/wjo.v9.i9.130
9. Vaughan MB, Xu G, Morris TL, Kshetri P, Herwig JX Predictable fibroblast tension generation by measuring compaction of anchored collagen matrices using microscopy and optical coherence tomography. Cell Adh Migr. 2019 Dec; 13(1):303-314. doi: 10.1080/19336918.2019.1644855

Реферати

АНАЛИЗ ЛАБОРАТОРНИХ ДАНИХ У ХВОРИХ НА КОНТРАКТУРУ ДЮПУИТРЕНА НА ЭТАПАХ ФОРМУВАННЯ ПАТОЛОГІЧНОГО ПРОЦЕСУ У ДОЛОННОМУ АПОНЕВРОЗІ

Гур'єв С.О., Іскра Н.І., Кузьмін В.Ю.,
Танасієнко П.В.

Визначення характерних особливостей загальнолабораторних даних хворих на контрактуру Дюпюитрена, які в минулому верифіковано зазнали впливу іонізуючого опромінення, показало, що у обстежених хворих на контрактуру Дюпюитрена має місце конкордатність фіброзного процесу в долонному апоневрозі та печінці і патологічний процес у печінці є однією з первинних патогенетичних ланок формування контрактури. Виявлено, що існує асоціація між ступенем фіброзного ураження печінки та біохімічними показниками крові хворих на контрактуру Дюпюитрена.

Ключові слова: контрактура Дюпюитрена, фіброз печінки, сполучна тканина, іонізуюче опромінення.

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АНАЛИЗ ЛАБОРАТОРНЫХ ИССЛЕДОВАНИЙ У БОЛЬНЫХ С КОНТРАКТУРОЙ ДЮПУИТРЕНА НА ЭТАПЕ ФОРМИРОВАНИЯ ПАТОЛОГИЧЕСКОГО ПРОЦЕССА В ЛАДОННОМ АПОНЕВРОЗЕ

Гурьев С.Е., Искра Н.И., Кузьмин В.Ю.,
Танасиенко П.В.

Изучение характерных особенностей данных лабораторных исследований у больных с контрактурой Дюпюитрена, которые в прошлом были верифицированы как подвергшиеся воздействию ионизирующего излучения, показало, что у обследованных больных с контрактурой Дюпюитрена имеет место конкордатность фиброзного процесса в ладонном апоневрозе и печени. При этом патологический процесс в печени является одним из первичных патогенетических звеньев формирования контрактуры. Выведено, что существует взаимосвязь между степенью фиброзного поражения печени и биохимическими показателями крови больных контрактуры Дюпюитрена.

Ключевые слова: контрактура Дюпюитрена, фиброз печени, соединительная ткань, ионизирующее облучение.

Рецензент Ляховський В.І.

M.O. Dmitriev, Yu.Yu. Trofimenko, O.Y. Cherkasova¹, V.V. Kernychnyi, I.V. Gunas
National Pirogov Memorial Medical University, Vinnytsya
¹Bogomolets National Medical University, Kyiv

FEATURES OF USING INDIVIDUALIZED STANDARD VALUES FOR THE INCISORS' POSITIONS ACCORDING TO C. STEINER IN UKRAINIAN YOUNG MEN AND GIRLS

e-mail: dmitriyevnik@gmail.com

The purpose of the study is to investigate the correctness of the use of the recommended indexes of the position of the central incisors according to the data obtained by S. Stainer for Ukrainian young men and women with orthognathic bite. Cephalometric analysis was performed using OnyxCeph 3D pro, statistical analysis, construction of polynomial and regression models was performed in MS Excell and "Statistica 6.0". Analysis of the distribution of angular and linear indices of the position of the central incisors in Ukrainian young men and women revealed significant variability with respect to the ANB angle. Therefore, to perform more accurate diagnosis and treatment planning for individual human characteristics for Ukrainian young men and women in the diagnostic cephalometric method S. Stainer it is recommended to use the developed prognostic models for determining the linear and angular indicators of the position of the central incisors of the upper and lower jaw.

Key words: central incisors, C. Stainer cephalometric analysis, Ukrainian young men and girls.

The work is a fragment of the research project "Current trends and innovative technologies in the diagnosis and treatment of odontopathology, diseases of periodontal tissues and oral mucosa", state registration No. 0118U005471.

The position of the frontal dental group is one of the most important factors that are considered when planning and evaluating the quality of dental interventions, whether prosthetics or orthodontic treatment. According to one of the recent Ukrainian study the prevalence of malocclusion in permanent dentition reaches an average of 84.33% [3]. The largest number of patients' complaints occurs with complaints about the non-aesthetic position of the frontal group of teeth or their exposure. To be able to plan treatment and evaluate the situation objectively, the physician must have clear geometric orientations of the position of the incisors of the upper and lower jaws relative to other facial structures. Historically, pioneers of orthodontic diagnostics have been offered various diagnostic approaches and given average indicative normative characteristics that were optimal from the perspective of researchers [11]. Over time, studies began to emerge that refined the mean values, considering racial, ethnic and gender characteristics [2, 6, 8, 9].

One of the most common and popular diagnostic methods preferred by orthodontists [6] is the analysis of lateral teleroentgenograms by S. Stainer, that also allows determining in detail the spatial position of incisors. But also many studies indicate the presence of ethnic and gender characteristics of Steiner indicators [4, 5, 12, 13].

The aim of the study – to investigate the correctness of the use of the recommended indicators of the position of the central incisors according to the data obtained by S. Stainer for Ukrainian young men and women with orthognathic bite.

Materials and methods. Using the Veraviewepocs 3D device Morita (Japan), for 38 young men (17 to 21 years of age) and 55 girls (16 to 20 years of age) with physiological occlusion, as close as possible to orthognathic, obtained and analyzed lateral teleroentgenograms according to C. Steiner method [11] (fig. 1-2).

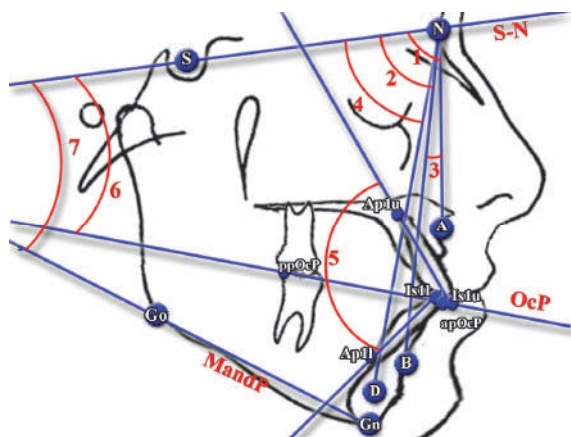


Fig. 1. Cephalometric indicators by C. Steiner: 1 – angle SNA; 2 – angle SNB; 3 – angle ANB; 4 – angle SND; 5 – inter-incisor angle II; 6 – angle SN-OcP; 7 – angle SN-GoGn.

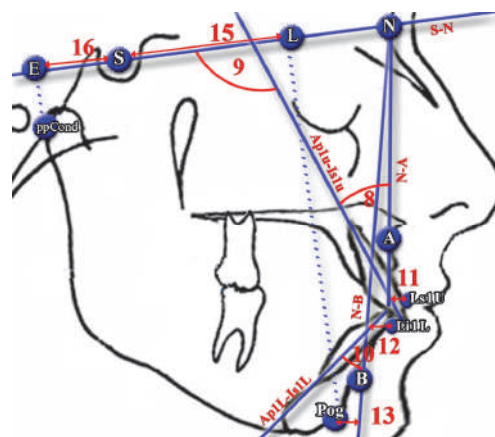


Fig. 2. Cephalometric indicators by C. Steiner: 8 – angle Max1-NA; 9 – angle Max1-SN; 10 – angle Mand1-NB; 11 – distance 1u-NA; 12 – distance 1l-NB; 13 – distance Pog-NB; 14 – Holdaway ratio, the difference between distances 1l-NB (12) and Pog-NB (13); 15 – distance S-L; 16 – distance S-E.

For convenience of demonstration, as well as the simplest method of approximation, the trend line, which in our case was a 6-degree polynomial function that describes the dependency and estimates the degree of approximation, we used MS Excel. Construction of regression models was carried out in the package "Statistica 6.0".

Results of the study and their discussion. The position of the frontal dental group is one of the most important factors to consider when planning and evaluating the quality of dental interventions. To be able to plan treatment and evaluate the situation objectively, the physician must have clear geometric orientations of the position of the incisors of the upper and lower jaws relative to other facial structures.

One of the most common and popular diagnostic methods for determining the spatial position of incisors is the analysis of lateral teleroentgenograms by S. Stainer, which in addition to the mean standard values, gave individualized standard values depending on the values of the ANB angle. In the diagram proposed by S. Stainer, the axes of the upper and lower incisors are symbolically indicated by the lines and the angular and linear values for each indicator are represented. For the upper incisor, the values for angle Max1-Na (left) and distance 1u-Na (right) for the lower incisor angle Mand1-NB (left) and distance 1l-NB (right) (fig. 3) are indicated at the top.

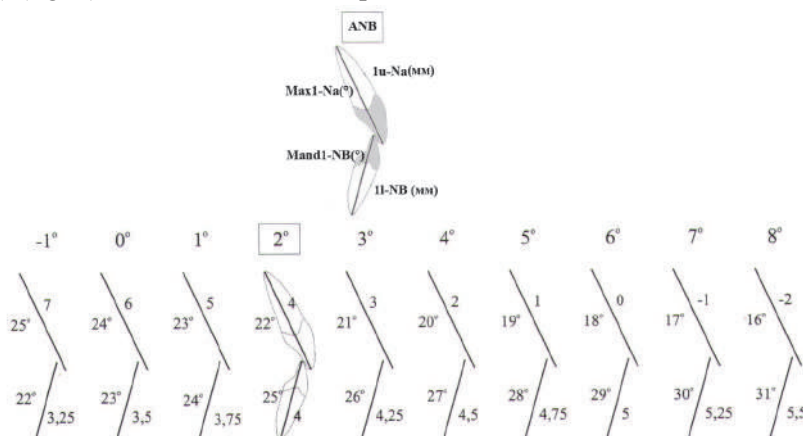


Fig. 3. Individualized standard incisors position values suggested by C. Stainer [10].

In the course of the study, we analyzed the distribution of position values of the upper central incisors relative to the NA line – Max1-Na angle, 1u-Na distance, and the lower central incisors relative to the NB line – Mand1-NB angle, and 1l-NB distance in 93 Ukrainian young men and women with physiological bite

that is as close as possible to the orthognathic. The obtained data are graphically represented in the form of graphs showing the distribution of the corresponding indexes of the position of the incisors (y-axis), depending on the values of the angle ANB (x-axis) (fig. 4a-4b).

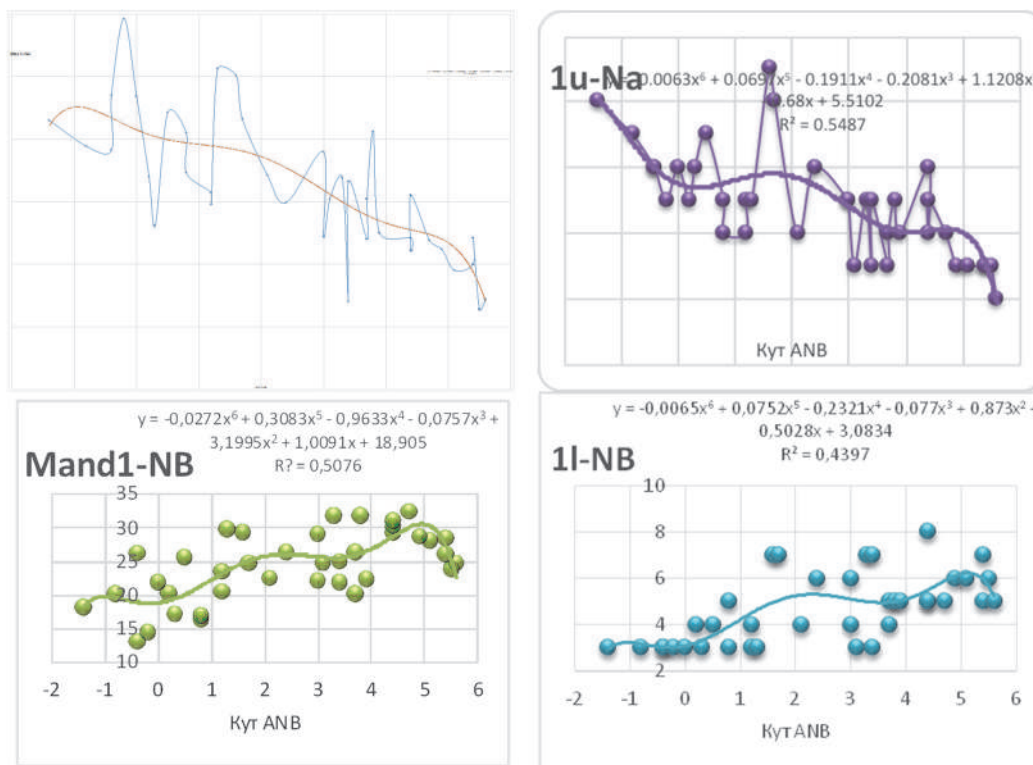


Fig. 4a. Distribution of values of indexes of position of the central incisors of the upper and lower jaws (Max1-Na, 1u-Na, Mand1-NB and 1l-NB) in Ukrainian young men with orthognathic occlusion depending on the values of the ANB angle. Notes: here and hereafter: R² – coefficient of determination; y – the value of the relevant index.

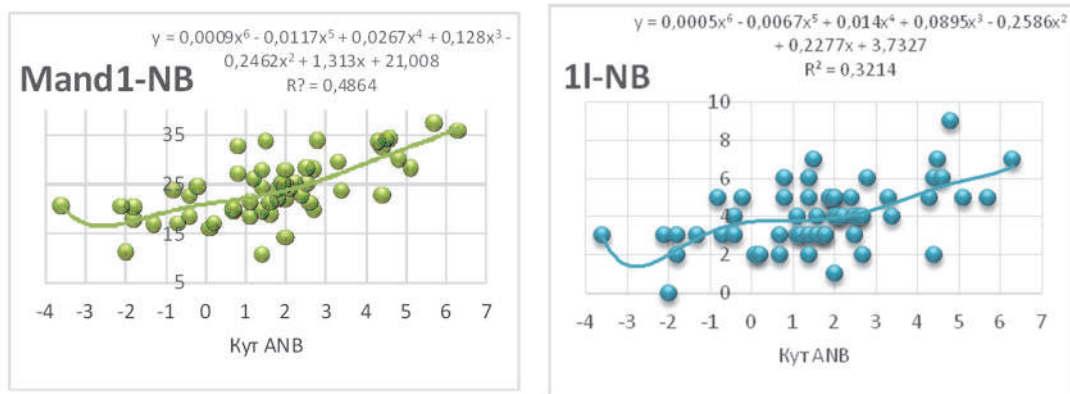


Fig. 4b. Distribution of values of indexes of the position of the central incisors of the upper and lower jaws (Max1-Na, Iu-Na, Mand1-NB and I1-NB) and the corresponding polynomial functions of their values depending on the values of the angle ANB for Ukrainian young women with orthognathic bite.

The graphs obtained show significant fluctuations in indicators that are difficult to clearly identify characteristic group values. However, the available trend lines show some dependence that can be mathematically determined either by a polynomial function, which for maximum accuracy must have the maximum acceptable number of orders, or by applying regression analysis, which may also consider the influence of other indicators of the S. Stainer methodology.

For comparison, we constructed sixth-order polynomial functions (having an approximation value of 0.32-0.58) and regression functions (an approximation reliability value of 0.46-0.77) of the indexes of the position of the central incisors of the upper and lower jaw for Ukrainian young men and women (table 1). As it can be seen from table 1, the use of direct stepwise regression analysis has increased the level of prediction of natural diagnostic values of the position of the central incisors of the upper and lower jaw for Ukrainian young men and girls.

Table 1

Polynomial and regression functions of indexes of position of central incisors of upper and lower jaw for Ukrainian young men and women.

Indexes	Polynomial functions	Regression functions
For young men		
Max1-NA	$= -0.013x^6 + 0.157x^5 - 0.586x^4 + 0.439x^3 + 0.919x^2 - 2.081x + 25.72$ (R ² =0.585)	$= 30.73 - 1.791*ANB - 0.399*SN-OCP$ (R ² =0.706)
Iu-Na	$= -0.006x^6 + 0.070x^5 - 0.191x^4 - 0.208x^3 + 1.121x^2 - 0.680x + 5.510$ (R ² =0.549)	$= -4.396 - 0.486*ANB + 0.167*SE + 0.084*SL + 0.086*SN-GOGN$ (R ² =0.768)
Mand1-NB	$= -0.027x^6 + 0.308x^5 - 0.963x^4 - 0.076x^3 + 3.199x^2 + 1.009x + 18.91$ (R ² =0.508)	$= 26.90 + 1.548*ANB - 0.363*SN-OCP - 0.621*POG-NB$ (R ² =0.542)
I1-NB	$= -0.007x^6 + 0.075x^5 - 0.232x^4 - 0.077x^3 + 0.873x^2 + 0.503x + 3.083$ (R ² =0.440)	$= -3.33 + 0.437*ANB + 0.117*SE + 0.115*SN-GONG + 0.146*SND$ (R ² =0.459)
For young women		
Max1-NA	$= 0.003x^6 - 0.030x^5 + 0.017x^4 + 0.482x^3 - 0.539x^2 - 3.387x + 26.11$ (R ² =0.524)	$= 27.71 - 2.036*ANB - 0.963*POG-NB$ (R ² =0.542)
Iu-Na	$= 0.0003x^6 - 0.005x^5 + 0.021x^4 + 0.034x^3 - 0.239x^2 - 0.590x + 6.321$ (R ² = 0.499)	$= 6.859 - 0.660*ANB - 0.306*POG-NB$ (R ² =0.503)
Mand1-NB	$= 0.001x^6 - 0.012x^5 + 0.027x^4 + 0.128x^3 - 0.246x^2 + 1.313x + 21.01$ (R ² =0.486)	$= 76.61 + 2.424*ANB - 2.064*POG-NB - 0.816*SNA + 0.282*SL$ (R ² =0.622)
I1-NB	$= 0.001x^6 - 0.007x^5 + 0.014x^4 + 0.089x^3 - 0.259x^2 + 0.228x + 3.733$ (R ² =0.321)	$= 2.731 + 0.362*ANB - 0.423*POG-NB + 0.085*SE$ (R ² =0.445)

Notes: x – value of angle ANB; ANB – angle ANB (°); POG-NB – angle POG-NB (°); SE – distance SE (mm); SL – distance SL (mm); SNA – angle SNA (°); SND – angle SND (°); SN-GOGN – angle SN-GOGN (°); SN-OCP – angle SN-OCP (°).

Summarizing the results, we see that the distribution of angular and linear indexes of the position of the central incisors in Ukrainian young men and women shows a great variability with respect to the ANB angle. The definite polynomial functions with 6 degrees have an approximation value of 0.32-0.59. The developed regression functions have a larger approximation value of 0.46-0.77 and consider all the requirements of modern medical statistics.

Analyzing the developed mathematical models, we can see that when determining the position of the central incisors of the lower and upper jaws in young men, 100 % of the models include the angle ANB and 50% of the models – angle SN_OCP. In young women, 100 % of models include a Pog_NB distance index, and 75 % of them – ANB angle.

Historically, modern medicine, and orthodontics is no exception, often uses simple averages that are easy to put into practice. Most standard diagnostic techniques [1, 11], as a rule, offer an average value and/or limit value. Our study of Ukrainian young men and women with normal occlusion showed

considerable variability and differences for the incisors' position, as other studies indicate. For example, M. B Gonzalez et al. [4] reasonably recommend the use of diagnostic values adapted to the Mexican population based on a Mexican ethnic group study that proves the existence of significant differences, in particular, the anterior location of the incisors of the upper and lower jaws, and reduction of the interincisor angle compared to the generally accepted European standards by the diagnostic methods of Ricketts, Steiner, Tweed and Arnett.

Significant differences of cephalometric indices of the position of the frontal group of teeth with S. Stainer indices are revealed, which show greater anterior teeth were more proclined and protruded, which caused the formation by E Hussien with co-authors [5] a normative base of measurements based on gender for Palestinian residents. Research by J.N. Sharma and others [13] except differences with the Europeans and the Japanese prove even the existence of significant differences by S. Stainer indices in residents of Nepal belonging to the Indo-Aryan and Mongoloid groups. The importance of considering age, apart from ethnic characteristics, is indicated by the research of A.S. Rathore et al. [12], which created a base of recommended values for mewari children.

Unlike most other diagnostic methods proposed [1, 11], in addition to the mean standard values, Stainer's method also provided individualized standard values depending on the nature of the ratio of the upper and lower jaw, which is characterized by the value of the angle ANB. Therefore, for each ANB angle value, S. Stainer proposed a set of values characterizing the positions of the upper and lower central incisors [1].

However, with increasing quality of treatment and increasing aesthetic requirements, more and more studies indicate the imperfection of existing standards [9] and the existence of variations in values across countries and ethnic groups. Therefore, we investigated the proposed S. Stainer dependence in Ukrainian young men and women with normal occlusion.

Thus, the recommendation of S. Stainer that the importance of considering the index of the location of the chin in relation to the line N-B (distance Pog_NB), in addition to the indicator of the angle ANB found valid and proven confirmation in the Ukrainian population of young women. In young men, the influence of the position of the occlusal plane relative to the base of the skull (S-N) – an indicator of the angle SN_OCP should be noted. Also interesting was the fact that for the index of the location of the crown of the lower central incisor to line N-B, the functions had a very low accuracy of description ($R^2 < 0.5$), and this indicates the natural variability of this index, regardless of the values of indicators considered within method C. Stainer.

Conclusions

1. The distribution of values of the angular and linear indexes of the position of the central incisors in Ukrainian young men and women show great variability with respect to the ANB angle, which makes the recommendation to use cautiously the normative data recommended by S. Stainer.
2. Regression models built with all the requirements of modern medical statistics provide greater opportunities for understanding the complex morphometric relationships of the structures of the craniofacial complex.
3. Developed prognostic models for determining the linear and angular indexes of the position of the central incisors of the upper and lower jaw should be used to conduct more accurate diagnostics and treatment planning for the consideration of individual human characteristics for Ukrainian young men and women in the diagnostic cephalometric method by S. Stainer.

References

1. Nettel F, Shults K. Prakticheskoe rukovodstvo po ortodonticheskoy diagnostike. Lvov: GalDent. 2006. 135. [in Russian]
2. Bronfman CN, Janson G, Pinzan A, Rocha TL. Cephalometric norms and esthetic profile preference for the Japanese: a systematic review. Dental Press J. Orthod. 2015; 20(6): 43-51.
3. Dmytrenko Maryna I., Nesterenko Oleh N. Results of follow-up study of occlusion state in Ukrainian schoolchildren. Journal of Stomatology (Poland). 2016; 69(6): 725-728.
4. Gonzalez MB, Caruso JM, Sugiyama RM, Schlenker WL. Establishing cephalometric norms for a Mexican population using Ricketts, Steiner, Tweed and Arnett analyses. APOS Trends in Orthodontics. 2013 Nov 16; 3(6):171-7.
5. Hussien E, Al-Khateeb S, Mowais MA. Palestinians norms of Steiner cephalometric analysis. World journal of orthodontics. 2010 Dec 1; 11(4):5-9.
6. Ji-Hwan K, Odontuya G, Bazar A, Shin-Jae L, Tae-Woo K. Comparison of cephalometric norms between Mongolian and Korean adults with normal occlusions and wellbalanced profiles. Korean J. Orthod. 2011; 41(1), 42-50.
7. Keim RG, Gottlieb EL, Vogels 3rd DS, Vogels PB. 2014 JCO study of orthodontic diagnosis and treatment procedures, part 1: results and trends. Journal of clinical orthodontics: JCO. 2014 Oct; 48(10):607-630.
8. Linjawi AI. Age- and gender-related incisor changes in different vertical craniofacial relationships. J Orthod Sci. 2016 Oct-Dec; 5(4):132-137.
9. Lombardo L, Perri A, Arreghini A, Latini M, Siciliani G. Three-dimensional assessment of teeth first-, second- and third-order position in Caucasian and African subjects with ideal occlusion. Prog Orthod. 2015; 16:11.
10. Navarro AC, Carreiro LS, Rossato C, Takahashi R, Lima CE. Assessing the predictability of ANB, 1-NB, P-NB and 1-NA measurements on Steiner cephalometric analysis. Dental press journal of orthodontics. 2013 Apr; 18(2):125-32.
11. Phulari B. An atlas on cephalometric landmarks. JP Medical Ltd; 2013 Mar 30.

12. Rathore AS, Dhar V, Arora R, Diwanji A. Cephalometric norms for mewari children using Steiner's analysis. International journal of clinical pediatric dentistry. 2012 Sep; 5(3):173.
13. Sharma JN. Steiner's cephalometric norms for the Nepalese population. Journal of orthodontics. 2011 Mar 1; 38(1):21-31.

Реферати

ОСОБЛИВОСТІ ВИКОРИСТАННЯ ИНДИВІДУАЛІЗОВАНИХ СТАНДАРТНИХ ЗНАЧЕНЬ ПОЛОЖЕНЬ РІЗЦІВ ЗА С. STAINER В УКРАЇНСЬКИХ ЮНАКІВ І ДІВЧАТ

Дмитрієв М.А., Трофіменко Ю.Ю., Черкасова О.В.,
Керничний В.В., Гунас І.В.

В роботі досліджено коректність використання рекомендованих показників положення центральних різців згідно даних, що отримані С. Stainer для українських юнаків і дівчат які мали фізіологічний прикус, максимально наближений до ортогнатичного. Цефалометричний аналіз проводився за допомогою програми OnyxCeph 3D pro, статистичний аналіз, побудова поліноміальної і регресійних моделей проводилося в MS Excell і "Statistica 6.0". Аналіз розподілу куткових та лінійних показників положення центральних різців у українських юнаків та дівчат виявив значну варіабельність по відношенню до кута ANB. Тому для проведення більш точної діагностики та планування лікування із врахування індивідуальних особливостей людини для українських юнаків та дівчат в діагностичній цефалометричній методиці С. Stainer рекомендовано використовувати розроблені прогностичні моделі визначення лінійних та куткових показників положення центральних різців верхньої та нижньої щелепи.

Ключові слова: центрльні різці, цефалометричний аналіз С. Stainer, українські юнаки та дівчата.

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ОСОБЕННОСТИ ИСПОЛЬЗОВАНИЯ ИНДИВІДУАЛІЗОВАНИХ СТАНДАРТНИХ ЗНАЧЕНИЙ ПОЛОЖЕНИЙ РЕЗЦОВ ПО С. STAINER У УКРАИНСКИХ ЮНОШЕЙ И ДЕВУШЕК

Дмитриев Н.А., Трофиненко Ю.Ю., Черкасова Е.В.,
Керничный В.В., Гунас И.В.

В работе исследовано корректность использования рекомендованных показателей положения центральных резцов согласно данным, полученных С. Stainer для украинских юношей и девушек которые имели физиологический прикус, максимально приближенный к ортогнатическому. Цефалометрический анализ проводился с помощью программы OnyxCeph 3D pro, статистический анализ, построение полиномиальной и регрессионных моделей проводилось в MS Excell и "Statistica 6.0". Анализ распределения угловых и линейных показателей положения центральных резцов в украинских юношей и девушек обнаружил значительную вариабельность по отношению к углу ANB. Поэтому для проведения более точной диагностики и планирования лечения с учетом индивидуальных особенностей человека для украинских юношей и девушек в диагностической цефалометрической методике С. Stainer рекомендуется использовать разработанные прогностические модели определения линейных и угловых показателей положения центральных резцов верхней и нижней челюсти.

Ключевые слова: центральные резцы, цефалометрический анализ С. Stainer, украинские юноши и девушки.

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M.V. Doroshenko-Kravchyk
Danylo Halytsky Lviv National Medical University, Lviv

NEWEST APPROACHES TO THE DIAGNOSIS OF HYPERPLASTIC PROCESSES IN GYNECOLOGY

e-mail: yashchenko_am@ukr.net

The efficacy of elastography as an additional diagnostic method in the ultrasound examination of the pelvic organs in patients with hyperplastic processes of the uterus and endometrium was studied. 75 women of reproductive age from 24 to 40 years with hyperplastic processes of the uterus and endometrium were examined. Of these, 20 women had diffuse-nodal, diffuse or nodal forms of uterine fibroids, 15 – endometrial hyperplasia, 17 – uterine polyps, 23 – adenomyosis. General clinical studies, ultrasound of the pelvic organs with elastography using General Electric Voluson E8 ultrasound apparatus were performed. At suspicion of an atypical etiology of processes, the histopathological study was carried out. It was shown that ultrasound elastography was an additional method of examination and allowed to differentiate hyperplastic processes of the endometrium from oncologic processes and to estimate the depth of invasion process, clarified the diagnosis of the myometrium condition in adenomyosis with clear verification of invasion sites. Verified the morphological etiology of uterine polyps. Diagnosed the condition of nodal diffuse proliferation in uterine leiomyoma to monitor conservative management and treatment.

Key words: elastography, proliferative processes, adenomyosis, leiomyoma, polyp.

The work is a fragment of the research project "Improving the monitoring of obstetric care in idiopathic miscarriage", state registration No. 0117U001080.

Hyperplastic processes account for a significant percentage of the pelvic organ pathology, the prevalence and frequency of which depends on many factors: neuroendocrine, immune, genetic, age-related, and adaptive [1, 2, 3, 4, 7, 8, 10, 11, 12]. In particular, it depends on: apoptosis processes, molecular genetic disorders, endodermal tissue growth factor, angiopoietin, cytokines [9, 12]. They are one of the causes of loss of reproductive function and reduced efficiency of women aged 34– 45 years [1, 2]. The urgency of the problem of hyperplastic process diagnosis is undeniable, as it is due to the high risk of malignancy. Diagnosis of these processes always has a comprehensive approach, taking into account

clinical, laboratory and instrumental research methods [1, 2, 5]. Today, ultrasound elastography is one of the most modern areas of ultrasound diagnostics, which is developing both in the technological direction and in application in daily medical practice [5]. Unfortunately, there are currently no international protocols for the use of elastography in gynecological practice, unlike such already available protocols for elastography of the liver and mammary glands.

The purpose of the study was to investigate the effectiveness of elastography as an additional diagnostic method in the ultrasound examination of the pelvic organs in patients with hyperplastic processes of the uterus and endometrium.

Materials and methods. 75 women of reproductive age from 24 to 40 years with hyperplastic processes of the uterus and endometrium were examined. Of these, 20 women had diffuse-nodal, nodal forms of uterine fibroids, 15 – endometrial hyperplasia, 17 – uterine polyps, 23 –adenomyosis. The study was carried out in accordance with the basic standards of the GCP (1996), the European Convention on Human Rights and Biomedicine of 04.04.1997, the Declaration of Helsinki of the World Medical Association on the Ethical Principles for Medical Research Involving Human Subjects (1964–2008), Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009. General clinical studies, ultrasound of the pelvic organs with elastography using General Electric Voluson E8 ultrasound apparatus were performed on the basis of the "DV" medical center. At suspicion of an atypical etiology of processes, the histopathological study was carried out. Ultrasound elastography is an additional diagnostic method to B2 mode, which evaluates the mechanical properties of tissues [5]. Therefore, it is possible to visually and virtually additionally palpate the examined organ.

It is impossible to carry out the examination without knowing its physical basis. Elasticity is the ability to resist tissue deformation. Accordingly, at the force impact, the tissue tries to return to the previous position, so the elasticity of the tissues is directly proportional to the force impulse and inversely proportional to the pressure difference [5, 6]. It is quantitatively determined by the elongated method, which describes the mechanical tissue according to the formula of the English scientist Robert Hooke, proposed in 1676. $E \text{ (kPa)} = \sigma / \varepsilon = (F/S) / (\Delta l / l_0)$. The main principle of elastography is mechanical irritation of the tissue, after which the device monitors the tissue response and the constructs the image (Fig. 1).

In gynecology, strain elastography is used as a non-invasive method of qualitative assessment of elasticity [3, 4]. Advantages of strain elastography: real-time visualization, availability of computing capabilities during the procedure. In order to quantify the qualitative method, elastography indices from 0-4 and a color mapping scale were used, which represented the nature of rigidity on a 5-scores system (fig. 1).

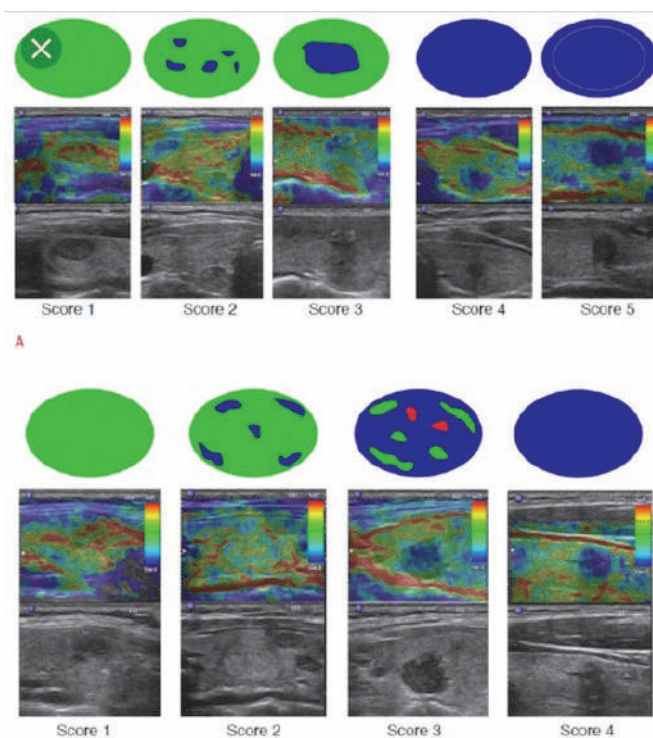


Fig. 1. An example of elastography indices on a 5-scores system (top row) and colour flow imaging scale (bottom row).

Regardless of the process localization, malignancy is characterized by a high accumulation of tissue rigidity with a high coefficient of deformation, and the color image is in the range of intense blue. The myometrium density in leiomyomas was higher than in the unchanged myometrium (fig. 2 a, b). It should be noted that the benign process of the myometrium was characterized by a blue-green-red type of imaging, and the elastography index is 2, while in patients with leiomyomas the elastography index was fixed as 1. Fibromatous nodes are elastographically harder than a normal myometrium and are clearly contoured (fig. 2 c, d). The elastography index of fibromatous nodes is 1, while in patients without changes in the myometrium this index is 2.

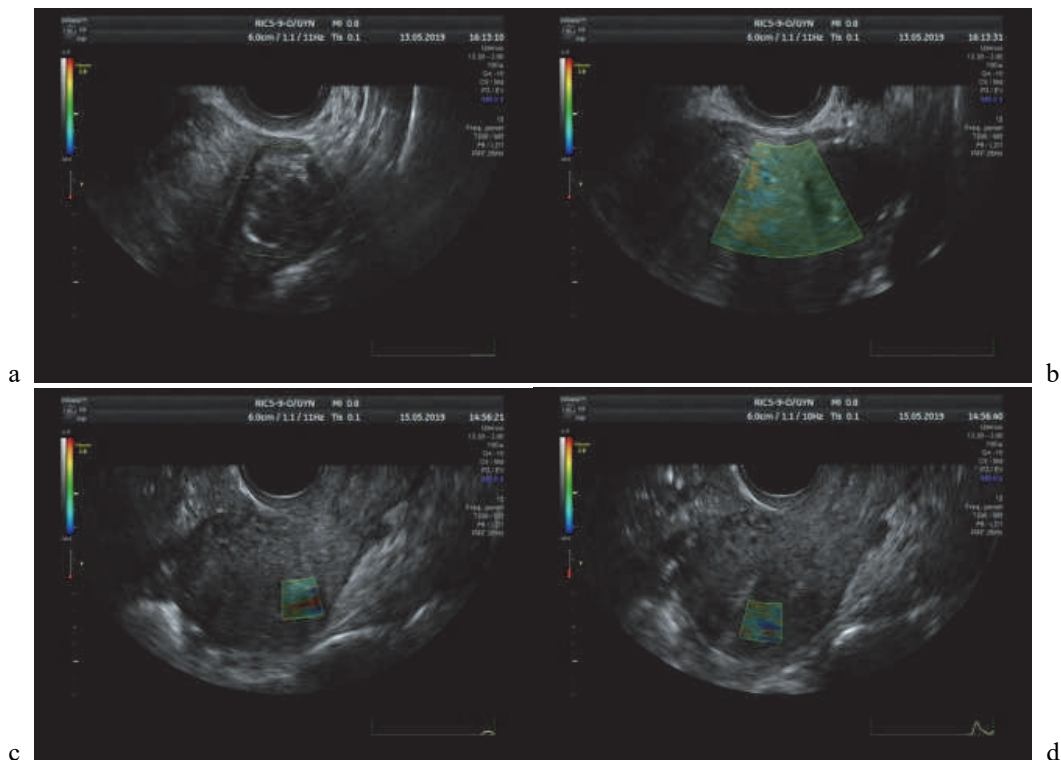


Fig. 2. a, b – elastography of patient K. with leiomyoma, a – changes in density, b – characteristic blue-green-red type of imaging; c, d – elastography index of fibromatous nodes in patient M., c – changes in density, d – changes in color.

Ultrasound examination of the pelvic organs with elastography in 23 patients with adenomyosis showed that the myometrium structure in adenomyosis is less dense than the structure of the normal myometrium. Thus, in adenomyosis, the elastography index was in the range of 3-5, which indicates a decrease in the myometrium density. Whereas an unchanged myometrium is characterized by an index of 2. For all 23 examined women with adenomyosis, a blue-red-green type of imaging was diagnosed, which indicates the absence of a tendency to degeneration (fig. 3 a, b).

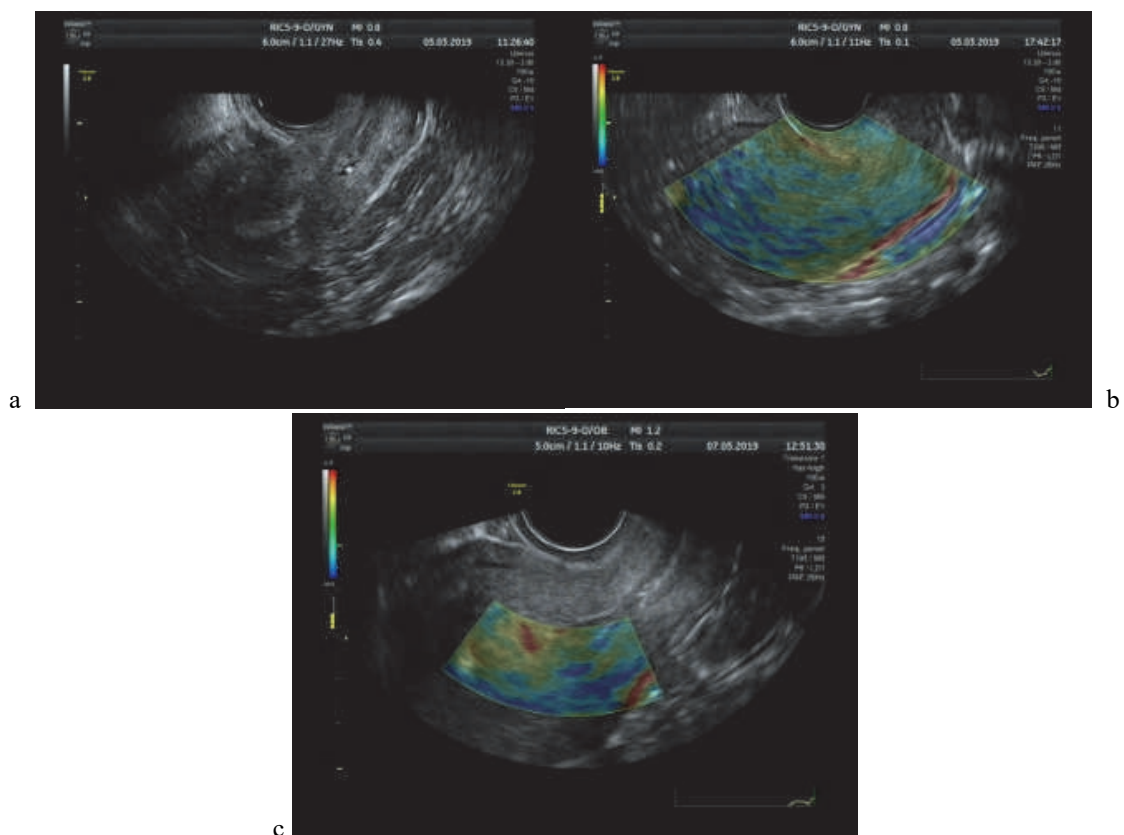


Fig.3. a, b – elastography of the endometrium of patient A. with adenomyosis without a tendency to atypical degeneration; c – elastography of the endometrium of patient H. with atypical hyperplasia.

In addition to the studies described above, we also examined 15 women with endometrial hyperplasia. It is shown that in normal endometrial hyperplasia without a tendency to atypical degeneration, the elastography index is 3-5 and has a blue-green-red type of imaging. In atypical endometrial hyperplasia, the elastography index decreases to 1-2, as well as the characteristic blue type of imaging (fig. 3 c).

After the diagnostic measures, patients with elastography index 1-2 were referred for histopathological examination of the endometrium, the results of which confirmed the process atypia.

When examining 15 women with endometrial polyps, it was found that uterine polyps are characterized by a blue-green-red type of imaging (fig. 4 a, b). The elastography index of polyps was 3-5. When diagnosing high density polyps with an elastography index of 1-2, a blue type of imaging was recorded. Such patients were referred for histopathological examination, which confirmed the atypia of morphological changes. Benign changes are softer than the structure of the normal endometrium. Polyps of benign origin are characterized by a blue-red-green type of imaging, elastography index is 3-5.

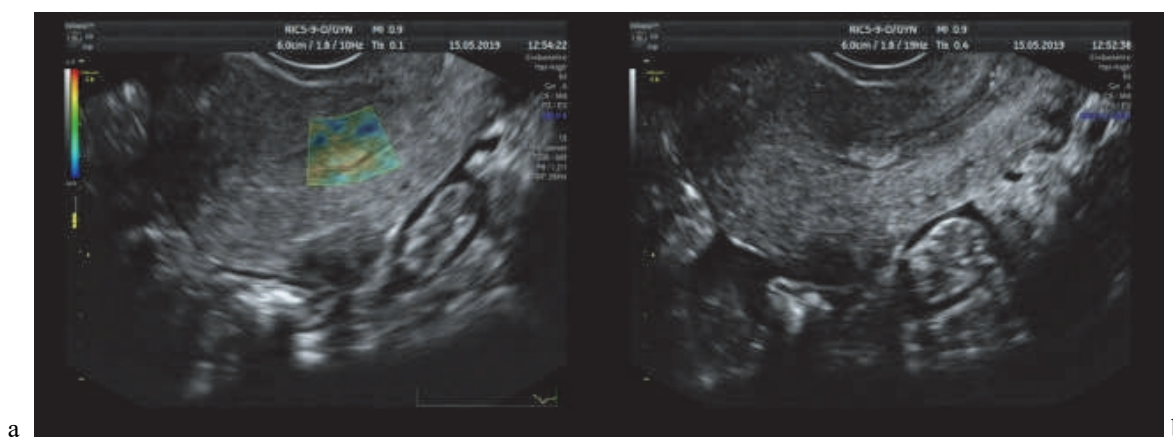


Fig. 4. a, b – elastography of patient A. with endometrial polyps, a – characteristic blue type of imaging, b – increased density of polyps.

The relevance of the diagnosis of endometrial pathology, in particular hyperproliferative processes, is primarily due to the high risk of their degeneration into malignant neoplasms and a steady tendency to increase in the incidence of this pathology, which according to [3, 4, 13] is 10-12% among women of perimenopause age.

Our comparative studies in various pathological processes such as leiomyoma, adenomyosis, endometrial hyperplasia, endometrial polyps have shown that endometrial tissues have different elastography index and different color. For example, patients in whom the density of endometrial polyps was associated with an index of 1-2 had a characteristic blue type of imaging. In patients with normal endometrial hyperplasia, the elasticity index was in the range of 3-5, whereas in atypical hyperplasia, the elasticity index varied and was 1-2. According to [1, 2], early diagnosis of endometrial hyperplastic processes is important both for the choice of treatment therapy and for the prevention of cancer. Sonoelastographic studies of patients with breast cancer performed [10] before treatment and after chemotherapy showed a significant reduction in the coefficient of deformation of breast tissue. Studies carried by the authors [8,10] also confirm our results and suggest that elastography can potentially be used as an early prognosis for the diagnosis and treatment of pathological processes.

Thus, our studies using ultrasound diagnostics with elastography have shown the prospects for the use of this method in gynecology, especially in hyperplastic processes.

Conclusion

Ultrasound elastography is an additional method of examination and allows to differentiate hyperplastic processes of the endometrium from oncological processes and to assess the depth of invasion. It estimates the depth of invasion process, clarified the diagnosis of the myometrium condition in adenomyosis with clear verification of invasion sites. Verified the morphological etiology of uterine polyps. Diagnosed the condition of nodal diffuse proliferation in uterine leiomyoma to monitor conservative management and treatment.

Prospects for further research. In order to improve diagnostics, it is planned to perform elastography of female genital organs with other pathological processes in the future.

References

1. Gazhonova VE, Belozeroва IS, Vorontsova NA, Nadolnikova TA. Sonoelastografiya v diagnostike giperplasticheskikh protsessov endometriya. Meditsinskaya vizualizatsiya. 2013; 6:57-65 [in Russian]
2. Gazhonova VE, Belozeroва IS, Vorontsova NA, Titov DS. Sonoelastografiya v diagnostike raka endometriya. Akusherstvo i ginekologiya; 2014; 1:54-58 [in Russian]
3. Golovko TS, Bakay OA. Vozmozhnosti elastografii v diagnostike novoobrazovaniy sheyki matki. Zdorovye zhenshchiny. 2014; 8 (94):112-117. [in Russian]
4. Diomidova VN, Zakharova OV, Petrova OV. Elastografiya sdvigovoy volnoy v otsenke endometriya i miometriya u zdorovykh zhenshchin reproduktivnogo vozrasta. Ultrazvukovaya i funktsionalnaya diagnostika. 2015; 5: 51-56. [in Russian]
5. Zubarev AV, Gazhonov VE, Churkina SO, Khokhlova EA, Panfilova EA. Metodicheskiye rekomendatsii po ispolzovaniyu innovatsionnogo metoda sonoelastografii dlya poiska raka razlichnykh lokalizatsiy. Metodicheskoye rukovodstvo. Moskva: Meditsina; 2009. 32s. [in Russian]
6. Mitkov VV, Khuako SA, Ampilogoва ER, Mitkova MD. Otsenka vosproizvodimosti rezultatov kolichestvennoy ultrazvukovoy elastografii Ultrazvukovaya i funktsionalnaya diagnostika. 2011; 2:115-120. [in Russian]
7. Rubtsova NA, Novikova YeG, Puzakov KB, Antipova VA. Magnitnorezonansnaya tomografiya v diagnostike raka sheyki matki. Rossiyskiy onkologicheskiy zhurnal. 2012; 2:39-45. [in Russian]
8. Frantsevych KA. Sonoelastografiya yak metodyka v alhorytmni diahnostryky patolohichnykh tvoren hrudnoyi zalozy. Visnyk Natsionalnoho tekhnichnoho universytetu Ukrayiny "Kyivskyy politekhnichnyy instytut". Ser.: Pryladobuduvannya. 2013; 45:180-190. [in Ukrainian]
9. Bailey C, Desmond KL, Czarnota GJ, Stanisz GJ. Quantitative magnetization transfer studies of apoptotic cell death. Magn Reson Med. 2011; 66:264-269.
10. Falou O, Sadeghi-Naini A, Prematilake S, Sofroni E, Papanicolau N, Iradji S, et al. Evaluation of neoadjuvant chemotherapy response in women with locally advanced breast cancer using ultrasound elastography. Transl. Oncol. 2013; 6(1):17-24.
11. Sadeghi-Naini A, Falou O, Hudson JM, Bailey C, Burns PN, Yaffe MJ, Stanisz GJ, Kolios MC, Czarnota GJ. Imaging innovations for cancer therapy response monitoring. Imaging Med. 2012; 4:311-327.
12. Stavridis S, Saidi S, Lekovski L, Dohceev S, Spasovski G. Screening for prostate cancer: a controversy or fact. Hippokratia. 2010; 14:170-175.
13. Yusupov K, Nedopekina E, Vikharova O. Use of elastography and gynekologic practice. Obstetrics and Gynecology. 2016; 11:22-27.

Реферати

НОВІ ПІДХОДИ ДО ДІАГНОСТИКИ ГІПЕРПЛАСТИЧНИХ ПРОЦЕСІВ У ГІНЕКОЛОГІЇ

Дорошенко-Кравчук М.В.

Вивчали ефективність застосування еластографії в якості додаткового методу діагностики при проведенні УЗД дослідження органів малого таза у пацієнток з гіперпластичними процесами матки і ендометрія. Обстежено 75 жінок репродуктивного віку від 24 до 40 років з гіперпластичними процесами матки і ендометрія. З них 20 жінок з дифузно-вузловий, дифузійної та вузловою формою міоми матки, 15-з гіперплазією ендометрія, 17-з поліпами ендометрія, 23 з аденоміозом. Проведено загальні клінічні дослідження, УЗД органів малого таза з використанням еластографії за допомогою УЗД апарату General Electric Voluson E8. При підозрі на атипичну етіологію процесів проводилися патогістологічне дослідження. Показано, що ультразвукова еластографія є додатковим методом обстеження і дозволяє диференціювати гіперпластичні процеси ендометрія від онкопроцесу і дає можливість оцінити глибину інвазії процесу, уточнює діагностику стану міометрія при аденоміозе з чіткою верифікацією ділянок проростання. Верифікує морфологічну етіологію поліпів ендометрія. Діагностує стан вузлових і дифузних розростань при лейоміомі матки для моніторингу консервативного ведення і лікування.

Ключові слова: еластографія, проліферативні процеси, ендометріоз, лейоміома, поліп.

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НОВЫЕ ПОДХОДЫ К ДИАГНОСТИКЕ ГИПЕРПЛАСТИЧЕСКИХ ПРОЦЕССОВ В ГИНЕКОЛОГИИ

Дорошенко-Кравчук М.В.

Изучали эффективность применения эластографии в качестве дополнительного метода диагностики при проведении УЗИ исследования органов малого таза у пациенток с гиперпластическими процессами матки и эндометрия. Обследовано 75 женщин репродуктивного возраста от 24 до 40 лет с гиперпластическими процессами матки и эндометрия. Из них 20 женщин с диффузно-узловой, диффузной и узловой формой миомы матки, 15-с гиперплазией эндометрия, 17-с полипами эндометрия, 23 с аденомиозом. Проведено общие клинические исследования, УЗИ органов малого таза с использованием эластографии с помощью УЗИ аппарата General Electric Voluson E8. При подозрении на атипичную этиологию процессов проводились патогистологическое исследования. Показано, что ультразвуковая эластография является дополнительным методом обследования и позволяет дифференцировать гиперпластические процессы эндометрия от онкопроцессов и дает возможность оценить глубину инвазии процесса, уточняет диагностику состояния миометрия при аденомиозе с четкой верификацией участков прорастания. Верифицирует морфологическую этиологию полипов эндометрия. Диагностирует состояние узловых и диффузных разрастаний при лейомиоме матки для мониторинга консервативного ведения и лечения.

Ключевые слова: эластография, пролиферативные процессы, эндометриоз, лейомиома, полип.

Рецензент Ліхачов В.К.

L.V. Zhyvotovska, Y.Y. Paida¹, V.V. Borysenko, L.A. Bodnar, N.A. Makarenko²

Ukrainian Medical Stomatological Academy, Poltava

¹Kamyanets-Podilskyi Tax Institute, Kamyanets-Podilskyi²Donetsk Law Institute, Ministry of Internal Affairs of Ukraine, Donetsk

CHARACTERISTICS OF CLINICAL AND PSYCHOPATHOLOGICAL INDICES IN ALCOHOL DEPENDENCE IN PERSONS WITH CONSTANT TYPE OF ALCOHOL ABUSE IN COMPLIANCE WITH BIOLOGICAL RHYTHMS

e-mail: lzhyvotovska@gmail.com

Among the current issues of modern addiction medicine is the problem of studying the psychopathological manifestations of mental and behavioral disorders due to alcohol consumption, their pathogenetic mechanisms and consideration of these factors in the development of therapeutic methods. As a result of psycho-emotional study, taking into account the biorhythm status, it was noted that in persons of evening type prevailed the high level of state and trait anxiety in comparison with morning and undifferentiated type ($p < 0.01$), severe depression was more common compared to the morning type ($p < 0.05$), anxious and dysthymic type of accentuation was prevailed, personality profile showed more pronounced social maladjustment compared to the morning and undifferentiated type of working capacity. The obtained results expand the possibilities of optimizing the complex therapy of this cohort of patients.

Key words: alcohol dependence, constant type of alcohol abuse, biorhythm status, state anxiety, trait anxiety, depression, individual psychological features.

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Irreversible medical-biological, social-economic, demographic, legal consequences of alcoholism of the population of Ukraine at the present stage gives every reason to put alcohol dependence on a par with other most dangerous medical and social problems that pose a real threat to the health of the nation. According to the WHO, the global average alcohol consumption is 6.1 liters per person per year, and in Ukraine this index is one of the highest in the world (15.6 liters per person per year). The annual mortality rate from alcohol-related consequences is about 40,000 people [11].

According to the statistics of the Ministry of Health of Ukraine, the number of patients in medical care dispensaries of Ukraine currently reaches 1 million people, and occupies one of the first places in the structure of emergency care disorders caused by alcohol dependence [5]. A significant increase in the number of alcohol consumers among the population, especially among young people [3], inevitably provokes a sharp increase in physical and mental morbidity, trauma, suicide attempts, aggressive behavior and criminal activity [9, 10].

Alcohol abuse is considered to be one of the main factors of the demographic and social crisis in Ukraine and as a national danger at the level of the individual, family, society [2, 4]. In recent years, under conditions of military and political instability in the east of the country, there has been a sharp increase in drug and mental diseases as a social response to long-term traumatic stress. Recent medical and social studies have revealed a strong correlation between the level of stress in society and the level of problems associated with alcohol [1].

At the same time, the clinical pathologic response of modern forms of alcohol dependence causes a significant complication of the clinical evidence. The appearance in the clinical evidence of heavy drinking practices indicates the special severity and malignancy of the addiction syndrome. Couping of heavy drinking practices is one of the most difficult problems of modern addiction medicine, which requires the implementation of individualized and differentiated treatment and rehabilitation programs [8, 12].

The study of clinical and psychopathological features of heavy drinking practices of alcohol dependence, taking into account biological rhythms, expands the possibilities in understanding the complex pathogenetic mechanisms that lead to the emergence of these conditions [13, 14, 15]. Performing biorhythm studies in patients with alcohol dependence is important for adequate selection and use of methods of therapy and psychological prophylaxis in order to achieve proper quality of remission [6, 7].

The purpose of the study was to investigate the clinical and individual psychological characteristics of patients with alcohol dependence with a constant type of alcohol abuse, considering the biorhythm status.

Materials and methods. We observed 226 patients with alcohol dependence, including 157 men and 69 women aged 19 to 63 years. Nosological diagnosis was based on the criteria of ICD-10 (1998) and

corresponded to the headings of mental and behavioral disorders due to alcohol consumption – F10.2-F10.4. Patients had a constant type of alcohol abuse with daily or almost daily heavy drinking on the background of which there were periods of increased alcohol abuse in maximum doses.

The examination was performed using clinical-psychopathological, clinical-anamnestic, biorhythm, psychopathological and statistical methods and was performed after the course of detoxification therapy. The main examination methods were clinical and psychopathological ones to assess the condition of patients, determine the features of the clinical evidence and the pathological process course, and clinical and anamnestic method, which included a retrospective analysis of clinical manifestations, study of anamnesis and medical history, as well as objective information obtained from relatives of patients, with a retrospective assessment of the period preceding the patient's request for medical assistance. Anamnestic data allowed to determine the duration of the disease, the type of alcohol abuse, the stage and nature of the dependence. A comprehensive psychodiagnostic study was performed using the Östberg's questionnaire (adapted by S. I. Stepanova, 1986) to determine the biorhythm type, K. Leonhard, H. Schmieschek questionnaire (according to D. Ia. Raigorodsky, 1998) to study the types of character accentuation, the "Minimult" method (adapted by V. P. Zaitsev, V. N. Koziulia, 1981) – a reduced multifactorial questionnaire to study the personality profile. Psycho-emotional studies have been performed using the Spielberger-Khanin scale (1976) to assess anxiety and the Montgomery-Asberg scale (MADRS, 1979) to assess depression. Methods of statistical processing of study results were carried out with calculations of mean value (M), standard deviation (σ). Student's T-test was used to compare the mean values of the normally distributed trait in the groups, and χ^2 Pearson's test was used to study the relationships between the indices.

Taking into account the assessment of biorhythm type on the Östberg's scale, three clinical groups were formed, representative by age and sex: Group 1 included 100 (44.2%) patients of morning working capacity (more than 77 scores), Group 2 – 70 (31.0%) persons of undifferentiated type (58-76 scores), Group 3 – 56 (24.8%) persons of the evening type (less than 57 scores).

Results of the study and their discussion. Analysis of the distribution of state anxiety (SA) and trait anxiety (TA) indices on the Spielberger-Khanin scale in all patients showed that high level (≥ 46 scores) of SA was observed in 102 (45.1%) patients, medium level (31-45 scores) – in 91 (40.3%), low level (≤ 30 scores) – in 33 (14, 6%). High levels of TA were observed in 93 (41.1%) patients, medium – in 122 (53.9%) and low – in 11 (4.9%).

Table 1 shows the distribution of the state and trait anxiety levels depending on the biorhythm type. It was found that in Group 3 respondents predominated (73.21 \pm 5.92%), which score of SA was high compared to Group 1 (30.0 \pm 4.58%, $\chi^2=27.033$, $p < 0.001$) and Group 2 (44.29 \pm 5.94%, $\chi^2=10.631$, $p = 0.002$). High levels of TA also dominated among patients of Group 3 (75.0 \pm 5.79%) in contrast to Group 1 (23.0 \pm 4.21%, $\chi^2 = 39.936$) and Group 2 (40.0 \pm 5.86%, $\chi^2 = 15.435$), $p < 0.001$. Average SA values were significantly more often observed in Group 1 than in Group 3 – 52.2 \pm 5.0% and 23.21 \pm 5.64%, respectively, $\chi^2=9.314$, $p=0.003$. Among patients in Group 3 there were no respondents with low SA, while 18.0 \pm 3.84% of patients in Group 1 and 21.43 \pm 4.90% in Group 2 had low SA ($p < 0.001$).

Table 1

Distribution of state and trait anxiety levels on the Spielberger-Khanin scale depending on biorhythm type

Anxiety levels		Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Total n (%)
State anxiety (SA)	more than 45 scores	30 (30%)	31 (44%)	41 (73%)	102 (45.1%)
	31-45 scores	52 (52%)	24 (34%)	15 (23%)	91 (40.3%)
	up to 30 scores	18 (18%)	15 (21%)	-	33 (14.6%)
Trait anxiety (TA)	more than 45 scores	23 (23%)	28 (40%)	42 (75%)	93 (41.1%)
	31-45 scores	71 (71%)	37 (53%)	14 (25%)	122 (53.9%)
	up to 30 scores	6 (6%)	5 (7%)	-	11 (4.9%)
Total		100	70	56	226

The distribution of SA and TA, taking into account the individual chronotype revealed statistically significant differences in SA in patients of Group 1 compared with Group 3 (43.9 \pm 1.7 and 51.7 \pm 1.5, $p < 0.001$), TA – in Groups 1 and 2 in comparison with Group 3 (39.3 \pm 1.9 and 37.4 \pm 1.4, respectively, and 46.9 \pm 1.5, $p = 0.002$). At the same time, in persons of morning type of working capacity the combination of average and high values of SA with high indices of TA was noted rather less often, than at persons of evening and undifferentiated type.

The Montgomery-Asberg scale revealed the presence of depressive symptoms in 139 (61.5%) patients, of whom 36 (15.9%) had mild depression (16-25 scores), 89 (39.4%) – moderate (26-30 scores), 14 (6.2%) – severe (> 30 scores). The analysis revealed that 89 people (39.4%) had a moderate level of

depression with an average indice of 28.1±0.7. The distribution of the depressive symptoms severity on the MADRS scale in patients depending on the biorhythm type is shown in fig. 1.

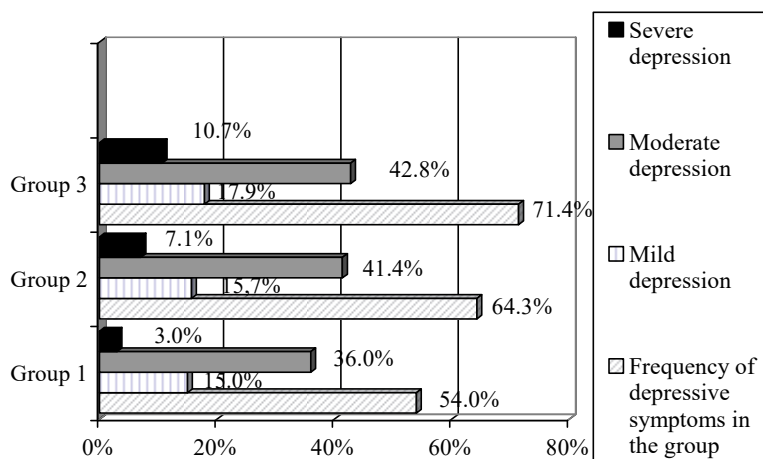


Fig. 1. Distribution of the depressive symptoms severity on the MADRS scale depending on the biorhythm type.

Comparison of the depression severity depending on the biorhythm status showed that in Group 3 compared with Group 1 were more frequent manifestations of depression (71.4±6.04% and 54.0±4.98%, respectively), $\chi^2=4.553$, $p=0.033$, and severe depression was more common (10.71±4.13% and 3.0±1.71%), $\chi^2=3.930$, $p=0.048$. Analysis of the depression distribution on the MADRS scale depending on the individual chronotype did not reveal statistically significant differences between the groups.

According to the Leonhard-Schmieschek questionnaire, 106 patients had a combination of two types of accentuations (46.9%), signs of one isolated accentuation were found in 57 (25.2%) people, less often there was a combination of three – in 52 people (23.9%) or even four accentuations – in 11 (4.9%) people. In patients of Group 1, a pronounced accentuation was pedantic (42.0±4.94%), and emotionally labile type (30.0±4.58%), in Group 2, emotionally labile type (40.0±5.86%) and dysthymic (30.0±5.48%) variants prevailed, Group 3 was dominated by dysthymic (53.57±6.66%) and anxious (32.14±6.24%) types of character accentuations with a minimum amount of pedantic (7.14±3.44%) and emotionally labile (16.07±4.91%), which is shown in Table 2.

Table 2

Distribution of character accentuations according to the Leonhard-Schmieschek questionnaire (over 18 scores) depending on the biorhythm type

Type of accentuation	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Total n (%)
Pedantic	42 (42%)	10 (14%)	4 (7%)	56 (24.7%)
Anxious	5 (5%)	19 (27%)	18 (32%)	42 (18.6%)
Dysthymic	26 (26%)	21 (30%)	30 (53%)	77 (34.1%)
Emotionally labile	30 (30%)	28 (40%)	9 (16%)	67 (29.6%)

It was found that the morning type was dominated by pedantic ($\chi^2 = 20.977$, $p < 0.001$) and emotionally labile ($\chi^2 = 3.927$, $p = 0,048$) type of accentuation, in persons of undifferentiated type in comparison with morning – anxious ($\chi^2=16.651$, $p<0.001$), and compared to the evening – emotionally labile type of accentuation ($\chi^2=8.588$, $p=0.004$), in the evening type – anxiety type of accentuation compared to the morning ($\chi^2=21.040$, $p<0.001$) and dysthymic compared to the morning ($\chi^2=11.222$, $p<0.001$) and undifferentiated type of working capacity ($\chi^2=7.175$, $p=0.008$).

According to the "Minimult" method, it was determined that this cohort of patients had a predominant personality profile with an increased and high level of results on the 2nd, 3rd, 7th and 8th scales with the code 273 (8). At the same time the high level of indices on the 2nd scale, combined with a significant increase in the 3rd, which is in a subordinate position to the 2nd scale, as well as increased 7th and 8th scales with a reduced 9th, indicates severe emotional discomfort, which is reflected in a constant feeling of tension, low mood with self-doubt, low self-esteem, low motivation to succeed and adaptation problems of a chronic nature. This type of profile reflects the properties of the hypostenic type of response and indicates a neurotic variant of maladaptation and decompensation of person towards increased inhibitory reactions.

In general, the indices on the scale F (reliability) were at the level of 65-75T, which reflected a high level of emotional stress and the need for help, and combined with moderately reduced indicators on the scale K (correction) in the range of 50-60T, which was associated with decreased self-control and showed a tendency to exaggerate rather than underestimate the degree of interpersonal conflict and the symptoms severity. There was an increase in the scale L (lie) in the range of 60-69T, which indicated a lack of self-understanding and low adaptive capacity. 23 people (10.2%) had an unreliable profile. According to the main scales, patients had a borderline profile with the highest scores up to 70-75T and other scales not

lower than 55T scores, in which the peaks reflected the accentuated features; wide range profile, in which, along with most scales that are on the same level, one, two or more were located much higher than others (15-20 T and above) with a different number of contrasting "peaks" and a profile with a rise on one or two distant scales, and on the other – the rise is less pronounced or absent, reflecting the maladaptation of the individual.

The personality profile of patients considering the biorhythm type is shown in fig. 2. In Group 1 with the profile code 23 (6), the combination of the profile peak on the 2nd and 6th scales reflects the presence of disharmony, as it reveals the coexistence of depressive tendencies and affective rigidity, which leads to a feeling of rupture of interpersonal ties and is accompanied by anxiety and depressive reactions. Disharmony is also indicated by the simultaneous desire to focus on external evaluation with the displacement of negative signals from others and a sense of hostility (a combination of scales 3 and 6). The combination of peaks on the 2nd, 3rd and 6th scales in this group of patients shows that they feel alienated, misunderstood and not involved in the social environment, and therefore prone to self-blame. Due to dissatisfaction and vulnerability, the perception of the social situation is a source of tension, prolonged negative emotions, depression, decreased activity (lowering the profile of the scale 9). In the morning type of working capacity there was also a decrease in the profile on a 4 scale, which indicates a high tendency to maintain permanent attitudes, interests and goals.

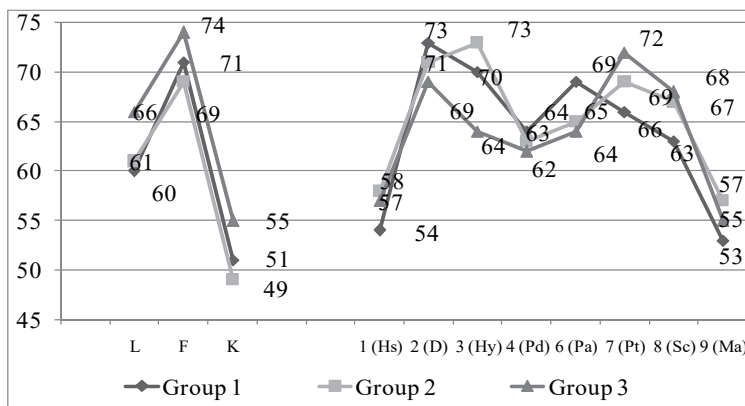


Fig. 2. The personality profile of patients according to the "Minimult" method considering the biorhythm type.

Profile code 32 (7) in patients of Group 2 had similarities with the profile code of respondents of Group 1, however, they had less affective rigidity and more prevalent anxiety. The combination of peaks on the 3rd and 2nd scales shows that demonstrative behavior and sense of insufficient attention and understanding from others are combined with negative emotions, which is a disharmonious manifestation of personality and leads to a violation of social adaptation.

The combination of the peaks of the 2nd and 7th scales indicates that the gloomy color of the situation and the feeling of failure are combined with a decrease in productivity, initiative and a sense of depression. The need for attention, recognition, and reduced social spontaneity lead to painful responses to negative signals from others (a combination of scales 3 and 7). The obtained profile also indicates the internal tension and pessimistic assessment of the future.

The personality profile in Group 3 was mostly highly distributed, with a profile code of 72 (8). The state of maladaptation, reflected in the profile by increasing the 7th scale, is characterized by sleep disorders, anxiety, a sense of confusion and nervousness. The combination of high 2nd, 7th and 8th scales with relatively low 9th characterizes the profile of the psychasthenic type. At the same time, the rise on the 2nd and 8th scales indicates a feeling of lack of communication with the environment, unsatisfied need for contact, which is expressed by increasing anxiety or depression. In general, the increase in the 2nd, 7th, 8th scales indicates that the tendency to focus on internal criteria and communication difficulties is combined with severe anxiety, which makes it difficult to realistically assess the situation with a sense of alienation and misunderstanding. Such feelings lead to depressive tendencies, often combined with irritability and anxiety or a feeling of increased fatigue and apathy.

The most significant differences in personality profiles were observed in persons of morning and evening types. There was a tendency to increase indicators on the 7th (72.3 ± 2.1 and 66.5 ± 1.9 , $p=0.042$) and 8th scales, and a decrease on the 3rd (64.9 ± 1.7 and 70.2 ± 2.0 , $p=0.045$) and 6th scales in Group 3 compared with Group 1, which indicated a more pronounced social maladaptation in the evening type. The personality profile in Group 2 occupied an intermediate position, approaching the indices in patients of Group 1, thus the difference of indices on the 3rd scale was statistically significant in comparison with Group 3 (73.1 ± 2.4 and 64.9 ± 1.7 , respectively, $p=0.006$).

In scientific studies of recent years there have been reported a propensity of evening-type individuals to depression and destructive behavioral patterns, including the use of psychoactive substances [15]. In persons with evening desynchrony, there are changes in brain function associated with reward, which correlates with higher levels of alcohol consumption and symptoms of alcohol dependence [14].

Conclusion

Thus, the results of the study allowed to distinguish the features of affective and personal manifestations in persons with a constant type of alcohol abuse in alcohol dependence, considering the biorhythm status. When analyzing the features of the affective sphere, taking into account the individual chronotype, it was noted that the evening type was dominated by high levels of SA and TA ($p < 0.01$), more common severe depression ($p < 0.05$), anxious and dysthymic type of accentuation were prevailed, the personality profile testified to more pronounced social maladaptation in comparison with the morning and undifferentiated type of working capacity. Affective disorders and individual psychological features of patients with heavy drinking states in disorders associated with alcohol consumption, depending on the individual chronotype, allowed to make an informed decision on the choice of methods and targets of psychotherapeutic influence in the creation of comprehensive personalized programs of treatment and rehabilitation measures.

References

1. Haponov KD. Alkoholna zalezhnist i sotsialnyy stres: biokhimični, neyrofizioloģični i psykhosotsialni mekhanizmy vzyayemovplyvu (ohlyad literatury). Ukrayinskyy visnyk psykhonevroloģiyi. 2018; 26(1):120-1. [in Ukrainian]
2. Detsyk OZ, Karpinets IM. Kompleks zakhodiv profilaktyky alkoholizmu na rivni pervynnoyi medychnoyi dopomohy. Aktualni pytannya farmatsevtichnoyi i medychnoyi nauky ta praktyky. 2013; 1(11):76-9. [in Ukrainian]
3. Kazakov OA. Suchasnyy stan problemy pidlitkovoho alkoholizmu. Svit medytsyny ta bioloģiyi. 2017; 2(60):63-5. [in Ukrainian]
4. Lytvynenko VV, Suchasni osoblyvosti formuvannya alkoholnoyi zalezhnosti u cholovikiv yak osnova yikh reabilitatsiyi. Scientific Journal "ScienceRise: Medical Science". 2019; 1(28): 42-4. [in Ukrainian]
5. Minko OI, Lisna NM, Markozova LM. Indyvidualno-psykholoģični osoblyvosti osib z alkoholnoyu zalezhnistyu ta yikh spivzaleznykh rodychiv, yakі vplyvayut na formuvannya terapevtichnoho alyansu. Ukrayinskyy visnyk psykhonevroloģiyi. 2018; 26(3):39-42. [in Ukrainian]
6. Sapozhnykov SP, Kozlov VA, Holenkov AV. Alkohol kak sotsialnyy desinkhronyzator sutochnykh osobennostey vnezapnoy serdechnoy smerty. Narkoloģyya. 2014; 10:80-5. [in Russian]
7. Sonnyk HT, Skrypnikov AN, Rud VA. Byorytmoloģicheskie issledovaniya v psykhyatrii: sostoyanie i perspektivy razvitiya. Psikihiatriya, psikhoterapiya i klinicheskaya psikholoģyya. 2012; 1(07):34-6. [in Russian]
8. Sosin IK, Skvira IM, Mitsura VM. Rannya diahnozyka alkoholnoyi zalezhnosti v praktytsi simeynoho likarya. Zdobutky klinichnoyi i eksperymentalnoyi medytsyny. 2016; 1(12):69-72. [in Ukrainian]
9. Sosyn YK, Chuev YuF. O narkoloģicheskoy situatsyy v Ukrainy. Ukrayins'kyy visnyk psykhonevroloģiyi. 2010;18(64):174. [in Russian]
10. Khrystuk EL. Problema alkoholnoyi adykttsiyi v suchasniy vitchyznyaniy psikholoģiyi. Naukovyy visnyk Lvivskoho derzhavnoho universytetu vnutrishnikh sprav. 2012; 2(2):69-73. [in Ukrainian]
11. Shuvera OV. Sudovo-farmatsevtichni osnovy udoskonalennya zakhodiv protydyiy pry alkoholniy zalezhnosti (F 10.2) [dysertatsiya]. Kharkiv: Khark. med. akad. pislyadypl. osv: 2017. 235 s. [in Ukrainian]
12. Aimetov KV, Vozny DV. Substantiation and analysis of adaptive model of medical-and-social rehabilitation of alcohol dependent persons introduction efficacy. Journal of Education, Health and Sport. 2016; 6(9):1015-27.
13. Close J. Are stress responses to geomagnetic storms mediated by the cryptochrome compass system? Proc. Royal Society. Biological sci. 2016. doi: 1098/rspb.2012.0324. Oxford, UK.
14. Hasler BP, Clark DB. Circadian Misalignment, Reward-Related Brain Function, and Adolescent Alcohol Involvement. Alcohol Clin Exp Res. 2013; 37(4):558–565.
15. Kivelä L, Papadopoulou MR, Antypa N. Chronotype and Psychiatric Disorders. Curr Sleep Med Rep. 2018; 4(2):94–103.

Реферати

**ХАРАКТЕРИСТИКА КЛІНІЧНИХ
ТА ПАТОПСИХОЛОГІЧНИХ ПОКАЗНИКІВ
ПРИ АЛКОГОЛЬНОЇ ЗАЛЕЖНОСТІ У ОСІБ
З ПОСТІЙНИМ ТИПОМ ЗЛОВЖИВАННЯ
АЛКОГОЛЕМ З УРАХУВАННЯМ БІОЛОГІЧНИХ
РИТМІВ**

**Животовська Л.В., Пайда Ю.Ю.,
Борисенко В.В., Боднар Л.А., Макаренко Н.А.**

Серед актуальних питань сучасної наркології залишається проблема вивчення психопатологічних проявів психічних і поведінкових розладів внаслідок вживання алкоголю, їх патогенетичних механізмів і врахування цих факторів в розробці терапевтичних методів впливу. В результаті дослідження психоемоційної сфери з урахуванням біоритмологічного статусу відзначено, що у осіб вечірнього типу переважав високий рівень реактивної та особистісної тривожності в порівнянні з ранковим і недиференційованим типом ($p < 0,01$), частіше зустрічалася важка депресія порівняно з ранковим типом ($p < 0,05$), переважали тривожний і дистимічний тип акцентуації, профіль особистості свідчив про більш виражену соціальну дезадаптацію порівняно з ранковим та недиференційованим типом працездатності. Отримані результати розширюють

**ХАРАКТЕРИСТИКА КЛИНИЧЕСКИХ
И ПАТОПСИХОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ
ПРИ АЛКОГОЛЬНОЙ ЗАВИСИМОСТИ У ЛИЦ
С ПОСТОЯННЫМ ТИПОМ ЗЛОУПОТРЕБЛЕНИЯ
АЛКОГОЛЕМ С УЧЕТОМ БИОЛОГИЧЕСКИХ
РИТМОВ**

**Животовская Л.В., Пайда Ю.Ю.,
Борисенко В.В., Боднар Л.А., Макаренко Н.А.**

Среди актуальных вопросов современной наркологии остается проблема изучения психопатологических проявлений психических и поведенческих расстройств вследствие употребления алкоголя, их патогенетических механизмов и учета этих факторов в разработке терапевтических методов воздействия. В результате исследования психо-эмоциональной сферы с учетом биоритмологического статуса отмечено, что у лиц вечернего типа преобладал высокий уровень реактивной и личностной тревожности по сравнению с утренним и недифференцированным типом ($p < 0,01$), чаще встречалась тяжелая депрессия по сравнению с утренним типом ($p < 0,05$), преобладали тревожный и дистимичный тип акцентуации, профиль личности свидетельствовал о более выраженной социальной дезадаптации по сравнению с утренним и недифференцированным типом работоспособности. Полученные результаты расширяют возможности

можливості оптимізації комплексної терапії даної когорти пацієнтів.

Ключові слова: алкогольна залежність, постійний тип зловживання алкоголем, біоритмологічний статус, реактивна тривога, особистісна тривожність, депресія, індивідуально-психологічні особливості.

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оптимизации комплексной терапии данной когорты пациентов.

Ключевые слова: алкогольная зависимость, постоянный тип злоупотребления алкоголем, биоритмологический статус, реактивная тревога, личностная тревожность, депрессия, индивидуально-психологические особенности.

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V. P. Ivanov, M. O. Kolesnyk, O. M. Kolesnyk, O. F. Bilonko, I. A. Niushko
National Pirogov Memorial Medical University, Vinnytsya

CHANGES IN EFFORT TOLERANCE INDICES IN PATIENTS WITH CHRONIC HEART FAILURE AND LATENT IRON DEFICIENCY ON THE BACKGROUND OF THE ORAL FERROTHERAPY

e-mail: mokolesnyk@gmail.com

It is known that iron deficiency (ID) in the case of chronic heart failure (CHF), regardless of the presence of anemia, contributes to the development of the skeletal muscle dysfunction, which results in a reduction of effort tolerance (ET) in patients. The objective of the study was to assess the changes in effort tolerance indices in patients with chronic heart failure, with reduced left ventricular ejection fraction and concomitant latent iron deficiency, on the background of a standard treatment combined with long-term oral ferrotherapy. The data obtained showed that the conducted additional oral ferrotherapy is accompanied by a substantial improvement in effort tolerance indices in patients with CHF as compared to the standard therapy alone. This demonstrates the feasibility of a latent ID 6-month oral ferroc correction to treat CHF with reduced LV EF in order to improve the patients' condition and working capacity.

Key words: chronic heart failure, latent iron deficiency, oral ferrotherapy

The study is a fragment of the research project "Prediction of the course and efficacy of various cardiovascular diseases treatment in combination with the pathology of other organs and systems", state registration No. 0120U100022.

In recent years, researchers have focused on the comorbidity of chronic heart failure (CHF). This is due to the fact that despite the use of modern treatment methods, the mortality of such patients reaches 30-60% within 3-5 years [14, 15]. Besides, the patients with CHF have a significantly lower quality of life, caused primarily by impairment of their physical activity [5], which, in turn, leads to significant medical, social, and economic challenges [2, 13]. In this regard, the issue of improving their physical condition, quality of life and prognosis remains relevant and can be addressed by improving the comorbidity diagnostics and treatment [2].

In previous years, researchers have focused more on the combination of CHF with a common manifest iron deficiency (ID), i.e. iron deficiency anemia (IDA), whereas the latent ID, even in the absence of anemia, is recorded in 45.6% of patients with CHF [10]. An important clinical aspect is that ID is significantly common among patients with cardiovascular morbidity, having nonspecific symptoms, and can be diagnosed only by determining the biochemical parameters of iron metabolism. Further, it is known that ID is a factor of unfavorable prognosis, impairment of physical activity and quality of life, as well as contributes to an increased number of hospitalizations [8].

ET decrease in these patients is due to the skeletal muscles disorders. In the human body, part of the iron is represented in the protein form – myoglobin, which is used to accumulate oxygen in the muscles. ATP in the muscles is formed by oxidative phosphorylation, which constantly requires a significant amount of oxygen. Accordingly, myoglobin provides oxygen redundancy and provides the ability of the muscles to contract for a long time. Lack of iron leads to the defects in the formation of iron-containing enzymes, which in turn is the cause of muscle hypotrophy and dysfunction, which is of clinical significance, especially in patients with latent iron metabolism disorders [6, 11].

The medicated correction of ID in the case of CHF brings positive changes in patients' condition. However, it has its own peculiarities. In previous studies, the benefits of intravenous administration over oral administration of iron have been demonstrated [9, 3]. However, these studies were conducted in patients with both absolute and functional ID, when known to activate proinflammatory cytokines in the case of functional ID worsen oral iron absorption. The question is whether positive changes in patients' condition with CHF and absolute ID with oral iron formulation will be obtained. Besides, a position of ferroc correction and its duration in patients with latent ID remains ambiguous. In view of disadvantages of oral ferroc correction, i.e. slow absorption in the gastrointestinal tract and its decreased level upon a slightest

possible inflammation in the case of CHF and due to blood congestion, in order to improve patients' physical functioning and general condition, oral ferrotherapy in patients with CHF and concomitant latent ID was prolonged in our study.

The purpose of the study was to assess the changes in effort tolerance indices in patients with chronic heart failure with reduced left ventricular ejection fraction and concomitant latent iron deficiency in the background of a standard treatment combined with long-term oral ferrotherapy.

Materials and methods. The study includes 60 patients with CHF with reduced left ventricular (LV) ejection fraction (EF) of the functional class (FC) II-III according to NYHA with concomitant latent ID. The patients with combined hypertensive and ischemic etiology of HF were enrolled in the study. Of them, 41 (68.3%) were men and 19 (37.1%) were women 68.3±0.63 years old. During the enrollment phase, all patients underwent general clinical examination according to 2016 ESC Guidelines for the diagnostics and treatment of acute and chronic heart failure with a compulsory laboratory testing of hemoglobin (Hb), red blood cells (Rbc), Rbc indices: MCV, MCH, MCHC and serum iron levels (SI), ferritin, total iron-binding capacity of serum (TIBC) and transferrin saturation (TS). The following criteria were used to diagnose the latent ID: 1) in the absence of signs of anemia, a decrease in serum iron (SI) in women < 11.5 µmol/l and in men < 13.0 µmol/l; 2) absolute ID – upon a decrease of SI and ferritin level < 100 ng/ml and 3) functional ID – upon a decrease of SI, ferritin levels of 100-300 ng/ml and transferrin saturation (TS) < 20% [7].

According to the study design, all patients received a standard therapy indicated by modern ESC recommendations, taking into account ischemic and hypertensive etiology of CHF and comorbid conditions, such as a trial fibrillation.

In order to avoid the possible impact of base treatment on the ferrotherapy outcomes, standard drug regimens were prescribed. Drug dosages were selected individually, in view of the patients' clinical condition. Two study groups were formed: besides the standard therapy, the patients in the 1st group (n=30) were prescribed oral ferrous sulfate at the dose of 320 mg, equivalent to 100 mg of bivalent iron and 60 mg of ascorbic acid, per day for 6 months; the patients in the 2nd group (n=30) received only a standard CHF therapy. The prescription of additional treatment was conducted among patients with absolute ID only. To determine the changes in effort tolerance (ET) indices in patients during treatment, the dynamics of the covered six-minute walk test distance was analyzed.

The groups of patients were compared by gender, age, main clinical characteristics, and treatment regimen.

Statistical processing of the obtained results was performed using Microsoft Office Excel and Statistica. Due to abnormal distribution of data, the obtained measurements are presented as a median (lower, upper quartile). The statistical significance of the difference in the measured parameters among groups was calculated according to Kruskal-Wallis ANOVA & Median test for all groups criterion, and the difference between the results of a 6-month treatment and the baseline values were calculated according to Wilcoxon matched pairs test criterion. The difference in the frequency of signs (%) was calculated by the χ^2 criterion. The difference was considered significant at $p < 0.05$.

Results of the study and their discussion. At the end of the study, the distribution of CHF FC according to NYHA among all patients demonstrated a decrease in the number of patients with FC 3 in the

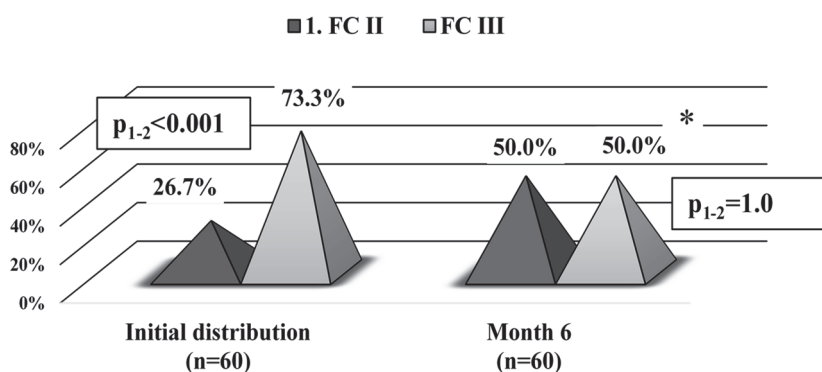


Fig. 1. Changes in CHF FC distribution according to NYHA among patients in the background of treatment. Note: "*" the difference of FC (%) on the background of a 6-month treatment as compared to the initial distribution was calculated by χ^2 criterion ($p < 0.001$).

background of the prescribed treatment in comparison with the initial distribution of the recording frequency of different FC (Fig. 1). Accordingly, the analysis of the dynamics showed that the overall decrease of FC according to NYHA on month 6 of treatment was reported for 14 (23.3%) patients. It should be noted that the clinical signs of CHF progression were not observed in any patient.

The assessment of FC changes on the background of treatment depending on a 6-month ferrotherapy (Fig. 2) did not identify any significant pattern $p > 0.05$, although a trend of increase in the cases of HF FC reduction was observed among patients who received iron supplements.

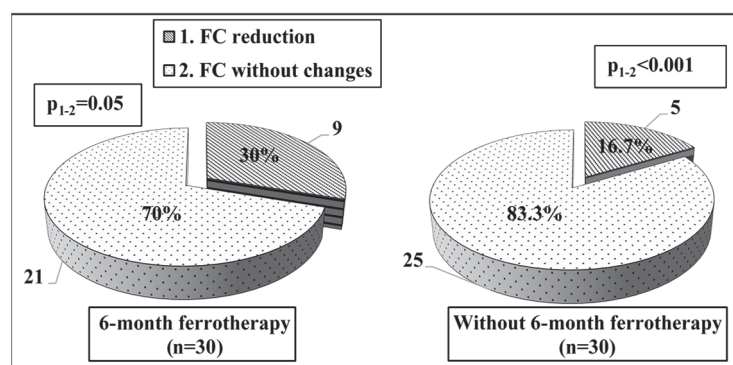


Fig. 2. Frequency of HF FC reduction cases according to NYHA depending on the 6-month ferrotherapy (in %). Note: The cross-group difference in % of cases with FC reduction depending on the 6-month oral ferrotherapy, which was calculated by χ^2 criterion, is insignificant ($p>0.05$).

increased over time. The following hematological changes, especially the decrease of SI (serum iron) and TS (transferrin saturation), in the group of patients who did not receive the iron supplements, demonstrate ID progression.

Table 1

Changes in the indicators of red blood growth in patients on the background of 6-months treatment (median, lower and upper quartile)

Hematological parameters	6-month ferrotherapy, n=30	Without 6-month ferrotherapy, n=30	p
Hb, g/l			
Baseline value	133 (130; 139)	135 (130; 146)	>0.05
6 th month	156 (150; 163)	121 (112; 132)	<0.001
Changes, %	+17.3 (+15.3; +17.2)	-9.7 (-14; -8)	<0.001
p _{iv-6}	<0.001	<0.001	
Rbc, $\times 10^{12}/l$			
Baseline value	4.59 (4.5; 5)	4.65 (4.4; 5)	>0.05
6 th month	4.8 (4.6; 5.2)	4.35 (4.2; 4.7)	<0.05
Changes, %	+4.57 (+2.22; +4)	-6 (-7.1; -4.5)	<0.001
p _{iv-6}	<0.001	<0.001	
MCV, fl			
Baseline value	84.6 (81.25; 86.7)	86.2 (81.3; 91.8)	>0.05
6 th month	87.4 (84.8; 89.8)	83.3 (80.4; 88.4)	<0.001
Changes, %	+3.3 (+4.3; +3.7)	-2 (-3.8; -1.1)	<0.001
p _{iv-6}	<0.001	0.01	
MCH, pg			
Baseline value	28.3 (27.3; 29.25)	29.4 (27.7; 30.1)	>0.05
6 th month	31.5 (29.9; 33.6)	27.4 (25.6; 28.4)	<0.001
Changes, %	+11.3 (+9.5; +14.8)	-4.3 (-7; -2.7)	<0.001
p _{iv-6}	<0.001	<0.001	
MCHC, g/l			
Baseline value	341 (331.1; 347.5)	340.3 (320.9; 351.1)	>0.05
6 th month	368.6 (348.8; 379.5)	326.9 (305.9; 343.6)	<0.001
Changes, %	+8.1 (+5.3; +9.2)	-2.1 (-5.7; -1.7)	<0.001
p _{iv-6}	<0.001	0.002	

Note: p_{iv-6} – significance of a difference between baseline values and after a 6-month treatment

The ET analysis among all patients with latent ID demonstrated that the indices of the covered six-minute walk test distance, as compared to the baseline values, increased by 10.5% (from 286.5 to 302.5 m, $p<0.001$) after 6 months of standard treatment.

Despite an overall increase of the covered six-minute walk test distance, 60 patients with latent ID on the background of the proper standard treatment and a half of patients, who received additional ferrotherapy, that is 16 (26.7%) patients, showed the covered distance reduction.

Changes in the indicators of iron metabolism in patients on the background of 6-months treatment (median, lower and upper quartile)

Hematological parameters	6-month ferrotherapy, n=30	Without 6-month ferrotherapy, n=30	p
1	2	3	4
SI (serum iron), umol/l			
Baseline value	8.7 (7.9; 9.6)	8.6 (8.5; 9.6)	>0.05
6 th month	23 (18; 25.9)	7 (5.9;8)	<0.001
Changes, %	+164 (+127.8; +169.8)	-17.3(-29.9; -7)	<0.001
p _{iv-6}	<0.001	<0.001	
Ferritin, µg/l			
Baseline value	70 (46; 78)	113 (78; 156)	<0.001
6 th month	144 (104; 167)	148 (65; 194)	>0.05
Changes, %	+105.7 (+126; +114)	+10.1(-13.9; 48.7)	<0.001
p _{iv-6}	<0.001	>0.05	
TS, %			
Baseline value	12.5 (11.8; 14.6)	13.9 (12.2; 17.6)	>0.05
6 th month	37.2 (31; 44.2)	10.5 (9; 15.1)	<0.001
Changes, %	+198 (+162.7; +202.7)	-20.7 (-36.4; -5.9)	<0.001
p _{iv-6}	<0.001	<0.001	
TIBC, umol/l			
Baseline value	67.5 (62.5; 73)	62.3 (56.4; 66)	>0.05
6 th month	58 (55.4; 64)	63 (55; 72)	>0.05
Changes, %	-13.4 (-11.36; -12.3)	3.6 (-8.9; 11.9)	<0.005
p _{iv-6}	<0.001	>0.05	

Note: p_{iv-6} – significance of a difference between baseline values and after a 6-month treatment

The changes in the covered six-minute walk test distance in 30 patients with latent ID on the background of a standard treatment and additional ferrotherapy over 6 months demonstrated an increase in

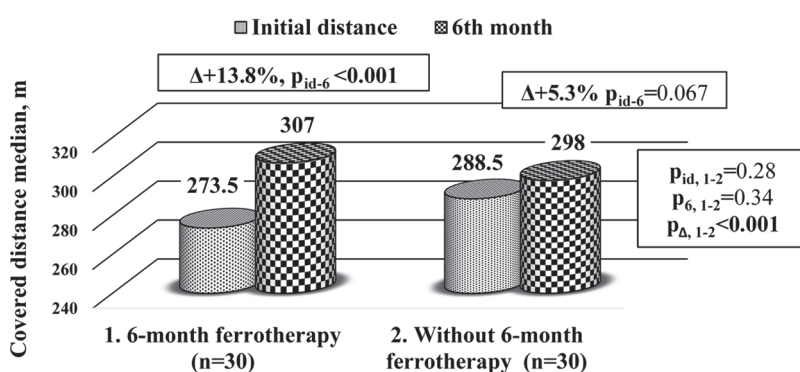


Fig. 3. The changes in the covered six-minute walk test distance in patients with CHF, with reduced LV EF and concomitant latent ID, on the background of 6-months treatment, median (lower, upper quartile). Notes: p_{iv-6} – significance of differences between the initial and post-treatment distance; p_{id,1-2} – significance of initial distance differences between two treatment groups; p_{6,1-2} – significance of distance differences after 6 months of observations between two treatment groups; p_{Δ,1-2} – significance of changes difference between two treatment groups.

covered six-minute walk test distance on the background of the prescribed treatment is rather interesting. It was identified that a greater frequency of cases with negative changes in the six-minute walk test occurred in the group of patients who received a standard treatment without ferrotherapy, namely 14 (46.7%) versus 2 (6.7%) patients, who received oral iron supplements, p<0,001 (Fig. 4).

Thus, this study shows that despite adequate standard treatment in patients with CHF with concomitant latent ID without ferrocorrection compared to patients who received iron supplementation noted a smaller percentage of frequency reduction of the HF FC by NYHA, less positive dynamics of the covered distance of 6-minute walk test, higher incidence of covered distance, which demonstrates lack of effective treatment in view of improving ET. The results obtained are probably due to negative changes in the indicators of red blood growth and iron metabolism, which took place due to the lack of ferrocorrection with the development of the above-mentioned mechanisms of influence of ID on the potentiation of skeletal muscle dysfunction. According to the hematological picture, not only a decrease in iron metabolism in patients who did not receive iron preparations was demonstrated, but also the progression of ID, in some

the actual distance by 13.8% (from 273.5 to 307 m, p<0.001) (Fig. 3). The analysis of changes in the covered distance among patients, who did not receive a 6-month therapy, did not demonstrate significant positive changes. Thus, as compared to the baseline values, the covered distance increased by 5.3% after 6 months (from 288.5 to 298 m, p=0.067) (Fig. 3).

From a practical point of view, the analysis of frequency of the cases in decrease in the

cases, with the development of manifestation – the appearance of anemic syndrome (as evidenced by a significant decrease in hemoglobin levels), which in turn also affects the reduction of ET in patients [4].

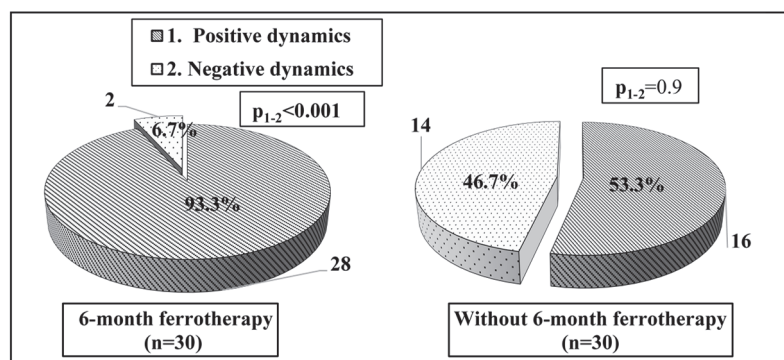


Fig. 4. Frequency of cases with negative changes in the six-minute walk test depending on whether a 6-month ferrotherapy was conducted or not (in %). Notes: The significance of intergroup differences in % of cases with negative changes in the six-minute walk test distance, depending on whether the 6-month oral ferrotherapy was conducted or not, was calculated by χ^2 criterion ($p < 0.001$).

agents [9]. The number of papers devoted to peroral ferrotherapy in CHF with differentiation of hematological variants is limited. It is known that due to reduced absorption of iron in the gastrointestinal tract, to replenish its reserves in the body, peroral ferrotherapy should last more than 3 months [1]. Despite this disadvantage, due to its availability, peroral iron therapy remains an alternative method of correcting ID [3], which is confirmed in our study.

Conclusion

The conducted additional oral ferrotherapy was accompanied by a more substantial improvement of effort tolerance indices in patients with CHF as compared to the use of the standard therapy alone. This demonstrates the feasibility of the latent ID 6-month oral ferrocorrection to treat CHF with reduced LV EF in order to improve the patients' condition and working capacity.

References

1. Amosova KM, Tsaralunha VM, Sydorova MM. Viddaleni klinikolaboratorni naslidky medykamentoznoyi korektsiyi zalizodefitytu u khvorykh na koronarohennu khronichnu sertsevu nedostatnist iz suputnoiu anemiieiu bez yavnykh prychny vtraty zaliza ta yiyi vplyv na funktsionalnyi stan khvorykh. Sertse i sudyny. 2013; 1(41): 101-9. [in Ukrainian]
2. Ivanov VP, Kolesnyk MO, Kolesnyk OM, Ivanova Yel. Anemii v rakursi problemy khronichnoi sertsevoi nedostatnosti: patohenez i laboratorna diahnozyka. Lvivskiy medychny chasopys. 2018; 2 (24): 69-76. [in Ukrainian]
3. Mozhina TL. Zhelezodefitsit v praktike semeynogo vracha. Zdorovya Ukrayiny XXI storichcha. 2017; 24: 44-45. [in Russian]
4. Voronkov L.G. Anemiya u patsiyenta z KhSN: yak otsiniuvaty ta likuvaty? Sertseva nedostatnist. 2015; 2: 5-13. [in Ukrainian]
5. Voronkov LG, Lutsak OO, Babykh PM, Liashenko AV. Predyktory yakosti zhyttia u khvorykh iz khronichnoyu sertsevoyu nedostatnistyu. Ukrainskiy medychny chasopys. 2011; 3: 86-88. [in Ukrainian]
6. Vydyborets SV. Optymalnyi vybir ionnykh i neionnykh preparativ zaliza pry likuvanni zalizodefitytynoy anemiyi u vahitnykh (pohliad na problemu). Zdorovye zhenshchynu. 2015; 8: 34-41. [in Ukrainian]
7. Anker SD, Kirwan BA, van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. Eur J Heart Fail. 2018; 20: 125-33.
8. Comin-Colet J, Enjuanes C, Gonzalez G, Torrens A, Cladellas M, Merono O, et al. Iron deficiency is a key determinant of health-related quality of life in patients with chronic heart failure regardless of anaemia status. Europ. J. of Heart Failure. 2013; 15: 1164-72.
9. Cunha GJL, Rocha BML, Menezes Falcão L. Iron deficiency in chronic and acute heart failure: A contemporary review on intertwined conditions. Eur J Intern Med. 2018; 52: 1-7.
10. Duygu K, Kadri MG. Iron deficiency and its treatment in heart failure: indications and effect on prognosis. E-Journal of Cardiology Practice. 2016; Available from: <https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-14/Iron-deficiency-and-its-treatment-in-heart-failure-indications-and-effect-on-prognosis>.
11. Dziegala M, Josiak K, Kasztura M, von Haehling S, Banasiak W, Anker SD, et al. Iron deficiency as energetic insult to skeletal muscle in chronic diseases. J Cachexia Sarcopenia Muscle. 2018; 9(5): 802-815.
12. Jankovska E, von Haehling S, Anker S, Macdougall I, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. Europ. Heart J. 2013; 34: 816-26.
13. Klip I, Comin-Colet J, Voors A. Iron deficiency in chronic heart failure: an international pooled analysis. Am. Heart J. 2013; 165: 575-82.
14. Mamas M, Sperrin M, Watson M. Do patients have worse outcomes in heart failure than in cancer? A primary carebased cohort study with 10-year follow-up in Scotland. Eur. J. Heart Fail. 2017; 19: 1095-1104.
15. Pocock SJ, Ariti CA, McMurray JV. Predicting survival in heart failure: a risk score based on 39372 patients from 30 studies. Eur. Heart J. 2013; 34: 1404-13.

Реферати

**ЗМІНИ ПОКАЗНИКІВ ТОЛЕРАНТНОСТІ
ДО ФІЗИЧНОГО НАВАНТАЖЕННЯ
У ХВОРИХ З ХРОНІЧНОЮ СЕРЦЕВОЮ
НЕДОСТАТНІСТЮ ТА ЛАТЕНТНИМ
ЗАЛІЗОДЕФИЦИТОМ**

НА ТЛІ ПЕРОРАЛЬНОЇ ФЕРРОТЕРАПІЇ
Іванов В.П., Колесник М.О., Колесник О.М.,
Білонько О.Ф., Ньюшко Т.Ю.

Відомо, що залізодефіцит (ЗД) при хронічній серцевій недостатності (ХСН), незалежно від наявності анемії, сприяє розвитку дисфункції скелетних м'язів, що приводить до зниження толерантності до фізичного навантаження (ТФН) у пацієнтів. Метою дослідження було оцінити зміни показників ТФН у хворих з ХСН зі зниженою фракцією викиду лівого шлуночка та супутнім латентним ЗД на тлі стандартного лікування в комбінації з тривалою пероральною ферротерапією. Отримані дані продемонстрували, що проведена пероральна ферротерапія супроводжується більш суттєвим покращенням показників ТФН у пацієнтів з ХСН, порівняно із застосуванням лише стандартного лікування. Це свідчить про доцільність 6-місячної феррокорекції латентного ЗД при лікуванні ХСН зі зниженою ФВ ЛШ, з метою покращення стану і працездатності таких пацієнтів.

Ключові слова: хронічна серцева недостатність, латентний залізодефіцит, оральна ферротерапія

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**ИЗМЕНЕНИЕ ПОКАЗАТЕЛЕЙ
ТОЛЕРАНТНОСТИ К ФИЗИЧЕСКОЙ НАГРУЗКЕ
У БОЛЬНЫХ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ
НЕДОСТАТОЧНОСТЬЮ И ЛАТЕНТНЫМ
ЖЕЛЕЗОДЕФИЦИТОМ НА ФОНЕ ПЕРОРАЛЬНОЙ
ФЕРРОТЕРАПИИ**

**Иванов В.П., Колесник М.О., Колесник О.М.,
Билонько О.Ф., Ньюшко Т.Ю.**

Известно, что железодефицит (ЖД) при хронической сердечной недостаточности (ХСН), независимо от наличия анемии, способствует развитию дисфункции скелетных мышц, что приводит к снижению толерантности к физической нагрузке (ТФН) у пациентов. Целью исследования было оценить динамику показателей толерантности к физической нагрузке у больных с хронической сердечной недостаточностью со сниженной фракцией выброса левого желудочка и сопутствующим латентным ЖД на фоне стандартного лечения в сочетании с длительной пероральной ферротерапией. Полученные данные продемонстрировали, что проведенная дополнительная пероральная ферротерапия сопровождается более существенным улучшением показателей толерантности к физической нагрузке у пациентов с ХСН по сравнению с применением только стандартной терапии. Это свидетельствует о целесообразности 6-месячной феррокоррекции латентного ЖД при лечении ХСН со сниженной ФВ ЛЖ, с целью улучшения состояния и работоспособности таких пациентов.

Ключевые слова: хроническая сердечная недостаточность, латентный железодефицит, оральная ферротерапия

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A.P. Kazmirchuk, O.I. Lashin, O.V. Druz, I.O. Chernenko
National Military Medical Clinical Center "Main Military Clinical Hospital",
Ministry of Defense of Ukraine, Kyiv

**BASIC PREDICTORS OF POST-TRAUMA STRESS DISORDER FORMATION AMONG
COMBATANTS**

e-mail: super-passa@ukr.net

In the present work, the authors identify predictors of the post-traumatic stress disorder (PTSD) formation among combatants. The study results include: a) tendency to express negative feelings through the form and content of verbal answers; b) unstable balance between the simultaneous desire for truthfulness and aggravation of PTSD symptoms, which provides a PTSD prognosis at the level of $\Sigma DC = 20.59 > 20$; c) combination of high level anxiety with a normal level of spontaneity, which ensures a PTSD forecast of $\Sigma DK = 15, 82 > 13$. Thus, an important component of the rehabilitation for combatants with PTSD is the creation of an appropriate therapeutic environment based on a patient-centered approach to potentiate the psychological, psychotherapeutic work aimed at restoring the relations between combatants, at the level of micro- and macro-environment.

Key words: combatants, post-traumatic stress disorder, post-stress mental disorder, combat mental trauma.

The work is a fragment of the research project "Substantiation of applying diagnostic and restorative psycho-physiological measures in the post-contusional period of servicemen", state registration No. 0118U00326.

The peculiarity of wars and military conflicts of today has become a manifestation of characteristic specific symptoms in many of its participants and in those occurring in the battle area, that are associated with the complex influence of physical, psychological, informational and other factors of war and related informational and cognitive influences on people. According to the WHO, 16.2% and 12.5% (out of 10% of citizens in 21 countries) suffer the consequences of war or traumatic injuries, respectively [1, 3, 9, 10]. Combat mental trauma (CMT) causes major disorders in combatant serviceman - mental maladaptation states - in 80% of cases, and among the wounded, according to the experience of local armed conflicts, mental disorders make almost 50% [2, 4, 5].

Stress-related mental disorders occurring during military operations are one of the major internal barriers to combativity and efficient performance of professional duties by combatants (up to the reduced

ability to participate in active combat), and subsequently to adaptation in ordinary life through the layering of new stresses associated with social maladaptation.

Therefore, selection of predictors of the post-traumatic stress disorder (PTSD) formation among combatants and development of effective strategies for their early diagnosis and prevention are pressing issues today.

The purpose of the study was to determine the predictors of PTSD formation among combatants based on the comparative analysis of psychiatric history indices.

Materials and methods. During 2016-2018, 150 servicemen in the Armed Forces of Ukraine (AFU) and in military unit A0139 were inspected in compliance with the principles of ethics and deontology, based on the informed consent to participate in the examination, on the basis of the psychiatry clinic at the National Military Medical Clinical Center "Main Military Clinical Hospital".

The sample was formed by the simple probabilistic sampling method (using the random numbers table), the required sample size was determined by the method of current assessing the differences significance by Rafales-Lamarck ($p < 0.05$ was accepted as the threshold confidence level) [2].

According to the criterion of PTSD presence/absence, combatants were divided into two comparison groups. Group 1 included 93 persons who were diagnosed with PTSD ($F 43.1$) by the criteria of MKH-10, group 2 consisted of 57 apparently healthy persons (without signs of PTSD). All of the surveyed were men, with an average age of 33.71 ± 1.34 years, mainly sergeants and unranked soldiers of the AFU, who served under the contract; the mean duration of their participation in the combat actions being 214.7 ± 41.55 .

The following study methods were used: clinical-psychopathological, clinical-anamnestic, psychodiagnostic (Buss-Durkee Hostility Inventory, BDHI, 1957), the technique for diagnosing general communicative tolerance by V.V. Boyko, and the empathy levels study by M. Yusupov [2, 5, 6].

Results of the study and their discussion. Predictors or markers of susceptibility-resistance to the PTSD formation in combatants were identified by analyzing the psychological, personality and behavioral characteristics of combatants. At the same time, the indices were taken into account according to the methods of psychodiagnostic research, which according to the scientific literature were associated with the development of PTSD.

As a result of the distribution analysis with determination of the ratio frequencies of a particular sing carriers by the comparison groups, the limit values of each index were set, after which it acquires the signs of a predictor for susceptibility or resistance to the PTSD formation. According to the Buss-Durkee Hostility Inventory, BDHI, 1957 [5, 6], it was found that the mean value of the aggressiveness index corresponded to the "social aggression" value and was significantly higher in comparison group 1 (19.60 ± 0.83 points versus 17.04 ± 0.31 at $p < 0.005$). Mean values of the hostility index were higher in the surveyed of the comparison group 2 ($p < 0.00001$), they exceeded the normative value by almost 2 times among PTSD combatants (11.57 ± 0.67 points) and by 3 times – the indices of apparently healthy combatants (17.08 ± 0.35 points) (table. 1).

Table 1

Mean values by the results of hostility and aggressiveness study (Buss-Durkee method)

Index, measuring units (points)	Mean values of the index*		p(t) **
	Group 1 (n=93)	Group 2 (n=57)	
Physical aggression	5.96±0.15	4.71±0.31	0.00019
Indirect aggression	5.59±0.21	5.67±0.22	0.39831
Irritability	6.01±0.28	4.84±0.27	0.00153
Negativism	3.75±0.14	5.85±0.29	<0.00001
Soreness	3.96±0.23	4.61±0.33	0.05233
Suspiciousness	6.65±0.28	4.76±0.27	<0.00001
Verbal aggression	8.12±0.33	4.84±0.25	<0.00001
Guilt feeling	5.96±0.21	7.19±0.27	0.00025
Hostility index	11.57±0.67	17.08±0.35	<0.00001
Aggressiveness index	19.60±0.83	17.04±0.31	0.00227

The most significant indices were those of MS - aggressiveness index > 21 points (MI = 1.87), the tendency of combatants to express negative feelings through the form (cry, scream) and the content of verbal responses (curse, threat) (verbal aggression > 8 points at MI = 1.26), hostility index > 13 points (MI = 1.20). In determining PTSD resistance, the most significant were ranges of the following features: irritability ≤ 5 points (MI = 0.78), negativism ≤ 2 points (MI = 0.67), physical aggression ≤ 5 points (MI = 0.62), verbal aggression ≤ 8 points (MI = 0.61), aggressiveness index ≤ 21 (MI = 0.60). It should be noted that the value of the latter corresponds to the normative value.

Distribution of the surveyed by diagnostic methods indices of the general communicative tolerance by V.V. Boyko and the study of the empathic tendencies level suggested by I.M. Yusupov and the levels of differences reliability in the intergroup comparison are presented in table. 2.

Table 2

Mean values of general communicative tolerance and the level of empathic tendencies

Index, measuring units (points)	Mean values of the index *		p(t) **
	Group 1 (n=93)	Group 2 (n=57)	
Method to diagnose general communicative tolerance (Boyko)			
Scale 1	6.29±0.50	4.37±0.40	0.00147
Scale 2	6.33±0.42	4.16±0.31	0.00003
Scale 3	8.21±0.51	4.27±0.35	<0.00001
Scale 4	7.68±0.47	3.09±0.22	<0.00001
Scale 5	4.99±0.44	3.41±0.14	0.00041
Scale 6	6.77±0.53	3.40±0.27	<0.00001
Scale 7	6.25±0.50	3.09±0.17	<0.00001
Scale 8	5.57±0.42	2.49±0.21	<0.00001
Scale 9	6.29±0.49	1.99±0.17	<0.00001
Scale 10	57.33±3.59	30.28±1.95	<0.00001
Empathy test by I.M. Yusupov. Empathic tendencies level	46.57±2.85	39.61±0.37	0.00838

Establishing the most significant predictors of PTSD among personality preferences in the communication process permitted, on the one hand, to determine the tendency of combatants to form this disorder, and, on the other, to determine the directions of psychotherapeutic work on correction and help combatants in dealing with problems of interpersonal interactions. The personal trends that contributed to the combatants' intolerance in communicating with other people influenced the development of PTSD to the greatest extent: scale 2 - using oneself as a standard in assessing other people's behavior and way of thinking (more than 2 points at MI = 1.45), scale 9 - inability to adjust to the character, habits and desires of others (more than 58 points at MI = 1.36), which testified to the intolerance of the combatant to others, scale 1 - rejection or misunderstanding of another person's individuality (more than 3 points at MI = 0.81), scale 3 - self-righteousness or conservatism in the estimates of others (more than or equal to 6 points with MI = 0.77), scale 4 - inability to hide or smooth out the unpleasant feelings in contact with an uncommunicative partner (more than 4 points at MI = 0.65).

Informative markers appeared to be: communicative tolerance is defined by scale 2 (see above) ≤ 4 points (at MI = 1.29), scale 1 ≤ 3 points (at MI = 1.04), scale 3 ≤ 6 points (at MI = 0.77), by scale 4 ≤ 4 (at MI = 0.73), by scale 8 (intolerance to physical or mental discomfort created by other people) ≤ 1 points (at MI = 0.59), by scale 9 ≤ 58 (for MI = 0.51). The data obtained indicate the need to include lessons on communication skills formation into treatment programs and rehabilitation training classes.

Very informative (which should be considered together with other predictors of PTSD) and a pathogenic marker that also influenced the communication problems of combatants was the level of empathic tendencies. It was a tendency for empathy registered at a level above average (more than 41 points (DC = 3.83 at MI = 0.76). This meant excessive "involvement" in another person's situation, empathy, compassion, which probably hindered the participants of local combat actions (PLCA) of performing their professional duties in combat circumstances. In its turn, the level of empathic tendencies lower than 41 points (DC = 3.48 at MI = 0.69) provided an adequate balance of sympathy for comrades, brothers and hostile attitude to the enemy.

Recent epidemiological studies have shown that military personnel involved in military conflict in the eastern region of Ukraine have different personality traits, and 30-40% of military personnel have psychopathological disorders, which are transformed into mental pathology, mainly of stressogenic origin. The most commonly diagnosed are acute reactions to the stress of the asthenic-depressive, asthenohypochondriacal and asthenic-neurotic nature (36.6-59.2%), PTSD (13.3-30.6%), disorders of adaptation (25.0-29.7%), organic affective and anxiety disorders (1.6%), psychotic (1.4%) and somatoform disorders (2.5%). This contingent of servicemen also has mental and behavioral disorders due to the use of alcohol and other psychoactive substances [7, 8, 11].

The works on PTSD also pay great attention to comorbid disorders such as depressive and anxiety disorders, mental and behavioral disorders due to alcohol and other psychoactive substances, which in 20% - 39% accompany PTSD [1, 3, 8]. However, despite the considerable achievements of recent decades, there are still a number of unresolved and rather controversial issues in the study of neurobiological and pathopsychological features of stress-related psychiatric disorders and comorbid pathology.

Conclusion

The study found that none of the psychological, personal, behavioral predictors by their mean contribution did not exceed the threshold of self-sufficiency in the PTSD prognosis ($DC > 13$), so the predisposition-resistance to the development of this disorder in a particular soldier can only be claimed when registering these markers (taking into account the desired level of reliability for such a conclusion).

Достатнього рівня значущості набули маркери схильності до ПТСР, які обумовлюють проблеми у спілкуванні комбатантів, комунікативний бар'єр. Також до найбільш значущих таких предикторів відносяться

The PTSD predisposition markers that cause combatants' communication problems, the communication barrier, have gained considerable significance. Also, the most significant predictors are:

- according to Buss-Durkee method - aggression index > 21 points ($MI = 1.87$), verbal aggression > 8 points, i.e. the tendency to express negative feelings through the form and content of verbal responses ($MI = 1.26$), hostility index > 13 points ($MI = 1.20$);

- a number of personal preferences in communication that promote intolerance in communication, and the level of empathy tendencies is higher than the mean normative (more than 41 points, $DC = 3.83$ at $MI = 0.76$).

Somatogenic and psychogenic factors related to combat circumstances, previous peaceful life, problems in interpersonal relationships (socio-demographic factors) have been found to have the greatest pathogenic impact.

References

1. Aymedov KV, Aseyeva YO, Tolmachov OA. Suchasna diahnostychna kontsepsiya posttravmatychnoho stresovoho rozladu. Arkhiv psykhiatriyi. 2016; 22(2): 128-129. [in Ukrainian]
2. Vasserman LI. () Psikhologicheskaya diagnostika i korrektsiya v somaticheskoy klinike: nauchno-prakticheskoe rukovodstvo. SPb: Rech. 2011. 270 s. [in Russian]
3. Voloshyn PV, Maruta NO, Shestopalova LF. Diahnozyka, terapiya ta profilaktyka medyko-psykholohichnykh naslidkyv boiovykh diy v suchasnykh umovakh: metod. rek. Kharkiv: 2014. 79 s. [in Ukrainian]
4. Kozhyna AM, Haichuk LM. Psykhoosvitni zakhody v umovakh hibrydnoyi viyny. Ukrainyskiy visnyk psykhonevrolohiyi. 2017; 25(1) 124–129. [in Ukrainian]
5. Metodyka rozrobky ta vprovadzhennia metodychnykh standartiv (unifikovanykh klinichnykh protokoliv) medychnoyi dopomohy na zadakh dokazovoyi medytsyny. Hakaz Ministerstva okhorony zdorovya Ukrainy vid 28 veresnia 2012 roku № 751, zareiestrovanyi v Ministerstvi yustytzii Ukrainy 29 lystopada za №2001/22313: dodatok 6. 2017; 25(1): 124. [in Ukrainian]
6. Raygorodskiy DY. Prakticheskaya psihodiagnostika. Metodiki i testy. Samara: "Bahrakh-M"; 2002. 2672 s. [in Russian]
7. Chernenko IO. Pokaznyky psykhiatrychnoho anamnezu yak markery rannoyi diahnozyky PTSR u uchasykiv lokalnykh boiovykh diy. United-journal. 2018; 21: 14-18. [in Ukrainian]
8. Shestopalova LF. Doslidzhennia transformatsiyi indyvidualno-psykholohichnykh osoblyvostey kombataniv, yaki perebuvaly u zoni ATO. Ukrainyskiy visnyk psykhonevrolohiyi. 2017; 25(1) 162. [in Ukrainian]
9. Badiuk MI, Shevchuk OS. The combat stress reaction as a scientific problem of the world, and its social and medical consequences. Clinical and Experimental Pathology. 2016; 4: 10-14.
10. Dalenberg C, Carlson EB. Dissociation in posttraumatic stress disorder part II: How theoretical models fit the empirical evidence and recommendations for modifying the diagnostic criteria for PTSD. Psychological Trauma: Theory, Research, Practice and Policy. 2016; 4: 51-67.
11. Kleim B, Ehlers A. Evidence for a curvilinear relationship between posttraumatic growth and posttrauma depression and PTSD in assault survivors. Journal of traumatic stress. 2009; 22(1): 45-52.

Реферат

ОСНОВНИ ПРЕДИКТОРИ ФОРМУВАННЯ ПОСТТРАВМАТИЧНОГО СТРЕСОВОГО РОЗЛАДУ СЕРЕД КОМБАТАНТІВ

Казмірчук А.П., Лашин О.І., Друзь О.В., Черненко І.О.

В дослідженні автори відокремлюють предиктори формування посттравматичного стресового розладу серед комбатантів. За результатами дослідження встановлено, що достатнього рівня значущості набули маркери схильності до ПТСР, які обумовлюють проблеми у спілкуванні комбатантів, комунікативний бар'єр. Також до найбільш значущих предикторів виявлено: а) схильність до виразу негативних почуттів через форму та зміст словесних відповідей; б) нестійка рівновага між одночасним прагненням до правдивості та агравації симптомів ПТСР, що забезпечує прогноз ПТСР на рівні $\Sigma ДК = 20,59 > 20$; в) сполучення високого рівня тривожності з нормальним рівнем спонтанності, що забезпечує прогноз ПТСР на рівні $\Sigma ДК = 15, 82 > 13$. Таким чином, важливою складовою реабілітації комбатантів з ПТСР є створення

ОСНОВНЫЕ ПРЕДИКТОРЫ ФОРМИРОВАНИЯ ПОСТТРАВМАТИЧЕСКОГО СТРЕССОВОГО РАССТРОЙСТВА СРЕДИ КОМБАТАНТОВ

Казмирчук А.П., Лашин А.И., Друзь О.В., Черненко И.А.

В работе авторы выделяют предикторы формирования посттравматического стрессового расстройства (ПТСР) среди комбатантов. По результатам исследования установлено, что достаточного уровня значимости получили маркеры предрасположенности к ПТСР: а) склонность к выражению негативных чувств через форму и содержание словесных ответов; б) неустойчивое равновесие между одновременным стремлением к правдивости и агравации симптомов ПТСР, что обеспечивает прогноз ПТСР на уровне $\Sigma ДК = 20,59 > 20$; в) сочетание высокого уровня тревожности с нормальным уровнем спонтанности, что обеспечивает прогноз ПТСР на уровне $\Sigma ДК = 15, 82 > 13$. Таким образом, важной составляющей реабилитации комбатантов с ПТСР является создание соответствующей терапевтической

відповідного терапевтичного середовища на тлі пацієнт-центрованого підходу задля потенціювання психологічної, психотерапевтичної роботи, спрямованої на відновлення взаємин комбатантів на рівні мікро- та макро-оточення.

Ключові слова: комбатанти, посттравматичний стресовий розлад, постстресовий психічний розлад, бойова психічна травма.

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среды на основе пациент-центрированного подхода для потенцирования психологической, психотерапевтической работы, направленной на восстановление отношений комбатантов на уровне микро- и макро-окружения.

Ключевые слова: комбатанты, посттравматическое стрессовое расстройство, постстрессовое психическое расстройство, боевая психическая травма.

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L.F. Kaskova, S.C. Novikova, N.M. Anopriyeva, A.A. Akzhitova
Ukrainian Medical Stomatological Academy, Poltava

CHANGES IN INDICES OF CHEMICAL COMPOSITION AND MINERALIZING PROPERTIES OF ORAL FLUID IN CHILDREN WITH INTESTINAL DYSBIOSIS

e-mail: n.nataliya86@gmail.com

The purpose of our work was to study the indices of calcium, inorganic phosphorus and mineralizing properties of oral fluid in 2-3 year-old children with intestinal dysbiosis. The results obtained allowed us to conclude that in the oral fluid of 2-3 years old children with intestinal dysbiosis there was a decrease in the content of calcium and inorganic phosphorus compared to similar indicators in healthy children. Thus, the rate of ionized calcium in the oral fluid was 0.23 ± 0.01 mmol/l, which is 1.6 times less than the corresponding indice in children of the control group (0.37 ± 0.02 mmol/l). The content of inorganic phosphorus in the oral fluid in children with intestinal dysbiosis was 4.38 ± 0.03 mmol/l, and in somatically healthy children it was 4.66 ± 0.03 mmol/l, which is correspondingly lower by 0.28 mmol/l. They also showed a decrease in the mineralizing potential of the oral fluid, which indicates the tendency of the erupted teeth to the enamel demineralization and increasing the prevalence of dental caries. The distribution of children by the level of mineralizing potential indicated that only 6.6% of children with intestinal dysbiosis have a high rate, which is more than 2 times worse than in the control group. The cooperation of a dentist and a pediatrician is necessary for the timely detection and prevention of dysbiosis emergence in children and, as a consequence, dental pathology – dental caries.

Key words: dysbiosis, oral fluid, children.

This work is a fragment of the research project "Improvement of methods of prevention and treatment of hard teeth tissues and periodontal tissues on the background of somatic pathology in children, taking into account socio-economic factors and psycho-emotional state", state registration No. 0119U102852.

In recent years, the number of children with caries developed in early childhood has been increasing [9, 11]. This is due to various local and general factors [2, 4, 6, 12], one of which is the child's diseases in the first years of life [9, 11].

Currently, the number of intestinal diseases has increased, which is caused by a violation of the qualitative and quantitative ratio of aerobic and anaerobic microflora in the lumen of this organ. This disease is called "intestinal dysbiosis" [5, 8]. Intestinal dysbiosis occurs more often and faster in infant children, any intestinal infection in them in 100% of cases is accompanied by dysbiosis. Modern epidemiological studies show that the population of the Earth to some extent have disorders in the microflora composition, which is the basis of the organism microecology [8].

Changes in the normal intestinal microflora in dysbiosis can lead to functional changes in the intestine, which leads to impaired absorption of nutrients, calcium and phosphorus, synthesis of a number of vitamins, and this adversely affects the formation of hard teeth tissues [1, 3].

The study of the condition of the hard teeth tissues and increasing their resistance in children with dysbiosis, arose because of the recent increase in clinical cases of the most acute aggressive early dental caries in children aged 1 to 5 years [9, 11]. There is a clear relationship between the intestinal flora and calcium and phosphorus metabolism, which, of course, affects the mineralization of hard teeth tissues, as well as the influence of these processes on the early caries occurrence in children with intestinal dysbiosis [1].

The purpose of the study was to study the indices of calcium and inorganic phosphorus in oral fluid and mineralizing properties of oral fluid in children with dysbiosis.

Materials and methods. The content of mineral components (calcium and inorganic phosphorus) in the oral fluid was determined in 80 children aged 2-3 years: 60 children had intestinal dysbiosis and 20 children were the control group (almost healthy children). Children with intestinal dysbiosis were registered with a pediatrician at the place of residence. Their diagnosis was determined by an infectious disease doctor on the basis of bacteriological examination during the child's stay at hospital, dental status was determined by the oral cavity examination. The content of ionized calcium and phosphorus in the oral fluid was determined using the kit "Reagent" (DAC – SpektroMed s.r.l., Moldova). The mineralizing potential of oral fluid (MPOL) was determined by its microcrystallization. Oral fluid was taken in an amount of 0.2-0.3 ml from the bottom of the oral cavity with a sterile pipette. Then at least three drops of

oral fluid were applied to the slide treated with alcohol and ether. Drying of microslides was performed at the room temperature. Dried drops of oral fluid were studied under a microscope (type MBS-9,10) at low magnification of 2x6. The MPOI evaluation was performed taking into account the total area of dried drops of oral fluid and expressed in the average score depending on the detected types of crystal formation. The mineralizing potential of oral fluid was evaluated on a scale: 0.0-1.0 – very low; 1.1-2.0 – low; 2.1-3.0 – satisfactory; 3.1-4.0 – high; 4.1-5.0 – very high.

The obtained results were processed by the Student's-Fisher's variational statistics method. The difference of indices at $p < 0.05$ was considered probable. All statistical processing of the results was performed using Microsoft Office Excel software package for a PC.

Results of the study and their discussion. Our studies showed that children aged 2-3 years with intestinal dysbiosis belong to the risk group, as evidenced by a decrease in the chemical composition of oral fluid in these children compared with similar indices in healthy children. Thus, the rate of ionized calcium in the oral fluid was 0.23 ± 0.01 mmol/l, which is 1.6 times less than the corresponding indice in children of the control group (0.37 ± 0.02 mmol/l) (table 1). The content of inorganic phosphorus in the oral fluid in children with intestinal dysbiosis was 4.38 ± 0.03 mmol/l, and in somatically healthy children it was 4.66 ± 0.03 mmol/l, which is correspondingly lower by 0.28 mmol/l.

Table 1

The content of calcium and inorganic phosphorus in the oral fluid of children (M \pm m)

Age of children in years	Groups of children	Number of children	Calcium, mmol/l	Phosphorus, mmol/l
2-3 years	Main	60	0.23 ± 0.01	4.38 ± 0.03
	Control	20	0.37 ± 0.02	4.66 ± 0.03
p			<0.01	<0.01

Note: p – the probability between the indices of the main and control groups.

The calcium content in the oral fluid of children affects the processes of enamel mineralization after the tooth eruption. The obtained data on the mineral components of the oral fluid in terms of calcium and inorganic phosphorus indicate a decrease in their concentration, which leads to the fact that the oral fluid ceases to perform remineralizing function, and leads to a carious process. The decrease in remineralizing properties of oral fluid in children with intestinal dysbiosis in comparison with healthy children is confirmed by indices of the mineralizing potential of oral fluid (table 2).

Table 2

Indices of the mineralizing potential of oral fluid in children (m \pm M)

Age in years	Groups of children	Number of children	Indices of mineralizing potential, scores			p ₂
			mean value	with caries	without caries	
2	Main	60	1.88 ± 0.09	1.43 ± 0.08 (n=30)	2.34 ± 0.12 (n=30)	<0.002
	Control	60	2.12 ± 0.10	1.71 ± 0.10 (n=30)	2.52 ± 0.12 (n=30)	<0.001
p ₁			<0.002	<0.002	<0.001	
3	Main	60	2.06 ± 0.10	1.70 ± 0.10 (n=30)	2.44 ± 0.14 (n=30)	<0.001
	Control	60	2.20 ± 0.11	1.69 ± 0.10 (n=30)	2.72 ± 0.14 (n=30)	<0.002
p ₁			<0.001	<0.001	<0.001	
Total	Main	120	1.97 ± 0.05	1.56 ± 0.06 (n=60)	2.39 ± 0.09 (n=60)	<0.001
	Control	120	2.37 ± 0.06	2.12 ± 0.10 (n=60)	2.62 ± 0.10 (n=60)	<0.001
p ₁			<0.01	<0.001	<0.002	

Notes: p₁ – the probability of data between indices of the main and control groups in each age period; p₂ – the probability of data between indices within the main and control groups in children with and without caries; n – number of children in the group.

According to the study results, the mean value of the mineralizing potential of oral fluid in children 2 years old with intestinal dysbiosis was 1.88 ± 0.09 scores, and in somatically healthy children – 2.12 ± 0.10 scores. The mineralizing potential indice of oral fluid in children 3 years old of the main group was 2.06 ± 0.10 scores, and in somatically healthy children – 2.20 ± 0.11 scores. We found that in children 2-3 years old of the main group the mean value of mineralizing potential was 1.97 ± 0.05 scores, which corresponds to a low level of microcrystallization, and in healthy children – 2.37 ± 0.06 scores, i.e. they have a satisfactory level. There is a probable difference in the studied indice in children with caries and without caries of both the main and control groups, but the indice in children with intestinal dysbiosis is always worse than in somatically healthy children ($p < 0.001$). Thus, the mineralizing potential indice of oral fluid in children 2-3 years old of the main group with caries was 1.56 ± 0.06 scores and corresponded to a low level of microcrystallization, without caries – 2.39 ± 0.09 scores and corresponded to a satisfactory level of microcrystallization. The mineralizing potential indice of oral fluid in children 2-3 years old in the control group with caries was 2.12 ± 0.10 scores, without caries – 2.62 ± 0.10 scores.

The distribution of children by the level of mineralizing potential indicated that only 6.6% of children with intestinal dysbiosis have a high rate, which is more than 2 times worse than in the control

group. A very low mineralizing potential is more common in children of the main group than in practically healthy children.

The study of oral fluid in children under three years of age is important for early detection of the causes of cariogenic situation in the oral cavity and subsequent preventive measures. The obtained data confirm that the composition and properties of the oral fluid are an important factor determining dental caries resistance. Enamel mineralization after the teeth eruption occurs under the influence of chemical components of oral fluid. Decreased concentration of calcium and inorganic phosphorus, deterioration of physical parameters of oral fluid leads to a decrease in enamel resistance and increase the prevalence of dental caries in infant children [1, 3, 7, 10, 12].

Conclusions

Studies have shown a decrease in calcium and inorganic phosphorus in the oral fluid of children 2-3 years old with intestinal dysbiosis compared with healthy children. They also have a decrease in the mineralizing potential of oral fluid, which causes the tendency of erupted teeth to enamel demineralization and increasing the prevalence of caries in these children. Therefore, preventive measures should be aimed at improving the studied indicators.

Prospects for further research lie in the fact that intestinal dysbiosis in children of 2-3 years old may be due to a violation of other components of the oral cavity homeostasis. Therefore, further comprehensive studying of this question will be expedient.

References

1. Bezvushko EV. Vmist mineralnykh komponentiv u rotoviy ridyni ditey, yaki prozhyvaiut u riznykh ekolohichnykh umovakh. *Novyny stomatolohii*. 2014; 1(78): 96 – 98. [in Ukrainian]
2. Dienha OV, Pynda MIA, Kovalchuk VV. Poshyrenist i intensyvnist kariiesu u ditei, yaki prozhyvaiut v umovakh defitsytu fluoru v pytnii vodi. *Visnyk problem biolohii i medytsyny*. 2014; 3(2):328-30. [in Ukrainian]
3. Kaskova LF, Ulasevych LP. Dynamika vmistu kaltsiyu i fosforu u rotoviy ridyni ditey doshkilnoho viku z hipertrofiieyu adenoyidiv z urakhuvanniam provedennia profilaktychnykh zakhodiv stosovno kariyesu. *Ukrainskyi stomatolohichniy almanakh*. 2017; 1:70-74. [in Ukrainian]
4. Luchynskyi MA. Vplyv nehatyvnykh faktoriv dovkillia na riven stomatolohichnoyi zakhvoriuvanosti dytiachoho naselennia. *Visnyk problem biolohii i medytsyny*. 2014; 1(2):221–23. [in Ukrainian]
5. Makarova SG, Namazova-Baranova LS. Kischechnaya mikrobiota i primeneniye probiotikov v praktike pediatria. *Chto novogo? Pediatricheskaya farmakologiya*. 2015. 12(1): 38–45. [in Russian]
6. Smolyar NI, Musiy-Sementsiv NI. Poshyrenist ta intensyvnist kariyesu molochnykh zubiv u ditey iz zahalnosomatychnoy patolohiyeyu. *Klinichna stomatolohiya*. 2013.; 3-4: 32–33. [in Ukrainian]
7. Stadnyk UO, Cherepiuk OM, Lysak TYu. Kharakterystyka deyakykh fizychnykh ta mikrobiolohichnykh vlastyvostey RR u ditey doshkilnoho viku v zalezhnosti vid intensyvnosti kariyesu tymchasovykh zubiv. *Visnyk problem biolohii i medytsyny*. 2016; 3(130):347–50. [in Ukrainian]
8. Stepanyan MI, Komarova EV. Disbioz kischechnika u detey rannego vozrasta i vozmozhnosti yego korrektsii. *Pediatricheskaya farmakologiya*. 2016; 13(6):592-596. [in Russian]
9. Khomenko LO, Bidenko NV. Ranniy kariyes tymchasovykh zubiv: perspektyvy vyrishennya. *Klinichna stomatolohiya*. 2011; 1-2 : 64-68. [in Ukrainian]
10. Chukhrai NL. Vzaiemoviazok mizh fizychnymy vlastyvostiamy rotovoyi ridyny u ditey ta rezystentnistiu emali. *Visnyk stomatolohii*. 2017; 2:41–45. [in Ukrainian]
11. Yakubova II., Kuzmina VA. Ranniy dytyachyy kariyes. *Stan problemy v Ukrayini. Sovremennaya stomatolohiya*. 2017; 1:48-53. [in Ukrainian]
12. Núñez FL, Sanz BJ, Mejía LG. Dental caries and early childhood development: a pilot study. *Rev Chil Pediatr*. 2015; 86(1): 38–42.

Реферати

ЗМІНА ПОКАЗНИКІВ МІНЕРАЛЬНОГО СКЛАДУ ТА МІНЕРАЛІЗУЮЧИХ ВЛАСТИВОСТЕЙ РОТОВОЇ РІДИНИ У ДІТЕЙ ІЗ ДИСБАКТЕРІОЗОМ КИШЕЧНИКУ
Каськова Л.Ф., Новікова С.Ч., Анопрієва Н.М., Акжитова Г.О.

Метою нашої роботи було вивчення показників вмісту кальцію, неорганічного фосфору та мінералізуючих властивостей ротової рідини у дітей 2-3 років з дисбактеріозом кишечника. Отримані результати дозволили зробити висновок, що у дітей 2-3 років з дисбактеріозом кишечника в ротовій рідині виявлено зниження вмісту кальцію і неорганічного фосфору в порівнянні з аналогічними показниками здорових дітей. Так показник іонізованого кальцію в ротовій рідині склав $0,23 \pm 0,01$ ммоль/л, що в 1,6 рази менше в порівнянні з відповідним показником у дітей контрольної групи ($0,37 \pm 0,02$ ммоль/л). Показник вмісту неорганічного фосфору в ротовій рідині у дітей з дисбіозом кишечника склав $4,38 \pm 0,03$ ммоль/л, а у

ИЗМЕНЕНИЯ ПОКАЗАТЕЛЕЙ МИНЕРАЛЬНОГО СОСТАВА И МИНЕРАЛИЗУЮЩИЕ СВОЙСТВА РОТОВОЙ ЖИДКОСТИ У ДЕТЕЙ С ДИСБАКТЕРИОЗОМ КИШЕЧНИКА
Каськова Л.Ф., Новикова С.Ч., Аноприева Н.М., Акжитова А.А.

Целью нашей работы было изучение показателей содержания кальция, неорганического фосфора и минерализующих свойств ротовой жидкости у детей 2-3 лет с дисбактериозом кишечника. Полученные результаты позволили сделать вывод, что у детей 2-3 лет с дисбактериозом кишечника в ротовой жидкости выявлено снижение содержания кальция и неорганического фосфора по сравнению с аналогичными показателями здоровых детей. Так показатель ионизированного кальция в ротовой жидкости составил $0,23 \pm 0,01$ ммоль/л, что в 1,6 раза меньше по сравнению с соответствующим показателем у детей контрольной группы ($0,37 \pm 0,02$ ммоль/л). Показатель содержания неорганического фосфора в ротовой жидкости у детей с дисбиозом кишечника составил $4,38 \pm 0,03$ ммоль/л, а у соматически здоровых детей

соматично здорових дітей дорівнює $4,66 \pm 0,03$ ммоль/л, що на $0,28$ ммоль/л відповідно нижче. Також в них спостерігалось зниження мінералізуючого потенціалу ротової рідини, що вказує на схильність зубів, які прорізалися, до демінералізації емалі і підвищення показників поширеності карієсу. Розподіл дітей за рівнем мінералізуючого потенціалу свідчить про те, що серед дітей з дисбактеріозом кишечника високий його показник мають лише $6,6\%$ дітей, що більше ніж в 2 рази гірше в порівнянні з контрольною групою. Для своєчасного виявлення та запобігання дисбактеріозу у дітей і, як наслідок, стоматологічної патології – карієсу зубів, необхідна співпраця стоматолога і педіатра.

Ключові слова: дисбактеріоз, ротова рідина, діти.

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равен $4,66 \pm 0,03$ ммоль/л, что на $0,28$ ммоль/л соответственно ниже. Также у них наблюдалось снижение минерализующего потенциала ротовой жидкости, что указывает на склонность зубов, которые прорезались, к деминерализации эмали и повышению показателей распространенности кариеса. Распределение детей по уровню минерализующего потенциала свидетельствует о том, что среди детей с дисбактериозом кишечника высокий его показатель имеют только $6,6\%$ детей, что более чем в 2 раза хуже по сравнению с контрольной группой. Для своевременного выявления и предотвращения дисбактериоза у детей и, как следствие, стоматологической патологии – кариеса зубов, необходимо сотрудничество стоматолога и педиатра.

Ключевые слова: дисбактериоз, ротовая жидкость, дети.

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A.G. Kyrychenko, V.M. Kornatsky¹, V.M. Serdiuk², S.V. Abramov, V.V. Ogorenko²
 Dnipro Medical Institute (Traditional and Non-Traditional Medicine), Dnipro
¹“National Scientific Centre “The Academician M.D. Strazhesko Institute of Cardiology”
 of the NAMS of Ukraine”, Kyiv, ²State Institution “Dnipropetrovsk Medical Academy
 of the Ministry of Health of Ukraine”, Dnipro

PREVENTION OF AUTONOMIC DISADAPTATION IN SERVICE MEMBERS

e-mail: grial2401@gmail.com

The autonomic nervous system (ANS) is the main regulator of maintaining homeostasis and organism adaptation to changes in the environment. Most often, autonomic dysfunction occurs under the conditions of chronic psychoemotional stress. To prevent emotion dysregulation and stress-related disorders in service members, the state of the autonomic nervous system was assessed by examining 145 military servicemen, considering the initial autonomic tone, autonomic reactivity and autonomic support of the individual. In most subjects there was tension and dysfunction of the ANS, which allowed us to recommend a more thorough study of its three main components in order to identify autonomic disorders and the allocation of these persons to the risk group for psychosomatic pathology.

Key words: autonomic nervous system, service member, tone, stress-associated disorders.

The work is a fragment of the research project “Development of a system of diagnostic, psychocorrectional, treatment, rehabilitation and preventive measures for patients with non-psychotic mental disorders and their family members”, state registration No. 0118U001281.

The autonomic nervous system (ANS) is the main regulator of maintaining homeostasis and organism adaptation to changes in the environment. Dysfunction leads to the development of autonomic dysregulation, which is a risk factor for many psychosomatic diseases, such as somatoform autonomic dysfunction, anxiety or panic neurosis, various paroxysmal conditions or stress-associated disorders, irritable bowel or stomach syndrome and others. Most often, autonomic dysfunction occurs under conditions of chronic psychoemotional stress or under certain conditions that lead to the development of physical or sexual impotence, emotional and psychological disorders [4, 6, 8, 12, 14].

In recent years, there has been a significant increase in the development of stress-related disorders in the service members (SM), who are within the anti-terrorist operation (ATO) conditions [1, 9, 10]. In this regard, the SM with signs of autonomic dysfunction most often have difficulties in adapting to the conditions of military service, which is manifested in the violation of military discipline, reduced professional efficiency, harmony of interpersonal relations and social status. In terms of military service, this leads to negative consequences: suicide attempts, conflicts within the military personnel, the unauthorized leaving of a military unit. This fact requires more attention to the state of SM health, which should be put forward to the autonomic state of persons participating in the ATO [5, 6, 7, 9]. Unfortunately, autonomic dysfunction in military conflict is regarded not as pathology but as a clinical normology, which, in our opinion, is not right given that the already low level of functioning should be regarded as preclinical disadaptation conditions.

The purpose of the study was to assess the state of the autonomic nervous system to prevent disadaptation and stress-related disorders in the service members.

Materials and methods. For this purpose, 145 servicemen aged 18 to 37 were examined. All service members underwent a clinical and neurological examination, assessing the autonomic status [2, 3,

13]. History of the present illness was studied in detail. Functional assessment of the ANS state was carried out taking into account its three main components: the initial autonomic tone, autonomic reactivity and autonomic support of the individual's activity.

ANS homeostasis was determined by clinical and electrophysiological parameters that characterize the initial autonomic tone (IAT), autonomic reactivity (AR) and autonomic support (AS) of organs and systems [3, 13]. Cardiointervalography (CIG) was used to determine IAT in addition to special research methods [3, 13]. To assess the ANS reactivity – cardiovascular tests (Prevel's orthostatic reflex and Dagnini-Aschner reflex) [3, 13]. Autonomic support of activity (ASA) was determined using a physical and mental work load test [2, 13, 15]. All ANS studies were performed in the morning, at the same time. Statistical processing was performed using parametric and nonparametric research methods, using Student's reliability with a significance level of $p < 0.05$.

Results of the study and their discussion. During the clinical and neurological examination of the SM the following complaints were identified: vertigo (27.9%), syncope (21%), intolerance to heat (28.9%) and cold (33.7%), liability to allergies (29.8%), increased sweating (36.3%), frequent abnormal bowel pattern (27.9%), nausea (22.1%), constipation (26.5%), increased oiliness of the skin (38.7%), cold hands (42.6%), warm and wet hands (44.8%). Periodic decrease in working capacity was found in 40%, decrease in attention or inattention – in 38.6%, dyssomnic disorders – in 27% of individuals. Feelings of anxiety, worry, or fear were found in 34% of individuals.

In 74% of individuals were identified manifestations of autonomic dysfunction, which were manifested by distal acrohypothermy, distal and diffuse hyperhidrosis or their combination, tachycardia, hyperthermia, hyperaesthesia or paresthesia in the extremities and others. Signs of autonomic dysfunction at the segmental level were found in 96 people (66%). The number of signs of autonomic dysfunction per serviceman averaged 3.4 ± 1.9 . The analysis of the difference in blood pressure in both arms revealed an initial asymmetry, which was unreliable ($p > 0.05$). Given the stress index in subjects aged 18–26 years, eutonia was observed in $58.6 \pm 4.1\%$ of cases, vagotonia – in $20.7 \pm 3.4\%$, and sympathicotonia – in $20.7 \pm 3.4\%$. In 27% there was a significant increase in systolic blood pressure ($p < 0.05$). At that time, diastolic blood pressure did not increase ($p < 0.05$). As it can be seen in fig. 1 the most common was the initial eutonia ($48.3 \pm 4.15\%$; $p < 0.001$), in $26.3 \pm 3.65\%$ – the initial vagotonia, in $25.4 \pm 3.55\%$ there was the initial sympathicotonia.

In the SM after direct participation in the combat conditions, the vagotonic orientation of the initial autonomic tone was 2 times more common ($p \leq 0.02$), especially it was increased in individuals from 25 to 36 years (35%) (fig. 2).

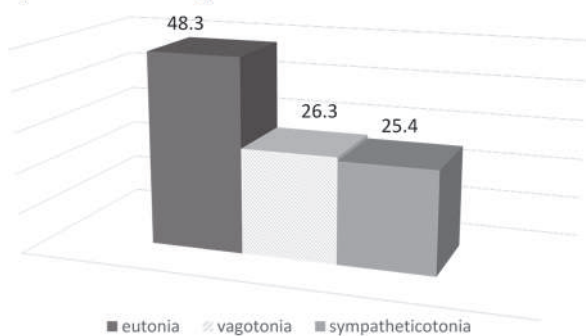


Fig. 1. Comparative diagram of indices (%) – the number of subjects) of autonomic tone in the SM

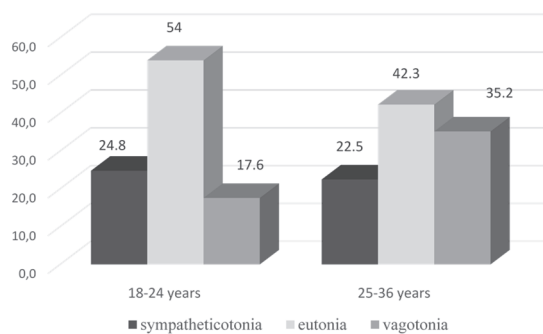


Fig. 2. Comparative diagrams of indices (%) – number of subjects) of autonomic tone depending on participation in combat action

Kerdo autonomic index decreased by 19% ($p < 0.05$). In the studied persons aged 18–24 years it was 34.1% ($p < 0.001$) higher than in persons aged 25–36 years – by 27% ($p < 0.05$). Heart rate, respiration rate and Hildebrandt coefficient did not change depending on age ($p > 0.05$). In subjects with sympathicotonia, along with SI increase above 90 RU, there was a significant increase in A-mode, ARI, AEI and a decrease in ΔX , Mo ($p < 0.001$), compared with the same indices in subjects with initial eutonia. In subjects with vagotonia there were inverse relationships, in the form of a decrease in SI (under 30 RU), A-mode, ARI, AEI and an increase in ΔX , Mo ($p < 0.001$).

During the study of ECG parameters, it was determined that sinus tachycardia was detected in $62 \pm 4.3\%$ of subjects, sinus bradycardia – in $30.3 \pm 4.2\%$, sinus arrhythmia – in $7.7 \pm 5.5\%$, respectively. Cardiac conduction disease in the form of incomplete first-degree AV block was observed in $12.4 \pm 2.7\%$, and incomplete blockade of the right branch of His bundle – in $23.6 \pm 4.3\%$. These manifestations were correlated with clinical manifestations, where the SM showed a tendency to sudden skin redness, increased blood pressure and diffuse hyperhidrosis.

After physical activity and a change in the SM's body position, the heart rate recovery was assessed as satisfactory in 28%, good – in 68%, unsatisfactory – in 4%. Instead, in subjects with vagotonia, there was an increase in the R-R and P-Q intervals, decreased P-wave and increased T-wave, QRST complex expanded for more than 0.38 sec.

The study of autonomic reactivity using the Prevel's orthostatic reflex showed that 58.6±4.1% of individuals had normal AR, 22.8±3.5% had excessive AR and 18.6±3.2% had insufficient AR. (fig. 3).

During the analysis of the orthostatic reflex test absolute values, a significant increase in heart rate (15.5 per minute, $p < 0.001$), increased systolic (10.1 mm Hg, $p < 0.001$) and diastolic (9.9 mm Hg, $p < 0.001$) arterial pressure were determined. After psycho-emotional stress and orthostatic reflex test systolic (by 24.0%, $p < 0.05$) and diastolic (by 19.0%, $p < 0.05$) blood pressure becomes higher in the examined individuals. During the Dagnini-Aschner reflex test, 51.0±4.15 % of individuals had normal AR, 20.7±3.36% had excessive AR, 19.3±3.65 % had insufficient AR, and 9.0±2.38 % had misdirected AR (fig. 3). In total, the parasympathetic Dagnini-Aschner reflex test caused a decrease in heart rate by 7-9 beats per minute in persons aged 18–26 years – $p < 0.001$. The study found no significant differences in changes in heart rate depending on age.

During the study of autonomic support of activity by means of a mental capacity test, in 56.6±4.1% of individuals the normal type was registered, in 17.2±3.1% – an excessive type and in 26.2 ± 3.6% – insufficient type of ASA (fig. 4).

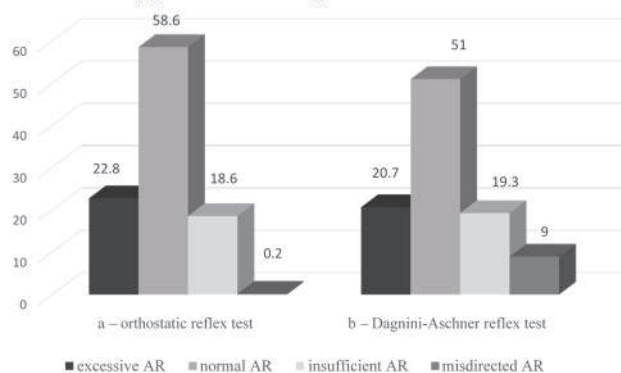


Fig. 3. Comparative diagrams of indices (% – number of examined subjects) autonomic reactivity in individuals aged 18–26 years and 27–36 years.

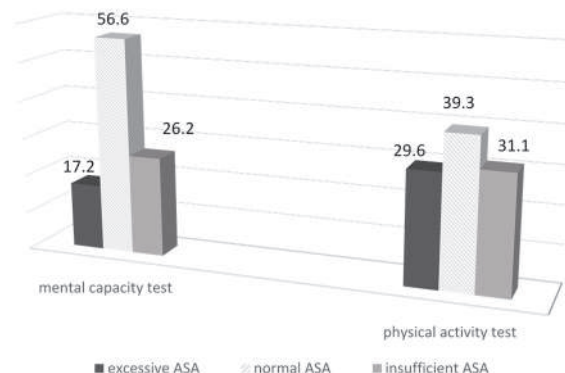


Fig. 4. Comparative diagrams of indices (% – number of examined subjects) autonomic support of activity in individuals aged 18–26 years.

In general, the subjects had a significant increase in heart rate by 15.7 minutes ($p < 0.001$). Age analysis did not reveal a significant difference in the mental capacity test.

During the physical activity test, the normal variant of ASA was observed in 39.3±4.0 % individuals, the excessive variant – in 29.6±3.8 %, and the insufficient variant – in 31.1±3.8 % (fig. 4). As can be seen, during physical activity there is no predominance of one or another variant of ASA ($p > 0.05$). In general, during this test in persons aged 18-26 years there was a significant increase in heart rate (18.4 per minute, $p < 0.001$), an increase in systolic (9.4 mm Hg, $p < 0.001$) and diastolic (6.1 mm Hg, $p < 0.001$) arterial pressure compared to the initial tone.

It was found that the level of diastolic blood pressure increase in individuals aged 18–26 years was slightly higher ($p < 0.001$), but in individuals aged 27–34 years the diastolic blood pressure increase in the test was significantly higher ($p < 0.001$) than in individuals aged 18–26 years. Other indices during the physical activity test did not depend on age.

Analysis of AR and ASA depending on the initial autonomic tone showed that in persons with initial eutonia during orthostatic test in 81.4±4.6 % of cases there was a normal AR, in 12.9±4.0% of cases – excessive AR and in 5.7±2.8 % – insufficient AR. During the Dagnini-Aschner test, normal AR was observed in 74.3±5.2 % of individuals, excessive AR – in 5.7±2.8 %, insufficient AR – in 11.4±3.8 %, and misdirected AR – in 8.6±3.3 %.

In individuals with initial sympatheticotonia, insufficient AR (59.5±8.1 %, $p < 0.001$) and normal AR (40.5±8.1 %, $p < 0.001$) were most often observed during the orthostatic test. At the same time, there was no excessive AR. The parasympathetic Dagnini-Aschner test in most cases revealed excessive AR (59.5±8.1 %; $p < 0.005-0.001$). In addition, in 24.3±7.0% of cases there was normal AR, in 13.5±5.6% – insufficient AR and in 2.7±2.6% – misdirected AR. In persons with initial vagotonia in the transition to orthostatic position, excessive AR was most often predominant (63.2±7.8%; $p < 0.01-0.001$). In 34.2±7.7 % of cases, there was normal AR and in isolated cases – insufficient AR. The Dagnini-Aschner test was normal in 34.2±7.7 % of individuals, insufficient – in 39.5±7.9%, misdirected – in 15.8±5.9%, and excessive – in 10.5±4.9%.

The study of ASA during a mental capacity test, considering the initial autonomic tone showed that in persons aged 18–26 years with eutonia at rest in 71.4±5.4% of cases there was a normal type of ASA, in 17.1±4.5% of cases – an insufficient type and in 11.5±3.8 % – an excessive one. In persons with initial euthonia during physical activity test, normal ASA was observed in 57.1±5.9% of cases, excessive – in 17.1±4.5% and insufficient – in 25.8±5.2%. At initial sympathicotonia (mental capacity test), normal ASA was found in 43.2±10.8% of individuals, excessive – in 13.6±5.6% and insufficient – in 43.2±10.8 %. During the physical activity test, normal ASA was registered in 21.6±6.7% of individuals, excessive – in 24.3±7.1% and insufficient – in 54.1±8.2 %. In subjects with initial vagotonia, normal ASA during the mental capacity test was found in 42.1±8.0%, excessive – in 31.6±7.6 % and insufficient – in 26.3±7.1 %. In the physical activity test, it was 23.7±6.9 %; 57.9±8.0% and 18.4±6.3% respectively.

Thus, the obtained data showed that along with the normal type of autonomic tone, half of the service members had vagotonia or sympathicotonia, which indicated a decrease in the reserve capacity of autonomic regulation and a tendency to disadaptation. These data coincide with the data of other researchers [4, 12]. Especially after the combat condition, vagotonic orientation was 2 times more often in the SM aged 25-36 years (35%), which manifested in various symptoms of autonomic dystonia syndrome with vagotonic predominance. These data are consistent with data from other researchers [4, 8, 9, 10, 11].

The obtained results suggest that the manifestations of the autonomic nervous system dysregulation, which were identified in 74% of service members, can lead to the development of disadaptation, which in turn additionally trigger a cascade of psycho-somatic disorders, which coincides with the data of other scientific studies [4]. This fact suggests that psychoneurological non-training can lead to the formation of stress-associated disorders, so it is necessary to take a more careful approach to determining the autonomic regulation indices, which directly affects the formation of psychoneurological stability to avoid difficulties in their adaptation. All this gives grounds to agree with the conclusions of other authors [9, 10, 12, 13, 15] on the need for a thorough study of the ANS functioning to develop preventive measures for disadaptation occurrence in SM, especially in combat conditions.

Conclusions

1. The study of the ANS functioning revealed that the presence of hypersympathicotonia mostly indicates intense adaptation, reduced reserve capacity of autonomic regulation, the presence of asympathicotonia or vagotonia indicates unsatisfactory adaptation, which in stressful conditions is usually manifested by syncopal states, vertigo, poor tolerance of physical and psychoemotional stress.

2. Imbalance of the autonomic nervous system increases the risk of disadaptation, especially in combat conditions, which in turn can further trigger a cascade of stress-related disorders. In this regard, for prevention, it is necessary to include in the SM examination by neurophysiological research methods to identify and clarify the nature of possible adaptive and recovery disorders.

3. When recruiting service members, the definition of automatic regulation should be approached in more detailed definition, which will avoid difficulties in adapting not only in the service, but also in combat conditions.

References

1. Bakhadova EM, Karpov SM, Apaguni AE, Karpova EN, Apaguni VV, Kaloiev AD. Otdalennyye posledstviya minno-vzryvnoy travmy na neurofiziologicheskoye sostoyaniye golovnoy mozga. Fundamentalnyye issledovaniya. 2014; 2: 28-33. [in Russian]
2. Berdieva DB. Metody issledovaniya fizicheskoy rabotosposobnosti u rabotnikov umstvennogo truda v dinamike rabocheho dnya [Internet]. Molodoy uchenyy. 2016; 11(115):1143-1145. Dostupno na URL: <https://moluch.ru/archive/115/30696/> [in Russian]
3. Kalenchits TI, Ryisevets EV, Antonovich ZhV. Funktsionalnyye nagruzochnyye proby (uchebno-metodicheskoye posobie). Minsk: BGMU; 2018. 36 s. [in Russian]
4. Karpov SM, Malevanets EV, Kaloiev AD, Shevchenko PP, Solomonov AD, Kireyeva OG. Psihonevrologicheskie proyavleniya v raznyye sroki u voennosluzhashchih srochnoy sluzhby. Fundamentalnyye issledovaniya. [Internet]. 2013;9(4):435–438. Dostupno na: <http://www.fundamental-research.ru/ru/article/view?id=32489> [in Russian]
5. Konstantinov VV, Dyakov VV. Charakteristiki identichnosti lichnosti i process socialno-psihologicheskoy adaptatsii. Teoriya i praktika obshchestvennogo razvitiya. 2015; 12: 482–486. [in Russian]
6. Korostii VI, Polishuk VT, Zavorotnii VI. Psihofarmakoterapiya v kompleksnomu likuvanni ta reabilitatsii posttravmatichnogo stresovogo rozladu. Mizhnarodnyi nevrologichnyi zhurnal. 2015; 6 (76): 59–71. [in Ukrainian]
7. Kulakova MV. Osobennosti ispolzovaniya metodov psihokorreksii s tselyu optimizatsii processa psihologicheskoy adaptatsii voennosluzhashchih, pohodyashchih sluzhbu po przyvu. Vestnik Kemerovskogo gosudarstvennogo universiteta. 2014; 3 (59): 1:127-130. [in Russian]
8. Malevanets EV, Karpov SM, Kaloiev AD. Processy adaptatsii sredi voennosluzhashchih srochnoy sluzhby. Klinicheskaya nevrologiya. 2013; 3:3–6. [in Russian]
9. Malevanets EV, Karpov SM, Kaloiev AD, Shevchenko PP, Solomonov AD, Kireeva OG. Psihonevrologicheskie proyavleniya v raznyye sroki u voennosluzhashchih srochnoy sluzhby. Fundamentalnyye issledovaniya. 2013; 9:655-660. [in Russian]
10. Malevanets EV, Kaloiev AD, Karpov SM. Adaptatsiya voennosluzhashchih k voennoy sluzhbe po rezul'tatam kardiointervalograficheskogo issledovaniya. Meditsinskiy vestnik Severnogo Kavkaza. 2013; 8 [4]: 47-50. [in Russian]
11. Mikhailov BV, Zinchenko OM, Fedak BS, Sarvir IM. Medyko-psihologichnyi suprovid osib z gostrymy rozladamy psyhiky i povedinky psyhogennoy pohodzhennya (metodichni rekomendatsiyi). Kharkiv; 2014. 28. [in Ukrainian]

12. Mikhailov BV. Rozlady psyhiky i povedinky ekstremalno-psyhologichnogo pohodzhennya. Psyhichne zdorov'ya. 2015; 2[47]: 9–18. [in Ukrainian]
13. Odinak MM, Litvinenko IV. Nervnye bolezni: uchebnik dlya studentov meditsinskih vuzov. Sankt-Peterburg: SpetsLit; 2020. 575 s. [in Russian]
14. Pulikov AS, Moskalenko OL, Meyngot YaYa. Otsenka vegetativnogo reagirovaniya organizma yunoshei v usloviyah Sibiri. Fundamentalnye issledovaniya [Internet] 2015; 1-2:332–336. Dostupno na: <http://www.fundamental-research.ru/ru/article/view?id=36898>. [in Russian]
15. Torgashov MN. Neurosomaticheskie problemy stressovyh vozdeistvii [disertatsiya] Ekaterinburg; Uralskiy Gosudarstvennyy Meditsinskiy Universitet; 2017. 337 [in Russian]

Реферати

**ЗАПОБІГАННЯ ВЕГЕТАТИВНОЇ
ДЕЗАДАПТАЦІЇ ВІЙСЬКОВИХ**

**Кириченко А.Г., Корнацкий В.М, Сердюк В.Н.,
Абрамов С.В., Огоренко В.В.**

Вегетативна нервова система (ВНС) є головним регулятором підтримки гомеостазу та пристосування організму до змін зовнішнього середовища. Найбільш часто вегетативна дисфункція виникає в умовах хронічного психо-емоційного стресу. Для запобігання виникнення дизрегуляції та стрес-асоційованих розладів у військових було проведено оцінку стану вегетативної нервової системи шляхом обстеження 145 військових з урахуванням вихідного вегетативного тону, вегетативної реактивності та вегетативного забезпечення діяльності особи. У більшості досліджуваних осіб відзначалися напруженість і дисфункція ВНС, що дозволяє рекомендувати більш ретельне дослідження трьох її основних складових з метою виявлення вегетативних порушень і виділення цих осіб в групу ризику по виникненню психосоматичної патології.

Ключові слова: вегетативна нервова система, військовослужбовець, тонус, стрес-асоційовані розлади.
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**ПРОФИЛАКТИКА ВЕГЕТАТИВНОЙ
ДЕЗАДАПТАЦИИ ВОЕННЫХ**

**Кириченко А.Г., Корнацкий В. М, Сердюк В.Н.,
Абрамов С. В., Огоренко В. В.**

Вегетативная нервная система (ВНС) является главным регулятором поддержания гомеостаза и приспособления организма к изменениям внешней среды. Наиболее часто вегетативная дисфункции возникает в условиях хронического психо-эмоционального стресса. Для предотвращения возникновения дизрегуляции и стресс-ассоциированных расстройств у военных была проведена оценка состояния вегетативной нервной системы путем обследования 145 военных с учетом исходного вегетативного тону, вегетативной реактивности и вегетативного обеспечения деятельности человека. В большинстве исследуемых лиц отмечались напряженность и дисфункции ВНС, что позволяет рекомендовать более тщательное исследование трех ее основных составляющих с целью выявления вегетативных нарушений и выделению этих лиц в группу риска по возникновению психосоматической патологии.

Ключевые слова: вегетативная нервная система, военнослужащий, тонус, стресс-ассоциированные расстройства.
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Yu. Z. Kotsiubynska¹, N.M. Kozan¹, H.M. Zelenchuk¹, S.V. Koliadenko², I.V. Vakar²
¹Ivano-Frankivsk National Medical University, Ivano-Frankivsk
²National Pirogov Memorial Medical University, Vinnytsya

**POSSIBILITY OF USING DERMATOGLYPHIC PARAMETERS OF THE MEDIUM
AND PROXIMAL FINGER FALANGES OF THE HANDS WITHIN THE REQUIREMENTS
OF DVI-INTERPOL**

e-mail: nmkozan@gmail.com

The study material was the dermatological parameters of the middle and proximal phalanges of the fingers that were obtained from 460 representatives of different ethno-territorial groups of the Carpathian region with the use of Futronic's FS80 USB 2.0 optical scanner, that were subjected to quantitative and qualitative study and processing by one- and multidimensional statistical analysis. The morphological structure peculiarities of the dermatoglyphic parameters of the middle and proximal finger phalanges have been studied; it is suggested to use "Complementary classification of skin patterns of middle and proximal phalanges of fingers" (Author's certificate of scientific work No. 74560); it is suggested to classify the dermatoglyphs of the middle and proximal phalanges of the fingers by the complexity of the morphological structure. Based on the performed research, a separate self-sufficient system of dermatoglyphic identification features was developed, which is able to increase and confirm the reliability of the complex identification examination results according to DVI Interpol criteria.

Key words: forensic medicine, identification of the person, dermatological parameters.

The work is a fragment of the research project "Forecasting of external recognizable human features based on a comprehensive study of dermatological features of hands and feet", state registration No. 0117U00477.

In international practice, the set of all integrative professional properties related to the identification of persons and the organization of forensic medical examinations, is conditioned and controlled by the international organization ICPO-Interpol, which combined not only intellectual human resources, but also a set of earned identification algorithms adapted to multifaceted catastrophes [1]. It is not superfluous to say that to the methodological approach Disaster Victim Identification (DVI), developed by Interpol, the

method of dermatoglyphic identification is included, due to its material ease, high informativeness, as well as the ability to get results within short time limits.

Among the problems of identifying an unknown person, along with improving the organization and technology of identification, one of the most important tasks is the development of new identification criteria and techniques that would help to bring the results closer to the most accurate, since none of the DVI Interpol method is 100 % reliable [2].

A great deal of scientific works in recent years has been devoted to the development and supplementation of existing identification dermatoglyphic criteria of the palms, feet and distal phalanges of the fingers and toes [7, 9].

Insufficient theoretical properties and applied methodological recommendations regarding to the use of dermatoglyphic parameters of the middle and proximal phalanges of the fingers for identification purposes, attracts attention and opens new prospects for study. In particular, scientific researches of Shpak L.Yu. [4], devoted to the study of the dermatoglyphic parameters of the middle and proximal phalanges of the fingers, which partially elucidate the interrelationships of the dermatoglyphic parameters of the distal, middle and proximal phalanges of the fingers, their sexual dimorphism, bilateral and digital variability, the symmetry of skin relief, as well as regularity of inheritance of patterns of middle and proximal phalanges. Author demonstrated the ability to use the dermatoglyphic parameters of the middle and proximal phalanges of the hand at the level with the parameters of the distal phalanges to identify a person for establishing kinship, as well as systematized and improved classification of patterns of comb pattern of the proximal and middle phalanges of the hand. Chistikina T.A, Zoroastrov O.M, Kolomys V.E [3] developed dermatoglyphic diagnostic complexes, studying the prevalence of finger patterns of distal, middle and proximal phalanges of fingers of the population of Tyumen region.

However, existing data do not provide a holistic view of the structure and significance of the interrelationships between the dermatoglyphs of the middle and proximal phalanges of the hands and with the human external recognition parameters, nor do they reveal the full identification potential of these connections.

The purpose of the study was to supplement the forensic identification criteria of DVI Interpol within the dermatoglyphic method by examining the morphological features of the dermatoglyphic parameters of the middle and proximal phalanges of the fingers; to form multifaceted classification schemes that will further facilitate the work of experts during the quantitative and qualitative study of the dermatoglyphs of the middle and proximal phalanges of the fingers and increase the competence of the forensic expert in conducting identification examinations.

Materials and methods. The dermatoglyphic parameters of the middle and proximal phalanges of the fingers were obtained from 260 male and female aged from 18 to 59, who identified themselves as representatives of the Hutsul, Boiko, Lemko, Opil, Pokut ethno-territorial groups, and control groups of persons, living at the territory of the Carpathian region. The criterion for inclusion in the study groups were voluntary consent of the individual, absence of genetic pathology, pathology of the endocrine system and musculoskeletal system, age 18-59 years. The exclusion criteria from study were the refusal from the study at any stage, the presence of genetic pathology, pathology of the endocrine system and the musculoskeletal system, age younger than 18 and over 59 years.

The scope and methods of work research do not contradict the basic principles of the Helsinki Declaration on Biometric Research (1974), adapted at the 41st Hong Kong International Assembly (1989), in which a person acts as their object. The basic principles such as respect for the individual, the awareness of the individual, the risk assessment of harm and benefit were adhered during the study.

The dermatoglyphs of the middle and proximal phalanges of the fingers were obtained by scanning them with a Futronic's FS80 scanner and improved by converting bitmaps to vector graphic objects, using the algorithm VeriFinger 6.6/MegaMatcher 4.4 Identification Technology Algorithm. The data obtained by quantitative and qualitative study of the morphological elements that form the dermatoglyphic parameters of the middle and proximal phalanges of the fingers of hands (type of papillary pattern, complexity of the morphological structure, directionality of the papillary lines), were subjected to one- and multidimensional statistical analysis.

Results of the study and their discussion. The palmar surface of the human hands is covered with different combinations of parallel, fan-shaped or diagonally arranged papillary lines, which form unique dermatoglyphic patterns for each person, which, in turn, are used as constant identification criteria for conducting forensic identification of an unknown person.

On the palmar surface of all fingers except the first finger, at the location of the metacarpophalangeal and phalangeal joints, there are three bending folds that delineate the papillary fields

of the dermatoglyphic parameters of the phalanges corresponding to the proximal, middle and distal phalanges. On the 1st finger of both hands are two bending folds, and, accordingly, they distinguish only two papillary fields, corresponding to the proximal and distal phalanx. It should be noted that the papillary field of the proximal phalanx on all fingers is limited by the metacarpo-phalangeale bending fold (plica flexoris metacarpo-phalangeale) and bending fold of proximal phalanx (plica flexoris proximal-phalangeale) The papillary field of the middle phalanx on all fingers except the 1st finger is limited by the proximal and flexural fold of the middle phalanx (plica flexoris media-phalangeale). The papillary field of the distal phalanx is limited by the distal edge of the phalanx and the bending fold of the middle phalanx. In the fields described above there is a papillary pattern, which is a complex relief pattern formed by alternation with a certain periodicity of ridge-like elevations (height 0.1-0.4 mm, width 0.2-0.7 mm), separated by shallow furrows – depressions (width 0.1-0.3 mm).

Dermatoglyphic relief on the middle and proximal phalanges is formed by papillary patterns without delta (fig. 1), in contrast to the dermatoglyphic parameters located on the distal phalanges (fig. 2).



Fig. 1. Without delta dermatoglyphs of the middle phalanges of the fingers.



Fig. 2. Delta dermatoglyphs of the distal phalanges of the fingers.

The image of the papillary pattern on the scan should be read in the distal-proximal direction along the axis of the finger phalanx. The lettering of the specific type of pattern is made by using the abbreviation of English marking with indication of papillary lines direction in the form of the index after the lettering in the side of I or V fingers (radial, ulnar), as well as considering the topography of the pattern with regard to the phalanx bending folds (proximal, distal). For example: radial wave (Vr), distal arc (Ad).

The lettering of the combined patterns is also made by using the abbreviation in English and is written through the oblique line. For example: double arc/with tilt (Da/L), double arc/with tilt (Da/L), distal arc/with tilt (L/Ad) with corresponding designation of papillary lines orientation.

For ease of use, we decided all known to us papillary images of middle and proximal phalanges of the fingers to group by the complexity of the morphological structure into 2 groups: simple and combined (Tab. 1).

Table 1

Types of dermatoglyphic parameters depending on the complexity of the dermatoglyphic structure

No.	Simple patterns	Combined patterns
1	Direct (S)	Distal arc/ with tilt (L/Ad)
2	With tilt (L)	Double arc (Da)
3	Distal sickles (Hd)	Proximal arc/with tilt (Ap/L)
4	Proximal sickles (Hp)	Double arc /with tilt (Da/L)
5	Distal arc (Ad)	Double sickle (Dh)
6	Proximal arc (Ap)	Featherlike (F)
7	Sickleshaped arc (Ah)	Closed pattern (Cl)
8	Wave (V)	Distal angle (Nd)
9		Proximal angle (Np)
10		Double angle (Dn)
11		Distal arc/angle (Nd/Ad)
12		Proximal arc/angle (Ap/Np).
13		Combined linear (L/S)
14		Wave/ direct (V/S)
15		Distal arc/direct (Ad/S)
16		Proximal arch/direct (Ap/S)

To systematize all known dermatoglyphic parameters of the middle and proximal phalanges of the fingers, we have developed the "Supplemented classification of skin patterns of the middle and proximal phalanges of the fingers" (Copyright Certificate No. 74560. Graphic image. Date of registration 07.11.2017) (fig. 3).

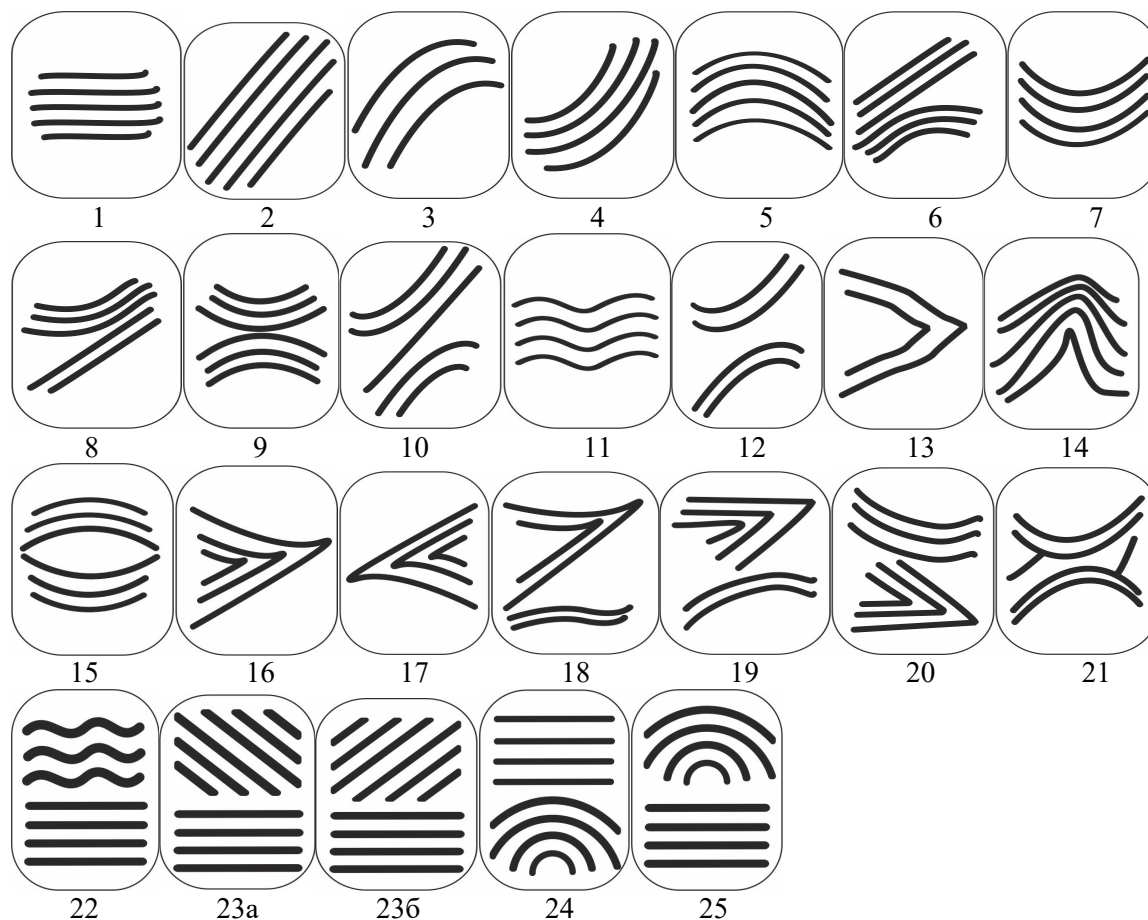


Fig. 3. Supplemented classification of skin patterns of the middle and proximal phalanges of the fingers

According to the proposed classification, among the patterns of the middle and proximal phalanges of the fingers are the following (fig. 3): 1) straight (S); 2) with a slope (L); 3) distal sickles (Hd); 4) proximal sickles (Hp); 5) distal arc (Ad); 6) distal arc/with tilt (L/Ad); 7) proximal arc (Ap); 8) proximal arc/with tilt (Ap/L); 9) double arc (Da); 10) double arc/with tilt (Da/L); 11) wave (V); 12) double sickle (Dh); 13) featherlike (F); 14) sickle shaped arc (Ah); 15) closed pattern (Cl); 16) distal angle (Nd); 17) proximal angle (Np); 18) double angle (Dn); 20) distal arc/angle (Nd/Ad); 21) proximal arc/angle (Ap/p); 22) wave/straight (V/S); 23) a, b combined linear (L/S); 24) distal arc/straight (Ad/S); 25) proximal arc/straight (Ap/S).

Studying the dermatoglyphs of the middle and proximal phalanges of the fingers, we came to the conclusion that the most poorly differentiated is straight (S) (No. 1) pattern, formed by straight parallel papillary lines and has middle location, with a slope (L) (No. 2), that is also constructed from parallel papillary lines, but these lines have already trend to be radially or ulnar oriented and the wave (V) (No. 11), which may have middle, ulnar, and radial positions. The sickles (Hd, Hp) (No. 3,4), as well as the arches (Ad, Ap) (No. 5,7), according to the orientation of the pattern relative to the phalanx bending folds (proximal, distal) are divided into proximal and distal and by directionality of the papillary lines, respectively, to the ulnar and radial. Sickles in their morphological structure are similar to arches, but there is the difference that allows to differentiate these two types of patterns - if the course of the arc begins at an angle of 45 degrees or less, then as a consequence, the beginning of the arc is extended. This causes that the "straight part" of the arch can occupy 2/3 of the width of the phalanx and, thus, to form a "sickle handle", and the rounded top part sharpens and forms a "sickle top". The specificity of the of the sickle shaped arc (Ah) is manifested in the fact that it is constructed of the top acute in parallel arcuate curved papillary lines (graphical representation of the described patterns can be seen in fig. 3 under the indicated numbers).

Combined patterns are the combination of simple patterns, the morphological elements of which may have different orientations according to the interphalangeal folds, as well as the papillary lines that form the patterns, can be directed to the ulnar or radial side (fig. 3 No. 6-25).

Established in 1923, INTERPOL currently encompasses 188 countries and is an excellent example of the collaboration of practitioners and scientists working together to bring crime and crime to the latest data and technology. One of the areas of this structure is DVI [14].

The dermatoglyphic method of investigation can be a great helper method for identifying victims of disasters, given its simplicity and cheapness. More and more research is expanding not only the theoretical base but also the geography of the use of dermatoglyphics, making it possible to answer more and more police questions [8, 13].

A dermatoglyphic examination of Kanuri residents living in northeast Nigeria revealed the following distribution of finger patterns: loops – 59.10 %, whorls – 33.80 % and arches – 7.07 %. The RD ratio was 12.85 and 12.49; the TRC index is 122.64 and 115.45 for men and women, respectively. These indicators are characteristic of other ethnic groups living in the northwest and eastern Nigeria [11].

The study of dermatoglyphics in the Asante tribe revealed that the most common pattern type among them is loops followed by whorls and arches. Differences in the frequencies of different types of patterns on different fingers were found in men and women of this tribe and a difference in TRC. In addition, researchers have noted the similarity of these indicators to the representatives of tribes living in Nigeria [5].

In addition, a possible tool for identifying a person's gender may be the density of skin ridges (RD). Indian researchers found that in all areas studied greater density of skin ridges were observed in women [6]. RD indicator can also be used to determine a person's ethnicity [12].

One promising area is the use of white lines counting on fingers. A survey of Hausa representatives revealed that the best indicator for identifying a person's gender is the difference in the white lines of the second and fourth fingers of the left and right hands [15].

In recent years, appears works, that allow to establish not only the ethnic but territorial identity of a person according to the modern administrative and territorial units. The largest contribution to discrimination between representatives of southern or other parts of Ukraine is made by the type of pattern on the fingers of the right hand and the asymmetry of the ridge count of the palmar lines [10].

Conclusion

Based on the foregoing, we can conclude that the dermatoglyphic parameters of the middle and proximal phalanges of the fingers are diagnostic features that can be used at the level with the dermatoglyphic parameters of the distal phalanges of the fingers in determining the dermatoglyphic constitution of an unknown person, and complement the identification algorithm DVI Interpol.

References

1. Kostenko YeYa. Prynstypy funktsionuvannya systemy DVI INTERPOL ta spetsializovanoho prohramnoho zabezpechennya PLASS DATA SOFTWARE u rozrizi miznarodnoyi spivpratsi ta pislyadyplomnoyi osvity spetsialistiv stosovno identyfikatsii osib. Sudovo-medychna ekspertyza. 2015; 2:16-28. [in Ukrainian]
2. Fedin IV, Chikun VI, Gorbunov NS, Khludneva NV. Problema identifikatsii cheloveka. Vestnik sudebnoy meditsyny. 2018; 7(1):56-60. [in Russian]
3. Chistikina TA, Zoroastrov OM, Kolomys VE. Kompleksnaya diagnostyka grup po ikh svoistvam na osnove dermatoglyfiki paltsev ruk. Sydebnaya ekspertyza. 2009; 52(5):11-4. [in Russian]
4. Shpak LYu. Dermatoglyfika falang paltsev kisti (antropologicheskkiye i sudebno-meditsinskiye aspekty) (avtoreferat). Moskva; 2003. [in Russian]
5. Awuah D, Dzogbefia VP, Chattopadhyay PK. Finger dermatoglyphics of the Asante population of Ghana. International Journal of Innovative Research and Advanced Studies. 2017; 4(4):333-6.
6. Dhall JK, Kapoor AK. Fingerprint ridge density as a potential forensic anthropological tool for sex identification. Journal of forensic sciences. 2016; 61(2):424-9.
7. Gunas VI. Modeling using discrimination analysis, priority of practical health in administrative-territorial regions of Ukraine on the basis of dermatoglyphic indicators features. World of Medicine and Biology. 2018; 63(1):9-14.
8. Mbaka G, Ejiwunmi A, Alabi O, Olatayo T. Digital dermatoglyphic variation and migratory pattern of ethnic Liberians. Egyptian Journal of Forensic Sciences. 2016; 6(4):416-21.
9. Mishalov V, Klimas L, Gunas V. Demographic variability indicators of somatically healthy men from different administrative and territorial regions of Ukraine. Current Issues in Pharmacy and Medical Sciences. 2016; 29(2):90-3.
10. Mishalov VD, Gunas VI. Discriminating models of dermatoglyphic priority of practically healthy men to southern or other administrative-territorial regions of Ukraine. Forensic-medical examination. 2018; 1:17-21.
11. Mohammed B, Garba SH, Adeyemi LB. Digital dermatoglyphics patterns of the Kanuri ethnic group of North Eastern Nigeria. International Journal of Innovation and Applied Studies. 2014; 9(2):985-8.
12. Nayak VC, Rastogi P, Kanchan T, Yoganarasimha K, Kumar GP, Menezes RG. Sex differences from fingerprint ridge density in Chinese and Malaysian population. Forensic science international. 2010; 197(1-3):67-9.
13. Neumann C, Evett IW, Skerrett J. Quantifying the weight of evidence from a forensic fingerprint comparison: a new paradigm. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2012; 175(2):371-415.
14. Sweet D. INTERPOL DVI best-practice standards--An overview. Forensic science international. 2010; 1-3:18-21.
15. Taura MG, Adamu LH, Asuku AY, Umar KB, Abubakar M. Adjacent digit fingerprint white line count differences: a pointer to sexual dimorphism for forensic application. Egyptian Journal of Forensic Sciences. 2019; 9(1):63.

Реферати

**МОЖЛИВІСТЬ ВИКОРИСТАННЯ
ДЕРМАТОГЛІФІЧНИХ ПАРАМЕТРІВ
СЕРЕДНІХ ТА ПРОКСИМАЛЬНИХ ФАЛАНГ
ПАЛЬЦІВ РУК У МЕЖАХ ВИМОГ
DVI-INTERPOL**

Коцюбинська Ю.З., Козань Н.М., Зеленчук Г.М.,
Коляденко С.В., Вакар Т.В.

Матеріалом дослідження були цифрові дерматогліфи середніх та проксимальних фаланг пальців рук, отримані від 260 представників різних етнотериторіальних груп Прикарпаття із застосуванням оптичного сканера Futronic's FS80 USB 2.0, які піддавалися кількісному та якісному вивченню та обробці методом одно- та багатомірного статистичного аналізу. У ході дослідження вивчено особливості морфологічної будови дерматогліфичних параметрів середніх та проксимальних фаланг пальців рук; розроблено «Доповнену класифікацію шкірних візерунків середніх та проксимальних фаланг пальців рук» (Авторське свідоцтво на науковий твір № 74560); запропоновано розділяти дерматогліфи середніх та проксимальних фаланг пальців рук за складністю морфологічної будови. На основі проведеного дослідження розроблено окрему самодостатню систему дерматогліфичних ідентифікаційних ознак, яка здатна підвищити та підтвердити достовірність результатів комплексної ідентифікаційної експертизи згідно критеріїв DVI Interpol.

Ключові слова: судова медицина, ідентифікація особи, дерматогліфичні параметри.

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**ВОЗМОЖНОСТЬ ИСПОЛЬЗОВАНИЯ
ДЕРМАТОГЛИФИЧЕСКИХ ПАРАМЕТРОВ СРЕДНИХ
И ПРОКСИМАЛЬНЫХ ФАЛАНГ ПАЛЬЦЕВ РУК
В ПРЕДЕЛАХ ТРЕБОВАНИЙ
DVI-INTERPOL**

Коцюбинская Ю.З., Козань Н.М., Зеленчук Г.М.,
Коляденко С.В., Вакар Т.В.

Материалом исследования были цифровые дерматоглифы средних и проксимальных фаланг пальцев рук, полученные от 260 представителей различных этнотерриториальных групп Прикарпатья с применением оптического сканера Futronic's FS80 USB 2.0, которые подвергались количественному и качественному изучению и обработке методом одно- и многомерного статистического анализа. В ходе исследования изучены особенности морфологического строения дерматоглифических параметров средних и проксимальных фаланг пальцев рук; разработано «Дополненную классификацию кожных узоров средних и проксимальных фаланг пальцев рук» (Авторское свидетельство на научное произведение № 74560); предложено разделять дерматоглифы средних и проксимальных фаланг пальцев рук по сложности морфологического строения. На основе проведенного исследования разработано отдельную самодостаточную систему дерматоглифических идентификационных признаков, которая способна повысить и подтвердить достоверность результатов комплексной идентификационной экспертизы согласно критериям DVI Interpol.

Ключевые слова: судебная медицина, идентификация личности, дерматоглифические параметры.

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N.V. Kuzminova, A.V. Ivankova, V.P. Ivanny, S.E. Lozinsky, I.I. Knyazkova, A.O. Gavrylyuk
National Pirogov Memorial Medical University, Vinnytsya,
Kharkiv National Medical University, Kharkiv

**STRUCTURAL AND FUNCTIONAL CHANGES OF THE HEART IN PATIENTS WITH
ESSENTIAL HYPERTENSION AND CONCOMITANT FREQUENT EXTRASYSTOLES**

e-mail: Kuzminova5517@gmail.com

The total of 156 patients (65 men and 91 women) with stage II hypertension (EH II) were examined, with an average age of 58.2 ± 0.9 years. The main clinical array consisted of 124 patients with frequent symptomatic supraventricular (SVE) (74 (59.7%) patients) or ventricular extrasystoles (VE) (50 (40.3%) pts) according to Holter monitoring of the electrocardiogram (HM ECG). The comparison group included 32 patients with EH II without cardiac arrhythmias. Echocardiographic evaluation of structural and functional changes of the heart showed that the presence of frequent extrasystoles was associated with an increase of right ventricular (RV) size and signs of its overload, more pronounced left ventricular hypertrophy (LVH), a significant decrease in LV systolic function and impaired myocardial relaxation with the prevalence of the rigid type of transmitral flow. Patients with EH II and frequent VE compared with patients with EH II and SVE had a more significant decrease in LV systolic function and more pronounced disorders of diastolic function, whereas patients with SVE had a more expressed LVH.

Key words: arterial hypertension, essential hypertension, supraventricular extrasystole, ventricular extrasystole, echocardiography, Holter ECG monitoring.

The study is a fragment of the research project "Metabolic risk factors, cardiovascular remodeling and functional status of the kidneys in patients with cardiovascular pathology. The options of pharmacological correction", state registration No. 0119U101849.

The most common cardiac arrhythmias in patients with arterial hypertension are atrial fibrillation (AF) and extrasystole. AH as an etiology of AF occurs in approximately 14% of patients due to a significant prevalence of AH in population. In the case of high BP levels, the risk of AF increases almost 5-fold [3, 7, 9]. While the circumstances of AF progression in patients with hypertension has been studied in great detail, the causes and mechanisms of extrasystoles is still studied insufficiently at the moment.

There is some controversy about the relationship of SVE and structural remodeling of the left ventricular (LV) myocardium. When some observed SVE independently of LVH in high systemic BP [12],

the others found some structural myocardial abnormalities after taking into account the circadian changes in BP. A greater number of SVE, an increased left atrium size, LV index of myocardial mass were found in patients with an inadequate nocturnal decrease in blood pressure (non-dippers) [2, 10].

To date, there is undeniable evidence of an association of diastolic dysfunction of the LV and the incidence of SVE in hypertension. A.V. Nedostup (2011) believes that SVE is less common in AH and manifests only in severe diastolic LV dysfunction with the development of mitral regurgitation [4]. In other studies, a positive correlation was found between the frequency of SVE and the time of isovolumetric relaxation and deceleration time of early diastolic blood flow. There was also an inverse correlation with the ratios of early and late diastolic LV filling [14].

The first reports of the onset of VE on the background of high BP and LVH were published by Messerli et al. (1984). It was found that patients with AH and ECG signs of LV hypertrophy showed a greater amount of VE than those without hypertrophy and hypertension. These data have been confirmed in several further studies [10, 13, 14]. It is considered that the combination of VE, LVH, and the ECG detected ST-segment depression is particularly dangerous. The question remains: is VE should be considered as a specific marker of malignant arrhythmias or as a marker of the severity of the disease?

It is known that LV hypertrophy in patients with hypertension is a pathomorphological basis for the development of electrical instability of the myocardium and cardiac arrhythmias. Increased myocardial stress on the background of hypertension, along with excessive post-loading, stimulate myocardial hypertrophy, its structural remodeling with a disproportionate increase in fibrotic tissue, reduction of coronary blood flow and the development of myocardial diastolic dysfunction [13]. Myocardial hypertrophy leads to the injury of the myocardial current of Ca^{2+} , Mg^{2+} , Na^+ , K^+ , which contributes to the prolongation of the action potential duration and can be a trigger of the re-entry mechanism, early postdepolarization, and trigger activity. Endothelial vascular dysfunction along with LVH plays a certain role in the genesis of arrhythmias [1, 11]. The presence of both significantly increases the risk of cardiac events in the future, including the risk of arrhythmia. However, there is insufficient evidence to suggest that extrasystole in patients with EH II is associated with certain structural changes in the myocardium, and further researches are required.

The purpose of the study was to assess the structural and functional changes of the myocardium in patients with stage II hypertension with concomitant extrasystoles.

Materials and methods. A thorough screening, collection of complaints and anamnesis, signing of the informed consent to participate in the study under principals of Helsinki Declaration preceded the study.

The study involved 124 patients with EH II and frequent extrasystole aged within 27 and 75 (mean age 58.2 ± 0.9) years. The comparison group included 32 patients with EH II without any arrhythmias. Their age ranged within 32 and 72 years (mean age 55.9 ± 1.7). There were 50 males (40.3%) and 74 (59.6%) females. The comparison group consisted of 15 (46.9%) men and 17 (53.1%) women. The statistical analysis between the main group and the comparison group showed that there were no significant differences ($p > 0.05$) by age and gender, which indicated the age and gender homogeneity of the examined patients [7].

Among the 124 patients with EH II and concomitant frequent extrasystole, 74 (59.7%) cases were referred to supraventricular (SVE) and 50 (40.3%) to ventricular extrasystole (VE). Arrhythmic history ranged from 1 to 27 years and averaged 8.06 ± 0.42 years. 30 patients (24.2%) in the main group experienced arrhythmia constantly during the last year as a variety of symptoms. The most common symptoms were missed heartbeat and pause in a heartbeat. Indeed, the vast majority of patients (94 (75.8%)) experienced episodic arrhythmias in the form of intermittent episodes.

All patients were examined at the inclusion stage by complete clinical, laboratory and instrumental methods to verify the main diagnosis and concomitant conditions. General clinical and anthropometric examination, office BP measurement, 12-lead ECG, HM ECG, and cardiac ultrasound were performed in all patients.

BP was measured according to the recommendations of the Ukrainian Society of Cardiologists (2013) using a sphygmomanometer "Microlife". Electrocardiography was performed according to the standard procedure in 12 leads on the electrocardiograph "UKARD" (Hungary).

Daily HM ECG was performed using the hardware and software "DiaCard" (JSC "Solvaig", Ukraine) according to the standard protocol [6]. Following parameters were determined for the assessment of the nature of the arrhythmia: the daily number of SVE and VE; maximal frequency of SVE and VE per 1 hour (SVE_1 and VE_1 respectively); a number of patients with paired and group VE (PVE) and their number in 24 hours.

Assessment of the structural-functional state of the heart was performed using echocardiography in one-dimensional and two-dimensional modes with color, pulse and constant-wave Doppler imaging by

the equipment «My Lab 25» (Italy) to the recommendations of the American Society of Echocardiography (ASE) and the European Society of Cardiovascular Imaging (EACVI) [8]. The type of LV geometric remodeling was determined according to A. Ganau (1992) method based on the parameters of LVMI and RWT. LV diastolic function was estimated based on the velocity of early (V_e , m/s) and late (V_a , m/s) diastolic blood flow measured by PW Doppler and followed by the calculation of V_e/V_a ratio [3].

Statistical processing of the study results was performed using software «Statistica» v. 12.0 by «StatSoft» company according to the recommendations for the processing of biomedical data. Comparisons of relative values (%) were performed using the criterion χ^2 . Mann-Whitney U test was used for the comparison of independent samples [5].

Results of the study and their discussion. The assessment of the structural and functional state of the heart by EchoCG showed that the patients with EH and frequent extrasystole (the main clinical group), compared with patients without heart rhythm disorders (comparison group) had a significant ($p = 0.002$) increase in RV size and RV/EDD ratio ($p = 0.004$). These findings to a certain extent indicated the right-sided overload in this group of patients (Table 1). The EDV/LVM ratio was significantly ($p = 0.02$) lower in the group of patients with arrhythmias compared to the patients without arrhythmia, which highlighted more expressed LVH in patients with extrasystole. The findings are consistent with those of other researchers who have found a relationship between the presence of LVH and the occurrence of cardiac arrhythmias [2, 10, 14]. It should be noted that the patients with arrhythmia had an increase in the incidence of the aortic valve (AV) fibrosis/calcification compared with patients without arrhythmias (44.4% vs. 25%, respectively, $p = 0.04$).

Table 1

Structural and functional state of the myocardium in patients with EH II depending on the presence of extrasystoles

EchoCG parameters	Comparison group (n=32)	Main group (n=124)	P
ESD, mm	33.8 (32.5; 36.9)	33.3 (31.0; 37.0)	0.43
EDD, mm	51.0 (47.4; 54.0)	50.0 (47.4; 54.0)	0.92
LA, mm	40.4 (38.0; 42.0)	40.0 (37.0; 43.0)	0.85
LAV, ml	70.0 (62.5; 73.5)	69.0 (66.0; 74.0)	0.88
LAI, mm/m ²	21.1 (19.4; 22.7)	20.7 (19.1; 22.8)	0.57
LA/EDD	0.79 (0.76; 0.82)	0.78 (0.73; 0.83)	0.35
RV, mm	24.9 (24.0; 28.4)	28.0 (25.3; 32.0)	0.002
RV/EDD	0.49 (0.46; 0.53)	0.55 (0.48; 0.63)	0.004
AoD, mm	32.8 (31.6; 34.3)	33.0 (30.0; 35.0)	0.89
PWD, mm	12.0 (11.3; 12.3)	12.0 (11.0; 13.0)	0.91
IVSD, mm	11.5 (10.1; 12.1)	12.0 (11.0; 12.9)	0.10
RWT	0.46 (0.40; 0.50)	0.47 (0.42; 0.50)	0.41
LVMI	146.0 (135.3; 159.0)	154.2 (131.0; 178.0)	0.42
EDV/LVM, ml/g	0.58 (0.54; 0.66)	0.55 (0.48; 0.61)	0.02
EF, %	60.3 (57.5; 63.5)	57.0 (53.0; 61.7)	0.04
CI, ml·min/m ²	3.4 (3.0; 3.8)	3.5 (3.0; 4.1)	0.86
V_e/V_a	1.45 (1.04; 1.59)	1.25 (0.89; 1.48)	0.04
Structural remodeling by Ganau			
Normal type	1 (3.1%)	9 (7.3%)	0.39
Concentric remodeling	0 (0)	6 (4.8%)	0.20
Concentric hypertrophy	19 (59.4%)	70 (59.7%)	0.97
Eccentric hypertrophy	12 (37.5%)	39 (31.5%)	0.51
Diastolic transmitral flow type			
Normal	8 (25.0%)	7 (5.6%)	0.0009
Rigid	22 (68.8%)	103 (83.1%)	0.07
Pseudonormal	2 (6.2%)	14 (11.3%)	0.40
Heart valves anomalies			
AV fibrosos/calcinosis	8 (25.0%)	55 (44.4%)	0.04
AV fibrosos/calcinosis	3 (9.4%)	13 (10.5%)	0.85
Mitral regurgitation	27 (84.4%)	96 (77.4%)	0.39
Aortal regurgitation	2 (6.3%)	19 (15.3%)	0.18
Tricuspid regurgitation	13 (40.6%)	67 (54.0%)	0.17

Notes (hereinafter):

1. ESD and EDD - end-systolic and end-diastolic dimensions; EDV - the end-diastolic volume of the left ventricle; LA - the anterior-posterior size of the left atrium; LAV - the volume of the left atrium, LAI - index of the left atrium, RV - the anterior-posterior size of the right ventricle; AoD is the aortic diameter; PWD - thickness of the posterior wall of LV in diastole; IVSD is the thickness of the interventricular septum in diastole; RWT is the relative wall thickness; LVMI – left ventricular myocardial mass index; SI - systolic index; EF - ejection fraction, V_e / V_a - early to late diastolic filling velocity, AV - aortic valve, MV - mitral valve;

2. Here and in the following tables the quantitative values are presented in the form of a median and an interquartile interval with the meanings of 25 and 75 percentiles;

3. The significance of intergroup differences calculated by the Mann-Whitney U Test

The study included only patients with no echocardiographic signs of LV systolic dysfunction (EF > 40%). However, it was noted that patients with EH II and frequent extrasystoles had a significantly ($p = 0.04$) lower EF compared with patients without cardiac arrhythmias (Table 1).

The diastolic variant of LV myocardial dysfunction was revealed among the patients (tables 1, 2). Diastolic dysfunction criteria were determined concerning novel recommendations for age-adjustment. In patients with frequent extrasystole, compared with patients without arrhythmias, there was a significant ($p = 0.04$) decrease in the value of the ratio of early to late diastolic filling rate (V_e / V_a). It was indicating to the more severe left ventricular myocardial relaxation disorders in patients with EH II and frequent extrasystoles. Our data to some extent are in the agreement with the results of other studies that evidenced the presence of pronounced diastolic dysfunction in patients with SVE on the background of AH [4, 13]. Echocardiographic signs of diastolic myocardial dysfunction were as often as 94.4% in patients with frequent extrasystoles versus 75.0% in those without arrhythmias. Only 5.6% of the main group had normal transmittal blood flow while the portion of such patients in the group of EH II without arrhythmias was equal to 25% ($p = 0.0009$). The rigid type of diastolic transmittal blood flow was found in 68.8% of the comparison group, compared with 83.1% in patients with arrhythmias ($p = 0.07$). It may be evidence of increasing diastolic dysfunction in the case of extrasystoles. Pseudonormal type of blood flow was reported in 6.2% of patients with hypertension and 11.3% of patients with both (VE and SVE) extrasystoles.

The analysis of LV structural-geometric remodeling by Ganau in different clinical groups evidenced that concentric hypertrophy of the LV in patients with EH II was significantly prevalent compared with other types of LV remodeling. It was true as in patients with, as in those without cardiac arrhythmias (59.4% and 59.7%, respectively). There was no significant difference in the prevalence of any type of LV remodeling between the main and the comparison groups (Table 1).

The results of the assessment of the structural-functional state of the heart depending on the type of extrasystoles showed that patients with frequent SVE, compared with patients with VE had significantly ($p = 0.04$) lower EDV/LVM ratio (Table 2), which indicated a more pronounced degree of LVH in patients with SVE. These findings coincide with the results of other researchers who described an increase in LVMI in patients with hypertension and SVE [2, 10]. However, we did not find in the literature any comparative analysis of the LV hypertrophy, depending on the variant of extrasystoles in patients with hypertension. Thus, further studies in this direction are required.

The size of RV and the ratio of RV/ESD) were significantly ($p < 0.05$) higher in patients with extrasystoles compared with patients with hypertension but without rhythm disorders (Table 2), which indicated a more pronounced overload of the right-sided heart departments in patients with extrasystoles. Simultaneously, there were no significant differences in those parameters in groups of patients with different types of extrasystoles (Table 2). It was noted that patients with SVE tended to increase RV ($p = 0.07$) compared with VE.

Patients with VE had a significantly lower EF value compared with patients with SVE (54.3 (50.2; 61.1) versus 57.0 (53.8; 63.4) %, respectively, $p = 0.02$).

Interesting that the V_e/V_a rate was significantly ($p = 0.03$) lower in the group of patients with frequent VE compared with patients with SVE, indicating more pronounced diastolic abnormalities in this category of patients. Our findings regarding the presence of apparent diastolic dysfunction in patients with arrhythmias coincide with other researchers' findings of the association between the presence of SVE in patients with hypertension and diastolic dysfunction [4, 13, 14].

The vast majority of patients with EH II and extrasystoles had transmitral blood flow disorders. A rigid type of transmitral blood flow was observed in most of the patients (81.1% of patients with SVE and 86.0% with VE), whereas only 8.1% of patients and 2.0% respectively had normal transmitral blood flow. Pseudonormal type of diastolic filling of the LV was observed in 10.8% of patients with SVE and 12.0% of patients with VE [2, 10].

Analysis of the structural-geometric remodeling of LV by Ganau in clinical groups showed no significant difference between groups of patients. It was noted that in patients of both clinical groups, concentric LVH was significantly more prevalent among different types of remodeling (reported in 54.1% of SVE and 60.0% of VE cases), eccentric LVH was defined in 33.8% and 28.0% respectively.

Table 2

Structural and functional state of the myocardium in the main group depending on different types of extrasystoles

EchoCG parameters	SVE (n=74)	VE (n=50)	P
EDS, mm	33.9 (31.0; 37.0)	33.1 (30.9; 36.0)	0.54
EDD, mm	50.0 (48.0; 55.0)	50.0 (47.2; 53.5)	0.29
LA, mm	40.0 (37.0; 43.0)	40.5 (38.0; 42.0)	0.85
LAV, ml	68.0 (66.0; 74.0)	69.5 (67.0; 73.0)	0.97
LAI, mm/m ²	20.7 (18.7; 22.8)	20.6 (19.4; 22.1)	0.94
LA/ESD	0.77 (0.72; 0.82)	0.79 (0.74; 0.85)	0.13
RV, mm	28.5 (26.0; 32.0)	27.9 (24.8; 30.9)	0.07
RV/ESD	0.54 (0.49; 0.64)	0.55 (0.48; 0.61)	0.59
AoD, mm	32.9 (27.0; 37.0)	33.2 (28.5; 37.0)	0.47
PWD, mm	12.0 (10.0; 13.1)	12.0 (10.0; 13.0)	0.73
IVSD, mm	12.0 (9.5; 14.0)	12.0 (9.8; 14.4)	0.23
RWT	0.47 (0.36; 0.55)	0.48 (0.42; 0.53)	0.76
LVMi	154.7 (108.5; 208.2)	152.6 (109.1; 198.4)	0.32
EDV/LVM, ml/g	0.52 (0.39; 0.68)	0.56 (0.42; 0.74)	0.04
EF, %	57.0 (53.8; 63.4)*	54.3 (50.2; 61.1)**	0.02
CI, ml·min/m ²	3.5 (2.5; 5.2)	3.5 (2.7; 4.7)	0.87
Ve/Va	1.34 (0.76; 1.51)*	1.18 (0.75; 1.34)**	0.03
Structural remodeling by Ganau			
Normal type	5 (6.8%)	4 (8.0%)	0.79
Concentric remodeling	4 (5.4%)	2 (4.0%)	0.72
Concentric hypertrophy	40 (54.1%)	30 (60.0%)	0.51
Eccentric hypertrophy	25 (33.8%)	14 (28.0%)	0.49
Type of transmitral blood flow			
Normal	6 (8.1%)	1 (2.0%)	0.14
Rigid	60 (81.1%)	43 (86.0%)	0.47
Pseudonormal	8 (10.8%)	6 (12.0%)	0.83
Heart valves anomalies			
AV fibrosos/calcinosis	5 (6.8%)	8 (16.0%)	0.09
AV fibrosos/calcinosis	33 (44.6%)	22 (44.0%)	0.94
Mitral regurgitation	57 (77.0%)	39 (78.0%)	0.89
Aortal regurgitation	15 (20.3%)	4 (8.0%)	0.06
Tricuspid regurgitation	34 (45.9%)	33 (66.0%)	0.02

Notes: 1. SVE - supraventricular and VE - ventricular extrasystole; 2. The significance of difference based the Mann-Whitney U Test

Based on the assessment of the structural and functional state of the valves in patients with different extrasystoles, it was established that in patients with VE compared with SVE there were a significantly higher number of cases of tricuspid regurgitation (66.0 versus 45.9 %, respectively, $p=0.02$) and a tendency to more incidence of fibrosis or calcification of AV. At the same time, the number of cases of aortic regurgitation was likely to increase in the group of patients with frequent SVE [4].

Thus, the study suggests that patients with EH II and frequent extrasystoles have certain structural and functional changes of the heart compared with patients with EH II but without rhythm disorders. Namely, there was an increase in the size of RV with signs of its overload, more pronounced LVH, a significant decrease in LV systolic function and impaired relaxation of the myocardium with the predominance of rigid type of transmitral blood flow. The assessment of the structural and functional state of the myocardium depending on the type of extrasystoles allow establishing some differences in patients with EH II and frequent VE compared with those with SVE. The had a more significant decrease in LV systolic function followed by the more pronounced impairment of diastolic, while patients with SVE had a slightly higher degree of LV hypertrophy.

Conclusions

1. The presence of frequent extrasystole in patients with EH II, regardless of its type, is associated with a significant increase in size and overload of RV, more pronounced LVH, the presence of diastolic

dysfunction, impaired transmitral blood flow and increase in the incidence of fibrosis and calcinosis of the aortal valve.

2. The presence of frequent SVE in patients with stage II GC is associated with a tendency to an overload of RV and a greater degree of LVH compared with patients with EH II and VE.

3. A more significant decrease in LV EF followed by more significant impairment of diastolic function was observed in patients with EH II and VE compared with patients with SVE. Also, the incidence of tricuspid regurgitation (66.0% vs. 45.9%, $p = 0.02$) and fibrosis/calcification of AV were more frequent in the group of EH II and VE.

Future researches of associative links between the presence of rhythm disorders and structural and functional changes of the myocardium in patients with EH II, revealing the pathogenic mechanisms of arrhythmias in patients with hypertension, will improve the diagnosis and treatment of such complicated patients.

References

1. Belenkov YuN, Mareev YuV. Serdechno-sosudystui kontinuum. Serdechnaya nedostatochnost. 2012; 1: 7-11. [in Russian]
2. Zharinov OI, Talaieva TV, Lishchyshyna OM, Bozhko LI, Hetman TV, Zalevskyi VP. [ta in.] Adaptovana klinichna nastanova, zasnovana na dokazakh. Fibryliatsiia peredserd. Rekomendatsii Robochoi hrupy z porushen rytmu sertsia Asotsiatsii kardiologiv Ukrainy. 2016: 11-7. [in Ukrainian]
3. Kovalenko VM, Dolzhenko MM., Potashev SV. Nastanovy z klinichnoi ekhokardiohrafii. 2018. 327s. [in Ukrainian]
4. Nedostup AV, Blahova OV. Kak lechyt arytmiyu. Narusheniya ritma i provodimosti v klynycheskoy praktike. 2011. 365s. [in Russian]
5. Rebrova OYu. Statysticheskyi analiz meditsynskikh dannykh. Primeneniye paketa prikladnykh programm STATISTICA. 2006. 312s. [in Russian]
6. Syhov OS, Lutai MI, Romanova OM. Ambulatorne EKH-monitoryuvannya. Rekomendatsiyi Asotsiatsiyi kardiologiv Ukrainy. 2010. 44s. [in Ukrainian]
7. Kuzminova NV, Ivankova AV, Ivanov VP, Lozinsky SE, Knyazkova II, Gavriluk AO. Daily blood pressure pattern disorders in patients with stage II essential hypertension and frequent premature beats. Svit medytsyny ta biolohiyi. 2020; 1(71): 72-7. <https://doi.org/10.26724/2079-8334-2020-1-71-72-77>
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L. [et al.] Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1-39.
9. Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB. [et al.] Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults. Canadian Journal of Cardiology. 2017; 33(5): 557-76.
10. Lip G, Coca A, Kahan T, Boriani G, Manolis AS, Olsen MH. [et al.] Hypertension and cardiac arrhythmias: a consensus document from the EHRA and ESC Council on Hypertension, endorsed by the HRS, Asia-Pacific Heart Rhythm Society APHRS and SOLEACE. Europace. 2017; 19 (6): 891-911. <https://doi.org/doi:10.1093/europace/eux091>.
11. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M. [et al.] 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J. Hypertens. 2013; 31(7): 1281-357.
12. Purmah Y, Proietti M, Laroche C, Mazurek M, Tahmatzidis D, Novo S. Rate vs. rhythm control and adverse outcomes among European patients with atrial fibrillation. Europace. 2017; 19 (3): 241-50. PMID: 28160483. DOI: 10.1093/europace/euw421.
13. Xu TY, Yang Y, Li JJ, Li Y, Wang JG. Left ventricular deformation in relation to the geometric pattern in hypertensive patients. Medicine. 2019; 98(4): 1-6.
14. Zeng Z, Zhou R, Liang O. Comparison of arrhythmias different left ventricular geometric patterns in essential hypertension. J. Tongji. Med. Univ. 2011; 21 (2): 93-6.

Реферати

СТРУКТУРНО-ФУНКЦІОНАЛЬНІ ЗМІНИ СЕРЦЯ У ХВОРИХ НА ГІПЕРТОНІЧНУ ХВОРОБУ І СУПУТНЮ ЧАСТУ ЕКСТРАСИСТОЛІЮ

**Кузьміна Н.В., Іванкова А.В., Іванов В.П.,
Лозинський С.Є., Князькова І.І., Гаврилюк А.О.**

Обстежено 156 хворих (65 чоловіків та 91 жінка) на гіпертонічну хворобу II стадії (ГХ II), середній вік $58,2 \pm 0,9$ років. Основний клінічний масив склали 124 з них, які за даними холтеровського моніторингу електрокардіограми мали часту симптомну суправентрикулярну (СВЕ) (74 (59.7%) пацієнти) або шлуночкову екстрасистолю (ШЕ) (50 (40.3%) осіб). До групи порівняння увійшли 32 хворих на ГХ II ст. без порушень серцевого ритму. Оцінка структурно-функціональних змін серця за даними ехокардіографії показала, що наявність частої екстрасистолії асоційована із збільшенням розміру ПШ з ознаками його перевантаження, більш виразнішою ГЛШ,

СТРУКТУРНО-ФУНКЦИОНАЛЬНЫЕ ИЗМЕНЕНИЯ СЕРДЦА У БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ И СОПУТСТВУЮЩЕЙ ЧАСТОЙ ЭКСТРАСИСТОЛИЕЙ

**Кузьмина Н.В., Иванкова А.В., Иванов В.П.,
Лозинский С.Э., Князькова И.И., Гаврилюк А.А.**

Обследовано 156 больных (65 мужчин и 91 женщина) гипертонической болезнью II стадии (ГБ II), средний возраст $58,2 \pm 0,9$ лет. Основной клинический массив составили 124 из них, которые по данным холтеровского мониторинга электрокардиограммы имели частую симптомную суправентрикулярную (СВЭ) (74 (59.7%) пациента) или желудочковую экстрасистолию (ЖЭ) (50 (40.3%) особ). В группу сравнения вошли 32 больных ГБ II ст. без нарушений сердечного ритма. Оценка структурно-функциональных изменений сердца по данным эхокардиографии показала, что наличие частой экстрасистолии ассоциирована с увеличением размера правого желудочка (ПЖ) с признаками его перегрузки, более выраженной гипертрофией левого желудочка (ГЛЖ),

достовірним зменшенням систолічної функції ЛШ та погіршенням релаксаційної здатності міокарда з переважанням ригідного типу трансмітрального кровотоку. У пацієнтів із ГХ II стадії та частою ШЕ порівняно з хворими на ГХ II стадії та СВЕ визначені більш суттєві зменшення систолічної функції ЛШ на фоні більш виразних порушень діастолічної функції серця, в той час як у хворих з СВЕ спостерігався дещо більший ступінь гіпертрофії ЛШ.

Ключові слова: артеріальна гіпертензія, гіпертонічна хвороба, суправентрикулярна екстрасистоля, шлуночкова екстрасистоля, ехокардіографія, холтеровське моніторування ЕКГ.

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достовірним зниженням систолічної функції ЛЖ і ухудшенням релаксаційної здатності міокарда з переважанням ригідного типу трансмітрального кровотоку. У пацієнтів с ГХ II стадії та частою ЖЭ по сравнению с больными ГХ II стадии и СВЭ определено более существенное снижение систоліческой функции ЛЖ на фоне более выраженных нарушений диастоліческой функции сердца, в то время как у больных с СВЭ наблюдалась несколько большая степень гипертрофии ЛЖ.

Ключевые слова: артериальная гипертензия, гипертоническая болезнь, суправентрикулярная экстрасистолия, желудочковая экстрасистолия, эхокардиография, холтеровское мониторирование ЭКГ.

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V.O. Lefterov, O.V. Timchenko, O.M. Tsilmak, I.I. Ignatieva
National University "Odessa Law Academy", Odessa

SIMULATION AND PSYCHOLOGICAL TRAININGS AS METHODS OF PREVENTING EMOTIONAL BURNOUT IN DOCTORS

e-mail: lefterov.vasil@gmail.com

The article analyzed the problem of emotional burnout in doctors, as well as the features of using and implementing medical simulation tools in the training process of medical specialists. The results of an empirical study of the simulation and psychological training effects on the psychological correction and the burnout syndrome prevention in doctors were presented. It was found that after these trainings doctors have reduced rates of emotional exhaustion, depersonalization, and improved well-being and mood. It was recommended to perform diverse psychological trainings and other psychological support and consulting procedures in the simulation training system.

Key words: medical simulation tools, simulation training, psychological training, burnout syndrome, psychological correction and prevention.

The work is a fragment of the research project "To develop a scientifically sound system for assessing the safety of hospitals in Ukraine", state registration No. 0118U003654.

Achieving true professional competence and skill of a doctor is preceded by a long and painstaking process of training and practical activities, associated with significant psychological stress and potential risks of emotional burnout. Words of the founder of modern medical ethics, Hippocrates: "Aliis inserviando consumer — Giving light to others, I burn myself" not only determined the purpose of a true healer, but also reflected the psychological energy-consuming nature of the doctor's activity. This explains why the medical profession occupies one of the first places in terms of the risk of burnout syndrome [2, 12, 14].

Burnout syndrome is characterized by a pronounced combination of disturbance symptoms in the mental, somatic and social spheres of life. It is generally accepted that this is a pathological condition associated with defatigation, a state of exhaustion of vitality.

Numerous empirical studies confirm the emotional exhaustion typicality in doctors, leading to disturbances in communication and self-regulation, which can lead to negative personality changes. Thus, I.P. Nazarenko found that altruistic, practical and aesthetic types of emotional orientation are characterized by a low level of formation of burnout symptoms. At the same time, the hedonistic type of emotional orientation (associated with satisfying the need for physical and mental comfort) increases the risk of burnout, especially in people who work in psychiatry [9].

D. R. Mikov, A.M. Kulesh, S.V. Muraviov and other researchers empirically substantiated that the burnout syndrome of doctors is in a state of dynamic development and manifests itself in emotional disorders, affective states, anxiety, depression and the symptom of "driven into the corner" [8]. T.A. Vezhnovets and V.D. Pariy substantiated that the burnout syndrome prevention in medical workers should be carried out taking into account the characteristics of psycho-traumatic factors, depending on the type of work motivation [2].

The problem of preventing burnout in doctors is especially relevant today, in the context of the pandemic of the coronavirus COVID-19 pandemic. To minimize the emotional (professional) burnout syndrome of doctors, various methods of psychological correction and therapy are offered today, in

addition to creating adequate working and resting conditions for doctors, increasing their social status. At the same time, the possibilities of preventing and correcting the burnout in doctors through a complex of educational simulation and psychological trainings have not been sufficiently studied.

The modern system of training doctors introduces simulation methods that provide not only a high practical level of clinical training for future and current doctors, but, what is equally important, also the launch-updating of the psychological mechanisms for the formation of their necessary professional and personal competencies.

Among the special tools of medical simulation in the doctors training, there are: mannequins, phantoms, models, trainers, simulators, etc. Today, simulation methods in medicine are widespread throughout the world [13, 15].

Over the past decades, Ukraine has been actively introducing new simulation technologies in medical education. A systematic repetition of identical simulated situations with further debriefing allows you to consolidate the resulting communicative experience as a conscious skill [1].

Today, medical simulation methods are usually implemented in the form of simulation training. We focus specifically on group trainings, which means educational and training procedures organized in a special way. Training is a kind of informational and subject medium filled with training events, various simulation scenarios, games, debriefings, etc. for targeted professional psychological training of a specialist [7]. Without an educational training context, simulation tools are just expensive toys. It should be noted that individual simulation programs are also successfully used in medical simulations, but group ones are always more effective, both from an economic point of view and from the training quality.

The purpose of the study was to study the possibilities of simulation and psychological training methods in psychological correction and prevention of the burnout syndrome in doctors based on empirical psychological research.

Materials and methods. To achieve this, we organized an empirical study on the basis of the educational and innovative center for practical training of doctors at the Odessa National Medical University. The study involved three groups of family physicians and pediatricians, a total of 44 people, undergoing skill development in the form of simulation training lasting from 5 to 10 days. The study was performed in the period of 2015-2016 and included three experimental stages. At the first phase, a stating experiment was performed with the examined doctors: an “input” questionnaire and psychodiagnostic testing.

At the second phase, a formative experiment was performed by participating in the simulation training programs and in the specially designed psychological training “Candle”. In the process of simulation trainings, various clinical situations were simulated, including using the Standardized Patient method. For this, we used robotic mannequin-simulators of medium and high level of realism. The implementation of video feedback was obligatory, which allowed debriefings and psychological consultations for a detailed analysis and error analysis. The “Candle” training included a set of exercises and psychological techniques to consolidate the results of simulation training, psychological correction and prevention of emotional burnout. Among the training methods, a special place was occupied by exercises aimed at developing the emotional and value-semantic sphere of the physician’s personality, analysis of the experiences of his functional states, as well as reflection on the meaning of life in the past, present and future.

At the third study phase, an “output” questioning of the subjects was carried out immediately after the end of training, as well as repeated psycho diagnostic testing two months after simulation and psychological trainings.

“The diagnosis of professional burnout” methodology was used (K. Maslach, S. Jackson, adapted by N.E. Vodopyanova) as a method of psychodiagnostics, which allows one to identify both a general indicator of professional emotional burnout and makes it possible to analyze the results of the three burnout components: emotional exhaustion; depersonalization; reduction of personal achievements. We used the test version for medical professionals (doctors) [3]. To assess the severity of a particular psychoemotional state of the subjects, the “WAM Questionnaire: Well-being, Activity, and Mood” was used (V.A. Doskin, N.A. Lavrentieva, V.B. Sharay, M.P. Miroshnikov) [10].

To identify reliable relationships and differences between the compared indices, methods of mathematical statistics were used (Pearson correlation coefficient and Student's T-test), which increased the validity of the conclusions of the study. Processing of the obtained data was carried out using the statistical software package for SPSS 14.0 for Windows and the Microsoft Office for Windows XP Professional software package.

Results of the study and their discussion. As a result of our “input” and “output” questionnaires of participants in simulation and psychological trainings, it was found that the contents of the simulation training program largely corresponded to their professional needs and personal goals. 81.8% (36/44) of the

surveyed respondents rated the level of relevance and information content of the simulation trainings as high as possible, 90.9% (40/44) of the respondents noted a high level of practicality regarding their medical activities. An emotional assessment is also indicative, especially of the psychological part of the training. Thus, 95.5% (42/44) of doctors noted a comfortable environment and psychological support during the trainings, which contributed to the successful training and acquisition of both professional skills and the skills of emotional regulation, stress resistance and better adaptability.

The results of professional burnout diagnosis in doctors before simulation training and 2 months after it are presented in table 1. As we see from the doctors during the stating experiment (before the training), increased indices of professional burnout on the scales of "Emotional exhaustion" and "Depersonalization" were revealed. Moreover, a direct correlation was established between these scales and the scales of the WAM questionnaire methodology "well-being" ($r = 0.452$; $p = 0.003$) and "mood" ($r = 0.305$; $p = 0.046$). This indicated that the doctors have revealed states of emotional emptiness, manifestations of depression and apathy, as well as satiety from work, which began to harden them more. Many doctors have indifference, callousness and a decrease in emotional warmth in relations with colleagues and subordinates, which indicates the presence of signs of professional deformation. All this happened against the background of a depressed state and well-being (weakness, fatigue, lethargy, dullness, pessimism, frustration, dissatisfaction, etc. were noted).

Table 1

Comparative results of testing doctors according to the method of "Diagnosis of professional burnout"

Scales/Mean group values	Emotional exhaustion (maximum 54 scores)	Depersonalization (maximum 30 scores)	Reduction of personal achievements (maximum 48 scores)	Total score of professional emotional burnout
Before trainings	39.7	22.9	28.4	91
2 months after training	34.2	19.5	27.5	81.2
Student's <i>T</i> -test	-3.229	-2.44	-1.049	-2.16
Significance point <i>p</i>	0.003	0.021	0.301	0.043

Repeated psychodiagnostic testing two months after simulation and psychological training revealed a decrease in the level of professional burnout in doctors on almost all scales. A comparative statistical analysis by Student's *T*-test showed that significant decreases in burnout syndrome were recorded on the scales of "Emotional exhaustion" ($t = -3.229$; $p = 0.003$) and "Depersonalization" ($t = -2.44$; $p = 0.021$). In addition, two months after the training, "Total score of professional emotional burnout" significantly decreased in doctors ($t = -2.16$; $p = 0.043$) (table 1).

The results of the study on the "WAM Questionnaire: Well-being, Activity and Mood", presented in table 2, indicated that before the trainings, the emotional state level of doctors was "below average" on the scales "Mood" and "Well-being". Moreover, the ratio of all indices on the WAM questionnaire also showed the presence of fatigue and exhaustion in doctors, since in a rested person, without symptoms of emotional burnout, assessments of activity, mood and well-being are approximately equal.

Table 2

Comparative results of testing of doctors on the "WAM Questionnaire: Well-being, Activity, and Mood"

Scales/Mean group values	Well-being	Activity	Mood
Before trainings	3.75	4.80	4.15
2 months after training	4.55	4.92	4.9
Student's <i>T</i> -test	2.101	0.915	2.198
Significance point <i>p</i>	0.047	0.409	0.04

Diagnostics after the training revealed that doctors had a tendency to reduce adverse conditions, in some cases there was a significant increase in favorable conditions and approximately the same ratio of all indicators. So, a significant increase was recorded on the scales "Well-being" ($t = 2.101$; $p = 0.047$) and "Mood" ($t = 2.198$; $p = 0.04$), which indicated a significant improvement in well-being, increased satisfaction, optimism and cheerfulness of doctors as a result of participation in simulation and psychological trainings. Given the established correlation of the data of the WAM methodology scales with the scales "Emotional exhaustion" and "Depersonalization" of the "Diagnosis of professional burnout" methodology, it can be argued that psychological correction and prevention of symptoms of emotional burnout occurred as a result of the participation of doctors in the trainings. They become less susceptible to emotional emptiness, fatigue, apathy, are more open and caring, they show interest in colleagues and people around them, they improve their overall emotional background, well-being and mood.

Our results are comparable with the data of recent studies and publications. Thus, T.A. Vezhnovets and V.D. Pariy were studied the dominant symptoms of emotional burnout among medical professionals

(stress, resistance, and exhaustion) [2]; D.R. Mikov, A.M. Kulesh, S.V. Muraviov, V.G. Cherkasova, P.N. Chainikov, N.V. Solomatina had empirically found that about half of medical workers experience symptoms of emotional burnout, while more than a third of them had an emotional burnout in the stage of actual development [8]. D.A. Shkurupii, V.B. Lukzen, I.V. Bukharov substantiate the dependence of the emotional burnout in doctors of a surgical profile on their professional deformation [11]. These patterns are also reflected in our study. In addition, our experimental testing of the training effectiveness in the prevention of burnout in doctors confirmed the similar research results of N.V. Gafarova [4].

I. Koval substantiated the necessity of introducing a program of psychological training on therapeutic interaction [5]. The study results of I.P. Nazarenko showed that medical workers with a more developed value-sensory sphere, who have higher general indicators of life-meaning orientations, are less amenable to burnout [9]. This was confirmed by the results of our study: the proposed and carried out training "Candle" helped to correct the signs of professional deformation and the development of the value-semantic sphere, which in turn reduced the level of burnout among doctors.

Conclusions

Thus, the training of doctors by simulation medicine methods, which takes place in conjunction with psychological trainings, contributes not only to the professional development of doctors, but also to the prevention of burnout syndrome. Therefore, in the system of simulation training, it is recommended to perform various psychological trainings and other psychological support and consulting procedures aimed both at correcting maladaptive forms of behavior, and at developing doctors' skills of stress resistance, self-regulation, communicative skills, clinical and creative thinking, self-development motivation and other professionally significant psychological qualities.

References

1. Artiomenko VV, Semchenko OS, Yehorenko DA. Symuliatyivne navchannia v medytsyni: mizhnarodnyi ta vitchyzniani dosvid. Odeskyi medychnyi zhurnal. 2015; (6): 67–74. [In Ukrainian]
2. Vezhnovets TA, Parii VD. Syndrom emotsiinoho vyhorannia v medychnykh pratsivnykiv khirurhichnykh viddilen iz pozytsii kadrovoho menezhmentu. Ukraina. Zdorovya natsii [Internet]; 2016; (1-2): 41-47. Dostupno na: http://nbuv.gov.ua/UJRN/Uzn_2016_1-2_11 [In Ukrainian]
3. Vodopianova NE, Starchenkova ES. Sindrom vygoraniia. 2-e izd. SPb.: Piter; 2016. 336 s. [In Russian]
4. Gafarova NV. Sotsialno-psihologicheskii trening, napravlenyi na preodolenie professionalnogo vygoraniia i empiricheskaya proverka ego effektivnosti. Vestnik YuUrGU. Seriya «Psihologiya». 2013; 6 (2): 43-49. [In Russian]
5. Koval I. Syndrom emotsiinoho vyhorannia v likariv onkologichnoho profiliiu ta shliakhy yoho podolannia. Psykhosomatychna medytsyna ta zahalna praktyka [Internet]; 2017; 2 (1): 35-37. Dostupno na: <https://uk.e-medjournal.com/index.php/psp/article/view/25> [In Ukrainian]
6. Korpliakova NI, Tadieva EV, Isaev OI, Kuzina ZA. Sravnitelnoe izuchenie sindroma emotsionalnogo vygoraniia v praktike vrachey dermatovenerologov, kosmetologov. Zhurnal fundamentalnoy meditsyny i biologii. 2014; (3): 18-20. [In Russian]
7. Lefterov VO. Osobystisno-profesiinnyi rozvytok fakhivtsiv ekstremalnykh vydiv diialnosti zasobamy psikhologichnoho treninhu. Psykholohiia i suspilstvo. 2012; (2): 91-107. [In Ukrainian]
8. Mikov DR, Kulesh AM, Muraviov SV, Cherkasova VG, Chainikov PN, Solomatina NV. Osobennosti sindroma emotsionalnogo vygoraniia u medicinskih rabotnikov mnogoprofilnogo stacionara Vestnik Permskogo universiteta. Filosofiya. Psihologiya. Sociologiya. 2018; (1): 88–97. [In Russian].
9. Nazarenko IP. Syndrom emotsiinoho vyhorannia sered medychnykh pratsivnykiv psykhiatrychnoi sfery. Novosti medytsyny y farmatsyy, psykhyatriya [Internet]; 2011; (383). Dostupno na: <http://www.mifua.com/archive/article/20574> [In Ukrainian].
10. Raygorodskiy DYa. Prakticheskaya psihodiagnostika. Metodiki i testy. M.: Bahrah-M; 2015. 672 s. [In Russian].
11. Shkurupii DA, Lukzen VB, Bukharov IV. Syndrom profesiinoho vyhorannia u likariv khirurhichnoho profiliiu. Visnyk problem biolohii i medytsyny. 2014; 3, (2) (111): 97-100. [In Ukrainian]
12. Akaike Masashi, Miki Fukutomi, Masami Nagamune. Simulation Based Medical Education in Clinical Skills Laboratory. The Journal of Medical Investigation. 2012; 59 (1–2): 28–35.
13. Amofo E, Hanbali N, Patel A, Singh P. What are the significant factors associated with burnout in doctors? Occupational Medicine. 2015 March 2; (65): 117–121/ Available from: <https://doi.org/10.1093/occmed/kqu144>.
14. Rosen MA, Hunt EA, Pronovost PJ. In situ simulation in continuing education for the health care professions: a systematic review. J Contin Educ Health Prof. 2012; 32 (4): 243-254.
15. Shirom A, Nirel N, Vinokur AD. Work hours and caseload as predictors of physician burnout: the mediating effects by perceived workload and by autonomy. Appl Psychol. 2010; (59): 539–565.

Реферати

СИМУЛЯЦІЙНІ ТА ПСИХОЛОГІЧНІ ТРЕНІНГИ ЯК МЕТОДИ ПРОФІЛАКТИКИ ЕМОЦІЙНОГО ВИГОРАННЯ ЛІКАРІВ

Лєфтеров, В.О., Тімченко, О.В., Цільмак О.М., Ігнатєва, І. І.

У статті здійснюється аналіз проблеми емоційного вигорання лікарів, а також особливостей використання і впровадження засобів медичної симуляції в процес

СИМУЛЯЦИОННЫЕ И ПСИХОЛОГИЧЕСКИЕ ТРЕНИНГИ КАК МЕТОДЫ ПРОФИЛАКТИКИ ЭМОЦИОНАЛЬНОГО ВЫГОРАНИЯ ВРАЧЕЙ

Лєфтеров, В.О., Тімченко, О.В., Цільмак А.Н., Ігнатєва, І.І.

В статье проводится анализ проблемы эмоционального выгорания врачей, а также особенностей использования и внедрения средств медицинской симуляции в процесс

підготовки медичних фахівців. Наводяться результати емпіричного дослідження впливу симуляційних та психологічних тренінгів на психокорекцію і профілактику синдрому емоційного вигорання лікарів. Встановлено, що після зазначених тренінгів у лікарів значимо знижуються показники емоційного виснаження, деперсоналізації, поліпшується самопочуття і настрої. Рекомендовано проведення в системі симуляційного навчання різнопланових психологічних тренінгів та інших процедур психологічного супроводу та консалтингу.

Ключові слова: засоби медичної симуляції, симуляційний тренінг, психологічний тренінг, синдром емоційного вигорання, психокорекція та профілактика.

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підготовки медичних фахівців. Наводяться результати емпіричного дослідження впливу симуляційних та психологічних тренінгів на психокорекцію і профілактику синдрому емоційного вигорання лікарів. Встановлено, що після зазначених тренінгів у лікарів значимо знижуються показники емоційного виснаження, деперсоналізації, поліпшується самопочуття і настрої. Рекомендовано проведення в системі симуляційного навчання різнопланових психологічних тренінгів та інших процедур психологічного супроводу та консалтингу.

Ключевые слова: средства медицинской симуляции, симуляционный тренинг, психологический тренинг, синдром эмоционального выгорания, психокоррекция и профилактика.

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G.V. Nevoit, M.M. Potiazhenko, O.P. Mintser¹, N.I. Ignatenko², Yu.A. Kabernik²
 Ukrainian Medical Stomatological Academy, Poltava
¹P.L. Shupyk National Medical Academy of Postgraduate Education, Kyiv
² Football Club Vorskla, Poltava

BIOELECTRICAL IMPEDANCE DETERMINING BODY COMPOSITION AND HARDWARE-SOFTWARE RECORDING OF HEART RATE VARIABILITY DURING AN OBJECTIVE STRUCTURED CLINICAL EXAMINATION AS A DIAGNOSTIC TOOL

e-mail: umsainua@ukr.net

Practical issues of studying the role of electromagnetic phenomena of cardiac activity and impedance of body tissues in the diagnosis of the functional state of the human body are presented in the article. The purpose of the publication is to determine the clinical diagnostic potential and the appropriateness of applying the computerized methodology for a short record of heart rate variability and the body impedance measurement technique as an instrumental Objective Structured Clinical Examination. The article presents the results of a survey of functionally healthy people of different levels of fitness.

Key words: Non-communicable diseases, Objective Structured Clinical Examination.

The work is a fragment of the research project "Development of algorithms and technology for introducing a healthy lifestyle in patients with non-communicable diseases based on the study of psycho-emotional status", state registration No. 0116U007798.

Today, the concept of 4P-Medicine is one of the most promising models for modern Healthcare. Prediction, Prevention, Personalization, Participation - these are four basic principles of examination and treatment of patients according to modern approaches. Requirements for medical diagnostic procedures should increase. First of all, this applies directly to the communication between the doctor and the patient and the implementation of the Objective Structured Clinical Examination (OSCE) of the patient [6, 10, 14].

Therefore, the development of objective methods for diagnosing the functional state of the patient is extremely relevant. The current era of information technology and the computerization of the doctor's workplace has created technical capabilities for introducing fundamentally new computerized techniques for physical examination of patients during the initial examination of the patient and in the dynamics of treatment. The methodology of an OSCE of patients will comply with the principles of 4P-Medicine then to a greater extent [6,10,14]. Therefore, the issues of improving the diagnosis and management of patients with non-communicable diseases (NCDs) through the use of computerized methods of therapeutic examination and fundamentally new approaches to the study of electromagnetic phenomena in patients with NCDs are of interest for the further development of medicine and the practical part of healthcare.

We came to a preliminary conclusion in the course of a search study that it is electromagnetic oscillatory (wave) processes in the vascular system that are a synchronized indicator of the interaction between the central, autonomic nervous systems, humoral regulation and all organs, body tissues. It is necessary to consider cardiac activity as an integral electromagnetic wave cyclical phenomenon now. Thus, cardiac activity has a significantly greater diagnostic value in assessing the functional state of the body, and it is a source of complex parameters of the psychophysical potential, evaluating the prognostic value of the occurrence of adverse cardiovascular events. The method of assessing heart rate variability (HRV)

is considered by us as the most promising method for performing an OSCE in the 4P-Medicine Model. A short record of HRV (2-5 minutes) is an independent technique and it is characterized by non-invasiveness, simplicity and speed of execution. It allows you to assess the state of regulatory mechanisms in patients [3, 11, 12, 13].

A non-invasive method of monitoring the state of metabolism is necessary for working with patients according to the 4P-medicine model. Fat metabolism disorders play a key role in the pathogenesis of the onset and progression of NCDs. We suggest the use of Bioelectrical Impedance method (BIM) measurement with automatic of body composition calculation for this purpose [4,8,9].

Diagnostic equipment for HRV-short recording of and instruments for BIM determining body composition have been developed and certified in many countries of the world and in Ukraine. However, these methods are used very limited or not used at all in the practice of OSCE patients.

The purpose of the work was to determine the clinical diagnostic potential and the feasibility of OSCE patients of HRV-short recording of and BIM determining body composition as a tool procedure in functionally healthy individuals.

Materials and methods. An open, non-randomized, controlled study was performed at the Educational and practical Center of Biophotonics and Valeology of the Department of Internal Medicine and Emergency Medicine of the Ukrainian Medical Stomatological Academy (UMSA, Poltava, Ukraine). 82 functionally healthy individuals were recruited to participate in the present study. Following anamnesis, healthy individuals were familiarized with the experimental equipment and procedures. The functionally healthy football players of the teams of the main, additional, junior squads were examined during a routine medical examination (January 2020) of the Vorskla Football Club (Poltava, Ukraine) 60 people (median age – 20,5±4,7 years, men - 100%; Study Group 1 - persons engage in systematic sports at a professional level). Anamnesticly functionally healthy non-athletes - 23 post-graduate doctors (median age – 24,8±2,0 years, men - 78%; Study Group 2 - control) were examined for conducting the annual preventive training department strategy “Doctor in the fight against NCDs: start with yourself” (2020-2021). The study was approved by the Ethics Committee of the UMSA. It was carried out in compliance with all applicable ethical rules.

The formula of the methodology included the following methods of multiparameter diagnostics: 1) testing according to an adapted questionnaire with the determination of the psychological type of attitude towards a healthy lifestyle with the identification of predictors of the occurrence of NCDs; 2) BIM determining body composition; 3) HRV-short recording (background recording - 5 minutes and Orthostatic test - 3 minutes).

The formation of the healthy lifestyle components was calculated after testing according to the formula $N\% = X \cdot 100 / 54$ (where X is the total number of points scored) and it had the following point estimate: 0-27 (0-50%) points - low (object-passive) level (neglect of one's health occurs in the respondent on the background of insufficient awareness of a healthy lifestyle) 28-45 (52-74%) - medium (objectively -active) level (the respondent has a sufficient level of awareness about the healthy lifestyle, but neglects his health) 45-54 (76-100%) - high (subjective) level (sufficient awareness coincides with the implementation of the health-saving activities of the respondent). Testing assessed the presence/absence of bad habits (drinking, smoking), the level of physical activity (morning exercises, regular exercise), proper nutrition [2].

BIM determining body composition was performed on a Body Composition Monitor (model HBF-500-E, Omron Healthcare, Japan) according to the recommended measurement technique. The BIM monitor automatically calculates the following indicators: body weight (kg), Body Mass Index (BMI), Body Fat Percentage (BFP) (5.0-60.0% in 0.1% increments), Visceral Fat Level (VFL) (at 30 levels in increments of 1 level), Skeletal Muscle Percentage (SMP) (5.0-50.0% in 0.1% increments), Resting Metabolism (RM) (385-5000 kcal) [4,9].

HRV was assessed using a complex (model Poly-Spectr, Neurosoft Company, Ivanovo, Russia). Technical requirements and commercial recommendations for the implementation of the research methodology were observed. Blood pressure was measured before and after recording HRV. The analysis of the results of HRV recording was carried out automatically by the hardware-software complex Poly-Spectr. Evaluated automatic conclusion, indicators of Variational Pulsometry and Spectral Analysis (Total power (TP, mc^2); Very low frequency (VLF, mc^2 ;) - 0,0033-0,04 Гц; Low Frequency power (LF, mc^2) 0,04–0,15 Гц; High Frequency power (HF, mc^2) - 0,15–0,4 Гц; a ratio of Low Frequency to High Frequency (LF/HF ratio) [1,3,5,11].

The study used certified medical equipment that has the appropriate metrological conclusions. The data obtained were analyzed by groups and by personnel. Statistical analysis was performed using the Prism

5.0 software package. The data obtained are presented as average values with their average error ($M \pm m$). Mann-Whitney U-test was evaluated to determine the significance of differences between groups. Differences and correlations were considered significant at $p < 0.05$.

Results of the study and their discussion. A group analysis of indicators showed that respondents-athletes (group 1) have a higher level of psychological formation for a healthy lifestyle than non-athletes-young doctors (group 2). It was found that 47% of group 1 respondents have a high overall level of psychological type formation, 53% of the respondents have an average; 84% of the respondent of Group 2 have an average level, 4% of the respondent have a high level of formation of a healthy lifestyle. The following distribution of blocks takes place in Group 1: 1 block - 66% high level, 34% average level; 2 block - 57% high level, 40% average level, 3% low level; 3 block - 71% high level, 29% average level. The distribution of levels in Group 2 includes: 1 block - 26% high level, 61% average level, 13% low level; 2 block - 44% high level, 52% average level, 4% low level; 3 block - 87% average level, 13% high level of formation of a Healthy Lifestyle. The data obtained demonstrate greater awareness, awareness and implementation of health-preserving activities among athletes.

Understanding the importance and nature of health-preserving technology is a professional medical competency. The results obtained indicate a low level of these competencies among respondent doctors. The presence of respondents with bad habits, poor nutrition, and ignoring physical education in group 2 confirms this fact. So, 52% of respondents was drink strong alcoholic drinks, 65% of respondents was drink weak alcoholic drinks, 6% of respondents was drink energy drinks, 44% of respondents was smoke, 61% of respondents do not adhere to normotrophic nutrition, 35% of respondents consume more than 6 g of salt per day in group 1. These indicators are lower among respondents in group 2: 19%, 38%, 12%, 9%, 33% and 33%, respectively. Professional athletes accepted the group 1. 61% of the respondents do not exercise and 39% of the respondents never go in for sports in the control group. Significant changes in body composition were found in respondents of group 2. The averaged anthropometric data for the groups are given in Table 1.

Table 1

General Characteristics of the body composition

	Group 1 (n=60)	Group 2 (n=23)
Weight (kg)	73.54±9.22	74.48±12.07
Height (cm)	182±6.7	176.6±7.8
BMI	22.76±2.92	23.98±2.48
SMP (norm 42-54 %)	41.54±5.88	37.37±5.72*
BFP (norm 8-19.9%)	15.87±3.74	22.65±7.27*
VFL (norm 1-9 level)	4.27±1.10	6±2.42
RM	1742±67	1671±207

Note * - the difference is reliable at $p < 0.05$ between the characteristics Group 1. Group 2.

The obtained personified data made it possible to identify among the functionally healthy respondents such patients who need to correct their lifestyle and improve their health indicators clusters. 3 respondents had latent obesity with an increased BFP in group 1. We revealed obesity by BMI in 8 (33%) people, of which 5 (20%) of the respondents had a mild degree, 3 (13%) had a moderate degree in group 2. At the same time, obesity with an increase in BFP was detected in 11 (48%) of respondents: 4 (17%) of respondents had a high level of BFP, 7 (31%) of respondents had a very high level of BFP; 2 (8%) of respondents were diagnosed with visceral obesity.

The data obtained are a consequence of the presence of metabolic disturbances in these respondents and they are predictors of the occurrence of NCDs in the future in our opinion. A fundamentally important established fact is the presence of muscle mass deficiency in 16 (70%) of respondents in group 2. This confirms the fact of metabolic disturbance due to inactivity and this is another new early predictor of the occurrence of NCDs in the future, as we now believe. This fact is not accidental. As the results of a three-year retrospective analysis show, we recorded muscle deficit in more than half of the surveyed respondents (young doctor) annually, and we found that more than 30% of respondents (young doctor) showed impaired fat metabolism. 69 (54%) interns had impaired fat metabolism; BMI obesity was found in 31%, BFP obesity, was found in 17%, visceral obesity was found in 7% of people. 55 (93%) interns had a muscle deficit without gender differences [2,4].

We also believe that the levels of indicators of the electromagnetic activity of cardiac activity are another cluster that allows you to objectively assess the functional state of respondents and their level of fitness. Indicators of spectral characteristics of the electromagnetic parameters of cardiac activity and variational pulsometry are the most informative for assessing the functional state of respondents. Naturally, HRV is an individual diagnostic method that is sensitive to changes in neuro-humoral regulation and a

chronological change in indicators during the day according to the literature. At the same time, general patterns exist, which are also displayed in the averaged results by groups. Significant differences in the power of spectral characteristics for all indicators of the frequency spectrum were established by us (Table 2).

Table 2

General indicators of Spectral Characteristics of the Heart Rate Variability

	group 1 (n=60)		group 2 (n=23)	
	Background recording	Orthostatic test	Background recording	Orthostatic test
TP (mc ²)	24173±71872	7333±11772	2918±2042*	2614±1955**
VLF (mc ²)	8442±32908	3269±8946	935.5±858.2*	880.4±818.3**
LF (mc ²)	7369±29211	2918±3429	1080±808.7*	1413±1218**
HF (mc ²)	8362±14530	1146±2326	902.4±759.2*	320±251.7**
LF/HF ratio	1.024±1.071	6.656±5.078	1.433±0.925	6.003±5.591

Note * - the difference is reliable at $p < 0.0001$ between the indicators Background recording. ** the difference is reliable at $p < 0.0001$ between the indicators Orthostatic test.

So, the spectral activity indices were significantly higher in the main group and they corresponded to the normal range. Apparently, these significant differences are due to a higher level of metabolism of substances and a higher energy status as a result of systematic sports. Spectral indicators were reduced and there was no balance in the control group, which a personalized analysis of the results shows clearly. Low and very low overall activity of regulatory mechanisms occurs in 12 (50%) respondents in the control group and average activity is recorded in 8 (32%) respondents in the control group, while activity is high and above average in 32 (65%) and 17 (29%) of the respondents of the main group, respectively. A low level of regulatory disruption was found in 40 (69%) respondents in the main group, an average level of regulatory disruption occurred in 14 (24%) respondents in the main group versus group 2, where high and medium levels of regulatory disruption occurred in 25% and 50% of respondents, respectively. This indicates the presence of higher functional reserves among the respondents of the main group as a result of physical fitness, proper metabolism and the corresponding general energy status of the body. Therefore, the spectral characteristics and functional state are better in the main group (athletes) than in the control group (not athletes).

Finally, the task to study the clinical effectiveness of the proposed method was successfully achieved. The results obtained are completely consistent with the data available in science regarding the fact that the power of the HRV frequency spectrum reflects the power of regulation [1,5,7,15]. Reliably large values in athletes demonstrate this clearly (Tabl.2). It is known that chronic distress with sympathetic hyperactivation is recorded in patients with NCDs according to HRV [1,5,15]. This was not registered in the control group, but a reduced spectrum power indicates a decreased regulation of systemic recovery mechanisms in the absence of systematic sports. And this refers the respondents of the control group to the risk group for the occurrence of NCDs in the future. This once again confirms the importance of regular sports for the prevention of NCDs. Our results supplemented the data available in science as well, since they proved the presence of significant differences in cardiac activity and metabolism in functionally healthy young people with different physical activities. They showed that promising predictors of the occurrence of NCDs (spectral changes in the activity of the heart, impaired body composition) can occur in functionally healthy people. The state of functional health in a patient in his youth does not guarantee the absence of a hidden pathology of metabolism and regulation of the body, which will be part of his cardiovascular continuum in the future.

The attitude of doctors to their health is of great importance. If the doctor does not adhere to the principles of a Healthy Lifestyle, then he will not be convinced of the promotion of a Healthy Lifestyle among his patients, and he will become ill with NCDs in the future [2]. This confirms the value and relevance of applying our proposed methodology additionally. There are practically no studies of the assessment of the Health Status of doctors in the scientific literature.

Conclusions

1. A comprehensive study of the functional state of the body and assessment of respondents' lifestyle revealed that athletes have an objectively better functional state of the body, a better psychological type of attitude to a healthy lifestyle, a more correct Healthy Lifestyle than functionally healthy non-athletes.

2. It was found that tested and objective risk factors for the occurrence of NCDs and the formation of the preclinical phase of the disease occur in functionally healthy non-athletes. 3) New promising

predictors of the early occurrence of NCDs have been established: muscle deficiency, the phenomenon of a decrease in the spectral power of cardiac activity. 4) Instrumental impedance measurement and short recording of HRV methods have significant diagnostic potential and can be recommended for widespread use in the practice of OSCE patients. 5) The method of personalized diagnostics developed by us that determines the direction of correction of the way of life can be used to improve medical monitoring of patients, diagnostics, and it meets the main criteria of the 4P-medicine model.

Prospects of further research lie in the fact that these research results are intermediate. A deeper study of the possibilities of the HRV method in the clinic of internal diseases is planned.

References

1. Baevskiy RM. Prognozirovaniye sostoyaniy na grani normy i patologii. Kniga po Trebovaniyu. Moskva; 2014. 295 s. [in Russian]
2. Bondar OG, Potyazhenko MM, Nevoyt GV. Zdorovyy likar – shlyakh do peremohy nad khronichnymy neinfektsiynymy zakhvoryuvannyamy. Visnyk VDNZU «Ukrayinska medychna stomatolohichna akademiya». 2018; 2 (62):231-234 [in Ukrainian]
3. Mihaylov VM. Variabelnost ritma serdtsa (novyy vzglyad na staruyu paradigmu). OOO «Neurosoft». Ivanovo; 2017. 516 s [in Russian]
4. Nevoyt GV. Bioimpedansna otsinka skladu tila yak dotsilnyi suchasnyi biofizychnyi instrumentalnyi metod obyektivnoho obstezheniia patsiiientiv terapevtychnoho profilu i funktsionalno zdorovykh osib. Ukr. J. of Medicine, Biology and Sport. 2020; 1:156-160 [in Ukrainian]
5. Yabluchanskiy NI, Martynenko AV. Variabelnost serdechnogo ritma v pomoshch prakticheskomu vrachu. Dlya nastoyashchikh vrachev. Kharkov; 2010. 131 s. [in Russian]
6. Alonso SG, de la Torre Díez I, Zapirain BG. Predictive, Personalized, Preventive and Participatory (4P) Medicine Applied to Telemedicine and eHealth in the Literature. J Med Syst., 2019; 43, 140. Available from: <https://doi.org/10.1007/s10916-019-1279-4>
7. Arêas GPT, Caruso FCR, Simões RP, Castello-Simões V, Jaenisch RB, Sato TO et.al. Ultra-short-term heart rate variability during resistance exercise in the elderly. Brazilian Journal of Medical and Biological Research. 2018; 51(6): e6962. Available from: <http://dx.doi.org/10.1590/1414-431X20186962>
8. Ballesteros-Pomar M, Calleja-Fernández A, Díez-Rodríguez R, Vidal-Casariago A, Blanco-Suárez M. Comparison of different body composition measurements in severely obese patients in the clinical setting. Nutr. Hosp. 2012; 27(5):1626-1630.
9. BF500 Body Composition Monitor Instruction Manual. Omron Healthcare [Internet]. Available from: <https://www.manualslib.com/manual/718051/Omron-Bf500.html>
10. Flores M, Glusman G, Brogaard K, Price ND, Hood L. P4 medicine: how systems medicine will transform the healthcare sector and society. Per Med. 2013;10(6):565–576.
11. Javorka M, Krohova J, Czippelova B, Turianikova Z, Lazarova Z, Wiszt R, Faes L. Towards understanding the complexity of cardiovascular oscillations: insights from information theory. Comput Biol Med. 2018; 98:48–57.
12. McCraty R, Shaffer F. Heart rate variability: new perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. Glob Adv Health Med. 2015; 4(1):46–61.
13. Melo HM, Martins TC, Nascimento LM, Hoeller AA, Walz R, Takase E. Ultra-short heart rate variability recording reliability: The effect of controlled paced breathing. Ann Noninvasive Electrocardiol. 2018; 23(5): e12565.
14. P4 Medicine. European society of preventive medicine. [Internet]. Available from: <http://www.esprevmed.org/p4-medicine/>
15. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health. 2017; 5(258):1–17.

Реферати

БІОІМПЕДАНСНЕ ВИЗНАЧЕННЯ СКЛАДУ ТІЛА І АПАРАТНО-ПРОГРАМНИЙ ЗАПИС ВАРІАБЕЛЬНОСТІ РИТМУ СЕРЦЯ В СТРУКТУРІ ОБ'ЄКТИВНОГО КЛІНІЧНОГО ОБСТЕЖЕННЯ ЯК ДІАГНОСТИЧНИЙ ІНСТРУМЕНТ

Невойт Г.В., Потяженко М.М., Минцер О.П.,
Ігнатенко Н.І., Каберник Ю.А.

У статті розглянуті практичні питання дослідження електромагнітних феноменів серцевої діяльності та біоімпедансу тіла задля діагностиці функціонального стану людини. Мета публікація - визначення клінічного діагностичного потенціалу та доцільності застосування комп'ютеризованої методики короткого запису, варіабельності серцевого ритму та методики вимірювання імпедансу як доповнення до об'єктивного клінічного обстеження пацієнтів. У статті представлені результати обстеження функціонально здорових людей різних рівнів фізичної тренуваності.

Ключові слова: неінфекційні захворювання, клінічне об'єктивне обстеження.

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БИОИМПЕДАНСНОЕ ОПРЕДЕЛЕНИЕ СОСТАВА ТЕЛА И АППАРАТНО-ПРОГРАМНАЯ ЗАПИСЬ ВАРИАБЕЛЬНОСТИ РИТМА СЕРДЦА В СТРУКТУРЕ ОБЪЕКТИВНОГО КЛИНИЧЕСКОГО ОБСЛЕДОВАНИЯ КАК ДИАГНОСТИЧЕСКИЙ ИНСТРУМЕНТ

Невойт А.В., Потяженко М.М., Минцер О.П.,
Игнатенко Н.И., Каберник Ю.А.

В статье представлены практические вопросы изучения роли электромагнитных феноменов сердечной деятельности и импеданса тела в диагностике функционального состояния организма человека. Целью публикации является определение клинического диагностического потенциала и целесообразности применения компьютеризированной методики короткой записи вариабельности сердечного ритма и методики измерения импеданса тела в качестве дополнения объективного клинического обследования пациента. В статье представлены результаты обследования функционально здоровых людей разного уровня физической подготовки.

Ключевые слова: неинфекционные заболевания, клиническое объективное обследование.

Рецензент Катеренчук І.П.

V.V. Povoroznyuk¹, G.O. Kostromin^{1,2}, N.V. Zaverukha¹, D.F. Chebotarev

Institute of Gerontology, NAMS Ukraine, Kyiv

¹Ukrainian Scientific-Medical Center of Osteoporosis Problems, Kyiv

²Bogomolets National Medical University, Kyiv

AGE, BODY MASS INDEX, BODY COMPOSITION IN POSTMENOPAUSAL WOMEN WITH CHRONIC VENOUS DISEASE

e-mail: nataliyahryb@gmail.com

Chronic venous disease (CVD) is one of the common, though controversial problems in modern medicine. The aim of our study is to determine the association between age, body composition, obesity and CVD in postmenopausal women. We have examined 96 postmenopausal women aged 46-85 years (mean age – 66.19±0.96 years), that in accordance to the presence of CVD all women were divided in two groups. The diagnosis of CVD was established on C-category of clinical, anatomical and pathophysiological (CEAP) classification and vascular surgeon consultation. We have detected increases of CVD frequency with age in postmenopausal women (from 72 % in those aged 45-59 years to 84 % in those aged 75-89 years). A significant correlation between the total fat mass and age was determined in postmenopausal women with CVD. Significantly, higher values of body weight, BMI, total body fat, and lower extremity body fat were found in the oldest group with CVD compared to patients without CVD.

Keywords: chronic venous disease, risk factors, age, obesity, postmenopausal women.

The work is a fragment of the research project “10 years risk and incidence of osteoporotic fractures in the population of Ukraine: age and regional features”, state registration No. 0118U002899.

Chronic venous diseases (CVD) of the lower extremities are among of the most discussed problems of medicine. In the Western countries, approximately 3% of total health care costs are associated with venous disorders; chronic venous disorders occurring in 25-30% of women and 10-40% of men [2, 6, 11, 12]. In the recent decade, the active study of various aspects of this pathology is ongoing, but many questions remain unresolved. Among the well-known risk factors of CVD, there are age, sex, genetic factors, sedentary lifestyle, sedentary working, dietary aspects (consuming large amounts of farinaceous and meat foods) etc. [9, 10, 14, 15]. The data on association between obesity and CVD are still considered controversial. Some scientists believe there is a significant correlation between the BMI and clinical severity, according to the C-category of clinical, anatomical and pathophysiological (CEAP) classification [7]. Other scientists confirm that the body mass index and age are significant predictors of CVD's clinical grade, according to the C- category of the CEAP classification [10, 13]. On the contrary, a French epidemiological study did not reveal any relationship between the CEAP classification's C-category and obesity [1]. Today, there have been no such studies in Ukraine.

The purpose of the study was to examine the association of age, body composition (lean and fat masses), obesity and chronic venous diseases in postmenopausal women.

Materials and methods. The study was performed at D. F. Chebotarev Institute of Gerontology, NAMS Ukraine. The study was approved by the Institute's Ethical Committee (17.05.2017, Protocol № 5). All the examined signed a voluntary informed consent form to participate, being the subjects to the respective diagnostic examination procedures.

Our research involved 96 postmenopausal women. The subjects aged 46-85 years (mean age – 66.19 ± 0.96 years) were divided into groups, depending on the presence of CVD: the first group was made of 21 postmenopausal women without the CVD (age – 62.86 ± 2.05 years), the second group – 75 postmenopausal women with the CVD (age – 67.13 ± 1.05 years). According to the gerontological classification of age, women were divided into the following groups: middle-aged – 25 persons (26%) from 46 to 59 years (mean age – 54.4 ± 0.77 years), elderly – 46 persons (48%) of 61 - 74 years (mean age – 66.14 ± 0.56 years) and old - 25 (26%) persons of 75 - 85 years (mean age 78.16 ± 0.58 years).

The diagnosis of CVD was established based on the symptoms, clinical and ultrasound (if necessary) examinations of the lower extremities. All patients were examined by vascular surgeons. The following data were collected: demographic (age and sex) and anthropometric (weight, height, BMI) characteristics; personal anamnesis of venous thrombosis, pulmonary embolism and other health problems; current and previous therapy of cardiovascular diseases; history of venous thrombosis, as well as the results of clinical examination of the lower extremities. For the CVD assessment, we used the CEAP classification [7]. The C0s category, according to the CEAP classification (no deficiency or obstruction), was determined after excluding other possible causes of existing symptoms.

The BMI was computed by the ratio of body weight (kilograms) and height² (meters), expressed in kg/m² (WHO, 1998). Diagnosis of obesity was established when BMI was above 30 kg/m². The women were divided into three groups: I group – with a normal body weight (BMI 18.5 -24.9 kg/m²), II group – with an excessive weight (BMI 25.0 – 29.9 kg/m²), III group – with obesity (BMI is over 30.0 kg/m²). The

lean and fat masses were measured by the Dual-energy X-ray absorptiometry (DXA) with Hologic (Discovery WI, USA, 2015).

For the data processing purposes, "Statistika 6.0" (StatSoft, Inc. ©) was applied. We used variable and categorical metrics. A result was considered significant if p values were lower than 0.05 ($p < 0.05$). The

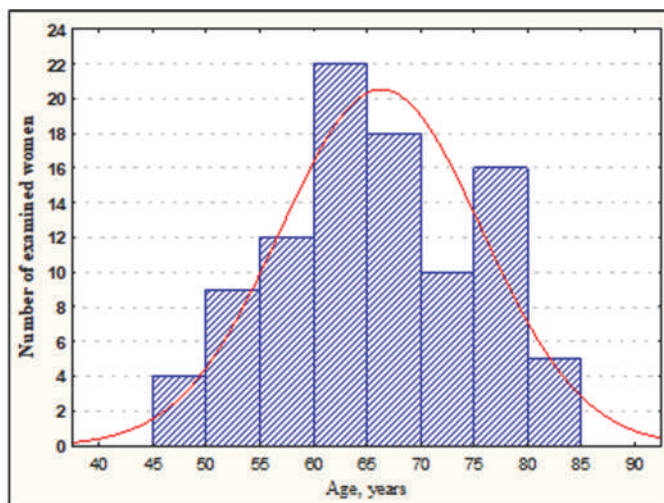


Fig. 1. Histogram of the observed women's distribution by age. Note: red line shows normal distribution

results are presented in the following manner: Mean values (M) \pm Standard Deviation (SD). For the data calculation we used: correlation, regression and ANOVA analysis. Intergroup differences were evaluated using the Scheffe test. The relationship between BMI and age, fat and lean mass was determined using linear regression.

Results of the study and their discussion. We have examined 96 postmenopausal women (age – 66.19 ± 0.96 years, height – 1.57 ± 0.007 m, weight – 76.77 ± 1.73 kg, BMI – 30.82 ± 0.63 kg/m²). The histogram of examined women depending on their ages is presented in fig. 1.

There were no differences observed among age, body mass and BMI across the examined groups depending on the presence of CVD (table 1).

Table 1

Anthropometric characteristics of the examined patients

Parameters	Group I	Group II	F	P
Age, years	62.86 \pm 2.05	67.13 \pm 1.06	3.54	0.06
Weight, kg	76.14 \pm 4.39	76.95 \pm 1.86	0.04	0.85
Height, cm	1.55 \pm 0.02	1.58 \pm 0.01	4.42	0.04
BMI, kg/m ²	31.66 \pm 1.64	30.59 \pm 0.67	0.48	0.51

Note: CVD - chronic venous disease, Group I – women without the CVD, Group II – postmenopausal women with the CVD.

The ratio of postmenopausal women with the CVD increased with age: from 72% in the group of 45-59 year-olds to 84% in the group of 75-89 year-olds (table 2).

Table 2

The distribution of examined women depending on the presence of CVD

Age group, yrs	Group I (n, %)	Group II (n, %)	Total
45-59	7 (28 %)	18 (72 %)	25 (100 %)
60-74	10 (22 %)	36 (78 %)	46 (100 %)
75-89	4 (16 %)	21 (84 %)	25 (100 %)
Total	21 (22 %)	75 (78 %)	96 (100 %)

Among the observed patients, 18% (17 of 96 persons) had a normal body weight, 28% (27 out of 96) were overweight and 54% (52 out of 96) had obesity. The CVD was diagnosed in 71% of patients with a normal body weight (12 out of 17), in 85% of patients with excessive weight (23 out of 27) and in 77% with obesity (40 out of 52) (table 3).

Table 3

Distribution of patients' BMI and age depending on the CVD presence

BMI	45-59 years		60-74 years		75-89 years	
	Without CVD	With CVD	Without CVD	With CVD	Without CVD	With CVD
18.5-24.9	1	4	1	4	3	4
25.0-29.9	1	5	2	11	1	7
>30	5	9	7	21	0	10
Total	7	18	10	36	4	21

Note. CVD - chronic venous disease

There were revealed no differences of lean and fat mass depending on the presence of CVD (fig. 2). In the elderly group of patients with and without the CVD, there were found significant differences in the parameters of body weight ($p = 0.009$), BMI ($p = 0.005$), total fat mass ($p = 0.024$), total lean mass ($p = 0.003$) and lean legs' mass ($p = 0.002$) (table 4).

Anthropometric characteristics, lean and fat mass of the examined patients depending on the presence of CVD and age

	45-59 years			60-74 years			75-89 years		
	Without the CVD	With the CVD	p	Without the CVD	With the CVD	p	Without the CVD	With the CVD	p
age	52.6±4.43	55.1±3.5	0.143	64.4±2.76	66.6±3.5	0.106	77.0±1.83	78.3±3.04	0.394
height	1.55±0.07	1.62±0.06	0.02	1.55±0.1	1.58±0.06	0.22	1.54±0.07	1.56±0.07	0.567
weight	88.3±25.68	78.4±16.44	0.261	76.9±9.1	78.0±17.1	0.843	53.0±8.6	73.9±14.04	0.009
BMI	36.1±8.56	29.9±6.67	0.065	32.2±4.36	31.1±6.05	0.598	22.5±3.14	30.3±4.8	0.005
TFM	41.6±16.0	35.3±11.58	0.285	33.7±4.98	33.9±10.79	0.966	16.9±6.42	30.9±11.08	0.024
TLM	43.2±9.75	41.1±5.26	0.486	42.1±5.78	42.2±6.98	0.945	33.6±2.29	42.0±4.89	0.003
LFM	13.5±1.89	12.8±5.0	0.753	10.1±2.05	11.8±4.09	0.216	6.6±2.22	10.4±4.6	0.123
LLM	13.5±3.13	13.0±2.1	0.686	13.0±1.95	15.8±16.29	0.605	10.4±0.59	13.0±1.66	0.002
n	7	18		10	36		4	21	

Note. CVD - chronic venous disease, TFM - total fat mass, TLM - total lean mass, LFM – legs’ fat mass, LLM – legs’ lean mass.

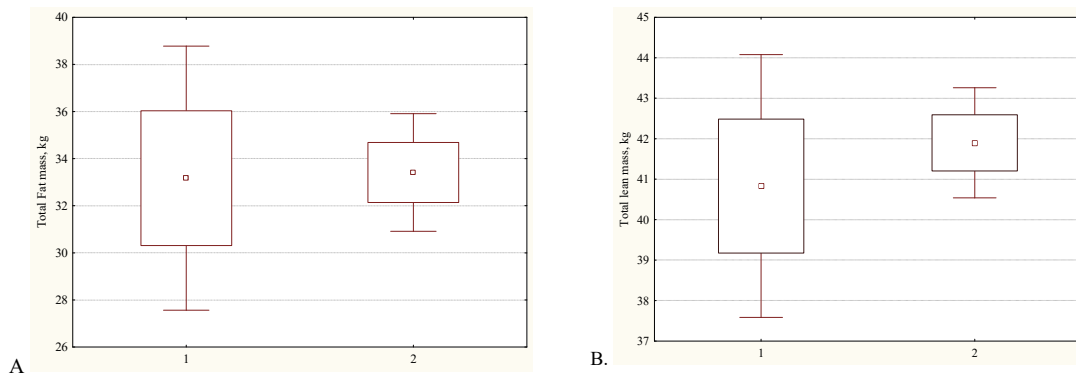


Fig. 2. Body composition of the postmenopausal women depending on the presence of CVD

Note. CVD - chronic venous disease, A. – Total fat mass, B. – Total lean mass; 1 – women without the CVD, 2 – postmenopausal women with the CVD.

Correlation and regression analyses of relations between fat mass and age are shown in fig. 3.

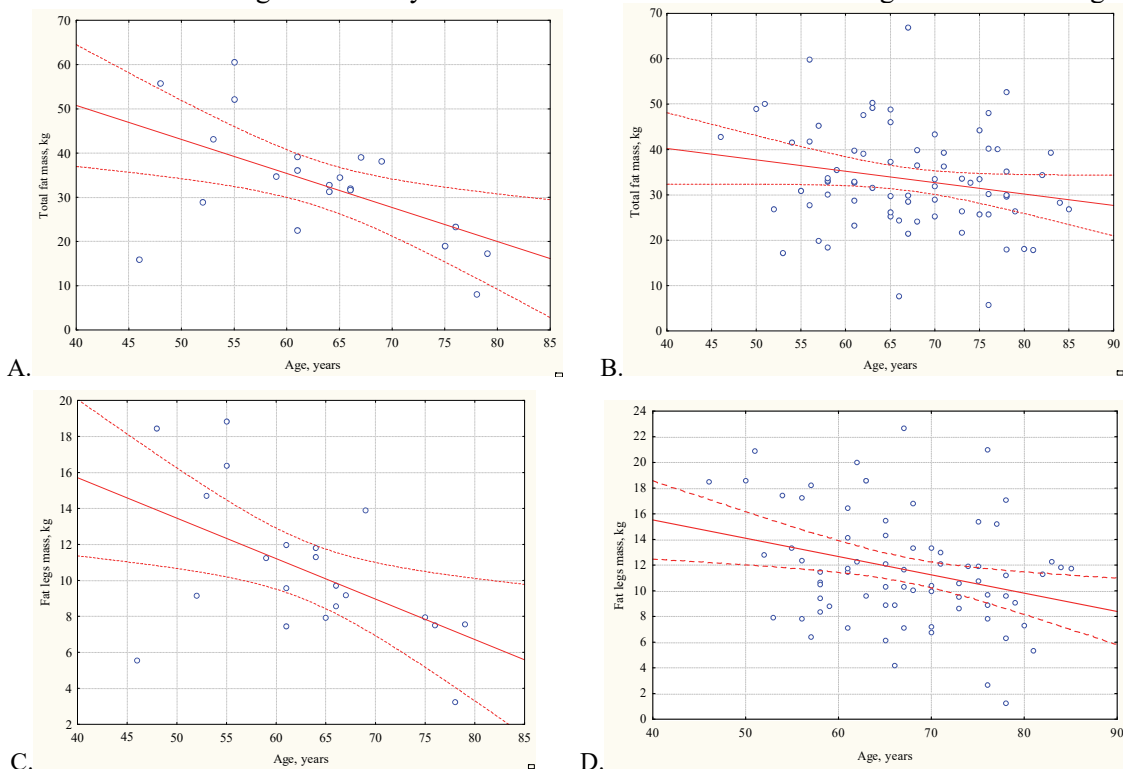


Fig. 3. Correlation between fat mass and age in postmenopausal women depending on the presence of CVD

Note. CVD - chronic venous disease. A. – Postmenopausal women without the CVD; total fat mass, kg = $81.51 - 0.77 * \text{Age, years}$ ($r=-0.55$; $t=-2.87$; $p=0.09$). B. – Postmenopausal women with the CVD; total fat mass, kg = $50.26 - 0.25 * \text{Age, years}$ ($r=-0.21$; $t=-1.82$; $p=0.07$). C. – Postmenopausal women without the CVD; Fat legs’ mass, kg = $24.71 - 0.23 * \text{Age, years}$ ($r=-0.52$; $t=-2.66$; $p=0.02$). D. – Postmenopausal women with the CVD; Fat legs’ mass, kg = $21.23 - 0.14 * \text{Age, years}$ ($r=-0.29$; $t=-2.66$; $p=0.009$).

In postmenopausal women without CVD, there was a significant correlation between BMI and age, unlike in postmenopausal women with CVD, where this association was not confirmed (fig. 4).

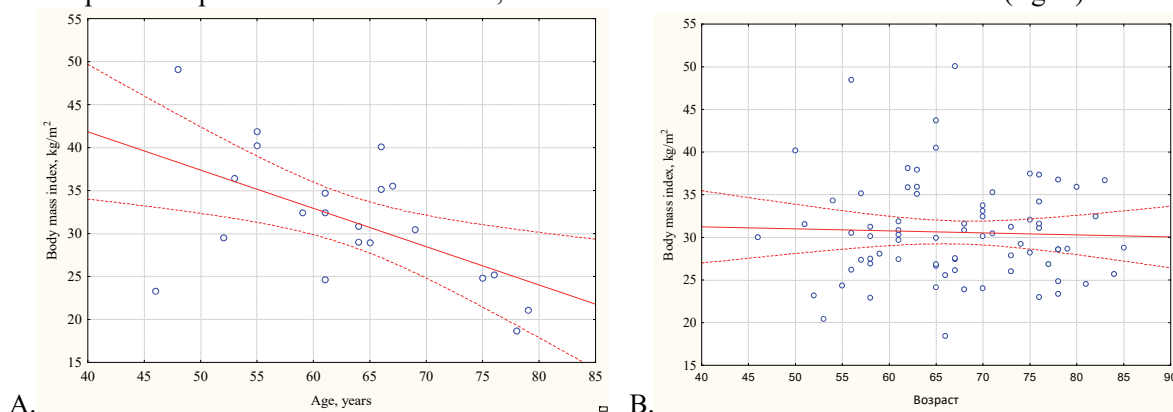


Fig. 4. Correlation between body mass index and age in postmenopausal women depending on the presence of chronic venous diseases. Note. CVD - chronic venous disease. A. – Postmenopausal women without the CVD; Body mass index, $\text{kg/m}^2 = 59.68 - 0.45 * \text{Age}$, years ($r=-0.55$; $t=-2.93$; $p=0.009$). B. – Postmenopausal women with the CVD; Body mass index, $\text{kg/m}^2 = 32.29 - 0.24 * \text{Age}$, years ($r=-0.37$; $t=-0.32$; $p=0.75$).

The CVD is an umbrella concept including morphological and functional disorders of the venous system, such as varicose, post-thrombotic disease of the lower extremities and angiodysplasia (phlebodysplasia). It is usually manifested by a discomfort in lower extremities, cosmetic defects and, in certain cases, it may be life-threatening [5].

The Framingham Study showed that the CVD incidence increased with age, regardless of gender. About 10% of women and 1% of men were diagnosed with the CVD in the age group of up to 30 years, while in the persons over 70 years, the prevalence reached 77% and 57%, respectively [12].

According to a large number of studies presented in the literature, advancing age of the patients has been associated with a higher chance of CVD developing [4, 12]. The results of our study support this fact: the incidence of CVR in postmenopausal women increased with age (from 72% in women aged 45-59 years to 84% in women of 75-89 years).

In the literature, the issue of excessive weight being a risk factor for CVD is deemed controversial. There is a significant correlation between an excessive weight or obesity and the severity of CVD's category C (clinical manifestations), according to the CEAP classification, unlike in the patients with a normal body weight. However, this association was independent of age and gender. Danielsson et al. detected a significant association between the clinical severity, according to C of CEAP classification, and BMI [3]. In the Study of San Diego Population, an increased waist circumference was associated with the CVD in males and females, and the increased body weight was a risk factor for a moderate CVD, though just in females. Obesity is a risk factor for venous thrombosis [8]. In addition, deep obstruction is significantly more common in patients with an excessive weight and obesity than in patients with a normal body weight [15].

In a number of papers, pregnancy is considered in the context of an excess body weight, being a risk factor for the CVD [9, 10, 15]. In this case, the probability of CVD developing gets higher with an increased number of pregnancies [4, 12]. In 2015, the Iranian scientists studied the incidence of CVD among the hairstylists. 197 women of 18-68 years were examined, 47.7% of them were diagnosed with the CVD. In this study, no significant association was found between the CVD and body weight of the participants. However, the CVD significantly correlated with patients' ages (OR=1.08; 95% CI: 1.03, 1.13); family history of the CVD (OR=1.99; 95% CI: 1.03, 3.82), blood pressure (OR=4.41; 95% CI: 1.63, 11.90); and duration of standing (OR=2.34; 95% CI: 1.05, 5.22) [4]. Similar results were obtained by the Japanese scientists who examined 1,198 nurses aged 19-50 years. They found no correlation between the CVD's development and BMI. However, they revealed the following risk factors for the CVD: women's age (OR = 1.317; 95% CI: 1.196, 1.450), time spent standing (OR=1.712, 95% CI: -2.423, 1.209) and family history of the CVD (OR=2.706, 95% CI: 1.444, 5.073). By contrast, the main protective factors were: wearing elastic stockings (OR= 0.052, 95% CI: 0.025, 0.107), resting with legs raised (OR=0.201, 95% CI: 0.095, 0.425), and physical exercise (OR=0.141, 95%CI: 0.072, 0.274). Moreover, age of the nurses ($r=0.47$, $P < 0.01$) and their length of work ($r=0.51$, $P < 0.01$) were linearly associated with the CVD [13].

Our research is limited by the fact that all the examined patients had such comorbidities, as osteoporosis, osteoarthritis, and back pain. However, in the literature, there is evidence of a possible relationship between the knee joints osteoarthritis and CVD. In addition, in the group of 75-89 year-olds, there were only 4 patients with no signs of lower extremity CVD. It may be interpreted as a confirmation of the reference data stating that the number of CVD cases increases with age.

Conclusions

We have detected an increase of the CVD frequency with age in the examined Ukrainian postmenopausal women. Significantly higher body weight, BMI, total body fat, and lower extremity body fat were found in the oldest group with the CVD compared to the patients without the CVD. A significant correlation was further revealed between the total fat mass and age in the postmenopausal women with the CVD.

A significant correlation between BMI and age was only observed in the postmenopausal women without the CVD.

References

1. Benigni JP, Cazaubon M, Tourneroc A. Is obesity an aggravating factor in chronic venous disease? Results of a French epidemiological study in male patients. *Int Angiol.* 2006; 25: 297-303.
2. Clark A, Harvey I, Fowkes FG. Epidemiology and risk factors for varicose veins among older people: cross-sectional population study in the UK. *Phlebology.* 2010 Oct; 25(5):236-40. doi: 10.1258/phleb.2009.009045.
3. Danielsson G, Eklof B, Grandinetti A, Kistner RL. The influence of obesity on chronic venous disease. *Vasc Endovascular Surg.* 2002; 36:271-6.
4. Ebrahimi H, Amanpour F, Haghghi NB. Prevalence and Risk Factors of Varicose Veins among Female Hairdressers: A Cross Sectional Study in North-east of Iran. *JRHS.* 2015 May; 15(2):119-23
5. Erding L, Shuyan C, Weiwei Z, Ying Y. Influencing factors for lower extremity varicose veins in female nurses in East China. *Biomedical Research. An International Journal of Medical Sciences.* 2017; 28(20):9039-45.
6. Feodor T, Baila S, Mitea IA, Branisteanu DE, Vittos O. Epidemiology and clinical characteristics of chronic venous disease in Romania. *Exp Ther Med.* 2019 Feb; 17(2):1097-1105. doi: 10.3892/etm.2018.7059.
7. International Union of Phlebology. Vein consult program (Observational, multicentric, descriptive survey of chronic venous disease). *Eur J Vasc Endovasc Surg.* 1996. 12: 487-492. Available from: <http://www.veinconsult.com/background/>
8. Klovaite J, Benn M, Nordestgaard BG. Obesity as a Causal Risk Factor for Deep Venous Thrombosis: A Mendelian Randomization Study. *J Intern Med.* 2015 May; 277 (5): 573-84. doi: 10.1111/joim.12299
9. Mahapatra S, Ramakrishna P, Gupta B, Arumalla A, Para MA. Correlation of obesity and comorbid conditions with chronic venous insufficiency. Results of a single-centre study. *The Indian Journal of Medical Research.* 2018 May; 147(5):471. doi: 10.4103/ijmr.IJMR_1844_16
10. Musil D, Kaletova M, Herman J. Age, body mass index and severity of primary chronic venous disease. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2011; 155:367-71.
11. Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. *International Journal of Angiology.* 2012; 31(2):105-115.
12. Seliverstov EI, Avakyants IP, Nikishkov AS, Zolotukhin IA. Epidemiology of Chronic Venous Disease. *Flebology.* 2016; 1:297-303.
13. Vlajinac HD, Marinkovic JM, Maksimovic MZ, Matic PA, Radak DJ. Body Mass Index and Primary Chronic Venous Disease e A Cross-sectional study. *Eur J Vasc Endovasc Surg.* 2013 Mar; 45(3):293-8. doi: 10.1016/j.ejvs.2012.12.011.
14. Vuylsteke ME, Thomis S, Guillaume G, Modliszewski ML, Weides N, Staelens I. Epidemiological Study on Chronic Venous Disease in Belgium and Luxembourg: Prevalence, Risk Factors and Symptomatology. *European Journal of Vascular and Endovascular Surgery.* 2015; 49(4):432-439. doi: 10.1016/j.ejvs.2014.12.031.
15. Willenberg T, Schumacher A, Amann-Vesti B, Jacomella V, Thalhammer C, Diehm N. Impact of obesity on venous hemodynamics of the lower limbs. *J Vasc Surg.* 2010 Sep; 52(3):664-8. doi: 10.1016/j.jvs.2010.04.023

Реферати

ВІК, ТІЛОБУДОВА ІНДЕКС МАСИ ТІЛА В ЖІНОК У ПОСТМЕНОПАУЗАЛЬНОМУ ПЕРІОДІ ІЗ ХРОНІЧНИМ ЗАХВОРЮВАННЯМ ВЕН НИЖНІХ КІНЦІВОК

Поворознюк В.В., Костромін Г.О., Заверуха Н.В.

Хронічне захворювання вен (ХЗВ) є однією з найбільш поширених, хоча й суперечливих проблем сучасної медицини. Метою дослідження є визначення зв'язку між віком, тілобудовою, ожирінням та ХЗВ у жінок у постменопаузальному періоді. Обстежено 96 жінок віком 46-85 років (середній вік 66,19±0,96 років), яких розподілено на дві групи відповідно до наявності ХЗВ. Діагноз ХЗВ був встановлений на основі клініко-етіолого-анато-патофізіологічної класифікації (СЕАР) та консультації судинного хірурга. Виявлено, що частота ХЗВ у жінок у постменопаузальному періоді зростає зі збільшенням віку обстежених (від 72% жінок віком 45-59 років до 84% жінок 75-89 років). У жінок з наявним ХЗВ визначено вірогідну кореляцію між загальною жировою масою та віком. У жінок із ХЗВ у старечому віці виявлено вірогідно більші значення показників маси тіла, ІМТ, загальної жирової маси та жирової маси нижніх кінцівок у порівнянні з пацієнтами без ХЗВ.

Ключові слова: хронічне захворювання вен, фактори ризику, вік, ожиріння, жінки у постменопаузальному періоді.

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ВОЗРАСТ, ТЕЛОСТРОЕНИЕ, ИНДЕКС МАССЫ ТЕЛА У ЖЕНЩИН В ПОСТМЕНОПАУЗАЛЬНОМ ПЕРИОДЕ С ХРОНИЧЕСКИМ ВЕНОЗНЫМ ЗАБОЛЕВАНИЕМ НИЖНИХ КОНЕЧНОСТЕЙ

Поворознюк В.В., Костромин Г.А., Заверуха Н.В.

Хроническое заболевание вен (ХЗВ) является одной из распространенных, хотя и неоднозначных проблем в медицине. Цель нашего исследования - определить связь между возрастом, телостроением, ожирением и ХЗВ у женщин в постменопаузальном периоде. Обследовано 96 женщин в возрасте 46-85 лет (средний возраст - 66,19 ± 0,96 года), которые были разделены на две группы в зависимости от наличия хронического венозного заболевания. Диагноз ХЗВ был установлен на основе клинико-этиоло-анато-патофизиологической классификации (СЕАР) и консультации сосудистого хирурга. Обнаружено увеличение частоты ХЗВ с возрастом у женщин в постменопаузальном периоде (с 72% в возрасте 45-59 лет до 84% в 75-89 лет). Значительная корреляция между общей жировой массой и возрастом была определена у женщин в постменопаузальном периоде с ХЗВ. У женщин с ХЗВ в старческом возрасте выявлено достоверно более высокие значения показателей массы тела, ИМТ, общей жировой массы и жировой массы нижних конечностей по сравнению с пациентами без ХЗВ.

Ключевые слова - хроническое заболевание вен, факторы риска, возраст, ожирение, женщины в постменопаузальном периоде.

Рецензент Ляховський В.І.

O.O. Pushko, N.V. Lytvynenko
Ukrainian Medical Stomatological Academy, Poltava

PECULIARITIES OF NEUROCOGNITIVE STATUS OF PATIENTS IN THE ACUTE ISCHEMIC STROKE PHASE OF DIFFERENT HEMISPHERIC LOCALIZATION

e-mail: olexandrpushko@gmail.com

The article considers the peculiarities of neurocognitive status in patients after acute ischemic stroke of different hemispheric localization. Left-sided hemispheric stroke revealed a higher frequency and higher degree of cognitive impairment (mean score for Mini Mental State Examination was 21.3 ± 0.61 , for Montreal Cognitive Assessment – 18.22 ± 0.9) compared with right-sided hemispheric localization of ischemic focus (mean score for MMSE – 24.05 ± 0.52 , for MoCa – 21.35 ± 0.84) with a statistically significant difference between groups of patients as a whole and by specific blocks of subtests. It was also found that right-sided hemispheric strokes were characterized by a higher frequency and higher degree of anxiety and depressive disorders (mean score for Beck Depression Inventory was 15.1 ± 0.87 , for the state anxiety scale – 37.6 ± 1.71 , for the trait anxiety scale – 36.55 ± 1.73) compared with the left-sided hemispheric localization of acute cerebrovascular accident (mean score for BDI was 11.61 ± 0.71 , for the state anxiety scale – 29.78 ± 0.95 , for the on the Spielberger-Khanin trait anxiety scale – 30.87 ± 1.0) with a statistically significant difference between the groups.

Key words: brain infarction, ischemic stroke, acute period, hemispheric peculiarities, neurocognitive disorders.

The work is a fragment of the research project “Clinical and pathogenetic optimization of diagnosis, prognosis, treatment and prevention of complicated disorders of the central nervous system, as well as neurological disorders in somatic pathology”, state registration No. 0116U004190.

According to the World Health Organization, stroke is a clinical syndrome of the rapid development of signs of focal or total loss of brain function that lasts 24 hours and more or leads to death in the absence of non-vascular causes. Every year, more than 16 million stroke cases and more than 5 million fatal cases from the disease are registered in the world, and according to experts, by 2030 is expected about 23 million strokes and about 7.8 million fatal cases [2, 7].

For today, ischemic stroke is an important and complex medical and social problem, as post-stroke disability is one of the leading causes of disability in the adult population of most countries. The main components of the clinical evidence of ischemic stroke are movement, sensory processing, mental and cognitive disorders. According to a number of sources, about 80% of people who have suffered a stroke remain disabled, and about a quarter of them need constant care. Cerebrovascular pathology in general occupies one of the first places in the structure of morbidity and mortality of the population in developed countries and occupies a prominent place among the causes of acquired cognitive deficiency, especially multi-infarct dementia. Problems of neurocognitive deficiency in patients with acute focal brain lesions are still insufficiently considered [4, 11, 12, 14].

In recent years, there has been an increase in the prevalence of post-stroke cognitive impairment [1, 6]. Prospective studies show an increase in the risk of developing dementia after stroke by almost 10 times [3, 13].

Impaired right-sided hemispheric activation is associated with depression, which is accompanied by high levels of anxiety, while low levels of anxiety and depression are more typical for left-sided hemispheric dysfunction [5, 9]. Observations of patients after stroke (ischemic and/or hemorrhagic) revealed worse dynamics of recovery of speech and cognitive functions in left-sided hemispheric stroke localization and more pronounced disorders of social adaptation in patients with right-sided hemispheric localization of the focus [8, 10].

The **purpose** of the study was to identify and evaluate the hemispheric peculiarities of neurocognitive status of patients in the acute ischemic stroke phase in one of the carotid arterial system.

Materials and methods. 43 patients (27 men and 16 women) with a diagnosis of acute hemispheric ischemic stroke were examined during the study. The mean age was 59.81 ± 1.28 years. Right-sided hemispheric ischemic stroke was observed in 20 patients (46.5%, Group 1), left-sided hemispheric – in 23 patients (53.5%, Group 2). Control group consisted of 16 apparently healthy individuals (10 men and 6 women, CG). The mean age was 59.5 ± 1.74 years.

The study was performed on the basis of the Municipal Enterprises “M.V. Sklifosovsky Poltava Regional Clinical Hospital” and “1st Poltava City Clinical Hospital”.

Study entry criteria: the presence of clinically and neuroimagingly confirmed non-lacunar hemispheric ischemic stroke and a signed form of informed consent to participate in the study. Exclusion criteria from the study were: the presence of clinically and neuroimagingly confirmed intracranial hemorrhage, lesions of two or more systems; global aphasia, decompensated psychopathological syndrome, the presence of somatic disease in the decompensation phase and oncological pathology.

All patients underwent comprehensive neuropsychological testing. The examination period was 3-7 days of the studied cerebrovascular accident. Assessment of neurocognitive status was performed using a short scale of mental status assessment (Mini Mental State Examination, MMSE; Folstein M., 1975), Montreal scale of cognitive assessment (Montreal Cognitive Assessment, MoCa; Nasreddine Z., 1996, 2005), Beck Depression Inventory scales (Beck Depression Inventory, BDI; Beck A., 1961), Spielberger-Khanin state and trait anxiety questionnaire (SA and TA, respectively) (STAI, Spielberger C., 1983). According to the results of MMSE, 28-30 scores were evaluated as the absence of cognitive impairment (CI), 24-27 – precognitive impairment (PCI), 20-23 – mild cognitive impairment, 11-19 – moderate cognitive impairment. For MoCa, less than 26 scores were assessed as manifestations of cognitive impairment. According to BDI, 0-9 scores were interpreted as the absence of depressive symptoms (DS), 10-15 – mild depressive symptoms (subdepression), 16-19 – moderate depressive symptoms, 20-29 – severe depressive symptoms, 30 or more scores – severe depression. According to STAI, 0-30 scores were assessed as mild anxiety, 31-45 – as moderate anxiety, 46 or more scores – as severe anxiety.

Statistical processing of the obtained data was performed using the software package "SPSS", "Statistica 6.0", methods of descriptive statistics and statistical analysis. In particular, descriptive statistics are presented as the mean±standard error of the mean; the Mann-Whitney U-test was used to assess intergroup differences. Differences were considered statistically significant at $p < 0.05$.

The study was complied with the Rules of Humane Treatment of Patients in accordance with the requirements of the Tokyo Declaration of the World Medical Assembly, the requirements of the International Recommendations of the Declaration of Helsinki of Human Rights, "Council of Europe Convention on Human Rights and Biomedicine", the Law of Ukraine "Fundamentals of the legislation of Ukraine on Health Care" as amended, Orders of the Ministry of Health of Ukraine, the Code of Ethics of Physicians of Ukraine and the Code of Ethics of Scientists of Ukraine.

Results of the study and their discussion. Comparing groups by age and sex, no statistically significant differences were found.

Studying the neurocognitive status by the Mini Mental State Examination in the control group, the mean score was 28.19 ± 0.25 , whereas in patients with right-sided hemispheric stroke – 24.05 ± 0.52 ($p < 0.01$), with left-sided hemispheric stroke – 21.3 ± 0.61 ($p < 0.01$) with a statistically significant difference between Groups 1 and 2 ($p < 0.05$).

Analyzing the structure of cognitive disorders on a short scale of mental status assessment, it was found that in the group with right-sided hemispheric ischemic stroke, normal cognitive indices was observed in 5% of patients, precognitive impairment – in 45%, mild cognitive impairment – in 45%, moderate cognitive impairment – in 5%; in the group with left hemispheric localization of the ischemic focus, normal indices of the cognitive sphere were absent, precognitive impairment was observed in 22%, mild cognitive impairment – in 61%, moderate cognitive impairment – in 17%, whereas in the control group precognitive impairment was observed in 25%, and in 75% of individuals there were normal indices of the cognitive sphere. The distribution of patients by the degree of cognitive impairment is shown in fig. 1.

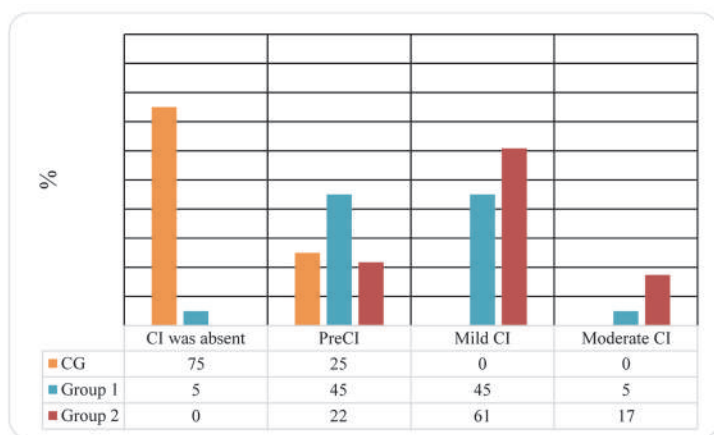


Fig. 1. MMSE: distribution of patients by the degree of cognitive impairment.

The most significant differences were found between the groups of right- and left-sided hemispheric ischemic stroke on the "Attention and calculation", "Execution of a 3-stage command" subtests of the MMSE scale, which indices were significantly lower in the group with right-sided hemispheric stroke, while in the group with left-sided hemispheric ischemic stroke the lowest score was observed for the "Memory" and "Language" subtests. The obtained data are shown in fig. 2a.

Between patients with right-sided hemispheric stroke and the control group, a statistically significant difference was found in the "Attention and calculation" (2.35 ± 0.22 vs. 4.56 ± 0.16), "Memory" (2.95 ± 0.05 vs. 2.56 ± 0.16), "Execution of a 3-stage command" (3.4 ± 0.27 vs. 5.56 ± 0.13) subtests of the MMSE scale ($p < 0.05$), whereas in the group with left-sided hemispheric stroke and control group – all of them were statistically significantly different ($p < 0.05$), except for the "Attention and calculation" subtest ($p = 0.08$).

According to the Montreal Cognitive Assessment scale, the mean score in the control group was 27.56 ± 0.29 scores, while in patients with right-sided hemispheric stroke – 21.35 ± 0.84 ($p < 0.01$), with left-

sided hemispheric stroke – 18.22 ± 0.9 ($p < 0.01$) with a statistically significant difference between groups of patients with right- and left-sided hemispheric ischemic stroke ($p < 0.05$).

There were also statistically significant differences between the groups of right- and left-sided hemispheric ischemic stroke for all subtests of the MoCa scale, while between patients with right-sided hemispheric stroke and the control group the most significant difference was found in the “Visuospatial/executive” (2.25 ± 0.22 vs. 4.81 ± 0.1), “Attention” (2.9 ± 0.28 vs. 5.06 ± 0.14), “Abstraction” (1.15 ± 0.15 vs. 2.0) ($p < 0.01$) subtests, and was not detected in the “Naming” ($p = 1$) subtest. In the group with left-sided hemispheric stroke and control group – by the “Language” (0.91 ± 0.17 vs. 2.13 ± 0.13), “Delayed recall” subtests (0.96 ± 0.19 vs. 4.56 ± 0.13) ($p < 0.01$) and was not detected in the “Abstraction” subtest ($p = 0.14$). The obtained data are shown in fig. 2b.

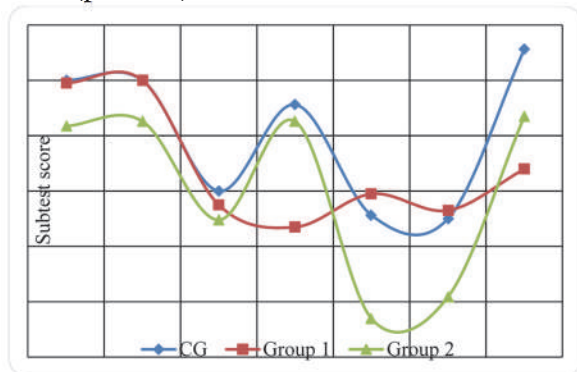


Fig. 2a. MMSE: distribution by subtests: 1 – orientation to time, 2 – orientation to place, 3 – registration, 4 – attention and calculation, 5 – recall, 6 – language, 7 – execution of a 3-stage command. Note: * – index of the level of statistical significance between Groups 1 and 2 $p < 0.05$.

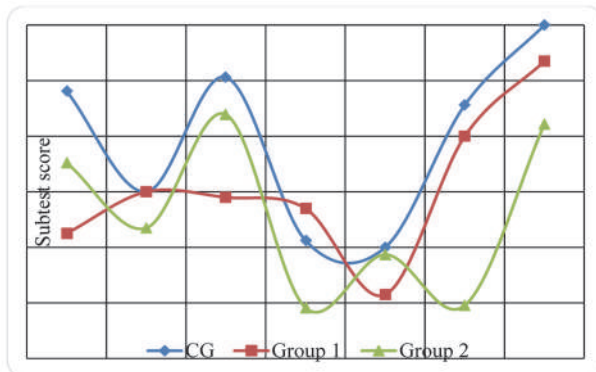


Fig. 2b. MoCa: distribution by subtests: 1 – visuospatial/executive, 2 – naming, 3 – attention, 4 – language, 5 – abstraction, 6 – delayed recall, 7 – orientation. Note: * – index of the level of statistical significance between Groups 1 and 2 $p < 0.05$.

In the study of anxiety and depressive disorders on the Beck Depression Inventory scale in patients of the control group, the mean score was 7.75 ± 0.69 , whereas in patients with right-sided hemispheric stroke – 15.1 ± 0.87 ($p < 0.01$), with left-sided hemispheric stroke – 11.61 ± 0.71 ($p < 0.01$) with a statistically significant difference between Groups 1 and 2 ($p < 0.01$).

Analyzing the structure of depressive symptoms on the Beck Depression Scale, it was found that in the group with left-sided hemispheric ischemic stroke depressive symptoms were absent in 30%, mild depressive symptoms were observed in 48%, moderate – in 22% of patients. In the group with right-sided hemispheric ischemic stroke depressive symptoms were absent in 10%, mild depressive symptoms were observed in 30%, moderate – in 55%, severe depressive symptoms – in 5%, while in the control group mild depressive symptoms were observed in 25%, and in 75% of patients depressive symptoms were absent. The distribution of patients by the degree of depressive symptoms is shown in fig. 3.

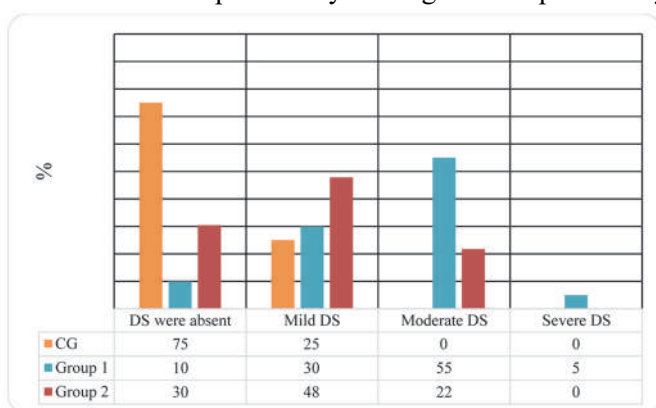


Fig. 3. BDI: distribution of patients according to the degree of depressive symptoms.

37.6 ± 1.71 and 36.55 ± 1.73 , respectively, which was statistically significantly different from the control group ($p < 0.01$), with a statistically significant difference between patients in the right- and left-sided hemispheric ischemic stroke groups ($p < 0.05$).

Analyzing the anxiety syndrome structure on the Spielberger-Khanin state and trait anxiety scale, it was found that in the group with right-sided hemispheric ischemic stroke the state (situational) anxiety was mild in 35% of patients, moderate – in 45%, severe – in 20%, as well as the trait anxiety level (35%, 45%, 20%, respectively). In the group with left-sided hemispheric ischemic stroke, state anxiety was mild

There were also statistically significant differences in the structure of the anxiety syndrome between the groups of right- and left-sided hemispheric stroke. According to the results of Spielberger-Khanin state and trait anxiety questionnaire, the mean score for state anxiety in the control group was 28.19 ± 0.73 , and for trait anxiety it was 29.06 ± 0.53 . In patients with left-sided hemispheric stroke, the mean score was 29.78 ± 0.95 on the scale of state (situational) anxiety ($p = 0.23$) and 30.87 ± 1.0 scores on the trait anxiety scale ($p = 0.16$), whereas in the group with hemispheric stroke –

in 52% of patients, moderate – in 48%; mild level of trait anxiety was found in 74%, moderate – in 22%, high – in 4% of patients with left-sided hemispheric localization of the ischemic focus, while in the control group a mild level of state anxiety was observed in 75%, moderate – in 25%, and trait anxiety was moderate in 12.5%, mild – in 87.5% of patients. The distribution of patients according to the degree of state and trait anxiety is shown in fig. 4a and fig. 4b, respectively.

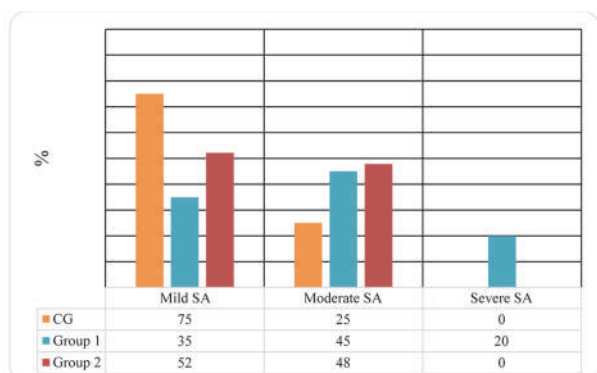


Fig. 4a. STAI: distribution of patients according to the degree of state anxiety.

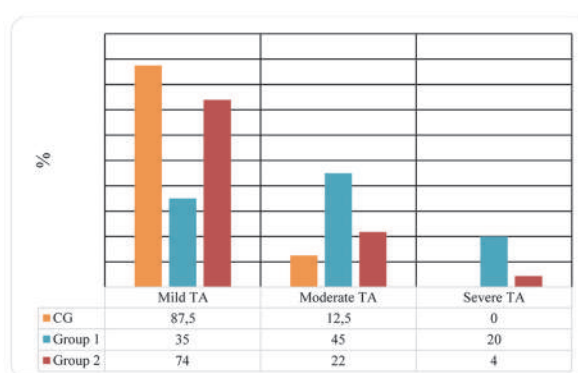


Fig. 4b. STAI: distribution of patients according to the degree of trait anxiety.

The analysis of the obtained results shows that in patients with left-sided hemispheric ischemic stroke there is probably a higher frequency and higher degree of post-stroke cognitive impairment with speech dysfunction, memory impairment, compared with the right-sided hemispheric localization of the ischemic focus, which is characterized by cognitive dysfunction with a predominant impairment of attention, abstract thinking, visuospatial/executive skills and a higher frequency and higher degree of anxiety and depressive disorders [5, 6, 9, 10].

The concept of stroke lateralization can play a key role in optimizing therapeutic and rehabilitation measures in patients with hemispheric ischemic stroke to achieve maximum recovery.

These results do not claim priority, are preliminary in nature and require further study.

Conclusion

The acute phase of hemispheric ischemic stroke is characterized by neurocognitive disorders of varying severity. Right-sided hemispheric ischemic stroke is significantly more often associated with varying degrees of anxiety and depressive disorders and cognitive dysfunction with a predominant impairment of attention, abstract thinking, executive skills, which significantly complicates their social adaptation, while the left-sided hemispheric localization of acute cerebrovascular accident significantly more often leads to cognitive impairment with speech dysfunction, memory impairment.

References

1. Levin OS. Sovremennyye podkhody k diagnostike i lecheniyu postsulnykh kognitivnykh narusheni. Sovremennaya terapiya v psikiatrii i nevrologii. 2014; 1:40-6 [in Russian]
2. Mischenko TS. Epidemiologiya tserebrovaskulyarnykh zbolevaniy i organizatsiya pomoshchi bolnym s mozgovym insultom v Ukraine. Ukrayinskyi visnyk psikhonevrolohiyi. 2017; 25(90):22-4 [in Russian]
3. Bejot Y, Aboa-Eboule C, Durier J, Rouaud O, Jacquin A, Ponavoy E, et al. Prevalence of earle dementia after first-ever stroke: a 24-year population-based study. Stroke. 2011; 42:607-12.
4. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019; 139(10):56-528.
5. Chun HYY, Whiteley WN, Dennis MS, Mead GE, Carson AJ. Anxiety after stroke the importance of subtyping. Stroke. 2018; 49(3):556-64.
6. Dichgans M, Leys D. Vascular Cognitive Impairment. Circulation Research. 2017; 120:573-91.
7. Katan M, Luft A. Global burden of stroke. Seminars in Neurology. 2018; 38(02):208-11.
8. Knapp P, Campbell Burton CA, Holmes J, Murray J, Gillespie D, Lightbody CE, et al. Interventions for treating anxiety after stroke. Vol. 2017, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd. 2017; 5:4-35.
9. Manna CB, Tenke CE, Gates NA, Kayser J, Borod JC, Stewart JW, et al. EEG hemispheric asymmetries during cognitive tasks in depressed patients with high versus low trait anxiety. Clinical EEG and Neuroscience. 2010; 41(4):196-202.
10. Mosch SC, Max JE, Tranel D. A matched lesion analysis of childhood versus adult-onset brain injury due to unilateral stroke: another perspective on neural plasticity and recovery of social functioning. Cognitive and Behavioral Neurology. 2005; 18(1):5-17.
11. Rangaraju S, Frankel M, Jovin TG. Prognostic value of the 24-hour neurological examination in anterior circulation ischemic stroke: A post hoc analysis of two randomized controlled stroke trials. Interventional Neurology. 2015; 4:120-9.
12. Strozzyk D, Dickson DW, Lipton RB, Katz M, Derby CA, Lee S, et al. Contribution of vascular pathology to the clinical expression of dementia. Neurobiology of Aging. 2010; 31(10):1710-20.
13. Sun JH, Tan L, Yu JT. Post-stroke cognitive impairment: epidemiology, mechanisms and management. Annals of Translational Medicine. 2014; 2(8):80.
14. Thrift AG, Thayabaranathan T, Howard G, Howard VJ, Rothwell PM, Feigin VL, et al. Global stroke statistics. International Journal of Stroke. 2017; 12(1):13-32.

Реферати

ОСОБЛИВОСТІ НЕЙРОКОГНІТИВНОГО СТАТУСУ ПАЦІЄНТІВ У ГОСТРОМУ ПЕРІОДІ МОЗКОВОГО ІШЕМІЧНОГО ІНСУЛЬТУ РІЗНОЇ ПІВКУЛЬОВОЇ ЛОКАЛІЗАЦІЇ

Пушко О.О., Литвиненко Н.В.

У статті розглянуто особливості нейрокогнітивного статусу пацієнтів після перенесеного гострого ішемічного інсульту різної півкульової локалізації. При лівопівкульовому інсульті виявлено більшу частоту й вищий ступінь когнітивних порушень (середній бал за Mini Mental State Examination 21,3±0,61, за Montreal Cognitive Assessment 18,22±0,9) порівняно з правопівкульовою локалізацією ішемічного вогнища (середній бал за MMSE 24,05±0,52, за MoCa 21,35±0,84) зі статистично значимою різницею між групами пацієнтів у цілому та за окремими блоками субтестів. Також виявлено, що для правопівкульових інсультів характерна більша частота й вищий ступінь тривожно-депресивних порушень (середній бал за Beck Depression Inventory 15,1±0,87, за шкалою реактивної тривожності 37,6±1,71 та 36,55±1,73 за шкалою особистісної тривожності) порівняно з лівопівкульовою локалізацією гострого порушення мозкового кровообігу (середній бал за BDI 11,61±0,71, за шкалою реактивної тривожності 29,78±0,95 та 30,87±1,0 за шкалою особистісної тривожності Спілбергера-Ханіна) зі статистично значимою різницею між групами.

Ключові слова: інфаркт мозку, ішемічний інсульт, гострий період, півкульові особливості, нейрокогнітивні порушення.

Стаття надійшла 31.07.2019 р.

ОСОБЕННОСТИ НЕЙРОКОГНИТИВНОГО СТАТУСА ПАЦИЕНТОВ В ОСТРОМ ПЕРИОДЕ МОЗГОВОГО ИШЕМИЧЕСКОГО ИНСУЛЬТА РАЗЛИЧНОЙ ПОЛУШАРНОЙ ЛОКАЛИЗАЦИИ

Пушко А.А., Литвиненко Н.В.

В статье рассмотрены особенности нейрокогнитивного статуса пациентов после перенесенного острого ишемического инсульта различной полушарной локализации. При левополушарном инсульте выявлено большую частоту и большую степень когнитивных нарушений (средний балл по Mini Mental State Examination 21,3±0,61, по Montreal Cognitive Assessment 18,22±0,9) по сравнению с правополушарной локализацией ишемического очага (средний балл по MMSE 24,05±0,52, по MoCa 21,35±0,84) со статистически значимой разницей между группами пациентов в целом и по отдельным блокам субтестов. Также выявлено, что для правополушарных инсультов характерна большая частота и более высокая степень тревожно-депрессивных нарушений (средний балл по Beck Depression Inventory 15,1±0,87, по шкале реактивной тревожности 37,6±1,71 и 36,55±1,73 по шкале личностной тревожности) по сравнению с левополушарной локализацией острого нарушения мозгового кровообращения (средний балл по BDI 11,61±0,71, по шкале реактивной тревожности 29,78±0,95 и 30,87±1,0 по шкале личностной тревожности Спилбергера-Ханина) со статистически значимой разницей между группами.

Ключевые слова: инфаркт мозга, ишемический инсульт, острый период, полушарные особенности, нейрокогнитивные нарушения.

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S.V. Rymsha, N.V. Ratsyborynska-Polyakova, A.O. Gavrylyuk
National Pirogov Memorial University, Vinnytsya

FEATURES OF LONG-TERM MENTAL DISORDERS IN THE VICTIMS OF CHERNOBYL ACCIDENT

e-mail: ratsiborinska@gmail.com

The purpose of the work was to study the features of the clinical structure, the pathopsychological and pathophysiological mechanisms of mental disorders formation in the victims of the Chernobyl accident in the long term. The study of the mental status in the liquidators - III groups of complex survey - 202 persons – liquidators of the Chernobyl disaster, that worked in 1988 in 30 – kilometer zone, the radiation level ranged from 0.2 to 25 Gy - took into account the system of risk factors, which included social, radiological, medical aspects, social factors including hypokinesia, unsustainable diet, smoking, alcohol consumption and radiological factors. In the affected by the Chernobyl accident in 1986 long-term consequences for mental health were revealed, mental disorders were found to be dependent on the dose and the relationship between the severity of lesions and radiation symptoms. The study of the liquidators' health can extend the understanding of the relationship between PTSD, depression, risk of internal diseases and recovery. According to our data, the central element in the structure of psychopathological manifestations is psycho-vegetative syndrome with affective accompaniment. Thus, the conclusion was made that psychosocial effects of stress as a result of Chernobyl disaster shows how important it is to continue monitoring of the mental health in the population to establish the relationship between mental well-being, physical illness and mortality.

Key words: Chernobyl catastrophe, liquidators' health status, radiation damage, mental disorders due to irradiation.

The work is a fragment of the research project "Scientific substantiation of diagnostic and therapeutic rehabilitation measures for endogenous and exogenously-organic psychotic and non-psychotic mental disorders", state registration No. 0116U000856.

In the twentieth century, the most frightening and stigmatizing of all technogenic disasters were the nuclear bombings in Hiroshima and Nagasaki and the catastrophes at nuclear power plants at Three Mile Island and Chernobyl. After them revealed the changes in the psyche, such as stigmatization, anxiety, depression and the manifestations of post-traumatic stress disorder (flashbacks and psychic numbing), that lasted sufficiently long, and were associated with a sense of risk for the health, independently of the

objective physical consequences [7, 8, 13]. Liquidators, working at the station in the spring and summer of 1986, have reported long-term effects on mental health, such as increased suicidal activity [14] and significantly higher levels of depression, post-traumatic stress disorder and severe headache comparing to the cohort of liquidators with control geographic age and gender matched group [9]. Domestic studies have found a dose-dependent relationship between the severity of radiation damage and the manifestations of symptoms of post-traumatic stress. The study of the health status of liquidators allows us to expand our understanding of the relationship between PTSD, depression and the risk of cardiovascular diseases, recovery [12] and other conditions [10]. Particular attention we should pay to the presence of symptoms of post-traumatic stress in elderly respondents, especially in woman who survived the evacuation [4]. All these data coincide with the findings of the report of the consequences of the Chernobyl accident, which states that the health status of the inhabitants of the contaminated territories we can describe as bad and the state of health services complicates the evaluation of the explicit consequences for the affected population [3, 112]. Meanwhile, most people with common psychiatric symptoms turn to medical institution to doctors of different specialties, but not to psychiatrists [14]. According to the State Register of Ukraine (SRU) and the Clinical and Epidemiological Register (CER) of the State Institution «Scientific Center of Radiation Medicine of the Academy of Medical Science of Ukraine» the liquidators and evacuees had high levels of cerebrovascular diseases. In addition, the influence of radiation in small doses is a significant risk factor for accelerated aging, irradiation of the thyroid gland at doses >300 mGy is a significant risk factor of the development of cardiovascular and cerebrovascular diseases. Also, at doses >2 mGy — it is a risk factor for mental disorders and diseases of peripheral nervous system. External exposure of the whole body at a dose >250 mGy is a factor of neuropsychiatric and vascular diseases [12]. Thus, the Chernobyl catastrophe has led to long-term neurological and psychopathological consequences, for which established radiation risks exist. Therefore, it is necessary to continue lifelong neurological, psychiatric and epidemiological studies with dosimetry.

The purpose of the work was to study the features of the clinical structure, the pathopsychological and pathophysiological mechanisms of mental disorders formation in the victims of the Chornobyl accident in the long term.

Materials and methods. We had the III groups of complex survey - 202 persons – liquidators of the Chernobyl disaster, that worked in 1988 in 30 – kilometer zone, the radiation level ranged from 0,2 to 25 Gr. All respondents gave informed consent to participate in the study, as evidenced by the relevant documents. The Committee on Bioethics reviewed the materials of the research work of the Department of Psychiatry, Narcology and Psychotherapy with a course on VNMU "Scientific substantiation of diagnostic and therapeutic rehabilitation measures for endogenous and exogenously-organic psychotic and non-psychotic psychiatric disorders" (a fragment of which is this article). As a result of the examination, it was found that the research materials do not contradict the basic bioethical standards of the Declaration of Helsinki adopted by the General Assembly of the World Medical Association, the Council of Europe Convention on Human Rights and Biomedicine (1977), in accordance with the provisions of WHO, International Council of Medical Sciences Ethics (1983), Council of Europe Convention on the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes, 18.03.1986, EEC Directive 609 of 24.11.1986. and Order of the Ministry of Health of Ukraine No. 281 of 01.11.2000. Group I - 30 patients underwent stationary investigation and treatment at the regional center of radiation protection of the population for the asthenic variant of psycho-organic syndrome with diencephalic crises. They stayed in 30-kilometer zone - from 6 month to 1 year. Dose of less than 5 rem was in 9 people (30,0%), 5-10 rem- in 2 people (6,7%), 11-15 rem - in 4 people (13,3%), 16-20 rem - y 2 people (16,7%), 21-25 rem - in 7 people (23,3%), more than 25 rem - in 6 people (20,0%). Thus, the patients received a “small” dose of radiation – up to 100 rem. The related specialists: neurologist, therapist, endocrinologist and ophthalmologist examined the patients. Neurologist diagnosed discirculatory encephalopathy in all the patients. Group II - 35 patients, with organic depressive disorder F 06.32 by ICD-10. Diagnosis of depressive organic disorder based on the clinical-psychopathological, pathology-psychological, electroencephalographic investigations, findings of neurologic, ophthalmologist, therapist. Group III - 137 patients (men) with hypochondriac and phobic syndrome in the structure of residual-organic disorders of radiation origin. The observation group included Chernobyl disaster liquidators in 1986 and continued to work with rotation method on the contaminated area. The irradiation dose was 0.025 - 0,03 Gy. Individual irradiation dose based on the official notations in medical documentation. The study of the mental state of liquidators took into account the system of risk factors, which included social, radiological, medical aspects. Social factors included hypokinesia, unsustainable diet, smoking, alcohol consumption. Radiological factors included external and internal radiation doses. Medical and clinical factors were the changes in

different organs and systems, confirmed by therapists, medical and functional – tolerance to physical activity, reduction of performance indications. We did not exclude from anamnestic data the level of stress in the work with rotational method, which manifested in insufficient preparation for work in extreme conditions, unusual physical and psychological stress, and difficulties in adapting to new living conditions, work, subjective perceptions of the victims of Chernobyl disaster about the inadequacy and unevenness of social benefits. The long duration of stress, lack of information about the radiation background and the received dose of irradiation led to further mental disorders and somatic pathology. All surveyed I-III groups were practically healthy to participate in the work of Chernobyl disaster elimination and did not seek medical help. The medical documentation (outpatient cards, certificates of medical commissions) confirmed it. All patients were male; the age was from 50 to 65 years. The exclusion criteria were diabetes, myocardial infarction or stroke in anamnesis, tumors, convulsive syndrome, malignant hypertension and angina pectoralis, alcoholism, dementia, severe somatic diseases, endogenous mental disorders. Each patient underwent a preliminary interview about the research objectives and agreed to use personal data.

Results of the study and their discussion. The patients with verified acute radiation sickness develop post-radiation organic and psychiatric disorders. The vegetative vascular and visceral stage of neurological and psychiatric pathology (3-5 years after irradiation) changed to cerebral-organic, cerebral-vascular and somatogenic neurological and psychiatric disorders ($\geq 5-10$ years after irradiation). Apathetic variant of organic personality disorder (microvascular neurological symptoms, personality changes, negative psychopathological symptoms, depression, and cognitive deficiency) is characteristic for long-term effects of acute radiation sickness [12]. The problem of health status of Chernobyl disaster liquidators remains relevant due to the significant spread of CNS diseases, which manifest by a wide range of psychiatric disorders from asthenic states to the exhaustion of adaptive capacity of brain structures. If in the first (1987-1989) years of the post-accident period the vegetative-vascular dystonia prevailed among the list of diseases, then, from 1992 to the present day, the early development of hypertension and cerebral atherosclerosis are dominant. They lead to cerebral blood circulation disorders, and, gradually, to the encephalopathy. Pathogenic mechanisms of development of cerebrovascular disorders of Chernobyl disaster liquidators manifest as a combination of discirculatory encephalopathy syndrome and hydrocephalic-hypertension syndrome. Radiation factors influence the central parasympathetic mechanisms, that lead to the deep brain systems lesion (brain stem, hypothalamus, rhinencephalon), that are important structural formations of the limbic-reticular complex. These systems refer to as vegetative trans-segmental formations, which lack specific vegetative centers, but have integrative systems, that regulate vegetative support of various forms of behavior. Vegetative disorders have both paroxysmal and permanent nature. Paroxysmal autonomic disorders are vegetative crises (sympathetic-adrenal, vago-insular and mixed), in modern literature, they refer to as panic attacks. Permanent vegetative disorders are not absolute stable indicators, but their frequent fluctuations, that we cannot record clinically, as they do not reach the level of vegetative crisis. Since 1990, the scientists covered the severity of psychiatric disorders in persistent vegetative-vascular dystonia and distinguished asthenic, asthenic-neurotic, asthenic-hypochondriac and asthenic-depressive syndrome. The mentioned data indicate the adverse impact of radiation on the mental health of large populations affected by the Chernobyl disaster. Over time, the number of people with organic brain disorders among the affected liquidators tend to increase, and the symptomatology – to enrich. In this regard, we devote our study to the transformation of chronic fatigue syndrome into an asthenic variant of psycho-organic syndrome with diencephalic crises. We can trace the correlation between the duration of work at the CNPP, the radiation dose and the severity of psychopathological symptoms. Among the variants of psycho-organic syndrome non-psychotic forms as a hypersthenic type of asthenic or dysthymic depression with predominance of affective disorders in combination with intelligence and memory disorders without severe intellectual deficiency. The common manifestations of it are the following: general inhibition of mental processes, narrowing of the circle of interests, monotonous hypothymia in combination with pessimistic assessment of the surrounding, dissatisfaction with own inability, weakness, it does not have daily fluctuations and is not due to external factors. Thus, ICD-10 classifies them as F 06.32 – organic depressive disorders. The spreading of combined cerebral-vascular pathology with perceptual-cognitive, cerebral asthenic, affective and personal disorders determine the further search for new approaches and medicaments with multicomponent pharmacological effects that regulate metabolic, neurotransmitter disorders in the organism, and reveal adaptation and compensation abilities.

Patients in I group with psycho-vegetative syndrome noted, that one of the obligatory symptoms at the beginning of the disease was persistent fatigue with impaired performance, which occurred on the

background of somatic well-being and lasted more than 6 months. Patients associated the onset of their disease with the effects of exogenous factors (radiation). Patients had the highest latency of sleep (time to fall asleep) and the lowest duration of sleep with frequent awakenings during the night. Headaches and sleep disorders were, undoubtedly interrelated, and one symptom exacerbated the severity of the other. Disturbances of night sleep aggravated the headache, which gradually influenced falling asleep and changed the character of the night sleep. On this background the patients noted a progressive decline in ability to work, so they often smoked to improve mental activity, and occasionally consumed alcoholic beverages to "reveal" the psychological stress. Clinical features of the disorders were due to hypertensive, hypotonic, cardiac type of vegetative-vascular dystonia and proceeded in the form of sympathetic adrenal and vago-insular crises. The main features of vegetative manifestations are the presence of both subjective and objective disorders and effects on different systems. Central to the study is the investigation of the autonomic crisis manifestations. In 21 patients (70%) sympathetic adrenal activity increased in the first half of the day, resulting in patients complaining of palpitations at rest, weight loss, white dermographism, pain and unpleasant sensations in the heart area, increasing of blood pressure, numbness and cooling in the extremities. In nine patients (30%), there were vago-insular crises, which included increased sweating, hyperthermia of the skin, red dermographism, bradycardia, tugs in the heart area, arrhythmia, pressure in the chest, and feeling of lack of air, shortness of breath, polyuria, and spastic constipation. The vegetative crisis appeared suddenly, within a few minutes developed the complex of symptoms of vegetative disorders, accompanied with a feeling of fear and anxiety. Duration of the attack - 20-30 minutes. Patients regarded their condition, as severe cardiac pathology. In intermittent period, the phobic-anxious component of emotional disorders prevailed. In addition to the mentioned above symptoms, functional neurotic components of the crisis ("feeling of lump in the throat", "numbness, weakness in the extremities", "increasing of the chills to the degree of tremor") – occurred in 15 patients (50%). Emotional-affective components (fear of death, which transformed into feeling of unreasonable fear) occurred in 12 patients (40%). Feeling of internal tension, irritability, vulnerability and frequent complaints of hypersensitivity to external stimuli (especially sound and light) appeared periodically. Cognitive components in the structure of crisis: feeling of "derealization", "depersonalization", sense of remoteness of sounds ("as in an aquarium") – in three patients (10%). Subsequently, all patients noted the attachments of ideation-level symptoms of asthenic disorders, which manifested with intellectual impairment: memory impairment, increased time for concentration, impaired playback in memory of events of one's own life, errors in performing mathematical operations. In the structure of psycho-vegetative syndrome, all patients had cephalic and insomnia syndromes. In 18 patients (60%) - cardiac, and in 12 patients (40%) – hyperventilation syndrome. According to the Spielberger test, patients had high levels of both reactive - 48 points, and personal anxiety - 53 points. Depression level (Beck test) was one, 5 points, indicating that 25 patients (83%) had subdepressive condition. The results of the questionnaire showed that the clinical manifestations of the psycho-vegetative syndrome amounted to 45 points on the vegetative questionnaire. Hyperventilation syndrome - 43 points. Asthenic questionnaire - 18 points. Sleep Quality Assessment Questionnaire - 17 points. The quality of life indicator reduced to 35%. The objective score for well-being in VAS was 1.6. Patients with headache slept less than those in the control group (6.1 versus 6.7 hours). In addition, they were more likely to wake up at night (1.98 and 0.96 times, respectively), at the same time, the patients felt correspondingly tired in the morning (100% vs. 36%). The clinical condition of the majority of patients of the II group with organic depression before the start of treatment was determined by a combination of cerebral asthenic phenomena (headaches, dizziness, tinnitus, hypertension, fatigue, exhaustion, sleep disorders), cognitive disorders of varying degrees (difficulties of concentration, impairment of the short- and long-term memory, intellectual productivity, general activity), as well as affective disorders (irritability, internal tension, fussiness, mood swings with anxiety, hypothyria), the severity of which was different. In 60.7% on initial stage occurred cephalgia, tension, cognitive, dyssomnia, vegetative disorders, increased hypersthenic type fatigue and fatigue during normal workload, decreased performance, which met the criteria of discirculatory encephalopathy (DEP) I stage. Page with DEP II stage reported emotional lability with decreased sad mood (dysthymia), intellectual and memory dysfunction, social and professional maladaptation. In 13, aggression, and intellectual accompanied 3% of patients with DEP III stage, dysthymic depression and memory disorders resembled pseudo-dementia. In the clinical manifestations, responders of the group III, as a component of the summation syndrome in investigated patients, reported manifestations of the cerebral asthenic complex of symptoms (irritability, fast mental and physical exhaustion, sensitivity, weather-sensitive migraine-type headache,

and dizziness, faint). They also reported hypochondriac overvalued ideas, and has the basis of poly-organ organic pathology, affecting cardiovascular, digestive, muscular-skeletal systems and manifested by palpitations, blood pressure fluctuations, hyperhidrosis, unpleasant physical sensations without clear localization, with diffuse, and in some cases migratory character. In addition, patients complained of unpleasant isolated sensations (contraction, flipping, pressure), coming from different parts of the body, or separate organs (senestopathies). Senestopathies were located in the chest and muscular-skeletal system. Argumentation of hypochondriac manifestations based on paresthesia's, senestopathies, pains, which had a long course, so patients had a tendency of self-observation, and underwent multiple investigations at doctors of different profiles. Therefore, they formed a stable confidence in the incurability of the disease, loss of hope for recovery, the idea of the futility of the future. Thus, based on the previous system we can establish the correlation between hypochondriac and phobic symptoms, namely: the onset of fear of death, fainting, and oncological disease (respectively thanato-, vertigo-, and cancerophobia). We noted following cognitive disorders: difficulty of concentration of attention, decreased short- and long-term memory, loss of ability to learn new information, which led to intellectual disability and the transition to the disability group.

The analysis of the structure and prevalence of long-term mental disorders in the victims of Chernobyl accident, their clinical typology and the peculiarities of these states were presented in the professional literature are in the agreement with our research [1, 2, 5, 6, 11, 13]. Thus, the typical clinical manifestations in patients with psycho-vegetative syndrome at the initial stage were the following complaints: mental and physical fatigue, rapid decrease in concentration of attention, increased irritability, increasing headache by type of compression or migraine, unilateral by localization, throbbing, insomnia at night and drowsiness during the day, which to some extent coincides with the results of other researchers [1, 2, 5]. Headaches and sleep disorders progressed and were not associated with somatic disease. Beside the mentioned complaints, there were usually the signs of vegetative-vascular disorders. Analysis of the clinical and psychological examination showed, that the most frequent vegetative manifestations were in the cardiovascular, respiratory system, gastrointestinal disorders were less likely to occur. Psycho-vegetative manifestations of this contingent of individuals tend to be resistant to progressiveness with the addition of symptoms of intellectual and memory impairment. The clinical condition of the majority of patients with organic depression before the start of treatment was determined by a combination of cerebral asthenic phenomena, cognitive disorders of varying degrees, as well as affective disorders, the severity of which was different. Responders of the with summation syndrome reported manifestations of the cerebral asthenic complex of symptoms. In our previous studies (1994-1998), we also noted a correlation of somatic-vegetative disorders with psychopathological symptoms in the liquidators of the consequences of the Chernobyl accident, which to some extent coincides with results of some scientists [6, 12].

Conclusion

On basis of the research, we can formulate the concept of post-Chernobyl syndrome as a polymorphic complex of symptoms, which includes psychopathological and neurological manifestations, related to the consequences of Chernobyl catastrophe. Mental disorders, correlated with somatic pathology, present in Chernobyl catastrophe liquidators, are exogenous-organic and progressive. These disorders had following stages: the initial period (vegetative dysfunctions) included sympathetic-adrenal and vago-insular crises, the final stage – intellectual and memory decline. In the I half of the day a sympathetic-adrenal crisis was noted in the clinical manifestations of vegetative disorders. In the II half of the day, the activity of parasympathetic nervous system was increased, resulting in vago-insular crises. The clinical manifestations of sympathetic-adrenal and vago-insular crises, aggravated by affective disorders: phobic, anxious, and depressive. The obtained results show, that psycho-vegetative syndrome with affective components is a central link in the structure of psychopathological manifestations. Thus, the psychosocial impact of stress in the Chernobyl disaster shows the importance of continuing to monitor the mental health of the population in order to establish a link between mental well-being, somatic illness and mortality.

References

1. Bromet E.J. Posledstviya chernobyil'skoy katastrofyi dlya psichicheskogo zdorovya - «Vestnik Assotsiatsii psichiatrov Ukrainyi» (02) 2012 - <http://www.mif-ua.com/archive/issue-34084/> - [In Russian].
2. Burtovaya EYu, Kantina TE, Litvinchuk EA, Cheban AYU, Akleev AV. Kharakteristika otdalennykh astenicheskikh rastroystv u lits, podverghshikhsya khronicheskomu radiatsionnomu vozdeystviyu. Klinicheskie, biologicheskie, psikhologicheskie aspekty

- psikhiatrii i narkologii. Materialy mezhrregionalnoy nauchno-prakticheskoy konferentsii s mezhdunarodnym uchastiem pod redaktsiyey D.M. Ivashinenko. 2016; 13-18. Dostupno na: elibrary.ru. [in Russian]
3. Vaynshteyn LA, Stozharov AN, Hayashida N, Takahashi J. Psikhologicheskie podkhody i analiz stressovykh sostoyaniy cheloveka pri deystvii radiatsionnogo faktora. Big Data and Advanced Analytics. 2019; 5: 92-99. [in Russian]
4. Kostyuchenko SI. Analiz obsuzhdeniya v fokus-gruppakh problem, svyazannykh so zdoroviyem i posledstviyami Chernobylskoy katastrofy, sredi zhitel'ey Beloy Tserkvi. Vestnik Assotsiatsii psikhiatrov Ukrainy. 2013; (01). Dostupno na: <http://www.mif-ua.com/archive/issue-34119/> - [in Russian].
5. Adams R.E., Guey L.T., Gluzman S.F., Bromet E.J. Psychological wellbeing and risk perceptions of mothers in Kyiv, Ukraine, 19 years after the Chernobyl disaster // Int. J. Soc. Psychiatry. - 2011 Nov. - 57(6). - 637-645.
6. Bromet E.J. Emotional consequences of nuclear power plant disasters. 2014; 106(2): 206-10.
7. Bromet E.J., Guey L.T., Taormina D.P., Carlson G.A., Havenaar J.M., Kotov R., Gluzman S.F. Growing up in the shadow of Chernobyl: adolescents' risk perceptions and mental health // Soc. Psychiatry Psychiatr. Epidemiol. — 2011 May. — 46(5). — 393402.
8. Bromet E.J., Havenaar J.M., Guey L.T. A 25 year retrospective review of the psychological consequences of the Chernobyl accident // Clin. Oncol. - 2011. - 23. - 297-305.
9. Bromet E.J. Mental health consequences of the Chernobyl disaster. J. Radiol. Prot. 2012; 32(1): 71-75.
10. Fukasawa M, Kawakami N, Umeda M, Miyamoto K, Akiyama T, Horikoshi N, Yasumura S, Yabe H. Environmental radiation level, radiation anxiety, and psychological distress of non-evacuee residents in Fukushima five years after the Great East Japan Earthquake: Multilevel analyses - SSM - Population Health journal. 2017. Available at: 2352-8273/© 2017. - P.1-12 - home page: www.elsevier.com/doi.org/10.1016/j.ssmph.2017.09.002.
11. Kim Y., Tsutsumi A., Izutsu T., Kawamura N., Miyazaki T., Kikkawa T. Persistent distress after psychological exposure to the Nagasaki atomic bomb explosion // Br. J. Psychiatry. - 2011. - 199. - 411-16.
12. Loganovsky KN, Zdanevich NA. Cerebral basis of posttraumatic stress disorder following the Chernobyl disaster. CNS Spectrums. 2013; 18(2): 95-102. doi: 10.1017/S109285291200096X. Epub 2013 Feb 27.
13. Matsuoka Y., Nishi D., Nakaya N., Sone T., Noguchi H., Hamazaki K., Hamazaki T., Koido Y. Concern over radiation exposure and psychological distress among rescue workers following the Great East Japan Earthquake // BMC Public Health. - 2012 May 15; 12: 249.
14. Samet JM, Patel SS The Psychological and Welfare Consequences of the Chernobyl Disaster: A Systematic Literature Review, Focus Group Findings, and Future Directions, April 18, 2011 Available at: <http://globalhealth.usc.edu> and www.greencross.ch.

Реферати

ОСОБЛИВОСТІ ВІДДАЛЕНИХ ПСИХІЧНИХ ПОРУШЕНЬ У ПОСТРАЖДАЛИХ ВІД АВАРІЇ НА ЧАЕС

Римша С.В., Рациборинська-Полякова Н.В., Гаврилук А.О.

У постраждалих внаслідок аварії на ЧАЕС 1986 року виявлені віддалені наслідки для психічного здоров'я, виявлена залежність від дози та взаємозв'язок між важкістю радіаційного ураження та проявами порушень психіки. Вивчення стану здоров'я ліквідаторів дозволяє розширити розуміння взаємозв'язку між ПТСР, депресією, ризиком внутрішніх захворювань та одужанням. За нашими даними центральною ланкою в структурі психопатологічних проявів є психовегетативний синдром з афективним супроводженням. Психосоціальний вплив стресу в результаті Чорнобильської катастрофи свідчить наскільки важливо продовжувати моніторинг психічного здоров'я населення з метою встановлення взаємозв'язку між психічним благополуччям, соматичними захворюваннями і смертністю.

Ключові слова: Чорнобильська катастрофа, стан здоров'я ліквідаторів, радіаційне ураження, психічні розлади внаслідок опромінення.

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ОСОБЕННОСТИ ОТСРОЧЕННЫХ ПСИХИЧЕСКИХ РАССТРОЙСТВ У ПОСТРАДАВШИХ ОТ АВАРИИ НА ЧАЭС

Рымша С.В., Рациборинская-Полякова Н.В., Гаврилук А.А.

У пострадавших вследствие аварии на ЧАЭС в 1986 году выявлено отдаленные последствия для психического здоровья, выявленная зависимость от дозы и взаимосвязь между тяжестью радиационного поражения и проявлениями нарушений психики. Изучение состояния здоровья ликвидаторов позволяет расширить понимание взаимосвязи между ПТСР, депрессией, риск внутренних заболеваний и выздоровлением. По нашим данным центральным звеном в структуре психопатологических проявлений является психовегетативный синдром с аффективным сопровождением. Психосоциальное воздействие стресса в результате Чернобыльской катастрофы свидетельствует, насколько важно продолжать мониторинг психического здоровья населения с целью установления взаимосвязи между психическим благополучием, соматическими заболеваниями и смертностью.

Ключевые слова: Чернобыльская катастрофа, состояние здоровья ликвидаторов, радиационное поражение, психические расстройства вследствие облучения.

Рецензент Єрошенко Г.А.

K.V. Rudenko, V.V. Lazoryshynets, O.M. Trembovetska, L.O. Nevmerzhytska,
M.O. Tregubova, P.A. Danchenko¹
Amosov National Institute of Cardiovascular Surgery NAMS of Ukraine
¹Bogomolets National Medical University

THE RESULTS OF SURGICAL TREATMENT OF PATIENTS WITH HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY AS A RISK FACTOR OF SUDDEN CARDIAC DEATH

e-mail: polinadanchenko12@gmail.com

The study includes 250 consecutive symptomatic patients with hypertrophic obstructive cardiomyopathy who underwent surgical extended myectomy, resection of anomalous chordal structures, mobilization of the papillary muscles and plication of the anterior mitral valve leaflet. The purpose of the study is to analyze the effectiveness of this technique and the immediate results of surgical correction. The results showed a statistically significant decrease of systolic pressure gradient on the left ventricular outflow tract, mitral regurgitation and an improvement in NYHA functional class. Sudden cardiac death (SCD) risk stratification was performed in 235 patients. The results of the study showed that the multi-stage correction allows to influence all links of pathological manifestation of the disease, but the question is how to predict the risk of SCD in already operated patients and how to protect them from life-threatening events?

Key words: hypertrophic cardiomyopathy, extended septal myectomy, surgical correction, sudden cardiac death

The work is a fragment of the research project "To improve the system of primary and secondary prevention of sudden cardiac death in patients with hypertrophic cardiomyopathy", state registration No. 0119U002019.

Hypertrophic cardiomyopathy (HCM) was initially described in living patients in 1959 by Morrow and Braunwald in a case series of 3 patients [10]. HCM is the most common sudden cardiac death (SCD)-related cardiomyopathy. The long-standing estimated prevalence has been 1 in 500 [7], with one study estimating the prevalence as high as 1 in 200 [14]. HCM is one of the most common causes of SCD in young athletes [5, 8].

In Ukraine, SCD statistics, both among general population and young people and athletes, remain uncertain. However, taking into account the prevalence of the disease (1:500 cases), the estimated number of patients with both obstructive and non-obstructive forms of HCM is about 75 thousand people.

The program on the study of the features of HCM diagnostics and treatment was established at the Amosov National Institute of Cardiovascular Surgery NAMS of Ukraine in 1993 when different methods of HCM treatment were applied. In the period from 1993 to 2019 there were applied and studied practically all invasive and non-invasive methods of HCM correction: dual-chamber (DDD) pacemaker implantation, classic Morrow technique, Bokeria-Borysov surgery, isolated mitral valve (MV) replacement, MV replacement with myotomy-myectomy, alcohol septal ablation (ASA). According to the analysis of the early and long-term results, implantation of dual-chamber pacemaker has shown its ineffectiveness and is now compared with placebo effect [9]. In addition, a considerable number of postoperative complications has attracted our attention in the surgical treatment group (iatrogenic complete AV block, iatrogenic defect of the interventricular septum (IVS), as well as damage of the aortic valve (AV) leaflets).

In view of the above, we are faced with the question of finding the optimal surgical treatment of HCM, which would be characterized by a minimal level of postoperative complications and, at the same time, high efficiency in reducing the risk of SCD.

In 2016, we implemented and completed the method of treatment of patients with HCM, proposed by Italian cardiac surgeon Paolo Ferrazzi (Monza, Italy), which presents a comprehensive multi-stage surgical approach to the HCM treatment.

The purpose of the work was to investigate the effectiveness of this technique, as well as to explore the early results of surgical correction in patients with obstructive HCM.

Materials and methods. The study included 250 consecutive symptomatic patients with obstructive HCM who underwent surgical extended myectomy, resection of the anomalous chordal structures, mobilization of the anterior and posterior groups of papillary muscles (PM) and plication of the anterior mitral leaflet (AML) in a period from 2016 to 2019.

The inclusion criteria for surgical treatment involved: systolic pressure gradient (SPG) on the left ventricle outflow tract (LVOT) ≥ 50 mmHg at rest or on physical exertion (or Valsalva maneuver) as well as heart failure symptoms resistant to medical therapy. Clinical features of 250 patients who were included to the study are presented in table 1.

Baseline characteristics of 250 examined patients

Parameters (N of patients = 250)	
Demographic data	
Age (years), mean±SD (median)	50.1±14.7(54)
Males, n (%)	126 (50.4)
Clinical features	
NYHA functional class III or IV, n (%)	93 (37.2%)
Previous ASA, n (%)	16 (6.4%)
Paroxysmal or persistent AF, n (%)	32 (12.8)
Pre-operative echocardiographic data	
SPG on LVOT at rest or on exertion, mmHg (mean±SD)	92.8±30.7
Moderate or severe MR, n (%)	182 (72.8%)
AF – atrial fibrillation; ASA – alcohol septal ablation; LVOT – left ventricle outflow tract; MR – mitral regurgitation; NYHA – New York Heart Association; SD – standard deviation; SPG – systolic pressure gradient.	

For the purpose of SCD risk stratification and according to the European Society of Cardiology (ESC) guidelines on HCM treatment all patients older than 16 years old mandatory underwent HCM SCD risk calculation in a 5-year period with the help of calculator developed by ESC (HCM risk-SCD calculator) [9]. According to the guidelines, patients with HCM were divided into 3 groups accordingly: low-risk group (SCD risk <4%), moderate-risk group (SCD risk ≥ 4 and <6%) and high-risk group (SCD risk $\geq 6\%$). In-hospital mortality included any death within 30 days after surgery.

An important component of preoperative planning in the adult group was routine computed tomography (CT) imaging with contrast and CT angiography or MRI with gadolinium (fig. 1A, 1B). In case of anomalies or coronary artery lesions, patients were referred for cardiac catheterization. In the children's group, a CT or MRI study was performed with gadolinium with subsequent calculations of the size of the right ventricle (RV), left ventricle (LV) and IVS to detect structural abnormalities, degree of fibrotic process and congenital heart defects.

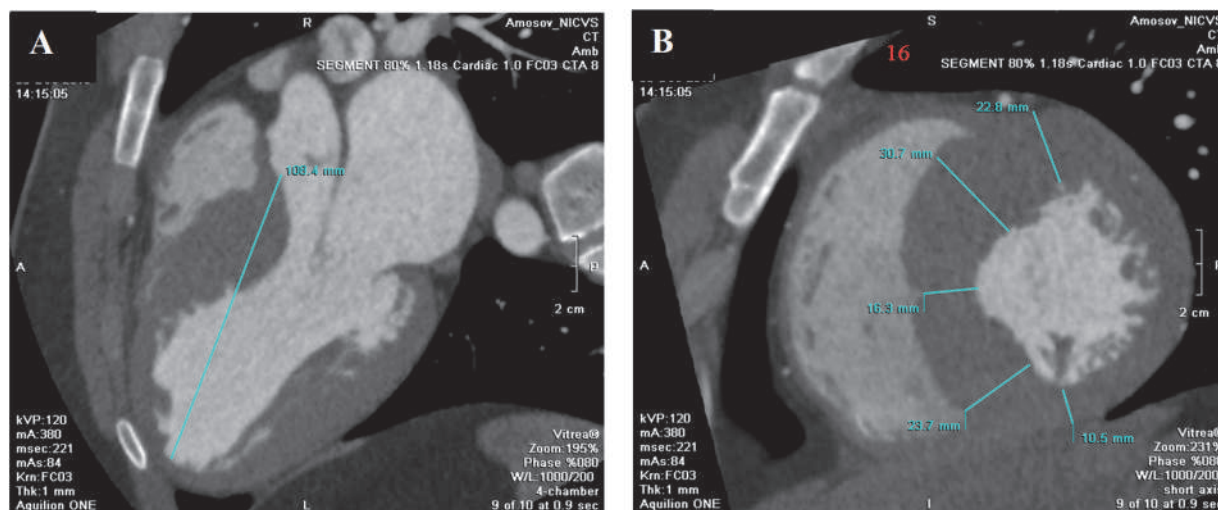


Fig. 1. Mandatory preoperative CT planning where the distance from the aortic annulus to the apex of the LV (LV depth) (A) and the dimensions of the LV and IVS at a distance of every 8 mm from the aortic annulus along the short axis are measured (B)

Surgical correction included a series of several mandatory steps: extended myectomy, resection of anomalous chordal structures of the MV, PM mobilization and, in case of necessity, AML plication with reduction of its area.

After induction of anesthesia, intraoperative transesophageal echocardiography (TEE) was performed to determine the extent of myectomy, as well as to assess the morphology of the MV and the presence of associated primary MV anomalies. TEE was repeated in the operating room immediately after stopping the cardiopulmonary bypass for the assessment of residual gradient on the LVOT and regurgitation on aortic and mitral valves, as well as for the detection of possible surgical complications such as iatrogenic perforation of the IVS or coronary fistula (fig. 2A, 2B).

Septal myectomy (often referred to as "extended myectomy" in modern literature) was performed during cardiopulmonary bypass with mild general hypothermia. Using the exposure through the oblique aortotomy the myectomy was begun from two longitudinal incisions in the basal part of the IVS, 2-3 mm below the AV, gradually continuing the resection more distally, to the base of the PM (equatorial zone), creating a trapezoidal muscular band which is wider towards the apex than at the subaortic level.

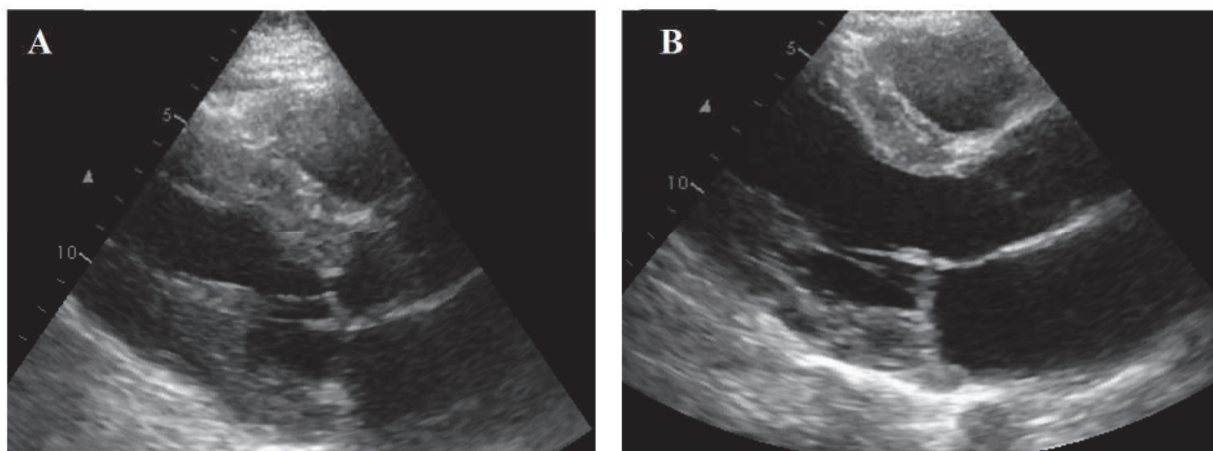


Fig. 2. Intraoperative TEE images before (A) and after (B) procedure, elimination of obstruction on the LVOT by excision of the fibromuscular band and resection of secondary (pathological) chordae.

In patients with LVOT obstruction accompanied by mid-ventricular obstruction due to hypertrophied PM or muscular bundles, an additional small resection was made at the base of the PM. After removal of the cardiac muscle (myectomy), an intervention on the subvalvular mitral apparatus was performed. Fibrous and muscular structures that connect PM with IVS or LV free wall were present practically in all patients with HCM and were limiting the mobility of the PM. Such structures, that can be identified only at the time of surgery, were systematically resected in each of the examined patient for the purpose of improvement of the PM mobility (PM mobilization). Anomalous chordal structures (pathological secondary chordae) or fibrous attachments between the AML and PM were found in the majority of patients with HCM. These structures routinely underwent resection, which increased the area of coaptation of the MV leaflets and prevented the phenomenon of systolic anterior motion (SAM) in the postoperative period. In cases of diastasis between the places of attachment of the primary chordae to the edge of the MV leaflet over 5 mm, this area was plicated.

The medians of the study were calculated according to the reverse Kaplan–Meier method. Comparisons of continuous variables were performed with the Wilcoxon test. Analyses of change for parameters evaluated before surgery and at the most recent evaluation were performed by means of the McNemar change test and sign test, for binary and continuous variables, respectively. All reported P-values are two-sided. SPSS statistical software (SPSS, Chicago, IL, USA) and MS Excel (Microsoft, Redmond, WA, USA) were used for the calculations.

Results and discussion. In this cohort study, the age of the patients ranged from 7 months to 78 years old (mean 50.1 ± 14.7 , median – 54 years). Among them, 12 patients were younger than 18 years old, and eight patients <12 years old. Out of 250 patients included to this study, 93 (37.2%) were in NYHA III–IV functional class at the moment of surgery.

The average cross clamp time accounted 80 ± 10.3 minutes. Septal myectomy was accompanied by AML plication in 146 (58.4%) and MV replacement in 3 (1.2%) out of 250 patients involved in the study. MV replacement was performed in patient with degenerative changes of the leaflets due to severe mitral regurgitation (MR) according to TEE data, as well as occurrence of the acute phase of infective endocarditis in late post-operative period. Other procedures that accompanied septal myectomy, including manipulations on the subvalvular apparatus, are listed in table 2.

Out of 250 patients studied, four (1.6%) underwent implantation of a cardioverter defibrillator (ICD) in the postoperative period to prevent SCD, while 10 (4%) patients underwent pacemaker implantation due to complete AV block. The average length of the in-hospital stay was 10 ± 3 days. The follow-up examination was performed at 3 months, 1, 3 and 5 years after surgery.

Reoperations were performed in 2 patients (0.8%) after 15 and 25 months accordingly after septal myectomy and involved MV replacement due to infective endocarditis.

Table 2

Surgical procedures that accompanied septal myectomy in 250 studied patients

Coronary artery bypass grafting, n (%)	24 (9.6)
Mitral valve replacement, n (%)	3 (1.2%)
AML plication, n (%)	146 (58.4%)
TV annuloplasty, n (%)	5 (2)
AVR, n (%)	6 (5)
ICD implantation, n (%)	4 (1.6)
Robisecek procedure	1 (0.4)
MV subvalvular apparatus	
Resection of the secondary(pathological) chordal attachments between AML and PM of the LV, n (%)	241 (96.4)
Resection of the anomalous ingrown PM to AML, n (%)	11 (4.4)
Resection of fibro-muscular structures between PM and IVS or LV free wall, n (%)	175 (70)
AML – anterior mitral leaflet; AVR – aortic valve replacement; ICD – implantable cardioverter-defibrillator; IVS – interventricular septum; LV – left ventricle; MV – mitral valve; PM – papillary muscle; TV – tricuspid valve	

Out of 250 patients studied, 4 (1.6%) died in the early post-operative period. In total, one case of death associated with chronic respiratory failure in a 65-year-old patient 11 months after surgery and one case of a SCD in a 20-year-old patient 13 months after correction were recorded during follow-up (table 3).

Table 3

Main cardiovascular events after septal myectomy in 250 studied patients

Early (≤30 days after myectomy), n (%)	
Mortality	4 (1.6)
Pacemaker implantation	6 (2.4)
Left bundle branch block	7 (2.8)
Late (≥30 days after myectomy), n (%)	
Pacemaker implantation	4 (1.6)
ICD implantation	4 (1.6)
MV repair	0
MV replacement	2 (0.8)
Cardiovascular death	0
Sudden cardiac death	1 (0.4)
Acute cerebrovascular event (ischemic stroke)	0
Respiratory failure	1 (0.4)
ICD – implantable cardioverter-defibrillator; MV – mitral valve	

The following clinical and echocardiographic evaluation of the patients' condition was performed at the base of our Institute. The SPG on the LVOT was assessed before and after surgical intervention. According to the data obtained, the SPG decreased from 92.8 ± 30.7 mmHg (range 50-235 mmHg) before the surgery to 19.3 ± 8.7 mmHg after correction ($p < 0.001$). 17 patients (6.8%) had residual (≥ 30 mmHg) SPG on the LVOT at rest or on exertion. Out of 250 patients studied, 44 (17.6%) had residual SPG ≥ 25 mmHg. Data on NYHA functional class before and after surgery were evaluated in each of the patients involved in the study. Out of 250 patients, 93 (37.2%) of whom were in NYHA functional class III-IV prior to surgery, 154 (61.6%) improved their functional class to I-II at the last evaluation ($p < 0.001$). In addition, there was performed the assessment of MR by echocardiographic examination in patients before and after surgery and distributed on a scale from 0 to 4 (0 – MR is absent, 1 – mild MR, 2 – moderate MR, 3 – moderate-to-severe MR, 4 – severe MR). According to the results of transthoracic echocardiography done after surgery, patients with grade 3 and 4 MR were not identified. 25 (10%) patients with a 2 (moderate) degree of MR were observed, whereas before surgery, the number of patients who had moderate or severe MR was 182 (72.8%) out of 250 individuals ($p < 0.001$).

Among the group of patients included in the study, 16 (6.4%) patients had previously undergone ASA, which proved to be ineffective, and therefore, due to high residual SPG, patients were shown to have surgery. In the post-operative period, all 16 patients (100%) had a satisfactory clinical result of correction – SPG on the LVOT in each of them was < 25 mmHg.

The mandatory and the most important stage of the study was SCD risk stratification at 5-year period. Given the exclusion criteria that make it impossible to calculate the risk, out of 250 patients enrolled in the study, the risk of SCD was calculated in 235 individuals (95.2%). Out of 235 patients, 131 (55.7%)

were at low risk, 77 (32.8%) were at moderate risk, 27 (11.5%) were at high risk. In the high-risk group, the average percentage of SCD risk before surgery was 8.43%, while after correction the indicator was 3.78% ($p < 0.002\%$).

The guidelines of the American College of Cardiologists (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC) have recognized surgical septal myectomy as the gold standard and the primary method of treatment for patients with obstructive HCM.

Up to date, one of the largest series of patients who have undergone septal myectomy is registered in the Cleveland Clinic [2]. This study of a series of 699 patients operated from January 1997 to December 2007 showed the excellent efficacy and safety of the procedure with continuous improvement in symptoms. The mean preoperative maximum LV thickness was 2.2 ± 0.5 cm compared to 1.7 ± 0.5 cm after surgery. The mean preoperative SPG at rest and the peak SPG were 61 and 103 mmHg respectively, in contrast to the average peak gradient of 32 mmHg after surgery. No 30-day mortality was observed, and pacemaker implantation was required only by 7% of patients. In their population, 96% of patients remained asymptomatic or minimally symptomatic (81% NYHA class I and 15% NYHA class II) for an average follow-up of 6.2 years, and freedom from reoperation was 97%.

A critical factor is that HCM still remains to be a complex pathology and therefore requires multistage correction. In order not only to reduce the risk of SCD, but also to provide the patient with an adequate quality of life that will not differ from the quality of life of healthy people, the disappearance of symptoms of heart failure and improve well-being, we have to perform all mandatory stages of correction: extended septal myectomy, resection of secondary (pathological) chordae of the AML, mobilization of the PM and plication of the AML.

Our study has shown that by itself, the myectomy procedure can reduce the risk of SCD in patients with obstructive HCM. This view is shared by Schaff and colleagues [13], who in their work reported that the survival of patients after septal myectomy was higher than the survival of non-operated patients, and this better result was partly due to greater freedom from SCD.

Despite such advances, the issue of SCD prevention remains open. Does septal myectomy actually reduce SCD risk in patients with obstructive HCM? A recent study by Desai and colleagues [2] describes the risk of SCD in a group of 1809 patients with obstructive HCM and compares the observed rates of life-threatening events with those predicted in two different risk models. In addition, 64% of patients underwent septal myectomy. The authors observed a small correlation between the calculated risk score and the actual rates of SCD. In the group of patients who were predicted to be at high risk (9%) of developing SCD or ICD discharge, the 5-year event rate was 4.8%. In addition, life-threatening events were similar among the 3 categories of SCD risk, and after 5 years of follow-up, approximately two-thirds of the events occurred in patients previously classified as low-risk, calculated using the ESC SCD risk calculator.

Standard risk assessment according to the guidelines of the American Heart Association and the American College of Cardiology also had low predictive value, since 65% of events after 5 years occurred in patients without risk factors.

Thus, it is not surprising that the risk models developed for the heterogeneous population of patients with HCM cannot be applied to patients after myectomy, and there are several possible explanations for this. The ESC risk calculator includes SPG, left atrial size, and maximum LV wall thickness in addition to other clinical variables. It is expected that the risk score calculated for the patient with obstruction will change after the gradient on LVOT is relieved.

In addition, the follow-up of patients after myectomy confirms that gradient relief is associated with both a decrease in left atrial size and LV mass [11, 12, 13]. Thus, it is expected that the calculated risk of SCD for an individual patient will change after septal myectomy. Therefore, the question remains: how can one predict the risk of SCD in already operated patients? And how to protect operated patients from life-threatening events?

Conclusion

HCM is a complex pathology which contains several pathophysiological mechanisms that lead to heart failure and high risk of SCD. Multi-stage correction such as extended myectomy, resection of anomalous chordal structures of the MV, mobilization of the PM and plication of the AML allows to influence all links of pathological manifestation of the disease. Surgical septal myectomy not only effectively reduces SPG on the LVOT, decreases the degree of MR and improves the patient's functional class, but also significantly reduces the risk of SCD in patients with obstructive HCM.

References

1. Delmo Walter EM, Javier MF, Hetzer R. Long-term outcome of simultaneous septal myectomy and anterior mitral leaflet retention plasty in hypertrophic obstructive cardiomyopathy: the Berlin experience. *Ann Cardiothorac Surg.* 2017; 6(4):343–352. doi:10.21037/acs.2017.03.08
2. Desai MY, Bhonsale A, Smedira NG, Naji P, Thamilarasan M, Lytle BW, et al. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. *Circ.* 2013; 128(3):209–16.
3. Finocchiaro G, Papadakis M, Robertus JL. Etiology of sudden death in sports. insights from a United Kingdom Regional Registry *J Am Coll Cardiol* 2016; 67:2108-2115.
4. Harmon KG, Asif IM, Maleszewski JJ. Incidence, cause, and comparative frequency of sudden cardiac death in National Collegiate Athletic Association Athletes: a decade in review. *Circ* 2015; 132:10-19.
5. Marian AJ, Braunwald E. Hypertrophic Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circ Res.* 2017; 121(7):749–770.
6. Maron BJ, Haas TS, Ahluwalia A, Murphy CJ, Garberich RF. Demographics and Epidemiology of Sudden Deaths in Young Competitive Athletes: From the United States National Registry. *Am J Med.* 2016; 129(11):1170–1177.
7. Maron BJ, Nishimura RA, McKenna WJ, Rakowski H, Josephson ME, Kieval RS. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy: a randomized, double-blind, crossover study (M-PATHY). *Circ.* 1999; 99 (22): 2927-33.
8. Maron BJ. Clinical Course and Management of Hypertrophic Cardiomyopathy. *N Engl J Med.* 2018; 379(7):655–668.
9. Morrow AG, Braunwald E. Functional aortic stenosis; a malformation characterized by resistance to left ventricular outflow without anatomic obstruction. *Circ* 1959; 20:181-189.
10. Nguyen A, Schaff HV, Nishimura RA, Dearani JA, Geske JB, Lahr BD, et al. Determinants of reverse remodeling of the left atrium following transaortic myectomy. *Ann Thorac Surg.* April 18, 2018.
11. Nguyen A, Schaff HV, Nishimura RA, Dearani JA, Geske JB, Lahr BD, et al. Does septal thickness influence outcome of myectomy for hypertrophic obstructive cardiomyopathy? *Eur J Cardiothorac Surg.* 2018; 53:582-9.
12. O'Mahony C, Jichi F, Pavlou M. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014; 35: 2010-2020.
13. Schaff HV, Nguyen A. Does septal myectomy reduce risk of sudden cardiac death in patients with hypertrophic cardiomyopathy? *J Thorac Cardiovasc Surg.* 2018; 156(2):748–749.
14. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspectives on the prevalence of hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2015; 65:1249-1254.

Реферати

**РЕЗУЛЬТАТИ ХІРУРГІЧНОГО
ЛІКУВАННЯ ПАЦІЄНТІВ З ОБСТРУКТИВНОЮ
ФОРМОЮ ГІПЕРТРОФІЧНОЇ КАРДІОМІОПАТІЇ
ЯК ФАКТОРУ РИЗИКУ РАПТОВОЇ
СЕРЦЕВОЇ СМЕРТІ**

**Руденко К.В., Лазоришинець В.В., Трембовецька О.М.
Невмержицька Л.О., Трегубова М.О., Данченко П.А.**

Дослідження включає 250 послідовних симптоматичних пацієнтів з обструктивною формою гіпертрофічної кардіоміопатії (ГКМП), яким було виконано хірургічну розширену мієктомію, резекцію аномальних хордальних структур, мобілізацію папілярних м'язів та пликацію передньої стулки мітрального клапана. Мета роботи – провести аналіз ефективності даної методики, а також вивчити безпосередні результати хірургічної корекції у пацієнтів з обструктивною ГКМП. Результати роботи показали статистично значуще зниження систолічного градієнта тиску на вихідному тракті лівого шлуночка, зменшення ступеня мітральної регургітації та покращення функціонального класу NYHA. У 235 пацієнтів проведено стратифікацію ризику раптової серцевої смерті (РСС). Результати дослідження показали, що проведення багатоетапної корекції дозволяє вплинути на всі ланки патологічного прояву даного захворювання, проте постають питання, як спрогнозувати ризик виникнення РСС у вже прооперованих пацієнтів і як захистити їх від життєзагрозливих подій?

Ключові слова: гіпертрофічна кардіоміопатія, розширена септальна мієктомія, хірургічна корекція, раптова серцева смерть.

Стаття надійшла 22.06.2019 р.

**РЕЗУЛЬТАТЫ ХИРУРГИЧЕСКОГО
ЛЕЧЕНИЯ ПАЦИЕНТОВ С ОБСТРУКТИВНОЙ
ФОРМОЙ ГИПЕРТРОФИЧЕСКОЙ
КАРДИОМИОПАТИИ КАК ФАКТОРА РИСКА
ВНЕЗАПНОЙ СЕРДЕЧНОЙ СМЕРТИ**

**Руденко К.В., Лазоришинец В.В., Трембовецкая Е.М.,
Невмержицкая Л.А., Трегубова М.А., Данченко П.А.**

Исследование включает 250 последовательных симптоматических пациентов с обструктивной формой гипертрофической кардиомиопатии (ГКМП), которым была выполнена хирургическая расширенная миэктомия, резекция аномальных хордальных структур, мобилизация папиллярных мышц и пликация передней створки митрального клапана. Цель работы – провести анализ эффективности данной методики, а также изучить непосредственные результаты хирургической коррекции у пациентов с обструктивной ГКМП. Результаты работы показали статистически значимое снижение систолического градиента давления на выходном тракте левого желудочка, уменьшение степени митральной регургитации и улучшение функционального класса NYHA. У 235 пациентов проведено стратификацию риска внезапной сердечной смерти (ВСС). Результаты исследования показали, что проведение многоэтапной коррекции позволяет повлиять на все звенья патологического проявления данного заболевания, однако возникают вопросы, как спрогнозировать риск возникновения ВСС у уже прооперированных пациентов и как защитить их от жизнеугрожающих событий?

Ключевые слова: гипертрофическая кардиомиопатия, расширенная септальная миэктомия, хирургическая коррекция, внезапная сердечная смерть

Рецензент Старченко І.І.

O.V. Savchuk, N.V. Hasiuk¹, O.V. Klytynska², G.A. Yeroshenko³, M.S. Zaliznyak¹
 Interregional Academy of Personnel Management, Kiev, Ukraine, ¹Ternopil State Medical
 University, Ternopil, Ukraine, ²Uzhhorod National University, Uzhgorod, Ukraine
³Ukrainian academy of medical dental, Poltava, Ukraine

CLINICAL AND MORPHOLOGICAL ASPECTS OF COMPLEX TREATMENT OF GENERALIZED PERIODONTITIS

e-mail: gasyuk.natasha@gmail.com

The article presents scientific data on the substantiation of clinical effectiveness of the effectiveness of the use of the drug “Jen-metrohelur” in the complex treatment of generalized periodontitis. Thus, according to our clinical and morphological studies, the use of “Jen-metrohelur” in the treatment of generalized periodontitis is clinically effective. The justification for this provision is the results of complex clinical and morphological observations, positive dynamics of changes in PMA index (49.32 ± 1.98) and periodontal Russell index (3.89 ± 0.54) and changes in the functional status of segmental leukocytes in the dynamics of treatment. So, according to the results of our clinical and morphological studies, the use of the medication “Jen-metrohelur” in the treatment of generalized periodontitis is clinically effective. This provision suggests that in the generalized periodontitis, cells of the inflammatory process together with disorganized cells of the epithelium, connective tissue of the gums and periodontium and bacteria form specific kinds of infiltrates in the periodontal tissues, the nature of these infiltrate initiates the incidence of relapses in the generalized periodontitis in patients.

Keywords: generalized periodontitis, gums, periodontal pockets, cells.

The article was made within the framework of the research work of the «Development of new individualized approaches to the diagnosis, treatment and prevention of dental diseases in patients with primary and secondary lesions of oral tissues based on the study of their pathogenetic mechanisms», №0117U003024.

Currently, periodontal diseases is an important issue of contemporary dentistry, since it is accompanied by pronounced morphofunctional disorders of the dentoalveolar system and is characterized by polyetiology and cascade of metabolic disorders [2].

The prevalence of generalized periodontitis in various countries is quite high [1].

Various systematic and clinical-morphological forms of generalized periodontitis are distinguished, depending on the etiology, the nature of the clinical course and immune response [8, 10]. The polymorphic clinical manifestations of this nosology are associated with different composition of the subgingival microflora. Factors, affecting antimicrobial response and updated metabolic status of the body are also crucial [4, 5, 7].

The problem of early diagnosis of generalized periodontitis, the development of effective measures for its prevention and treatment, aimed at achieving long-lasting positive outcomes, is one of the leading places in the priority areas of the development of state-of-the-art dentistry [11].

The issue of expanding indications for medical prophylaxis of periodontal tissue lesions and its complications in the risk groups is relevant to date.

Recent publications highlight the need to develop a special complex of diagnostic and therapeutic periodontal interventions, which includes professional oral hygiene with grinding-in and polishing of the dental cervixes and roots, surgical interventions in the periodontal tissues with the use of tissue-compatible osteoplastic agents for alveolar bone regeneration, orthodontic and prosthetic treatment on indications [9].

This provision initiates the search for a comprehensive approach in the treatment of generalized periodontitis by expanding and applying the spectrum of medications of local action.

The purpose of the study was at substantiation the clinical effectiveness of the use of “Jen-metrohelur” (JenDental-Ukraine LLC) medication in the complex treatment of generalized periodontitis.

Methods and Material. During the first visit, dental status was studied using the conventional criteria; the resulting data were subsequently recorded in the 0-43/o outpatient card of a dental patient with mandatory indication of the oral hygien index, calculated according to J.C. Green, J.R. Wermillion (1964), and papillary-marginal-alveolar (PMA) index, C. Parma modification (1960).

ENT-diseases, gastrointestinal diseases, biliary diseases, cardio-vascular diseases, diabetes mellitus and other endocrine lesions, purulent-septic processes, tuberculosis, smoking, excessive use of alcohol and spicy food, use of chewing gum were excluded in the patients at the time of the study, taking into account their past medical histories.

The material was collected from periodontal pockets of patients with exacerbated generalized periodontitis during their first visit and in the dynamics of treatment with “Jen-metrohelur” medication, using a sickle-shaped burnisher. Subsequently, the collected material was applied to a sterile slide. Drying of the smears was carried out by the method of dry fixation at room temperature, open air access, followed by Romanowsky-Giemsa staining and morphological quantitative and qualitative analysis of cellular composition.

“Jen-metrohelur” (JenDental-Ukraine LLC) medication consists of four active ingredients, namely chlorhexidine diacetate, metronidazole benzoate, hydrocortisone acetate and methyluracil, which are present in the most active form in the biopolymer matrix, which provides a prolonged release of ingredients into the surrounding soft tissues.

The findings of clinical and complex morphological studies were analyzed using a number of methods of biological statistics. The statistical processing of the resulting data was carried out using the licensed StatSoft *Statistica* software.

Absolute quantitative indices obtained during the examination of patients were processed by mathematical statistics with the calculation of the mean sample values (M) and errors of mean values (m) in the groups of subjects [3].

Parametric methods were applied to the indices with normal distribution. Compliance with the normal distribution was verified by the Shapiro-Wilk test [3]. In the cases where the distribution was not statistically different from normal, the statistical probability of changes in the indices in the independent samples was determined using the Student’s t-test. Differences were considered significant in conventional error in biomedical studies, $p < 0.05$ [3].

Results and Discussion: Patients with exacerbated generalized periodontitis complained of pain, bleeding and discomfort in the gums. The dental examination of patients revealed bright hyperemia and edema of the gingival papillae and gingival margin, and in some cases of the alveolar part of the gums. The depth of periodontal pockets ranged from (5.55 ± 0.13) , mainly in the area of the interdental fissure; the teeth were stable or with Class I, rare Class II teeth mobility. They were diagnosed with symptomatic gingivitis of the catarrhal clinico-morphological form and a recession of the gums with baring of dental cervixes and roots. The PMA index was (61.28 ± 2.33) , the Russel periodontal index was (4.23 ± 0.12) .

Periodontal pockets were filled with granulations and palpable serous-purulent exudate. Minor supra- and sub-gingival hard calculus deposits and significant dental plaque were found in periodontal pockets and on the dental crowns surface, respectively.

During the first visit of a patient with exacerbated Stage I- II generalized periodontitis, after performing professional oral hygiene using an ultrasonic scaler (or by mechanical method, if necessary), followed by polishing the roots, antiseptic sanitization with 0.05% chlorhexidine solution and drying of periodontal pockets with paper pins, the gel was administered into each periodontal pocket using a plastic nozzle, included in the kit. Initially, the gel was first administered into the deepest compartment of the periodontal pocket, subsequently filling the pocket to the gingival edge (Fig. 1, Fig. 2).

The patients were recommended to avoid drinking and taking food within 30 minutes after administration of the gel. Similar procedures were continuously performed for 14 days, with a daily interval.



Fig. 1 Administration of the gel into the deepest compartment of periodontal pocket using the plastic nozzle.



Fig. 2 Administration of the gel using the plastic nozzle, filling the periodontal pocket up to the gingival edge.

On day 14, clinical signs of positive dynamics were observed that were manifested by the absence of gingival pain, bleeding and unpleasant sensations. General clinical examination revealed slightly

cyanotic gums, no gingival edema except for palpable swollen gingival papillae. No exudate was detected in periodontal pockets on both jaws. The depth of periodontal pockets was (4.01 ± 0.11) . The values of the PMA index (37.32 ± 1.68) and the periodontal Russel index (3.25 ± 0.14) were significantly changed compared to the previous values of the above indices recorded during the first visit, $p < 0.05$.

The study of cellular composition of periodontal pockets of patients with exacerbated generalized periodontitis revealed hematogenous and epithelial cells at their first visit. Notably, single basal cells, which are normally absent, were found among the epitheliocytes [1]. They had a prismatic shape, elongated nucleus, peripheral nucleolus, sharp basophilia of the cytoplasm. The appearance of single basal cells makes it possible to confirm the severe epithelial lesions caused by the inflammatory process and demonstrates the course and severity of generalized periodontitis in the subjects. Signs of cytopathology were visualized in the cells in the form of numerous plasmolemma usurae. The peculiarity of the cytograms of the subjects was the absence of parabasal epitheliocytes, and, thereby, the cells of the second stage of differentiation.

The presence of intermediate cells was characteristic of cytograms of periodontal pockets. The cells, stained by Romanowsky-Giemsa, had a polygonal shape, optically clear cytoplasm, an eccentric elongated nucleus (Fig. 3a).

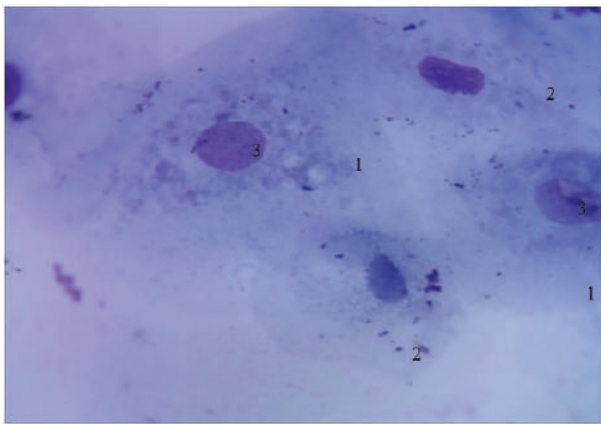


Fig. 3a. Cellular composition of the periodontal pocket in exacerbated generalized periodontitis. Romanowsky-Giemsa stain. Lens: 100×magnification; ocular lens: 10×magnification. 1 – intermediate cell; 2 – superficial cell; 3 – nucleus of intermediate cell.

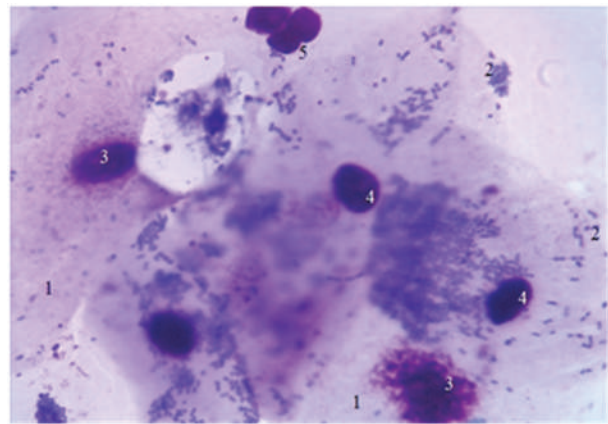


Fig. 3b. Cellular composition of the periodontal pocket. Romanowsky-Giemsa stain. Lens: 100×magnification; ocular lens: 10×magnification. 1 – type I superficial cell; 2 – type II superficial cell; 3 – nuclei of type I superficial cell; 4 – pyknotic nucleus of type II superficial cell; 5 – segmentonuclear leukocyte.

Noteworthy, intermediate epitheliocytes, which predominate in the cellular composition of subjects with intact gums [1] and are an indicator of normal maturation and differentiation of epitheliocytes, occur in the cytograms of this anatomical localization in a much smaller amount. The above indicates a disorder in the epithelium maturation caused by inflammatory process.

In the cellular composition of periodontal pockets superficial cells of two types are visualized and their identification is determined by the state of the nucleus (Fig. 3b).

Type I superficial epitheliocytes are represented by cells, which size is slightly larger than the intermediate ones. They had a clearly contoured centric nucleus of normal size.

Type II superficial cells, represented by superficial epitheliocytes with size, similar to Type I cells, though with pyknotic nucleus are characterized by clear contours, uncolored vacuoles, karyolysis and fragmentation with subsequent elimination from the cytoplasm.

The above findings suggest that prolonged inflammatory process in the periodontium causes disorders of epithelial keratinization, characterized by the absence of all representatives of the epithelial cell differon and altered ratio of cell types.

The findings of the study have been histologically and karyometrically confirmed at the stage of the analysis of histological structure of periodontal pockets [6]. A large number of neutrophilic granulocytes have been identified within hematogenous cells in periodontal pockets. In the exacerbated generalized periodontitis, the cellular composition of cytograms changes and is characterized by the predominance of neutrophilic granulocytes. It should be noted that most of them are degeneratively altered and were in a state of lysis, with hypersegmented nuclei, without junctions between them and specific granularity was absent.

Notably, quite numerous microbial compositions were visualized even in the cytoplasm of some cells in the form of cytoplasmic inclusions (Fig. 4a).

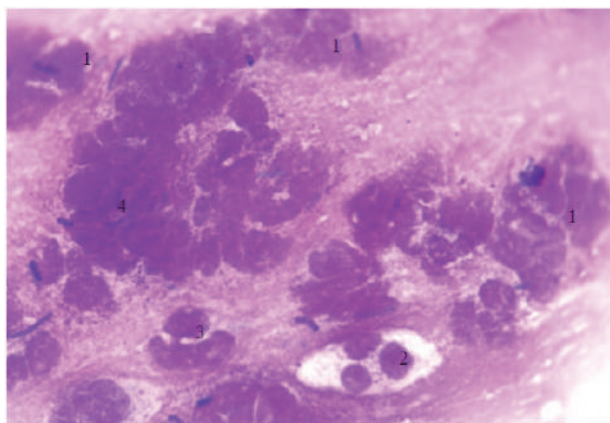


Fig. 4a. Cytogram of periodontal pocket in exacerbated generalized periodontitis. Romanowsky-Giemsa stain. Lens: 100×magnification; ocular lens: 10×magnification: 1 – lysed neutrophilic leucocyte; 2 – segmented nucleus; 3 – phagocytic-active neutrophilic leucocyte; 4 – cytoplasmic inclusions.

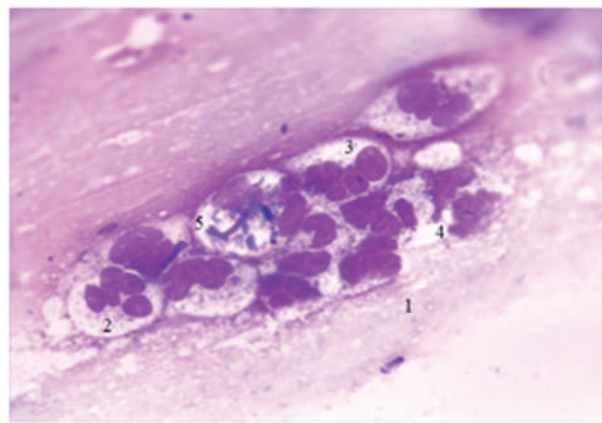


Fig. 4b. Cellular composition of the periodontal pocket after treatment with “Jen-metrohelur” (JenDental-Ukraine LLC) medication. Romanowsky-Giemsa stain. Lens: 100×magnification; ocular lens: 10×magnification: 1 – neutrophilic leukocytes; 2 – segmented nucleus; 3 – granularity; 4 – phagocytized neutrophilic leukocyte; 5 – inclusions of leukocyte cytoplasm.

On day 14 of treatment, the epithelial component of the cellular composition of the periodontal pockets remained unchanged, given that the number of cells with elements of cytopathology decreased, though the functional composition of neutrophilic granulocytes underwent significant changes.

The use of “Jen-metrohelur” (JenDental-Ukraine LLC) medication in the complex of local interventions enabled neutrophilic granulocytes to form cell clusters in the cellular composition of periodontal pockets. The number of lysed leukocytes decreased with clear visualization of the contours of phagocytic- active cells. Nuclei retained segmentation, and intra-cytoplasmic microorganisms were isolated (Fig. 4b).

Importantly, lymphocytes with large orbicular centric nucleus that occupied most of the cell were visualized in the cellular composition. The nucleus contained a significant amount of heterochromatin.

The above suggest correlation between cellular and humoral immunity of periodontal pockets, primarily due to polymorphonuclear leukocytes. These cells play a leading role in inflammatory responses and in protecting the body from the effects of foreign factors, including bacteria and their toxins.

The findings of the study with regard of restructuring of the cellular composition of periodontal pockets are confirmed by the several studies of predecessors [8] and show that penetration of periodontal pathogens leads to the formation of cytokines, a complex of highly active compounds, in the periodontal tissues, which are able to modify the activity of polymorphonuclear leukocytes and reduce their specific bactericidal properties. Of note, cytokines affect the periodontal tissues. Moreover, they cause subsequent activation of the cells that were involved in synthesis of cytokines, inhibit tissue repair and resynthesis of connective tissue, made by fibroblasts [6].

Conclusions

Thus, the findings of our clinical and morphological studies show that the use of “Jen-metrohelur” (JenDental-Ukraine LLC) medication in the complex treatment of generalized periodontitis is clinically effective, that is verified by the findings of the main clinical studies, as well as positive dynamics of changes in the PMA index (49.32 ± 1.98) and periodontal Russel index (3.89 ± 0.54) compared with the values of the above parameters at the first visit, and the findings of morphological study that showed a change in the functional status of segmentonuclear leukocytes in the dynamics of treatment. This provision suggests that, in generalized periodontitis, inflammatory cells, together with disorganized epithelial cells, connective tissue of the gums and periodontium, and bacteria form specific types of infiltrate in periodontal tissues, and the nature of these infiltrates initiates the recurrence rate of generalized periodontitis in patients.

References:

1. Gasyuk NV, Yeroshenko GA, Paliy OV. Suchasni uyavlennya pro etiologiyu ta patohenez khvorob parodonta. Svit medicini ta biolohiyi. 2013; 2 (38): 203-207. [in Ukrainian]
2. Shylyvskyy IV, Nemesh OM, Honta ZM. Suchasni pohlyady na etiologiyu ta patohenez zapalnykh zakhvoryuvan parodonta, yikh vzayemozvyazok iz patolohiyeyu sechovydilnoyi systemy (ohlyad literatury ta vlasni doslidzhennya). Bukovynskyy medychnyy visnyk. 2016; 20 (1): 224-227. [in Ukrainian]
3. Truhachova N. Meditsinskaya statistika. Fenikss. 2016; 336. [in Russian]
4. Ban A, Nemeth ZF, Szauter A, Soos S, Balasko M. Prevalence and severity of chronic paradontitis and oral mucosal lesions in chronic obstructive lung disease. Orvosi hetilap. 2018; 159 (21): 831-6.
5. Cheremisina VF; Berezhnyakova AI. Correlation of cytokine products levels in regulation mechanisms of bone tissue remodeling processes in paradontitis. World of medicine and biology. 2018; 64 (2):181-5.

6. Gasyuk NV, Yeroshenko GA. Feature of cellular composition of the gums in generalized periodontitis. World of medicine and biology. 2015, 1 (48): 17–20.
7. Kornman K S. The «innovator's dilemma» for periodontists. J. Periodontol 2010; 81: 646–649.
8. Kutepov IV, Lyashev YD, Artyushkova EB, Solin AV, Serikov VS, Lyashev AY, et al. Correction of acute parodontitis with indolicidin analogues. Bulletin of experimental biology and medicine. 2019; 167(1):47-9.
9. Müller F, Shimazaki Y, Kahabuka F, Schimmel M. Oral health for an ageing population: the importance of a natural dentition in older adults. Int Dent J. 2017;67(2):7-13.
10. Schmalz G. Release of prostaglandin E2, IL-6 and IL-8 from human oral epithelial culture models after exposure to compounds of dental materials. Eur. J. Oral. Sci. 2010; 108: 442-448.
11. Xiao L. New paradigms in inflammatory signaling in vascular endothelial cells. Am. J. Physiol. Heart Circ. Physiol. 2014; 306: 3: 317 – 325.

References

**КЛІНІКО-МОРФОЛОГІЧНІ АСПЕКТИ
КОМПЛЕКСНОГО ЛІКУВАННЯ
ГЕНЕРАЛІЗОВАНОГО ПАРОДОНТИТУ**
Савчук О.В., Гасюк Н.В., Клітинська О.В.,
Єрошенко Г.А., Залізняк М.С.

В статті приведені наукові дані стосовно обґрунтування клінічної ефективності використання препарату “Jen-metrohelur” у комплексному лікуванні генералізованого пародонтиту. В результаті комплексних клініко-морфологічних спостережень, показана позитивна динаміка змін індексу РМА ($49,32 \pm 1,98$) та пародонтального індексу за Расселом ($3,89 \pm 0,54$), а також зміни функціонального стану сегментарних лейкоцитів у динаміці лікування. Це положення дозволяє припустити, що при генералізованому пародонтиті клітини запального процесу разом з дезорганізованими клітинами епітелію, сполучної тканини власної пластинки ясен та бактеріями утворюють специфічні види інфільтратів, природа цих інфільтратів ініціює захворюваність рецидиви генералізованого пародонтиту у пацієнтів.

Ключові слова: генералізований пародонтит, ясна, пародонтальні кишені, клітини.

Стаття надійшла 15.05.2019 р.

**КЛИНИКО-МОРФОЛОГИЧЕСКИЕ АСПЕКТЫ
КОМПЛЕКСНОГО ЛЕЧЕНИЯ
ГЕНЕРАЛИЗОВАННОГО ПАРОДОНТИТА**
Савчук О.В., Гасюк Н.В., Клитинская О.В.,
Ерошенко Г.А., Залізняк М.С.

В статье приведены научные данные о обоснование клинической эффективности использования препарата “Jen-metrohelur” в комплексном лечении генерализованного пародонтита. В результате комплексных клиничко-морфологических наблюдений, показана положительная динамика индекса РМА ($49,32 \pm 1,98$) и пародонтального индекса по Расселу ($3,89 \pm 0,54$), а также изменения функционального состояния сегментоядерных лейкоцитов в динамике лечения. Это положение позволяет предположить, что при генерализованном пародонтите клетки воспалительного процесса вместе с дезорганизованными эпителиоцитами, клетками соединительной ткани собственной пластинки десны и бактериями образуют специфические виды инфильтратов, природа этих инфильтратов определяет течение и периодичность обострений генерализованного пародонтита у пациентов.

Ключевые слова: генерализованный пародонтит, десна, пародонтальные карманы, клетки.

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**K.V. Sedykh, S.M. Shevchuk, V.V. Shevchuk, Y.O. Klymenko
Poltava V.G. Korolenko National Pedagogical University, Poltava**

PECULIARITIES OF PSYCHOSOCIAL MALADJUSTMENT IN WOMEN RAISING CHILDREN WITH MENTAL AND PHYSICAL DISABILITIES

e-mail: S_Sevchuk@online.ua

Theoretical study of scientific sources allowed to define the concept of "child with mental and physical disabilities", their classification and generalize views on the phenomenon of maladaptation. An empirical study of psychosocial maladjustment of women raising children with mental and physical disabilities involved 274 mothers who have children of different ages with developmental disorders. The study lasted from June 2018 to March 2019 in the Podilsky district of Poltava, where 110 women were interviewed, in Lubny and Lubny district – 112 women and Kozelshchyna district of Poltava region – 52 women. Based on the analysis of the obtained results, it was found that in urban localities the number of mothers with signs of psychological maladjustment is lower (in Podilsky district of Poltava – 56-61%, in Lubny and Lubny district – 72.5-73%) than in rural areas (in Kozelshchyna district – 91-95%).

Key words: psychosocial adaptation, psychological maladaptation, child with limited mental and physical abilities.

The work is a fragment of the research project “Psychology of personality development in the educational space”, state registration No. 0119U002283.

In recent years, there has been a significant increase in the number of children with mental and physical disabilities who need lifelong state assistance, which is possible with effective cooperation with their parents. As mental and physical lesions, personal interests and aptitudes, these children can study, receive professional education and in the future be more or less adapted to social life. Modern medical and social policy of the state is aimed at helping people with mental and physical disabilities, provides them

with a number of complexes and rehabilitation measures. In Ukraine, as for the 2018-2019 school year, 11,866 students received general secondary education in inclusive classes; 6,230 students – in special classes; 37,787 students – in special schools; 12,115 students with special educational needs received the individual form of education; 8,417 inclusive classes are open in 3,790 secondary schools. The analysis of the dynamics shows that during 2016-2019 the number of inclusive classes increased by 3.1 times, the number of schools with inclusive classes – by 2.5 times, and the number of children receiving education there increased by 2.8 times [7].

The problem of children with mental and physical disabilities was considered by such domestic and foreign psychologists: I. Bekh, V. Bondar, V. Zasenka, Yu. Dolynnyi, D. Lubovsky, T. Iegorova, N. Kyseliyova, H. Kobernyk, O. Kuts, V. Lapshyn, I. Levchenko, O. Mastiukova, V. Pavlukhina, H. Popov, B. Puzanov, V. Syniov, Ie. Sobotovych, L. Fomichova, O. Khokhlyna, I. Chukhriy, M. Yarmachenko and others. Most sources present different types of classifications of children with mental and physical disabilities. According to the classification of V. Lapshyn and B. Puzanov, children with mental and physical disabilities have developmental disorders: hearing, vision, speech, musculoskeletal system, mental defectiveness, mental retardation, behavioral disorders, complex disorders of psychophysical development, as well as children with so-called complex defects (blind deaf-mute, deaf or blind children with mental retardation). H. Kobernik and V. Syniov developed their own classification of children with disabilities: children with persistent hearing impairment; with visual impairment; with persistent disorders of intellectual development on the basis of organic lesions of the central nervous system; with severe speech disorders; with complex disorders; with musculoskeletal disorders; with mental retardation; with psychopathic behaviors. The International Classification of Mental and Behavioral Disorders highlights mental retardation; mental development disorders; behavioral and emotional disorders that begin in childhood and adolescence; behavioral disorders; mixed behavioral and emotional disorders; emotional disorders specific to childhood; tic disorders; other behavioral and emotional disorders that begin in childhood and adolescence [6].

Studying problems of families raising children with developmental disabilities was carried out in the studies of V. Vyshnevsky, M. Holubeva, O. Horetska, I. Dzhugli, N. Mazurova, O. Makarenko, I. Mamaichuk, Ie. Mastiukova, K. Milutina, H. Mishina, A. Moskovkina, K. Ostrovska, L. Pechnikova, L. Solntseva, A. Spivakovska, V. Tkachova, M. Khimki, S. Khorosh, V. Chaves, H. Yusupova and others. The presence in the family of a child with mental and physical disabilities leads to a change in relationships within the family, as well as with society, which is associated with the psychological characteristics of the child's condition, as well as the presence of significant emotional stress in family members due to prolonged exposure to traumatic factors [4]. Most parents in this situation become helpless, and qualitative changes in such families are manifested on the psychological, social and somatic levels. Adaptive disorders are the most common in the system of psychological and psychiatric care. The development of adaptive disorders largely depends on the quantitative and qualitative characteristics of stress on the organism (strength and intensity of stress factors) and their individual significance for a particular person. The somatic state of the organism and the level of psychological protective barriers of the personality also play a role [5]. Thus, to date, certain approaches to the study of this problem have been formed, but the problems of psychosocial maladjustment in mothers raising children with mental and physical disabilities remain unstudied.

The purpose of the study was a comprehensive analysis of the peculiarities of psychological maladjustment in mothers living in Poltava region and raising children with mental and physical disabilities.

Materials and methods. During 2018–2019, a study was performed on the psychosocial maladjustment level of 274 mothers living in Poltava region and raising children with mental and physical disabilities. The scientific bases of the study were the theoretical provisions of medical and social psychology. In particular, the method of diagnosis of socio-psychological adaptation by K. Rogers and R. Diamond [3] and the scale for a comprehensive assessment of the degree of psychosocial maladjustment in various spheres, described by L. Herasymenko and A. Skrypnikov [1].

Results of the study and their discussion. Psychosocial maladjustment is a failure in the mechanisms of mental adaptation in acute or chronic emotional stress, resulting in partial or complete inability to adapt to social conditions and perform the usual role in society due to limited mental functioning. Maladjustment process unfolds on the principle of "vicious circle", where the trigger is mostly a sharp change in living conditions, the presence of a stable traumatic situation, which leads to the failure of adaptive mechanisms [1]. As of June 1, 2019, the number of children with mental and physical

disabilities in Poltava region was 4077 people. The distribution of children with developmental disorders by administrative-territorial units of the region is illustrated in table 1.

Table 1

**Number of children with mental and physical disabilities in the Poltava region,
as of June 1, 2019**

Administrative-territorial unit	Number of children with mental and physical disabilities
Velyka Bahachka district	58
Hadiach district	135
Hlobyne district	112
Hrebinka district	74
Dykanka district	57
Zinkiv district	84
Karlivka district	108
Kobeliaky district	111
Kozelshchyna district	60
Kotelva district	78
Kremenchuk district, Horishni Plavni, Kremenchuk	717
Lokhvytsia district	119
Lubny district Lubny	261
Mashivka district	72
Myrhorod district, Myrhorod	147
Novi Sanzhary district	109
Orzhytsia district	68
Pyriatyn district	60
Poltava district, Poltava	1234
Reshetylivka district	69
Semenivka district	69
Khorol district	106
Chornukhy district	37
Chutove district	43
Shyshaky district	89
Total in the region	4077

The hypothesis of the study was to identify the features of psychosocial maladjustment development at the regional level, taking into account various factors that determine its manifestations in women raising children with mental and physical disabilities.

Table 2

**Number of mothers with social and psychological maladjustment, raising children with mental
and physical disabilities**

Administrative-territorial unit	Number of studied mothers raising children with mental and physical disabilities, n	Number of mothers with social and psychological maladjustment, %
Podilsky district, Poltava	110	56
Lubny district and the city of Lubny	112	73
Kozelshchyna district	52	95

According to the results of methods of social and psychological adaptation diagnosis by K. Rogers and R. Diamond (table 2), it was established that the largest number of mothers with social and psychological maladjustment in Poltava region lives in Kozelshchyna district (95%), and the smallest – in the Podilsky district of Poltava (56 %).

The obtained results were confirmed by using the scale of psychosocial maladjustment by L. Herasymenko and A. Skrypnikov (table 3).

The scale of comprehensive assessment provides for six areas of psychosocial maladjustment: social and economic, social and informational, social and professional, interpersonal, family and parental. These areas are grouped into macro-social, meso-social and micro-social levels. The macro-social level includes social and economic and social and informational maladjustment. It was found that in Podilsky district 10.35% of mothers showed signs of social and economic maladjustment, in Lubny district – 12.46%, and in Kozelshchyna district – 14.46%. Since a child with developmental disabilities requires

significant financial expenditures for medical and psychological and pedagogical measures, the problem of material support is unresolved, as most of the interviewed women are unemployed, but they are constantly busy caring for the child. However, treatment and the search for new methods to improve the child's condition require significant financial resources.

Manifestations of social and informational maladjustment were recorded at the level of 9.79 % in the Podilsky district of Poltava, 10.87 % in Lubny district and 14.90% in Kozelshchyna district. These women have disorders of adaptation in the social environment as a result of the information factor, some women are not sufficiently aware of the peculiarities of their children's development, that is, they know the diagnosis, but do not pay due attention to the correction of these defects.

Table 3

Average indices of psychosocial maladjustment of mothers raising children with mental and physical disabilities according to the results of the method of L. Herasymenko and A. Skrypnikov

Scopes of psychosocial maladjustment	Mean values, $M \pm m$					
	Podilsky district of Poltava		Lubny district and the town of Lubny		Kozelshchyna district	
	No signs of maladjustment	With signs of maladjustment	No signs of maladjustment	With signs of maladjustment	No signs of maladjustment	With signs of maladjustment
Social and economic	14.84±2.03	31.01±2.13	13.45±2.41	37.39±3.24	7.31±2.81	43.39±4.54
%	4.95%	10.35%	4.48%	12.46%	2.44%	14.46%
Social and information	13.96±1.98	29.36±2.06	13.93±2.54	32.61±3.82	3.81±2.76	44.71±4.03
%	4.65%	9.79%	4.64%	10.87%	1.27%	14.9%
Social and professional	15.65±1.98	28.34±2.86	14.24±1.96	34.36±4.01	4.64±2.63	45.98±2.44
%	5.22%	9.45%	4.75%	11.45%	1.55%	15.33%
Interpersonal	14.96±1.54	30.41±2.84	14.48±2.02	38.36±3.64	4.89±2.61	46.71±2.20
%	4.97%	10.1%	4.83%	12.8%	1.63%	15.57%
Family	13.01±3.41	31.48±3.06	13.03±2.04	36.84±2.31	2.46±4.84	46.07±2.46
%	4.33%	10.5%	4.34%	12.28;	0.82%	15.35%
Parental	14.45±2.86	32.41±3.64	13.38±2.01	37.81±2.54	2.64±4.40	47.5±2.02
%	4.82%	10.8%	4.46%	12.6%	0.88%	15.8%
Total number of women	86.87±13.8	183.01±16.60	81.89±12.9	217.37±19.5	82.75±20.05	275.11±17.6
Total %	29%	61%	27.5%	72.5%	8.59%	91.41%

Indices of meso-social maladjustment indicate a social and professional and interpersonal adaptation disorder. The interviewed women of Kozelshchyna and Lubny districts and Podilsky district of Poltava have signs of social and professional maladjustment, 15.33%, 11.45% and 9.45% respectively. Such mothers are characterized by a violation of the implementation of their professional functions. Almost 90% of them are unemployed because they are forced to leave their professional activities, such women are professionally unrealized, do not have a positive dynamics of their career development. Caring for children eliminates or limits their professional activities, distorts their life goals and leads to the emergence of their own inferiority complex.

In the interpersonal sphere, almost 15.57% of women of Kozelshchyna, 12.8% of Lubny district and 10.1% of Podilsky district in Poltava have signs of maladjustment. After the birth of children with mental and physical disabilities, they became unfriendly and selective in contacts, narrowed the circle of their friends and even relatives due to the characteristic features of the child's condition and development, and even their fear or shame. The women did not deny the presence of anxiety, fear of communicating with other people, wary attitude towards all those who pay attention to their children.

Family and parental maladjustment are indicators of the micro-social level. 15.35% of respondents in Kozelshchyna, 10.5% in Lubny district and 12.28% in Podilsky district of Poltava have the signs of family maladjustment. As a result of the birth of a child with developmental disabilities, the already formed style of intra-family relations was disrupted, the expectations of family members related to the future of children were in vain, and a new understanding, acceptance of the situation and the acquisition of new values took a long period. It was found that most of these families are incomplete: 64–73% of women raise children on their own (the husband left the family after learning of the child's diagnosis, or they have the status of a single mother) and only 27–36% of women raise such children with their husbands. Although they noted that the main burden of child care is on them. Children's diseases, their mental state is psychogenic for parents, but primarily for mothers. The interviewed women

complained of fluctuations in blood pressure, insomnia, frequent and severe headaches, and thermoregulatory disorders. The older becomes the child with mental and physical disabilities (longer psychopathologic situation), the greater the deterioration of their mothers' health is: menstrual disorders, early menopause; frequent colds and allergies; cardiovascular and endocrine diseases; early graying; gastrointestinal problems. In addition, 60–68% of women noted conflicts with their parents or with the husband's parents due to the peculiarities of their child.

Parental maladjustment was typical for 15.8% of women surveyed in Kozelshchyna district, 12.6% in Lubny district and 10.8% in Podilsky district of Poltava. For such women, the birth of a child with mental and physical disabilities was perceived as the greatest grief and caused long-term stress, which had a strong deforming effect on worldviews and values. Interviewed women often had tantrums, depressed mood, fear for the future of their children, confusion, fatigue, loss of interest in themselves and others, aggression and tension, which can be a sign of maternal deprivation.

The results of the analysis of the psychosocial maladjustment scale results by L. Herasymenko and A. Skrypnikov, taking into account the maximum level of maladjustment of 300 scores, allowed to determine the average indices of psychosocial maladjustment in mothers raising children with mental and physical disabilities: Podilsky district of Poltava – 61% of 110 women surveyed, Lubny district and Lubny – 72.5% of 112 respondents and Kozelshchyna district – 91.41% of 52 respondents. In addition, the results of this method found that the highest levels of psychosocial maladjustment, regardless of the territorial affiliation of the surveyed women were interpersonal (10.1%–15.57%), family (10.5% –15.35%) and parental (10.8% –15.8%) relations.

Thus, the study results mainly confirmed and expanded the conclusions of V. Vyshnevsky and V. Tkachova that the birth of a child with mental and physical disabilities, and then its upbringing, education and communication is a long-term pathogenic psychological factor on the mother's personality, which can undergo significant changes, as depressive experiences can be transformed into neurotic personality development [8]. In addition, the results correlated with the research of O. Horetska [2], K. Milutina [4], S. Khorosh and L. Solntseva [8] regarding the fact that parents of children with disabilities use negative ways of communication; authoritarianism is often used in control. The conclusions of O. Horetska and K. Milutina on the preference for overprotection, symbiotic connection and emotional alienation were supplemented by ideas about the impact on the formation of this type of education, deterioration of psychosomatic and somatic health of mothers of such children.

Because our study included meso- and macro-level of maladjustment, its results expanded scientific understanding of the effects of economic and social systems on the behavior of women raising children with mental and physical disabilities, not just personal and family factors. The described influences are proved by the comparative analysis of results of a diagnostical technique of social and psychological adaptation by K. Rogers, R. Diamond and a scale of a comprehensive assessment of degree of psychosocial maladjustment in various spheres (L. Herasymenko, A. Skrypnikov).

The largest number of mothers with psychosocial maladjustment, who raise children with mental and physical disabilities, lived in Kozelshchyna district (91–95%), and the smallest – in Podilsky district of Poltava (56–61%).

It is reasonable to assume that this is influenced not only by the personal characteristics of mothers but also by social conditions, in particular the presence or absence of various organizations to provide assistance to families raising children with mental and physical disabilities. According to our data, all of these administrative-territorial units have Inclusive Resource Centers, but in addition in Lubny there was the Center for Development of Inclusive Type "Kozachok", Creative Center "Harmony", Center for Early Development "Smart", mini-school "Orange Sun", Development Center for preschoolers "Steps", Family Counseling Center "Arctur", Center for Modern Education "New Children", "Montessori Family", Center for Preschool Intellectual and Aesthetic Development of the Child "Indigo" and others, and in Poltava: Children's Club "Smile", Child Development Studio "Dzyha", Center for Correction and Child Development "Piznayko", Child Development Center "Wunder-child", Children's Development Center "Family House", Montessori Center "Sunflower", Family Development Center "Magic Key", Development Center "Child. Harmony. World", Children's Development Center "Chomusyky", Private School and Children's Development Center "Magic World", Children's Development Center "Happy Childhood", Family Center "Seven Palms", Family Psychological Counseling Center "Seven Elephants", Children's Development Center "Eureka" etc. Such organizations provide assistance not only to children, but also to parents.

Conclusions

On the basis of theoretical and empirical study of psychosocial maladjustment of mothers, raising children with mental and physical disabilities the comparison of indices in three administrative-territorial units of the Poltava region was carried out (Podilsky district of Poltava, Lubny and Lubny district and Kozelshchyna district) and it was found that in urban settlements the number of mothers with signs of psychosocial maladjustment is less than in rural areas by 30-39%. Prospects for further research are to study parent-child relationships in families raising children with mental and physical disabilities.

References

1. Herasymenko LO, Skrypnikov AM, Isakov RI. Diahnostyka psykhosotsialnoi dezadaptatsii zhinkov z depresyvnymy rozladamy. Svit medytyny ta biolohiyi. 2019; 1:34-38. [in Ukrainian]
2. Horetska O. Psykholohichni osoblyvosti stavlennia batkiv do ditei z osoblyvymy potrebamy. Osvita rehionu. 2013; 2: 289-294 [in Ukrainian]
3. Lemak MV, Petryshche VYu. Metodyka doslidzhennia sotsialno – psykholohichnoyi adaptatsii K. Rodzhersa - R. Daimonda. Metodychne vydannia Psykholohu dlia roboty. Diahnostychni metodyky. Uzhhorod Vydovnytstvo OleksandryHarkushi. 2011:85-90[in Ukrainian]
4. Miliutina KL. Vplyv batkivskoho stavlennia do ditei z rozladamy autystychnoho spektru na perspektyvu inkliuzyvnoho navchannia. Naukovyi visnyk Khersonskoho derzhavnogo universytetu. Seriya Psykholohichni nauky. 2017; 5(1): 98-102. [in Ukrainian]
5. SamoiloVA OV. Suchasni pohliady na problemu rozladiv adaptatsii (ohliad naukovo literatury). Psykhiatriia, nevrolohiia ta medychna psykholohiia. 2018; 9: 32-37. [in Ukrainian]
6. Stasiuk L. Teoretychni aspekty rozvytku ditei doshkilnoho viku z osoblyvymy potrebamy. Pedahohichni chasopys Volyni. 2015; 1:75-80. [in Ukrainian]
7. Statystychni dani [Elektronnyi resurs]. Dostupno na: <https://mon.gov.ua/storage/app/media/inkliuzyvne-navchannya/statistika-inklyuziya.pdf>. [in Ukrainian]
8. TkachioVA VV. Semia rebenka s ohranychennymy vozmozhnostyamy zdorovia: dyahnostyka y konsultyrovanye. Moskva: Natsyonalny knyzhnyi tsentr. 2014. 160 s. [in Russian]

Реферати

ОСОБЛИВОСТІ ПСИХОСОЦІАЛЬНОЇ ДЕЗАДАПТАЦІЇ У ЖІНОК, ЯКІ ВИХОВУЮТЬ ДІТЕЙ З ОБМЕЖЕНИМИ ПСИХОФІЗИЧНИМИ МОЖЛИВОСТЯМИ

Седих К.В., Шевчук С.М., Шевчук В.В., Клименко Ю.О.

Теоретичний аналіз наукових джерел дозволив визначити поняття «дитини з обмеженими психофізичними можливостями», їх класифікації та узагальнити погляди на явище дезадаптації. До емпіричного дослідження психосоціальної дезадаптації жінок, які виховують дітей з обмеженими психофізичними можливостями було залучено 274 матері, які мають дітей різного віку з вадами розвитку. Дане дослідження тривало з червня 2018 по березень 2019 р. на території Подільського району м. Полтави, де було опитано 110 жінок, у м. Лубни та Лубенському районі – 112 жінок та Козельщинському районі Полтавської області – 52 особи. На підставі аналізу отриманих результатів встановлено, що у міських населених пунктах чисельність матерів, які мають ознаки психологічної дезадаптації менша (у Подільському районі м. Полтави 56–61 %, у м. Лубни та Лубенському районі – 72,5–73%), ніж у сільських (у Козельщинському районі – 91–95%).

Ключові слова: психосоціальна адаптація, психологічна дезадаптація, дитина з обмеженими психофізичними можливостями.

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ОСОБЕННОСТИ ПСИХОЛОГИЧЕСКОЙ ДЕЗАДАПТАЦИИ У ЖЕНЩИН, КОТОРЫЕ ВОСПИТЫВАЮТ ДЕТЕЙ С ОГРАНИЧЕННЫМИ ПСИХОФИЗИЧЕСКИМИ ВОЗМОЖНОСТЯМИ

Седых К.В., Шевчук С.Н., Шевчук В.В., Клименко Ю.А.

Теоретический анализ научных источников позволил определить понятие «ребенка с ограниченными психофизическими возможностями», их классификации и обобщить взгляды на явление дезадаптации. К эмпирическому исследованию психосоциальной дезадаптации женщин, воспитывающих детей с ограниченными психофизическими возможностями были привлечены 274 матерей, имеющих детей разного возраста с нарушениями развития. Данное исследование продолжалось с июня 2018 по март 2019 г. на территории Подольского района г. Полтавы, где было опрошено 110 женщин, в г. Лубны и Лубенском районе – 112 женщин, Козельщинском районе – 52 человек. На основании анализа полученных результатов обнаружено особенность, что в городских населенных пунктах численность матерей, имеющих признаки психосоциальной дезадаптации меньше (в Подольском районе г. Полтавы 56–61%, в г. Лубны и Лубенском районе – 72,5–73%), чем в сельских (в Козельщинском районе – 91–95%).

Ключевые слова: психосоциальная адаптация, дезадаптация, ребенок с ограниченными психофизическими возможностями.

Рецензент Скрипніков А.М.

H.B. Semenyna, K.L. Shatylovykh, I.V. Fartushok, O.S. Komissarova¹, O.M. Yurchyshyn²
 Danylo Halytsky Lviv National Medical University, Lviv,
¹Shupyk National Medical Academy of Postgraduate Education, Kyiv,
²I. Horbachevsky Ternopil National Medical University, Ternopil

A NEW APPROACH TO THE COMBINATION THERAPY OF POLYCYSTIC OVARY SYNDROME

e-mail: yaroslavbuchko@gmail.com

The article presents the results of hormonal parameters and metabolic homeostasis in women with polycystic ovary syndrome (PCOS) and a treatment method developed on this basis. 67 women with PCOS (main group) and 50 healthy women (control group) were under the supervision. The results showed that in women with PCOS hormonal and metabolic disorders are significant, among which a prominent place is occupied by disorders of central regulation of ovarian function, hyperandrogenism, hypoprogesteronemia, insulin resistance on the background of impaired adrenal response to change. Taking into account the pathophysiological multifactority of PCOS and in order to avoid polypharmacy, patients with PCOS were offered a combined drug based on myo-inositol in combination with Lagerstroemia speciosa extract, vitamin D3, methyl folate and chromium. The treatment lasted for 3 months. Clinical evidence of treatment efficacy was spontaneous ovulation (25%) and positive attempts to induce ovulation in resistant patients (40%), probably due to improved ovum quality, hormonal balance, and reduced incidence of insulin resistance. As a result of treatment, 64% (43/67) of patients with PCOS had a menstrual cycle improvement. 33% (22/67) of women reported a reduction in hyperandrogenic dermatopathy. No side effects were observed during treatment.

Key words: polycystic ovary syndrome, myo-inositol, treatment.

The study is a fragment of the research project "Improving the monitoring of obstetric care in idiopathic miscarriage", state registration No. 0117U001080.

Polycystic ovary syndrome (PCOS), which incidence reaches 15% in women of reproductive age, is the most common cause of menstrual disorders, ovarian dysfunction and infertility [1]. The course of the disease is associated with insulin resistance (IR) and compensatory hyperinsulinemia (HI), which are central complications of PCOS. HI plays a leading pathogenetic role in hyperandrogenism (HA) and nonovulation in PCOS in both obese and slim women [11]. According to some provisions, patients with PCOS have a high risk of developing diabetes [9] and increased risk of cardiovascular profile: hypertension, dyslipidemia, subclinical inflammation and atherosclerosis [13].

Due to the specific pathophysiological role of insulin in the treatment of PCOS, sensitizers such as metformin, pioglitazone, and troglitazone were prominent. However, metformin, used in therapeutic doses, showed some side effects: in particular, diarrhea, flatulence, nausea. Because of this, a number of patients can not apply this method of treatment for a long time. Therefore, in recent years there has been an active search for other therapeutic corrections for IR and HI [8]. Recent studies have shown that one of the mechanisms of insulin deficiency is provoked by a mediator such as inositol phosphoglycan, and that a lack of myo-inositol in inositol phosphoglycans causes IR [4,5]. For these reasons, application of inositol-containing drugs in the treatment of metabolic disorders is appropriate.

The purpose of the study was to determine the effectiveness of hormonal and metabolic disorders correction in women with PCOS, taking into account the complex pathophysiology of the disease.

Materials and methods. 67 women with PCOS (main group) and 50 healthy women (control group) were under the supervision. PCOS was diagnosed according to the Rotterdam (ESHRE/ASRM) criteria (2003) [1]. The age of patients in both groups ranged from 23 to 29 years. Ultrasonographic examination was performed using the Aloka SSD-2000 apparatus. The presence of hirsutism was assessed on the Ferriman-Gallwey scale.

Determination of estradiol (E₂), progesterone (Pg), free testosterone (T_f), total testosterone (T_t), androstenedione (A), free androgen index (FAI), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxyprogesterone (17-OHP), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), insulin, cortisol (C), anti-mullerian hormone (AMH), inhibin B was performed by "ECLIA" electrochemiluminescence assay using automatic analyzers and reagents Cobas 6000 of "Roche Diagnostics" company (Switzerland). Venous blood glucose was determined by enzyme-linked immunosorbent assay using a Cobas 6000 analyzer and test system from Roche Diagnostics (Switzerland). Surrogate indices were calculated to assess IR, β -cell function, and insulin sensitivity [1]. The conclusion on IR was made on the HOMA index (>3.0): fasting glucose (mmol/l) \times fasting immunoreactive insulin (mcU/ml)/22.5 and Caro: fasting glucose (mg/dL)/fasting immunoreactive insulin (mcU/ml). To determine the metabolic characteristics, patients of control (n = 50)

and PCOS groups (n = 67) were divided into subgroups depending on body mass index (BMI): I – BMI less than 25 kg/m², II – BMI more than 25 kg/m² [1].

Patients with PCOS were treated with the combined drug myoxin oro (PharmaSuisse Lab. Str., Italy) based on the activating substances of myo-inositol 2000 mg, methylfolate 400 µg, banaba extract (*Lagerstroemia speciosa*) 48 mg, vitamin D₃ 1000 IU and 40 µg of chromium. The drug was prescribed for 1 sachet twice a day for three months. Examination of patients was performed before treatment and after three months, evaluated complaints, hyperandrogenic dermopathy, metabolic and hormonal parameters, changes in menstrual and reproductive functions.

The study provided for measures to ensure human health, human dignity and moral and ethical standards in accordance with the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine and relevant laws of Ukraine (conclusion of the Danylo Halytsky LNMU Commission on Bioethics).

Statistical processing of the obtained data was performed using standard methods of descriptive and categorical statistics and a package of certified programs Statistica for Windows 13.0 (Statsoft Inc., USA).

Results of the study and their discussion. Clinically, the combination of ovulation disorders and HA was the most typical for women with PCOS: oligo-/amenorrhea – in all patients, 100% (67/67), hirsutism – in 74% (50/67), infertility – in 100% (67/67).

Hormonal examination of women with PCOS showed a significant increase of LH in peripheral blood (p=0.0001), ovarian androgens, including the biologically active fraction of free androgens (p = 0.00001), a tendency to decrease the level of E₂ (p = 0.016) and insufficient content of Pg (p = 0.0053) (table 1).

Table 1

The state of hormonal balance in the examined women

Index	Control group (n=50)	PCOS (n=67)
LH, mIU/ml	3.3±0.7	11.7±1.7* p=0.0001
FSH, mIU/ml	4.7±1.3	5.5±2.1
PRL, ng/ml	10.1±2.7	9.87±0.73
DHEA-S, mcg/ml	177.2±18.7	237.6±22.3
E ₂ , pmol/l	163.0±17.9	91.7±17.6* p=0.016
SHBG, nmol/l	97.8±13.2	33.1±8.5* p=0.0001
T, nmol/l	1.3±0.1	3.7±0.3* p=0.00001
FAI	1.3±0.2	11.2±2.5* p=0.0001
Pg, nmol/l	65.0±16.4	18.4±3.5* p=0.0053
C, nmol/l	253.0±65.8	280.1±71.7
17-OHP, ng/ml	0.50±0.16	1.61±0.67
A, nmol/l	2.6±0.40	14.1±4.41* p=0.009
AMH, ng/ml	2.1±0.3	7.6±1.7* p=0.0012
Inhibin B, ng/ml	113.0±13.0	129.0±21.7

Note. * – the difference is significant compared to the control group.

According to our data, HA in PCOS was 76% (51/67), subnormal level of T_f was detected in 58% (39/67) of patients, T_t – in 34% (23/67), and DHEA-S – in 33% (22/67). Simultaneous increase of all three hormones was observed in 18% (12/67) of patients. AMH levels in the control group and in patients with PCOS differed significantly (p = 0.0012).

The results of metabolic studies revealed HI in 41% (16/39) of patients with PCOS and normal body weight and in 78% (22/28) of patients with PCOS and obesity (Table 2).

Table 2

Surrogate indices of fasting IR, M ± m

Indices	Control group		Main group	
	I, n = 28	II, n = 22	I, n = 39	II, n = 28
CARO	10.98±0.91	15.72±5.49	13.84±2.15	8.34±0.90 p ₁ =0.0375 p ₃ =0.0168
HOMA	1.28±0.09	4.29±1.36 p ₁ =0.0278	1.70±0.81	7.46±1.37 p ₁ =0.0001 p ₃ =0.0003
IR-HOMA	1.53±0.11	5.13±1.65 p ₁ =0.0293	2.04±0.14	4.13±0.95 p ₁ =0.0067 p ₃ =0.0293

Note. p₁ – reliability of the difference compared with subgroup I of the control group; p₂ – reliability of the difference compared with the subgroup II of the control group; p₃ – reliability index of the difference compared with subgroup I of the main group.

IR was more common in overweight patients due to the synergistic effect of HI inherent in obesity and PCOS. IR was more typical for patients with the male type of adipose tissue distribution at a value of WHR>0.85. Such a clinical sign as "acanthosis nigricans" was observed only in patients with IR and male obesity – in 39% (11/28).

According to the results of metabolic examinations, it should be said that the clinical phenotype of PCOS with excess body weight was characterized by fasting IR on the background of reduced insulin sensitivity, and the clinical phenotype of PCOS with normal body weight was characterized by a tendency to abdominal fat accumulation in the absence of excess body weight. These changes are possible risk factors for the formation of cardiovascular disease in women with PCOS, type II diabetes, and gestational diabetes during pregnancy [13].

Studies after treatment in patients of the main group showed a decrease in the content of LH ($p = 0.0078$), LH/FSH, T_e ($p = 0.0014$), FAI ($p = 0.0477$), A ($p = 0.0257$), AMH ($p = 0.008$), IR ($p = 0.0150$), HOMA index ($p = 0.0455$) and CARO ($p = 0.0105$) (table 3).

Table 3

Hormonal balance in women with PCOS before and after treatment, n = 67

Index	Before treatment	After treatment
LH, mIU/ml	11.7±1.7	6.1±1.3, $p=0.0078$
FSH, mIU/ml	5.5±2.1	4.9±1.8
PRL, ng/ml	9.87±0.73	8.03±0.43, $p=0.0285$
DHEA-S, mcg/ml	237.6±22.3	205.1±18.7
E ₂ , pmol/l	91.7±27.6	104.9±11.5
SHBG, nmol/l	33.1±8.5	43.0±7.6
T, nmol/l	3.7±0.3	2.1±0.4, $p=0.0014$
FAI	11.2±2.5	5.7±1.2, $p=0.0477$
Pg, nmol/l	18.4±3.5	23.3±2.7
C, nmol/l	280.1±71.7	271.0±80.1
17-OHP, ng/ml	1.61±0.67	1.03±0.52
A, nmol/l	14.1±3.41	6.2±1.01, $p=0.0257$
AMH, ng/ml	7.6±0.9	5.0±0.4, $p=0.008$
HOMA	5.72±1.11	3.04±0.75, $p=0.0455$
CARO	11.09 ±1.15	7.14 ±1.03, $p=0.0105$

Note: p –reliability of the difference in indices before and after treatment.

In 25% (17/67) of patients with PCOS who received myo-inositol-containing combination drug, spontaneous ovulation was restored, but any spontaneous pregnancies did not occur during the observation. During ovulation induction in the first cycle, 40% (27/67) of patients became pregnant (previously clomiphene-resistant), and 28% (19/67) of women continued to attempt reproductive function. 31% (21/67) of women had no reproductive intentions at the time of observation. As a result of treatment, 64% (43/67) of patients with PCOS had a menstrual cycle correction. 33% (22/67) of women reported a reduction in the manifestations of hyperandrogenic dermatopathy. Thus, myo-inositol is not only an effective but also a safe alternative in the treatment of patients with PCOS, as no side effects have been observed. The obtained positive effect can be explained by recalling the basics of clinical biochemistry of the drug components.

Myo-inositol plays an important role in the signaling pathways of cells [15]. Recent studies have shown that the effect of myo-inositol in PCOS may be associated with improved insulin sensitivity and a subsequent increase in intracellular glucose uptake [12]. According to the authors, during the preparation of patients with PCOS for in vitro fertilization, it was found that the use of myo-inositol and folic acid can increase the ovum number from 29 to 68.1% [14].

The problem of folic acid deficiency is relevant for our country, as it is necessary for the division and growth of new cells in the body, for the synthesis of melatonin and the metabolism of several important amino acids, is involved in cell DNA replication [3] and is necessary for patients with reproductive intentions. Corosolic acid, which is part of *Lagerstroemia speciosa*, effectively reduces the glucose content in human blood [10]. Ellaginatinin in *Lagerstroemia speciosa* (Lagerstremin) served as an insulin receptor agonist [6]. It was proposed that vitamin D status be associated with an androgenic profile in women with PCOS [7]. Pub Med, SCOPUS, and Google Scholar reported on six clinical trials involving 183 participants aged 18-41. Vitamin D supplementation has been shown to significantly reduce total testosterone, but did not affect free testosterone or SHBG levels [2]. The biological role of chromium, which is to regulate carbohydrate metabolism and blood glucose levels, is important since chromium is a component of low molecular weight organic complex – a glucose tolerance factor. Chromium normalizes the permeability of cell membranes to glucose, the processes of its application by cells and deposition, and in this regard functions together with insulin. It is believed that chromium forms a complex with insulin that regulates blood glucose levels. Chromium increases the sensitivity of cellular tissue receptors to insulin, facilitating their interaction and reducing the organism's need for insulin. High chromium deficiency can cause a diabetic condition [8].

Given that the PCOS pathophysiology is multicomponent, the disease is not limited to reproductive pathology and health problems in patients with age are exacerbated, hormonal drugs for them have limited administration, the application of myo-inositol in combination with methyl folate, Lagerstroemia speciosa, vitamin D₃ and chromium may be an alternative therapeutic option.

Conclusions

1. In women with PCOS hormonal and metabolic disorders are significant, among which a prominent place is occupied by disorders of central regulation of ovarian function, hyperandrogenism, hypoprogesteronemia, insulin resistance on the background of impaired adrenal response to change.

2. Taking into account the pathophysiological multifactority of PCOS and in order to avoid polypharmacy, patients with PCOS were offered a combined drug based on myo-inositol.

3. Clinical evidence of treatment efficacy with a drug based on myo-inositol in combination with Lagerstroemia speciosa extract, vitamin D₃, methylfolate and chromium is a reduction in the manifestations of hyperandrogenic dermatopathy, spontaneous ovulation (25%) and positive attempts to induce ovulation in resistant patients (40%), probably due to improved ovum quality, hormonal balance, and reduced incidence of insulin resistance.

Prospects for further research will concern the comparison of the effectiveness of the proposed treatment of PCOS with other therapeutic regimens.

References

1. Semenyna HB. Endokrynni ta obminno-metabolichni porushennya v zhinok iz syndromom polikistoznykh yayechnykv i novi mozhlyvosti yikhnyoyi korektsiyi. Reproduktyvna endokrynolohiya. 2016; 6(32):69-76.[in Ukrainian]
2. Azadi-Yazdi M, Nadjarzaden A, Khosravi-Boroujeni H, Salehi-Abargouei A. The effect of vitamin D supplementation on the androgenic profile in patients with polycystic ovary syndrome: systematic review and meta-analysis of clinical trias. Horm Metab Res. 2017; 49(3):174-179.
3. Eichholzer M, Tonz O, Zimmermann R. Folic acid: a public-health challenge. Lancet. 2016; 367:1352-1361.
4. Gard D, Tal R. Inositol treatment and ART outcomes in women with PCOS. Int J Endocrinol. 2016; 201:1-9.
5. Genazzani AD, Prati A, Santogni S. Differential insulin response to myo-inositol administration in obese polycystic ovarian syndrome patients. Gynecol Endocrinol. 2012; 28:969-973.
6. Hayashi T, Maruyama H, Kasai R, Hattori K, Takasuga S, Hazeri O et al. Ellagitannins from Lagerstroemia speciosa as activators of glucose transport in fat cells. Planta Med. 2012; 68(2):173-175.
7. Irani M, Seifer DB, Grazi RV, Irani S, Rosenwaks Z, Tal R. Vitamin D decreases serum VEGF correlating with clinical improvement in vitamin D-deficient women with PCOS: a randomized placebo-controlled trial. Nutrients. 2017; 9(4):334.
8. Iuorno MJ, Nestler JE. Insulin-lowering drugs in polycystic ovary syndrome. Obstet Gynecol Clin N Am. 2011; 128:453-464.
9. Kamenov Z, Kovarov G, Gateva A, Carlomagno G, Genazzani AD. Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance. Gynecol Endocrinol. 2015; 31(2):131-135.
10. Miura T, Takagi S, Ishida T. Management of diabetes and its complications with Banaba and corosolic acid. Evid Based Compl Alternat Med. 2012; 3(28):44-49.
11. Nestler JE, Jakubowicz DJ. Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian p450c17 alfa activity and serum androgens. J Clin Endocrinol Metab. 2017; 82:4075-4079.
12. Papaleo E, Unfer V, Baillargeon J.P. Myo-inositol in patients with polycystic ovary syndrome : a novel method for ovulation induction. Gynecol Endocrinol. 2017; 123:700-703.
13. Paradisi G, Steinberg HO, Hempfling A. Polycystic ovary syndrome is associated with endothelial dysfunction. Circulation. 2011; 103:1410-1415.
14. Simi G, Genazzani AR, Obino MR. Inositol and in vitro fertilization with embryo transfer. Int J Endocrinol. 2017; 217:1-5.
15. Venturella R. Assessment of the modification of the clinical, endocrinol and metabolic profile of patients with PCOS treated with myo-inositol. Minerva Ginecol. 2010; 64:239-243.

Реферати

НОВИЙ ПІДХІД ДО КОМПЛЕКСНОГО ЛІКУВАННЯ СИНДРОМУ ПОЛІКІСТОЗНИХ ЯЄЧНИКІВ

Семенина Г.Б., Шатилович К.Л., Фартушок Т.В., Комісарова О.С., Юрчишин О.М.

У статті представлені результати обстеження гормональних параметрів та обмінно-метаболического гомеостазу у жінок з синдромом полікістозних яєчників (СПКЯ) та розроблений на цій підставі метод лікування. Під спостереженням знаходилось 67 жінок з СПКЯ (основна група) та 50 здорових жінок (контрольна група). Результати показали, що у жінок з СПКЯ гормональні та обмінно-метаболическі порушення є вагомими, серед яких чільне місце посідають порушення центральної регуляції функції яєчників, гіперандрогенія, гіпопрогестеронемія, інсулінорезистентність на тлі порушеної адреналової реакції на зміни. Приймаючи до уваги багатofакторність патофізіології СПКЯ з метою уникнення фармакологічної поліпрагмазії пацієнткам з

НОВЫЙ ПОДХОД К КОМПЛЕКСНОМУ ЛЕЧЕНИЮ СИНДРОМА ПОЛИКИСТОЗНЫХ ЯИЧНИКОВ

Семенина Г.Б., Шатилович К.Л., Фартушок Т.В., Комиссарова О.С., Юрчишин О.М.

В статье представлены результаты обследования гормональных параметров и обменно-метаболического гомеостазу у женщин с синдромом поликистозных яичников (СПКЯ) и разработан на этом основании метод лечения. Под наблюдением находилось 67 женщин с СПКЯ и 50 здоровых женщин. Результаты показали, что у женщин с СПКЯ гормональные и метаболические нарушения весомые, среди которых главным образом есть нарушения центральной регуляции функции яичников, гиперандрогения, гипопрогестеронемия и инсулинорезистентность на фоне нарушенной адреналовой реакции на изменения. Принимая во внимание многофакторность патофизиологии СПКЯ с целью предупреждения фармакологической полипрагмазии

СПКЯ було запропоновано комбінований препарат на основі міо-інозитулу в комбінації з екстрактом *Lagerstroemia speciosa*, вітаміном D3, метилфолатом і хромом. Лікування тривало упродовж 3 місяців. Клінічним підтвердженням ефективності лікування є самостійні овуляції (25%) та позитивні спроби індукції овуляції у резистентних пацієток (40%), ймовірно, за рахунок покращання якості яйцеклітин, гормонального балансу та зменшення частоти інсулінорезистентності. У результаті лікування у 64%(43/67) пацієток з СПКЯ відбулось врегулювання менструального циклу. 33% (22/67) жінок повідомили про зменшення проявів гіперандрогенної дерматії. Побічних ефектів у ході лікування не спостерігали.

Ключові слова: синдром полікістозних яєчників, міо-інозитол, лікування.

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пациентки с СПКЯ был предложен комбинированный препарат, содержащий мио-инозитол, экстракт *Lagerstroemia speciosa*, витамин D3, метилфолат и хром. Лечение продолжалось в течении трёх месяцев. Клиническим подтверждением эффективности лечения были самостоятельные овуляции (25%), положительные результаты индукции овуляции у резистентных в прошлом пациенток (40%), вероятно, за счет улучшения качества яйцеклеток, гормонального баланса и уменьшения частоты инсулинорезистентности. В результате лечения у 64% (43/67) пациенток с СПКЯ произошло урегулирование менструального цикла. 33% (22/67) женщин сообщили об уменьшении проявлений гиперандрогенной дерматии. Побочных эффектов в ходе лечения не наблюдалось.

Ключевые слова: синдром поликистозных яичников, мио-инозитол, лечение.

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P.I. Tkachenko, O.B. Dolenko, N.M. Lokhmatova, S.O. Bilokon, Yu.V. Popeln
Ukrainian Medical Stomatological Academy, Poltava

STATE OF THE PALATE TISSUES REPARATIVE REGENERATION IN CHILDREN AFTER RADICAL URANOSTAPHYLOPLASTY

e-mail: olgadolenko500@gmail.com

The purpose of the work was to study the state of the soft palate tissues reparative regeneration after radical uranostaphyloplasty by assessing the clinical situation and morphological structure of the palatine mucosal periosteal flaps. A sophisticated complex of interrelated homeostasis disorders, which occurs after uranostaphyloplasty, significantly affects the process of scar formation and the nature of wound healing. The study of reparative regeneration processes in soft palate tissues on the 13-14th and 29-30th days after radical uranostaphyloplasty permits to predict the probability of forming a dense scar at early stages and to influence this process using the individual plan of treatment and prevention and rehabilitation measures for this category of patients.

Key words: palate, soft tissues, children, uranostaphyloplasty, reparative regeneration.

The work is a fragment of the research project «Integrative-differentiated substantiation for the selection of optimal methods for surgical interventions and volume of medical measures in surgical pathology of maxillofacial area», state registration No. 0116U003821.

Labial cleft and fissured palate remain widespread forms of congenital defects, and surgery is an integral part of their treatment comprehensive support. Surgical treatment of congenital clefts is accompanied by significant blood loss and intense nociceptive stimulation, which is largely due to traumatic surgery, profuse vascularization and a high concentration of nerve endings in this area. A complex set of interrelated homeostasis disorders that occurs after uranostaphyloplasty significantly affects the process of scar formation and the nature of wound healing [1, 2, 4].

Data reported in the literature indicate that the formation and reorganization of the scar lasts for a long time after scarring and epithelialization of the wound tissue surface, and therefore, in the short term after the wound epithelialization, the scar cannot be considered a complete physiological formation [7].

It is proved that the mechanism of sequential scar remodeling is based on a stable balance between the processes of the formed collagen destruction under the action of collagenase and the new collagen synthesis. When the intensity of collagenosynthesis prevails over collagenolysis, the normal process of scar formation is disturbed and it acquires hypertrophic properties, enlarges in volume and protrudes over the surface of the tissues surrounding it. Such scars cause various secondary deformations and functional disorders [5, 9].

Some scientists believe that one of the reasons for such scars formation after surgery is the presence of disturbances in the histological structures architectonics of the mucous membrane tissues in the area of the operating field. The leading role in the pathogenesis of pathological scarring is played by the disruption of close corporate links between tissue basophils, monocytes, and fibroblasts against the background of general and local autosensitization. Information about the recovery of the epithelium in the area of the postoperative wound healing is questionable, the period of 10 to 25 days is reported [8].

Recent studies have shown that the regeneration of tissues injured after uranostaphyloplasty, and then the function of the palatine-pharyngeal complex, is directly influenced by the state of the muscle

components of the soft palate, namely by the level of myogenin and myostatin mRNA expression. It has been found that with age the level of myogenic potential in a patient decreases, which was a medical-genetic justification of recommendations for early surgery and for determination of the preoperative medication correction algorithm to obtain higher functional results of surgical treatment [2].

However, at present there is no explicit methodological concept regarding the application of preventive components in this case aimed at preventing gross scarring. Indications and contraindications to the purposeful pharmacological correction of the scar formation process itself have not been determined, which has prompted us to carry out scientific work in this direction with the purpose of developing further pathogenetically justified preventive measures [11].

The purpose of the work was to study the reparative regeneration of the palate soft tissues after radical uranostaphyloplasty by assessing the clinical situation and morphological structure of the palatine mucosal- periosteal flaps.

Materials and methods. The results of the clinical work are based on the analytical generalization of a comprehensive examination in 27 children with congenital unilateral cleft palate at the age of 2 to 5 years (11 girls, 16 boys). Among these, in 15- (55.5%) the cleft defect was left-sided and in 12 ones - (44.5%) right-sided. The clinical examination included a visual examination and assessment of the wound condition on the 13th-14th and the 29th-30th days after surgery.

Substrate for morphological study were bioplates from scar tissue of the palate obtained in the area of the vascular-nerve bundle's exit, which were collected on the 13th-14th and the 29th-30th days from the time of uranostaphyloplasty by means of the needle to collect material proposed by the authors (fig. 1).

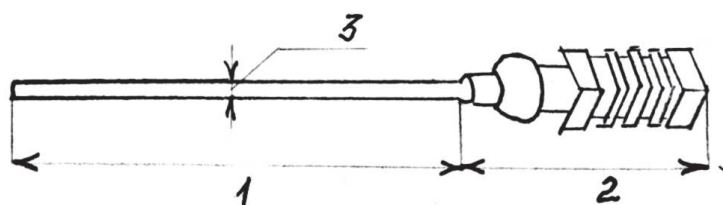


Fig. 1. Needle for taking soft tissue biopsies of the palate.

For its manufacture, a special needle was used for blood transfusion with a diameter of 3 mm, changing the angle of its bevel to 90° and making a fine sharpening at the end of the working part, which permitted to receive enough material for further morphological study.

For further study of the structural elements, it was subjected to pre-fixation in 4% solution of glutaric aldehyde in phosphate buffer at pH 7.4 for 60 min at the temperatures of 4°C. From the scar palatine tissues contained in EPON-812, semi-thin sections were obtained with MPS-2 rotary microtome and stained with a fresh 0.1% solution of methylene blue [3].

For the purity of the study, radical uranostaphyloplasty was performed by a single surgeon - Professor Tkachenko P.I. according to the method proposed by Professor Kharkov L.V. using one type of suture material. Medical support was carried out in compliance with the recommendations presented in the protocols of providing medical care for this category of patients [6].

Results of the study and their discussion. The studies presented in this paper are a continuation of our previous scientific work, where we studied the clinical situation in children with congenital malformations and the morphological structure of the mucosa-periosteal flaps of the palate before surgery and in the early postoperative period (on the 6th-7th days) after performing radical uranostaphyloplasty [4].

It is known that the structure of the oral mucosa changes strictly depending on the age. Each age period is characterized by its own inherent features, which must be taken into account when performing uranostaphyloplasty, when we are dealing with tissues compromised by the phenomena of dysontogenic disorders.

We also established it when these children revealed the presence of vacuolar dystrophy in the stratum spinosum of the biopsy epithelium sampled immediately before surgery, which, in our opinion, is a consequence of the combined effect of the microcirculatory bed disorders and increased antigenic load on the underdeveloped palatine tissue structures. Reduction of keratinization phenomena and manifestations of dystrophic processes in the epithelium in the form of acanthosis, testified to their modified response to physical load against the background of impaired chewing function and impaired blood circulation. Of course, these features of the mucous membrane structure in children with congenital malformations are a prerequisite for defective scar formation and epithelial regeneration in this area.

When comparing the results of morphological studies on biopsy specimens taken with unilateral, bilateral perforating and isolated medial palate clefts, we did not establish significant differences in their structure. As both methods of surgery were used in both observation groups, the healing in the postoperative period was followed by primary intension along the median line of the palate and by secondary intention in other areas.

It should be reminded that on the 6-7th day the wound along the medial line in the area of hard and soft palate is covered by a layer of fibrin, its edges had a crown of hyperemia up to 2 mm wide and were immersed compared to the surrounding tissues. In some areas, the bone tissue remained partially denuded.

Microscopically during this period of observation, pronounced leukocyte infiltration prevailed, which indicated the presence of an inflammatory component in the wound. It is necessary to point to the unity of the inflammatory and actually reparative components in a holistic reaction, since the proliferative phase of inflammation is also reparative. The inflammation and regeneration are separated conditionally, all phases of the process are overlapped. Conditionally separated are also regeneration and fibrosis, especially in the case of substitutional regeneration (fig. 2).

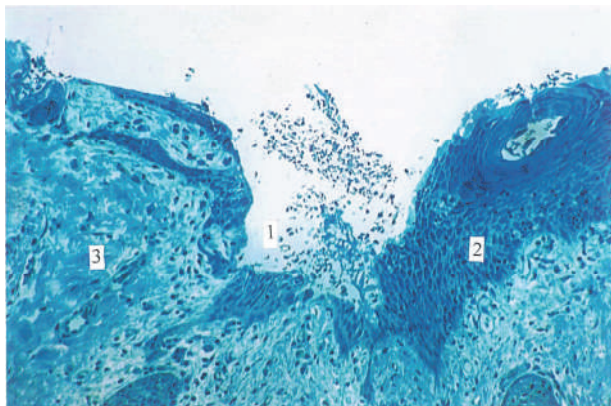


Fig. 2. Micrograph of a wound biopsy surface fragment in the area of surgical intervention in a child with congenital right cleft of palate on the 6th day. Patient B., medical history No. 2224. Semifine section. $3b \times 900$. Stain - methylene blue. The wound canal (1), epithelium infiltration (2), edema and swelling of collagen fibers in connective tissue (3) are determined.

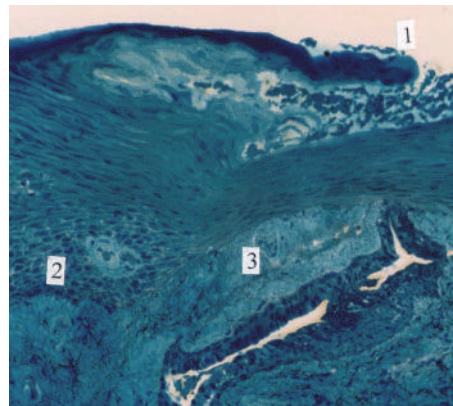


Fig. 3. Micrograph of a wound biopsy surface fragment in the area of surgical intervention in a child with congenital right cleft of the palate on the 13th day. Patient B., medical history No. 2224. Semifine section. $3b \times 900$. Stain - methylene blue. The wound canal (1), epithelial growth on top of the fibrin-erythrocyte clot (2), basal layers of the epithelium (3), connective tissue (4) are determined.

In the clinical aspect, on the 13th-14th day of the postoperative period, in most patients the crown of hyperemia around the scar was slightly pronounced, and the wound canal was completely filled with granulations, the volume of which increased, they were compacted over the entire surface and slightly overtopped the surrounding tissues level.

At that time, in two patients (7.4%) with unilateral perforating cleft, complete suture line disruption was observed in the area of the uvula, and in one case (3.7%), postoperative complication was observed in the form of partial divergence of sutures in the superficial layer of the mucous membrane of the oral cavity. hard and soft palate. Another patient (3.7%) was also found to have a partial suture line disruption in the same area with the formation of a residual defect.

In the morphological aspect, on the 13th-14th day, 87% of microslides showed initial signs of hemodynamic normalization in the operation area. At this time of the observation, the fibrous structures began to prevail over cellular elements. Thus, at this time in the wound there was a transformation of granulation tissue into connective tissue (fig. 3).

In parallel with the development of connective tissue and subsequent vascularization of the wound, the process of epithelialization is completed. It should be noted that in 34% of microslides the epithelium was infiltrated into the leukocyte-necrotic layer, i. e., in these cases there was no strong epithelialization, which indicated the inability of the granulation tissue to accept the epithelial structures on itself and the imperfection of its cellular composition at the time of observation.

In 66% of the microslides young granulation tissue was found, which filled both the primary and secondary defects that arose after the rejection of the microbotic zone and the wound surface cleansing. At this time of observation, the processes of concentric contraction of the wound edges to the center due to migration of the mucous membrane surrounding the defect to the granulation tissue and due to the off-wound intercalation, that means hyperplasia and hypertrophy of the mucous membrane, were taking place.

On the 29th-30th days, 15 children (55.6%) showed slight manifestations of swelling and hyperemia in separate isolated sites of scar tissue, which mostly had a pink color and was at the level of the surrounding unchanged soft tissue of the palate. The medial line scar became flatter and more flexible within the soft palate and the uvula.

On the 29-30th day of the postoperative period in all microslides there were signs inherent in the third phase of the wound healing process according to Shekhter A.B., namely the formation and rearrangement (remodeling or resimulation) of the scar [7].

During this period, the number of fibroblasts compared to collagen fibers reduced significantly. In 89% of microslides there were signs of the final stage in granulation tissue maturation, which was characterized by the development of collagen fibers, a gradual decrease in the number of blood vessels and cellular elements, the dehydration of tissues with the prerequisites for the restructuring of young connective tissue into the mature fibrous tissue. The edges of the wound were connected by a scar, which was

characterized by the presence of fibrous collagen tissue, without a characteristic orientation of connective tissue fibers in the scar. In this case, bundles of collagen fibers were presented in different directions (fig. 4).

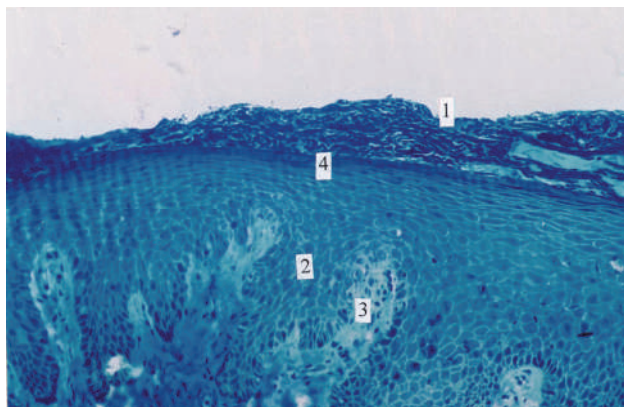


Fig. 4. Micrograph of a wound biopsy surface fragment in the area of surgical intervention in a child with congenital right cleft of the palate on the 30th day. Patient B., medical history No. 2224. Semifine section. $3b \times 900$. Stain - methylene blue. The epithelium surface is covered with fibrin (1), epithelial papilla (2), connective tissue papilla with the blood vessel (3), surface layers of the epithelium (4).

imperfection of its cellular composition and the inability of its scar tissue to accept it. In all other cases, the processes of concentric contraction of the wound edges to the center were observed due to migration of the mucous membrane surrounding the defect onto the granulation tissue and due to the off-wound intercalation.

On the 29th-30th day of observation, the scar tissues in their bulk had a pink color and were at the level of surrounding unchanged soft tissues of the palate. The medial line scar became flatter and more flexible within the soft palate and the uvula.

Morphologically, at this time, there was a slowing in the marginal epithelialization of the wound, which could contribute to the precocious maturation of granulation tissue and to the preconditions for the formation of denser scars.

In general, our results are consistent with those of other researchers [1, 4, 6, 10]. With regard to inflammation and adaptive responses, our findings correlate with the results of the analysis of intercellular interactions performed by Russian colleagues [7]. In Ukraine, the problems of the palatine soft tissues regeneration after uranostaphyloplasty were studied by Kharkov L.V. and Egorov R.I. [5, 6]. These researchers have studied in detail the energy processes and the level of myogenic potential in the tissues of the palate in children with its cleft. The results obtained by these authors were supplemented by the data on the healing process features in the postoperative wound at different stages of the palatine tissues regeneration after radical uranostaphyloplasty with support of traditional medical means, which are widely used in medical institutions of our country. Foreign colleagues [9, 10] note similar clinical and morphological characteristics of the wound process in the early postoperative period.

Conclusion

The study of the reparative regeneration state in the palatine soft tissues on the 13th-14th and the 29th-30th days after the radical uranostaphyloplasty by assessing the clinical situation and morphological structure of the palatine periosteal flaps permits to predict the probability of dense scar formation at early stages. It permits to deliberately influence this process by designing treatment and preventive and rehabilitation measures for individual treatment in this category of patients.

References

1. Hulyuk AH, Kohan LB, Demyd OI, Kryklyas VH, Dmytriyeva NB. Medyko-sotsialna rehabilitatsiya ditey z pryrodzhenoyu patolohiyeu oblychchya. Visnyk stomatolohiyi. 2015; 2: .54-60. [in Ukrainian]
2. Yehorov RI. Otsinka efektyvnosti veloplastyky v zalezhnosti vid metodyky operatsiyi ta stanu myaziv myakoho pidnebinnya [dysertatsiya]. Kyiv: Nats. med. un-t im. O.O.Bohomoltsya; 2017. 21s. [in Ukrainian]
3. Karupu VYa. Elektronnaya mikroskopiya.- Kyiv: Vyshcha shkola; 1984. 240 s. [in Russian]
4. Tkachenko PI, Dolenko OB, Lokhmatova NM, Bilokon SO, Dobroskok VO. Kliniko-morfologichna kharakterystyka ranovoho protsesu v rannomu pislyaoperatsynomu periodi pislya radykalnoyi uranostafiloplastyky. Svit medytsyny ta biolohiyi. 2018; 4(66): 113- 117. [in Ukrainian]
5. Kharkov LV, Yegorov RI. «Vozmozhnosi regeneratsii myshts myagkogo neba pri yego nesrashchenii v zavisimosti ot miogennogo potentsiala stvolovykh kletok», Azerbaijan Medical Journal. 2016; 4: 147-154. [in Russian]
6. Kharkov LV. Khirurgicheskoye lecheniye vrozhdennykh nezarashcheniy neba. Kyiv: Vyshcha shkola; 1992.- 210s. [in Russian]
7. Shekhter AB, Serov VV. Vospaleniye, adaptivnaya reaktsiya i disregeratsiya (analiz mezhkлетochnykh vzaimodeystviy). Arkhiv patologi. 1991; 7: 7-14. [in Russian]

8. Abdel-Aziz M, Khalifa B, Shawky A. Trans-oral endoscopic partial adenoidectomy does not worsen the speech after cleft palate repair. *Braz.J. Otorhinolaryngol.* 2016; 83 (4): 422-426.
9. Bhuskute AA, Tollefson TT. Cleft lip repair, nasolabial molding, and primary cleft rhinoplasty. *Facial Plast Surg Clin North Am.* 2016; 24 (4): 453-466.
10. De Ladeira PRS, Alonso N. Protocols in cleft lip and palate treatment: systematic review. *Plast Surg Int [Internet].* 2012. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3503280/>
11. Mostafa NZ, Doschak MR, Major PW, Talwar RJ. Reliable critical sized defect rodent model for cleft palate research. *Craniofacial Surg.* 2014; 42(8): 1840-1846.

Реферати

СТАН РЕПАРАТИВНОЇ РЕГЕНЕРАЦІЇ ТКАНИН ПІДНЕБІННЯ У ДІТЕЙ ПІСЛЯ РАДИКАЛЬНОЇ УРАНОСТАФІЛОПЛАСТИКИ

Ткаченко П.І., Доленко О.Б., Лохматова Н.М., Білоконь С.О., Попело Ю.В.

Метою роботи стало вивчення стану репаративної регенерації м'яких тканин піднебіння після проведення радикальної ураностафілопластики шляхом оцінки клінічної ситуації і морфологічних структур піднебінних слизово-окисних клаптів. Комплекс взаємообумовлених порушень гомеостазу, який виникає після проведення ураностафілопластики, значно впливає на процес формування рубця і характер загоєння рани. Вивчення процесів репаративної регенерації м'яких тканин піднебіння на 13-14 і 29-30 добу після проведення радикальної ураностафілопластики дає можливість на ранніх етапах спрогнозувати ймовірність формування грубого рубця і вплинути на цей процес шляхом підбору індивідуального плану лікувально-профілактичних і реабілітаційних заходів для цієї категорії хворих.

Ключові слова: піднебіння, м'які тканини, діти, ураностафілопластика, репаративна регенерація.

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СОСТОЯНИЕ РЕПАРАТИВНОЇ РЕГЕНЕРАЦІЇ ТКАНЕЙ НЁБА У ДЕТЕЙ ПОСЛЕ РАДИКАЛЬНОЇ УРАНОСТАФИЛОПЛАСТИКИ

Ткаченко П.И., Доленко О.Б., Лохматова Н.М., Белоконь С.А., Попело Ю.В.

Целью работы стало изучение состояния репаративной регенерации мягких тканей нёба после проведения радикальной ураностафилопластики путём оценки клинической ситуации и морфологической структуры нёбных слизисто-надкостничных лоскутов. Сложный комплекс взаимообусловленных нарушений гомеостаза, который возникает после проведения ураностафилопластики, значительно влияет на процесс формирования рубца и характер заживления раны. Изучение процессов репаративной регенерации мягких тканей нёба на 13-14 и 29-30 сутки после проведения радикальной ураностафилопластики даёт возможность на ранних этапах спрогнозировать вероятность формирования грубого рубца и повлиять на этот процесс путём подбора индивидуального плана лечебно-профилактических и реабилитационных мероприятий для этой категории больных.

Ключевые слова: небо, мягкие ткани, дети, ураностафилопластика, репаративная регенерація.

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P.I. Tkachenko, K.Yu. Rezvina, A.I. Shvets, Yu.V. Popelo
Ukrainian Medical Stomatological Academy, Poltava

FREQUENCY AND STRUCTURE OF BENIGN SOFT TISSUE FORMATIONS IN THE MAXILLOFACIAL AREA

e-mail: ekadiomina@gmail.com

The article considered our own observation results and retrospective analysis of archival material of the Maxillofacial Department of M.V. Sklifosovsky Poltava Regional Clinical Hospital and Surgical Department of the Poltava City Children's Clinical Hospital from 2008 to 2018. It was found that among adults the number of patients with benign soft tissue formations of the face and neck is 4.9%, and in children – 7.8% of the total number of inpatients. Most of them were bronchiogenic cysts of the lateral part of the neck (152 – 26.3%) and atheromatous plaques (147 – 25.4%). They mostly occurred at the age of 22 to 60 years, men suffered more often (205 - 35.5%). The largest number of discrepancies in the diagnosis at the prehospital phase were patients with epidermal cysts – 38 (7.9%). As for pediatric population, their number was 7.8% of the total number of inpatients. Neoplasms of dysontogenetic origin predominate, among which the most common were dermoid cysts – 92 patients (32.4%) and haemangiomas – 74 patients (26%). Less common were ranulae – 36 cases (12.7%), bronchiogenic cyst – 17 cases (6%) and atheromatous plaque – 16 cases (5.6%). They were found more often in the nursery age – from 1 to 3 years.

Key words: adults, children, benign formations, tumor-like formations, cysts of the maxillofacial area, soft tissues.

The work is a fragment of the research project "Integrative-differentiated substantiation of the choice for optimal methods of surgical interventions and scope of treatment in surgical pathology of the maxillofacial area", state registration No. 0116U003821.

According to various authors, the proportion of cystic lesions ranges from 25% to 40% in the structure of the maxillofacial area diseases, including within the Poltava region. Benign tumors and tumor-like neoplasms of the soft tissues of the face and neck account for 29% of all human tumors, of which 25% are cysts of the lateral surface of the neck. [1, 2, 4, 5].

There is no separate classification of maxillofacial tumors in the modern literature. Currently, oral and maxillofacial surgeons most often use O.O. Kolesov (primary tumors and tumor-like formations of

facial bones); I.I. Yermolaev (odontogenic tumors and tumor-like formations) and V.V. Panikarovskiy (salivary gland tumors) classifications [3, 4, 5].

The proportion of their nosological forms is diagnosed in patients of different ages, but the ratio and clinical manifestations of individual diseases can vary significantly [7, 9, 10]. It should be noted that between true tumors and cystic lesions of the maxillofacial area there is a similarity of clinical manifestations during the initial examination, while after additional and pathomorphological studies, their essence differs significantly [6, 7, 8]. Therefore, with high probability, it is possible to assert about discrepancy of diagnoses at various examination stages in these patients. In addition, cases of recurrence and postoperative complications were determined, which is associated with topographic and anatomical features of the maxillofacial area. Therefore, in order to improve and enhance the effectiveness of surgical care for patients with this pathology, a significant place is given to the use of the latest diagnostic methods, which made it possible to carry out a differential diagnosis, establish a final diagnosis and plan the surgery scope.

The purpose of the work was to perform a retrospective analysis of archival material to establish the frequency and structure of benign soft tissue tumors in adults and pediatric population of Poltava region to plan organizational measures to provide them with specialized care.

Materials and methods. In accordance with this purpose, we analyzed the archival material relating to 12,850 medical history sheets of patients who were hospitalized in the Department of Maxillofacial Surgery of the M.V. Sklifosovsky Poltava Regional Clinical Hospital. In addition, a similar situation was studied in relation to 3,642 medical history sheets of inpatients of the Surgical Department of the Poltava City Children's Clinical Hospital from 2008 to 2018.

We performed a detailed analysis of the content of all case histories for the respective years, the cystic formations percentage to the total number of patients with benign cysts of different anatomical localization and established their frequency.

Results of the study and their discussion. Studying archival materials of the Department of Maxillofacial Surgery, the content of the presented case histories and our own observations allowed establishing the number of patients with benign soft tissue formations of the maxillofacial area, which amounted to 636 patients (4.9%) of the total number of treated. Their distribution by nosological form of the disease, age and sex are presented in table 1.

Table 1

Distribution of benign soft tissue formations of the face and neck by age and sex in adults

Sex, Age, Nosology	male, 16-21		female, 16-20		male, 22-35		female, 21-35		male, 36-60		female, 36-55		male, 61-74		Total	
	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
Bronchiogenic cyst	10	1.6	10	1.6	46	7.2	35	5.5	25	3.9	26	4.1	-	-	152	23.9
Dermoid cyst	-	-	2	0.3	37	5.8	29	4.6	12	1.9	3	0.5	1	0.2	84	13.2
Epidermal cyst	-	-	1	0.2	23	3.6	10	1.6	9	1.4	2	0.3	1	0.2	46	7.2
Median neck cyst	12	1.9	13	2	8	1.3	7	1.1	8	1.3	9	1.4	-	-	57	9
Salivary gland cyst	2	0.3	2	0.3	19	3	2	0.3	-	-	-	-	1	0.2	26	4.1
Haemangioma	2	0.3	4	0.6	2	0.3	2	0.3	35	5.5	15	2.4	4	0.6	64	10
Lymphangioma	-	-	-	-	1	0.2	3	0.5	3	0.5	3	0.5	-	-	10	1.6
Atheromatous plaque	4	0.6	3	0.5	10	1.6	20	3.1	61	9.6	34	5.3	15	2.4	147	23.1
Ranula	15	2.4	17	2.7	6	0.9	5	0.8	-	-	3	0.5	4	0.6	50	7.9
Total	45	7.1	52	8.2	152	23.9	113	17.8	153	24	95	15	26	4.1	636	100

It was found that the most common nosological units among patients were bronchiogenic cyst of the neck – 152 patients (23.9%) and atheromatous plaque – 147 patients (23.1%). Fewer patients were treated with dermal cyst of the neck – 84 patients (13.2%), haemangioma – 64 cases (10%), median cyst of the neck – 57 patients (9%), ranula – 50 patients (7.9%). Epidermal cyst occurred in 46 patients (7.2%), salivary gland cyst was found in 26 patients – (4.1%), and lymphangioma accounted for the smallest number – only in 10 patients (1.6%).

Regarding age, the largest number of such diseases was detected in young and middle-aged people – from 22 to 60 years and it affected 418 patients (65.7%), most of whom were male – 305 (48%). Regarding topographical anatomy localization, most neoplasms were localized on the neck in 376 (59.2%) cases, in the cheeks – in 76 (12%), in the frontal area – in 73 (11.4%), in the temporal area – in 70 (11%), in the lower lip area – in 26 (4.1%), in the upper lip – in 15 patients (2.3%).

For further study, we took 480 (75.5%) of the 636 patients, which were fully examined, according to our algorithm [5]. A comparative analysis of the correspondence between the clinical diagnosis and the data obtained during additional examination methods: ultrasound, cytological, biochemical and histological.

Comparative analysis revealed that out in 108 (22.4%) of 480 patients, the clinical diagnosis did not coincide with the final one after additional studies. Among the analyzed number of case histories, 22.4% of discrepancies between the established diagnoses were revealed during the initial treatment with clinical ones. The largest number of such cases was in the group of patients with epidermal cyst of the lateral part of the neck – 38 people (7.9%), bronchiogenic cyst of the lateral part of the neck accounted for 28 people – (5.8%), with ranula – 12 (2.5%) and dermal cyst of the lateral part of the neck – 10 (2.1%) (table 2).

According to our observation regarding the discrepancy of diagnoses at different study phases for each nosological form of the disease, it was found that in patients with bronchiogenic cysts at the initial treatment such a diagnosis was established in 105 cases (21.9%), and after histological examination of the operative material such a diagnosis was confirmed only in 77 cases (16%).

Table 2

Comparative analysis of the diagnosis conformity at the phases of examination

Nosological form	Initial examination		After ultrasound		After cytological examination		After histological examination		Discrepancy	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Bronchiogenic cyst	105	21.9	87	18.1	84	17.5	77	16	28	5.8
Dermoid cyst	79	16.5	86	17.9	79	16.4	89	18.5	10	2.1
Epidermal cyst	39	8.1	50	10.4	86	17.9	77	16	38	7.9
Median neck cyst	50	10.4	47	9.8	46	9.6	46	9.6	4	0.8
Salivary gland cyst	16	3.3	15	3.1	12	2.5	14	2.9	2	0.4
Haemangioma	58	12.1	51	10.6	50	10.4	50	10.4	8	1.7
Lymphangioma	3	0.6	3	0.6	3	0.6	7	1.5	4	0.8
Atheromatous plaque	100	20.8	105	21.9	90	18.8	102	21.3	2	0.4
Ranula	30	6.3	36	7.5	30	6.3	18	3.8	12	2.5
Total	480	100	480	100	480	100	480	100	108	22.4

In patients with a dermoid cyst at the initial examination such diagnosis was established in 79 cases (16.5%), after a morphological study it concerned in 89 patients (18.5%). The diagnosis of epidermoid cyst at the initial treatment was established in 39 patients (8.1%), but after histological examination its features were found in 77 cases (16%). A lower percentage of discrepancy between the primary and final diagnosis was found in patients with median neck cyst – 50 (10.4%) at the initial treatment, and 46 cases (9.6%) after histological examination of postoperative material. Also, minor deviations were observed in patients who were diagnosed with a salivary gland cyst in 16 cases (3.3%) at the initial treatment, and 14 cases (2.9%) after morphological examination. With regard to haemangiomas, at the initial treatment it was diagnosed in 58 people (12.1%), and after histological examination in 50 (10.4%). In patients with lymphangioma at the initial treatment, such a diagnosis was established in 3 patients (0.6%), after histological examination of the surgical material, the number of patients increased to 7 (1.5%). A comparative analysis of the clinical diagnosis and the results of postoperative morphological examination of removed tumors revealed that in 108 cases (22.4%) there was a discrepancy between the primary and final diagnoses.

Recurrence after the surgery was recorded in 12 patients (1.9%) of the total number of operated patients. In 8 patients (66.7%) it occurred after removal of the median neck cyst, and in 4 patients (33.3%) – after removal of the bronchiogenic cyst.

The analysis of the archive material of the Surgical Department of the Poltava City Children's Clinical Hospital, which we performed for a certain period, allowed us to state that the number of children with benign soft tissue formations of the maxillofacial area was 284 patients (7.8%) of the total number of treated patients, which structure is presented in table 3.

According to our estimates, the most common nosological forms in childhood were dermoid cysts – 92 patients (32.4%) and haemangiomas – 74 patients (26%). Less common were ranulae – 36 cases (12.7%), bronchiogenic cyst – 17 cases (6%) and atheromatous plaque – 16 cases (5.6%). They were found more often in the nursery age – from 1 to 3 years.

Regarding the localization of the soft tissues neoplasms of the maxillofacial area, in 71 cases (25%) the pathological focus was localized in the neck, in the forehead pathological focus – in 34 cases (12%), in the soft tissues of the oral cavity – in 34 cases (11.8%), in the lower lip area – in 24 cases (8.4%), in cheeks

– in 24 cases (8.4%), in the upper lip – in 20 cases (7.1%), in the chin – in 10 cases (3.5%). It should be noted that in 68 cases (23.8%) haemangiomas covered several anatomical areas.

Table 3

Distribution of benign soft tissue formations of the face and neck by age and sex in pediatric population

Sex, age Nosological form	Early infancy, up to 1 year		Infancy, 1-3 years		Nursery, 3-7 yrs		School age, 7-13 yrs		Adolescence, 13-17 yrs		Total	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Bronchiogenic cyst	–	–	8	2.8	5	1.8	2	0.7	2	0.7	17	6
Dermoid cyst	26	9.15	19	6.7	21	7.4	18	6.3	8	2.8	92	32.4
Epidermal cyst	–	–	5	1.8	3	1	4	1.4	1	0.3	13	4.6
Median cyst	–	–	2	0.7	2	0.7	10	3.5	–	–	14	4.9
Salivary gland cyst	–	–	–	–	3	1	5	1.8	7	2.5	15	5.3
Haemangioma	37	13	25	8.8	2	0.7	6	2.1	4	1.4	74	26
Lymphangioma	3	1.1	–	–	4	1.4	–	–	–	–	7	2.5
Atheromatous plaque	5	1.8	–	–	3	1	8	2.8	–	–	16	5.6
Ranula	–	–	7	2.5	6	2.1	8	2.8	15	5.3	36	12.7
Total	71	25	66	23.3	49	17.2	61	21.5	37	13	284	100

Recurrences of neoplasms after planned surgery were observed in 17 cases (6%). Of these, 8 patients (47%) had a cystectomy for a median neck cyst and 4 patients (23.6%) had a haemangioma and 5 patients (29.4%) had a ranula removed.

Comparative analysis of diagnoses at the initial treatment and after histopathological examination revealed that 44 children (15.5%) found a discrepancy between the clinical diagnosis and the primary. The most common diagnostic errors were found in epidermoid cysts – 17 patients (39%), lymphangiomas – 14 patients (32%) and dermal cysts – 13 patients (29%).

In fundamental works, monographs of both domestic and foreign specialists periodically provide data on the study of the frequency and prevalence of various nosological forms of benign tumors. But the statistics of monitoring the health of the population need constant updating due to the variability of diseases in different regions, and this allows to some extent to objectively assess the situation and plan a program of specialized medical care.

Congenital cysts of the neck are quite rare. Comparative analysis of statistical data with indicators of A.A. Kolesov, Yu.I. Vorobyov, N.N. Kasparova [4] allowed us to state certain changes in the frequency and prevalence of these neoplasms of the lateral side of the neck in adults and children. According to the authors (for more than 20 years), 51 patients (27 males and 24 females) with median and lateral cysts and fistulas of the neck were observed. Among them, median cysts and fistulas of the neck were observed in 24 patients, and lateral cysts and fistulas of the neck were observed in 27 patients. The mean age of these patients was 23.5 years. For the period from 2008 to 2018 in Poltava, 152 patients (23.9%) with bronchiogenic cysts and 57 (9%) with median neck cysts were hospitalized. The mean age of this category of patients was 25 years for bronchiogenic cysts and 17 years for median neck cyst.

Dermal cysts, according to A.M. Solntsev, V.S. Kolesov [5] had 50 (47.3%) patients with localization in the area of the bottom of the oral cavity out of 106 patients observed with epidermoid and dermoid cysts of the maxillofacial area. The second most common were dermoid cysts of the neck – 22 (20.8%) patients. Regarding our own observations, there were 84 patients with dermoid cysts (13.2%), which indicates an increase in the number of patients with this pathology in contrast to epidermoid cysts, the number of which in A.M. Solntsev [5] accounted for 56 (52%) patients, according to our observations – 46 patients (7.2%). The mean age ranged from 21 to 35 years.

Cysts of the salivary glands are quite rare. We observed 26 patients (4.1%) with ectopic salivary gland cysts of the lateral side of the neck and 50 (7.9%) patients with ranulas. The mean age of patients with salivary gland cysts was 25 years, with ranula – 16-21 years. According to the results of A.M. Solntsev, V.S. Kolesov [5], 86 patients were observed (35%) with ranulas, 9 (3.7%) patients with cysts of the submandibular salivary gland. According to the age criterion, ranulas manifested at the age of 24.3 years, salivary gland cysts – at 30 years. Accordingly, it can be argued that the number of patients with salivary gland cysts has increased in contrast to patients with ranula, whose number has decreased.

Regarding the prevalence and incidence of haemangiomas, lymphangiomas and atheromatous plaques, data were not given even in more modern sources, which emphasizes the feasibility and relevance of our work.

Conclusions

1. It was found that among adults the number of patients with benign formations of soft tissues of the face and neck was 4.9%. Most of them were bronchiogenic cysts of the lateral part of the neck (152 – 26.3%) and atheromatous plaques (147 – 25.4%). They mostly occurred at the age of 22 to 60 years, men suffered more often (205 - 35.5%). The largest numbers of discrepancies in the diagnosis at the prehospital phase were patients with epidermal cysts – 38 (7.9%).

2. Neoplasms of dysontogenetic origin predominated in pediatric population, among which the most common were dermoid cysts – 92 patients (32.4%) and haemangiomas – 74 patients (26%). Less common were ranulae – 36 cases (12.7%), bronchiogenic cyst – 17 cases (6%) and atheromatous plaque – 16 cases (5.6%).

Prospects for further research are based on the fact that the analysis of archival material has permitted establishing the number of discrepancies in diagnoses at the initial treatment stage with the final clinical diagnosis. This indicates the need for additional examination methods according to our algorithm to properly assess the situation and plan the necessary measures.

References

1. Dyomina KYu. Kliniko-immunohistokhimichna kharakterystyka bichnykh kist shyyi [dysertatsiya]. Poltava, 2007. 160 s. [in Ukrainian]
2. Zaretskaya AS. Analiz rezultatov diagnostiki i ambulatornogo lecheniya patsiyentov s obshirnymi odontogennymi polostnymi obrazovaniya v chelyustnykh kostyakh [dissertatsiya] Stomatologiya. Moskva, 2011. 79 s. [in Russian]
3. Kiselev AS, Pazhetnev AR. Brankhiogennyye kisty i svishchi litsa i shei. Rossiyskaya otorinolaringologiya. 2007; 5: 91-95. [in Russian]
4. Malanchuk VO, Konchak AV. Dobroyakisni pukhlyny ta pukhlynopodibni urazhennya shchelepno-lytsevoyi dilyanky ta shyyi. Navchalnyi posibnyk. Kyiv: Lohos. 2011; 1. 669s. [in Ukrainian]
5. Tkachenko PI, Rezvina KYu. Alhorytm obstezhennya khvorykh z kistamy bichnoyi dilyanky shyyi. Svit medytsyny ta biolohiyi. 2011; 1: 104-107. [in Ukrainian]
6. Tkachenko PI, Rezvina KYu, Shvets AI, Kostrikov AV. Informatyvni diahnostychnykh zakhodiv na etapakh obstezhennya khvorykh z bichnymi kistamy shyyi. Aktualni problemy suchasnoyi medytsyny. 2018; 18, 1(61): 240-244. [in Ukrainian]
7. Starchenko II, Bilokon SO. Morfolohichna kharakterystyka shchytoyazykovoyi i zobno-hlotkovoyi protok yak mozhlyvykh dzherel rozvytku kist shyyi. Global scientific unit, 2014. The European scientific and practical congress. Prague (Czechrepublic). 2014: 77-78. [in Ukrainian]
8. Charous DD, Charous MT, Spiegel JR. Third branchial pouch cyst presenting as a lateral neck mass in an adult. Ear, Nose & Throat J. 2006; 85 (11): 754-759.
9. Greenberg Sh, Boscolo E, Adini I. Corticosteroid Suppression of VEGF-A in Infantile Hemangioma. Derived Stem Cells. N. Engl. J. Med. 2010; 362: 1005-1013.

Реферати

ЧАСТОТА ТА СТРУКТУРА ДОБРОЯКІСНИХ УТВОРЕНЬ М'ЯКИХ ТКАНИН ЩЕЛЕПНО-ЛИЦЕВОЇ ДІЛЯНКИ

Ткаченко П.І., Резвіна К.Ю., Швець А.І., Попело Ю.В.

В статті розглядаються результати власних спостережень та ретроспективного аналізу архівного матеріалу щелепно-лицевого відділення Полтавської обласної клінічної лікарні ім. М.В. Скліфосовського та хірургічного відділення дитячої міської клінічної лікарні м. Полтави з 2008 по 2018 роки. Встановлено, що серед дорослих кількість пацієнтів з доброякісними утвореннями м'яких тканин обличчя та шиї складає 4,9%, а у дітей 7,8% від загальної кількості стаціонарних хворих. Більшість із них припадає на бронхіогенні кісти бічної ділянки шиї (152 – 26,3%) та атероми (147 – 25,4%). Вони переважно зустрічаються у віці від 22 до 60 років, частіше хворіють чоловіки (205 – 35,5%). Найбільшу кількість невідповідностей діагнозу на догоспітальному етапі складають хворі з епідермоїдними кістами – 38 (7,9%). Щодо дітей, їх кількість складає 7,8% від загальної кількості стаціонарних хворих. Превалюють новоутворення дизонтогенетичного походження, серед яких найпоширеніші дермоїдні кісти – 92 хворих (32,4%) та гемангіоми – 74 хворих (26%). Рідше зустрічалися ранула – 36 випадків (12,7%), бронхіогенна кіста – 17 випадків (6%) та атерома – 16 випадків (5,6%). Їх виявляли частіше в ясельному віці – від 1 до 3 років.

Ключові слова: дорослі, діти, доброякісні утворення, пухлиноподібні утворення, кісти щелепно-лицевої ділянки, м'які тканини.

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ЧАСТОТА И СТРУКТУРА ДОБРОКАЧЕСТВЕННЫХ ОБРАЗОВАНИЙ МЯГКИХ ТКАНЕЙ ЧЕЛЮСТНО-ЛИЦЕВОЙ ОБЛАСТИ

Ткаченко П.И., Резвина К.Ю., Швець А.И., Попело Ю.В.

В статье рассматриваются результаты собственных наблюдений и ретроспективного анализа архивного материала челюстно-лицевого отделения Полтавской областной клинической больницы им. М.В. Скліфосовского и хирургического отделения детской городской клинической больницы г. Полтавы с 2008 по 2018 годы. Установлено, что среди взрослых количество пациентов с доброкачественными образованиями мягких тканей лица и шеи составляет 4,9%, а у детей 7,8% от общего количества стационарных больных. Большинство из них приходится на бронхиогенные кисты боковой области шеи (152 - 26,3%) и атерома (147 - 25,4%). Они преимущественно встречаются в возрасте от 22 до 60 лет, чаще болеют мужчины (205 - 35,5%). Наибольшее количество несоответствий диагноза на догоспитальном этапе составляют больные с эпидермоидными кистами – 38 (7,9%). В отношении детей, их количество составляет 7,8% от общего количества стационарных больных. Превалируют новообразования дизонтогенетического происхождения, среди которых самые распространенные дермоидные кисты – 92 больных (32,4%) и гемангиомы - 74 больных (26%). Реже встречались ранулы - 36 случаев (12,7%), бронхиогенная киста - 17 случаев (6%) и атерома - 16 случаев (5,6%). Их обнаруживали чаще в ясельном возрасте - от 1 до 3 лет.

Ключевые слова: взрослые, дети, доброкачественные образования, опухолевидные образования, кисты челюстно-лицевой области, мягкие ткани.

Рецензент Старченко І.І

D.A. Shkurupii, A.I. Mogylnyk, E.G. Sunnik, N.O. Udovyt'ska
Ukrainian Medical Stomatological Academy, Poltava

STATE OF GASTROINTESTINAL MUCOSAL PROTECTION IN NEUROLOGICAL PATIENTS IN CRITICAL STATE

e-mail: d.a.shkurupiy@gmail.com

An observational clinical study was performed with 50 adult participants. The main group consisted of 30 patients with cerebrovascular diseases of the cerebrovascular diseases, which required the organization of intensive care. In the main group, on the 1st day of observation, the level of glycosaminoglycans was higher in 70% (21/30) cases. On the 7th day of observation, this indicator was higher in 100% (30/30) cases. Correlations between the increase in the concentration of glycosaminoglycans and their age, the severity of the condition in accordance with APACHE II, and the start time of enteral nutrition were established. Thus, in neurological patients in critical condition, the protection system of the gastrointestinal mucosa is in a state of functional tension.

Key words: glycosaminoglycans, gastrointestinal tract, vascular syndromes of brain in cerebrovascular diseases, intensive care.

The article is a fragment of research project "Individualization of anesthesiology support and intensive care of patients for purposes of organ protection", state registration No. 0119U103321.

Patients of intensive care (IC) units always have some degree of central nervous system disturbance, which is associated with both primary brain damage as a result of vascular syndromes of brain in cerebrovascular diseases, traumatic brain injury, exogenous neurotoxic effects, and secondary injuries main reasons of which are universal mechanisms of critical state that develop due to extra-cerebral causes [2].

The survival and rehabilitation of such patients is closely related to the functioning of the gastrointestinal tract (GIT). Firstly, its functioning affects the energetic plastic supply of the nervous system in the context of changed quantitative and qualitative characteristics of nutritional needs. Secondly, the existence of vegetative, immune and metabolic relationships between the brain and the gastrointestinal tract has been proven. Thirdly, under conditions of the critical state of the gastrointestinal tract, it becomes the target of the pathogenetic mechanisms of the critical state [4, 13].

The latter fact is crucial in the lesion of the mucous membrane of the GIT. In this case, the mechanisms of its protection come to absolute or relative impairment. An example of a violation of such protection can be the so-called stress ulcers of the gastrointestinal mucosa of the GIT [5, 9].

Protective mechanisms of the gastrointestinal tract enclose three groups of factors: preepithelial, which are represented in the layer of epithelial mucus; epithelial, which are conditioned by the physical and chemical properties of epitheliocytes, and subepithelial, which include adequate hemocirculation and acid-base balance of mucus membrane of the GIT [1].

An important factor in preepithelial protection are glycosaminoglycans (GAG), which are a major component of the extracellular matrix and constitute heteropolysaccharides consisting of repeating disaccharide units of uranic acid or galactose and amino sugar residues. Disorders of their function are considered as a component of interactions of microbiota and macroorganism, links of sepsis and systemic inflammatory response [8, 10].

The purpose of the work was to evaluate the status of gastrointestinal mucosal protection in neurological patients in critical state by analyzing GAG level.

Materials and methods. An observational clinical study has been performed with 50 adult participants. The main group consisted of 30 patients with vascular syndromes of brain in cerebrovascular diseases (headings of the International Classification of Diseases of the X revision "Vascular brain syndromes in cerebrovascular diseases (G46)"), which required the organization of IC. The control group consisted of 20 practically healthy individuals. The criteria of exclusion from the study were conditions that could affect the level of GAG, namely, the presence of chronic gastrointestinal diseases, dermatoses, collagenoses in the life anamnesis.

Patients or their legal representatives gave written informed consent to participate in the study prior to the study starting date. During the study the patients' rights were respected in accordance with the requirements of the Helsinki Declaration, 1975, as amended in 2005.

Photocolorimetric determination of the GAG level in the blood was conducted by the orcin method. The dynamics of changes in GAG level has been evaluated for over 7 days of IC, and correlations of GAG level with clinical data such as age, gastrointestinal failure GIF severity on a scale The Working

Group on Abdominal Problems) (WGAP), patient gender, APACHE II severity score, onset of enteral nutrition, and mortality were determined.

Statistical materials were represented by non-parametric statistics methods, free of distribution, and were described by the mean values of absolute indexes through the median, upper and lower quartiles "Me (50L; 50U)", relative values - through the percentage and number of cases in the cohort "% (n/N)", absolute values - through the Mann-Whitney test indicating the statistical significance of the result «U; p», relative values - through the Pearson test (χ^2), connection - through the according to Spearman's correlation. We represented the dynamics of indicators through the criterion of signs "G; z; p». P = 0.05 was considered as the limited level of the latter one [3].

Results of the study and their discussion. The concentration of GAG in the control group and in the main group in the dynamics of the 1st and the 7th days of IC is shown in fig. 1.

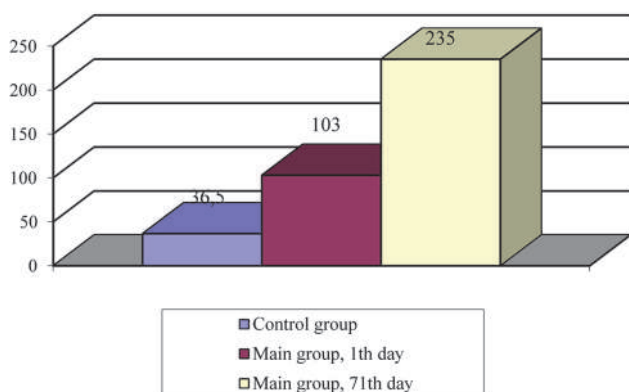


Fig. 1. Concentration of GAG in the control group and in the main group in the dynamics of the 1st and the 7th days of IC.

As the data of fig. 1 show, in the control group the level of GAG in serum was 36,5 (22,5; 88,5) mg/l. In the main group on the 1st day of observation this indicator was equal to 103 (78; 145) mg/l ($U=687,5$; $p<0,01$), which was observed in 70% (21/30) of cases. On the 7th day of observation, this indicator reached 235 (132; 369) mg/l, which was significantly higher both in relation to the control group ($U=936,5$; $p<0,01$) and to the 1st day of observation ($U=522,5$; $p=0,02$). At the same time, an increase in the level of the studied indicator was observed in 100% (30/30) of cases.

The dynamics of these changes are a consequence of disturbance of local homeostasis of gastrointestinal mucosal protection, which is a consequence of stress compensatory reactions of the body through sympathicotonia, massive release of glucocorticosteroids, catecholamines and other stress hormones into the bloodstream. As a consequence, a systemic inflammatory reaction of the body develops, causing bowel ischemia and tissue hypoxia. Due to impaired intestinal motility, failure of enteral nutrition, in most cases, neurologic patients in critical condition develop gastrointestinal insufficiency, characterized by impaired motor, suction, secretory and barrier functions of the gastrointestinal tract. The absence of peristalsis leads to loss of colonization resistance of the intestine, mucosal atrophy, translocation of pathogenic and opportunistic microflora, as a consequence - bacteremia and the development of sepsis. Disorders of the motor and decrease the intestinal functions of the intestine contributes to the accumulation of fluid in the lumen of the intestine and stretching its loops. And the increase in pressure in the lumen of the intestine leads to increased disturbance of the microcirculation in its wall, ischemia and increased intra-abdominal pressure [6, 13].

The level of GAGs in the dynamics decreased in 13% of cases (4/30), and increased in 87% of cases (26/30) ($G=86,7$; $z=3,83$; $p<0,001$), which indicates the progressing of the mucosal protection system intension.

On the 1st day of observation, GIF on the WGAP scale was observed in 30% of cases (10/30), and on the 7th day this indicator became already 80% (24/30) ($\chi^2=13,3$; $p<0,001$). At the same time, the evaluation indicators of the development of this pathology in the dynamics also differed: in 10% of patients (3/30) the manifestations of GIF decreased, in 23% (7/30) remained without dynamics, in 67% (20/30) progressed ($G=84,2$; $z=2,75$; $p=0,006$). These data indicate the progression of GIF.

The correlation links of GAG concentration in the main group with clinical characteristics and data of the course of the IC stage on the 1st day of observation were:

- with age: $R=0,35$, $p=0,02$;
- with the gender: $R=-0,07$, $p=0,65$;
- with the severity of the condition on a scale APACHE II: $R=0,2$, $p=0,15$;
- with GIF severity on a scale WGAP: $R=0,18$, $p=0,18$;
- with the starting time of enteric nutrition: $R=-0,17$, $p=0,27$;
- with fatality cases: $R=0,08$, $p=0,72$.

Correlations links of GAG concentration in the main group with clinical characteristics and data of the course of the IT stage on the 7th day of observation were equal to 11.

- with age: $R=0,8$, $p<0,01$;

- with the gender: $R=0,3$, $p=0,35$;
- with the severity of the condition on a scale APACHE II: $R=0,4$, $p=0,01$;
- with GIF severity on a scale WGAP: $R=0,38$, $p=0,02$;
- with the starting time of enteric nutrition: $R=0,4$, $p=0,02$;
- with fatality cases: $R=-0,3$, $p=0,38$.

This data prove the existence of statistically significant relationships, indicate a presence of statistically significant correlation between the increase in GAG concentration and age, the severity of state according to APACHE II and the time of onset of enteral nutrition. In this case proceeding from the data in the Table 1, during treatment, the statistical link between growing GAG levels and age increased. On the 7th day of observation the links between APACHE II severity and enteral nutrition time on the 1st day was not statistically significant, and gender and mortality rates were not statistically related to the change of indicator under the study.

The gastrointestinal mucosal protection system in neurological patients in a critical state is in the state of functional tension, as evidenced by an increase in GAG levels. It is the pathogenetic mechanisms of the development of the critical state that cause the development of gastrointestinal insufficiency, which is both the cause and the consequence of the violation of mucosal protection, which leads not only to the violation of nutrient absorption, but also to the disruption of the intestinal barrier function for microorganisms. In critical conditions, there are common mechanisms that lead to mucosal damage and the development of gastrointestinal insufficiency. The most significant mechanisms can be considered ischemic damage, tissue hypoxia, paresis, intraperitoneal hypertension, syndrome of excess bacterial colonization of the intestine. They are closely intertwined and reinforce each other's actions. Intestinal ischemia, together with tissue hypoxia, are classic links in the pathogenesis of critical conditions, manifestations of which are manifested at all levels of the organization of the whole organism. Ischemia develops as a result of the critical state of redistribution of blood flow between organs and systems: most of the arterial blood is distributed in favor of the respiratory, cardiovascular, nervous systems, while the intensity of blood flow in the bowel is reduced. The spasm of the vessels of the intestinal wall leads to a decrease in the volumetric rate of blood flow, the opening of arteriovenous anastomoses and a decrease in perfusion of the tissues of the intestine, especially its mucous membrane. Vasoconstriction in the system of organs of the gastrointestinal tract is much higher than in others, which leads to a disproportionate decrease in blood flow in the intestine in relation to cardiac output and, accordingly, increased manifestations of hypoxia at the tissue and cellular levels. Disturbance of intestinal microcirculation caused by abdominal compartment syndrome, increases ischemia, intestinal edema, leads to the development of microthrombosis, which promotes active microbial translocation from the intestine, causing a clinical picture of systemic inflammation and sepsis. However, intestinal bacterial translocation, which is inherent in patients in critical conditions, not only implements the mechanisms of endotoxicosis and immune changes; there are data on its effect on the structural and functional qualities of microglia, permeability of the blood-brain barrier, memory processes, the development of depression [9, 11].

This may be due to a change in the composition of the intestinal microbiota, for which these compounds create a barrier protecting the macro organism from bacterial translocation [15]. However, the high risk of infection realization caused, in particular, by group B streptococci and *S. agalactiae* in the elderly people and patients with diabetes is associated with their interaction with GAG, which explains the dependence of changes in their concentration with age [7].

The role of enteral nutrition in maintaining the intestinal mucosal barrier has been proven. Accordingly, its absence requires a tension on the protective mechanisms of the gastrointestinal tract, especially against the background of ischemia and hypoxia [14], which explains the association of changes in GAG levels with the time of enteral nutrition and the severity of APACHE II. Statistics show that about one-third of all inpatients are malnourished. And among patients hospitalized for emergency indications, in the vast majority of cases, malnutrition remains unrecognized, which is an aggravating factor in the effectiveness of treatment and leads to poor clinical prognosis and recovery [12]. Therefore, providing protection of vital functions and stabilization of the patient's condition, it will allow to reduce dysmetabolic disorders in the gastrointestinal tract, to start early enteral nutrition and to achieve the necessary nutritional support by enteral route against the background of hypercatabolism and increased need for nutrients.

Conclusion

Thus, in neurological patients in critical state, the gastrointestinal mucosal protection system is in a state of functional tension, as evidenced by an increase of GAG levels in blood serum. These changes

progress over the IC period, which is also related to the age of the patient, the severity of the state on the APACHE II scale and the starting time of enteral nutrition.

Prospects for further research are to develop methods of improving the quality of gastrointestinal mucosal protection in neurologic patients in critical state on the basis of the obtained data.

References

1. Milyukov VE, Dolgov EN, Nguen KK, Polunin SV. Faktory agresii i zashchity slizistoy obolochki zheludka pri ostroy tonkokishechnoy neprokhodimosti. Vestnik eksperimentalnoy i klinicheskoy khirurgii. 2012; 5(3): 596-600. [in Russian]
2. Nikonov VV, Kursov SV, Yakovtsov IZ, Zagurovskiy VM, Chernov AL, Savitskaya IB, et al. Problemy nedifferentsirovannoy terapii u bolnykh s sindromom ostroy tsebralnoy nedostatochnosti (analiticheskiy obzor). Chast 1 /. Meditsina neotlozhnykh sostoyaniy. 2016; 1(72): 30-8. [in Russian]
3. Petry A., Sebyn K, editors. Nagliadnaya meditsinskaya statistika: ucheb. posobiye. Moskva: HEOTAR-Medya; 2015. 216 s. [in Russian]
4. Teriv PS, Shkurupii DA. Tsynk-zalezni vplyvy pry intensyvni terapii u khvorykh z nevrolohichnoiu patolohiieiu. Visnyk problem biolohii i medytsyny. 2014; 2: 3 (109): 48-52. [in Ukrainian]
5. Buendgens L, Koch A, Tacke F. Prevention of stress-related ulcer bleeding at the intensive care unit: Risks and benefits of stress ulcer prophylaxis. World J Crit Care Med. 2016 Feb 4;5(1):57-64. doi: 10.5492/wjccm.v5.i1.57.
6. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015; 28(2):203–209.
7. García B, Merayo-Llodes J, Martín C, Alcalde I, Quirós LM, Vazquez F. Surface proteoglycans as mediators in bacterial pathogens infections. Front Microbiol. 2016 Feb 24; 7:220. doi: 10.3389/fmicb.2016.00220.
8. Hakansson AP, Orihuela CJ, Bogaert D. Bacterial-host interactions: physiology and pathophysiology of respiratory infection. Physiol Rev. 2018 Apr 1; 98(2):781-811. doi: 10.1152/physrev.00040.2016.
9. Haussner F, Chakraborty S, Halbgebauer R, Huber-Lang M. Challenge to the intestinal mucosa during sepsis. Front Immunol. 2019 Apr 30; 10:891. doi:10.3389/fimmu.2019.00891.
10. Kawai K, Kamochi R, Oiki S, Murata K, Hashimoto W. Probiotics in human gut microbiota can degrade host glycosaminoglycans. Sci Rep. 2018 Jul 13; 8(1):10674. doi: 10.1038/s41598-018-28886-w.
11. Lerner A, Neidhöfer S, Matthias T. The gut microbiome feelings of the brain: A perspective for non-microbiologists. Microorganisms. 2017; 5(4):66. doi: 10.3390/microorganisms5040066
12. Lew CCH, Wong GJY, Cheung KP. The association between nutritional adequacy and 28-day mortality in the critically ill is not modified by their baseline nutritional status and disease severity. Crit Care. 2019; 23(1):222. Published 2019 Jun 18. doi:10.1186/s13054-019-2500-z
13. Miller I. The gut-brain axis: historical reflections. Microb Ecol Health Dis. 2018 Nov 8; 29(1):1542921. doi: 10.1080/16512235.2018.1542921.
14. Nadatani Y, Watanabe T, Shimada S, Otani K, Tanigawa T, Fujiwara Y. Microbiome and intestinal ischemia/reperfusion injury. J Clin Biochem Nutr. 2018 Jul; 63(1):26-32. doi: 10.3164/jcbs.17-137.
15. Shmagel A, Demmer R, Knights D, Butler M, Langsetmo L, Lane NE, et al. The Effects of glucosamine and chondroitin sulfate on gut microbial composition: a systematic review of evidence from animal and human studies. Nutrients. 2019 Jan 30; 11(2). pii: E294. doi: 10.3390/nu11020294.

Реферати

СТАН ГАСТРОІНТЕСТИНАЛЬНОГО МУКОЗАЛЬНОГО ЗАХИСТУ У НЕВРОЛОГІЧНИХ ПАЦІЄНТІВ У КРИТИЧНОМУ СТАНІ Шкурупій Д.А., Могильник А.І., Сонник Є.Г., Удовичка Н.О.

Проведене обсерваційне клінічне дослідження за участю 50 дорослих осіб. Основну групу склали 30 пацієнтів з наявністю гострих порушень мозкового кровообігу, які потребували організації інтенсивної терапії. Контрольну групу склали 20 практично здорових осіб. Встановлено, що концентрація глікозаміногліканів в основній групі була вищою за контрольну в 70% (21/30) випадків на 1-у добу і в 100% (30/30) випадків на 7-у добу спостереження. Також встановлені статистично значимі зв'язки між зростанням концентрації глікозаміногліканів, віком, тяжкістю стану за шкалою APACHE II, часом початку ентерального харчування. Отримані дані свідчать про напруження системи гастроінтестинального мукозального захисту у обстежених хворих.

Ключові слова: глікозаміноглікани, шлунково-кишковий тракт, гостре порушення мозкового кровообігу, інтенсивна терапія.

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СОСТОЯНИЕ ГАСТРОИНТЕСТИНАЛЬНОЙ МУКОЗАЛЬНОЙ ЗАЩИТЫ У НЕВРОЛОГИЧЕСКИХ ПАЦИЕНТОВ В КРИТИЧЕСКОМ СОСТОЯНИИ Шкурупий Д.А., Могильник А.И., Сонник Е.Г., Удовичка Н.О.

Проведено обсервационное клиническое исследование с участием 50 взрослых лиц. Основную группу составили 30 пациентов с наличием острых нарушений мозгового кровообращения, нуждающихся в организации интенсивной терапии. Контрольную группу составили 20 практически здоровых лиц. Установлено, что концентрация гликозаминогликанов в основной группе была выше контрольной в 70% (21/30) случаев на первый день и в 100% (30/30) случаев на седьмой день наблюдения. Также установлены статистически значимые связи между ростом концентрации гликозаминогликанов, возрастом, тяжестью состояния по шкале APACHE II, временем начала энтерального питания. Полученные данные свидетельствуют о напряжении системы гастроинтестинальной мукозальной защиты у обследованных больных.

Ключевые слова: гликозаминогликаны, желудочно-кишечный тракт, острое нарушение мозгового кровообращения, интенсивная терапия.

Рецензент Дельва М.Ю.

I.V. Yanishen, O.L. Fedotova, N.L. Khlystun, P.L. Yushchenko, A.Y. Dolia
Kharkiv National Medical University, Kharkiv

THE EFFECT ANALYSIS OF THE DOUBLE-LAYER BASES IN REMOVABLE DENTURES WITH OCCLUSIVE PART ON THE MICROCIRCULATORY STATE OF THE DENTURE FOUNDATION AREA VESSELS

e-mail: helennochka@i.ua

The purpose of this work was to determine the effect of double-layer bases in removable dentures with occlusive part on the microcirculatory state of the denture foundation area vessels compared to the effect of dentures made of ordinary base resin. To achieve this purpose, 20 patients with post-traumatic defects of the maxillary bone were examined and orthopedically treated. The method of laser Doppler flowmetry was used to study the characteristics of blood circulation. The generalized analysis of microcirculatory parameters showed the absence of negative effect on the hemodynamic characteristics of the microvasculature in the denture foundation area tissues in the manufacture of removable structures with double-layer bases, which is a major factor in preventing the development of functional and structural changes that occur both from pressure and indirectly through neuroreflex mechanisms.

Key words: microcirculation of vessels, double-layer basis, removable denture, occlusive part, mucous membrane of the oral cavity.

The work is a fragment of the research project "Optimization of methods for diagnosis and treatment of basic dental diseases", state registration No. 0119U002899.

From the numerous literature data [3, 8], it is obvious that even the most modern non-removable dentures will not be able to replace removable dentures for a long time. However, they can injure denture foundation area tissues due to the inevitable pressure on the mucous membrane. Analyzing the factors that affect the duration of removable dentures operation, and noting their cumulative nature, we can state the discrepancy of the five-year period of their application with the period of clinical well-being. Recent studies show that repeated and subsequent orthopedic treatment with newly made removable dentures application, change the hemodynamic characteristics of the denture foundation area tissues [4, 9, 10]. These changes can negatively affect the prognosis of effective functioning of the denture. Due to this, double-layer bases of removable dentures become increasingly used. This technique is especially useful in such complex clinical cases as the maxillary bone defects, which are combined with the maxilla and maxillary sinuses, when it is necessary to make a removable denture with an occlusive part. According to M.A. Rebrova, the leading role in the functional and structural changes development in the denture foundation area tissues belongs to vascular disorders that occur both from pressure and indirectly through neuroreflex mechanisms [2, 8, 11].

Currently, a method of computer registration of capillary blood flow in the mucous membrane of the denture foundation area with the preservation of fragments of video in the database is developed in dentistry. The high resolution of the obtained video fragments allows not only to see the state of microvessels, but also to calculate the linear and volumetric rates of capillary blood circulation by canals: arterial, venous and transitional [6, 7].

The purpose of this work was to determine the effect of double-layer bases in removable dentures with occlusive part on the microcirculatory state of the denture foundation area vessels compared to the effect of dentures made of ordinary base resin.

Materials and methods. The study was performed on the basis of the Department of Prosthetic Dentistry of the University Dental Center of Kharkiv National Medical University.

Deontological aspects are resolved within the framework of the current legislation of Ukraine, the Law of Ukraine "On Medicinal Products", 1996, Art. 7, 8, 12, Principles of ICH GCP (2008), Order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009 "On approval of the Rules for performing clinical trials and examination of clinical trial materials and the Standard Regulations on the Ethics Commission" as amended; Declaration of Helsinki of the World Medical Association. The study was performed with minimal psychological losses on the part of patients. Patients were fully informed about the purpose and methods of the study, the potential benefits and risks, as well as possible discomfort during diagnosis and treatment. All ethical requirements are met in accordance with maintaining the confidentiality of information obtained during the study. The work was considered and approved by the Commission on Bioethics of KhNMU of the Ministry of Health of Ukraine.

20 patients, aged 39 to 56 years, with post-traumatic defects of the maxillary bone were examined and orthopedically treated. They were divided into 2 groups: I – control group (n=10, 8 men, 2 women),

patients, whose removable dentures were made with occlusive part of the ordinary base resin; II – main group (n=10, 6 men, 4 women) patients, whose removable dentures were made with occlusive part and two-layer bases.

The method of laser Doppler flowmetry (LDF) using a multifunctional laser diagnostic complex "LAKK-02" was used to study the characteristics of blood circulation. The measurement was performed before dental prosthetics and at different times after the imposition of removable dentures: 1 day, 1 month and 6 months. Operation of the "LAKK-02" complex was performed in the "LDF+spectrophotometry" mode. Before starting the study, the signal was calibrated according to the manufacturer's instructions.

Capillary blood circulation indices were measured in a state of complete physical and mental rest in a room with a temperature of 20-22 °C. During the Doppler imaging, the patient was in a sitting position, the head was fixed on the headrest. Records were performed in the area of the muco-gingival junction at the level of the interdental gingiva from the vestibular surface. The duration of each measurement ranged from 30 to 60 seconds. Each indicator in the subject was determined three times in the same examination area, taking into account biometric and chronometric characteristics, and considering their average value.

The study evaluated the following characteristics: by the method of laser Doppler flowmetry (LDF) – the microvascular flow index (MFI) according to the following formula:

$MFI = C \times Nrbc \times Vav.$, where:

C – coefficient of proportionality (constant),

Nrbc. – the number of red blood cells in the volume of tissue probing,

Vav. – the average speed of red blood cells.

The MFI parameter determines the dynamic characteristic of blood microcirculation – the change in blood flow per unit of time in the studied volume of tissue of about 1 mm³ in relative blood perfusion units (BPU). LDF signal has a constant and time-varying components associated with the tone of microvessels.

The database formation based on the results of randomized controlled trials was carried out in Microsoft Excel, 2007. Statistical processing of the study results was performed using the "STATISTICA V. 8.0" software package. We calculated the arithmetic mean value of the quantitative indices presented in the text as (M±m), where M is the sample mean, m is the error of the mean. The results of the qualitative index description (frequency of withdrawal) were expressed in percentage. In all statistical analysis procedures, the achieved significance level (p) was calculated, and the critical significance level in this study was assumed to be 0.05. The hypothesis of equality of general means in the two compared groups was tested using the nonparametric Wilcoxon-Mann-Whitney test for independent samples, and the percentages were performed using the chi-squared test [1].

Table 1

Microcirculatory indices in the mucous membrane of the denture foundation area of patients with post-traumatic defects of the maxillary bone

Indices	Control group, ordinary base resin (n=10)				Main group, double-layer removable dentures (n=10)			
	Treatment stages							
	Before imposition	1 day	1 month	6 months	Before imposition	1 day	1 month	6 months
Microcirculatory index, M, BPU	16.9±0.32	23.2±0.4 ^a	21.8±0.51	20.3±0.75	17.14±0.54	16.8±0.19 ^a	17.2±0.35	17.3±0.22
Flaxmotion index, FMI	1.51±0.13	1.05±0.19 ^b	1.11±0.09 ^c	1.19±0.08 ^c	1.4±0.2	1.42±0.28 ^b	1.46±0.13 ^c	1.53±0.15 ^c
Intravascular resistance, R, %	5.39±0.31	3.28±0.42	3.39±0.29	3.49±0.38 ^d	5.41±0.2	5.48±0.41	5.36±0.28	5.46±0.44 ^d
Vascular tone, %	91.6±3.15	84.3±2.75 ^b	83.1±4.16	79.6±3.84 ^d	94.8±2.53 ^b	92.9±3.2	93.6±2.91	94.3±4.1 ^d

^a – significant differences between groups I and II on the first day at the level of p<0.01;

^b – significant differences between groups I and II on the first day at the level of p<0.05;

^c – significant differences between groups I and II after 1 and 6 months at the level of p<0.05;

^d – significant differences between groups I and II after 6 months at the level of p<0.01.

Results of the study and their discussion. As a result of our study, we found a reliably significant (p<0.01) increase in the microcirculatory index value (Fig. 1, Table 1) in the control group of patients immediately on the first day of denture application from 16.9 BPU up to 23.2 BPU, indicating an increase in vascular perfusion and a decrease in their tone, which further decreased due to the compensatory response of the organism, while in patients of the main group a significant difference in indices at different stages of measurement was not observed.

Determination of the flaxmotion index (FMI) (Fig. 2) showed the variability of perfusion in the control group – on the first day the index significantly ($p<0,05$) decreased from 1.51 to 1.05, later it increased after 1 month only by 0.06 and after 6 months by 0.08, but it did not return to the initial level. For the main group, the flaxmotion index increased slightly with each subsequent measurement, but no significant difference between the stages was found – no variability was observed throughout the study. Comparing the FMI of both groups in 1 and 6 months after dental prosthetics, we recorded a significant ($p<0.05$) difference in results in favor of double-layer removable dentures.

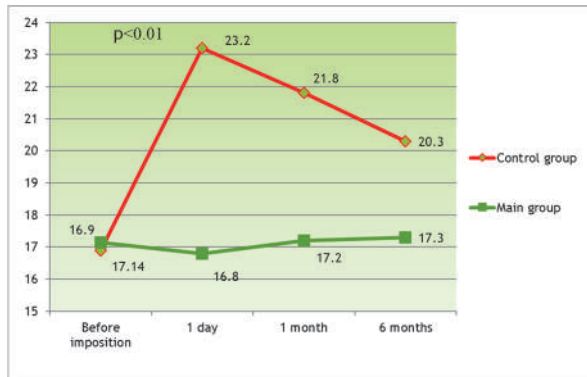


Fig. 1. Microcirculatory index (M), BPU

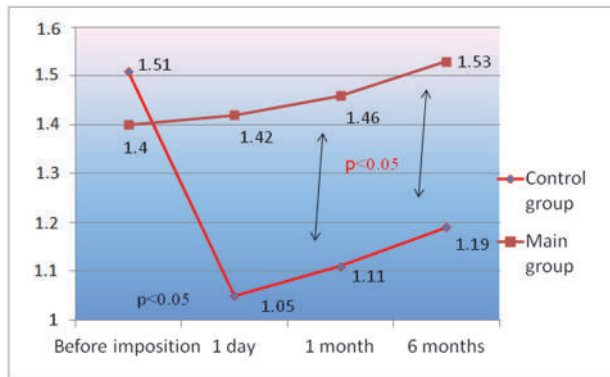


Fig. 2. Flaxmotion index, (FMI)

Indices of intravascular resistance (Fig. 3) ranged from 3.28% to 5.48%. As we had suspected, using double-layer removable dentures, we did not see significant changes from stage to stage and for this parameter, while in the control group there was a significant ($p<0.05$) decrease in the 2nd stage of the study, at the 3rd and 4th stages it increased slightly (possibly due to compensatory reactions), but remained significantly lower than the measurement before dental prosthetics. As a result – a significant ($p<0.01$) difference between the main and control groups 6 months after dental prosthetics.

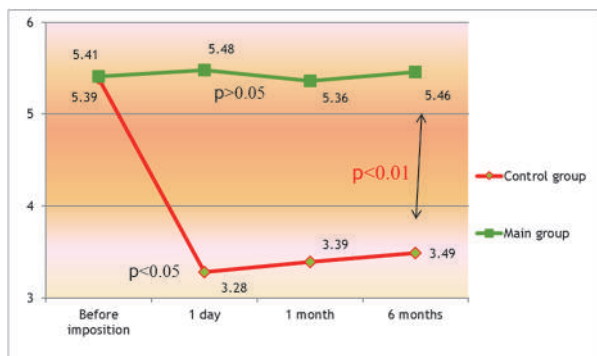


Fig. 3. Intravascular resistance, R, %

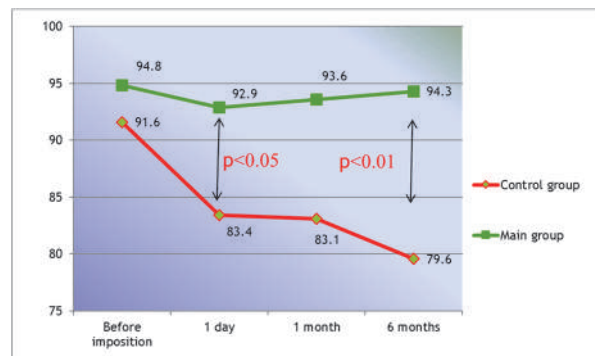


Fig. 4. Vascular tone, VT, %

The next studied parameter was a vascular tone (Fig. 4). From the obtained data we see a significant ($p<0.05$) difference between the groups already at the 2nd stage, and a year later the difference becomes significant at the level of 99.9%.

Thus, we see that a number of previous studies have focused on studying the effect of partial or full removable dentures on the state of the oral mucosa [3, 4]. Other studies were aimed at analyzing the relationship between the microcirculation of oral tissues and general diseases of the organism [6, 7]. We were the first to use the method of laser Doppler flowmetry to control the quality of orthopedic treatment of patients with post-traumatic defects of the maxillary bone using occlusive dentures with a double-layer base.

Therefore, a generalized analysis of the microcirculatory parameters in the mucous membrane of the denture foundation area of patients with post-traumatic defects of the maxillary bone showed that in comparison with standard manufacturing of partial removable dentures with an occlusive part, manufacturing of removable dentures with double-layer bases had a number of essential advantages. In particular, our study proved the lack of negative impact on the hemodynamic characteristics of the microcirculatory flow of the denture foundation area tissues, which is fundamental in the functional and structural changes development that occur both from pressure and indirectly through neuroreflex mechanisms, and this will undoubtedly have a positive effect on the prognosis of the denture functioning.

Conclusions

1. When using double-layer removable dentures with an occlusive part, the microcirculatory index did not change significantly ($p>0.05$).
2. No significant blood perfusion variability was observed when determining the flaxmotion index.
3. A significant ($p<0.01$) difference between the intravascular resistance indices of the main and control groups 6 months after dental prosthetics was determined.
4. After 1 year of dentures application, a significant difference in the "Vascular tone" index was recorded between the studied groups at the level of 99.9%.

The performed study made it possible to clearly demonstrate the effect of two-layer removable dentures with an occlusive part on the microcirculatory state of the denture foundation area vessels and compare it with the effect of dentures made of ordinary base resin. Prospects for further research. Further research will focus on ways to improve the occlusal efficiency of patients with partial maxillary adentia and a defect of the hard palate and alveolar process to improve their quality of life.

References

1. Zhmurov VO, Maltsev VI, Yefimtseva TK, Kovtun LI. Obrobka danykh ta analiz rezultativ klinichnykh vyprobuvan likarskykh zasobiv. Ukrayinskyi medychnyi chasopys. 2011; 6:34-38. [in Ukrainian]
2. Mikhaylova VV, Libikh DA. Dinamika izmeneniy mikroциркуляtsii slizistoy obolochki polosti rta u patientsov s paresteziy v processe ortopedicheskogo stomatologicheskogo lecheniya. Parodontologiya. 2014; 3(72): 51-53. [in Russian]
3. Rozhko MM. Stomatolohiya. Kyiv: Medytsyna. 2013. Book 1: 872. [in Ukrainian]
4. Akazawa H, Sakurai K. Changes of blood flow in the mucosa underlying a mandibular denture following pressure assumed as a result of light clenching. Journal of Rehabilitation. 2012; 29:336-340.
5. Ali MM, Khalifa N, Alhajj MN. Quality of life and problems associated with obturators of patients with maxillectomies. Head Face Med. 2018; 14(1):22-25.
6. Canjau S, Miron MI, Todea CD. Laser Doppler flowmetry evaluation of gingival microcirculation recovery in gingivitis. Archives Balkan Med Union. 2015; 50(3):354-359.
7. Hinrichs JE, LaBelle LL, Aeppli D. An evaluation of laser Doppler readings obtained from human gingival sulci. J Periodontol. 2015; 66:171-176.
8. Rogers SN, Lowe D, McNally D, Brown JS, Vaughan ED. Health-related quality of life after maxillectomy: a comparison between prosthetic obturation and free flap. J Oral Maxillofac Surg. 2013; 61(2):174-181.
9. Vincent A, Burkes J, Williams F, Ducic Y. Free Flap Reconstruction of the Maxilla. Semin Plast Surg. 2019; 33(1):30-37.
10. Yanishen IV, Biryukova MM, Diudina IL, Krychka NV, Kuznetsov RV. Employment of functional tests in multivariable modeling of plastic dentures in patients with complete absence of teeth. Medical Education. 2017; 6:1794-1499.
11. Yetzer J, Fernandes RJ. Reconstruction of orbitomaxillary defects. Oral Maxillofac Surg. 2013; 71(2):398-409.

Реферати

**АНАЛІЗ ВПЛИВУ ДВОШАРОВИХ БАЗИСІВ
ЗНІМНИХ ПРОТЕЗІВ З ОБТУРУЮЧОЮ
ЧАСТИНОЮ НА СТАН МІКРОЦИРКУЛЯЦІЇ
СУДИН ПРОТЕЗНОГО ЛОЖА**

**Янішен І.В., Федотова О.Л., Хлїстун Н.Л.,
Ющенко П.Л., Доля А.В.**

Метою даної роботи було визначення впливу двошарових базисів знімних протезів з обтуруючою частиною на стан мікроциркуляції судин протезного ложа порівняно з впливом протезів, які виготовлені зі звичайної базисної пластмаси. Для досягнення поставленої мети було обстежено та проведено ортопедичне лікування 20 пацієнтів із посттравматичними дефектами верхньої щелепи. Для вивчення характеристик кровотоку застосовували метод лазерної доплерівської флоуметрії. Узагальнений аналіз параметрів мікроциркуляції показав відсутність негативного впливу на гемодинамічні характеристики мікроциркуляторного русла тканин протезного ложа при виготовленні знімних конструкцій із двошаровими базисами, що є основним фактором профілактики розвитку функціональних і структурних змін, які виникають як від тиску так і опосередковано через нервово-рефлекторні механізми.

Ключові слова: мікроциркуляція судин, двошаровий базис, знімний протез, обтуруюча частина, слизова оболонка порожнини рота.

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**АНАЛІЗ ВЛИЯНИЯ ДВУХСЛОЙНЫХ БАЗИСОВ
СЪЕМНЫХ ПРОТЕЗОВ С ОБТУРИРУЮЩЕЙ
ЧАСТЬЮ НА СОСТОЯНИЕ МИКРОЦИРКУЛЯЦИИ
СОСУДОВ ПРОТЕЗНОГО ЛОЖА**

**Янішен І.В., Федотова О.Л., Хлїстун Н.Л.,
Ющенко П.Л., Доля А.В.**

Целью данной работы было определение влияния двухслойных базисов съемных протезов с обтурирующей частью на состояние микроциркуляции сосудов протезного ложа по сравнению с влиянием протезов, изготовленных из обычной базисной пластмассы. Для достижения поставленной цели было обследовано и проведено ортопедическое лечение 20 пациентов с посттравматическими дефектами верхней челюсти. Для изучения характеристик кровотока применяли метод лазерной доплеровской флоуметрии. Обобщенный анализ параметров микроциркуляции показал отсутствие негативного влияния на гемодинамические характеристики микроциркуляторного русла тканей протезного ложа при изготовлении съемных конструкций с двухслойными базисами, что является основным фактором профилактики развития функциональных и структурных изменений, которые возникают как от давления так и опосредованно через нервно-рефлекторные механизмы.

Ключевые слова: микроциркуляция сосудов, двухслойный базис, съемный протез, обтурирующая часть, слизистая оболочка полости рта.

Рецензент Аветіков Д.С.

I.V. Gubar^{1,2}, V.E. Lavrynenko², S.M. Chuchrai, S.I. Savosko, L.M. Sokurenko²,
O.L. Apykhtina¹, O.P. Yavorovsky
Bogomolets National Medical University, Kyiv, ¹SI "Kundliev Institute of Occupational Health",
NAMS of Ukraine, Kyiv, ²Educational and Scientific Center "Institute of Biology and Medicine"
of Taras Shevchenko National University, Kyiv

CARDIOVASOTOXIC EFFECT OF DIFFERENT SIZES LEAD NANOPARTICLES INTRODUCTION

e-mail: ginna5@ukr.net

Cardiovascular toxicity of Pb compounds NP (nanoparticles) 26-34 nm and 50-80 nm in size was investigated in the experiments. Morphological and morphometric methods were used to detect structural changes in the heart and aorta after 30 and 60 injections of Pb compounds NP. The results of the experiments indicate damage to the myocardium, which consists in increasing of the interstitial space between the fibers of cardiomyocytes, dystrophy of cardiomyocytes, stasis of blood in the microvessels of the heart ventricles. A greater sensitivity of the atrial myocardium to the toxic effects of Pb compounds NP was detected. Structural changes of the aorta consisted in a stratification of elastic membranes, a decrease in the density of the connective tissue of the adventitious layer, which tended to progressive changes.

Key words: lead, Pb, nanoparticles, morphological changes, aorta, myocardium.

The work is a fragment of the research project "Investigation of the heavy metal nanoparticles toxic effects, search and substantiation of preventive measures", state registration No. 0116U000497, and "Changes in internal organs and regulatory systems under the conditions of experimental damage and historical aspects of histology, cytology and embryology development in Ukraine", state registration No. 0116U000121.

The development of new technologies and nanomaterials is a prerequisite for technological advancement in various industries [7]. The significant increase in environment and workspaces pollution by heavy metal nanoparticles, in particular the lead PbS NP (nanoparticles), one of the most common and highly toxic metals, is worrying [10]. The small size, shape, chemical composition, charge, structure of NP as well as the large surface area determine their unique properties as a promising material for the manufacture of temperature-sensitive sensors, detectors, photoresistors, selective sensors; in flexible optoelectronics - as high-performance photodetectors; in the third generation solar elements as quantum dots, which greatly increases the efficiency of solar energy conversion; as well as in the composition of various polymer films and nanoporous matrices, abrasive treatment of lead materials, etc [12, 14].

Lead compounds are characterized by pronounced neurotoxicity, hepatotoxicity, nephrotoxicity, gonadotoxicity and cardiotoxicity and are indicated by blood indices [6]. Lead can have direct and indirect toxic effects on cardiovascular system [13]. Experimental studies have shown its high affinity to be accumulated in blood vessels, stimulate the production of reactive oxygen species, the development of oxidative stress and impaired nitric oxide metabolism, resulting in the development of endothelial dysfunction [15].

The nanoscale and the properties of the surfaces of NP allow coming into direct contact with proteins and individual cell structures of the body at the molecular level. Overcoming cellular barriers and damaging cell structures, NP can disrupt functions and even lead to cell death of all organs and tissues. At the same time, numerous experimental data do not give an unambiguous answer to the dangerous effects of NP on human health, since NP toxicity depends on their characteristics (including size, method of stabilization, etc.) [2]. This determines the relevance of the study of the effects of nanoparticles on the body and the assessment of potential risks

The purpose of the study was to examine features of morphological changes in the organs of the cardiovascular system under the action of lead sulfide nanoparticles of different sizes and lead nitrate (ionic form) in the experimental model of intoxication.

Materials and Methods. In this work lead compounds are used in nanoform: NP of lead sulfide (PbS NP) with 26-34 nm and 50-80 nm average size and in ionic form: lead nitrate (Pb(NO₃)₂) which is readily soluble in water. Lead sulfide NP were obtained by chemical synthesis using a sodium polyphosphate stabilizer (NaPO₃)_n. NP size was determined by electron microscopy.

The study was conducted on mature male Wistar rats 160-180 g. The animals were kept in vivarium on a standardized diet with free access to drinking water. The rats were divided into 3 experimental groups and control group. The first experimental group was injected with 26-34 nm PbS NP (PbS_{26-34nm} NP group), the second – 50-80 nm PbS NP (PbS_{50-80nm} NP group), the third – with Pb(NO₃)₂ ionic form ((NO₃)₂ group); the control group received a physiological solution. These substances were administered intraperitoneally daily 5 times a week (simulation of a working week) in 0,94 mg/kg/day dose adjusted to lead [1]. Histological examinations were performed after 30 injections (1.5 months) and 60 injections (3 months). To study the morphological changes, the internal organs of the experimental rats were taken after decapitation under mild ether anesthesia. The heart and aorta were fixed in 10% neutral formalin (phosphate buffer, PBS). The fixed frontal tissues were dehydrated and embedded in paraffin. Paraffin sections were made on a Thermo Microm HM 360 microtome. The sections were deparaffinized and stained with hematoxylin and eosin, using Picro-Mallory method, which can reveal collagen. The micropreparations were examined on an Olympus BX51 microscope. Morphometric analysis was performed using Carl Zeiss software (AxioVision SE64 Rel.4.9.1), magnification × 200, × 400. Aorta wall thickness (mkm), tunica adventitia of aorta thickness (mkm), comparative amount of collagen fibers in tunica adventitia (%), number of elastic membranes in tunica media (conventional units) were examined. The statistical study was performed in Origin Lab version 8.0 using the non-parametric Kruskal-Wallis test, because normal distribution of data was not proven. Data are presented as medians with smaller and larger quartiles (M [Q1-Q3]). The difference was considered statistically significant at P < 0.05.

All manipulations with animals were carried out in accordance with the provisions of European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1985). The study meets bioethical requirements. The experiment plan is approved by the Bioethics Commission of State Institution "Kundiiev Institute of Occupational Health of the National Academy of Medical Sciences of Ukraine" (Minutes № 5, session of bioethics commission from 23.11.2017).

Results of the study and their discussion. In all tested heart samples of the control and experimental groups, the overall morphological structure of the heart was preserved. The endocardium, myocardium, and epicardium were recorded in the ventricles and atria. In the control group, the myocardium is represented by densely oriented fibers of cardiomyocytes. Cardiomyocyte nuclei and intercalated discs are recorded. There is almost no intercellular space between the fibers. Morphological differences were found in myocardium of the atria and ventricles: in the ventricles the fibers are oriented more straightforwardly, whereas in the atria they are often tortuous (nuclei of cardiomyocytes in the atria are larger). There are microvessels (arterioles, venules, capillaries), in the myocardium, their density is higher in the ventricles.

Morphological features of structural disorders of the heart were established in the experimental groups (Fig. 1). In the endocardium of the hearts of all 3 groups after 30 and 60 injections, no structural changes were detected; endotheliocytes and structurally preserved valves (including the aortic valve) were recorded. The epicardium is morphologically represented by a thin layer of connective tissue with elastic elements, as in the control groups, without structural changes. The ventricular and atrial myocardium was heterogeneous, like in the control, had a greater thickness and density in the ventricles, represented by bundles of cardiomyocytes, between which thin layers of collagen fibers were detected (when stained by the Picro-Mallory method). The density of collagen fibers was higher around medium- and large-caliber myocardial vessels, but without a clear difference in control groups. Some morphofunctional differences were found between the comparison groups. Thus, after 30 injections of Pb(NO₃)₂, less collagen fibers were detected in the ventricular myocardium, whereas no qualitative changes were observed in the atria compared to the control. In all 3 experimental groups, a lower density of cardiomyocyte nuclei was observed in the investigated areas of the ventricles, as well as a decrease in the tinctorial properties of the cardiomyocytes cytoplasm in the atria and dystrophic changes at the cellular level, in particular destructive contractile myocyte processes, this is an evidence of toxic effects both PbS NP and Pb(NO₃)₂.

After 60 injections, structural changes in the myocardium of experimental group animals were more pronounced. Increased interstitial space between cardiomyocyte fibers, stasis in ventricular myocardial microvessels, atrial damage, and dystrophic cardiomyocyte changes were observed. In the group with expose PbS₅₀₋₈₀, local dystrophic myocardial changes (destructive changes of cardiomyocytes with loss of histological structure of the myocardium) were established between the ventricle and the atria. In the atrial epicardium of group with expose Pb(NO₃)₂, focal accumulation of mast cells was detected, which could indicate their infiltration / migration, but no other types of leukocytes (neutrophils,

lymphocytes, etc.) were detected. In general, in all experimental groups progressive damage to the myocardial cardiomyocytes, to a greater extent in the atria, was revealed.

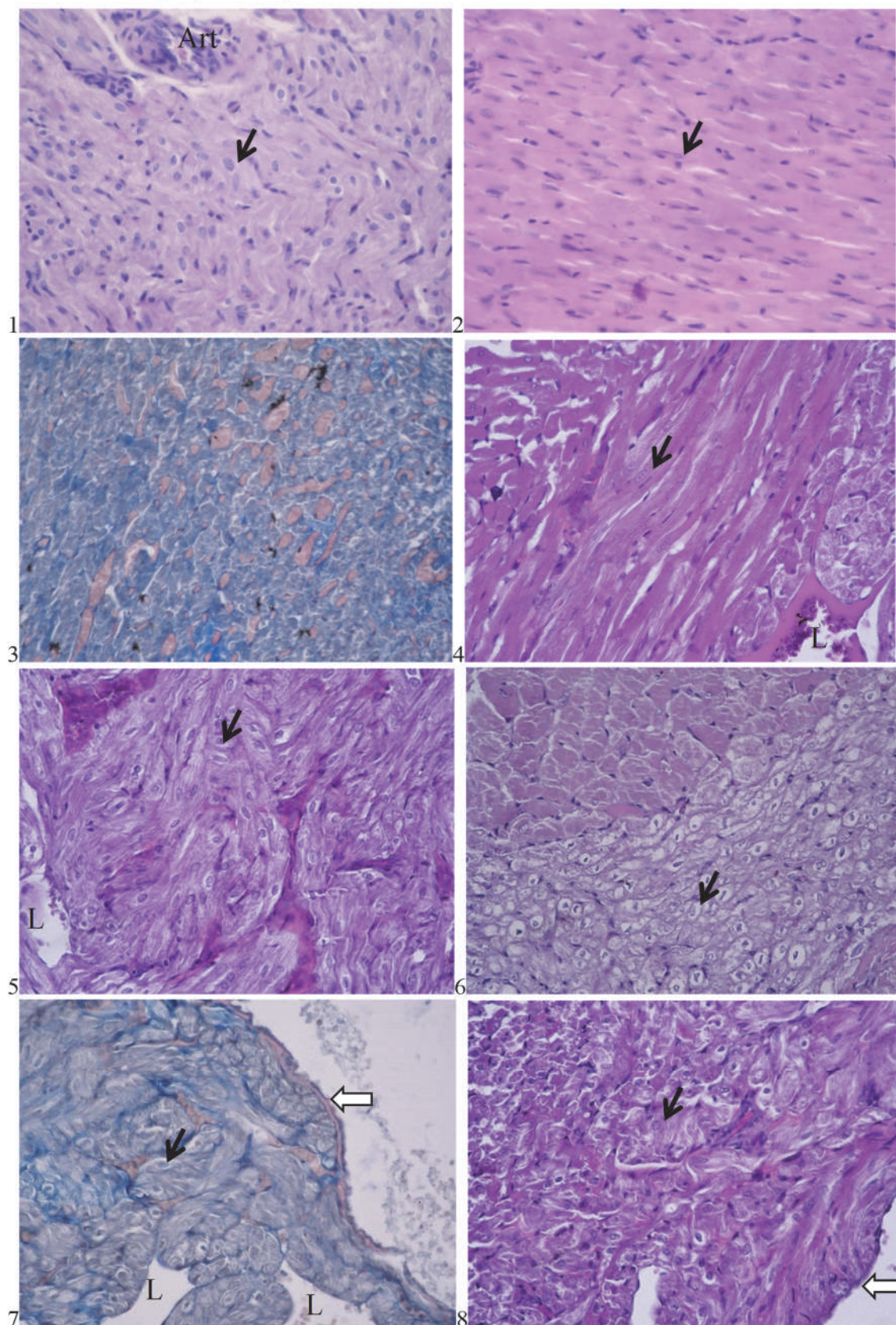



Fig. 1. Damage to the myocardium of the rat's heart against the background of exposure to Pb compounds. Significant structural changes in the atrial myocardium and partial damage to the fibers of the cardiomyocytes in the ventricle, blood filling, erythrocytic stasis of the microvessels. Increasing interstitial space between cardiomyocytes. Note: 1, 2 - atria and ventricle of the control group; 3, 4 - ventricle of PbS_{26-34nm} NP group after 30 and 60 injections; 5, 6 - atria of the PbS_{50-80nm} NP group after 30 and 60 injections; 7, 8 - atrium of Pb(NO₃)₂ group after 30 and 60 injections: cardiomyocyte nuclei;  the epicardium; Art - artery; L - atrial / ventricular lumen. Hematoxylin-eosin (1, 2, 4, 5, 6, 8), Picro-Mallory (3, 7); obj. 40, oc. 10.

In the control and experimental groups, the histological structure of the aortic wall had similar morphological features. All three tunicae were registered – inner (intima), middle (media) and outer (adventitia). In the control group, the elastic membranes of the tunica media were tightly oriented, with nuclei of smooth muscle cells registered between them (fig. 2). The adventitia was represented by a fibrous connective tissue; adipose tissue was often detected around the aorta. The results of aortic wall morphometry are shown in table 1.

After 30 injections of PbS_{26-34nm} and PbS_{50-80nm} NP group, a decrease in rats' aortic wall thickness as well as in connective tissue density in the adventitious layer was detected. After 30 injections of Pb(NO₃)₂, on the contrary, a local increase in the density of collagen fibers and fibroblasts was observed (the connective tissue density in the adventitia of the PbS_{50-80nm} NP group was lower). The morphometric study confirmed the morphological changes: the thickness of the aortic wall statistically significantly decreased in both PbS NP groups, compared to control. In PbS_{50-80nm} NP group, the thickness of the adventitial layer is less than that of PbS_{26-34nm} NP group and Pb(NO₃)₂ (Table 1). In the Pb(NO₃)₂ group, quantitative and morphological changes in aorta were less pronounced (wall thickness decreased, but the relative content of adventitia remained at the level of statistical error). Slight reduction in the number of elastic membranes in tunica media of aorta is observed in all groups, especially with PbS_{26-34nm} NP and Pb(NO₃)₂ expose.

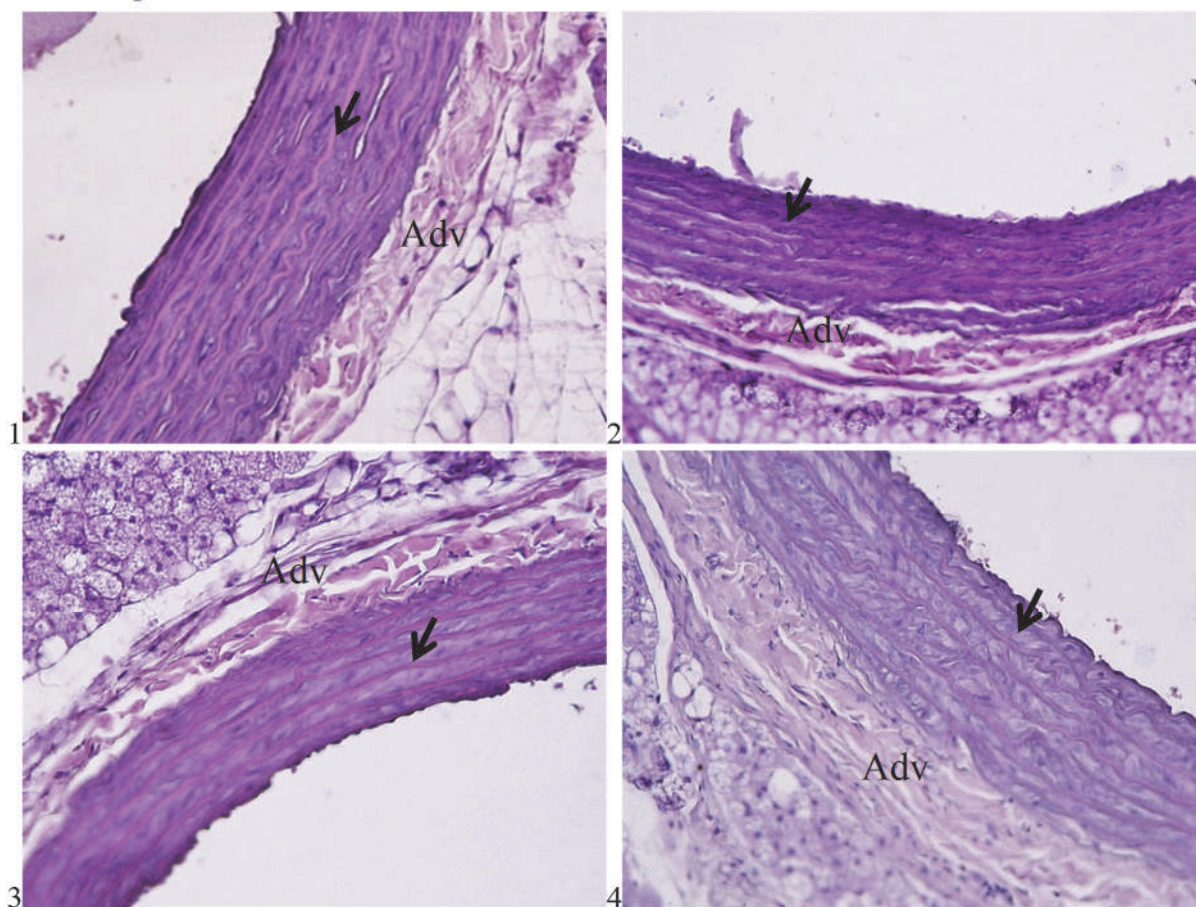


Fig. 2. Structural changes of the aorta after 60 injections of Pb compounds. Changes in the density of structural elements in the tunica media. Note: 1 - control group; 2 - PbS_{26-34nm} NP group; 3 - PbS_{50-80nm} NP group; 4 - Pb(NO₃)₂; ← elastic membranes of tunica media; Adv - adventitia. Hematoxylin-eosin, obj. 40, oc. 10.

After 60 injections, all structural samples showed similar structural changes as in the previous term, as well as the tendency of decreasing density of the structural elements of the adventitia after the introduction of Pb. Additionally, focal disorganization of the tunica media (delamination, edema, reduction of cell nuclei between elastic membranes) and areas of reduced density of elastic membranes were revealed in all experimental group. Especially these manifestations are significant in PbS_{26-34nm} NP and Pb(NO₃)₂ experimental animal groups. After 60 injections of PbS_{50-80nm} NP, the tendency of the aortic wall thickness to increase due to the development of structural changes (loosening of collagen fibers) of the adventitial layer and elastic membranes in the tunica media was established.

Currently, there is insufficient data on the toxic effects of lead NPs on the cardiovascular system, so it is important to study the features of cardiovascular toxicity in order to prevent possible negative effects

of lead nanoparticles on the health of the population. Ferreira de Mattos G. et al. explain the morphofunctional disorders of the heart in people affected by lead poisoning, disorders of cardiac excitability, the appearance of a negative inotropic effect, and increased diastolic tension [5]. But debatable is the question of the dependence of lead NP toxicity on their size. Thus, Qingzhao et al. express a view of the dependence of a greater degree of lung lesion by NP of smaller size, in particular 30 nm [11]. Luhovsky S.P. et al. found that 12.5 nm PbS NP compared to 100 nm NP have a greater area of interaction with the structural elements of the skin and thus increases the permeability through the skin and toxic effects on the liver, kidneys and heart [9]. It is already established that Pb NP accumulate in tissues, crystallize, are phagocytosed by siderophages, causing hydropic dystrophy of organ cells having dose-dependent toxicity [3]. Lebedová J. et al. found that lungs and kidneys are more sensitive to Pb NP than liver and brain, and Pb NP toxicity was correlated with oxidation and decreased glutathione [8]. The latter is explained by the development of oxidative stress and a decrease in the activity of antioxidant enzymes, which leads to dystrophic and proteolytic processes [11]. In our own experiments, we found damage to the myocardium and the aorta wall due to the action of Pb compounds in nanoscale and ionic form, and observed a tendency for progressive morphological changes after 60 injections, which was manifested by a decrease in the number of nuclei of cells in the walls of some of medium caliber vessels in myocardium and blood filling of ventricle capillaries. The decreasing of the density of cardiomyocyte cytoplasm (in the inner layers of the myocardium, while the outer layers remained more compact) may indicate a damage of the cardiomyocytes contractile elements and their destruction against the background of NP Pb exposure.

Table 1

Results of morphometric investigation of the aortic wall in control and experimental groups (Me [Q1-Q3])

Group	Aorta wall thickness, mkm	T.adv. thickness, mkm	Comparative amount of collagen fibers in t.adv., %	Number of elastic membranes in t.media, conv. un.
Control group	230.1 [220.7-240.7]	97.3 [85.3-110.7]	42.2 [38.3-46.1]	11 [10.2-11]
PbS _{26-34nm} NP – 30 injections	199.0 [185.5-220.0] *	70.2 [63.8-71.9] *	35.3 [29.2-38.8] *	8 [8-9]
PbS _{50-80nm} NP – 30 injections	193.4 [171.9-200.4] *	57.1 [42.1-60.8] * P<0.05 до Pb1. Pb3	29.3 [24.5-30.4] * P<0.05 до Pb1	9 [9-9]
Pb(NO ₃) ₂ – 30 injections	193.2 [171.6-205.4] *	85.9 [67.0-99.6]	44.6 [38.0-47.7]	8 [8-9]
PbS _{26-34nm} NP– 60 injections	183.2 [176.2-201.8] *	51.1 [46.1-62.6] *	28.4 [25.0-31.8] *	9[9-9]
PbS _{50-80nm} NP – 60 injections	215.5 [200.1-223.3]	82.8 [60.6-96.3] P<0.05 до Pb1	38.3 [30.2-43.1]	9 [8-10]
Pb(NO ₃) ₂ – 60 injections	197.0 [192.1-198.2] *	68.2 [56.4-72.1] *	34.6 [29.3-36.3] *	8[8-8]

Note: * - statistically significant differences compared to control (P <0.05)

Our results are confirmed by other authors. Thus, dystonic changes of arteries and capillaries (paretic enlargements and spasmodically constricted vessels), blood stasis in capillaries, red blood cells aggregation and development of cardiomyocyte dystrophy in the form of appearance of cells with signs of their contractural damage were revealed [9]. One of the long-term effects of lead toxicity on cardiovascular system is the restructuring of the connective tissue of the aorta, capillaries, and myocardium, which is identical to changes in accelerated aging of these organs. As a result of the damage to an elastic carcass of vessels there was development of aortic delamination and its aneurysm [4]. Disorganization of the aortic tunica media was detected in the PbS_{50-80nm} and Pb(NO₃)₂ groups, as well as changes in connective tissue in all study groups. According to the results of the morphometric study after the introduction of Pb NP there was found statistically significant decrease of the thickness of its wall, after 30 and 60 injections (an average of 15.6% and 14.3%), which is associated with a decrease in the thickness of the adventitious layer and a slight reduction in the number of elastic membranes in its tunica media. This may indicate a suppression of the development (morphogenesis) of the connective tissue against the background of Pb NP exposure.

Conclusion

Prolonged administration of PbS_{26-34nm} NP and PbS_{50-80nm} NP groups to rats caused damage to the myocardium and structural changes of the aorta wall, which consist in cardiomyocyte dystrophy,

delamination of the elastic membranes of tunica media in aorta, and a decrease in the content of connective tissue in tunica adventitia.

References

1. Aleksyichuk VD, Sokurenko LM, Omelchuk ST. Peculiarities of lead sulfide and nitrate nanoparticles influence on organisms of experimental animals in different research periods and methods of its negative impact correction. *World of medicine and biology*. 2015; 4 (54): 97-101. [in Ukrainian]
2. Casals E, Vazquez-Campos S, Bastus N, Puentes V. Distribution and potential toxicity of engineered inorganic nanoparticles and carbon nanostructures in biological systems. *Trac-Trends in Analytical Chemistry*. 2008; 27: 672-683. doi: 10.1016/j.trac.2008.06.004.
3. Dumkova J, Smutna T, Vrlíkova L, Le Coustumer P, Večeřa Z, Dočekal B, Mikuška P, Čapka L, Fictum P, Hampl A, Buchtová M. Sub-chronic inhalation of lead oxide nanoparticles revealed their broad distribution and tissue-specific subcellular localization in target organs. *Part Fibre Toxicol*. 2017; 14(1): 55.
4. Feng L, Yang X, Shi Y, Liang S, Zhao T, Duan J, Sun Z. Co-exposure subacute toxicity of silica nanoparticles and lead acetate on cardiovascular system. *Int J Nanomedicine*. 2018; 13: 7819-7834.
5. Ferreira de Mattos G, Costa C, Savio F, Alonso M, Nicolson GL. Lead poisoning: acute exposure of the heart to lead ions promotes changes in cardiac function and Cav1.2 ion channels. *Biophys Rev*. 2017; 9(5): 807-825.
6. Grandjean P. Even low-dose lead exposure is hazardous. *Lancet*. 2010; 376: 855-856. doi: 10.1016/S0140-6736(10)60745-3.
7. Jeevanandam J, Barhoum A, Chan YS, Dufresne A, Danquah MK. Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. *Beilstein J Nanotechnol* 2018; 9: 1050-1074. <https://doi.org/10.3762/bjnano.9.98>
8. Lebedová J, Nováková Z, Večeřa Z, Buchtová M, Dumková J, Dočekal B, Bláhová L, Mikuška P, Míšek I, Hampl A, Hilscherová K. Impact of acute and subchronic inhalation exposure to PbO nanoparticles on mice. *Nanotoxicology*. 2018; 12(4): 290-304.
9. Luhovsky SP, Didenko MM, Melnik NA. Morphofunctional changes in internal organs of rats upon chronic exposure of micro and nanoparticles of inorganic lead compounds on their intact skin. *Ukrainian Journal of Modern Problems of Toxicology*. 2017; 3: 34-47.
10. Pietroiusti A, Magrini A. Engineered nanoparticles at the workplace: current knowledge about workers' risk. *Occupational Medicine*, 65(2); 2015: 171-173. <https://doi.org/10.1093/occmed/kqu194>.
11. Qingzhao Li, Xiaoli Hu, Yuping Bai, Mohamed Alattar, Dong Ma, Yanhua Cao, Yulan Hao, Lihua Wang, Chunyang Jiang. The oxidative damage and inflammatory response induced by lead sulfide nanoparticles in rat lung. *Food and Chemical Toxicology*. 2013; 60: 213-217.
12. Ren Z, Sun J, Li H, Mao P, Wei Y, Zhong X, Hu J, Yang S, Wang J. Bilayer PbS Quantum dots for high-performance photodetectors. *Adv Mater*. 2017; 29(33). doi: 10.1002/adma.201702055. Epub 2017.
13. Skoczynska A, Skoczynska M. Low-Level exposure to lead as a cardiovascular risk factor. In: Gasparyan A, editor. *Cardiovascular Risk Factors*. Croatia: InTech Open; 2012. doi: 10.5772/30808.
14. Tchapyguine M, Mikkela MH, Mårzell E, Polley C, Mikkelsen A, Zhang W, Yartsev A, Hetherington CJ, Wallenberg LR, Björneholm O. Metal-passivated PbS nanoparticles: fabrication and characterization. *Phys Chem Chem Phys*. 2017; 8-19(10): 7252-7261. doi: 10.1039/c6cp06870g.
15. Yavorovsky OP, Karlova OO, Sheiman BS. Toxicokinetic mechanisms of endothelial dysfunction formation as an early clinical manifestation of chronic lead poisoning. *Ukrainian medical journal Heart & vessels*. 2015; 3(51): 92-98.

Реферати

КАРДИОАЗОТОКСИЧНИЙ ЕФЕКТ ВВЕДЕННЯ НАНОЧАСТИНОК СВИНЦЮ РІЗНИХ РОЗМІРІВ

Губар І.В., Лавриненко В.Є., Чухрай С.М., Савосько С.І., Сокуренько Л.М., Апихтіна О.Л., Яворовський О.П.

У експериментах досліджували кардіоазотоксичну дію НЧ (наночастинок) свинцю розміром 26-34 нм та 50-80 нм. Морфологічні та морфометричні методи були використані для виявлення структурних змін серця та аорти через 30 і 60 введень НЧ Pb. Результати експериментів вказують на пошкодження міокарду серця, які полягають у збільшенні інтерстиційного простору між волокнами кардіомиоцитів, дистрофії кардіомиоцитів, стази крові у мікросудинах шлуночків серця. Виявлено більшу чутливість міокарду передсердь до токсичної дії НЧ Pb. Структурні зміни аорти полягали у розшаруванні еластичних мембран, зменшенні щільності сполучної тканини адвентиційної оболонки та мали тенденцію до прогресуючих змін.

Ключові слова: свинець, Pb, наночастинки, морфологічні зміни, аорта, міокард.

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КАРДИОАЗОТОКСИЧЕСКИЙ ЭФФЕКТ ВВЕДЕНИЯ НАНОЧАСТИЧЕК СВИНЦА РАЗЛИЧНЫХ РАЗМЕРОВ

Губарь И.В., Лавриненко В.Е., Чухрай С.Н., Савосько С.И., Сокуренько Л.М., Апихтина Е.Л., Яворовский А.П.

В экспериментах исследовали кардиоазотоксическое действие НЧ (наночастиц) свинца размером 26-34 нм и 50-80 нм. Морфологические и морфометрические методы были использованы для обнаружения структурных изменений сердца и аорты через 30 и 60 введений НЧ Pb. Результаты экспериментов указывают на повреждения миокарда сердца, которые заключаются в увеличении интерстициального пространства между волокнами кардиомиоцитов, дистрофии кардиомиоцитов, стаза крови в микросудах желудочков сердца. Виявлено большую чувствительность миокарда предсердий к токсическому действию НЧ Pb. Структурные изменения аорты заключались в расслоении эластических мембран, уменьшении плотности соединительной ткани адвентициальной оболочки и имели тенденцию к прогрессирующим изменениям.

Ключевые слова: свинец, Pb, наночастицы, морфологические изменения, аорта, миокард.

Рецензент Єрошенко Г.А.

A.Ye. Demkovych, Yu.I. Bondarenko, P.A. Hasnuk, I.O. Sukhovolets
I. Horbachevsky Ternopil National Medical University, Ternopil

PHAGOCYtic ACTIVITY OF PERIPHERAL BLOOD NEUTROPHILS IN MECHANISMS OF EXPERIMENTAL BACTERIAL-IMMUNE PERIODONTITIS DEVELOPMENT

e-mail: demkovushae@tdmu.edu.ua

One of the important links that leads to injure in all structures of the periodontium and formation of inflammation of varies severity is phagocytic activity of polymorphonuclear leukocytes. The purpose of the study was to evaluate pathogenic role of neutrophils activity in the experimental bacterial-immune inflammation in periodontium. The article shows the results of studies on the spontaneous and activated test with nitroblue tetrazolium on the 7th, 14th and 30th days of the bacterial-immune inflammation in periodontal tissues. In this paper, the results of neutrophils activity changes in the process of formation and chronification of the inflammation in the tissues of periodontal complex are presented. It was established that the nature of the experimental inflammation course in periodontal tissues depending on the peculiarities of phagocytic activity changes in blood neutrophils. In this condition the spontaneous test with nitro blue tetrazolium of blood neutrophils accompanied the growth and indices of the oxygen-dependent metabolism reserve decreased in the induced nitro blue tetrazolium test, the coefficient of blood neutrophils metabolic activation in the rats with inflammatory process in periodontium and testified about metabolic reserves depletion of these cells and disorder of phagocytic activity.

Key words: phagocytosis, bacterial-immune periodontitis, neutrophils, immune system.

The work is a fragment of the research project "Systemic and organic violations due to the actions of extraordinary factors on the body, mechanisms of their development and pathogenetic correction", state registration No. 0116 U003390.

Inflammatory diseases of periodontal tissues idespread in the all world, and Ukraine is one of the countries with a high incidence of chronic generalized periodontal disease. According to various authors, there is a further increase of periodontal disease in our country in last years, which has both general medical and social significance [3].

The development and progression of inflammatory diseases of the periodontium is now considered not so much as a local inflammation as well as reaction of the whole organism to the bacterial invasion in the periodontal tissues. It is known that the development of periodontitis is a result of an imbalance between the microflora of the oral cavity, that is, microbiote, and immune protection of the body [12]. It should also take into account the activity of inflammatory cells and adequacy of mechanisms of resistance [8, 11]. The bacterial factor is not enough for development of inflammation one, should be a combined of pathogenetic factors. There is means fixing of them not only in the tissues of periodontium, but also in all organism, from that depends on effectiveness of standard therapy [6].

Now, much evidence has been accumulated that the risk of systemic diseases may increase as a result of periodontal disease. This concerns, for example, coronary heart disease, myocardial infarction, stroke, arteriosclerosis. There is a necessity in deep and comprehensive study of the disorder features of immunological processes in the mechanisms of this pathology development as one of important parts of pathogenesis [9]. It is generally known that one of the key links in the phagocytosis immunity is, which is considered not only as an antiinfectious immunity tool, but also as a universal effector that responds to numerous signals about destabilization of the body's internal environment and is one of key pathogenetic links in the development of immune and inflammatory reactions [10].

The purpose of the study was to determinate the pathogenetic role of neutrophils activity for the experimental bacterial-immune inflammation in periodontium.

Materials and methods. The studies were performed with the use of non-linear, clinically healthy white rat males weighing 150-200 g in the conditions of vivarium. Experiments were carried out in compliance with the general rules and regulations of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), and the "General Ethical Principles of Animals Experimentation" (Kyiv, 2001). Animals were kept throughout the observation period on a standard diet, balanced by elements of food with free access to water. The rats were randomly divided into four groups: I group (n = 10) – intact animals; II group (n = 8) – animals with bacterial-immune inflammation in the periodontium on the 7th day of the experiment; III group (n = 8) – animals with bacterial-immune inflammation in the periodontium on the 14th day of the experiment, IV group (n = 8) – animals with bacterial-immune inflammation in the periodontium on the 30th day of the experiment.

The experimentally modelled bacterial-immune periodontitis was produced in the rats by injection into periodontal tissues complex mixture of microorganisms diluted in protein (egg white). A complete

Freund's adjuvant was injected in the animal's paw simultaneously with the introduction of the pathogen to enhance the immune response. To IV group of animals was injected pathogen with adjuvant repeatedly on the 14th day. Thus, an increase in the reproduction efficiency of bacterial-immune periodontitis was achieved [2]. On the 30th day of the study, rats were killed by bleeding under thiopental anesthesia. Blood was taken for further research in which the bactericidal action of neutrophils was determined using the nitro-blue tetrazolium reduction test (NBT-test) [4].

The spontaneous NBT-test was performed with phagocytes which were cultivated in the presence of nitro blue tetrazolium without prior activation of cells, while carrying out an induced NBT-test, an activator of phagocytic reaction was added to the culture medium. The reaction was evaluated by a result of counting 100 neutrophils with the presence of granules and grains of diformasan in the cytoplasm. In the cytoplasm of the cells, which reacted positively with nitro blue tetrazolium, precipitation of granular diformasan blue-violet color was recorded. In the negative reaction with NBT, granulates of diformasan in the cytoplasm of the cells were absent. Reserve possibility of oxygen-dependent metabolism was determined for index of reserve and metabolic activation coefficient.

The results were statistically processed using the software STATISTICA Version 10.0 ("Statsoft", USA) [5]. The reliability of the difference in values between independent quantitative values was determined with the normal distribution by criterion U-criterion Mann-Whitney [7].

Results of the study and their discussion. In a result of this research was found for early stage of inflammation in the periodontium, which included period from the 1st to the 7th day of the experiment, excessive increase of the number formazan-positive neutrophils (by 1.83 times; $p < 0.01$) in the spontaneous nitro blue tetrazolium test (NBT-test) as compared to the intact animal group (table 1, fig. 1).

Table 1

Indices of spontaneous NBT-test of rat's blood neutrophils for different periods of modelled inflammation development in the periodontium (M±m)

Groups of animals	Duration of the experiment (days)	Number of the rats	Spontaneous NBT-positive test, %
Control, intact rats	-	10	14.39±0.84
Animals with periodontal inflammation	7	8	26.34±1.07 $p_1 < 0.01$
	14	8	22.54±0.90 $p_1 < 0.01$; $p_2 < 0.05$
	30	8	19,80±0.72 $p_1 < 0.01$; $p_2 < 0.01$; $p_3 > 0.05$

Note 1: p_1 – index of differences relative to intact animals. 2: p_2 – index of differences relative to animals with bacterial-immune periodontal inflammation on the 7th day of the experiment. 3: p_3 – index of differences relative to animals with bacterial-immune periodontal inflammation on the 14th day of the experiment.

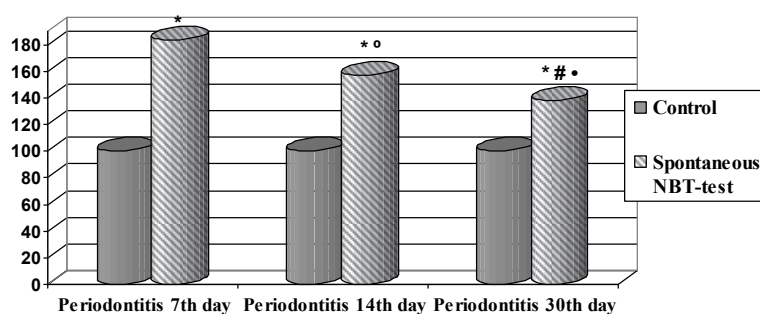


Fig. 1. – Changes in the indices of spontaneous NBT-test in the rats blood neutrophils in conditions of modelled bacterial-immune periodontal inflammation (% of control).

Note 1: * – differences between the control rats ($p < 0.01$). 2: # – differences between rats with periodontal inflammation on the 7th day of the research ($p < 0.01$). 3: ° – differences between rats with periodontal inflammation on the 7th day of the research ($p < 0.05$). 4: • – differences between rats with periodontal inflammation on the 14th day of the research ($p > 0.05$).

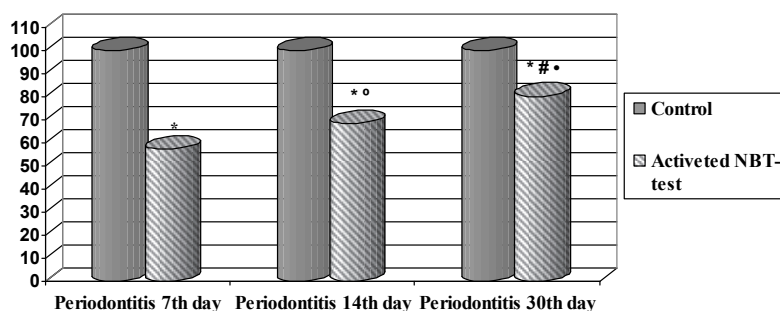
Studying the presence of diformasan-positive cells in activated NBT-test in the animals with experimental modelled bacterial-immune inflammation on the 14th day of the pathological process in the periodontium, number of neutrophils with these properties was found increased (by 1.19 times; $p < 0.05$) compared to animals, which were studied on the 7th day, and decreased compared to the results of the intact group (by 1.47 times ($p < 0.01$)).

The activated NBT-test characteristics functional activity of phagocytes and affects their readiness for complete phagocytosis in the presence of antigenic stimuli [1]. In a process of perform an activated NBT-test opposite-directed results were obtained (table 2, fig. 2). The number of diformasan-positive neutrophils was found decreased in the rats, which was enquire on the early stage (7th day) of the experimental periodontitis (by 1.75 times; $p < 0.01$), compared to the control rats.

Indices of activated NBT-test of rats blood neutrophils for different periods of modelled inflammation development in the periodontium (M±m)

Groups of animals	Duration of the experiment (days)	Number of the rats	Activated NBT-positive test, %
Control, intact rats	-	10	31.07±1.01
Animals with periodontal inflammation	7	8	17.81±0.69 $p_1 < 0.01$
	14	8	21.20±0.74 $p_1 < 0.01; p_2 < 0.05$
	30	8	24.93±0.52 $p_1 < 0.01; p_2 < 0.01; p_3 < 0.01$

Note 1: p_1 – index of differences relative to intact animals. 2: p_2 – index of differences relative to animals with bacterial-immune periodontal inflammation on the 7th day of the experiment. 3: p_3 – index of differences relative to animals with bacterial-immune periodontal inflammation on the 14th day of the experiment.



Periodontitis 7th day Periodontitis 14th day Periodontitis 30th day

Fig. 2. – Changes in the indices of activated NBT-test in the rats blood neutrophils in conditions of modelled bacterial-immune periodontal inflammation (% of control).

Note 1: * – differences between the control rats ($p < 0.01$). 2: # – differences between rats with periodontal inflammation on the 7th day of the research ($p < 0.01$). 3: ° – differences between rats with periodontal inflammation on the 7th day of the research ($p < 0.05$). 4: • – differences between rats with periodontal inflammation on the 14th day of the research ($p < 0.01$).

In comparison of diformasan-positive cells amount in spontaneous NBT-test on the 30th day of experimental periodontitis development, were found reduced their in relation with the 14th day, but the data statistically were doubtful ($p > 0.05$), at the same time meant were significantly lower (by 1.33 times; $p < 0.01$), in comparison with the 7th day of the study. However, this indicators was also significantly higher in comparison to the intact group of animals (by 1.38 times; $p < 0.01$).

It should be noted that number of diformasan-positive neutrophils in activated NBT-test of the experimental animals with periodontitis on the 30th day of the experiment was also lower (by 1.25 times; $p < 0.01$) in relation to indicator of the intact animals. However, the indicated data were higher according to those obtained in rats on the 7th (by 1.40 times; $p < 0.01$) and 14th (by 1.18 times; $p < 0.01$) days of experiment.

The coefficient of metabolic activation of phagocytes also changed. Thus, on the 7th day of bacterial-immune periodontal inflammation, it was decreased, if compared to the intact rats (by 1.79 times; $p < 0.01$) (table 3).

As it can be seen from table 3, it means that metabolic activation of phagocytic neutrophils was found decreased (by 1.46 times; $p < 0.01$) on the 14th day of the study as compared to the control group of rats. It should be noted that this index increased on the 14th day of the study in relation to the 7th day (by 1.23 times; $p < 0.05$) (fig. 3).

Table 3

Indices of oxygen-dependent metabolic reserve and coefficient of metabolic activity of animals blood phagocytes for different periods of modelled inflammation development in the periodontium (M±m)

Experiment conditions and indices	Control, intact rats	Animals with periodontal inflammation		
		7	14	30
Duration of the experiment (days)	-	7	14	30
Number of the rats	10	8	8	8
Reserve of the oxygen-dependent metabolism	2.24±0.17	0.69±0.05 $p_1 < 0.01$	0.98±0.07 $p_1 < 0.01; p_2 < 0.05$	1.27±0.04 $p_1 < 0.01; p_2 < 0.01; p_3 < 0.05$
Coefficient of metabolic activation	29.23±1.91	16.31±0.78 $p_1 < 0.01$	20.07±0.81 $p_1 < 0.01; p_2 < 0.05$	24.13±0.52 $p_1 < 0.01; p_2 < 0.01; p_3 < 0.01$

Note 1: p_1 – index of differences relative to intact animals. 2: p_2 – index of differences relative to animals with bacterial-immune periodontal inflammation on the 7th day of the experiment. 3: p_3 – index of differences relative to animals with bacterial-immune periodontal inflammation on the 14th day of the experiment.

The performed studies showed that coefficient characterizing the activity of blood neutrophils on the 30th day of the study was higher, as compared to the groups of rats with experimental inflammations on the 7th and 14th day of the study, respectively (by 1.48 times; $p < 0.01$ and by 1.20 times; $p < 0.01$). But, it increased (by 1.21 times; $p < 0.01$) than in the group of animal without periodontitis (fig. 3).

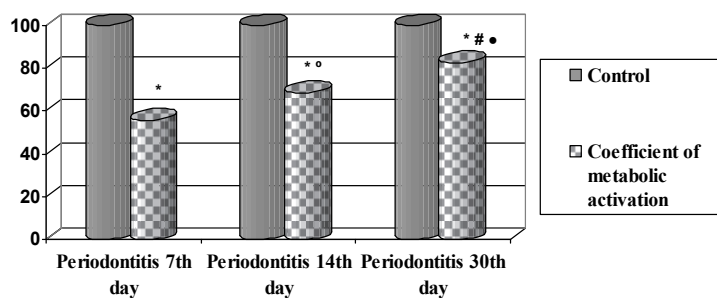


Fig. 3. – Changes in the indices of metabolic coefficient activation in the rats blood neutrophils in conditions of modelled bacterial-immune periodontal inflammation (% of control).

Note 1: * – differences between the control rats ($p < 0.01$). 2: # – differences between rats with periodontal inflammation on the 7th day of the research ($p < 0.01$). 3: ° – differences between rats with periodontal inflammation on the 7th day of the research ($p < 0.05$). 4: • – differences between rats with periodontal inflammation on the 14th day of the research ($p < 0.01$).

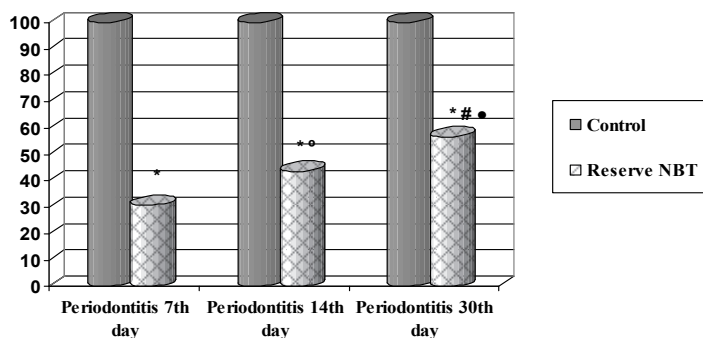


Fig. 4. – Changes in the indices of oxygen-dependent metabolic reserve in the rats blood neutrophils in conditions of modelled bacterial-immune periodontal inflammation (% of control).

Note 1: * – differences between the control rats ($p < 0.01$). 2: # – differences between rats with periodontal inflammation on the 7th day of the research ($p < 0.01$). 3: ° – differences between rats with periodontal inflammation on the 7th day of the research ($p < 0.05$). 4: • – differences between rats with periodontal inflammation on the 14th day of the research ($p < 0.05$).

Conclusions

1. Increased indices of spontaneous test with nitro blue tetrazolium of blood neutrophils in experimental animals with bacterial-immune modelled periodontitis indicate the predominance of their oxygen-dependent bactericidal activity and presence in the blood of activators that can stimulate the functional activity of these phagocytes.
2. Reduced indices of induced NBT-test of oxygen-dependent metabolism, metabolic reserve rate of blood neutrophils in the rats with inflammatory process in the periodontium is a result of metabolic reserves depletion of these cells and of phagocytic processes disorder.

References

1. Demkovych AYe, Bondarenko YuI. Patohenetichni osnovy modelyuvannya parodontytu u tvaryn. Zdobutky klinichnoyi i eksperymentalnoyi medytsyny. 2015 Sich; 1(22):54-57. [in Ukrainian]
2. Dimitrova AG, Kolenko YuG. Otsenka effektivnosti razlichnykh immunomodulyatorov v kompleksnom lechenii generalizovanogo parodontita u lits molodogo vozrasta (18-25 let). 2013; 2:38-39. [in Russian]
3. Nagoev BS, Kambachokova ZA. Funktsionalno-metabolicheskaya aktivnost neitrofilnykh granulocytov u bolnykh retsidiviruyushhey gerpeticheskoy infektsiyey. Zhurnal infektologii. 2011; 3(3):38-41. [in Russian]
4. Orlov AI. Struktura neparametricheskoy statistiki (obobshchayushchaya statya). Zavodskaya laboratoriya. Diagnostika materialov. 2015; 81(7):62-72. [in Russian]
5. Chernyshov VP, Stamboli LV, Osypchuk DV, Donskoi B.V. Laboratorna diagnostyka khronichnoyi granulomatoznoyi khvoroby: porivnyannya dvokh metodiv. Eksperymentalna ta klinichna fiziologiya i biokhimiya. 2016; 2:77-83. [in Ukrainian]
6. Bayani M, Pourali M, Keivan M. Possible interaction between visfatin, periodontal infection, and other systemic diseases: A brief review of literature. Eur J Dent. 2017 Jul-Sep; 11(3):407-410.
7. Berger RL, Casella C. Hypothesis Testing in Statistics. International Encyclopedia of the Social & Behavioral Sciences. 2015; 11:491-493.
8. Genco RJ, Garcia WS, Compton R. Risk factors for periodontal disease. Risk assessment and periodontal prevention in primary care. Periodontol 2000. 2016; 71(1):10-21.
9. Hajishengallis G. Immunomicrobial pathogenesis of periodontitis: keystone, pathobionts, and host response. Trends Immunol. 2014; 35(1):3-11.
10. Herrmann JM, Meyle J. Neutrophil activation and periodontal tissue injury. Periodontol 2000. 2015 Oct; 69(1):111-127.
11. Hirschfeld J. Dynamic interactions of neutrophils and biofilms. J Oral Microbiol. 2014 Dec 17; 6:26102.
12. Thumbigere-Math V, Michalowicz BS, Hodges JS. Periodontal disease as a risk factor for bisphosphonate-related osteonecrosis of the jaw. J. Periodontol. 2014; 2(85):226-233.

Реферати

ФАГОЦИТАРНА АКТИВНІСТЬ НЕЙТРОФІЛІВ КРОВІ В МЕХАНІЗМАХ РОЗВИТКУ ЕКСПЕРИМЕНТАЛЬНОГО БАКТЕРІАЛЬНО-ІМУННОГО ПАРОДОНТИТУДемкович А.Є., Бондаренко Ю.І., Гасюк П.А.,
Сухоалець І.О.

Однією із важливих ланок в механізмах розвитку, що призводять до ушкодження структурних компонентів пародонтального комплексу та розвитку запального процесу з різним ступенем тяжкості, є фагоцитарна активність лейкоцитів. Мета дослідження полягала в оцінці активності нейтрофілів крові при експериментальному змодельованому бактеріально-імунному пародонтиті. У статті наведені результати досліджень показників спонтанного та активованого тесту з нітросинім тетразолієм на 7-му, 14-ту і 30-ту добу експериментального бактеріально-імунного запалення в пародонті. При цьому наводяться дані щодо характеру змін фагоцитарної активності нейтрофілів у процесі формування і хронізації запального вогнища в пародонтальних тканинах. Також встановлено, що характер перебігу даного змодельованого запального процесу запалення в пародонтальних тканинах залежав від особливостей змін фагоцитарної активності нейтрофілів крові. При цьому запальний процес супроводжувався підвищенням спонтанного тесту з нітросинім тетразолієм нейтрофілів крові та зниженням показників індукованого НСТ-тесту, резерву оксиген-залежного метаболізму, коефіцієнта метаболічної активації нейтрофілів крові щурів із запальним процесом у пародонті та свідчив про виснаження метаболічних резервів даних клітин і порушення процесів фагоцитозу.

Ключові слова: Фагоцитоз, нейтрофіли, імунна система, бактеріально-імунний пародонтит.

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ФАГОЦИТАРНАЯ АКТИВНОСТЬ НЕЙТРОФИЛОВ КРОВИ В МЕХАНИЗМАХ РАЗВИТИЯ ЭКСПЕРИМЕНТАЛЬНОГО БАКТЕРИАЛЬНО-ИМУННОГО ПАРОДОНТИТАДемкович А.Е., Бондаренко Ю.И., Гасюк П.А.,
Сухоалець И.О.

Одной из важных звеньев в механизмах повреждения структур пародонтального комплекса и формирования воспалительного процесса с различной тяжестью, является фагоцитарная активность лейкоцитов. Цель исследования заключалась в оценке активности нейтрофилов крови при экспериментальном моделированном бактеріально-імунном воспалении в пародонте. В статье показаны результаты исследований полученных показателей спонтанного и активированного теста с нитросиним тетразолием на 7-ые, 14-ые и 30-ые сутки экспериментального пародонтита. При этом приводятся данные о характере изменений активности нейтрофилов в процессе формирования и хронизации воспалительного очага в тканях пародонта. Установлено, что характер течения экспериментального воспаления в тканях пародонтального комплекса зависит от особенностей изменений фагоцитарной активности нейтрофилов. При этом воспалительный процесс сопровождался повышением спонтанного теста с нитросиним тетразолием нейтрофилов крови и снижением показателей индуцированного НСТ-теста, резерва кислород-зависимого метаболизма, коэффициента метаболической активности нейтрофилов крови крыс с воспалительным процессом в пародонте и свидетельствовал об истощении метаболических резервов данных клеток и нарушении процессов фагоцитоза.

Ключевые слова: Фагоцитоз, нейтрофилы, иммунная система, бактеріально-імунный.

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I.Ya. Dzyubanovskiy, B.M. Vervega¹, S.R. Pidruchna, N.A. Melnyk
HSEE "I.Ya. Horbachevskiy Ternopil National Medical University, MOH of Ukraine", Ternopil
¹Danylo Halytskyi Lviv National Medical University, Lviv

MORPHOLOGICAL CHANGES IN RAT HEART MUSCLE IN EXPERIMENTAL PERITONITIS AGAINST THE BACKGROUND OF DIABETES MELLITUS

e-mail: danaverveha@gmail.com

The purpose of the work was to study the morphological changes in the heart muscle of rats with modeled acute peritonitis against the background of diabetes mellitus compared to animals with experimental widespread acute peritonitis. Structural changes of cardiomyocytes (focal intracellular myocytolysis and pycnotically altered nuclei), pronounced perivascular edema, focal dystrophic-necrotic changes, polymorphocellular infiltrates, which were located in the stroma, perivascularly and around the necrotically altered cardiomyocytes, were revealed. Structural changes of cardiomyocytes and disturbances in all links of the microhemocirculatory bed, which were manifested in dystonia and paresis of vessels, changes in rheological properties of blood were more pronounced in the conditions of comorbid pathology.

Key words: acute peritonitis, diabetes mellitus, morphological changes of the heart muscle.

The work is a fragment of the research project "Pathogenetic features of the allergic and inflammatory processes course and their pharmacocorrection", state registration No. 0116U004503.

The urgency of timely diagnosis and treatment of widespread acute peritonitis (WAP) against the background of diabetes mellitus (DM) is due to long-term disability, complicated course and high mortality [7, 10]. One of the main provisions in all modern concepts of various diseases' pathogenesis, including WAP, is the cell membrane structure damage. As a consequence, complex morphofunctional changes of the internal organs lead to the development of complications, which are the main causes of lethality in

peritonitis [2, 3, 8, 9]. The inability of the body's defenses to localize infectious factors and to provide adequate excretion of toxins due to the pathogenetic features of diabetes causes the development of multiple organ failure syndrome in these patients [1, 6]. These factors are universal for various critical conditions and affect the course of the disease. Animals with experimental models of WAP and acute inflammation of the peritoneum against the background of DM were used to elucidate structural changes in the heart muscle.

The purpose of the work was to study the morphological changes in the rat heart muscle with simulated WAP against the background of DM compared to animals with experimental WAP.

Materials and methods. The experiment was performed on 48 white rats, which were divided into two groups: the main group - 24 animals with simulated WAP against the background of DM, the comparison group - 24 animals with modeled WAP. All the compared groups of animals were representative by weight, sex and age. Euthanasia of rats was performed under thiopental anesthesia on the 1st, 3rd and 7th days after the injection of feces. As a result of death during the experiment, the number of animals in the groups at the time of euthanasia was accordingly different.

This experimental study was carried out in compliance with the general rules and regulations of the European Convention for the Protection of Vertebrate Animals, which are used for research and other scientific purposes (Strasbourg, 1986), the General Ethical Principles of Experiments on Animals (Kyiv, 2001), and the Law of Ukraine "On the Protection of Animals from Cruel Treatment" (2006).

Experimental DM was induced by means of intraperitoneal administration of streptozotocin produced by "Sigma" in the fasting state at the dose of 60 mg/kg, which was dissolved in a sodium citrate buffer solution (pH 4.5). Glucose studies were carried out at 9:00 with free access of experimental animals to food and water during the night period. Insulin (0.2 IU subcutaneously two to five times a week) was administered to rats throughout the observation period.

After 2 weeks upon the use of streptozotocin in the venous blood of rats, which were obtained from the tail vein, glucose content was determined, and in the subsequent studies, only the rats with glucose content of more than 300 mg/L were observed.

14 days after the use of streptozotocin, animals of the main group were administered a 10% solution of filtered stool suspension into the abdominal cavity at the dose of 0.5 ml per 100 g of body weight. Thus, peritonitis was induced by the model proposed by V.A. Lazarenko et al. (2008) [5].

This model of peritonitis by its etiological factors, clinical manifestations and the course phases is close to a similar process in humans. The faecal suspension was obtained by mixing isotonic solution and stool obtained from the feces of 2-3 intact animals, then it was filtered twice through a double layer of gauze. The resulting suspension was injected into healthy rats in a puncture manner no later than 20 min after its preparation. In order to avoid damage to the internal organs when the faecal suspension was introduced into the abdominal cavity, the animals were kept upright, with the caudal end up. Using the method of puncture of the ventral wall in the center of the midline of the abdomen, directing the end of the needle alternately into the right and left hypochondrium, right and left iliac areas, the equal amount of faecal suspension was introduced.

Histological examination of the heart tissues was performed, they were fixed in 10% neutral formalin solution and Lilly fixator, followed by embedding in paraffin. The sections obtained by means of the sledge microtome were stained with hematoxylin and eosin, by Heidenhain and by Shabadash. The nature and depth of morphological changes were determined using Olimpus microscope and the histological slide imaging system.

Results of the study and their discussion. In the histological study of myocardial tissue in animals with simulated WAP, on the 1st day of the experiment, we found a slightly pronounced blood filling of arterial vessels in the epicardium and a slight expansion and vascular venous type congestion. In addition, there was indolent perivascular edema and single diapedetic hemorrhages. In some fields of view polymorphocellular elements were observed. The stroma was sharply loosened by edema, which also extended to the intercellular spaces (fig. 1). Some stromal vessels were somewhat dilated, irregularly filled with blood. In most fields of view, cardiomyocytes were well visualized. However, in several specimens, single cells with optically empty cytoplasm were encountered in the myocardial thickness.

In animals with WAP, cell infiltrates were observed both perivascularly and in myocardial stroma (fig. 2). In addition, hemorrhages localized within the thickness of the myocardium could be detected in individual specimens. Certain areas with necrotic altered cardiomyocytes were surrounded by polymorphocellular infiltrates.

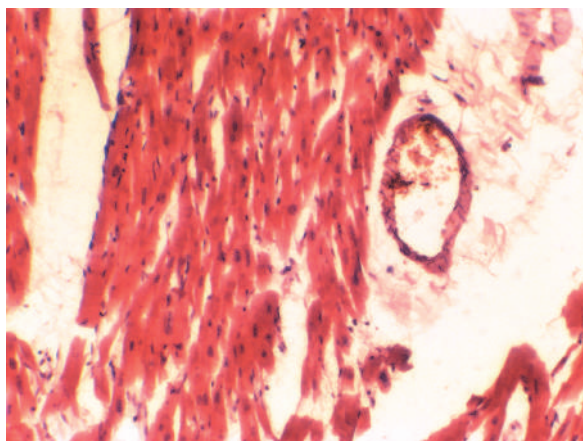


Fig. 1. - Histological structure of the myocardium in an animal with WAP on the 1st day of the experiment. Staining with hematoxylin and eosin. $\times 200$

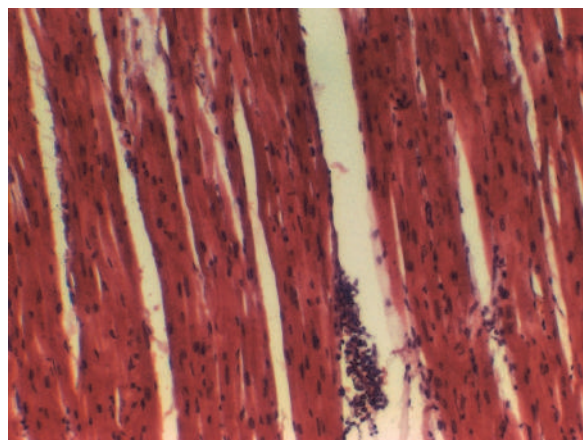


Fig. 2. - Histological structure of the myocardium in an animal with WAP against the background of DM on the 1st day of the experiment. Staining with hematoxylin and eosin. $\times 200$

In the comparison group on the 3rd day of observation pronounced blood filling of blood vessels of the arterial type in the epicardium and expansion and full blood vessels of the venous type were revealed. In addition, moderate perivascular edema was observed, with diapedetic hemorrhages and polymorphocellular elements in some places. In the animals of the main group, there was pronounced edema of the perivascular stroma, which contained single erythrocytes and polymorphic cells (fig. 3). Cell infiltrates were visualized both in the perivascular areas and in the stroma of the myocardium, whose vessels were slightly enlarged and irregularly filled with blood. In some animals, hemorrhage in the thickness of the myocardium and single cells with focal intracellular myocytolysis and pycnotically altered nuclei were found. In the endocardium, there were single aggregations of lympho- and histiocytes.

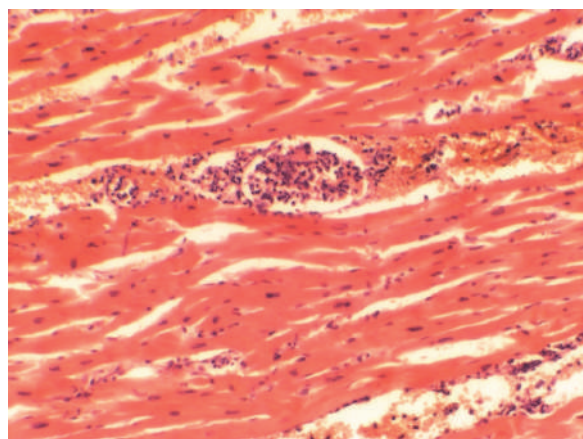


Fig. 3. - Histological structure of the myocardium of an animal with WAP against the background of DM on the 3rd day of the experiment. Staining with hematoxylin and eosin. $\times 200$

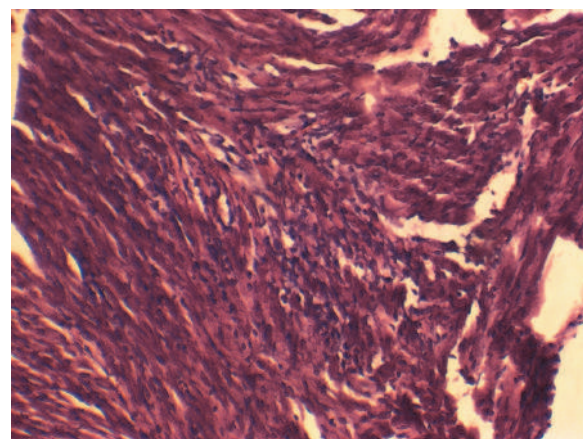


Fig. 4. - Histological structure of the myocardium in an animal with WAP against the background of DM on the 7th day of the experiment. Staining with hematoxylin and eosin. $\times 180$

On the 7th day of experimental WAP modeling, the myocardial stroma of the animals in the comparison group was moderate, loosened, containing single erythrocytes and polymorphocellular elements. Stromal vessels were irregularly blood-filled. Cardiomyocytes were well visualized in the vast majority of visual fields.

Accordingly, the pathological changes that occurred at all levels of the microhemocirculatory bed, in animals with WAP against the background of diabetes mellitus, were manifested by dystonia and angioparesis. Changes in the rheological properties of blood, namely blood stasis, formation of cellular aggregates in the lumen of vessels were observed. Plasma separation was seen in individual vessels. Dystonic manifestations and overflow of vessels with blood led to active transudation of liquid blood into perivascular spaces. The perivascular stroma was loosened by edema extending to the intercellular layers, disintegrating the muscle layers.

In animals of the main group, in the thickness of the myocardium, it was found that individual cardiomyocytes had fuzzy contours, areas of compact placement of cells alternated with the foci of their loosening. Longitudinal sections showed wide fields of disordered placement, tortuous path, and myocyte fragmentation (fig. 4). The cross-striation was fuzzy, unevenly pronounced, cytoplasm was heterogeneous, irregular in color. Somewhere between cardiomyocytes small cell infiltrates were noted. In some specimens, a small number of cells with cleared cytoplasm were identified and changes in the structure of

nuclei were observed, indicating that the presence of focal dystrophic-necrotic changes. Small areas with necrotic altered cardiomyocytes were surrounded by polymorphocellular infiltrates.

Our data are consistent with the results of I.Ya. Hushul [4], who revealed congestion of veins, venules and irregularly pronounced edema of interstitium in predominantly subendocardial compartments for 24 and 48 hours from the time of WAP modeling. The onset of pronounced interstitial edema, which we found early in the WAP modeling period against the background of DM, and the rapid increase of the discirculatory phenomena in the hemomicrocirculatory bed of the heart, combined with hypertransudation throughout the experiment, indicate that DM is significantly deepens and accelerates the processes of organ dysfunction.

Conclusion

The onset of pronounced interstitial edema at the early stages of widespread acute peritonitis modeling against the background of diabetes mellitus and a rapid increase in structural changes of cardiomyocytes, discirculatory phenomena in the haemomicrocirculatory bed of the heart in combination with hypertransudation throughout the experiment indicate a rapid generalization of the process caused by the comorbid pathology which deepens and accelerates the organ dysfunction processes.

References

1. Churpii IK, Pyptiuk OV, Churpii KL. Funktsionalnyi stan pechinky u khvorykh na perytonit. Naukovyi visnyk Uzhhorodskoho universytetu. Ser.: "Medytsyna". 2011; 2(41): 290-293. [in Ukrainian]
2. Dziubanovskiy IYa, Mihenko BO, Poliatsko KH. Syndrom poliiorhannoyi nedostatnosti u khvorykh na hostryi poshyrenyi perytonit. Klinichna anatomiya ta operatyvna khirurgiya. 2014; 2: 56-60. [in Ukrainian]
3. Herasymchuk MR, Zaiats LM. Novi pohliady na otsinku hostroho lehenevoho ushkodzhennia na foni eksperymentalnoho perytonitu. Visnyk morfolohiyi. 2012; 3: 63-68. [in Ukrainian]
4. Hushul IYa. Patomorfologichni zminy vnutrishnikh orhaniv pry hostromu poshyrenomu perytoniti na tli raku tovstoyi kyshky v eksperymenty. Eksperymentalna i klinichna medytsyna. 2016; 2(71): 64-68. [in Ukrainian]
5. Lazarenko VA, Lipatov VA, Blinkov YuYu, Skorikov DV. Eksperimentalnaya model rasprostranennogo kalovogo peritonita. Chelovek i yego zdoroye. 2008; 4: 129-132. [in Russian].
6. Polyovyi VP, Karatieieva SIu, Palianytsia AS. Analiz faktoriv ta mekhanizmiv nespetsyfnichnoho ta spetsyfnichnoho imunnoho protyinfektsiynoho zakhystu u khvorykh na TsD z hniyno-zapalnymy protsesamy pry zastosuvanni ozonoterapiyi. Khirurgichna perspektyva. 2010; 4: 108-112. [in Ukrainian]
7. Coronel F, Cigarrán S, Herrero JA. Morbidity and mortality in diabetic patients on peritoneal dialysis. Twenty-five years of experience at a single centre. Nefrologia. 2010; 30(6): 626-632. doi: 10.3265/Nefrologia.pre2010.Jul.10553.
8. Gerasymchuk MR, Zayats LM, Cherkasova VV. The role of endogenous intoxication and neutrophils in mechanisms of acute lung injury in case of experimental peritonitis. Vestnik KazNMU. 2013; 5: 76-80.
9. Mačiulienė A, Maleckas A, Kriščiukaitis A, Mačiulis V, Vencius J, Macas A. Predictors of 30-Day In-Hospital Mortality in Patients Undergoing Urgent Abdominal Surgery Due to Acute Peritonitis Complicated with Sepsis. Med Sci Monit. 2019; 25: 6331-6340. doi: 10.12659/MSM.915435.
10. Popejoy MW, Long J, Huntington JA. Analysis of patients with diabetes and complicated intra-abdominal infection or complicated urinary tract infection in phase 3 trials of ceftolozane/tazobactam. BMC Infect Dis. 2017; 17(1): 316. doi: 10.1186/s12879-017-2414-9.

Реферати

МОРФОЛОГІЧНІ ЗМІНИ В СЕРЦЕВОМУ М'ЯЗІ ШУРІВ ПРИ ЕКСПЕРИМЕНТАЛЬНОМУ ПЕРИТОНІТІ НА ТЛІ ЦУКРОВОГО ДІАБЕТУ
Дзюбановський І.Я., Вервега Б.М., Підручна С.Р., Мельник Н.А.

Метою дослідження було вивчення морфологічних змін у серцевому м'язі шурів при змодельованому гострому поширеному перитоніті на тлі цукрового діабету порівняно із тваринами з експериментальним гострим поширеним перитонітом. Виявлено структурні зміни кардіоміоцитів (осередковий внутрішньоклітинний міоцитоліз та пікнотично змінені ядра), виражений периваскулярний набряк, вогнищеві дистрофічно-некротичні зміни, поліморфноклітинні інфільтрати, які розташовувалися у стромі, периваскулярно та навколо некротично змінених кардіоміоцитів. Структурні зміни кардіоміоцитів та порушення у всіх ланках мікрогемодинамічного русла, які відображались у дистонії і парезі судин, зміни реологічних властивостей крові були більш вираженими в умовах коморбідної патології.

Ключові слова: гострий поширений перитоніт, цукровий діабет, морфологічні зміни серцевого м'язу.

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МОРФОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ В СЕРДЕЧНОЙ МЫШЦЕ КРЫС ПРИ ЭКСПЕРИМЕНТАЛЬНОМ ПЕРИТОНИТЕ НА ФОНЕ САХАРНОГО ДИАБЕТА
Дзюбановский И.Я., Вервега Б.М., Подручная С.Р., Мельник Н.А.

Целью исследования было изучение морфологических изменений в сердечной мышце крыс при смоделированном остром распространенном перитоните на фоне сахарного диабета по сравнению с животными с экспериментальным острым распространенным перитонитом. Выявлены структурные изменения кардиомиоцитов (внутриклеточный миоцитоліз и пикнотически измененные ядра), выраженный периваскулярный отек, очаговые дистрофически-некротические изменения, полиморфноклеточные инфильтраты, которые располагались в строме, периваскулярно и вокруг некротические измененных кардиомиоцитов. Структурные изменения кардиомиоцитов и нарушения во всех звеньях микрогемодинамического русла, которые отображались в дистонии и парезе сосудов, изменения реологических свойств крови были более выраженными в условиях коморбидной патологии.

Ключевые слова: острый распространенный перитонит, сахарный диабет, морфологические изменения сердечной мышцы.

Рецензент Єрошенко Г.А.

O.Yu. Isayenko, O.V. Knysh, I.M. Ryzhkova¹, O.V. Kotsar², G.I. Dyukareva³
 SI "I.I. Mechnikov Institute of Microbiology and Immunology, NAMS of Ukraine", Kharkiv
¹Kharkiv State Zoo-Veterinary Academy, Kharkiv
²Kharkiv National Medical University, Kharkiv
³Kharkiv State University of Food Technology and Trade, Kharkiv

ANTIBIOFILM ACTIVITY OF LACTOBACILLUS RHAMNOSUS GG AND SACCHAROMYCES BOULARDII METABOLITES IN RELATION TO POLYRESISTANT GRAM-NEGATIVE MICROORGANISMS

e-mail: el_isaenko@ukr.net

In order to avoid the chronic forms of diseases development and to effectively treat patients with acute manifestations of infections it is necessary not only to fight pathogenic microorganisms with antibacterial drugs, but also to learn how to influence the pathogens biofilm formation. In this work, the study of the antibiofilm activity of the original metabolites of *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*, obtained by cultivating probiotics in disintegrated microorganisms, was carried out. The antibiofilm effect of probiotic substances concerning strains polyresistant to antibacterial drugs (*Pseudomonas aeruginosa* PR, *Klebsiella pneumoniae* PR, *Lelliottia amnigena* (*Enterobacter amnigenus*) PR) is dependent on the activity of *L. rhamnosus* GG and *S. boulardii* filtrates and on the individual sensitivity of the pathogens test culture. Statistically significant reduction of the biofilms formation by pathogens' microbial cells occurred with the use of metabolites of bacteria and of fungi ($p < 0.03$). High antibiofilm properties inherent in the combination of saccharomyces and lactobacilli metabolites, with the exception of the polyresistant *K. pneumoniae* culture, which tended to reduce biofilm formation. The disintegrated *L. rhamnosus* GG and *S. boulardii* were inferior to the activity of these pathogens as to their antibiofilm properties.

Key words: biofilms, products of lactobacilli and saccharomyces metabolism, gram-negative microorganisms polyresistant to antibacterial drugs.

The work is a fragment of the research project "Study of biological and physico-chemical preconditions for the development of anti-diphtheria agents based on probiotic strains metabolites", state registration No. 0116U000864.

In recent decades, the ability to effectively treat patients with bacterial diseases is rapidly faltering: intractable diseases are replenished due to the reduced activity of antibiotics and, as a result, emergence of pathogens resistant to antimicrobial drugs. The problem of fighting against resistant microorganisms continues aggravating and is acquiring the global significance. According to the World Health Organization (WHO), due to the misuse and excessive use of antibiotics, the time may come when widespread infections and minor injuries are likely to become fatal again [3, 8, 13]. WHO published a list of antibiotic-resistant "priority pathogens" ("supermicrobs"): *Acinetobacter*, *Pseudomonas*, various species of *Enterobacteriaceae* (*Klebsiella*, *E. coli*, *Serratia*, *Proteus*).

Pathogenic microorganisms contained in biofilms are almost not sensitive to antibiotics [2]. It was established that the formation of biofilms is going on in stages: bacteria join each other in a few minutes, within 2-4 hours they form dense colonies of microscopic size, within 6-12 hours they become tolerant to biocides, after 2-4 days, depending on the microorganism's species and the conditions of its cultivation, lose planktonic forms of bacteria and create complete biofilm colonies, which are characterized by high resistance to biocides, and, with mechanical destruction applied, have the ability to quickly recover and within 24 hours to re-create a mature biofilm [1, 7]. The presented dynamics of the mature microorganism biofilm formation, testifies to the complexity of its formation process and to the difficulty of affecting the bacteria being inside. According to the literature, 60% of all chronic and recurrent infections occurred with the participation of biofilms [4, 6, 7, 11].

Consequently, in order to avoid the development of chronic disease forms and to effectively treat patients with infections caused by bacteria and fungi, it is necessary to fight against pathogenic and polyresistant opportunistic microorganisms, as well as to develop means affecting the pathogens biofilm formation [3]. Studies of recent years show the promising use of substances that can suppress the biofilm formation of *Staphylococcus aureus* and *Staphylococcus epidermidis* opportunistic bacteria, based on of lactobacilli metabolites (*Lactobacillus plantarum* L3 and *Lactobacillus fermentum* 97) [2].

The purpose of the study was to substantiate the promising application of *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* metabolism products against the biofilm forming activity of polyresistant gram-negative microorganisms to design the new generation antimicrobials.

Materials and methods. Probiotic strains were used to obtain metabolic products: *Lactobacillus rhamnosus* (LGG®) ATCC 53103 derived from the PREEMA® symbiotic (Schonen, Switzerland) and *Saccharomyces boulardii* CNCM I-745, isolated from BULARDI® drug (Schonen, Switzerland).

Ultrasonic disintegrates of lactobacilli (L) and saccharomycetes (S) were derived from suspensions of microorganisms with an optical density of 10.0 units by McFarland (Densi-La-Meter, PLIVA-Lachema Diagnostika, Czech Republic). The metabolic products deriving from lactobacillus (ML) and saccharomycetes (MS) was carried out by cultivating a probiotic in its own disintegrate according to the procedure [9]. The original products of microorganism metabolism were obtained by introducing saccharomycetes suspension into the ultrasonic lactobacilli (LS) disintegrate, or by adding a mixture of lactobacilli and saccharomycetes cells to the lactobacilli disintegrate (MLS) [9].

Were used as test-strains polyresistant to antibacterial drugs: *Pseudomonas aeruginosa* PR (*P. aeruginosa* PR), *Klebsiella pneumoniae* PR (*K. pneumoniae* PR), *Lelliottia amnigena* (*Enterobacter amnigenus*) (*L.amnigena* (*E.amnigenus*) PR) and *Pseudomonas aeruginosa* (*P. aeruginosa*) and the reference strain of *Pseudomonas aeruginosa* ATSC 27853 (*P. aeruginosa* ATSS 27853). Concentration microbial cells complied $1,5 \times 10^7$ CFU / ml [8, 12].

The study of the metabolic complexes impact on the process of biofilm formation was performed by means of spectrophotometric method in polystyrene flat-bottom 96-well plates (TOV Eximcargotrade, Ukraine) [12]. To each well was added 110 μ l of TSB (trypticase-soy broth) with 1% glucose. To the experimental wells, 30 μ l of metabolites were added, and to the control ones - a physiological solution of sodium chloride. Bacterial cultures were introduced in the amount of 10 μ l into the experimental and positive control wells (control of culture), and into the negative control wells (control of medium), test cultures suspension was replaced with sodium chloride physiological saline solution. Incubation was carried at a temperature of 37 ° C. for 24 hours. The contents of the wells being removed, the plates were washed three times with 0.1 M phosphate-saline buffer (FSB, pH 7.2) and dried at 60° C for 60 minutes. After fixation, the biofilms were stained with 1% solution of crystal violet (150 μ l / well) followed by thorough washing and addition of 150 μ l of 96 ° ethanol (30 minutes at room temperature). Changes in the optical densities were measured using Erba LisaScantem EM. The degree of biofilm formed was calculated according to the formula:

$$OD_{exp} = OD_{av} - OD_{cut}, \text{ where} \\ OD_{cut} = OD_{av.neg/c} + (3 \times SD_{neg/c}), \text{ where}$$

OD_{exp} - optical density of the experimental strain, OD_{av} - average test strain, OD_{cut} - cut off value, $OD_{av.neg/c}$ - average negative control, $SD_{neg/c}$ - standard deviation of negative control [12]. The study was carried out three times in three replicates. Statistical processing of the study results was carried out with a personal computer using Excel 2010 software package (Microsoft, USA). The mean values of the obtained indices (M) with standard deviations (m) were calculated. The significance of the difference between the indices obtained was determined using the Student's criterion (t). The presented differences of the results processed were reliable and amounted $p < 0.03$ and $p < 0.05$.

Results of the study and their discussion. Probiogenic metabolic products developed by the authors have a broad spectrum of action and possess high antimicrobial activity compared to many obligate pathogenic and opportunistic gram-positive and gram-negative microorganisms. Studying the antibiofilm properties of the original biologically active *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* complexes' effects on the biofilm formation by gram - negative microorganisms polyresistant to antimicrobial agents is carried out for the first time.

In determining the degree of biofilms formation by pathogens, according to the literature, the researchers measured the optical density of the wells content according to different wavelengths of 492 nm, 570 nm, 620 nm, etc. Our preliminary analysis of the experiments on studying the ability of the *Pseudomonas aeruginosa* (*P. aeruginosa*) circulating strain to form a biofilm in 96-well microplates was carried out with measurements of optical densities available at three wavelengths: 578 nm, 630 nm, and using the double reading option of 578 nm + 630 nm (Table 1). Depending on the light filter's wavelength, the excellent indices of absolute values for the optical density of the *P. aeruginosa* eluates were observed, both in the control and in the experimental samples. Despite the different values of the optical density, the initial intensity of the pathogen biofilm formation and the change in the biofilm formation degree under the influence of the *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* samples, measured at the same wavelength, answered to the changes between similar indices fixed with other wavelengths applied.

Using the obtained results on the *Pseudomonas aeruginosa* strain's ability to biofilm formation by means of three-wavelengths light filters, it was concluded that any wave may be used to determine the optical density of the experimental microorganisms eluates. Consequently, further experiments on the effects of the *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* test substances on the biofilms formation by bacterial test cultures were carried out using filters with the wavelength of 630 nm.

Optical density of biofilm formation by *Pseudomonas aeruginosa* strain after exposure to lactobacilli and saccharomycetes metabolism products when using light filters with different wavelengths (OD_{exp})

Wavelength, nm	C	Structural components and metabolite compounds, (M±m)					
		L. rhamnosus			S. boulardii		
		L	ML	MLS	S	MS	LS
578	1.903± 0.004*	1.49± 0.006*	0.916± 0.012**	1.305± 0.013**	1.323± 0.0123**	1.614± 0.007*	1.377± 0.012**
630	0.736± 0.011**	0.219± 0.013**	0.161± 0.009**	0.343± 0.013**	0.435± 0.014**	0.533± 0.006*	0.703± 0.011**
578+630	2.095± 0.003*	1.577± 0.013**	0.915± 0.01**	1.881± 0.009**	1.362± 0.005**	1.859± 0.006*	2.067± 0.006*

Note: C- control, L - disintegrate (structural components) of lactobacilli, ML - metabolites (metabolic compounds) of lactobacilli, MLS - combination of saccharomycetes and lactobacilli metabolites, S - disintegrate (structural components) of saccharomycetes, MS - metabolites (metabolic compounds) of saccharomycetes grown on saccharomycetes, LS - metabolites (metabolic compounds) of saccharomycetes grown on lactobacilli; the differences are statistically significant compared to the control indices: * - p<0.02; ** - p<0.05

The results of studying the work on determining the effect of lactobacilli filtrates and saccharomycetes metabolic products on the biofilm formation in two representatives of *Pseudomonas aeruginosa* showed a different degree of biofilms formation inhibition by pathogens (fig. 1). Thus, one of the selected representatives, *P. aeruginosa* ATCC, was sensitive to all the studied samples of *L. rhamnosus* GG and *S. boulardii*. The maximum statistically reliable inhibition of biofilms formation by the reference strain among the studied probiotic substances was observed with the use of lactobacilli (ML) metabolites: the reduction was more than by 100 times (p = 0.03).

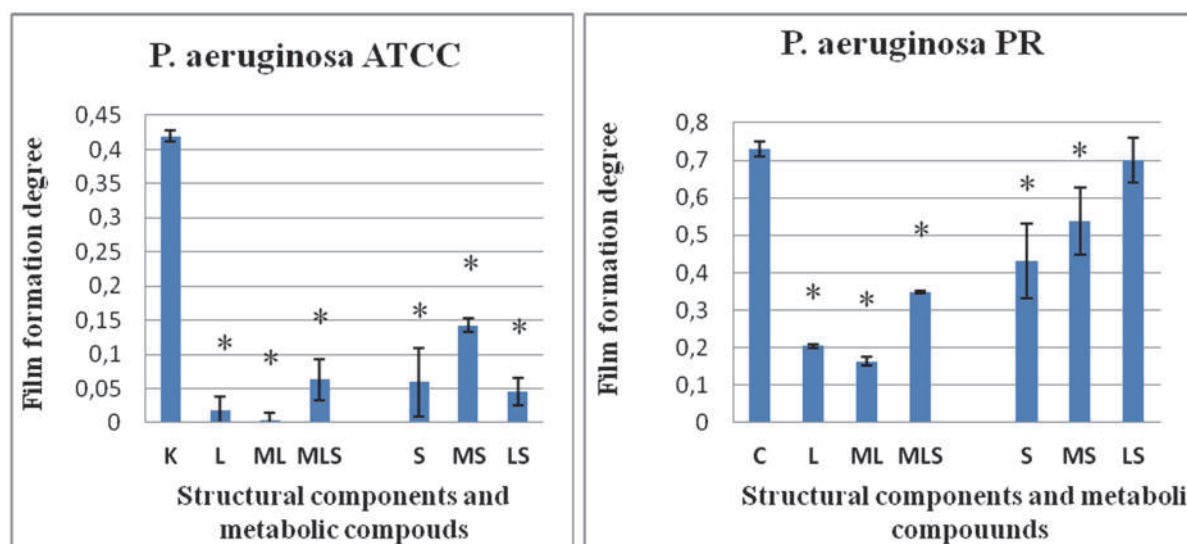


Fig. 1. Optical density of biofilm formation by *P. aeruginosa* ATSS 27853 and the *P. aeruginosa* PR polyresistant strain after the impact of lactobacilli and saccharomycetes metabolites. Note: C- control, L - disintegrate (structural components) of lactobacilli, ML - metabolites (metabolic compounds) of lactobacilli, MLS - combination of saccharomycetes and lactobacilli metabolites, S - disintegrate (structural components) of saccharomycetes, MS - metabolites (metabolic compounds) of saccharomycetes grown on saccharomycetes, LS - metabolites (metabolic compounds) of saccharomycetes grown on lactobacilli; *the differences are statistically significant compared to the control indices: - p<0.03.

Biofilm formation of the second microorganism, *P. aeruginosa* PR, which is polyresistant to antibacterial drugs, was reduced under the impact of all experimental samples except for the metabolites of saccharomycetes grown on lactobacilli (LS): the pseudomonade culture was insensitive to the said samples. The greatest inhibition of the biofilms formation is performed by opportunistic pathogens, among the presented *L. rhamnosus* GG and *S. boulardii* filtrates, has been established with the use of bacterial metabolites (ML).

The performed experiments permitted to establish that, regardless of the pseudomonade strain, the more pronounced antibiotic effect was observed after incubation of microbial cells with metabolites of lactobacilli (ML).

The results of studying the antibiofilm activity of *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* compared to the *K. pneumoniae* PR polyresistant strain differed from the previous data (figure 2). The use of both types of disintegrators (saccharomycetes (S) and lactobacilli (L)) did not cause statistically significant changes in the biofilm formation of the selected opportunistic microorganism. Under the influence of lactobacilli and saccharomycetes (MLS) metabolites combination, there was observed a tendency to reduce the biofilms formation by a polyresistant strain, however, no significant

differences between the experimental and control samples were observed. The statistically significant reduction in the biofilm formation by *K. pneumoniae* PR was established after application of metabolites samples: ML - by 1.7 times ($p = 0.01$), MS - by 1.3 times ($p = 0.01$), and LS - by 1.6 times ($p = 0.02$). Determination of the most active filtrate among *L. rhamnosus* GG, *S. boulardii* disintegrates, metabolites of lactobacilli and saccharomycetes, mixture of bacteria and fungi probiotic strains metabolites, which reduces the formation of biofilms by the *K. pneumoniae* polyresistant strain, confirmed the results of the performed pseudomonades studies. A more pronounced inhibition of the biofilm formation by opportunistic cultures was observed after the preliminary microbial cells incubation with *L. rhamnosus* GG (ML) metabolites samples.

Polyresistant strain of *L.amnigena* (*E.amnigenus*) PR was more sensitive to the lactobacilli and saccharomycetes metabolites (fig. 2). As the study results showed, all experimental filtrates produced an adverse effect on the pathogen's biofilm formation. The complete suppression of the above culture biofilm formation was observed after the use of bacteria and fungi (L, S) disintegrates, *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* (ML, MS) metabolites and combination of saccharomycetes and lactobacilli (MLS). Antibiofilm action of the saccharomycetes metabolites grown on lactobacilli (LS) on the selected test culture was manifested by the biofilm formation reduced by 2.2 times ($p = 0.006$).

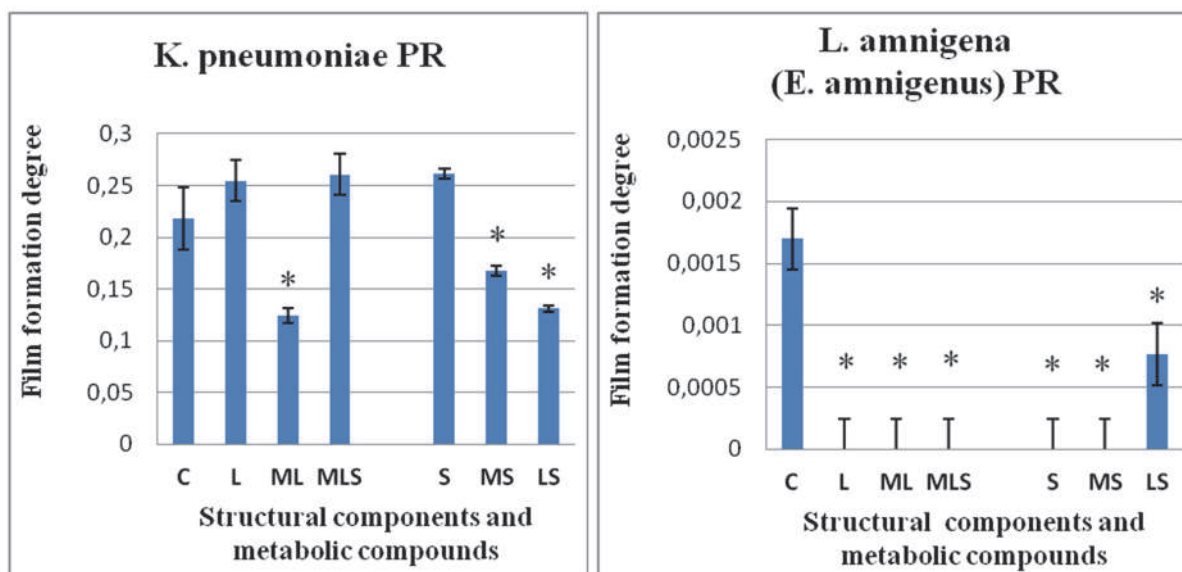


Fig. 2. Optical density of biofilm formation by polyresistant strains of *K. pneumoniae* PR and *L.amnigena* (*E.amnigenus*) PR impacted with metabolic products of lactobacilli and saccharomycetes. Note: C- control, L - disintegrate (structural components) of lactobacilli, ML - metabolites (metabolic compounds) of lactobacilli, MLS - combination of saccharomycetes and lactobacilli metabolites, S - disintegrate (structural components) of saccharomycetes, MS - metabolites (metabolic compounds) of saccharomycetes grown on saccharomycetes, LS - metabolites (metabolic compounds) of saccharomycetes grown on lactobacilli; *the differences are statistically significant compared to the control indices: - $p < 0.03$.

The results of the high antibiofilm activity of metabolites obtained by the author's method coincide with the data of other researchers [5, 8, 12, 13]. The degradation by peptide substances of biofilms *Pseudomonas aeruginosa* is known after 4 hours, but the concentration of the pathogen was less than own in 10-fold (2×10^6) [8]. In the following experiment, the effect on an even smaller number of pathogen microbial cells (0.5×10^5 CFU / ml) was studied in contrast to our own study (1.5×10^7 CFU / ml) [5]. The installed lack of effectiveness of the 1-hour effect of biologically active substances *Lactobacillus jensenii* and *Lactobacillus rhamnosus* on the pre-formed biofilms of antibiotic resistant strains of *Acinetobacter baumannii*, *Escherichia coli* and *Staphylococcus aureus* [13]. The increase in incubation time to ~ 18 hours was accompanied by degradation of 75 - 99.9% of the biofilms of all three pathogens. The data are consistent their own work pronounced antibiotic effect on antibiotic resistant strains of microorganisms and incubation time. A similar duration of exposure was tested by Osama et al. [12]. They also established the anti-film activity of metabolites of *Lactobacillus rhamnosus* EMCC 1105, but at a lower concentration of the microorganism (2×10^5 CFU / ml). In the previous own work the expressed anti-biofilm properties of metabolic complexes of lactobacilli and saccharomycetes were obtained in relation to pre-formed biofilms *Corynebacterium ulcerans* tox + 112, *Corynebacterium diphtheriae* gravis tox + 108; *Pseudomonas aeruginosa* ATCC 27853 with a high concentration of microbial cells (1.5×10^7 CFU / ml). The decrease in optical density of the formed biofilm of all tested strains occurred in 1.3 - 5.3 times depending on the strain and the test substances [11].

Conclusions

1. All the selected bacterial test cultures to various extents are sensitive to samples of *L. rhamnosus* and *S. boulardii*. The antibiotic effect of metabolic products on polyresistant to anti-bacterial drugs strains depends on the activity of lactobacilli and saccharomycetes metabolic products and on the individual sensitivity of the pathogens test culture.

2. Comparative characteristics of the *L. rhamnosus* GG and *S. boulardii* filtrates impact on the biofilm formation by the presented gram-negative strains showed that, under the same conditions of the experiment performed, the statistically significant reduction in the biofilms formation by microbial pathogens cells occurred with the use of bacteria and fungi metabolites obtained by means of cultivation on their own disintegrates ($p < 0.03$). The combination of saccharomycetes and lactobacilli metabolites possesses high antibiofilm properties, which is established due to a significant reduction of the biofilms formation by selected test strains, except for the polyresistant *K. pneumoniae* culture, which tended to reduce its biofilm formation. Other metabolic products of *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*, in terms of their antibiofilm properties against the said pathogens, were inferior to the above mentioned ones.

Prospects for further research lie in the comprehensive study of disintegrates and original metabolic products of L. rhamnosus GG and S. boulardii in order to apply them in development of new generation antimicrobials against pathogenic and polyresistant to antibacterial drugs opportunistic pathogens.

References

1. Glushanova NA, Blinov AI, Alekseeva NB. Bakterialnye bioplenki v infektsionnoy patologii cheloveka. Meditsina v Kuzbasse. 2015: 30–35. [in Russian]
2. Rybalchenko OV, Bondarenko VM, Orlova OG, Larionov IV, Fialkina S.V. Dezorganizatsiya bioplenok klinicheskikh shtammov stafilokokkov metabolitami laktobatsill. Zh. mikrobiol., epidemiol. i immunobiol. 2010; 6: 66-70 [in Russian]
3. Antibiotic resistance. WHO, Fact sheets, Detail. 2018 Feb 5. <http://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance>.
4. Arciola CR, Campoccia D, Speziale P, Montanaro L, Costerton JW. Biofilm formation in Staphylococcus implant infections. Biomaterials. 2012; 33(26):5967-82. doi: 10.1016/j.biomaterials.2012.05.031.
5. Atlas RM. Handbook of Microbiological Media. – 4th edition. – London New York: Boca Raton: CRC Press, 2010. – 2040 p.
6. Chen H, Wubbolts RW, Haagsman HP, Veldhuizen EJA. Inhibition and eradication of *Pseudomonas aeruginosa* biofilms by host defence peptides. Sci Rep. 2018; 8(1): 10446. doi: 10.1038/s41598-018-28842-8.
7. Gladkikh PG. Importance of microbiofilms in infection pathology of human (review). Vestnik novykh meditsinskikh tekhnologiy. 2015; 1. doi: 10.12737/7834.
8. Fukuda K. As the world stands on the edge of a post-antibiotic era, the time has come for decisive action. WHO, Media centre. 2015 May 27. <http://www.who.int/mediacentre/commentaries/antibiotic-resistance/en/>
9. Isayenko OY, Knysh OV, Babych YM, Ryzhkova TN, Dyukareva GI. Effect of disintegrates and metabolites of *Lactobacillus rhamnosus* and *Saccharomyces boulardii* on biofilms of antibiotic resistant conditionally pathogenic and pathogenic bacteria. Regulatory Mechanisms in Biosystems. 2019; 10(1): 3–8. doi: 10.15421/021901.
10. Osama DM, Elkhatib WF, Tawfeik AM, Aboulwafa MM, Hassouna NA. Antimicrobial, antibiofilm and immunomodulatory activities of *Lactobacillus rhamnosus* and *Lactobacillus gasseri* against some bacterial pathogens. International Journal of Biotechnology for Wellness Industries. 2017; 6(1), 12-21. doi: <http://dx.doi.org/10.6000/1927-3037.2017.06.01.2>.
11. Sambanthamoorthy K, Feng X, Patel R, Patel S, Paravanitana C. Antimicrobial and antibiofilm potential of biosurfactants isolated from lactobacilli against multi-drug-resistant pathogens. BMC Microbiol. 2014;14:197. doi: 10.1186/1471-2180-14-197.
12. Stepanović S, Vuković D, Hola V. Quantification of biofilm in microtiter plates: overview of testing conditions and practical recommendations for assessment of biofilm production by staphylococci. APMIS. 2007; 115(8): 891-899. doi:10.1111/j.1600-0463.2007.apm_630.x.
13. WHO publishes list of bacteria for which new antibiotics are urgently needed. WHO, News Releas. 2017 Feb 27. <http://www.who.int/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed>.

Реферати

**АНТИБІОПЛІВЧНА АКТИВНІСТЬ ПРОДУКТІВ
МЕТАБОЛІЗМУ LACTOBACILLUS RHAMNOSUS
GG I SACCHAROMYCES BOULARDII
ПО ВІДНОШЕННЮ ДО ПОЛІРЕЗИСТЕНТНИХ
ГРАМНЕГАТИВНИХ МІКРООРГАНІЗМІВ**
Исаенко О.Ю., Книш О.В., Рыжкова Т.М.,
Коцар О.В., Дюкарева Г. І.

Щоб уникнути розвитку хронічних форм захворювань та ефективно проводити лікування хворих з гострими проявами інфекцій необхідно не лише боротися з патогенними мікроорганізмами за допомогою антибактеріальних препаратів, а й навчитися впливати на біоплівкоутворення збудників. В роботі проведено вивчення антибіоплівочної активності оригінальних продуктів метаболізму *Lactobacillus rhamnosus* GG і *Saccharomyces boulardii*, отриманих шляхом

**АНТИБІОПЛЕНОЧНАЯ АКТИВНОСТЬ
ПРОДУКТОВ МЕТАБОЛИЗМА LACTOBACILLUS
RHAMNOSUS GG И SACCHAROMYCES BOULARDII
ПО ОТНОШЕНИЮ К ПОЛІРЕЗИСТЕНТНЫМ
ГРАМОТРИЦАТЕЛЬНЫМ МІКРООРГАНІЗМОВ**
Исаенко Е.Ю., Книш О.В., Рыжкова Т.Н.,
Коцарь Е.В., Дюкарева Г.И.

Чтобы избежать развития хронических форм заболеваний и эффективно проводить лечение больных с острыми проявлениями инфекций необходимо не только бороться с патогенными микроорганизмами с помощью антибактериальных препаратов, но и научиться влиять на био пленкообразование возбудителей. В работе проведено изучение антибиопленочной активности оригинальных продуктов метаболізма *Lactobacillus rhamnosus* GG и *Saccharomyces boulardii*, полученных путем культивирования

культивування пробіотиків у дезінтеграції мікроорганізмів. Антибіоплівочний ефект пробіотичних речовин відносно полірезистентних до антибактеріальних препаратів штамів (*Pseudomonas aeruginosa* PR, *Klebsiella pneumoniae* PR, *Lelliottia amnigena* (*Enterobacter amnigenus*) PR) має залежність від активності фільтратів *L. rhamnosus* GG та *S. boulardii* та від індивідуальної чутливості тест-культури збудників. Статистично значуще зменшення утворення біоплівок мікробними клітинами патогенів відбувалося при застосуванні метаболітів бактерій і грибів ($p < 0,03$). Високими антибіоплівочними властивостями володіє комбінація метаболітів сахароміцетів та лактобактерій, за винятком полірезистентної культури *K. pneumoniae*, у якій спостерігалась тенденція до зменшення біоплівкоутворення. Дезінтеграції *L. rhamnosus* GG і *S. boulardii* за своїми антибіоплівочними властивостями відносно даних збудників поступалися активністю.

Ключові слова: біоплівки, продукти метаболізму лактобактерій і сахароміцетів, полірезистентні до антибактеріальних препаратів грамнегативні мікроорганізми.

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пробиотиков в дезинтеграции микроорганизмов. Антибиопленочный эффект пробиотических веществ относительно полирезистентных к антибактериальным препаратам штаммов (*Pseudomonas aeruginosa* PR, *Klebsiella pneumoniae* PR, *Lelliottia amnigena* (*Enterobacter amnigenus*) PR) зависит от активности фильтрата *L. rhamnosus* GG и *S. boulardii* и от индивидуальной чувствительности тест-культуры возбудителей. Статистически значимое уменьшение образования биопленок микробными клетками патогенов происходило при применении метаболитов бактерий и грибов ($p < 0,03$). Высокими антибиопленочными свойствами обладает комбинация метаболитов сахаромисетов и лактобактерий, за исключением полирезистентной культуры *K. pneumoniae*, у которой наблюдалась тенденция к уменьшению биопленкообразования. Дезинтеграция *L. rhamnosus* GG и *S. boulardii* по своим антибиопленочным свойствам в отношении данных возбудителей уступали активностью.

Ключевые слова: биопленки, продукты метаболизма лактобактерий и сахаромисетов, полирезистентные к антибактериальным препаратам грамотрицательные микроорганизмы.

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L.M. Kolinko, L.E. Vesnina
Ukrainian Medical Stomatological Academy, Poltava

ENERGY VALUE OF DIETARY INTAKE AND ITS CONFORMITY TO DAILY NEEDS IN YOUNG PEOPLE

e-mail: ludmilakolinko17@gmail.com

The paper presents the energy value of dietary intake of people with different body weight and its compliance with daily energy needs. 96 people of both gender aged 18-25 have been involved into the study. In the groups with normal body weight, overweight (body mass index of 25.00-29.99 kg/m²) and Class I obesity (body mass index of 30.00-34.99 kg/m²) nutritional status has been studied by the method of 24-hour nutrition reproduction, as well as basal metabolism and recommended daily energy dietary intake. The energy value of the dietary intake of the subjects of both gender with overweight and Class I obesity significantly exceeded the energy value of the dietary intake of controls. In the group with overweight, the level of positive energy balance in male subjects on a weekday was 16.02%, in male subjects and female subjects on a weekend day was 26.47% and 24.46%, respectively. In male subjects with obesity, the level of positive energy balance on a weekday was 20.09%, on a weekend day was 33.92%, whereas in female subjects with obesity it was 10.48% and 37.28% on a weekday and a weekend day, respectively. Strong to moderate correlation has been established between anthropometric and energy metabolism values.

Keywords: overweight, Class I obesity, energy value of dietary intake, energy metabolism, positive energy balance.

The work is a fragment of the research project "Comprehensive study of the pathogenetic role of M1 and M2 macrophages subpopulations in the development of chronic obstructive pulmonary disease for the development and justification of personalized therapy based on body weight", state registration No. 0117U005252.

The rapid increase in the number of overweight and obese people is attracting the attention of health professionals, since the above conditions are the precursors for the formation of a large number of diseases, namely, diabetes mellitus, metabolic syndrome, cardiovascular disease, diseases of the musculoskeletal system [8].

Recently, the nutrition pattern of the population worldwide has changed in the direction of the predominance of products high in fat and carbohydrates but poor in microelements and low quality nutrients. The current diet contains predominantly highly refined foods, long-term storage products, fast food, which contributes to the development of metabolic disorders, leading to overweight and obesity [9]. Young people may be one of the most vulnerable groups in terms of weight gain and obesity, given the numerous lifestyle factors that can potentially affect health [15]. These are energy imbalance, hypodynamia, significant emotional stress, chronic insomnia, irregular nutrition, inadequate distribution of the daily dietary intake, the presence of bad habits, etc. [5, 6].

Energy imbalance, caused by constant increased energy consumption with food and low levels of its expenditure is one of the main factors in the formation of overweight and obesity [10]. Information on studying the compliance of the energy value of the dietary intake with the energy needs of young people is quite limited.

The purpose of the study was to determine the energy value of the dietary intake of young people with different body mass and its compliance with daily needs.

Materials and methods. The study was conducted with the permission of the Commission on Bioethics of the Ukrainian Medical Stomatological Academy. Informed consent was signed by the subjects before the start of the study. 96 people of both gender aged 18-25 have been selected. Anthropometric parameters (height, body weight, waist circumference (WC) and thighs circumference (TC) and their ratio) were determined by standard methods.

Based on the BMI, calculated according to the equation: $BMI = W/H^2$, where W is body weight (kg), H is the height (m), the subjects have been assigned into three groups of 32 people. The control group involved subjects with normal weight with BMI of 18.50 - 24.99 kg/m², the group with overweight involved subjects with BMI of 25.00 - 29.99 kg/m², the group with Class I obesity involved subjects with BMI of 30.00 - 34.99 kg/m². All groups were gender-balanced.

To estimate the nutritional status of the subjects, the method of 24-hour reproduction of nutrition [4] on weekdays and weekend has been used. For optimal reproduction of information in the nutrition diaries, data on food consumption were recorded for the day before the survey and the next day off. The name, the meal composition, method of cooking, culinary processing was recorded. To estimate the amount of consumed food, the album with photos of main dishes, fast food and beverages was used, where each product was provided in different options in size and weight. During the survey, the subjects chose the appropriate option of products and dishes. The nutrient content and energy value were determined using the tables.

The value of the basal metabolic rate (BMR) was calculated by the Mifflin-St Jeor equation [13]: men: $BMR = 10,0 \times \text{body weight (kg)} + 6,25 \times \text{height (cm)} - 5,0 \times \text{age (years)} + 5$;

women: $BMR = 10,0 \times \text{body weight (kg)} + 6,25 \times \text{height (cm)} - 5,0 \times \text{age (years)} - 161$.

The recommended daily energy dietary intake to maintain the existing body weight was calculated by the EER equation [11]: Estimated Energy Requirement (EER) = BMR × PAC, where PAC is the physical activity coefficient. Data on the amount of daily physical activity were recorded by the respondents in the observation sheet. We used PAC of 1.4, which corresponds to the minimum energy expenditure.

The STATISTICA 10 software package (Stat Soft Inc, USA) was used for statistical processing of the resulting data. The arithmetic mean (M), its mean accuracy (m) was determined. Correlations of values were determined by Spearman correlation coefficient. The means were compared using the Student's t-test. The indices were considered statistically significant in $p < 0.05$.

Results of the study and their discussion. Taking into account the peculiarities of energy metabolism of men and women, the study groups were further divided by gender. Anthropometric studies have shown the following differences. The body weight of male subjects in the group with overweight and Class I obesity was by 29.70% and 53.98%, respectively, higher compared to controls and the body weight of female subjects in the group with overweight and Class I obesity was by 26.90% and 47.64%, respectively, higher compared to controls (table 1).

Table 1

Anthropometric values of the study groups (M±m)

Values	Men			Women		
	with normal body weight n=16	with overweight n=16	with Class I obesity n=16	with normal body weight n=16	with overweight n=16	with Class I obesity n=16
Age, years	19.50±0.56	19.88±0.42	20.94±0.60	19.31±0.45	19.13±0.39	20.25±0.46
Height, cm	177.63±1.01	180.78±1.53	181.53±0.85	165.94±1.56	166.25±1.25	165.19±1.70
Body weight, kg	69.41±1.29	90.03±2.19*	106.88±1.65***	60.73±1.28	77.06±1.18*	89.66±1.76***
BMI, kg/m ²	22.01±0.32	27.48±0.24*	32.49±0.38***	22.04±0.31	27.90±0.28*	32.78±0.27***
WC, cm	75.47±0.97	87.66±1.35*	100.16±1.24***	70.56±0.87	82.06±0.90*	90.22±1.42***
TC, cm	95.03±3.76	109.00±5.22*	115.00±5.38***	95.88±1.71	108.94±1.15*	117.78±1.26***
WC/TC ratio	0.79±0.01	0.81±0.01	0.87±0.02***	0.74±0.01	0.75±0.01	0.77±0.02

Notes herein after in Tables 1-3: * - $p < 0,05$ compared to individuals with normal body weight; ** - $p < 0,05$ compared to individuals with overweight.

BMI was by 24.85% and 47.61% higher in male subjects with overweight and Class I obesity, respectively, and by 26.59% and 48.73% higher in female subjects with overweight and Class I obesity, respectively, compared to controls ($p < 0.05$) (table 1). Importantly, the values of WC and TC in male and female subjects with overweight and Class I obesity were significantly higher compared to controls. The WC/TC ratio was by 10.13% higher in men with Class I obesity compared to controls ($p < 0.05$) (table 1).

The analysis of the dietary intake was performed in two days: a weekday and a weekend day, which can usually differ in the amount and mode of nutrition. The analysis of the nutritive value of daily dietary intake based on food diaries showed the following results (table 2). In male subjects with overweight, the energy value of dietary intake was by 27.04% on a weekday, and by 38.16% significantly higher on a weekend day, compared to controls. The energy value of dietary intake of male subjects with Class I obesity was by 42.89% higher on a weekday compared to controls ($p<0.05$). On a weekend day, male subjects with obesity consumed by 58.97% more calories compared to the control group ($p<0.05$) (table 2).

In the group of female subjects with overweight, the nutritive value was by 32.28% significantly higher the nutritive values in controls on a weekday and by 25.99% higher the values in controls on a weekend day (table 2).

Table 2

Energy value of daily dietary intake in the subjects (M±m)

Values	Men		
	with normal body weight n=16	with overweight n=16	with Class I obesity n=16
Energy value, kcal weekday	2475.16±260.11	3144.42±158.84*	3536.78±243.12*
Energy value, kcal weekend day	2480.98±176.58	3427.63±138.32*	3944.01±331.74*
Indices	Women		
Energy value, kcal weekday	1715.29±132.21	2268.97±99.997*	2578.03±59.60*.**
Energy value, kcal weekend day	2147.81±186.62	2706.01±136.70*	3203.35±131.72*.**

On a weekday, in the female subjects with Class I obesity, the energy value of consumed food was by 50.30% significantly higher the values of the controls and by 13.62% higher the values of the group with overweight (Table 2). Similarly, the nutritive value of the dietary intake on a weekend day was by 49.15% higher the values of controls and by 18.38% higher the values of the group with overweight ($p<0.05$).

The value of the basal metabolic rate has been determined to estimate the minimal energy required to maintain overall health. The value of the basal metabolic rate in male subjects with overweight was by 13.09% ($p<0.05$) higher the values of controls (Table 3). The value of the basal metabolic rate in obese subjects was by 22.90% and 8.67% higher the values of controls and group with overweight, respectively ($p<0.05$).

Table 3

The value of the basal metabolic rate and recommended daily dietary energy intake in the subjects of the study groups (M±m)

Values	Men			Women		
	with normal body weight n=16	with overweight n=16	with Class I obesity n=16	with normal body weight n=16	with overweight n=16	with Class I obesity n=16
basal metabolic rate, kcal/day	1711.72± 17.21	1935.82± 29.99*	2103.63± 21.05***	1386.80± 24.36	1553.06± 18.30*	1666.73± 28.60***
recommended daily dietary energy intake, kcal/day	2396.41± 24.09	2710.15± 41.99*	2945.09± 29.47***	1941.52± 29.90	2174.29± 25.62*	2333.43± 40.04***

In female subjects with overweight the basal metabolic rate was by 11.99% significantly higher the rate of controls (Table 3). In subjects with Class I obesity the basal metabolic rate was by 20.19% higher the rate of controls and by 7.32% higher the rate of the group with overweight ($p<0.05$).

The survey has shown that almost all subjects led a passive lifestyle and were not involved in active rest and physical activities, which gave us a basis for using the physical activity coefficient of 1.4 when calculating the recommended daily dietary energy intake. In male subjects with overweight, the value of recommended daily dietary energy intake was by 13.09% higher the value of controls ($p<0.05$). In the obese subjects the level of daily dietary energy intake was by 22.90% significantly higher the values of controls and by 8.67% higher the values of the group with overweight (Table 3).

In female subjects with overweight the value of the recommended daily dietary energy intake was by 11.99% higher the value of controls ($p<0.05$). In the obese subjects the daily dietary energy intake was by 20.19% higher the values of controls and by 7.32% higher the values of the group with overweight ($p<0.05$) (Table 3).

Subsequently, the comparison of the values of the recommended daily dietary energy intake and the rates of energy value of the dietary intake in controls of both gender showed no significant difference between the energy value of dietary intake on a weekday and a weekend day and recommended daily dietary energy intake (Table 4).

The difference between the recommended daily dietary energy intake and energy value of the dietary intake in the subjects of the study groups (M±m)

Values	Men			Women		
	with normal body weight n=16	with overweight n=16	with Class I obesity n=16	with normal body weight n=16	with overweight n=16	with Class I obesity n=16
Recommended daily dietary energy intake, kcal/day	2396.41± 24.09	2710.15± 41.99	2945.09± 29.47	1941.52± 29.90	2174.29± 25.62	2333.43± 40.04
Energy value, kcal Weekday	2475.16± 260.11	3144.42± 158.84*	3536.78± 243.12*	1715.29± 132.21	2268.97± 99.99	2578.03± 59.60*
Energy value, kcal weekend day	2480.98± 176.58	3427.63± 138.32**	3944.01± 331.74**	2147.81± 186.62	2706.01± 136.70 **	3203.35± 131.72**

Notes: * - $p < 0,05$ – compared between the values of recommended daily dietary energy intake and the values of energy value on a weekday;
** - $p < 0,05$ – compared between the values of recommended daily dietary energy intake and the values of energy value on a weekend day.

On a weekday, in male subjects with overweight and obesity the energy value of dietary intake was by 16.02% and 20.09%, respectively, higher the value of recommended daily dietary energy intake ($p < 0.05$). On a weekend day, in male subjects with overweight and obesity the energy value of dietary intake was by 26.47% and 33.92%, respectively, higher the value of recommended daily dietary energy intake ($p < 0.05$). On a weekend day, in female subjects with overweight the energy value of dietary intake was by 24.46% higher the value of recommended daily dietary energy intake (Table 4). In female subjects with Class I obesity the energy value of dietary intake on a weekday and a weekend day was by 10.48% and 37.28%, respectively, higher ($p < 0.05$).

Correlation analysis has been carried out to establish correlations between the study values. The findings of the analysis have shown strong positive correlations between the values of the basal metabolic rate/recommended daily dietary energy intake in male subjects of control group and body weight ($r = 0,920$, $p < 0,05$) and TC ($r = 0,926$, $p < 0,05$). The positive moderate correlations between the values of the basal metabolic rate and daily dietary energy intake were derived from the BMI ($r = 0,594$, $p < 0.05$) and WC ($r = 0,501$, $p < 0.05$).

Positive strong correlations between the values of the basal metabolic rate/ recommended daily dietary energy intake and the value of the body weight ($r = 0.991$, $p < 0.05$), WC ($r = 0.702$, $p < 0.05$) and TC ($r = 0.805$, $p < 0.05$) and moderate correlations with BMI ($r = 0.649$, $p < 0.05$) have been established in the group of male subjects with overweight. Positive strong correlations between the value of the basal metabolic rate and value of the body weight ($r = 0,970$, $p < 0,05$) and moderate correlations with BMI ($r = 0.553$, $p < 0.05$) have been noted in the group of male subjects with Class I obesity. The similar correlations between the value of the recommended daily dietary energy intake and the value of the body weight ($r = 0.970$, $p < 0.05$) and BMI ($r = 0,553$, $p < 0,05$) have been formed.

The formation of the correlations between the values of the basal metabolic rate and recommended daily dietary energy intake in female subjects of control group have been noted: positive strong correlations with body weight ($r = 0,938$, $p < 0,05$) and TC ($r = 0,786$, $p < 0,05$) and negative moderate correlation with the value of the WC/TC ratio ($r = -0,500$, $p < 0,05$). Strong positive correlations between the values of the basal metabolic rate/ recommended daily dietary energy intake and body weight ($r = 0,939$, $p < 0,05$) and ($r = 0,954$, $p < 0,05$) have been established in female subjects with overweight and Class I obesity, respectively.

The energy that a person receives from food should cover energy expenditure due to the energy value of nutrients. Taking into account such factors as the age, gender, body weight and height, type of activity, amount of load, nutrient value of the dietary intake should provide the physiological need of the body for energy balance.

Daily energy expenditure is determined on the basis of the basal metabolism, physical and mental activity, digestive processes and nutrient absorption expenditure. The findings of our study showed a significant difference in the actual energy consumption on a weekday from the recommended daily dietary energy intake in the male subjects with overweight and subjects of both genders with obesity. On a weekend day, subjects of both gender with overweight and obesity also consumed more energy than needed according to the recommended daily dietary energy intake. Excess energy gradually leads to the formation of a positive energy balance and weight gain, when fat accumulation occurs in fat depots. In the group with overweight, the level of positive energy balance in male subjects on a weekday was 16.02%, in male subjects and female subjects on a weekend day was 26.47% and 24.46%, respectively. In male subjects with Class I obesity, the level of positive energy balance on a weekday was 20.09%, on a weekend day was 33.92%, whereas in female subjects with Class I obesity it was 10.48% and 37.28% on a weekday and a weekend day, respectively.

The peculiarities of nutrition were noteworthy. In the subjects of both gender with overweight and obesity, the diet was monotonous, with no clear intervals between meals. In most subjects of these groups, the last meal was too late without enough intervals between the last meal and sleep. Excessive consumption of coffee, cakes, sandwiches, fast food and small amount of vegetables and fruits was observed. Respondents consumed food that was cooked outside home, in public facilities, more often on weekdays, though some respondents did this both on weekdays and weekend.

Currently, rather irrational diet and specificities, namely, late dinners, excessive consumption of carbohydrates and fats due to mostly high-calorie foods is characteristic to young people, which, along with the lack of proper knowledge on nutrition science and other factors contribute to weight gain and obesity [3,5]. On the other hand, poor physical activity, increasing exposure to hypokinesia and hypodynamics lead to decreased motor-visceral reflexes, slow metabolism. Working conditions, the nature of working activities, lack of willpower and/or lack of its detection in relation to appetite control, lack of conscious attitude to nutrition contribute to the development of nutritional disorders [3]. According to our data, weight gain and obesity leads to a decrease in quality of life at a young age [2].

Excessive nutrition alters the cellular metabolic repertoire. According to current data, macrophages are the key cells in maintaining adipocyte homeostasis and central mediators of adipose-induced inflammation in the adipose tissue and insulin resistance. The microenvironment of the adipose tissue influences the increase in proliferation of macrophages, which in turn cause its chronic inflammation, regardless of its number [7]. Adipose tissue macrophages demonstrate metabolic activation, as evidenced by correlations with BMI [12]. Low-intensity chronic inflammation in the adipose tissue leads not only to increase in the number of macrophages but also affects their properties, mediating the influence on adipocyte function, cytokine synthesis, signs of subpopulation phenotype [14]. Generally, inflammation, formed during obesity in the adipose tissue, can serve as a regulatory signal of energy metabolism at the local and systemic level [1].

Conclusion

Thus, the findings of the study show that the energy value of the dietary intake of subjects of both gender with overweight and Class I obesity significantly exceeds the energy value of the dietary intake of controls. The formation of a positive energy balance between the recommended daily dietary energy intake and the energy value of the dietary intake of subjects of both gender with overweight and obesity has been established. A positive energy balance requires physiological correction by reducing the consumption and energy value of food and increasing energy expenditure by increasing physical activity.

References

1. Kaidashev YP. Yzmeneniye obraza zhyzny, narusheniye enerhetycheskogo metabolizma y sistemnoe vospaleniye kak faktory razvitiya bolezni tsyvylyzatsyy. Ukr med chasopys. 2013;5(97):103-8. [in Russian].
2. Kolinko LM, Vesnina LE. Doslidzhennia yakosti zhyttia molodykh osib z riznoi masoiu tila. Visnyk problem biolohii i medytsyny. 2019;1(153):366-372. [in Ukrainian].
3. Kozik NM, Stratiichuk NA, Pylyp HM, Lohush LH. Doslidzhennia osoblyvosti kharchuvannia studentiv vyshchoi shkoly yak skladovoi sposobi zhyttia. Molodyi vchenyi. 2017 Berez;3.1(43.1):172-6. [in Ukrainian].
4. Nykytiuk DB, Martynchuk AN, Baturyn AK, Safronova AM, Baeva ES, Keshabaiaants EE. Sposob otsenky yndyvudualnoho potrebeleniya pyshchy metodom 24-chasovoho (sutochnoho) vosproyzedveniya pytanyia. Moskva: FHBUN FYTs pytanyia y byotekhnolohyy. 2016. 36 s. [in Russian]
5. Tymofiichuk IR, Semenenko SB, Savchuk TP, Pidubna AA, Boreiko LD, Semenenko VV. Analiz kharchovykh ratsioniv studentiv-medykiv na osnovi pryntsyupiv ratsionalnoho kharchuvannia. Yednye zdorovia ta problemy kharchuvannia Ukrainy. 2019;1(50):54-8. doi: 10.33273/2663-9726-2019-50-1-54-58 [in Ukrainian].
6. Yushkovskaya O. Prichiny i osobennosti vozniknoveniya yzbytochnoy massy tela u studentov s uchetom gendernykh razlichiy. Slobozhanskyi naukovy-sportyvnyi visnyk. 2017; 1(57):127-31. doi:10.15391/snsv.2017-1.022. [in Russian].
7. Amano SU, Cohen JL, Vangala P, Tencerova M, Nicoloro SM, Yawe JC, et al. Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation. Cell Metab. 2014 Jan 7;19(1):162-171. doi: 10.1016/j.cmet.2013.11.017.
8. Djalalinia S, Qorbani M, Peykari N, Kelishadi R. Health impacts of Obesity. Pak J Med Sci. 2015; 31(1):239-242. doi: 10.12669/pjms.311.7033
9. Garcia G, Sunil TS, Hinojosa P. The fast food and obesity link: consumption patterns and severity of obesity. Obes Surg. 2012 May; 22(5):810-8. doi: 10.1007/s11695-012-0601-8.
10. Hall KD, Heymsfield SB, Kemnitz JW, Klein S, Schoeller DA, Speakman JR. Energy balance and its components: implications for body weight regulation. Am.J. Clin. Nutr. 2012; 95(4): 989-994. doi:10.3945/ajcn.112.036350.
11. Harris Benedict formula for women and men. GottaSport.com. Retrieved on 2011-10-27.
12. Kratz M, Coats BR, Hisert KB, Hagman D, Mutskov V, Peris E, et al. Metabolic dysfunction drives a mechanistically distinct proinflammatory phenotype in adipose tissue macrophages. Cell Metab. 2014 Oct 7;20(4):614-25. doi:10.1016/j.cmet.2014.08.010.
13. Mifflin MD, St Jeor ST, Hill LA, Scott BJ, Daugherty SA, Koh YO. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990 Feb;51(2):241-7. doi: 10.1093/ajcn/51.2.241.
14. Russo L, Lumeng CN. Properties and functions of adipose tissue macrophages in obesity. Immunology. 2018 Dec;155(4):407-417. doi: 10.1111/imm.13002.
15. Stroud C, Walker LR, Davis M, Irwin CE Jr. Investing in the health and well-being of young adults. J Adolesc Health. 2015 Feb;56(2):127-9. doi: 10.1016/j.jadohealth.2014.11.012.

Реферати

ЕНЕРГЕТИЧНА ЦІННІСТЬ ХАРЧОВОГО РАЦІОНУ ТА ЇЇ ВІДПОВІДНІСТЬ ДОБОВИМ ПОТРЕБАМ У МОЛОДИХ ОСІБ

Колинько Л.М., Веснина Л.Е.

У роботі визначено енергетичну цінність харчового раціону осіб із різною масою тіла та її відповідність добовим потребам в енергії. Обстежено 96 осіб обох статей 18-25 років. У групах з нормальною масою тіла, з підвищеною (індекс маси тіла 25,00-29,99 кг/м²) та ожирінням I ступеня (індекс маси тіла 30,00-34,99 кг/м²) вивчався харчовий статус методом 24-годинного відтворення харчування, основний обмін та рекомендоване добове споживання енергії. Енергетична цінність харчового раціону осіб із підвищеною масою тіла та ожирінням I ступеня обох статей достовірно перевищувала енергетичну цінність раціону осіб контрольної групи. Рівень позитивного енергетичного балансу в групі з підвищеною масою тіла у робочий день становив 16,02% у чоловіків, у вихідний день 26,47% у чоловіків, 24,46% у жінок. У чоловіків з ожирінням рівень позитивного енергетичного балансу у робочий день становив 20,09%, у вихідний 33,92%, у жінок у робочий день 10,48%, у вихідний 37,28%. Між показниками антропометрії та енергетичного обміну виявлені сильні та середньої сили зв'язки.

Ключові слова: підвищена маса тіла, ожиріння I ступеня, енергетична цінність харчового раціону, енергетичний обмін, позитивний енергетичний баланс.

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ЭНЕРГЕТИЧЕСКАЯ ЦЕННОСТЬ ПИЩЕВОГО РАЦИОНА И ЕГО СООТВЕТСТВИЕ СУТОЧНЫМ ПОТРЕБНОСТЯМ У МОЛОДЫХ ЛИЦ

Колинько Л.М., Веснина Л.Е.

В работе определена энергетическая ценность пищевого рациона лиц с разной массой тела и ее соответствие суточным потребностям в энергии. Обследовано 96 человек обоего пола 18-25 лет. В группах с нормальной массой тела, с повышенной (индекс массы тела 25,00-29,99 кг/м²) и ожирением I степени (индекс массы тела 30,00-34,99 кг/м²) изучался пищевой статус методом 24-часового воспроизведения питания, основной обмен и рекомендованное суточное потребление энергии. Энергетическая ценность пищевого рациона лиц с повышенной массой тела и ожирением I степени обоих полов достоверно превышала энергетическую ценность рациона лиц контрольной группы. Уровень положительного энергетического баланса в группе с повышенной массой тела в рабочий день составлял 16,02% у мужчин, в выходной день 26,47% у мужчин, 24,46% у женщин. У мужчин с ожирением уровень положительного энергетического баланса в рабочий день составлял 20,09%, в выходной 33,92%, у женщин в рабочий день 10,48%, в выходной 37,28%. Между показателями антропометрии и энергетического обмена выявлены сильные и средней силы связи.

Ключевые слова: повышенная масса тела, ожирение I степени, энергетическая ценность пищевого рациона, энергетический обмен, положительный энергетический баланс.

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Y.Y. Kuzmenko, L.O. Stechenko, S.M. Chuhrai, H.I. Kozak, I.M. Olinyk¹
Bogomolets National Medical University, Kyiv

¹National University of Ukraine on Physical Education and Sport, Kyiv

MORPHOFUNCTIONAL FEATURES OF RENAL GLOMERULAR CAPILLARIES IN CONDITIONS OF CONGENITAL HYPOTHYROIDISM IN THE AGE ASPECT

e-mail: lostechenko@gmail.com

Blood capillaries of rat renal glomeruli were studied 14, 50 and 100 days after the development of congenital hypothyroidism. It was found that on day 14 after the onset of hypothyroidism 7-day-old rats had a decrease in morphometric parameters of the number of capillaries and their area in comparison with age control in the absence of any marked morphological changes. In 45-day-old rats 50 days after the development of this pathology in glomerular blood capillaries changes in quantitative indicators had not reached critical values, while the presence of both destructive-dystrophic and compensatory processes were noted morphologically. 100 days after the development of pathology changes in blood capillaries became more pronounced than in the previous period. Destructive-dystrophic changes of a part of capillaries and the phenomena of necrosis and apoptosis were observed in the presence of compensatory-adaptive processes.

Key words: blood capillaries, kidneys, rats, congenital hypothyroidism.

The work is a fragment of the research project "Changes of internal organs and regulatory systems under conditions of experimental damage", state registration No. 0116000121.

Congenital hypothyroidism is one of the most complex and important problems among endocrinological pathology in children leading to a dangerous developmental disorder of almost all organs and systems, and without timely diagnosis and treatment to severe disability of a child. According to neonatal screening data incidence of congenital hypothyroidism in Ukraine ranges from 1/2500 to 1/4000 of newborns and peaks in the regions with severe iodine deficiency [2]. At present fatal changes in the body, growth and development retardation of a child can be prevented by timely prescription of thyroid hormone replacement therapy, therefore the study of this pathology is relevant [4,5,12]. It is known that during embryogenesis thyroid hormones directly or indirectly affect the development and physiology of kidneys causing significant changes in renal function, such as decreased sodium reabsorption in the proximal tubules, impaired concentrating capacity of distal tubules, decreased uric acid excretion,

decreased renal circulation and glomerular filtration [7-8]. In our earlier studies we found that thyroid hormone deficiency significantly affects the weight of the rats kidney at different ages and leads to impaired maturation of all its structural components [3].

Given the above, the study of morphogenesis, regeneration, viability of the kidneys as the main organ body homeostasis maintaining in conditions of thyroid hormone deficiency is relevant and up-to-date.

The purpose of the study was to reveal the peculiarities of the structure of renal glomerular blood capillaries in conditions of congenital hypothyroidism in the course of the experiment.

Materials and methods. Kidneys of Wistar rats which were kept in standard conditions of Bogomolets NMU vivarium were studied. In keeping, animal care, and procedures the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Scientific Purposes (Strasbourg, 1985) and the General Ethical Principles for Animal Experiments, approved by the 1st National Congress on Bioethics were observed. (Kyiv, 2001). Congenital hypothyroidism in experimental animals was simulated by thyroid suppression with a thyrostatic drug mercazolil, which has been administered daily at a dose of 20 mg / kg of body weight dissolved in water throughout the experiment. Pregnant females were administered the drug orally from the 14th day of prenatal fetal development and after birth the experimental animals had been receiving it with breast milk and then with their food. Peculiarities of thyroid hormone deficiency effect were determined in rats 7, 45 and 100 days old. Juvenile 7-day-old rats; young sexually and physiologically immature 45-day-old rats; sexually and physiologically mature 100 day-old rats served the control for experimental animals. The hypothyroidism condition was determined by enzyme-linked immunosorbent assay by the content of free thyroxine in blood plasma on the device "Sunrise RC" TEKAN company at the time when the animals were sacrificed. The cortical substance of the kidney was used as the material for electron microscopic examination. Kidney pieces were fixed with 2.5% glutaraldehyde solution on phosphate buffer with postfixation in 1% osmium tetroxide solution and treated following the conventional procedures. Sections were made on an LKB III (Sweden) ultramicrotome. The preparations were studied and photographed on an electron microscope PEM-125K. Morphometry of blood capillaries (bulk density, quantitative density and area) was done on a PEM-125K electron microscope using «KAPPA» software. The mean value, the mean value error, the standard deviation, and the accuracy factor were calculated for each indicator. Statistical processing of the obtained data was performed using the parametric Student's t test and the non-parametric Kolmogorov-Smirnov test according to the principles of variation statistics.

Results of the study and their discussion. 14 days after the beginning of the experiment thyroid hormone deficiency was confirmed in 7-day-old rats by a decrease in plasma thyroxine levels up to 3.44 ± 0.49 pmol / L versus 7.98 ± 0.71 pmol / l in the age control.

A decrease in the number of capillaries alongside the increase of their size was observed in this age group of rats, making the volume they occupy in the renal corpuscle equal to that in the statistically identical age control, i.e. $5.79 \pm 82\%$ of corpuscle volume (table 1).

The lumens of the capillaries were often obturated with formed elements of blood: erythrocytes, lymphocytes, and leukocytes. In renal corpuscles with incomplete differentiation processes the glomerular capillaries were lined with endothelial cells with large nuclei and there was no differentiation into the nucleus-containing and peripheral zones. This seems to be the reason for the increased size of the capillaries in comparison with the control. A few glomerular capillaries have dilated lumens and endothelial cells cytoplasm differentiated into the nucleus-containing and peripheral zones (fig. 1. A). The basal membrane of endothelial cells in immature glomeruli still remains incompletely formed and quite thinned even at the sites of bifurcations (fig. 1B).

Table 1

Morphometric parameters of the renal glomerular capillaries in rats with CHT, M \pm m

Groups of animals	Bulk density of the capillaries %	Quantitative density * $10^{-6} \mu\text{m}^3$	Area of capillaries * $10^2 \mu\text{m}^2$
7 days	5.79 ± 1.82	$15.95 \pm 1.49^*$	$4.16 \pm 0.23^*$
control	6.82 ± 0.97	19.42 ± 1.61	3.60 ± 0.21
45 days	$9.56 \pm 1.92^*$	29.51 ± 2.63	3.16 ± 0.28
control	14.74 ± 2.20	33.35 ± 4.34	3.64 ± 0.32
100 days	$9.15 \pm 1.09^*$	$20.17 \pm 2.16^*$	$2.21 \pm 0.18^*$
control	16.9 ± 0.9	33.69 ± 1.9	3.15 ± 0.17

*significant difference in comparison with the control ($P \geq 0.05$)

According to enzyme-linked immunosorbent assay findings the level of free thyroxine in blood plasma of 45-day-old rats 50 days after the initiation of the experiment was significantly lower than in the

age control ($3.96, \pm 0.46$ pmol / L vs $7.63 \pm 0,99$ pmol / L, respectively.). The morphometric characteristics of the glomerular capillaries indicate a decrease in the bulk density of the capillaries, with the absolute number of glomerular capillaries and their area decreasing to a lesser extent (table 1).

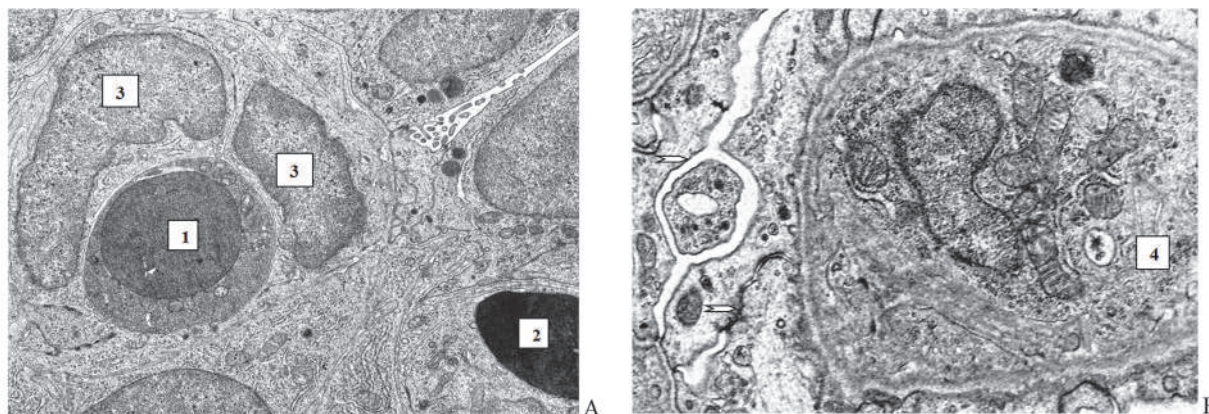


Fig. 1. Glomerular blood capillaries of a 7-day-old rat 14 days after the onset of CHT. Erythroblast (1), erythrocyte (2) in the lumen of the glomerular capillaries. Endothelial cell nuclei (3), peripheral areas (↑) of endothelial cells, mesangial cell (4). Electron microscope images. Magnification: A-10000, B-16000.

At the electron microscopy level heteromorphic structure in the endothelium of blood glomerular capillaries is noted: in some glomeruli endotheliocytes do not differ from those in control animals, but most of them contain a significantly thinned peripheral zone with a large number of fenestrae, which may indicate the development of adaptive processes in the endothelium (fig. 2. A, B). It should be noted that such a thinning of the cytoplasm leads to a decrease in the number of organelles and a disorder of metabolic processes in the endothelium.

Nuclear-containing zones are quite rare, but there occur cells with a pyknotically changed nucleus, extremely few organelles and a partially lysed plasma membrane, which may indicate the development of apoptotic changes in the endothelium (fig. 2 A). Some endothelial cells have signs of biosynthetic activity, namely: nuclei with predominance of euchromatin, endoplasmic reticulum tubules, Golgi complex, and polysomes not only around the nucleus, but also in the peripheral areas that have moderately or slightly increased thickness with no fenestra (fig. 2A, B). Others have signs of dystrophic and destructive processes: such as, local edema of the endothelial cells cytoplasm and their mitochondria with formation of vacuoles containing edematous fluid or microclasmatous outgrowths with their subsequent separation into the lumen (fig. 2. A).

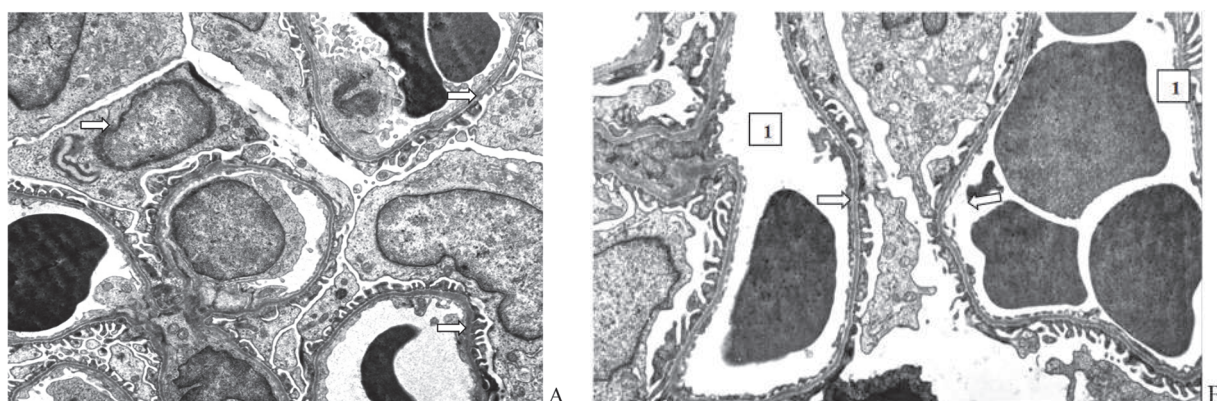


Fig. 2. Blood capillaries of a 45-day-old rat 50 days after the onset of CHT. Lumens of glomerular capillaries (1). Peripheral areas (↑) of endothelial cells. Electron microscopic images. Magnification: A, B-10000.

100 days after the development of CHT significantly less free thyroxine in comparison with the previous observation periods was found in the blood plasma of experimental rats, i.e. 2.77 ± 0.76 pmol / L, which is three times lower than in the age control (8.58 ± 0.72 pmol / L).

The lumens of the glomerula capillaries are slightly dilated and contain formed blood elements. The endothelial cells that line them have a clear division into the nuclear-containing and peripheral zones (fig. 3 A, B). As a rule, the karyoplasm of endothelial cells has high electron density, which makes them dark (fig. 3 A). In cases of the greatest compaction of karyoplasm the nuclei are reduced in sizes, pyknomorphic and flattened (fig. 3 B). The shrinkage of the nuclei can explain the detachment of endothelial cells from the basement membrane. In some capillaries, endothelial desquamation is also found

in the peripheral areas. Cells with pyknomorphic nuclei are significantly thinned, have single organelles, mainly lysosomes and the Golgi complex, in which autophagosomes are formed (fig. 3A).

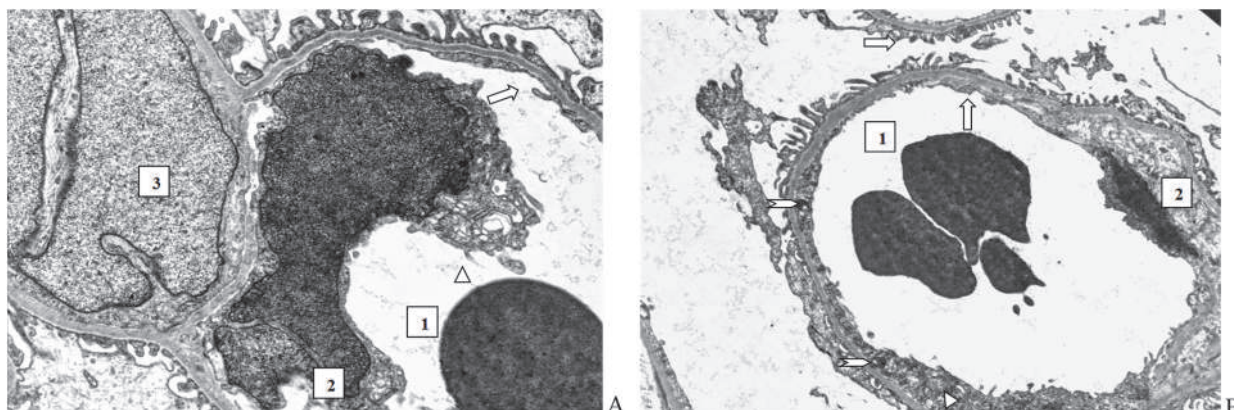


Fig. 3. Fragments of the renal corpuscle glomerular capillaries of 100 days old rats 100 days after the onset of CHT. Lumen of capillaries (1), pyknomorphic nucleus (2), peripheral areas (↑) of endotheliocytes, lysosome (△) mitochondria (†). Electron microscopic images. Magnification: A-14000, B-8000.

Regarding the indicators characterizing the glomerula capillaries, noteworthy is a decrease in all their values studied in comparison with age control. The degree of differences from control during the development of CHT is the greatest in 100-day-old rats (fig. 4).

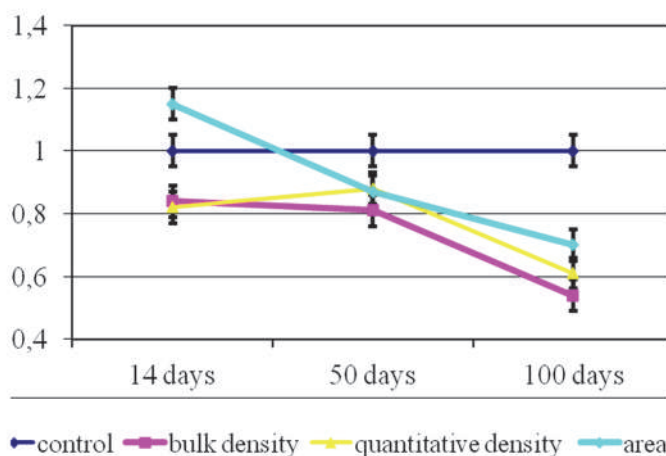


Fig. 4. Dynamics of changes in the indicators characterizing the glomerular capillaries of the renal corpuscles in rats with CHT in conventional units in relation to the control taken as 1.

In 45-day-old rats after 50 days of development of congenital hypothyroidism qualitative differences from age control in the glomerular blood capillaries are not widespread, and changes in quantitative indicators do not reach critical values. This gives grounds to believe that in the glomerular blood capillaries both destructive-dystrophic and compensatory processes are observed at the same time, with the latter prevailing. It should be noted, however, that apoptosis in the kidney of 45-day-old rats 50 days after the onset of CHT is not significantly pronounced. This statement is based on the absence of apoptotic bodies and cell compaction can be reversible.

100 days after the CHT development, changes in the kidney become more pronounced in comparison with the previous terms. In glomerular blood capillaries against the background of active destructive processes there is a failure of the compensatory ones.

Conclusion

In the course of the experiment, under the conditions of thyroid hormone deficiency, a number of morpho-functional changes develop in the glomerular blood capillaries.

At the early stages of hypothyroidism development in case of its congenital form, the main feature of the kidney is the retarded maturation of both the entire kidney and the differentiation of its components, in particular the glomerular blood capillaries. Prevailing in the glomerulus in the presence of the formed capillaries are the capillaries, whose endotheliocytes have a large nucleus, surrounded mainly by ribosomes and single mitochondria and almost no peripheral thinned area. Morphometrically, a decrease in the number of capillaries compared to control animals was found.

In 45-day-old rats after 50 days of CHT development, changes in quantitative parameters (number of capillaries and their area) do not significantly exceed those in control animals, which may indicate the predominance of compensatory changes in the internal lining of capillaries over the destructive-dystrophic ones.

100 days after CHT development, the changes in the kidney become more pronounced than in the previous period. Destruction of glomerular capillaries is observed, which leads to a decrease in both quantitative and bulk densities. These changes are based on apoptosis and necrosis of endothelial cells of the part of glomerular capillaries; desquamation of the endothelial lining, local expansion and loosening of the basement membrane, which leads to the damage to their integrity in particular and trophic disorders in general are observed in the other part of the capillaries.

References

1. Dzugkoev ST, Mozhayeva IV, Tokayeva EA. Mekhanizmy razvitiya endotelialnoy disfunktsii i perspektivy korreksii. Fundamentalnye issledovaniya. 2014, 4(1): 198-199. [in Russian]
2. Zelinska NB, Larin AS. Patologiya shitopodibnoyi zalozy u dityachoho naseleण्या Ukrayiny. Klinichna endokrinolohiya ta endokrynna khirurhiya. 2016; 3: 76-80. [in Ukrainian]
3. Kuzmenko YuYu, Koveshnikov VG. Dinamika organometrychnykh pokaznykiv nyrok shchuriv v umovakh vrodzhenoho hipotyreoza. Ukrayinskyi medychnyi almanakh. 2012; 15 (5):179-181.
4. Mamenko ME. Hipotyreoz u ditey. Dityachyi likar. 2013; 3(24):32-39.
5. Orlova MM. Vikovi osoblyvosti funktsiy nyrok u patsiyentiv z manifestnym hipotyreozom. Fundamentalni doslidzhennya. 2012; 4:347-351.
6. Chuhray S.M. Ultrastruktura krovonosnykh kapilyariv miokarda statevozirlikh shchuriv iz vrodzhenym hipotyreozom. Svit medytyny ta biolohiyi. 2010; 4: 164 – 168.
7. Basu G, Mohapatra A. Interaction between thyroid disorders and kidney disease. Indian J Endocrinol Metab. 2012 Mar; 16(2):204-213.
8. Iglesias P, Bajo MA, Selgas R, Díez JJ. Thyroid dysfunction and kidney disease: An update. Rev Endocr Metab Disord. 2017 Mar; 18(1):131-144.
9. Kriz W. Fenestrated Glomerular Capillaries Are Unique. J Am Soc Nephrol. 2008; 19: 1439-1440.
10. Kroemer G, Galluzzi L, Vandenabeele P. Classification of cell death: recommendations of the Nomenclature Committee on Cell Death. 2009. Cell Death. Differ. 2009; 16(1): 3.
11. Sorribas V, Lötscher M, Loffing J, Biber J. Cellular mechanisms of the age-related decrease in renal phosphate reabsorption. Kidney Int. 1996; 50(3): 855 - 63.
12. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol. 2015;. 3(4):286—95.

Реферати

МОРФОФУНКЦИОНАЛЬНІ ОСОБЛИВОСТІ КАПЛІАРІВ СУДИННОГО КЛУБОЧКА НИРОК В УМОВАХ ВРОДЖЕНОГО ГІПОТИРЕОЗУ У ВІКОВОМУ АСПЕКТІ

Кузьменко І.І., Стеченко Л.О., Чухрай С.М., Козак Г.І., Олійник Т.М.

У щурів досліджено кровоносні капіляри судинних клубочків нирок через 14, 50 і 100 днів розвитку вродженого гіпотиреозу. Встановлено, що на 14 добу від початку розвитку гіпотиреозу в 7-ми денних щурів на тлі відсутності виражених морфологічних змін відзначається зменшення морфометричних показників кількості капілярів і їх площі в порівнянні з віковим контролем. У 45-ти добових щурів через 50 днів розвитку цієї патології в кровоносних капілярах судинних клубочків зміни кількісних показників не набувають критичних величин, а морфологічно відзначаються як деструктивно-дистрофічні, так і компенсаторні процеси. Через 100 днів розвитку патології зміни в кровоносних капілярах набувають більшої виразності в порівнянні з попереднім терміном. На тлі компенсаторно-приспосувальних процесів відзначаються деструктивно-дистрофічні зміни частини капілярів та явища некрозу і апоптозу.

Ключові слова: кровоносні капіляри, нирки, щури, вроджений гіпотиреоз.

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МОРФОФУНКЦИОНАЛЬНЫЕ ОСОБЕННОСТИ КАПИЛЛЯРОВ СОСУДИСТЫХ КЛУБОЧКОВ ПОЧЕК В УСЛОВИЯХ ВРОЖДЕННОГО ГИПОТИРЕОЗА В ВОЗРАСТНОМ АСПЕКТЕ

Кузьменко І.І., Стеченко Л.О., Чухрай С.М., Козак Г.І., Олійник Т.М.

У крыс исследованы кровеносные капилляры сосудистых клубочков почек через 14, 50 и 100 суток развития врожденного гипотиреоза. Установлено, что на 14 сутки от начала развития гипотиреоза в 7-ми дневных крыс на фоне отсутствия выраженных морфологических изменений отмечается уменьшение морфометрических показателей количества капилляров и их площади в сравнении с возрастным контролем. У 45-ти суточных крыс через 50 суток развития этой патологии в кровеносных капиллярах сосудистых клубочков изменения количественных показателей не приобретают критических величин, а морфологически отмечаются как деструктивно-дистрофические, так и компенсаторные процессы. Через 100 суток развития патологии изменения в кровеносных капиллярах приобретают большую выразительность по сравнению с предыдущим сроком. На фоне компенсаторно-приспособительных процессов отмечаются деструктивно-дистрофические изменения части капилляров и явления некроза и апоптоза.

Ключевые слова: кровеносные капилляры, почки, крысы, врожденный гипотиреоз.

Рецензент Єрошенко Г.А.

T.V. Lakhtadyr, E.V. Cherkasov, I.M. Yaremenko, A.N. Grabovoy, K.V. Shepitko
 Bogomolets National Medical University, Kyiv
 Ukrainian Medical Stomatological Academy, Poltava

STRUCTURAL MANIFESTATIONS OF ER-STRESS IN THE NEPHRON HAEMOCAPILLARY ENDOTHELYCYTES IN EXPERIMENTAL BURN DISEASE IN RATS

e-mail: anatomi@ukr.net

Studies on structural manifestations of ER-stress, apoptosis and necrosis in endothelial cells of nephron hemocapillaries in experimental burn disease in rats (caused by burn injury of the skin with an area of 21-23% of the body surface) have shown indisputable protector and therapeutic advantages of intravenous colloidal hyperosmolar solutions infusion over the isotonic solution infusion, which was 0.9% NaCl solution. The most vulnerable organelle in endothelial cells of nephron hemocapillaries in experimental burn disease and in detoxification therapy performed is a granular endoplasmic reticulum, therefore an important evidence of the used detoxification solutions efficacy is the nature of the ER-stress course. Under the conditions of intravenous colloidal hyperosmolar solutions infusion (lactoprotein with sorbitol and HAES-LX-5%), normalization of ER stress is observed, accompanied by apoptotic changes of endothelial cells, but it is not accompanied by necrosis of endothelial cells. The consequence of the endothelial cells necrosis in the kidney hemocapillaries is the formation of paravascular hemorrhages and lympho-leukocyte infiltrates, which is evidence of impaired filtration and reabsorption functions of the kidneys, as well as of the inflammatory process progress in the kidneys.

Key words: burn disease, detoxification solutions, nephron hemocapillaries.

The work is a fragment of the research project "Morphological features and changes of the digestive tract organs in experimental skin burn injury", state registration No. 0119U101618.

It is recognized that the main factors of burn disease (BD) are endogenous intoxication, dyscirculatory hypoxia and histotoxic ischemia [17], therefore, in the BD treatment, intravenous detoxification infusion is used to prevent the development of severe toxic, hypoxic, and reperfusion damage to cells and tissues, which efficacy is the subject of clinical and experimental studies [4, 10, 7, 8].

For this purpose, different types of crystalloid and colloidal solutions are used. Ongoing discussions on the use of colloidal and crystalloid solutions have now turned to the debate on the optimal type of colloidal solutions, which solutions based on hydroxyethyl starch of different generation are attributed to, but even they are subject to debate on the presence or absence of hydroxyethyl starch nephrotoxic effects [10,1]. Determining the mechanisms of reactive and destructive changes of kidney cells under the action of toxicants and factors of various diseases led to the revision in many aspects on the problem of nephrotoxic damage to the kidney and involvement of hemomicrocirculation changes, stress of endoplasmic reticulum (ER-stress) in cells, necrosis, apoptosis, autophagy in this process. [2, 3, 9, 11, 12]. Meanwhile, the study of molecular and cellular manifestations of ER-stress, apoptosis, and necrosis in nephron hemocapillaries endothelial cells (HE) in burn disease (BD) under the effect of various detoxification solutions infusion has not recently been the subject of special studies.

The purpose of the work was to study the structural manifestations of ER-stress, apoptosis and necrosis in nephrons HE in experimental burn disease in rats under the effect of infusion: a typical isotonic crystalloid solution (0.9% NaCl solution), complex protein-saline hyperosmolar solution (lactoprotein with sorbitol) and the recently developed hydroxyethyl starch of the third generation colloidal-hyperosmolar HAES-LX-5% solution.

Materials and methods. Structural manifestations of ER-stress, apoptosis and necrosis in HE of nephrons with BD in rats were studied under the effect of various detoxification solutions infusion, namely: 0.9% NaCl solution, lactoprotein with sorbitol and HAES-LX-5%, on 105 white rat- males weighing 155-160 grams.

The experiment on the burn injury, infusion of solutions and a number of related study procedures was performed on the basis of the problematic research laboratory of functional morphology and development genetics at Vinnytsia Pirogov Memorial National Medical University, which is certified by the State Pharmacological Center at the MOH of Ukraine (Certificate No. 003/10 dated 11.01. 2010) and the laboratory of the Pharmacology Department at Vinnitsa Pirogov Memorial National Medical University, which is certified by the State Pharmacological Center at the MOH of Ukraine (certificate No. 000679 dated 11.01.2008).

Keeping in the vivarium and all manipulations with rats were carried out in full compliance with the provisions of the "General Ethical Principles for Animal Experiments", approved by the First National Congress on Bioethics (Kyiv, 2001), with strict adherence to the recommendations of the "European

Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Council of Europe, Strasbourg, 1986).

The experimental rats were divided into seven groups (15 animals in each): group I - intact rats; groups II, III and IV - rats without BD induction, which were administered a separate intravenous infusion of 0.9% NaCl solution, lactoprotein with sorbitol and HAES-LX-5% at the dose of 10 ml/kg; groups V, VI and VII - rats with BD, which under the same scheme were administered an intravenous infusion of the studied solutions.

For BD modeling, an experimental burn skin injury (T) was performed by pressing four heated copper plates (two plates on each side, each area being 13.86 cm²) for 10 minutes to the shaved lateral surfaces of the rat's body, which were previously held for 6 minutes in water at a permanent temperature of 100°C. To determine the damage degree in T, the severity index was used, which took into account the parameters of the burns area and depth, as well as the total skin area of the burned. The calculation data show that T covered 21-23% of the animal body surface, which was quite sufficient for the formation of II-III degree burns, the development of moderate-severity burn shock, and the BD initiation.

Intravenous infusion of solutions at the dose of 10 ml/kg was performed within 5 minutes into the caudal vena cava after the catheter was inserted under aseptic conditions through the femoral vein. The course of infusion therapy lasted 7 days (the first intravenous infusion was performed 1 hour after the induction of T, subsequent injections were carried out once a day). Induction of T, catheterization of the great vessels was performed under anesthesia caused by intraperitoneal administration of propofol at the dose of 60 mg/kg. Biological sampling from rats for morphological examination of the kidneys was performed under conditions of deep thiopental intraperitoneal anesthesia in 14, 21 and 30 days after T. For histological and electron microscopic studies, the sampled biopsies were processed according to the conventional method. Hemotoxylin-eosin stained histological specimens were examined on an Olympus BX51 microscope. Ultra-thin sections were made using LKB-3 ultramicrotome (Sweden), contrasted on copper support meshes with uranyl acetate and lead citrate according to Reynolds. Electron microscopic study was performed using PEM-125K electron microscope.

Results of the study and their discussion. The performed study showed that T and BD caused by it lead to significant structural changes in hemocapillaries of the vascular glomerulus (component of the filtration apparatus) and hemocapillaries of the peritubular vascular network (PH) (component of the reabsorption apparatus) of nephrons after 14, 21 and 30 days (at the stages of late BD toxemia and septicotoxemia, which manifestations were largely offset by timely infusion therapy). During this period of time, the process of destruction and structural restructuring in nephrons of experimental burned rats does not attenuate, but is only modified.

It is established that already 14 days after T under the conditions of 0.9% NaCl solution infusion (rats of group V) manifestations of mosaic reactive and destructive changes in blood vessels walls, kidney stroma and parenchyma are registered. The dilatation and / or collapse of the blood-filled and / or hollow lumens of the peritubular circulatory network vessels and hemocapillaries of the vascular glomerulus were detected. The phenomena of interstitial edema and erythrocytes diapedesis are observed. Particular destruction of PH is recorded, as well as the formation of paravasal edema, hemorrhage, lympho-leukocyte infiltrates.

After 21 days of observation in the renal cortex of group V rats an interstitial edema was revealed, which had mainly perivascular localization. Deformation and destruction of the granular endoplasmic reticulum (GER), vacuolation of the cytoplasm, and partial exfoliation of the EH PH are observed. Sometimes subtotal or even total destruction of the wall in individual PH is observed, followed by the formation of paravasal hemorrhages.

The lumen of most peritubular blood vessels is filled with sludged erythrocytes. The presence of PH with a destroyed wall and paravasal interstitial hemorrhages is combined with the occurrence of hemolyzed erythrocytes and cellular detritus in the lumen of the nephron tubules with the damaged wall. The erythrocyte hemorrhage site contains the remnants of the destroyed cells, therefore it is difficult in most cases to determine the extent of damage to the wall of peritubular blood vessels located in that area. Attention is drawn to the hemocapillaries of the vascular glomerulus, whose endothelial cover is locally completely disintegrated by apoptosis (anoikis) of the EH. The lumen of such microvessels is clouded by apoptotic altered EH that have completely or partially lost contact with the basement membrane. The nucleoplasm and cytoplasm in such apoptotic EH are condensed, the nuclear membrane is in many places invaginated, chromatin in the state of marginal aggregation (fig. 1).

Under the conditions of intravenous infusion of lactoprotein with sorbitol (group VI rats), 14 days after the T, nephrons PH are structurally preserved. The EH is characterized by the cytoplasmic zonation, which arises due to the organelle hypertrophy of the protein-synthesizing apparatus. In particular,

hypertrophied, long, branched, but prone to parallel placement to each other, expanded and filled with small-globular contents granular endoplasmic reticulum (GER) localized in the adjacent to the nucleus, elongated and thickened area of organelles. The peripheral, refined area of fenestra localization is also long and, as a rule, contralateral to the nuclear zone of the EH cytoplasmic organelles (fig. 2.).

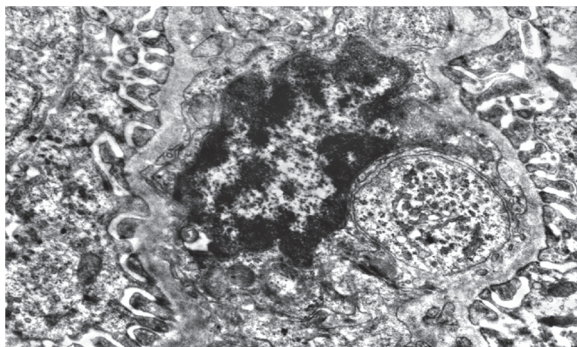


Fig. 1. Hemocapillary of the vascular glomerulus with disintegrated endothelial cover of the rat renal cortex 21 days after T under the conditions of administering 0.9% NaCl. 1 - nucleus of apoptotic EH; 2- apoptotic body; 3- basement membrane; 4- cytotrabecule; 5- podocyte cytopodia. Electronic micrograph. Magn. 35000.

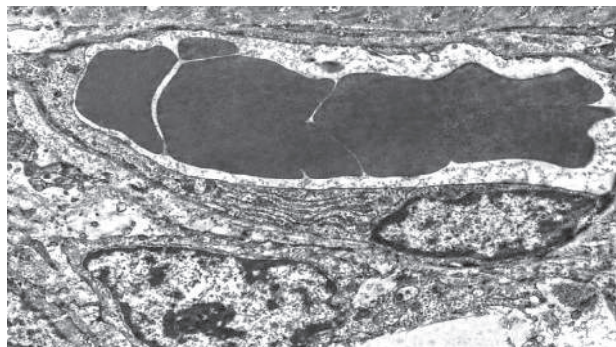


Fig. 2. Hypertrophy of the parallel tubes of the GER (marked with a single arrow) in the cytoplasm of the peritubular vascular network EH in the rat renal cortex 14 days after T under the conditions of administering lactoprotein with sorbitol. Electronic micrograph. Magn. 10000.

Electron microscopic studies of the renal cortex in animals of group VI 14 days after T showed that changes in all components of the filtration barrier occur in renal corpuscles, but they are less pronounced than in rats administered 0.9% NaCl solution. The enlargement of hemocapillary lumens of the vascular glomerulus and their moderate blood flow were observed. In the nuclear zone, the EH cytoplasm looks swollen, vacuolated and cleared, but a clear fenestration of the cytoplasmic areas remains.

In some peritubular areas (fig. 3), signs of interstitial edema (in the form of enlightenment of the basic amorphous substance) are noted, as well as intracellular edema, autophagic changes, vacuolation, necrosis of the interstitial cells and individual EH. Vacuolization and intracellular edema of EH are also observed without concomitant signs of perivascular edema and are the result of the vacuum transformation of the tubules of the GER, whose membranes lose their attached ribosomes. This is combined with manifestations of hemomicrocirculatory disorders.

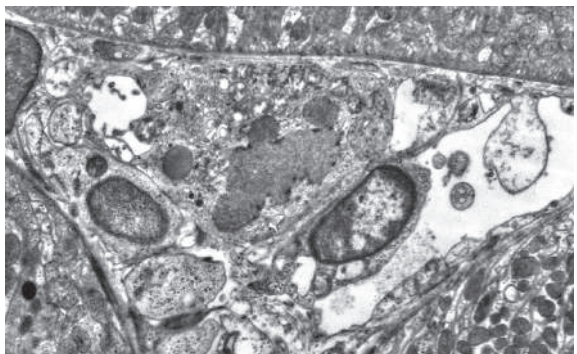


Fig. 3. Intracellular edema and vacuolation of EH in the rat renal cortex 21 days after T under the conditions of lactoprotein with sorbitol administration. Electronic micrograph. Magn. 25000.

The results of the morphological study on the structural components of the renal cortex 30 days after the T in group VI, indicate their high survivability. Perivascular edema is insignificant, PH are partially enlarged and blood filled. In the renal cortex there are hypertrophied renal corpuscles, some of them having small sizes. The hemocapillaries of the vascular glomerulus in the enlarged renal corpuscles are located tightly and blood-filled. In hemocapillaries of vascular glomeruli, apoptotic (anoikis) changes of EH are noted, but most of the renal corpuscles in their ultrastructure are similar to those in the control rats' kidney.

Morphological study of the rat kidneys in group VII 14 and 21 days after T showed that administration of HAES-LX-5% solution prevents the development of destructive changes in nephrons. Morphological study of the rat kidneys in group VII with T under the condition of HAES-LX-5% administration after 30 days of the experiment sometimes permitted to detect areas of renal cortex that do not differ from those in the control (unburned) animals. The prevalence and mutual arrangement of mitochondria, ribosomes, polysomes, GER tubules and Golgi complex in the EH indicate their coordinated and adjusted functioning.

The studies performed have shown the absolute positive advantages of intravenous infusion of colloidal-hyperosmolar solutions over infusion of isotonic solution, which is 0.9% NaCl solution. There are also differences in the influence on the renal cortex structure of lactoprotein with sorbitol and HAES-LX-5% in burned rats. We have found that the most vulnerable organelle of EH in nephrons with BD and detoxification therapy is GER. According to current concepts, GER (endoplasmic reticulum) is a membrane network that extends throughout the cell cytoplasm and is adjacent to the nuclear membrane.

It is a site of protein synthesis and transport, its assembly and coagulation, protein degradation, lipid and steroid synthesis, carbohydrate metabolism and calcium storage. GER consists of functional subdomains that have unique biophysical structure, which requires coordination in response to changes in the intracellular environment. Proteins are synthesized in ribosomes that are attached to the membranes of the GER tubules. Once inside the GER tubules, proteins undergo post-translational modification and acquire their correct three-dimensional shape (collapsed). Excessive increase in protein synthesis can lead to overloading of protein coagulation mechanisms in the GER tubules lumens, which results in imbalance of coagulation and accumulation of misfolded (folded) proteins [1, 13], which causes the stress state of GER (endoplasmic reticulum stress or ER-stress) [2].

Recent kidney studies [15] have found that acute kidney injury caused by renal ischemia-reperfusion leads to accumulation of unfolded and misfolded proteins in the lumen of the kidney GER and to development of ER stress. Under these conditions, prolonged ER stress activates the apoptotic cell death pathway, eliminating dysfunctional cells. According to M. Yanetall [15], modulation of ER stress in renal cells can be ensured by successful implementation of a therapeutic strategy for treatment of acute renal disease. This is why it is now widely accepted that ER stress plays a major role in acute and chronic structural damage to the kidneys, but also promotes cellular adaptation and nephroprotection [3, 15].

In our previous studies [8], the role of mitochondria in providing reactive rearrangement of nephron epithelial cells in BD was established, as well as the role of such phenomenon as mitophagy in this process [11]. The latest (as of publication date) literature review [9] on cellular and molecular mechanisms of renal toxicity discusses the role of mitochondria and GER in the signaling pathways of renal cell death, but the role of ER stress in the regulation of renal EH death under the conditions of toxicant exposure remains beyond the researchers' attention.

We have found that under the conditions of BD development (which component and factor is endogenous intoxication), structural changes of the GER occur in the EH of the vascular glomerulus and the pretubular vascular network of nephrons. Under the conditions of the applied detoxification solutions, hypertrophy (expansion of the lumen and the branching degree) of GER tubules overfilled with electron-dense content, which, taking into account the research literature data, indicates the tension of protein synthesis structural mechanisms and creation of conditions for the adaptive [ER] stress development. The second stage of the ER-stress development is the loss of attachment of most ribosomes to the tubule membranes of hypertrophied GER (which may indicate an attempt to restore normal EH function by stopping protein translation).

Such a scenario of ultrastructural transformations is not a preventer of EH apoptosis, but it is a preventer of necrosis. In the worst case of the ER-stress scenario, GER tubules released from the attached ribosomes are fragmented into vacuoles that merge with each other. The caused excessive vacuolation of the cytoplasm results in the necrotic death of EH, which is caused by both the deficiency of correctly folded proteins and an excess of misfolded proteins that provide a cytotoxic effect.

It should be noted that there is a continuing debate in the research literature about the presence or absence of nephrotoxic effects produced by infusion colloid-electrolyte-hyperosmolar solutions based on hydroxyethyl starch of different generation [5, 10, 14]. The data obtained indicate the nephroprotective properties of a new (based on third generation hydroxyethyl starch HES 130 / 0.4) balanced HAES-LX-5% plasma substitute, which provides a cytoprotective effect on the EH structure of nephrons in rats with BD.

Conclusion

The studies performed have shown the indisputable positive advantages of intravenous infusion of colloid-hyperosmolar solutions over infusion of isotonic solution, which is 0.9% NaCl solution. There are also differences in the influence of lactoprotein with sorbitol and HAES-LX-5% on the structure of nephrons in burned rats.

The most vulnerable organelle of nephron EH in BD and in the detoxification therapy performed is GER, therefore an important evidence of the used detoxification solutions' efficacy is the nature of the ER-stress in them. Under the conditions of intravenous infusion of colloid-hyperosmolar solutions (lactoprotein with sorbitol and HAES-LX-5%), ER-stress is normalized, accompanied by apoptotic changes in the EH, but it is not accompanied by the EH necrosis (which, by definition, is unprogrammed, randomized, and prone to unmanaged distribution of the process).

The consequence of renal EH necrosis is the formation of paravasal hemorrhages and lympho-leukocyte infiltrates, which is evidence of impaired filtration and reabsorption functions of the kidneys, as well as the progress of the inflammatory process in the kidneys. Such structural changes are particularly dangerous because, under the conditions of burn endogenous intoxication, the detoxification function of the kidneys is impaired.

The prospects for further scientific research in this field are to study the effects of different colloidal infusion solutions on the structure of nephrons in various pathological conditions.

References

1. Adams C J, Kopp MC, Larburu N, Nowak PR, Ali MMU. Structure and Molecular Mechanism of ER Stress Signaling by the Unfolded Protein Response Signal Activator IRE1. *Front. Mol. Biosci.* 2019; 6, 11. doi: 10.1111/fmolb.2019.00011
2. Cybulsky AV. Endoplasmic reticulum stress, the unfolded protein response and autophagy in kidney diseases. *Nat Rev Nephrol.* 2017; 13 (11), 681-696. doi: 10.1038/nrneph.2017.129
3. Gallazzini V, Pallet N. Endoplasmic reticulum stress and kidney dysfunction. *Biol Cell.* 2018; 110 (9), 205-216. doi: 10.1111/boc.201800019
4. Huai-Wu He. Colloids and the Microcirculation. *Anesthesia and Analgesia.* 2017; 126 (5): 1. doi: 10.1213/ANE.0000000000002620
5. Kansir AS, Johansen JK, Pedersen EB. The effect of 6% hydroxyethyl starch 130/0.4 on renal function, arterial blood pressure, and vasoactive hormones during radical prostatectomy: a randomized controlled trial. *Anesth Analg.* 2015; 120 (3), 608-618. doi: 10.1213/ANE.0000000000000596
6. Keck M, Herdon D, Komolz LP. Pathophysiology of burns. *WienMedWochenschr.* 2009; 159, 327-336. doi: 10.1136/bmj.328.7453.1427
7. Kovalchuk O, Cherkasov E, Dzevulska I, Raminsky R, Korsak A, Sokurenko L. Dynamics of morphological changes of rats adenohypophysis in burn disease. *Georgian Medical News.* 2017; (270), 104-108. PMID:28972493
8. Lachtadyr TV. Structural changes of the rat kidney cortical substance in the long-term period after burn injury of the skin under conditions of HAES-LX_5% infusion. *Emergency Medicine.* 2019; 5(100), 96-100. DOI: <https://doi.org/10.22141/2224-0586.5.100.2019.177023>
9. Lillie Marie A, Barnett BS, Brain S, Cummings, PhD. Cellular and Molecular Mechanisms of Kidney Toxicity. *Seminars in Nephrology.* 2018; 39(2), 141-151. DOI: <https://doi.org/10.1016/j.semnephrol.2018.12.004>
10. Mohanan M, Rajan S, Kesavan R, Mohamed ZU, Ramaiyar, SK, Zumar L. Evaluation of renal function with administration of 6% hydroxyethyl starch and 4% gelatin in major abdominal surgeries: a pilot study. *AnesthEssays Res.* 2019 Apr-Jun, 13(2), 219-224. doi:10.4103/aer.AER 25
11. Pickles S, Vigie P, Youle RJ. Mitophagy and quality control mechanisms in mitochondrial maintenance. *Curr Biol.* 2018 Feb 19, 28(4), R170-R185. doi:10.1016/j.cub.2018.01.004
12. Taniguchi M, Yoshida H. Endoplasmic reticulum stress in kidney function and disease. 2016 *Opin Nephrol Hypertens*, 2016; 24 (4), 345-350. doi: 10.1097/MNH.0000000000000141
13. Wang M, Kaufman RJ. Protein misfolding in the endoplasmic reticulum as a conduit to human disease. *Nature.* 2015; 529, 326-335. doi: 10.1038/nature17041
14. Weiskopf RB. Lack nephrotoxicity of hydroxyethyl starch 130/0.4 when used in surgery. *Anesthesiology.* 2015; 123(2), 482-483. doi: 10.1097/ALN.0000000000000719
15. Yan M., Sho S, Guo C, Tang C, Dong Z. Endoplasmic reticulum stress in ischemic and nephrotoxic acute kidney injury. *AnnMed.* 2018; 50 (5), 381-390. doi: 10.1080/07853890.2018.1489142

Реферати

**СТРУКТУРНІ ПРОЯВИ ЕР-СТРЕСУ
В ЕНДОТЕЛІОЦИТАХ ГЕМОКАПІЛЯРІВ
НЕФРОНІВ ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ
ОПІКОВІЙ ХВОРОБИ У ЩУРІВ**

**Лахтадир Т.В., Черкасов Е.В., Яременко Л.М.,
Грабовий А.Н., Шепітько К.В.**

Проведені дослідження структурних проявів ЕР-стресу, апоптозу і некрозу в ендотеліальних клітинах гемокапілярів нефронів при експериментальній опіковій хворобі у щурів (викликаній шляхом нанесення опікової травми шкіри площею 21-23% поверхні тіла) засвідчили безумовні протекторні та лікувальні позитивні переваги внутрішньовенної інфузії колоїдно-гіперосмолярних розчинів над інфузією ізотонічного розчину, яким є 0,9% розчин NaCl. Найбільш вразливою органелою ендотеліальних клітин гемокапілярів нефронів при експериментальній опіковій хворобі та здійсненій дезінтоксикаційній терапії є гранулярна ендоплазматична сітка, тому важливим свідченням ефективності застосованих дезінтоксикаційних розчинів є характер перебігу в них ЕР-стресу. За умов внутрішньовенної інфузії колоїдно-гіперосмолярних розчинів (лактопротеїну з сорбітолом та HAES-LX-5%) відбувається нормалізація ЕР-стресу, що супроводжується апоптозними змінами ендотеліальних клітин, але не супроводжується некрозом ендотеліальних клітин. Наслідком некрозу ендотеліальних клітин гемокапілярів нирок є утворення паравазальних кровоизливів та лімфо-лейкоцитарних інфільтратів, що є свідченням порушень фільтраційної та реабсорбційної функцій нирок, а також прогресу запального процесу в нирках.

Ключові слова: опікова хвороба, дезінтоксикаційні розчини, гемокапіляри нефронів.

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**СТРУКТУРНЫЕ ПРОЯВЛЕНИЯ ЕР-СТРЕССА
В ЭНДОТЕЛИОЦИТАХ ГЕМОКАПИЛЛЯРОВ
НЕФРОНОВ ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ
ОЖОГОВОЙ БОЛЕЗНИ У КРЫС**

**Лахтадыр Т.В., Черкасов Э.В., Яременко Л.М.,
Грабовой А.Н., Шепитько К.В.**

Проведенные исследования структурных проявлений ЕР-стресса, апоптоза и некроза в эндотелиальных клетках гемокапилляров нефронов при экспериментальной ожоговой болезни у крыс (вызванной нанесением ожоговой травмы кожи площадью 21-23% поверхности тела) показали безусловные протекторные и лечебные положительные преимущества инфузии коллоидно-гиперосмолярных растворов над инфузией изотонического раствора, которым является 0,9% раствор NaCl. Наиболее уязвимой органеллой эндотелиальных клеток гемокапилляров нефронов при экспериментальной ожоговой болезни в условиях осуществленной дезинтоксикационной терапии является гранулярная эноплазматическая сеть, поэтому важным свидетельством эффективности применяемых дезинтоксикационных растворов является характер течения в них ЕР-стресса. При инфузии коллоидно-гиперосмолярных растворов (лактопротеин с сорбитолом и HAES-LX-5%) происходит нормализация ЕР-стресса, которая сопровождается апоптозными изменениями эндотелиальных клеток, но не сопровождается некрозом эндотелиальных клеток. Результатом некроза эндотелиальных клеток гемокапилляров почек становится образование паравазальных кровоизлияний и лимфо-лейкоцитарных инфильтратов, что свидетельствует о нарушении фильтрационной и реабсорбционной функции почек, а также о прогрессе воспалительного процесса в почках.

Ключевые слова: ожоговая болезнь, дезинтоксикационные растворы, гемокапилляры нефронов.

Рецензент Єрошенко Г.А.

P.H. Lykhatskyi, L.S. Fira, I.B. Ivanusa, D.B. Fira
I. Horbachevsky Ternopil National Medical University, MOH of Ukraine, Ternopil

DEVELOPMENT OF OXIDATIVE STRESS AND INFLAMMATORY PROCESSES IN RATS UNDER NITRITE-TOBACCO INTOXICATION AND AFTER THE USE OF ENTEROSORPTION

e-mail: luhatsky@ukr.net

Intoxication rats of tobacco smoke was simulated in sealed chamber by burning 6 cigarettes (within 45 days). 24 and 72 hours before the end of the experiment, animals were injected with sodium nitrite at the dose of 45 mg/kg body weight, enterosorbent Carboline at the dose of 400 mg/kg (within 30 days). Increase in the content of met- and carboxyhemoglobin in rats' blood of all age groups during the experiment was noted. Immature rats were the most sensitive to simultaneous toxicant damage. The blood serum of affected old rats showed the highest content of C-reactive protein (3.3 times higher than the normal). Carboline had most effect on this index at the end of the study. In blood serum of affected rats in all age groups, shift in the cytokine balance towards pro-inflammatory processes was observed (increase in the content of interleukin-6 and decrease in interleukin-4). Enterosorbent had the most effect on the cytokine balance in mature rats.

Key words: nitrite-tobacco intoxication, meth- and carboxyhemoglobin, cytokines, C-reactive protein

The work is a fragment of the research project "Biochemical mechanisms of metabolic disorders under the conditions of administering toxicants of different genesis", state registration No. 0115U003359.

Smoking is a socio-economic phenomenon and one of the important health problems in Ukraine and around the world, as it is available to everybody and is therefore widespread. The spread of smoking in Ukraine is a significant threat to public health, the cause of disability and pre-terminal death [5]. Active and passive tobacco smoking can cause the formation of many active forms of oxygen - hydrogen peroxide, epoxides, nitrogen oxide (NO), nitrogen dioxide, peroxy nitrite (ONOO-). The latter activate the processes of free radical oxidation in the body. Exposure to cigarette smoke is known to activate circulating immunocytes in the lungs, which then release pro-inflammatory cytokines. Cytokines are formed by almost all cells of the body for intercellular interaction and regulation of biochemical processes in the cell [8]. Important role in the pathogenesis of toxic lesions in the body is given to the imbalance of cytokines.

A significant environmental and medical-biological problem in the agro-industrial regions of Ukraine is the combined effect on the human and animal body of inorganic nitro compounds, which is accompanied by cases of nitrate-nitrite intoxication. Under the influence of sodium nitrite, the first link in the pathogenesis is hemoglobin. The effect of sodium nitrite is manifested primarily in the oxidation of oxyhemoglobin to methemoglobin (MetHb) and a sharp increase in the intensity of free radical reactions [4].

Due to the summation of environmental risk factors, a chronic inflammatory process can occur, in which all organs and tissues are involved.

The growing number of diseases and pathological conditions, where a significant role is played by disorders of oxidative processes, immune and inflammatory responses, causes the emergence and deepening of endogenous intoxication manifestations.

The way out of this situation can be the widest possible and at the same time careful involvement of enterosorbents in treatment and prevention measures. Among the significant number of sorbents currently used in clinical practice, a significant place belongs to the "Carboline" drug. It is an inorganic, multifunctional enterosorbent based on tissue carbon fiber, which exhibits pronounced sorption and detoxification properties [1].

The purpose of this work was to study the content of hemoglobin derivatives and cytokine balance in rats of different ages with tobacco nitrite intoxication after enterosorption.

Materials and methods. The experiments were performed on white outbred male rats, which were kept on the standard diet of the vivarium of Ternopil National Medical University. Rats are divided into three age categories: the first - immature with a body weight of 60-80 g, the second - mature with a body weight of 180-200 g, the third - old rats with a body weight of 300-320 g. Each age group consisted of two subgroups - intact control and research group. The rats of the experimental groups were exposed to tobacco smoke for 45 days. Experimental animals were divided into 4 more groups. One of them was administered sodium nitrite at the dose of 45 mg/kg body weight 24 h before the end of the experiment, the other was administered sodium nitrite 72 h before euthanasia. Two more groups after being damaged with the both toxicants were intragastrically administered Carboline enterosorbent at the dose of 400 mg/kg body weight for 30 days (starting from the 15th day of tobacco smoke intoxication and daily until the end of the experiment) [1]. The model of chronic exposure to tobacco smoke was implemented using a airtight

chamber with a capacity of 30 liters, which permitted to fumigate the animals in free behavior. Tobacco smoke from the burning of 6 Prima Silver (Blue) cigarettes (containing 0.6 mg of nicotine and 8 mg of tar) was delivered into the chamber through openings. There were simultaneously 6 animals in the chamber for 6 minutes. Animals of the control group were also kept in the airtight chamber for 6 minutes, but were not exposed to tobacco smoke [9]. 45 days after the onset of tobacco smoke, exposure, the animals were sacrificed by euthanasia under thiopental anesthesia.

In our study we used the general principles of animal experiments, consistent with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes [11].

Blood and serum were sampled for the study. The content of methemoglobin (MetHb) in the reaction with acetone cyanhydrin [7] and carboxyhemoglobin (HbCO) in the reaction with potassium hexacyanoferrate (III) was determined in the blood [2]. Enzyme-linked immunosorbent assay was used to determine the level of proinflammatory cytokine, interleukin 6 (IL-6) [8] and anti-inflammatory - interleukin 4 (IL-4) [13]. The concentration of these cytokines in the serum of peripheral blood was assessed by solid-phase enzyme-linked immunosorbent assay with the RT-2100C immunoassay analyser. Test systems and control sera IL-6 and IL-4 produced by the manufacturer (Russia) were used in compliance with the relevant protocols to the test systems. To determine the concentration of cytokines the ULAB-108UA spectrophotometer was used, the wavelength being 450 nm. The concentration of cytokines studied according to the calibration curve of the respective standards was expressed in picograms per 1 ml of blood serum (pg/ml). The content of C-reactive protein (C-RP) was determined by the turbidimetric method, the principle of which is the appearance of turbidity due to the formation of insoluble immunocomplexes antigen-antibody (latex agglutination reaction). The intensity of the turbid solutions formation is recorded at 340 nm [10].

Statistical processing of the obtained data was performed using the program "STATISTICA 6.0" using the ANOVA parametric criterion and nonparametric Wilcoxon test for related samples. The changes were considered reliable at $p \leq 0.05$ [6].

Results of the study and their discussion. It is known that nitrate-containing compounds, as strong oxidants, have an effect on hematological parameters, converting bivalent heme ferrum into trivalent, forming a pathological form of hemoglobin - methemoglobin (MetHb) or hemoglobin, which is unable to reverse the addition of oxygen, which further causes hypoxia and is the main marker of the intoxication severity with nitrogen-containing compounds [4].

Prolonged smoking changes the oxygen balance of the blood and the utilization of oxygen by tissues. Carbon monoxide blocks myoglobin and impairs oxygen transport to mitochondria. The concentration of methemoglobin (HbCO) in the blood grows, which contributes to the development of acute circulatory failure of muscle tissue, tissue hypoxia, damage to vascular cells and increasing risk of atherosclerotic changes in blood vessels of all diameters [5].

Study on the content of MetHb in the blood of rats affected by sodium nitrite against the background of tobacco intoxication, showed its increase in all age groups during the experiment. After the damage with the both toxicants, the most sensitive were immature rats, in which this index increased sharply and was the highest by the end of the experiment – by 3.3 times higher compared to the control animals (table 1).

Table 1

Content of methemoglobin and carboxyhemoglobin (g/l) in the blood of different ages rats affected by sodium nitrite against the background of tobacco intoxication, and after the use of Carboline enterosorbent ($M \pm m$; $n = 6$)

Term of study, day/hours	Groups of experimental animals		
	Immature rats	Mature rats	Senile rats
	Methemoglobin		
Control rats	1.53±0.14	1.50±0.15	1.41±0.07
45 day of TS+24 hours SN	4.53±0.15*	3.64±0.09*	3.98±0.11*
45 day of TS+24 hours SN +Carboline	3.64±0.09**	3.37±0.09	3.49±0.06**
45 day of TS+72 hours SN	5.02±0.18*	4.01±0.20*	4.10±0.17
45 day of TS+72 hours SN +Carboline	3.85±0.15**	3.55±0.12	3.64±0.09
	Carboxyhemoglobin		
Control rats	0.0148±0.0012	0.0207±0.0016	0.0188±0.0017
45 day of TS+24 hours SN	0.0428±0.0040*	0.0328±0.0028*	0.0408±0.0026*
45 day of TS+24 hours SN +Carboline	0.0402±0.0029	0.0293±0.0025	0.0358±0.0028
45 day of TS+72 hours SN	0.0448±0.0038*	0.0311±0.0022*	0.0437±0.0035*
45 day of TS+72 hours SN +Carboline	0.0387±0.0019	0.0273±0.0022	0.0391±0.0032

Note: * - reliable changes between control and toxic animals; ** - reliable changes between affected rats and rats receiving carboline; TS - tobacco smoke; SN - sodium nitrite.

During this term of the study, the content of MetHb in the blood of mature rats increased by 2.7 times, in senile rats - by 2.6 times, compared to the level of control animals.

After the use of Carboline, the content of MetHb in the blood of immature animals decreased by 76%. Carboline had a similar effect on the process of methemoglobin formation in the groups of mature and senile rats.

One more index that characterizes the pathological changes in the body of animals after exposure to tobacco smoke and contributes to the deepening of hypoxia is carboxyhemoglobin. Carbonyl, or carbon monoxide contained in tobacco smoke, has the ability to bind the respiratory pigment of blood - hemoglobin. The resulting carboxyhemoglobin is not able to carry oxygen; as a result, tissue respiration processes are impaired [2].

By the end of the experiment, the HbCO content in the blood of immature rats (under the action of the both toxicants) has increased the most - by 3 times higher than the normal, in mature rats- by 1.5 times and in the senile - by 2.3 times higher than the level of animals in the control group.

When Carboline was used for 30 days, a tendency to decrease the carboxyhemoglobin content in the affected rats was observed, but no reliable changes were observed in any study period in all age groups of animals.

Therefore, the results obtained permit to note that the most sensitive to the simultaneous damage by sodium nitrite and tobacco smoke are immature rats, in which the content of methemoglobin and carboxyhemoglobin after the exposure is the highest. The Carboline enterosorbent used by us selectively had a positive effect on these indices in rats of different age groups.

The key mechanism for the development of lung diseases is inflammation, which occurs under the influence of various non-specific stimuli (tobacco smoke, air pollutants, etc.). Pulmonary inflammation, mediated by the accumulation of various cells (neutrophils, macrophages), is accompanied by oxidative stress, which supports inflammation [3].

The study of C-protein content is one of the most acceptable markers of early diagnosis and monitoring of inflammatory disease [3]. C-RP is a representative of several functional groups: mediators, transport proteins, immunomodulators. It is a highly sensitive but nonspecific acute phase index that is produced in response to most forms of tissue damage, infection, or inflammation.

We have studied the content of C-RP in the blood serum of rats in different age groups affected by sodium nitrite against the background of tobacco intoxication. The highest content of this index was registered in the blood serum of senile rats, in which by the end of the experiment it increased by 3.3 times (fig. 1).

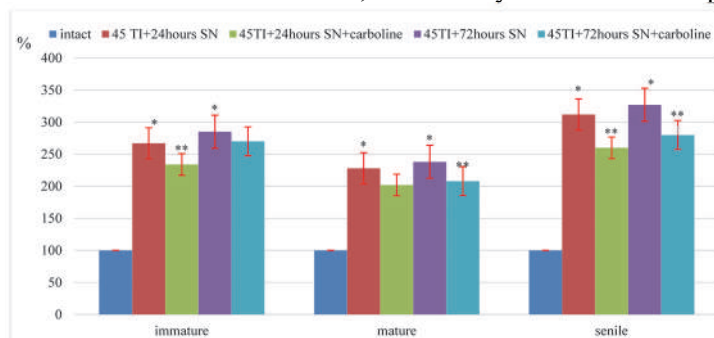


Fig.1. Content of C-reactive protein in the blood serum of rats at different ages under conditions of nitrite-tobacco intoxication and after the use of Carboline, %.

Note: * - reliable changes between control and toxicant affected animals; ** - reliable changes between affected rats and rats receiving carboline.

It is known that the synthesis and secretion of C-RP takes place in the liver and is regulated by proinflammatory cytokines, primarily by IL-6, but it can be produced by macrophages, lymphocytes. It should be noted that the peak concentration of C-RP correlates with the maximum increase in the concentration of IL-6 [12].

Based on the above, it was advisable to study the cytokine balance in smoke-toxicated and sodium nitrite-affected rats of different ages. Damage of rats with sodium nitrite against the background of 45-day intoxication of TS led to an increase in the content of proinflammatory cytokine IL-6 in the blood serum of rats in all experimental groups (table 2).

The highest content of IL-6 was observed in the serum of immature rats, which increased by 4.6 times at the end of the experiment. By the end of the experiment, after the damage induced by both toxicants, the content of proinflammatory cytokine in the blood serum of mature rats increased by 3.5 times, in the senile - by 2.6 times compared to the intact control group.

From the data presented in fig. 1 it can be seen that throughout the experiment, the content of C-RP increased. Carboline was effective at the late stages of the study (under its influence, the content of C-RP reliably decreased in this group of animals). Similar changes in the C-RP content were observed in the blood serum of immature and mature rats after the induced damage and carboline administration. More resistant to such changes were mature rats, in which this index increased the least after the damage.

Content of pro-inflammatory IL-6 and anti-inflammatory IL-4 (pg/l) in the blood serum of rats at different ages affected by sodium nitrite against the background of tobacco intoxication, and after the use of Carboline enterosorbent (M ± m; n = 6)

Term of study, day/hours	Groups of experimental animals		
	Immature rats	Mature rats	Senile rats
	proinflammatory IL-6		
Control rats	1.91±0.28	3.00±0.30	4.14±0.17
45 day of TS+24 hours SN	7.74±0.35*	9.35±0.32*	10.94±0.21*
45 day of TS+24 hours SN +Carboline	6.96±0.20	8.77±0.13	9.88±0.29**
45 day of TS+72 hours SN	8.87±0.21*	10.50±0.26*	10.90±0.31*
45 day of TS+72 hours SN +Carboline	7.89±0.34	8.94±0.23**	9.11±0.23**
	anti-inflammatory IL-4		
Control rats	1.98±0.04	1.45±0.03	1.36±0.02
45 day of TS+24 hours SN	1.13±0.04*	1.02±0.03*	0.90±0.03*
45 day of TS+24 hours SN +Carboline	1.14±0.02	1.08±0.03	0.96±0.04
45 day of TS+72 hours SN	0.90±0.02*	0.85±0.03*	0.75±0.02*
45 day of TS+72 hours SN +Carboline	0.96±0.02	0.96±0.04**	0.77±0.03

Note: * - reliable changes between control and toxicated animals; ** - reliable changes between affected rats and rats receiving carboline.

Efficacy of Carboline used was manifested mainly in the groups of mature and senile rats, in the blood serum of which by the end of the experiment the content of IL-6 reliably decreased ($p \leq 0.05$).

The basis for the development of the inflammatory process is the launch of the cytokine cascade, which includes, on the one hand, pro-inflammatory cytokines, on the other hand - anti-inflammatory mediators. The balance between the two oppositely directed groups of cytokines, mainly, determines the nature of the course and outcome of the disease. IL-4 has been shown to have a potent anti-inflammatory effect and plays a key role in the inflammatory response, as well as reducing the inflammatory functions of monocytes and macrophages.

We studied the content of IL-4 in the blood serum of rats affected by sodium nitrite against the background of tobacco intoxication, and the effect of the Carboline enterosorbent drug (table 2).

By the end of the study, the content of anti-inflammatory cytokine was most pronounced in the blood serum of immature rats - by 2.2 times, while in mature and senile rats - by 1.7 and 1.8 times, respectively (compared to the control).

Carboline did not show a positive effect on this index in the groups of immature and senile animals. In the group of mature rats, the content of IL-4 in the blood serum reliably increased ($p \leq 0.05$).

Oxidative stress and accumulation of toxic products of exogenous and endogenous origin in the body of affected rats, which we had found before, led to the development of inflammatory processes with their deepening depending on the age of the animals. This is confirmed by an imbalance of pro- and anti-inflammatory cytokines and an increase of the acute phase protein - C-reactive protein in the blood serum.

Our data are consistent with the literature [15], which shows that smokers have an impairment of the hemoglobin transport function in the blood, and in particular, an increase in oxygen-inactive forms of hemoglobin, particularly ligands such as methemoglobin and sulfhemoglobin. In addition, nitrate-containing compounds, as strong oxidants, have an effect on hematological parameters, forming a pathological form of hemoglobin - methemoglobin [14]. Some authors attribute a significant role in the development of metabolic disorders under the influence of cigarette smoke to carbon monoxide and oxidizing gases. Carbon monoxide reduces the transport of oxygen in the blood and its availability to the myocardium by increasing the level of carboxyhemoglobin in the blood [5], which is consistent with the observed increase in meth- and carboxyhemoglobin under the conditions of rats' damage with sodium nitrite against tobacco intoxication.

There is evidence suggesting that tobacco smoke can cause inflammation, in particular through the induction of pro-inflammatory cytokines. Proinflammatory cytokines are produced mainly by activated macrophages and are involved in the regulation of inflammatory reactions [15]. The observed increase in the content of interleukin-6 and decrease in the content of interleukin-4 under the conditions of nitrite-tobacco intoxication confirms the literature data on the imbalance in the content of pro- and anti-inflammatory cytokines in smokers.

Among the biomarkers that reflect changes in inflammation, acute phase proteins that appear in blood plasma 4-6 hours after tissue damage by various factors, including C-reactive protein, are of great importance [10]. We noted a reliable increase in this index in the blood serum of rats in our experiment, which was more pronounced in senile animals.

The use of Carboline enterosorbent was effective in nitrite-tobacco intoxication, which, in our opinion, indirectly affected the hematological parameters and led to the suppression of inflammatory activity in the toxicated body.

Conclusions

1. Simultaneous damage to rats induced with sodium nitrite and tobacco smoke leads to the activation of free radical processes, as indicated by the increased content of methemoglobin in the blood of rats at all ages. Along with this, there is an increase in carboxyhemoglobin in animals of different ages. Immature rats were the most sensitive to toxicants. Immature rats were sensitive to the effects of the Carboline enterosorbent (probably, the methemoglobin content decreased, which is a consequence of the free radical process activation after the damage).

2. Under the conditions of nitrite-tobacco intoxication in the blood serum probably the content of C-reactive protein increased, which was most pronounced in senile animals. In addition, there was a shift in the balance between cytokines towards pro-inflammatory processes, as indicated by an increase in the content of pro-inflammatory interleukin and a decrease in the content of anti-inflammatory interleukin after the damage. Carboline was effective in influencing C-reactive protein content in immature and senile rats, probably reducing it at the end of the study. In mature rats, enterosorbent led to a probable restoration of serum cytokine imbalance after intoxication with both toxicants.

3. The obtained results confirmed the possibility of including Carboline enterosorbent in complex treatment regimens for intoxications caused by chemical compounds, as well as by smoking.

References

1. Andreychyn SM, Lototska SV. Efektyvnist zastosuvannya enterosorbentu «Karbolayn» pry likuvanni khvorykh na khronichne obstruktyvne zakhvoryuvannya lehen. Journal of Education, Health and Sport. 2015; 5(5):125-130. doi: 10.5281/zenodo.17463. [in Ukrainian]
2. Velyhotsky DV, Stelmakh NV, Mamilov SO, Yesman SS. Aparatno-prohramnyyy kompleks dlya neinvazyvnoho diahnostuvannya karboksyhemoglobinu v potokakh krovi. Visnyk KrNU imeni Mykhayla Ostrohradskoho. 2012; 72(1):71-74. [in Ukrainian]
3. Volkova LI, Timofeyeva AV. C-reaktivnyy belok kak pokazatel sistemnogo vospaleniya u bolnykh khronicheskoy obstruktyvnoy boleznyu legkikh. Sovremennyye problemy nauki i obrazovaniya. 2013; 6:122-138. [in Russian]
4. Hunchak VM. Do toksykologiyi nitrativ i nitrytiv u tvaryn. Naukovyy visnyk LNUVMBT imeni SZ. Hzytskoho. 2013; 57(3):62-70. [in Ukrainian]
5. Kvasha NA. Meditsynskiye aspekty tabakokureniya. Zdorovya Ukrayiny. 2010; 20(249):40-41. [in Russian]
6. Shelamova MA, Insarova NI, Leshchenko VG. Statisticheskiy analiz mediko-biologicheskikh dannykh s ispolzovaniyem programmy EXCEL. Minsk: BGMU. 2010; 96 s. [in Russian]
7. Arakaki LS, Ciesielski WA, Thackray BD, Feigl EO, Schenkman KA. Simultaneous Optical Spectroscopic Measurement of Hemoglobin and Myoglobin Saturations and Cytochrome aa3 Oxidation In Vivo. Appl Spectrosc. 2010; 64(9): 973-979. doi: 10.1366/000370210792434387.
8. Chen Z, Li R, Xie Z, Huang G, Yuan Q, Zeng J. IL-6, IL-10 and IL-13 are associated with pathogenesis in children with Enterovirus 71 infection. Int. J. Clin. Exp. Med. 2014 Sep; 7(9):2718-2723.
9. Churg A, Wright J. Animal models of cigarette smoke-induced chronic obstructive pulmonary disease. Expert Rev Respir Med. 2010;4(6):723-34. doi: 10.1586/ers.10.68.
10. Deng ZC, Zhao P, Cao C, Sun SF, Zhao F, Lu CY, et al. C-reactive protein as a prognostic marker in chronic obstructive pulmonary disease. Exp Ther Med 2014; 7:443-6. doi: 10.3892/etm.2013.1441.
11. Gross D, Tolba RH. Ethics in Animal-Based Research. Eur Surg Res. 2015 Apr; 55(1-2), 43-57. doi:10.1159/000377721.
12. Hubeau C, Kubera JE, Masek-Hammerman K, Williams CM. Interleukin-6 neutralization alleviates pulmonary inflammation in mice exposed to cigarette smoke and poly(I:C). Clin. Sci.(Lond). 2013 Nov; 125:483-493. doi: 10.1042/CS20130110.
13. Nam J, Park K, Park E, Lee YB, Lee HG, Baik HH, et al. Interleukin-13/-4-induced oxidative stress contributes to death of hippocampal neurons in $\alpha\beta 1$ -42-treated hippocampus in vivo. Antioxid Redox Signal. 2012 Jun; 16(12):1369-83. doi: 10.1089/ars.2011.4175.
14. Taylor CT, Moncada S. Nitric oxide, cytochrome c oxidase, and the cellular response to hypoxia. Arterioscler Thromb Vasc Biol. 2010 Apr; 30(4):643-7. doi: 10.1161/atvbaha.108.181628.
15. Wilson KM, Wesgate SC, Pier J, Weis E, Love T, Evans K, et.al. Secondhand smoke exposure and serum cytokine levels in healthy children. Cytokine. 2012 Oct; 60(1):34-7. doi: 10.1016/j.cyto.2012.06.236

Реферати

РОЗВИТОК ОКИСНОГО СТРЕСУ ТА ЗАПАЛЬНИХ ПРОЦЕСІВ В ОРГАНІЗМІ ЩУРІВ ЗА УМОВ НІТРИТНО-ТЮТІОНОВОЇ ІНТОКСИКАЦІЇ ТА ПІСЛЯ ЗАСТОСУВАННЯ ЕНТЕРОСОРБЦІЇ

Лихацький П.Г., Фіра Л.С., Івануса І.Б.

Ураження тютюновим димом моделювали у герметичній камері від горіння 6 сигарет протягом 6 хв (45 днів). За 24 та 72 год до закінчення експерименту тваринам вводили натрію нітрит у дозі 45 мг/кг маси тіла, ентросорбент Карболайн - у дозі 400 мг/кг (30 днів). Відмічено збільшення вмісту мет- та карбоксигемоглобіну у крові щурів усіх вікових груп впродовж експерименту. Найбільш чутливими до

РАЗВИТИЕ ОКИСЛИТЕЛЬНОГО СТРЕССА И ВОСПАЛИТЕЛЬНЫХ ПРОЦЕССОВ В ОРГАНИЗМЕ КРЫС В УСЛОВИЯХ НИТРИТНО- ТАБАЧНОЙ ИНТОКСИКАЦИИ И ПОСЛЕ ПРИМЕНЕНИЯ ЭНТЕРОСОРБЦИИ

Лихацкий П.Г., Фира Л.С., Ивануса И.Б.

Интоксикацию крыс табачным дымом моделировали в герметичной камере от горения 6 сигарет (45 дней). За 24 и 72 ч до окончания интоксикации животным вводили натрия нитрит в дозе 45 мг / кг массы тела, энтеросорбент Карболайн – в дозе 400 мг / кг (30 дней). Отмечено увеличение содержания мет- и карбоксигемоглобина в крови крыс всех возрастных групп на протяжении эксперимента. Наиболее чувствительными к

одночасного ураження токсикантами є статевонезрілі щури. Найвищий вміст С-реактивного протеїну зареєстровано у сироватці крові щурів старшого віку, у яких він підвищився в 3,3 раза. Карболайн виявився ефективним в останні терміни дослідження. Після ураження спостерігався зсув балансу між цитокинами в сторону прозапальних процесів, на що вказувало підвищення вмісту прозапального та зниження вмісту протизапального інтерлейкіну. У статевозрілих щурів ентеросорбент призвів до вірогідного відновлення дисбалансу цитокинів у сироватці крові після ураження.

Ключові слова: натрію нітрит, тютюновий дим, метгемоглобін, карбоксигемоглобін, цитокини, С-реактивний протеїн

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одновременному поражению токсикантами были неполовозрелые крысы. В сыворотке крови пораженных старых крыс отмечено наиболее высокое содержание С-реактивного протеина (в 3,3 раза выше нормы). Карболайн оказал эффективное влияние на этот показатель в конце исследования. В сыворотке крови пораженных крыс всех возрастных групп наблюдался сдвиг цитокинового баланса в сторону провоспалительных процессов (повышение содержания интерлейкина-6 и снижение интерлейкина-4). Наиболее эффективное влияние оказал энтеросорбент на цитокиновый баланс у половозрелых крыс.

Ключевые слова: нитритно-табачная интоксикация, мет- и карбоксигемоглобин, цитокины, С-реактивный протеин

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Ye.O. Loza, M.I. Marushchak, O.V. Denefil, D.S. Avetikov¹, O.O. Kulyanda
I. Horbachevsky Ternopil National Medical University, Ternopil
¹Ukrainian Medical Stomatological Academy, Poltava

BIOCHEMICAL FEATURES OF POSTOPERATIVE SKIN WOUNDS HEALING AGAINST THE BACKGROUND OF DIABETES MELLITUS IN RATS WITH DIFFERENT WAYS OF WOUND CLOSURE

e-mail: doctorloza@gmail.com

The study is devoted to identifying the features of free radical processes changes in skin homogenate of the rats with diabetes mellitus, after using different methods of surgical wounds closing. Analysis of the results suggests that the use of skin glue significantly reduces the intensity of the free radical oxidation course in the cells of scarred skin tissues in animals with simulated diabetes mellitus compared to the application of nodal sutures to the wound under similar conditions.

Key words: free radical oxidation, oxidative stress, abnormal scar.

The work is a fragment of the research project "Systemic and organ disorders due to emergency factors effect on the body, mechanisms of their development and pathogenetic correction", state registration No. 016U003390.

Diabetes mellitus (DM) is considered to be one of the most important non-communicable diseases worldwide and is also one of the global health challenges of the 21st century [3]. It ranks fourth among the major causes of death in developed countries [15].

In 2017, 1,270,929 cases of diabetes were registered in Ukraine. Today, almost 50% of diabetes cases are undiagnosed. Development of late complications leads to a significant reduction in quality of life, reducing its duration by 10-30%, disability, increased mortality of patients by 2-3 times and significant budget expenditures for their treatment. The number of patients with diabetes mellitus is increasing by 5-7% annually. Such indices indicate a non-infectious epidemic of diabetes.

Wound healing is a coordinated process that goes through certain stages with different types of cells and their waste products participating, which regulate the healing process. It is proved that in patients with DM there is the wound healing process disorder, but not all features of this process in diabetes mellitus are completely understood.

At the same time, the quality and structure of the material, the chemical composition of the suture material effect the reaction of tissues to their introduction, as well as the final result of the operation. Free radical oxidation (FRO) is an important biochemical conversion process of lipids, proteins, nucleic acids and other compounds under the action of free radicals, and peroxide oxidation of lipids (LPO) and proteins is one of the further consequences [2, 13]. At all stages of the FRO, due to the interaction of free radicals and biological macromolecules, numerous intermediate products are formed. Such peroxidation compounds, in their excess, are characterized by pronounced cytotoxic activity. As a result, the processes of energy production in the cell are suppressed, the synthesis of proteins and nucleic acids is disrupted, which in its turn leads to the formation of pathological scar tissue.

The purpose of the study to identify the features of free radical processes changes in the skin homogenate of rats in different ways of surgical wounds closing, in the conditions of diabetes mellitus.

Materials and methods. An experiment was performed on 60 adult male rats weighing 240-280 g. The rats were simulated diabetes mellitus by intraperitoneal administration of streptozotocin

("Sigma", USA) at the dose of 65 mg/kg body weight. 15 minutes before administration of streptozotocin the animals were intraperitoneally administered nicotinamide at the dose of 230 mg/kg body weight. All animals were obese, which was caused by keeping the animals on a high-fat diet for 4 weeks. By determining the concentration of glucose in the blood with ContourNext (USA) glucometer, the development of type 2 DM was confirmed. Under the thiopental anesthesia (40 mg/kg body weight), all experimental animals underwent straight incisions 2 cm long in the anterior-lateral region of the abdomen. In experimental group I (30 rats) surgical sutures "Vikril5 / 0" were used to close the postoperative wound. In experimental group II (30 rats) "Dermabond" skin glue (Ethicon, USA) was applied. Animals were sacrificed on the 3rd, 7th, 28th days after surgery by overdose of thiopental anesthesia (90 mg/kg body weight of rats).

The scarred skin pieces homogenate and the homogenate supernatant were under study.

To determine the degree of free radical oxidation processes activation, the content of reactive oxygen species (ROS) [5], lipid hydroperoxides (LHP) [5], diene conjugates (DC) and triene conjugates (TC) [1] and indices of blood plasma proteins oxidative modification were determined (OMP₃₇₀ and OMP₄₃₀) [10].

In order to study the antioxidant defense system, the activity of superoxide dismutase (SOD) in the supernatant was determined by the method of Chevari S. et al. [12]. Catalase activity was determined by the method of Korolyuk M.A. [6], sulfhydryl groups (SH groups) – according to Ellman G.L. [14].

Statistical processing of the obtained data was carried out by standard methods of variation statistics using a package of statistical software. The results are given as (M±m), where M is the mean value of the index, m is the standard error. The significance of discrepancies between the studied indices was determined using the Student's t-test.

Results of the study and their discussion. Our study showed that the activity of free-radical oxidation (FRO) increased during the wound process against the background of diabetes mellitus. However, in the skin homogenates of the animals treated with "Dermabond", all values were significantly lower than in the group of animals treated with interrupted sutures during all study periods. Thus, the number of ROS was greater in animals of group I, compared to those of group II, on the 3rd, 7th and 28th days of the experiment. They also showed a gradual decrease from the beginning of the study to the last time interval, the gradient of decrease being more significant in group II (table 1). The content of diene and triene conjugates in the skin homogenate of group I rats exceeded that of animals in group II on the 3rd day. In group I, the content of DC was (10.77±0.23) relative units (RU)/kg, TC - (9.72±0.41) RU/kg, in II - (7.66±0.37) RU/kg and (7.53±0.37) RU/kg, respectively. On days 7 and 28, a linear decrease in the content of primary LPO products was observed in both experimental groups I and II. Lipid hydroperoxides (LHP) content was also higher in group I rats, compared those in group II, on the 3rd day of the experiment and significantly decreased on the 7th and 28th days in the both groups of animals.

Table 1

Indices of free radical oxidation in the skin homogenate of rats with simulated diabetes mellitus using suture material and skin glue in the dynamics

Index		ROS, %	DC, RU/kg	TC, RU/kg	LHP, RU/h
Intact animals		19.20±0.37	4.05±0.08	4.09±0.18	5.05±0.06
Day 3	Group I	90.76±1.26	10.77±0.23	11.49±0.55	9.72±0.41*
	Group II	74.67±1.06*	7.66±0.37*	9.71±0.19*	7.53±0.37*
Day 7	Group I	88.27±2.08	9.88±0.56	9.29±0.39	7.20±0.38*
	Group II	43.93±1.31*	6.82±0.29*	7.84±0.20*	6.24±0.35*
Day 28	Group I	50.1±3.21	5.65±0.26	8.76±0.26	5.13±0.21
	Group II	29.07±0.95*	5.46±0.16	6.51±0.26*	4.93±0.23*

Notes. Henceforward in the tables: * - the difference is significant between experimental groups I and II within one day

The content of OMP₃₇₀ and OMP₄₃₀ products in the skin homogenate of group I animals was by 2.3 and 1.5 times higher, respectively, similar to skin of those in group II on the 3rd day of the experiment. A slight decrease in these indices occurred in both experimental groups on day 7. On day 28, the content of OMP₃₇₀ products in the skin homogenate of group I animals was by 3.6 times higher than the same index in the skin of group II animals (table 2).

Analysis of all indices permits to state that in the skin of animals treated with glue, the intensity of FRO processes is much lower compared to the imposition of interrupted sutures. Given the strengthening of the LPO processes, which cause the phenomena of primary and secondary alteration when using suture material to close wounds in rats with diabetes mellitus, the beginning of reparative mechanisms in them is delayed.

Indices of proteins oxidative modification in skin homogenate against the background of diabetes mellitus using suture material of skin glue in the dynamics

Group/Index, %		OMP ₃₇₀	OMP ₄₃₀
Intact animals		1.70±0.06	0.33±0.46
Day 3	Group I	7.25±0.20	2.79±0.10
	Group II	3.12±0.10*	1.84±0.09*
Day 7	Group I	6.78±0.17	2.10±0.11
	Group II	2.67±0.11*	1.42±0.09*
Day 28	Group I	5.83±0.26	1.69±0.06
	Group II	1.62±0.04*	1.02±0.06

At the early stages of scar formation (on the 3rd day), we observed an increase in the activity of the antioxidant defense system in the two groups presented. In the groups of animals to which interrupted sutures were applied, the activity of superoxide dismutase (SOD) and catalase was much higher than in the skin of the animals to which the glue was applied, and amounted to (199.81±7.59) RU and (175.02±8.31) kat/kg, respectively. Such data indicated the inevitable start of free radical oxidation due to the traumatic factor against the background of diabetes mellitus. A significant decrease in all parameters was determined in the skin of experimental animals of the both groups on the 7th day of the experiment. However, this difference in the change of SOD activity data was higher in group II animals than in the group treated with the skin glue, where the index decreased by 1.4 times, while in group I the this index decreased by 1.15 times (table 3).

Table 3

Indices of the antioxidant defense system in the skin homogenate under the conditions of diabetes mellitus using suture material and skin glue

Index		SOD, RU	Catalase, kat/kg	SH-groups, mmol/L
Intact animals		71.45±2.28	35.05±2.91	37.50±2.02
Day 3	Group I	199.81±7.59	175.02±8.31	90.44±2.00
	Group II	118.57±3.51*	96.05±2.43*	68.50±1.42*
Day 7	Group I	173.19±7.05	146.72±7.19	71.50±2.77
	Group II	84.72±1.81*	74.28±1.83*	62.90±1.27*
Day 28	Group I	140.51±5.93	111.12±5.13	64.18±2.25
	Group II	83.18±2.29*	73.02±1.40*	62.27±1.33*

Similarly, the reduced glutathione indices were lower in rats of group II, compared to those in group I, on the 3rd and the 7th days from the beginning of the experiment.

Thus, in the animals in the wound process against the background of diabetes mellitus, the indices of FRO activity are much higher, compared to the control rats. The obtained data are confirmed by the results of other authors in the study of the oxidative-antioxidant system status of the liver in alloxandiabetic rats under the conditions of melatonin administration and in the study of the vanadium and chromium citrates effect on the antioxidant system in the blood of experimental rats [4, 9, 11]. The activity of superoxide dismutase and catalase, which are important components of the antioxidant system, in the skin homogenate of rats with diabetes mellitus is significantly reduced, compared to healthy animals. Similar activity of these indices was found in the study of the antioxidant defense system in rats under the action of carrageenan against the background of streptozotocin diabetes, as well as in the study of lipid peroxidation system and antioxidant defense enzymes in rats of different ages in experimental diabetes mellitus [7, 8, 11].

Conclusion

The use of skin glue significantly reduces the FRO intensity in the cells of scar tissue in animals with simulated diabetes mellitus compared to the imposition of interrupted sutures on the wound: in skin homogenates of animals, which were applied skin glue "Dermabond", all indices are significantly lower than in the group of animals which were imposed interrupted sutures during all terms of the study. In particular, in the long term of the study (the 28th day) the content of hydro lipid peroxides in experimental group I was 8.76±0.26 RU/kg, which is by 1.3 times more than in the animal group II - 6.51±0.26 RU/kg.

References

1. Vlizlo VV, Fedoruk RS, Ratykh IB. Laboratorni metody doslidzhen u biolohii, tvarynnytsvi ta veterynarnoyi medytsyni. Dovidnyk. Lviv: 2012. 761 s. [in Ukrainian]
2. Holovchak NP, Tarnovska AV, Kotsiumbas HI, Sanahurskyi DI. Protseyi perekysnoho oksynennia lipidiv u zhyvykh orhanizmakh: monohrafiia. Lviv: 2012. 250 s. [in Ukrainian]
3. Dedova II, Shestakova MV. Sakharnyy diabet: diagnostika, lecheniye, profilaktika. M.: 2011. 808 s. [in Russian]
4. Ivankiv YaI, Oleshchuk OM, Datsko TV, Fedoniuk LI. Osoblyvosti pokaznykiv prooksydantno-antyoksydantnoho homeostazu, vuhlevodnoho obminu ta morfolohichni zminy pechinky za umov vvedennia melatoninu pry eksperymentalnomu diabete 2 typu. Visnyk morfolohii. 2016; 2(22):253-8. [in Ukrainian]
5. Kamyshnikov VS. Spravochnik po kliniko-biokhimicheskim issledovaniyam i laboratornoy diagnostike. M.: 2004. 911 s. [in Russian]

6. Korolyuk MA, Ivanova LI, Mayorova IG. Metod opredeleniya aktivnosti katalazy. Lab. delo. 1988;1:16-8.[in Russian]
7. Levytyskyi VA, Zhurakivska OIa, Miskiv VA. Aktyvnist perekysnoho oksylennia lipidiv ta fermentiv antyoksydantnoho zakhystu u shchuriv riznoho viku pry eksperymentalnomu tsukrovomu diabete. Visnyk Ukrayinskoyi medychnoyi stomatolohichnoyi akademii: Aktualni problemy suchasnoi medytsyny. 2011; 4(36):103-6.[in Ukrainian]
8. Lisnianska NV. Osoblyvosti systemy antyoksydantnoho zakhystu shchuriv za umovy diyi karahinanu na tli streptozototsynovoho diabete. Visnyk medychnykh i biolohichnykh doslidzhen. 2019; 2:19-23.[in Ukrainian]
9. Luhinich NM, Herush IV, Hryhorieva NP. Stan prooksydantno-antyoksydantnoi systemy pechinky aloksandiabetychnykh shchuriv za umov vvedennia melatoninu. Medychna ta klinichna khimiia. 2019; 21(2):30-4. [in Ukrainian]
10. Meshchyshe IF. Metod vyznachennia oksyliuvalnoyi modyfikatsii bilkiv plazmy krovi. Bukovynskyi medychnyi visnyk. 1998; 2(1):156-8.[in Ukrainian]
11. Sushko OO, Iskra RYa. Vplyv tsytrativ vanadiyu ta khromu na antyoksydantnu systemu v krovi shchuriv iz eksperymentalnym diabetom Visnyk ONU. Biolohiya. 2019; 24(1):106-15.[in Ukrainian]
12. Chevri S, ChabaI, Sekey Y. Rol superoksidreduktazy v oksylitelnykh protsessakh kletki i metod opredeleniya yeye v biologicheskomo materiale. Lab. delo. 1985; 11:678-681.[in Russian]
13. Kurahashi T, Fujii J. Roles of antioxidative enzymes in woundhealing. J. Dev. Biol. 2015; 3:57-70.
14. Moffat JA, Armstrong PW, Marks GS. Investigations into the role of sulfhydryl groups in the mechanism of action of the nitrates. Canadian Journal of Physiology and Pharmacology. 1982; 60(10):1261-6.
15. Whiting DR, Guariguata L, Weil C, Shaw J. International Diabetes Federation. Diabetes Atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice. 2011; 94:311–321.

Резюме

БІОХІМІЧНІ ОСОБЛИВОСТІ ЗАГОСННЯ ПІСЛЯОПЕРАЦІЙНИХ РАН ШКІРИ НА ФОНІ ЦУКРОВОГО ДІАБЕТУ У ЩУРІВ ПРИ РІЗНИХ СПОСОБАХ ЗАКРИТТЯ РАН

Лоза С.О., Марушак М.І., Денефіль О.В.,
Аветіков Д.С., Кулянда О.О.

Дослідження присвячено вивченню особливостей змін вільнорадикальних процесів у гомогенаті шкіри щурів при різних способах закриття операційних ран, за умов цукрового діабету. Аналіз отриманих результатів дає змогу стверджувати, що застосування шкірного клею достовірно знижує інтенсивність перебігу ВРО у клітинах рубцевозміненних тканин шкіри тварин зі змодельованим цукровим діабетом порівняно із накладанням на рану вузлових швів за аналогічних умов.

Ключові слова: вільнорадикальне окиснення, оксидативний стрес, патологічний рубець.

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БИОХИМИЧЕСКИЕ ОСОБЕННОСТИ ЗАЖИВЛЕНИЕ ПОСЛЕОПЕРАЦИОННЫХ РАН КОЖИ НА ФОНЕ САХАРНОГО ДИАБЕТА У КРЫС ПРИ РАЗЛИЧНЫХ СПОСОБАХ ЗАКРЫТИЯ РАН

Лоза Е.А., Марушак М.И., Денефиль О.В.,
Аветиков Д.С., Кулянда О.О.

Исследование посвящено изучению особенностей изменений свободнорадикальных процессов в гомогенате кожи крыс при различных способах закрытия операционных ран, при сахарном диабете. Анализ полученных результатов позволяет утверждать, что применение кожного клея достоверно снижает интенсивность течения свободно радикальных процессов в клетках рубцово-измененных тканей кожи животных с смоделированным сахарным диабетом по сравнению с наложением на рану узловых швов при аналогичных условиях.

Ключевые слова: свободно радикальное окисление, оксидативный стресс, патологический рубець.

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G.S. Maslova, R.I. Skrypnyk, O.F. Gopko, I.M. Skrypnyk
Ukrainian Medical Stomatological Academy, Poltava

THE ROLE OF ARGININE/CITRULLINE CYCLE DISORDERS IN THE PATHOGENESIS OF DOXORUBICIN-INDUCED LIVER INJURY ASSOCIATED WITH NONALCOHOLIC STEATOHEPATITIS IN RATS

e-mail: maslovaas1708@gmail.com

The article presents the results of an experimental study aimed to investigate the features of arginine / citrulline cycle disorders associated with doxorubicin-induced liver injury in rats, concomitant with NASH. The study involved adult fertile outbred albino rats (n=30; male rats=15 (50%); female rats=15 (50%)) weighted 160-220 g. The rats were assigned into 3 groups: Group I (n=10) involved rats with NASH, administered with intraperitoneal 5 mg/kg doxorubicin for 3 days; Group II (n=10) involved rats without NASH, administered with intraperitoneal doxorubicin similar to Group I regimen; Group III (n=10) – control group. It has been shown that administration of doxorubicin in rats with NASH leads to disorders of arginine/citrulline cycle, which are characterized by inhibition of arginase activity and activation of citrulline synthesis.

Key words: arginine, citrulline, arginase, doxorubicin, hepatotoxic reactions, nonalcoholic steatohepatitis.

The work is a fragment of the research project "Development of methods for prevention and treatment of the drug-induced internal organs damages", state registration No. 0115U001087.

Doxorubicin, an anthracycline antibiotic, has been extensively used in oncology and oncohematology for over 30 years. Currently, it is considered one of the most effective antitumor drugs with pharmacological feature to accumulate in malignant cells. However, the use of doxorubicin is accompanied by a high risk of side effects due to its high toxicity [3, 8, 10, 13].

From the point of view of studying the toxicity of doxorubicin, certain features of its pharmacokinetics are important, namely the short half-life period lasted for 3-5 minutes, and the long semiejection period, ranging from 24 to 46 hours [12]. Therefore, the development of toxicity and its degree is dependent on the rate of administration of doxorubicin. Upon entry into the blood plasma, doxorubicin, similar to doxorubicinol, binds to blood proteins, penetrates into the cell by passive diffusion and accumulates in tumor cells in concentrations exceeding its extracellular ones by 10-1000 times [12, 15]. The high permeability properties of doxorubicin are due to its lipophilicity, and the preservation of high intracellular concentrations of the drug is due to its DNA-intercalating and binding characteristics [12, 14].

It has been confirmed that DNA is the major target for doxorubicin. The drug accumulates in the cell nucleus with intercalation in the double strand of DNA between base pairs, which leads to inhibition of nucleic acid synthesis. In addition, doxorubicin disrupts the function of nuclear proteins, primarily topoisomerases I, II and helicase, which leads to inhibition of DNA twisting and cell replication [3, 15]. Intercalation of doxorubicin into a DNA molecule inhibits the activity of DNA and RNA polymerases, suspending both DNA replication and RNA transcription. Hence, doxorubicin disrupts the repair of the DNA molecule, which leads to attenuation of cell development in the G1 and G2 phases of the cell cycle and initiation of apoptosis [12].

An important element of the toxicity of doxorubicin, as an antitumor drug, is the impact on both tumor and healthy cells of the body, which multiply rapidly [3, 12, 14, 15]. Moreover, free radicals cause drastic side effects associated with administration of the drug through the mechanisms that provide high antitumor efficacy of doxorubicin [3, 11, 13].

Doxorubicin-induced hepatotoxic reactions can be a significant limiting factor in the overall chemotherapy (CT) in the conventional treatment of cancer patients. Currently, numerous experimental and clinical studies have confirmed the toxic effects of doxorubicin on tissues of the heart, brain, kidneys, liver, pancreas [10, 15]. The probability of development of cytostatic-induced hepatotoxic reactions increases significantly in chronic diffuse hepatic diseases, including non-alcoholic steatohepatitis [5]. Pathogenetically, it is the oxidative stress that is the most studied mechanism of liver damage induced by doxorubicin and other anthracycline antibiotics [13]. Doxorubicin has been confirmed to be associated with an increased risk of hepatotoxic reactions, manifested by elevated blood serum activity of alanine and asparagine aminotransferases, alkaline phosphatase, gamma-glutamyltranspeptidase, bilirubin and its fractions [5]. However, the use of chemotherapeutic drugs, including doxorubicin, affects a number of essential liver functions, namely detoxification and regenerative functions, which can be investigated by determining the content of arginine and ways of its biotransformation.

Arginase is involved in the final stage of the urea cycle, during which arginine is converted to urea and ornithine. Arginase is considered as a marker of hepatotoxicity induced by pharmacological drugs; its altered activity is more sensitive test of liver dysfunction compared to traditional ones. A competitive pathway for the metabolism of L-arginine is the formation of nitric oxide (NO) and citrulline under the influence of NO synthases (NOS). Arginine / citrulline cycle reflects the features of the competitive interaction of arginase and NOS activity [2, 4]. Given the fact that the inducible form of NOS promotes the production of NO as a cytotoxic and anti-inflammatory agent, the study of the balance of arginase and NOS activity may be crucial in studying the pathogenesis of cytostatic-induced liver damage, including the use of doxorubicin.

The purpose of the paper was to study the features of arginine / citrulline cycle disorders associated with doxorubicin-induced liver damage in rats, concomitant with NASH.

Materials and methods. The study involved adult fertile outbred albino rats (n=30; male rats=15 (50%); female rats=15 (50%)) weighted 160-220 g. The study was carried out in two stages. At the first stage 10 rats (5 males and 5 females) were exposed to modeled NASH, induced by a high-calorie diet, containing 42.8% fats (per one animal a day: combination fodder-concentrate granulated 0.04 kg, 72.5% butter 0.01 kg, refined sunflower oil 0.01 kg, palm oil 0.01 kg; 4% aqueous solution of fructose was used as the sole source of liquid) for 9 weeks (from day 1 to day 63). 20 rats received a regular rations of vivarium (per one animal a day: combination fodder-concentrate granulated 0.04 kg, low-fat cheese 0.006 kg, carrots 0.02 kg, cabbage 0.015 kg) for 9 weeks (from day 1 to day 63). Experimental rats were divided into 3 groups:

Group I rats (n=10; males n=5; females n=5) were exposed to modeled NASH, induced by a high-calorie diet from day 1 to day 63, followed by administration of intraperitoneal 5mg/kg doxorubicin for 3 days (from day 64 to day 66) to reach the cumulative doze of 15 mg/kg;

Group II rats (n=10; males n=5; females n=5) were on a regular rations of vivarium from day 1 to day 63, followed by administration of intraperitoneal 5mg/kg/day doxorubicin from day 64 to day 66 to reach the cumulative doze of 15 mg/kg;

Group III rats (n=10; males n=5; females n=5) were on a regular rations of vivarium from day 1 to day 63, followed by administration of intraperitoneal 0.9% sodium chloride solution at a dose of 1 ml for 3 days (from day 64 to day 66).

Decapitation of rats was performed under thiopental anesthesia on day 67 of the observation. The concentration of arginine [6], citrulline [9] and arginase activity [1, 7] were determined in 10% homogenate of rat liver and blood.

The statistical program GraphPad Prism Version 5.00 (GraphPad Software, Inc., San Diego, CA, USA) was used for statistical processing of the resulting data and to carry out parametric and nonparametric statistical analysis. With the normal distribution of data, the results were presented in the form of arithmetic means (M) and their mean accuracy (m). Significance of differences was calculated using Student's t-test. Paired nonparametric methods of Wilcoxon and Mann-Whitney tests were used in the distribution that differs from the normal one. The relationship between the studied values was evaluated using Spearman's correlation analysis. The differences were considered significant when $p < 0.05$.

Results of the study and their discussion. Rats of experimental Group I and II, which were administered with doxorubicin, showed increased concentration of blood arginine by 2.3 and 2 times, respectively, compared to the control group ($p < 0.05$) (table 1). This fact can be explained both by the increased formation of arginine during the activation of protein catabolism, and by the violation of its availability to enzymes involved in biotransformation. Arginine reuptake by cells might be inhibited by ornithine as well as NOS inhibitors [2, 4]. Undoubtedly, the most important in inhibiting arginine metabolism is arginase, which is a regulatory enzyme that determines the predominance of arginine biotransformation pathways for the formation of NO or ornithine as a substrate for the synthesis of putrescine, spermidine and spermine [4].

Table 1

The rates of arginine, citrulline concentration and arginase activity in rat blood with doxorubicin-induced liver damage associated with NASH (M ± m)

Groups	Arginine, mmol/L	Arginase, $\mu\text{mol/mL}$	Citrulline, $\mu\text{mol/mL}$
I (n=10)	0.14±0.035*	13.90±1.53*&	423.4±22.40*
II (n=10)	0.12±0.01*	19.18±1.38*	439.4±13.00*
III (n=10)	0.06±0.01	41.24±6.51	627.8±51.72

Note: significant differences: * $p < 0.05$ – between the experimental Group I and II and the control group; & $p < 0.05$ – between the values of Group I and II.

In addition, arginase is considered a marker of drug-induced liver damage, which may be more sensitive than generally accepted rates used in routine clinical practice. Apparently, rats of Group I and II, which were administered intraperitoneally with doxorubicin, showed that the activity of blood arginase was by 2.9 and 2.1 time, respectively, lower, compared to Group III ($p < 0.05$) (Table 1). It has been established that in rats of Group I, which were initially exposed to modeled NASH upon reaching cumulative dose of 15 mg/kg doxorubicin, the activity of blood arginase was by 1.4 times lower compared to rats of Group II ($p < 0.05$) (table 1). Therefore, it is obvious that NASH leads to more severe doxorubicin-induced liver damage.

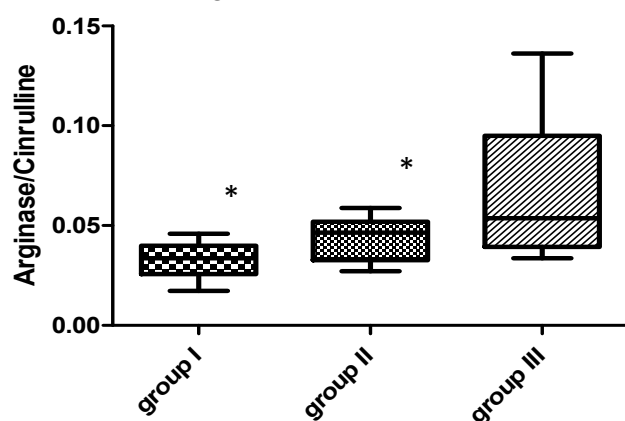


Fig. 1. The arginase / citrulline ratio in blood of rats with doxorubicin-induced liver damage associated with NASH. Note: * $p < 0.05$ – significant differences of values in rats of Group I and II compared to the control group.

Citrulline is a by-product of NO in the metabolism of arginine with the involvement of NOS. In rats of Group I and II, blood citrulline concentration was by 1.5 and 1.4 times, respectively, lower, compared to the control group ($p < 0.05$) (table 1). The arginase / citrulline ratio in rats of Group I with diet-induced NASH was by 2 times lower, compared to controls (0.03 ± 0.01 vs. 0.06 ± 0.01 ; $p < 0.05$) and by 1.3 times lower compared to rats of Group II (0.03 ± 0.01 vs. 0.04 ± 0.003 ; $p = 0.05$), which were administered with doxorubicin in the intact liver (fig. 1).

In rats of Group II, the arginine / citrulline ratio was by 1.5 times lower compared to controls (0.04 ± 0.003 vs. 0.06 ± 0.01 ; $p < 0.05$).

Consequently, the progression of NASH creates the preconditions for the development of doxorubicin-induced liver damage with violation of its detoxification function.

In the liver homogenate of rats of Group I and II, no significant deviations in arginine concentration, compared to the controls, were detected. However, arginase activity in rats of Group I and

II was by 1.6 and 1.7 times, respectively, lower, compared to Group III ($p=0.01$) (Table 2). Thus, the activity of arginase in the homogenate of liver and blood of experimental animals was reduced in equal proportions regardless of the presence of NASH, which indicates the high toxicity of doxorubicin with the risk for the development of hepatotoxic reactions.

However, in rats of Group I the concentration of citrulline in the liver homogenate was by 1.2 times higher compared with Groups II and III ($p<0.05$) (Table 2). Inverse correlation was found between the concentration of arginine and arginase activity in the liver homogenate of Group I rats ($r=-0.77$; $p<0.05$), as well as a direct correlation between the content of arginine and citrulline ($r=0.77$; $p<0.05$). This fact may indicate that NASH-related administration of doxorubicin is associated with the activation of the NOS-synthase pathway of arginine metabolism in liver tissue, primarily due to its inducible isoform, which creates an additional factor in hepatocyte damage.

Table 2

The rates of arginine, citrulline concentration and arginase activity in liver homogenate of rats with doxorubicin-induced liver damage associated with NASH ($M \pm m$)

Groups	Arginine, $\mu\text{mol/mL}$	Arginase, $\mu\text{mol/mL}$	Citrulline, $\mu\text{mol/mL}$
I (n=10)	0.31 ± 0.03	$1.62 \pm 0.23^*$	$68.54 \pm 3.37^*$
II (n=10)	0.29 ± 0.04	$1.54 \pm 0.12^*$	57.77 ± 2.41
III (n=10)	0.27 ± 0.02	2.61 ± 0.21	55.67 ± 1.23

Note: * $p<0.05$ – significant differences between the experimental groups I and II and control Group III ($p<0.05$).

From this point of view, it is of particular interest to determine the arginase / citrulline ratio in the liver homogenate. Hence, in rats of Group I and II the arginase / citrulline ratio was by 1.9 times (0.025 ± 0.004 vs. 0.047 ± 0.003) and 1.7 times (0.027 ± 0.004 vs. 0.047 ± 0.003), respectively, lower compared to Group III ($p<0.05$) (fig. 2). Therefore, administration of doxorubicin contributes to activation of the NOS-synthase mechanism and inhibition of the arginase pathway of arginine biotransformation in the liver tissues.

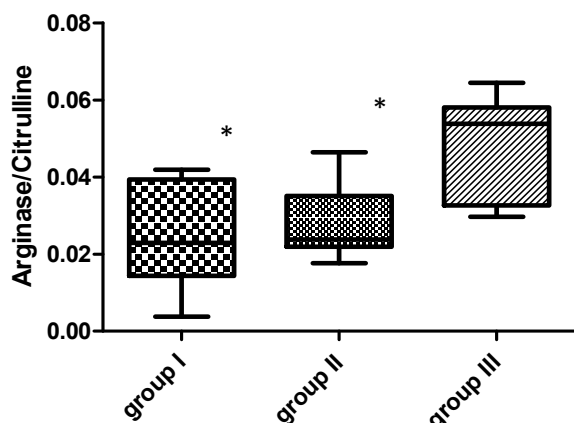


Fig. 2. The arginase / citrulline ratio in liver homogenate of rats with doxorubicin-induced liver damage associated with NASH

Note: * $p<0.05$ – significant differences of values in rats of Group I and II compared to the control group.

we can assume that doxorubicin accumulates in liver tissue, where the NOS pathway of arginine metabolism is activated, which creates a prerequisite for generating aggressive forms of oxygen as a powerful mechanism of pathogenesis of both NASH and doxorubicin-induced liver damage. Reducing the concentration of the blood citrulline may indirectly reduce the synthesis of NO in the endothelium with the formation of endothelial dysfunction as an additional factor in the occurrence of doxorubicin-induced lesions of organs and systems.

Administration of doxorubicin is associated with a decrease in arginase activity in the blood and liver homogenate, accompanied by a decrease in the arginase / citrulline ratio. Importantly, NASH potentiates the disruption of the arginase pathway of arginine biotransformation, leading to impaired detoxification function of the liver. The rate of arginase activity can be used in the clinical practice to evaluate detoxification function of the liver and diagnostics of drug-induced hepatotoxic reactions.

Conclusions

1. Administration of doxorubicin to rats with NASH leads to a decrease in arginase activity in the blood by 2.9 times and in the liver homogenate by 1.6 times, compared with the controls.

2. In the liver homogenate of rats administered with doxorubicin associated with NASH, an increase in the concentration of citrulline by 2 times compared to the control group and rats without NASH, administered with doxorubicin.

3. Decreased arginine / citrulline ratio in the blood and liver tissues of rats administered with doxorubicin indicate activation of the NOS mechanism of arginine metabolism, which is most associated with NASH.

References

1. Bojko OA, Lusenko VS. Vyznachennya aktyvnosti arginazy v tkanyakh. Fiziol zhurn. 1972; 18(5):703-5. [in Ukrainian]
2. Granik VG. Metabolizm L-arginina (obzor). Khimiko-farmaceuticheskiy zhurnal. 2003; 37(3):3-20. [in Russian]
3. Lymanecz TV, Maslova GS, Skrypnyk IM. Rol dysbalansu systemy oksydu azotu v rozvytku antracyklinovoyi kardiotoksychnosti u khvorykh na hostri leykemyi iz suputnyoyu ishemichnoyu khvoroboyu sertsya. Svit medytsyny ta biolohiyi. 2016; 3(57):35-40. [in Ukrainian]
4. Maksymchuk NO, Konovchuk VM. Metabolizm arginynu: perspektyvy klinichnoho vykorystannya (ohlyad literatury). Bukovynskiy medychniy visnyk. 2017; 21(1, 81): 205-10. [in Ukrainian]
5. Skrypnyk IM, Maslova GS. Nadmirna masa tila i ozhyrinnya yak vazhlyvi faktory ryzyku cytostatyk-indukovanykh urazhen pechinky u khvorykh na hostri leykemyi. Ukrayinskyi terapevtychnyi zhurnal. 2018; 2:21-5. DOI: <https://doi.org/10.30978/UTJ2018-2-21> [in Ukrainian]
6. Styuart Dzh, Yang Dzh. Shvachkina YuP, redaktor. Perevod s angl. Mishina GP. Tverdofaznyj sintez peptidov. Moskva: Mir; 1971. 129-130. [in Russian]
7. Khranov VA, Listopad GG. Modifikatsiya metoda opredeleniya ornitina po CHINARD i yeye ispolzovanie dlya kolichestvennogo opredeleniya syvorotochnoy arginazy. Laboratornoe delo. 1973; 10:591-2. [in Russian]
8. Abo-Salem OM, Abd-Ellah MF, Ghonaim MM. Hepatoprotective activity of quercetin against acrylonitrile – induced hepatotoxicity in rats. J Biochem Mol Toxicol. 2011; 25(6):386-92. doi: 10.1002/jbt.20406.
9. Boyde TR, Rahmatullah M. Optimization of Conditions for the Colorimetric Determination of Citrulline, Using Diacetyl Monoxime. Analytical Biochemistry. 1980; 107:424-31.
10. Chaudhary D, Khatiwada S, Sah SK, Tamang MK, Bhattacharya S, Jha CB. Effect of doxorubicin on histomorphology of Liver of Wistar Albino Rats. Journal of Pharmacy and Pharmacology. 2016; 4:186-190. doi: 10.17265/2328-2150/2016.04.005
11. Diamanti J, Mezzetti B, Giampieri F, Alvarez – Suarez JM, Quiles JL, Gonzalez-Alonso A, et al. Doxorubicin-induced oxidative stress in rats is efficiently counteracted by dietary anthocyanin differently enriched strawberry (*Fragaria × ananassa* Duch). J Agric Food Chem. 2014; 62(18):3935-43. doi: 10.1021/jf405721d.
12. Hilmer SN, Cogger VC, Muller M, Le Couteur DG. The hepatic pharmacokinetics of doxorubicin and liposomal doxorubicin. Drug Metab Dispos. 2004; 32(8):794-9.
13. Nagai K, Fukuno S, Oda A, Konishi H. Protective effects of taurine on doxorubicin – induced acute hepatotoxicity through suppression of oxidative stress and apoptotic responses. Anticancer Drugs. 2016; 27(1):17-23. doi: 10.1097/CAD.0000000000000299.
14. Prasanna PL, Renu K, Valsala Gopalakrishnan A. New molecular and biochemical insights of doxorubicin-induced hepatotoxicity. Life Sci. 2020; 250:117599. doi: 10.1016/j.lfs.2020.117599.
15. Pugazhendhi A, Edison TNJI, Velmurugan BK, Jacob JA, Karuppusamy I. Toxicity of doxorubicin (Dox) to different experimental organ systems. Life Sci. 2018; 200:26-30. doi: 10.1016/j.lfs.2018.03.023.

Реферати

РОЛЬ ПОРУШЕНЬ АРГІНІН/ЦИТРУЛІНОВОГО ЦИКЛУ В ПАТОГЕНЕЗІ ДОКСОРУБІЦІН-ІНДУКОВАНОГО УРАЖЕННЯ ПЕЧІНКИ НА ФОНІ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТУ У ЩУРІВ

Маслова Г.С., Скрипник Р.І., Гопко О.Ф., Скрипник І.М.

У статті представлені результати експериментального дослідження метою якого було дослідити особливості порушень аргінін/цитрулінового циклу на фоні доксорубіцин-індукованого ураження печінки у щурів із урахуванням супутнього неалкогольного стеатогепатиту (НАСГ). Дослідження проведені на 30 білих нелінійних статевозрілих щурах, із них 15 (50%) самців, 15 (50%) – самок вагою 160-220 г. Щури були розподілені на 3 групи: I (n=10) – щури із НАСГ, яким впродовж 3-х днів внутрішньочеревно вводили доксорубіцин із розрахунку 5 мг/кг/добу; II (n=10) – щури без НАСГ, яким вводили доксорубіцин аналогічно I групі; III (n=10) – група контролю. Показано, що ведення доксорубіцину на фоні НАСГ призводить до порушень у циклі аргінін/цитрулін, які характеризуються пригніченням активності аргінази та активацією синтезу цитруліну.

Ключові слова: аргінін, цитрулін, аргіназа, доксорубіцин, гепатотоксичні реакції, неалкогольний стеатогепатит.

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РОЛЬ НАРУШЕНИЙ АРГІНІН/ЦИТРУЛІНОВОГО ЦИКЛУ В ПАТОГЕНЕЗІ ДОКСОРУБІЦІН-ІНДУЦІРОВАНОГО ПОВРЕЖДЕННЯ ПЕЧЕНИ НА ФОНЕ НЕАЛКОГОЛЬНОГО СТЕАТОГЕПАТИТУ У КРИС

Маслова А.С., Скрипник Р.І., Гопко А.Ф., Скрипник І.Н.

В статті представлені результати експериментального дослідження, метою якого було дослідити особливості порушень аргінін/цитрулінового циклу на фоні доксорубіцин-індуцированого поразення печінки у крыс с учетом супутствующего неалкогольного стеатогепатита (НАСГ). Исследования проведены на 30 белых нелинейных половозрелых крысах, из них 15 (50%) самцов, 15 (50%) – самок, весом 160-220 г. Крысы были разделены на 3 группы: I (n=10) – крысы с НАСГ, которым в течение 3-х дней внутрибрюшинно вводили доксорубицин из расчета 5 мг/кг/сутки; II (n=10) – крысы без НАСГ, которым вводили доксорубицин аналогично I группе; III (n=10) – группа контроля. Показано, что введение доксорубицина на фоне НАСГ приводит к нарушениям в цикле аргинин/цитруллин, которые характеризуются угнетением активности аргиназы и активацией синтеза цитрулина.

Ключевые слова: аргинин, цитруллин, аргиназа, доксорубицин, гепатотоксические реакции, неалкогольный стеатогепатит.

Рецензент Костенко В.О.

S.S. Polishchuk, V.Ya. Skyba¹, I.S. Davydenko, S.M. Shuvalov², A.O. Gavrilyuk,
I.I. Yakovtsova³, B.C. Polishchuk
National Pirogov Memorial Medical University, Vinnytsya, ¹SI "Institute of Dentistry
and Maxillofacial Surgery of the National Academy of Medical Sciences of Ukraine", Odessa
²HSEE of Ukraine "Bukovinian State Medical University", Chernivtsi
³Kharkiv Medical Academy of Postgraduate Education, Kharkiv

HISTOLOGICAL CHANGES OF BONE TISSUE IN THE PERFORATION DEFECT SITE OF THE RAT MANDIBLE WHEN USING HEPATOPROTECTOR IN ODSTRUCTIVE HEPATITIS

e-mail: polischuk07@ukr.net

The purpose of the study was to experimentally investigate the features of reparative regeneration of the mandibular defect in rats with obstructive hepatitis against the background of hepatoprotector administration. An experimental study was performed on 60 white male Wistar rats, weighing 240-270 g. In the process of work, the rats were divided into 3 groups (20 rats in each one): control - included healthy rats with mandibular trauma; experimental group 1 - rats with jaw injury and simulated obstructive hepatitis; experimental group 2 - rats with mandibular injury + obstructive hepatitis + complex hepatoprotector. The experiment revealed that obstructive hepatitis impairs bone tissue healing in the site after the traumatic defect. The use of hepatoprotector, in experimental obstructive hepatitis, is a very effective measure for the processes of bone regeneration at the site of perforation.

Key words: experiment, rats, mandibular injury, obstructive hepatitis, hepatoprotector

The work is a fragment of the research project "Development of methods for surgical treatment of patients with pathology of the maxillofacial area, taking into account the correction of comorbidities", state registration No. 0118U005403.

The steady increase in the number of facial skeleton fractures and injuries of the maxillofacial area remains one of the important problems of today [2, 3, 4]. The problems of maxillofacial traumatology also include solution of the frequent complications' etiopathogenesis. Among facial injuries, the leading place is occupied by fractures of the upper and lower jaw in the structure of general traumatism. Fractures of the facial skeleton bones, among the injuries of the maxillofacial area, occur in 75-87% of cases [2, 3, 4, 6]. Among all examined and hospitalized patients, injuries of the maxillofacial area make about 15-38% [2, 3].

The increase in the total number of injuries also leads to an increase in the frequency of maxillofacial injuries and their complications. This is particularly true in patients with concomitant pathology [6], which can have a significant impact on the course of inflammatory processes. It should also be noted that an important factor in the development of inflammatory complications is the microbial factor. In the area of soft tissue wounds or fractures of the jaws there is a sequence of pathological local and general changes, which subsequently leads to complications (suppuration of bone wound, post-traumatic osteomyelitis, pseudarthrosis, abnormal mobility of bone fragments, secondary bleeding, post-traumatic sinusitis or neuritis, disturbed bite) [2, 3, 6].

Taking into account the above factors, the problem of complications should be considered and explained in the perspective of its association with the presence of comorbidities, including diseases of the liver and hepatobiliary system. This is primarily due to the high prevalence of liver disease, which occurs in almost 70% of the population [1, 5].

When the integrity of the maxillofacial area tissues is repaired, reparative regeneration of bone and soft tissue wound occurs due to the property of a living macroorganism to tissue repair, by forming a connective tissue matrix, followed by ossification of the fracture site with restoration of previous tissue structure [2, 3, 6]. An important task of dentists and maxillofacial surgeons in clinical settings, to improve the conditions of jaws fractures regeneration and recovery in inflammatory processes is to prevent the development of complications that may occur.

We have not found information about experimental studies of the maxillofacial tissues regeneration against the background of the hepatobiliary system pathology, and it needs further study and explanation.

The purpose of the work was to experimentally study the features of reparative regeneration of the mandible defect in rats with obstructive hepatitis against the background of hepatoprotector administration.

Materials and methods. We have performed an experimental study on 60 white male Wistar rats. Rats were on a common diet, had free access to water and food and standard living conditions in the cages of the vivarium at M.I. Pirogov VNMU. Age of animals was 5-6 months. The weight of rats ranged from 240 to 270 g.

A large number of mandibular fracture models in laboratory animals is known, but not all of these techniques permit to obtain objectification and standardization of the fracture, which in its turn will not permit to give an objective assessment [2, 3, 6]. In the experiment, we used the technique of causing a defect in the area of mandibular angle in rats with a surgical drill with a diameter of 1 mm, with the rotation rate of up to 10,000 revolutions per minute. This permitted to obtain a standard post-traumatic defect of the mandible and to objectively observe the regeneration processes [2, 6].

In the study process, the rats were divided into 3 groups:

1. Control - 20 rats - study of histological changes in the bone tissue of the mandible in healthy rats with trauma of the mandible at the site of the defect.

2. Experimental group 1 - 20 rats - study of histological changes in the bone tissue of the mandible in rats with trauma of the mandible at the site of the defect in obstructive hepatitis, obtained by ligation and transection of the common bile duct.

3. Experimental group 2 - 20 rats - study of histological changes in the bone tissue of the mandible in rats with trauma of the mandible at the site of the defect in obstructive hepatitis, obtained by ligation and transection of the common bile duct, which on the day of the jaw injury and the following two weeks, were added complex "Quertulin" hepatoprotector to the food at the dose of 200 mg per kilogram of rat weight.

"Quertulin" is a complex hepatoprotective drug containing quercetin bioflavonoid, inulin prebiotic, calcium citrate (permission of the Ministry of Health of Ukraine № 05.03.02. - 06/44464 dated 17.05.2012).

Inulin has an antidiabetic effect, stimulating the growth of probiotic microflora and eliminating the dysbiosis phenomena.

Quercetin has P-vitamin activity, antioxidative, membrane-protective and hepatoprotective action.

Calcium citrate is the most easily digestible form of calcium, which stimulates bone tissue mineralization, eliminating the osteoporosis phenomena.

In the course of the experimental study, we traced the features of post-traumatic mandibular bone defects regeneration. Quantitative assessment of histological changes was performed using the analysis of morphometric parameters: specific volume (in %) of fibroreticular tissue in the center of bone regeneration, specific volume (%) of blood vessels, specific volume (in %) of bone trabeculae in the center of bone regeneration, the number of osteoblasts in a certain area in the center of bone regeneration, specific volume (%) of bone marrow in the center of bone regeneration. The study was performed on the 7th, 14th, 30th, 60th days of the study.

The study was carried out in compliance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986), Council of Europe Directives 86/609 / EEC (1986), Law of Ukraine №3447-IV "On protection of animals from cruel treatment", general ethical principles of animal experiments, approved by the First National Congress of Ukraine on Bioethics (2001).

Numerical values are statistically processed with calculation of mean values (M) and standard error ($\pm m$). The probability of discrepancies in the mean values (p) was determined using the Student's t test. Discrepancies were considered reliable at $p < 0.05$.

Results of the study and their discussion. As a result of the experiment, in rats of the control group (n = 20), the features of bone damage regeneration in the area of the induced defect were observed. From the data in table 1, it is seen that the specific volume of fibroreticular tissue in the center of bone regeneration on the 7th day is predominant over other elements and makes about 91.4%.

Table 1

Morphometric parameters of regenerative tissues at the site of injury of the mandibular angle in the dynamics of the experiment in rats of the control group (n = 20)

Morphometric parameters	Day of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	91.4±0.94	56.3±0.71	48.2±0.51	12.4±0.22
specific volume (%) of blood vessels	3.2±0.05	2.0±0.05	1.6±0.05	0.5±0.01
specific volume (%) of bone trabeculae	1.8±0.04	12.9±0.84	48.0±0.19	72.2±0.68
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm^2	3.5±0.04	5.7±0.15	2.0±0.06	1.0±0.05
specific volume (%) of bone marrow	0	0	1.6±0.04	3.8±0.05

The presence of individual bone trabeculae in this period of the study is explained primarily not by their new creation, but by the remnants of former bone trabeculae that were at the site of perforation and damage before this injury. In addition, it is worth noting the increased number of osteoblasts per area unit of bone trabeculae. Such an increased concentration of them in the bone trabeculae indicates that the old bone trabeculae are also involved into the processes of bone regeneration at the defect site. The specific

volume of blood vessels on the 7th day of the experiment in the center of bone regeneration reaches 3.5%, and these blood vessels are located almost exclusively in the area of fibroreticular tissue.

We also found that on the 7th day there are no formed elements of bone marrow observed, although in fibroreticular tissue there is a significant presence of cells, which morphologically can be called lymphoid cells, which are round-shaped with a round nucleus and a narrow rim of the cytoplasm. It is known that cells with the above morphology can be either lymphocytes or stem (polypotent) cells, which in the future the elements of the bone marrow are formed of.

According to the data obtained, as can be seen from table 1, the specific volume of fibroreticular tissue in the center of bone regeneration in the dynamics of the experiment without external influence in animals of the control group decreases and on the 60th day is $12.4 \pm 0.22\%$ against $91.4 \pm 0.94\%$ on the 7th day. Along with this, in the dynamics of the experiment in the center of bone regeneration also decreases the specific volume of blood vessels, although on the 60th day these blood vessels are already localized not only in fibroreticular tissue, but also in the bone marrow, which is also already available on the 30th and moreover on the 60th day.

The specific volume of bone trabeculae up to the 14th day grows more than by 5 times compared to the seventh day, up to the 30th day it still grows and on the 60th day of the experiment the specific volume of bone trabeculae reaches more than 72 %, i. e. bone trabeculae in this period already constitute most of the elements in the bone regeneration zone (fig. 1).

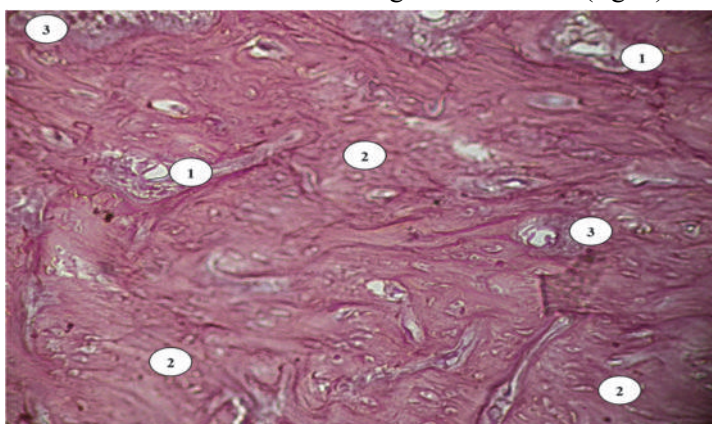


Fig. 1. Bone wound of the rat lower jaw at the site of its perforation on the 60th day of the experiment in the control group (n = 20). 1 - fibroreticular tissue. 2 - bone trabeculae. 3- bone marrow. Hematoxylin and eosin. Ob.10^x. Oc. 20^x.

The mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of $100 \mu\text{m}^2$ decreases at a relatively slow rate. It should be noted that on the 14th day compared to the 7th, there is no reliable decrease in the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit ($p > 0.05$), except that there is only a tendency to decrease, but on the 30th day compared to the 7th day, the changes, although not pronounced, are still statistically significant ($p < 0.05$).

The same can be noted on the 60th day of the experiment in rats of the control group, when the mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area has the lowest value among all periods of the experiment.

As mentioned above, the obvious elements of the bone marrow are only present in the histological materials of the damage area in the mandible of rats on the 30th and 60th day of the experiment. The bone marrow was dominated by hematopoietic elements at different stages of development with a predominance of lymphoid cells, single thin-walled slit-like blood vessels and individual lymphocytes. Thus, a certain sequence of histological changes and a sufficiently high activity of regenerative elements involved in the construction of new bone tissue and restoration of the bone defect were revealed.

Studies of histological changes in the bone tissue of the rat mandible at the site of its injury in obstructive hepatitis, showed that the specific volume of fibroreticular tissue in the bone regeneration center on the 7th day is dominant over other elements and is more than 90% (table 2).

Table 2

Morphometric parameters of mandibular tissues at the site of injury in obstructive hepatitis, without treatment in rats of experimental group 1 (n = 20)

Morphometric parameters	Day of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	92.1 ± 0.88	84.5 ± 0.73	74.6 ± 0.58	32.8 ± 0.24
specific volume (%) of blood vessels	3.7 ± 0.08	3.4 ± 0.09	3.2 ± 0.05	1.7 ± 0.02
specific volume (%) of bone trabeculae	1.4 ± 0.05	5.6 ± 0.14	14.8 ± 0.16	53.4 ± 0.64
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of $100 \mu\text{m}^2$	3.8 ± 0.08	3.5 ± 0.10	3.3 ± 0.06	2.8 ± 0.04
specific volume (%) of bone marrow	0	0	0	2.3 ± 0.06

Experimental data showed that the specific volume of fibroreticular tissue in the center of bone regeneration in rats of the experimental group 1 is almost no different from the control group on the seventh day.

Individual bone trabeculae in this period of the study are explained, of course, not by their new creation, but by the remnants of former bone trabeculae, which were at the site of perforation before the injury. The increased number of osteoblasts per area unit of bone trabeculae should also be noted. Such an increased concentration of them in the bone trabeculae indicates that the old bone trabeculae are also involved in the processes of bone regeneration in the defect site.

The specific volume of blood vessels on the 7th day of the experiment in the center of bone regeneration does not reach even four percent, and these blood vessels are located almost exclusively in the area of fibroreticular tissue. It should also be noted that on the 7th day there are no formed elements of the bone marrow, although in fibroreticular tissue there is a significant presence of cells, which morphologically should be called lymphoid cells. These lymphoid cells are round in shape with a round nucleus and a narrow rim of the cytoplasm. It is known that cells with the above morphology can be either lymphocytes or stem (polypotent) cells, which in the future the elements of the bone marrow are formed of.

As it can be seen from table 2, the specific volume of fibroreticular tissue in the bone regeneration center in the dynamics of the experiment with ligation of the common bile duct decreases and on the 60th day it is reduced by about three times compared to the 7th day.

In the dynamics of the experiment in the center of bone regeneration during ligation of the common bile duct, we found that the specific volume of blood vessels decreases, although on the 60th day these blood vessels are localized not only in fibroreticular tissue but also in bone marrow, which is also already available on the 60th day, although on the 30th day of the experiment the formed elements of the bone marrow in the center of bone regeneration can not be found, as in the previous periods of the experiment.

The specific volume of bone trabeculae up to the 14th day in rats of experimental group 1, grows more than by 4 times compared to the seventh day, and up to the 30th day it grows even more and on the 60th day of the experiment the specific volume of bone trabeculae is more than 50%, i. e. bone trabeculae in this period already make the most part of elements in the bone regeneration zone.

The mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of $100 \mu\text{m}^2$ decreases at a relatively slow rate. It should be noted that on the 14th day compared to the 7th day there is not a probable decrease in the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit ($p > 0.05$), except that there is only a downward trend, but on the 30th day compared to the 7th day, the changes, although not expressed morphologically, but still in the quantitative composition of cells are statistically significant ($p < 0.05$). Similar indices can be noted on the 60th day of the experiment, when the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit has the lowest value among all periods of the experiment (fig. 2).

As mentioned above, the obvious elements of the bone marrow during ligation of the common bile duct are only present in the histological materials of rats on the 60th day of the experiment. The bone marrow was dominated by hematopoietic elements at different stages of development with a predominance of lymphoid cells, single thin-walled slit-like blood vessels and individual lymphocytes.

Morphometric parameters in the study of jaws bone tissue in the animals of experimental group 2, show a positive effect of "Quertulin" on bone regeneration in the site of its defect (table 3).

Table 3

Morphometric parameters of the mandible hard tissues in the site of injury during ligation of the common bile duct in the dynamics of the experiment under correction with hepatoprotector, in rats of experimental group 2 (n = 20)

Morphometric parameters	Day of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	92.2±0.83	77.0±0.72	64.3±0.50	21.3±0.25
specific volume (%) of blood vessels	3.7±0.05	3.1±0.05	3.0±0.04	1.1±0.01
specific volume (%) of bone trabeculae	1.5±0.06	7.4±0.6	28.9±0.12	62.5±0.65
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of $100 \mu\text{m}^2$	3.7±0.09	4.6±0.13	2.7±0.04	1.2±0.03
specific volume (%) of bone marrow	0	0	0	2.8±0.05

The use of "Quertulin" significantly increases the proportion of bone marrow trabeculae on the 60th day compared to similar indices in experimental group 2 (fig. 3).

Morphometric data, presented in table 3, prove that the use of "Quertulin" as a means of correcting bone regeneration in the site of its perforation during ligation of the common bile duct, leads to accelerated regeneration rates from the 7th day of the experiment, as it is indicated by changes in the specific volume of fibroreticular tissue, blood vessels, bone trabeculae and bone marrow ($p < 0.05$) [6].

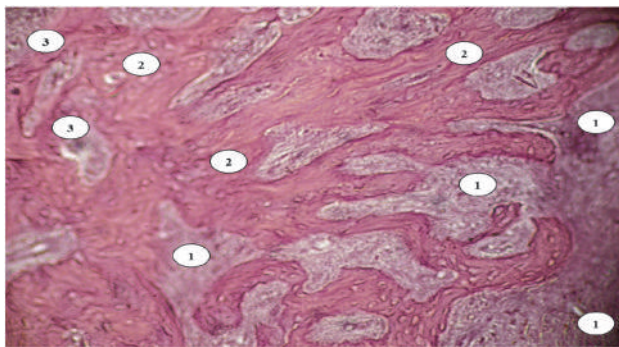


Fig. 2. Bone wound of the rat lower jaw in the site of its perforation during ligation of the common bile duct on the 60th day of the experiment in experimental group 1. 1 - fibroreticular tissue. 2 - bone trabeculae. 3- bone marrow. Hematoxylin and eosin.Ob.10^x. Oc. 20^x.

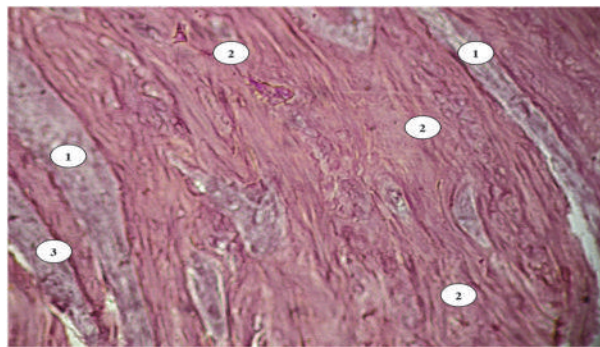


Fig. 3. Bone wound of the rat lower jaw in the site of its injury in obstructive hepatitis on the 60th day of the experiment under the correction with "Quertulin" in experimental group 2. 1 - fibroreticular tissue. 2 - bone trabeculae. 3- bone marrow. Hematoxylin and eosin.Ob.10^x. Oc.20^x.

The main patterns of changes in the dynamics of the experiment during ligation of the common bile duct were also preserved concerning the number of osteoblasts and bone trabeculae on the 30th day ($p < 0.05$). Concomitant liver pathology has a negative impact on regenerative processes in bone tissue [2, 3, 5]. Given the multifunctionality of the liver [1, 5], it is the control of its functions that becomes important in patients with traumatic injuries of the facial bones.

When using hepatoprotectors in the complex treatment of patients with fractures of the facial skeleton, one can reduce the number of complications and accelerate the fracture healing.

Conclusion

Експериментальне дослідження показало, що обтураційний гепатит погіршує загоєння кісткової тканини у ділянці після травматичного дефекту. Застосування комплексного гепатопротектора при експериментальному обтураційному гепатиті є досить ефективним заходом для процесів регенерації кістки в місці перфорації. У пацієнтів з переломом нижньої щелепи, при виявленні патології гепатобілірної системи, доцільно використовувати «Квертулін».

Experimental studies have shown that obstructive hepatitis impairs bone healing in the area after a traumatic defect. The use of a complex hepatoprotector in experimental obstructive hepatitis is a very effective measure for the processes of bone regeneration in the site of perforation. In patients with a fracture of the mandible, when pathology of the hepatobiliary system is detected, it is advisable to use "Quertulin".

References

1. Malanchuk VO, Lohvinenko IP, Malanchuk TO. Khirurhichna stomatolohiya ta shchelepno-lytseva khirurhiya: pidruchnyk.. Kyiv: LOHOS, 2011. 606 c. [in Ukrainian]
2. Moroz LV, Musayev EEO, Zaichko NV, Androsova OS, Hayduk OA. Vplyv vitaminu D na rezultaty likuvannya khronichnoho hepatytu C. Hepatolohiya. 2016; 4:42-50. [in Ukrainian]
3. Tymofeyev OO. Shchelepno-lytseva khirurhiya. Kyiv: VSV "Medytsyna", 2011. 752 s. [in Ukrainian]
4. Gutta R, Tracy K, Johnson C. Outcomes of mandible fracture treatment at an academic tertiary hospital: a 5-year analysis. J. Oral Maxillofac. Surg. 2014; 72; 3: 550–558.
5. Moroz LV, Bondaruk IYu, Popovich AA. Comparison of the diagnostic efficiency of various noninvasive methods for diagnosing liver fibrosis in patients with chronicviral hepatitis C. Journal of Education, Healthand Sport. 2019; 9(6): 546-555.
6. Polischuk SS, Davydenko IS, Shuvalov SM. Effect of the Forcalon histological changes of the rat's mandible bonet issue in the area of the traumatic defect at the pathology of the hepatobiliary system. Вісник морфології. 2018; 1(24): 47-55.

Реферати

ГІСТОЛОГІЧНІ ЗМІНИ КІСТКОВОЇ ТКАНИНИ У ДІЛЯНКІ ПЕРФОРАЦІЙНОГО ДЕФЕКТУ НИЖНЬОЇ ЩЕЛЕПИ ЩУРІВ ПРИ ВИКОРИСТАННІ ГЕПАТОПРОТЕКТОРА НА ТЛІ ОБТУРАЦІЙНОГО ГЕПАТИТУ
 Поліщук С.С., Скиба В.Я., Давиденко І.С., Шувалов С.М., Гаврилюк А.О., Яковцова І.І., Поліщук В.С.

Метою дослідження було експериментальне вивчення особливостей репаративної регенерації дефекту нижньої щелепи щурів при обтураційному гепатиті на тлі прийому гепатопротектора. Було проведено експериментальне дослідження на 60 білих щурах-самцях масою 240-270 г. У процесі роботи щури були розділені на 3 групи (по 20 щурів у кожній групі): контрольна - включала здорових щурів з травмою нижньої щелепи; дослідницька №1 - щури з травмою щелепи і

ГІСТОЛОГИЧЕСКИЕ ИЗМЕНЕНИЯ КОСТНОЙ ТКАНИ В ОБЛАСТИ ПЕРФОРАЦИОННОГО ДЕФЕКТА НИЖНЕЙ ЧЕЛЮСТИ КРЫС ПРИ ИСПОЛЬЗОВАНИИ ГЕПАТОПРОТЕКТОРА НА ФОНЕ ОБТУРАЦИОННОГО ГЕПАТИТА
 Полищук С.С., Скиба В.Я., Давыденко И.С., Шувалов С.М., Гаврилюк А.А., Яковцова И.И., Полищук В.С.

Целью исследования было экспериментальное изучение особенностей репаративной регенерации дефекта нижней челюсти крыс при обтурационном гепатите на фоне приема гепатопротектора. Было проведено экспериментальное исследование на 60 белых крысах-самцах линии Вистар массой 240-270 г. В процессе работы крысы были разделены на 3 группы (по 20 крыс в каждой группе): контрольная - включала здоровых крыс с травмой нижней челюсти; экспериментальная №1 - крысы с травмой

модельованим обтураційним гепатитом; дослідниця №2 - шури з травмою нижньої щелепи + обтураційний гепатит + комплексний гепатопротектор. В результаті експерименту виявили, що обтураційний гепатит погіршує загоєння кісткової тканини в області післятравматичного дефекту. Застосування гепатопротектора, при експериментальному обтураційному гепатиті, досить ефективно для процесів регенерації кістки в місці перфорації.

Ключові слова: експеримент, шури, травма нижньої щелепи, обтураційний гепатит, гепатопротектор. Стаття надійшла 28.06.2019 р.

челюсти и моделируемым обтурационным гепатитом; экспериментальная №2 - крысы с травмой нижней челюсти + обтурационный гепатит + комплексный гепатопротектор. В результате эксперимента обнаружили, что обтурационный гепатит ухудшает заживление костной ткани в области посттравматического дефекта. Применение гепатопротектора, при экспериментальном обтурационном гепатите, достаточно эффективно для процессов регенерации кости в месте перфорации.

Ключевые слова: эксперимент, крысы, травма нижней челюсти, обтурационный гепатит, гепатопротектор. Рецензент Шепітько В.І.

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V.Ya. Skyba¹, S.S. Polishchuk, I.S. Davydenko², O.I. Shtatko, S.M. Shuvalov, A.O. Gavrilyuk,
V.S. Polishchuk, O.O. Polishchuk
National Pirogov Memorial Medical University, Vinnytsya, ¹SI "Institute of Dentistry
and Maxillofacial Surgery of the National Academy of Medical Sciences of Ukraine", Odessa
²ISSE of Ukraine "Bukovinian State Medical University", Chernivtsi

DYNAMICS OF MORPHOMETRIC BONE CHANGES IN THE SITE OF MANDIBULAR PERFORATION DEFECT IN RATS WITH TOXIC HEPATITIS AND USE OF HEPATOPROTECTOR

e-mail: polischuk07@ukr.net

The purpose of the work was to experimentally study morphometric changes in the healing of perforation defect of the mandible in rats against the background of toxic hepatitis and the use of complex hepatoprotector. An experimental study was performed on 60 white male Wistar rats weighing 240-270 g. In the experiment process, the rats were divided into 3 groups (20 rats in each group): control - included healthy rats with mandibular trauma; experimental group 1 - rats with jaw injury and simulated toxic hepatitis; experimental group 2 - rats with trauma of the mandible + toxic hepatitis + complex hepatoprotector. The study of histological changes in the bone tissue of the mandible in the site of injury, in toxic hepatitis, justified the positive effect of hepatoprotector on changes in morphometric parameters. The experiment results revealed that toxic hepatitis worsened the morphometric parameters of the mandible perforation defect healing. It is particularly important that the complex hepatoprotector in toxic hepatitis increases the specific volume of bone trabeculae on the 30th and the 60th day and bone marrow on the 60th day, which indicates its positive effect on bone regeneration in the site of perforation.

Key words: experiment, rats, mandibular trauma, simulated toxic hepatitis, complex hepatoprotector.

The work is a fragment of the research project "Development of methods for surgical treatment in patients with pathology of the maxillofacial area, taking into account the correction of comorbidities", state registration No. 0118U005403.

Despite the scientific and technological progress and development of mankind in recent years, the number of injuries of the maxillofacial area and their complications still continues to grow [2, 3, 4, 5, 7, 8]. An important place is given to the solution and study of the possible etiopathogenesis of post-traumatic complications. Among the traumatic injuries of the face, the most common are fractures of the lower jaw, nasal bones, zygomaticoorbital complex, upper jaw. Injuries of the maxillofacial area make 15-38% among all examined and hospitalized in the clinic [2, 3, 5, 10, 11]. Maxillofacial fractures among all injuries of the facial skeleton occur in 75-87% of cases according to various authors [2, 3, 5, 6, 8, 11]. In addition, it is known that the share of maxillofacial injuries grows by 3-4% annually, both in our country and abroad. At the same time, about 80% of mandibular fractures occur in men of the most employable age - 20-40 years. This fact explains the urgency of the problem of treating fractures of the facial skeleton and their complications. Fractures of the facial skeleton bones are most frequently of transport and home accident origin [2, 5, 7].

The increase in the total number of injuries also leads to an increase in the frequency of maxillofacial injuries and their complications. All post-traumatic complications of non-gunshot mandible fractures can be divided into early (bone wound suppuration, secondary displacement of fragments, lymphadenitis, abscess, phlegmon, thrombophlebitis of facial veins) and late ones (post-traumatic osteomyelitis, sinusitis, delayed consolidation of fragments, pathological mobility of fragments, malunion, false joint, post-traumatic deformity). Of particular importance is the problem of post-traumatic complications in patients with comorbidities [1, 2, 3, 4, 6, 9], which can have a significant impact on the occurrence and course of post-traumatic inflammatory processes. It should also be remembered that the immediate cause of purulent-inflammatory complications is infection of the area affected by the microflora of the oral cavity and periapical foci of chronic infection. In the injury area there is a sequence of

pathophysiological local and general changes, which subsequently leads to the development of inflammatory processes [2, 3, 5, 8].

Taking into account the above factors, the problem of optimizing osteoreparative processes in fractures of the facial skeleton and prevention of complications should be explained in the context of their association with the presence of concomitant pathology, particularly diseases of the hepatobiliary system. This is primarily due to the high prevalence of liver disease, which occurs in almost 70% of the population [1, 3, 6, 9].

Functions performed by the liver lead to think about its connection with the occurrence of complications in traumatic injuries and inflammatory processes of the maxillofacial area, and in some cases to play one of the key factors. Osteoreparative processes occur due to the properties of a living organism to restore tissue by forming a connective tissue matrix, followed by the process of the fracture site ossification with restoration of the previous tissue structure [2, 3, 4, 5]. At the same time, all efforts of dental surgeons and maxillofacial surgeons should be aimed at improving the regeneration of jaw fractures and faster recovery by preventing development of post-traumatic complications.

In traumatic injuries or inflammatory processes of a maxillofacial site, patients' recovery, first of all, depends on a functional condition of the body which directly depends on the existence of the liver concomitant pathology. It may effect features of the mandible fractures healing, triggering mechanisms that include proliferation and differentiation of cells into osteogenic ones and the synthesis of osteoinductive factors. We have not found information on experimental studies concerning the regeneration of maxillofacial tissues against the background of the liver toxic damage and it needs further study.

The purpose of the work was to experimentally study morphometric changes in the healing of the mandible perforated defect in rats with toxic hepatitis and the use of complex hepatoprotector.

Materials and methods. The experimental study was performed on 60 white male Wistar rats. Rats were on a common diet, had free access to water and food and were kept under the standard living conditions in the vivarium of M.I. Pirogov VNMU. Age of animals was 5-6 months. The weight of rats ranged from 240 to 270 g.

Experimental models of mandibular injuries in laboratory animals have a long history and variety. In a detailed analysis, not all of these techniques can provide objectivity and standardization of the fracture, which, in its turn, will not permit to give an objective assessment of fracture healing and complications [2, 3, 4, 5, 10]. We selected an experimental model of mandibular injury by causing a defect in the area of the rat mandibular angle using a surgical drill with a diameter of 1 mm, which rotated at a speed of up to 10,000 revolutions per minute. The use of this technique permitted to obtain a standard post-traumatic defect of the mandible and to objectively observe the processes of post-traumatic regeneration [2, 3, 5].

In the process of work, the rats were divided into 3 groups:

1. Control - 20 rats - study of morphometric parameters of the mandibular bone tissue in healthy rats in the area of post-traumatic mandible defect.

2. Experimental group 1 - 20 rats - study of morphometric parameters of the mandibular bone tissue in healthy rats in the area of post-traumatic mandibular defect in toxic hepatitis, simulated by the administration of carbon tetrachloride per os.

3. Experimental group 2 - 20 rats - study of morphometric parameters of the mandibular bone tissue in healthy rats in the area of post-traumatic mandibular defect in toxic hepatitis, simulated by the administration of carbon tetrachloride per os, which on the day of the jaw injury and within the following two weeks were added "Quertulin" complex hepatoprotector to their food at a dose of 200 mg per kilogram of rat weight.

"Quertulin" is a complex drug of domestic production containing bioflavonoid quercetin, prebiotic inulin, calcium citrate (permission of the MOH of Ukraine No. 05.03.02. - 06/44464 dated 17.05.2012). Inulin has an antidiabetic effect, stimulating the growth of probiotic microflora, and eliminates the phenomena of dysbiosis. Quercetin has P-vitamin activity, antioxidative, membrane-protective and hepatoprotective action. Calcium citrate is the most easily digestible form of calcium, which stimulates bone tissue mineralization, eliminating the effects of osteoporosis.

In the course of the experimental study, we traced the features of post-traumatic mandibular bone defects regeneration. Quantitative assessment of histological changes was performed using the analysis of morphometric parameters: specific volume (in %) of fibroreticular tissue in the center of bone regeneration, specific volume (%) of blood vessels, specific volume (in %) of bone trabeculae in the center of bone regeneration, the number of osteoblasts in a certain area in the center of bone regeneration, specific volume (%) of bone marrow in the center of bone regeneration. The measurements were performed on the 7th, 14th, 30th, 60th days of the study.

The study was carried out in compliance with the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), Council of Europe Directives 86/609 / EEC (1986), Law of Ukraine №3447-IV "On protection of

animals from cruel treatment”, general ethical principles of animal experiments, approved by the First National Congress of Ukraine on Bioethics (2001).

Numerical values have been statistically processed with calculation of mean values (M) and standard error ($\pm m$). The reliability of discrepancies in the mean values (p) was determined using the Student's t test. Discrepancies were considered reliable at $p < 0.05$.

Results of the study and their discussion. During the experiment on 20 healthy rats of the control group, the features of bone damage regeneration were observed. Quantitative assessment of histological changes was performed using morphometric techniques. From the obtained data presented in table 1, it is noticeable that the specific volume of fibroreticular tissue in the center of bone regeneration on the 7th day is dominant over other elements and makes 91.4%, and on the 60th day it decreases to 12.4%.

Table 1

Morphometric parameters of regenerative tissues at the site of mandibular injury in the dynamics of the experiment in the control group rats (n = 20)

Morphometric parameters	Day of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	91.4 \pm 0.94	56.3 \pm 0.71	48.2 \pm 0.51	12.4 \pm 0.22
specific volume (%) of blood vessels	3.2 \pm 0.05	2.0 \pm 0.05	1.6 \pm 0.05	0.5 \pm 0.01
specific volume (%) of bone trabeculae	1.8 \pm 0.04	12.9 \pm 0.84	48.0 \pm 0.19	72.2 \pm 0.68
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm^2	3.5 \pm 0.04	5.7 \pm 0.15	2.0 \pm 0.06	1.0 \pm 0.05
specific volume (%) of bone marrow	0	0	1.6 \pm 0.04	3.8 \pm 0.05

Some single bone trabeculae (1.8%) in this period of the study are explained, of course, not by their new creation, but by the remains of former bone trabeculae, which were at the site of bone injury before the injury. The increased number of osteoblasts per area unit of bone trabeculae (3.5%) should also be noted. Such an increased concentration of them in the bone trabeculae indicates that the old bone trabeculae are also involved in the processes of bone regeneration in the defect site. The specific volume of blood vessels on the 7th day of the experiment in the center of bone regeneration reaches 3.5 percent, and these blood vessels are located almost exclusively in the area of fibroreticular tissue (fig. 1).

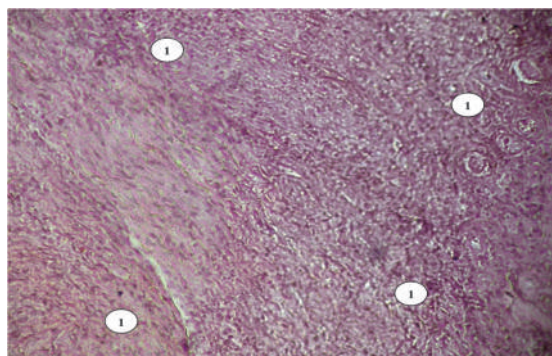


Fig. 1. Bone wound of the rat mandible is replaced by fibroreticular tissue (1), in the site of its perforation on the 7th day of the experiment in the control group. Hematoxylin and eosin. Ob.10x. Oc. 20x.

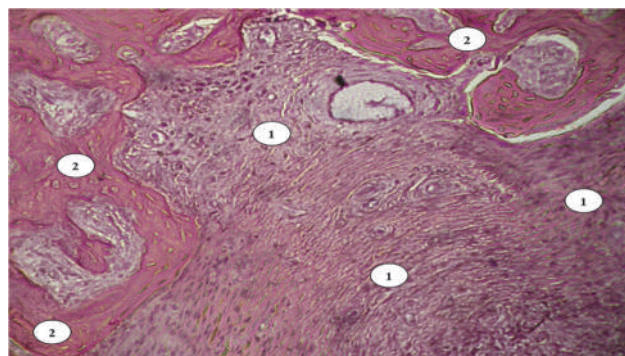


Fig. 2. Bone wound of the rat mandible in the site of its perforation on the 14th day of the experiment in the control group. 1 - fibroreticular tissue. 2 - bone trabeculae. Hematoxylin and eosin. Ob.10x. Oc. 20x.

It should also be noted that on the 7th day there are no formed elements of bone marrow, although in fibroreticular tissue there is a significant presence of cells, which morphologically can be called lymphoid cells, which have a round shape with a round nucleus and a narrow rim of the cytoplasm. It is known that cells with the above morphology can be either lymphocytes or stem (polypotent) cells, of which in the future the elements of the bone marrow are formed. In the dynamics of the experiment in the center of bone regeneration, the specific volume of blood vessels also decreases, and on the 60th day these blood vessels are localized not only in fibroreticular tissue, but also in the bone marrow, which is also manifested on the 30th and moreover on the 60th day.

The specific volume of bone trabeculae up to the 14th day grows more than by 5 times compared to the seventh day (fig. 2), up to the 30th day it still increases (fig. 3) and on the 60th day of the experiment the specific volume of bone trabeculae reaches more than 72 %, i.e. bone trabeculae in this period already make the most part of elements in the zone of bone regeneration (fig. 4).

The mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm^2 decreases at a relatively slow rate. It should be noted that on the 14th day compared the 7th, there is no reliable decrease in the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit ($p > 0.05$), except that there is only a tendency to decrease, but on the 30th day compared to the 7th day, the changes, although not pronounced, are still statistically significant ($p < 0.05$).

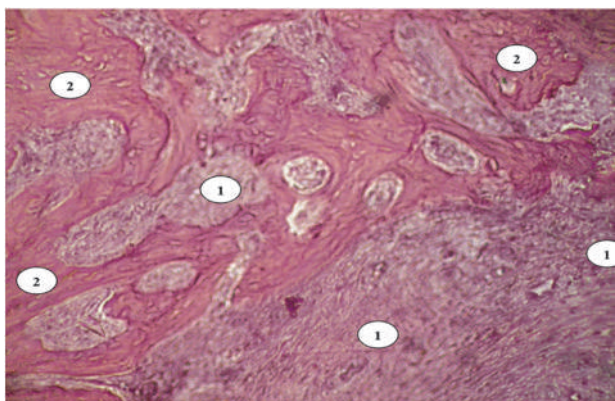


Fig. 3. Bone wound of the rat mandible in the site of its perforation on the 30th day of the experiment in the control group. 1 - fibroreticular tissue. 2 - bone trabeculae. Hematoxylin and eosin. Ob.10x. Oc. 20x.

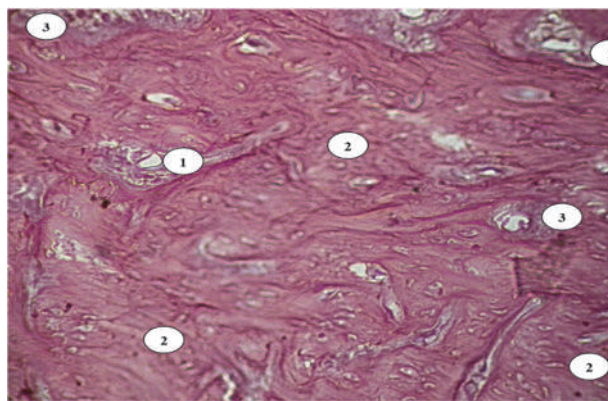


Fig. 4. Bone wound of the rat mandible in the site of its perforation on the 60th day of the experiment in the control group. 1 - fibroreticular tissue. 2 - bone trabeculae. 3- bone marrow. Hematoxylin and eosin. Ob.10x.Oc. 20x.

The same can be noted for the 60th day of the experiment, when the mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area has the lowest value among all periods of the experiment.

As it has been mentioned above, the obvious elements of the bone marrow are only present in the histological materials of the damaged area in the mandible of rats on the 30th and the 60th day of the experiment. The bone marrow was dominated by hematopoietic elements at different stages of development with a predominance of lymphoid cells, single thin-walled slit-like blood vessels and individual lymphocytes. Thus, a certain sequence of histological changes and a sufficiently high activity of regenerative elements involved in the construction of new bone tissue and replacement of the bone defect were revealed.

The mean data of morphometric parameters of the mandible hard tissues regeneration in the site of injury, in animals of experimental group 1, with toxic hepatitis in the dynamics of the experiment, without drug correction are presented in table 2.

The indices obtained, as it can be seen from table. 2, show a certain dynamics of regenerative processes in the area of mandibular injury, and show the negative impact of toxic experimental hepatitis on the healing processes.

Table 2

Morphometric parameters of the mandibular hard tissues in the site of injury in toxic hepatitis in the dynamics of the experiment without treatment, in rats of experimental group 2 (n = 20)

Morphometric parameters	Days of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	92.0±0.84	88.7±0.76	79.9±0.59	41.0±0.5
specific volume (%) of blood vessels	3.2±0.08	3.0±0.08	2.7±0.04	2.0±0.03
specific volume (%) of bone trabeculae	1.4±0.07	3.8±0.16	11.3±0.12	48.4±0.65
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm ²	3.7±0.05	3.6±0.10	3.5±0.07	2.8±0.05
specific volume (%) of bone marrow	0	0	0	1.6±0.02

The changes lie in the fact that in the dynamics of the experiment the specific volume of fibroreticular tissue and blood vessels gradually decreases, the mean number of bone trabeculae osteoblasts in the center of bone regeneration per area unit decreases, but at the same time the specific volume of bone trabeculae increases.

Table 3

Morphometric parameters of the mandibular hard tissues in the site of injury in toxic hepatitis in the dynamics of the experiment under correction with a complex hepatoprotector in rats of experimental group 2 (n = 20)

Morphometric parameters	Days of experiment			
	7	14	30	60
specific volume (%) of fibroreticular tissue	92.6±0.73	73.2±0.74	62.3±0.51	21.9±0.24
specific volume (%) of blood vessels	3.0±0.04	3.0±0.04	3.0±0.05	1.1±0.02
specific volume (%) of bone trabeculae	1.5±0.04	7.5±0.70	28.8±0.14	64.6±0.60
Mean number of bone trabeculae osteoblasts in the center of bone regeneration in the area of 100 μm ²	3.7±0.08	4.8±0.14	2.8±0.06	1.0±0.03
specific volume (%) of bone marrow	0	0	0	2.6±0.04

The proportion of bone trabeculae on the 60th day in animals of experimental group 1 is at the level of the 30th day in rats of the control group, which can indicate deterioration of bone wound healing almost twice. However, in toxic hepatitis, the mean number of bone trabeculae osteoblasts in the center of bone

regeneration per area unit shows the same dynamics. This also applies to the specific volume of bone marrow, which on the 60th day reaches the level of the 30th day in rats of the control group (tables 1, 2).

The experiment with drug correction of regenerative processes in toxic hepatitis by using “Quertulin” in rats of experimental group 2, as shown by morphometric data (table 3), had results that were statistically reliably different in fibrinolytic activity from the results of experimental rats in group 1 [3, 4]. There is a statistically reliable positive effect of complex hepatoprotector on the morphometric parameters of the mandibular regenerative tissues in the defected site [1, 3, 4].

The specific volume of fibroreticular tissue on the 7th day is almost unchanged, but there is a tendency to its sharp reduction on the 14th day. It is particularly important that “Quertulin” in toxic hepatitis increases the proportion of bone trabeculae on the 30th and 60th days and bone marrow on the 60th day [2, 5, 3]. The use of hepatoprotectors in the treatment of patients with fractures of the facial skeleton against the background of the liver toxic damage, will reduce the number of complications and accelerate the recovery of patients [1, 3, 9, 10].

Conclusion

Експериментальне дослідження показало, що токсичний гепатит погіршує морфометричну характеристику загоєння кісткової тканини у ділянці після травматичного дефекту. Використання комплексного гепатопротектора при експериментальному токсичному гепатиті є ефективним заходом для процесів регенерації кістки в місці перфорації, прискорюючи її майже вдвічі. У пацієнтів з травматичними переломом нижньої щелепи, при виявленні патології гепатобіліарної системи, доцільно використовувати «Квертулін», що дозволить скоротити терміни лікування та зменшити кількість ускладнень.

The experimental study showed that toxic hepatitis worsens the morphometric characteristics of bone healing in the area of post-traumatic defect. The use of a complex hepatoprotector in experimental toxic hepatitis is an effective measure for regeneration of bone in the site of perforation, accelerating it almost twice. In patients with traumatic fractures of the mandible, when pathology of the hepatobiliary system is detected, it is advisable to use “Quertulin”, which will reduce the duration of treatment and the number of complications.

References

1. Levitskiy AP, Demyanenko SA, Skidan MI, Pustovoyt PI. Effektivnost lecheniya khronicheskogo kataralnogo gingivita u bolnykh s gepatobiliarnoy patologiyey s ispolzovaniyem gepatoprotektora i prebiotika. *Innovatsiyi v stomatolohiyi*. 2013; 2: 5-9. [in Russian]
2. Malanchuk VO, Lohvinenko IP, Malanchuk TO. *Khirurgichna stomatolohiya ta shchelepno-lytseva khirurgiya: pidruchnyk*. Kyiv: LOHOS, 2011. 606 c. [in Ukrainian]
3. Moroz LV, Musayev EEO, Zaichko NV, Androsova OS, Hayduk OA. Vplyv vitaminu D na rezultaty likuvannya khronichnoho hepattytu C. *Hepatolohiya*. 2016; 4:42-50. [in Ukrainian]
4. Polishchuk SS, Davydenko IS, Shuvalov SM. Porivnyalne doslidzhennya histolohichnykh zmin kistkovoyi tkanyny nyzhnyoyi shchelepy shchuriv u dilyantsi travmatychnoho defektu pry patolohiyi hepatobiliarnoyi systemy. *Biomedical and biosocial anthropology*. 2017; 29:66-73. [in Ukrainian]
5. Tashchyan AE, Gulyuk AG, Makarenko OA. Stimulyatsiya mineralizatsii i kolagenoobrazovaniya v kostnoy tkani kryis s perelomami nizhney chelyusti s pomoshchyu preparata «osteovit». *Visnik stomatolohiyi*. 2012; 3: 5-8. [in Russian]
6. Tymofeyev OO. *Shchelepno-lytseva khirurgiya*. Kyiv: VSV “Medytsyna”, 2011. 752 s. [in Ukrainian]
7. Moroz LV, Bondaruk IYu, Popovich AA, Kulias SN. Comparison of the diagnostic efficiency of various noninvasive methods for diagnosing liver fibrosis in patients with chronic viral hepatitis C. *Journal of Education, Health and Sport*. 2019; 9(6): 546-555.
8. Polishchuk SS, Shuvalov SM. Influence of the dysfunction of the hepatobiliary system on the healing of the mandible fractures. *East European Scientific Journal*. 2018; 9 (37): 42-48.
9. Shankar DP, Manodh P, Devadoss P. Mandibular fracture scoring system: for prediction of complications *Oral Maxillofac. Surg*. 2012; 16(4): 355-360.
10. Vyas A, Mazumdar U, Khan F. A study of mandibular fractures over a 5-year period of time: A retrospective study. *Contemp. Clin. Dent*. 2014; 5(4): 452-455.
11. Yamamoto MK, D'Avila RP, Luz JG. Evaluation of surgical retreatment of mandibular fractures. *J. Craniomaxillofac. Surg*. 2013; 41(1): 42-46.

Реферати

ДИНАМІКА МОРФОМЕТРИЧНИХ ЗМІН КІСТКИ У ДІЛЯНКІ ПЕРФОРАЦІЙНОГО ДЕФЕКТУ НИЖНЬОЇ ЩЕЛЕПИ ЩУРІВ ПРИ ТОКСИЧНОМУ ГЕПАТИТІ ТА ВИКОРИСТАННІ КОМПЛЕКСНОГО ГЕПАТОПРОТЕКТОРА
Скиба В.Я., Поліщук С.С., Давиденко І.С., Штатсько О.І., Шувалов С.М., Гаврилюк А.О., Поліщук В.С., Поліщук О.О.

Метою дослідження було експериментальне вивчення морфометричних змін при загоєнні перфораційного дефекту нижньої щелепи щурів на фоні

ДИНАМИКА МОРФОМЕТРИЧЕСКИХ ИЗМЕНЕНИЙ КОСТИ В УЧАСТКЕ ПЕРФОРАЦИОННОГО ДЕФЕКТА НИЖНЕЙ ЧЕЛЮСТИ КРЫС ПРИ ТОКСИЧЕСКОМ ГЕПАТИТЕ И ИСПОЛЬЗОВАНИИ КОМПЛЕКСНОГО ГЕПАТОПРОТЕКТОРА
Скиба В.Я., Полищук С.С., Давыденко И.С., Штатско А.И., Шувалов С.М., Гаврилюк А.А., Полищук В.С., Полищук А.А.

Целью исследования было экспериментальное изучение морфометрических изменений при заживлении перфорационного дефекта нижней челюсти крыс на фоне

токсичного гепатиту та використання комплексного гепатопротектора. Було проведено експериментальне дослідження на 60 білих щурах-самцях лінії Вістар масою 240-270 г. В процесі роботи щурі були поділені на 3 групи (по 20 щурів у кожній групі): контрольна – включала здорових щурів з травмою нижньої щелепи; дослідна 1 – щурів з травмою щелепи та модельованим токсичним гепатитом; дослідна 2 – щурів з травмою нижньої щелепи + токсичний гепатит+комплексний гепатопротектор. Дослідження гістологічних змін кісткової тканини нижньої щелепи в ділянці травми, при токсичному гепатиті обґрунтувало позитивний вплив гепатопротектора на зміни морфометричних показників. В результаті експерименту виявили, що токсичний гепатит погіршує морфометричні показники загоєння перфораційного дефекту нижньої щелепи. Особливо важливим є те, що комплексний гепатопротектор при токсичному гепатиті збільшує питомий об'єм кісткових балок на 30 та 60 добу та кісткового мозку на 60 добу, що свідчить про його позитивний вплив на процеси регенерації кістки в місці перфорації.

Ключеві слова: експеримент, щурі, травма нижньої щелепи, модельований токсичний гепатит, комплексний гепатопротектор.

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токсического гепатита и использования комплексного гепатопротектора. Было проведено экспериментальное исследование на 60 белых крысах-самцах линии Вистар массой 240-270 г. В процессе работы крысы были разделены на 3 группы (по 20 крыс в каждой группе): контрольная - включала здоровых крыс с травмой нижней челюсти; экспериментальная № 1 - крыс с травмой челюсти и моделированным токсическим гепатитом; экспериментальная № 2 - крыс с травмой нижней челюсти + токсический гепатит + комплексный гепатопротектор. Исследование гистологических изменений костной ткани нижней челюсти в области травмы при токсическом гепатите обосновало положительное влияние гепатопротектора на изменения морфометрических показателей. В результате эксперимента обнаружили, что токсический гепатит ухудшает морфометрические показатели заживления перфорационного дефекта нижней челюсти. Особенно важно то, что комплексный гепатопротектор при токсическом гепатите увеличивает удельный объем костных балок на 30 и 60 сутки и костного мозга на 60 сутки, что свидетельствует о его положительном влиянии на процессы регенерации кости в месте перфорации.

Ключевые слова: эксперимент, крысы, травма нижней челюсти, моделированный токсический гепатит, комплексной гепатопротектор.

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Ye.V. Stetsuk, O.Ye. Akimov, K.V. Shepitka, A.N. Goltsev¹

Ukrainian Medical Stomatological Academy, Poltava

¹Institute for Problems of Cryobiology and Cryomedicine NAS of Ukraine, Kharkiv

STRUCTURAL ORGANIZATION OF STROMAL AND PARENCHYMAL COMPONENTS OF RAT TESTES DURING CENTRAL DEPRIVATION OF TESTOSTERONE SYNTHESIS ON THE 180 DAY OF THE EXPERIMENT

e-mail: stetsuk78@gmail.com

Prolonged central deprivation of testosterone synthesis may lead to biochemical and morphological changes in testes. Influence of prolonged testosterone deficiency on reactive nitrogen and oxygen species production, morphological changes in interstitial endocrinocytes and sustentocytes is not yet fully understood. The number of interstitial endocrinocytes is reduced in comparison with the control group, there are interstitial spaces between the convoluted tubules with a complete absence of interstitial endocrinocytes. Interstitial endocrinocytes are reduced in size, their nuclei are heterochromic. When we studied the structural organization of rat sustentocytes from the experimental group in comparison with the control group, we found that hyperplasia of the elements of the smooth endoplasmic reticulum was observed in the cytoplasm of the sustentocytes. The number of mitochondria in the cytoplasm of the sustentocytes decreased, the electron density of the mitochondrial matrix was lowered, protein structures were present either inside the vacuoles or independently located in the cell cytoplasm. Biochemical studies revealed increased NO production from inducible NO-synthase and development of oxidative stress. Experimental central deprivation of testosterone synthesis with diphereline on the 180th day of the experiment leads to shift of NO synthesis from constitutive NO-synthases to inducible NO-synthase and intensification of oxidative stress due to increase of superoxide anion-radical production and decrease in antioxidant protection.

Key words: testes, interstitial endocrinocytes, sustentocytes, NO-synthase, iNOS, cNOS, L-arginine, superoxide dismutase, rats.

The study is a fragment of the research project "Experimental morphological study of cryopreserved placenta transplants: action of diphereline, ethanol and 1% methacrylic acid on the morphofunctional status in a number of internal organs", state registration No. 0119U102925.

In developed European countries, there is a trend towards high sexual activity in older men and the late creation of a family with children, which has certain difficulties in connection with a decrease in testosterone production in old age [2, 10]. At the same time uncontrolled usage of testosterone leads to increase of prostate cancer incidence since androgens play key role in its development [4].

Diphereline is a potent treatment method for prostate cancer treatment, however we showed in our previous works that its usage leads to development of oxidative stress and changes in sustentocytes and interstitial endocrinocytes [3, 7, 14]. Minimal duration of diphereline intake in prostate cancer treatment

lasts half a year [6, 8, 9]. It is still unclear if the changes observed on 30th and 90th day of diphereline intake are not part of first adoptive reaction and not disappear later [11, 12].

The purpose of the study was to establish the microscopic organization of rat interstitial endocrinocytes and sustentocytes, to determine the sources of nitric oxide production and the intensity of oxidative stress in the testes in experimental central deprivation of testosterone synthesis with diphereline on the 180th day of the experiment.

Materials and methods. The experiments were carried out on 10 sexually mature male white rats of the Wistar line. Rats were divided into 2 groups: the control group (5) and the experimental group (5). Animals from experimental group were injected subcutaneously with diphereline (Triptorelin embonate) at a dose of 0.3 mg of the active substance/kg [5, 11, 12]. of body weight for 180 days, while control group received injection of saline [13].

Animals were kept in standard vivarium conditions of the Ukrainian Medical Stomatological Academy. Experimental animals were sacrificed in strict compliance with the provisions of the “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes”; (Strasbourg, 1986), as well as with the “General Ethical Principles of Animal Experiments” adopted by the First National Congress on Bioethics (Kyiv, 2001).

After an overdose of ketamine, the animals were decapitated, the prepared small pieces of the testes were fixed in a 2.5% glutaraldehyde solution (pH=7.2-7.4). Postfixation of the material was carried out with 1% solution of osmium (IV) oxide, followed by dehydration in propylene oxide and sample was embedded into the epoxy resins mixture. Ultrathin sections made with an ultramicrotome were contrasted with a 1% aqueous solution of uranyl acetate and lead citrate according to the Reynolds’ method and studied with an electron microscope [1].

Using standard methods, the material was imbedded in paraffin blocks, of which sections 4 μm thick were made and stained with hematoxylin and eosin. Histological preparations were examined using Biorex 3 light microscope with digital microfilter with software adapted for these studies (serial No. 5604).

All biochemical studies were carried out in 10% homogenate of testis tissue using Ulab 101 spectrophotometer [11, 12, 15].

General activity of NO-synthase (gNOS), activity of constitutive isoforms (cNOS), activity of inducible isoform (iNOS), activity of arginases and nitrite concentration [11, 12]. Basic production of superoxide anion radical ($O_2^{\cdot-}$), its production by the mitochondrial electron transport chain (ETC) and microsomal ETC was determined by the growth of diformazan concentration, formed in the reaction of $O_2^{\cdot-}$ with nitro blue tetrazolium [15]. Superoxide dismutase (SOD) and catalases activity was determined according to guidelines [15]. The concentration of free malondialdehyde (MDA) was determined by reaction with 1-methyl-2-phenylindole [15].

Statistical processing of the research results was carried out using the Microsoft Office Excel software and the Real Statistics 2019 extension to it. The nonparametric Mann-Whitney test was used to determine the statistical significance of differences between the groups. The difference was considered statistically significant at $p < 0.05$.

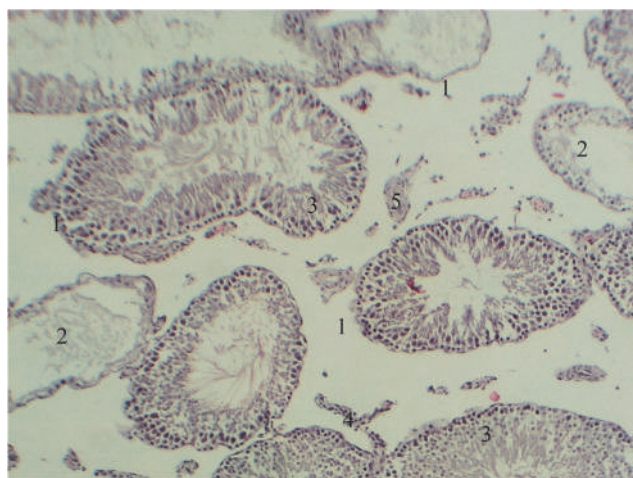


Fig. 1.a. Seminiferous tubules of experimental rat on the 180th day. Microimage. Stain: hematoxyline and eosine. Lens: 10; Ocular lens: 10. 1. Interstitial space - fibrosis. 2. Seminiferous tubule with single sustentocytes. 3. Spermatogenic epithelium of the unhealed tubule. 4. Interstitial cells. 5. The capillary in the Interstitial space with fibroblasts.

Results of the study and their discussion.

During morphological study of the experimental group of animals on the 180th day of the experiment, we found an increase in the interstitial space of the testes in comparison with the control group of animals (Fig.1a.) due to the proliferation of connective tissue (fibrosis). We determined an increased concentration of fibroblasts in the interstitial tissue, in some places it amounted to 14 cells in the field of view. The number of vessels is increased, they are full-blooded, the walls thickness increased, in some places with the marginal standing of leukocytes.

The number of interstitial endocrinocytes is reduced in comparison with the control group, there are interstitial spaces between the convoluted tubules with a complete absence of interstitial endocrinocytes (fig. 1a).

Interstitial endocrinocytes are reduced in size, their nuclei are heterochromic. Macrophages were also determined in the interstitial space. The number of parietal macrophages prevailed several times over interstitial. In the interstitium, macrophages were determined, which were located 1-2-3 (interstitial) closer to the vessel. Near the wall of convoluted seminiferous tubules, their number was up to 10-12 in the field of view. In the macrophage cytoplasm, secretory granules of various sizes and electron densities were detected. Also, rather large phagosomes containing fragments of dead cells were visualized in the cytoplasm of macrophages. (fig. 1.b). All parietal macrophages were in the phase of phagocytosis, which was not typical of interstitial macrophages.

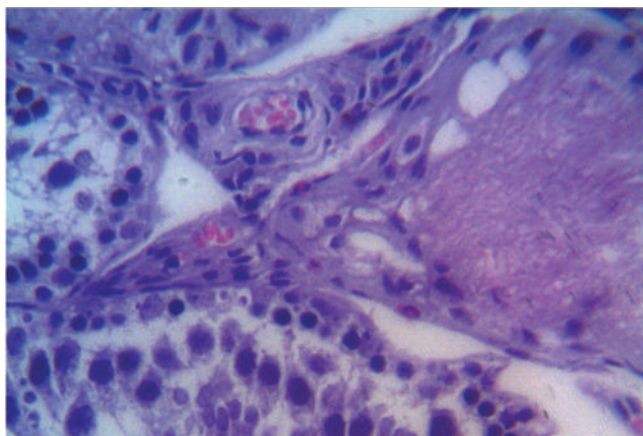


Fig. 1.b. Interstitial space of experimental rat on the 180th day. Microimage. Stain: hematoxyline and eosine. Lens: 40; Ocular lens:15.

The wall of the convoluted seminiferous tubules is compacted, convoluted due to interstitial fibrosis. In the structure of some convoluted seminiferous tubules from the spermatogenic epithelium of the basal layer, we detected following changes: a decrease in the population of both type A spermatogonia and type B spermatogonia. Discompletion and disorientation occurred in the adluminal layer, followed by desquamation of spermatids. Hypochromia and pycnosis were noted in the nuclei of spermatids.

Disorientation, discompletion of secondary and primary spermatocytes was determined in the ranks of spermatogenic epithelium. In most convoluted tubules, their desquamation was traced. Due to the complete or partial desquamation of spermatogenous epithelial cells from the basal membrane in the lumen of the tubules, "seed balls" were formed from undifferentiated cells. There were convoluted seminiferous tubules with a complete absence of spermatogenous epithelium and with single supporting cells (Sertoli cell-only syndrome; fig. 1.a.).

When we studied the structural organization of rat sustentocytes from the experimental group in comparison with the control group, we found that hyperplasia of the elements of the smooth endoplasmic reticulum was observed in the cytoplasm of the sustentocytes. Quite large phagosomes containing cell fragments were detected in the cytoplasm. In the cytoplasm of some spermatocytes and spermatids, deformation of the inner membranes and vacuolization of mitochondria appeared. The number of mitochondria in the cytoplasm of the sustentocytes decreased, the electron density of the mitochondrial matrix was lowered, protein structures were present either inside the vacuoles or independently located in the cell cytoplasm.

The total activity of NOS on the 180th day of central deprivation of testosterone synthesis increased by 51.9% when compared with the control group (tab. 1). At the same time, cNOS activity decreased 5.13 times, and iNOS activity increased 5.69 times. The concentration of nitrite in the testes of rats increases 3.44 times. The activity of arginases is reduced by 4.13 times. Thus, the increased production of nitric oxide under conditions of central deprivation of testosterone synthesis is ensured by the activity of the inducible NOS isoform. At the same time, an increase in iNOS activity with a decrease in the activity of the arginase pathway of L-arginine cleavage may indicate a change in the polarization of the macrophages of the testes with a predominance of the pro-inflammatory phenotype (M_1).

Table 1.

Nitric oxide cycle function during 180-day central testosterone synthesis deprivation ($M \pm m$)

Groups	Parameters				
	gNOS activity, $\mu\text{mol}/\text{min per g}$ of protein	iNOS activity, $\mu\text{mol}/\text{min per g}$ of protein	cNOS activity, $\mu\text{mol}/\text{min per g}$ of protein	Arginase activity, $\mu\text{mol}/\text{min per g}$ of protein	NO_2^- concentration, nmol/L
Control	0.54±0.04	0.13±0.02	0.41±0.03	2.48±0.05	3.83±0.25
Experimental	0.82±0.08*	0.74±0.08*	0.08±0.01*	0.60±0.02*	13.19±0.55*

Note: * - indicates that the difference is statistically significant when compared with control group ($p < 0.05$)

The basic production of O_2^- on the 180th day of the experiment increased 8.11 times when compared with the control group (tab. 2). Production of O_2 by mitochondrial ETC increased by 3.7 times, and that of microsomal ETC – by 2.4 times. SOD activity decreased by 2.7 times, meanwhile catalase activity did not change statistically significantly. MDA concentration in rat testes elevated by 3.15 times.

Oxidative stress markers in rat testes during 180-day central testosterone synthesis deprivation (M±m)

Groups	Parameters					
	SOD activity, c.u.	Catalase activity, nkat/g of tissue	Basic O ₂ ^{•-} production, nmol/s per g of tissue	Production of O ₂ ^{•-} from mitochondrial ETC, nmol/s per g of tissue	Production of O ₂ ^{•-} from microsomal ETC, nmol/s per g of tissue	Free MDA, μmol/g of tissue
Control	1.87±0.11	182.0±17.0	0.26±0.01	7.84±0.13	9.55±0.19	6.64±1.44
Experimental	0.70±0.17*	181.0±17.0	2.11±0.03*	28.75±1.62*	23.20±0.42*	20.91±0.25*

Note: * - indicates that the difference is statistically significant when compared with control group (p<0.05)

Thus, in the tissues of the testes under conditions of prolonged central deprivation of testosterone synthesis, oxidative stress develops, which on the 180th day of the experiment leads to the development of fibrosis in the testes. Change in the polarization of macrophages may be the reason for the development of oxidative stress in the testes, as evidenced by an increase in iNOS activity and a decrease in arginase activity.

Analyzing the changes described by us in dynamics, it is noteworthy that an increase in iNOS activity and a decrease in arginase activity is observed already from the first month of central deprivation of testosterone synthesis, does not change on the 3rd month of the experiment and continues on the 6th month [5, 6]. Therefore, changes in the polarization of macrophages (transition to the M₁ phenotype) may be the cause of the observed changes. Testosterone produced by interstitial endocrinocytes tends to inhibit the polarization of macrophages by the M₁ phenotype [11, 12].

However, in the tissues of the testes there are 2 populations of macrophages: resident (interstitial) and coming from the bone marrow (parietal). Based on the activities of iNOS and arginases, the number of parietal and interstitial macrophages in the control group, it can be concluded that under physiological conditions, the macrophages of the testes have an anti-inflammatory (M₂) phenotype. The contribution of interstitial and parietal macrophages to the development of morphological and biochemical changes in the testes during prolonged central deprivation of testosterone synthesis requires further study.

Controlling the polarization of testicular macrophages under conditions of prolonged central deprivation of testosterone synthesis may be a promising method for the pathogenetic correction of morphological and biochemical changes observed on 180th day of the experiment.

Conclusion

Experimental central deprivation of testosterone synthesis with diphereline on the 180th day of the experiment leads to shift of NO synthesis from constitutive NO-synthases to inducible NO-synthase and intensification of oxidative stress due to increase of superoxide anion-radical production and decrease in antioxidant protection. At the same time rat interstitial endocrinocytes decrease in number and volume. Their nuclei are heterochromic. Sustentocytes have hyperplasia of the elements of the smooth endoplasmic reticulum, much lesser amount of mitochondria with lower electronic density.

References

- Bahriy MM, Dibrova VA, Popadynets OH, Hryshchuk MI. Metodyky morfolohichnykh doslidzhen. Bahriy M.M., Dibrova V.A. redaktery. Vinnytsya: Nova knyha; 2016. 328s. [in Ukrainian]
- Almeida S, Rato L, Sousa M, Alves MG, Oliveira PF. Fertility and Sperm Quality in the Aging Male. *Curr Pharm Des.* 2017; 23(30): 4429-4437. doi: 10.2174/1381612823666170503150313.
- Atallah A, Mhaouty-Kodja S, Grange-Messent V. Chronic depletion of gonadal testosterone leads to blood-brain barrier dysfunction and inflammation in male mice. *J Cereb Blood Flow Metab.* 2017; 37(9): 3161-3175. doi: 10.1177/0271678X16683961.
- Hotta Y, Kataoka T, Kimura K. Testosterone Deficiency and Endothelial Dysfunction: Nitric Oxide, Asymmetric Dimethylarginine, and Endothelial Progenitor Cells. *Sex Med Rev.* 2019; 7(4): 661-668. doi: 10.1016/j.sxmr.2019.02.005.
- Liu FH, Yang DZ, Wang YF, Liang XP, Peng WM, Cao CA, Chen XG, Guo ZM. Making of the animal model with sterilized testes. *Zhonghua Nan Ke Xue.* 2007; 13(2): 125-9. [in Chinese].
- Merseburger AS, Hupe MC. An Update on Triptorelin: Current Thinking on Androgen Deprivation Therapy for Prostate Cancer. *Adv Ther.* 2016; 33(7): 1072-93. doi: 10.1007/s12325-016-0351-4.
- Mossadegh-Keller N, Sieweke M.H. Testicular macrophages: Guardians of fertility. *Cell Immunol.* 2018; 330: 120-125. doi: 10.1016/j.cellimm.2018.03.009.
- Rawla P. Epidemiology of Prostate Cancer. *World J Oncol.* 2019; 10(2): 63-89. doi: 10.14740/wjon1191.
- Rice MA, Malhotra SV, Stoyanova T. Second-Generation Antiandrogens: From Discovery to Standard of Care in Castration Resistant Prostate Cancer. *Front Oncol.* 2019; 9: 801. doi: 10.3389/fonc.2019.00801.
- Scovell JM, Khera M. Testosterone Replacement Therapy Versus Clomiphene Citrate in the Young Hypogonadal Male. *Eur Urol Focus.* 2018; 4(3): 321-323. doi: 10.1016/j.euf.2018.07.033.

11. Stetsuk YeV, Kostenko VO, Shepitko VI, Goltsev AN. Influence of the 30-days central deprivation of testosterone synthesis on the morphological and functional features of rat testicular interstitial endocrinocytes and sustentocytes. *World of Medicine and Biology*. 2019; 4(70): 228-233. doi: 10.26724/2079-8334-2019-4-70-228-233.
12. Stetsuk YeV., Akimov OYe., Shepitko KV., Goltsev AN. Morphofunctional features of rat testes interstitial endocrinocytes and sustentocytes after 90 days of central testosterone synthesis deprivation. *World of Medicine and Biology*. 2020; 1(71): 226-231. doi: 10.26724/2079-8334-2020-1-71-226-231.
13. Swelum AA, Saadeldin IM, Zaher HA, Alsharifi SAM, Alowaimier AN. Effect of sexual excitation on testosterone and nitric oxide levels of water buffalo bulls (*Bubalus bubalis*) with different categories of sexual behavior and their correlation with each other. *Anim Reprod Sci*. 2017; 181: 151-158. doi: 10.1016/j.anireprosci.2017.04.003.
14. Wenjing Y, Li L, Xiaofeng H, Guanghan K, Lifang L, Jishuai C, Chen X, Wei S, Wei C, Shanmin Z, and Shufang C. Levels of Leydig cell autophagy regulate the fertility of male naked mole-rats. *Oncotarget*. 2017 Nov 17; 8(58): 98677–98690. doi: 10.18632/oncotarget.22088.
15. Zhao Y, Liu X, Qu Y, Wang L, Geng D, Chen W, Li L, Tian Y, Chang S, Zhao C, Zhao X, Lv P. The roles of p38 MAPK → COX2 and NF-κB → COX2 signal pathways in age-related testosterone reduction. *Sci Rep*. 2019; 9(1): 10556. doi: 10.1038/s41598-019-46794-5.

Реферати

СТРУКТУРНА ОРГАНІЗАЦІЯ СТРОМАЛЬНИХ ТА ПАРЕНХИМАТОЗНИХ КОМПОНЕНТІВ СІМ'ЯНИКІВ ЩУРІВ ПРИ ЦЕНТРАЛЬНОЇ ДЕПРИВАЦІЇ СИНТЕЗУ ТЕСТОСТЕРОНА НА 180 ДЕНЬ ЕКСПЕРИМЕНТУ

Стецюк Є.В., Акімов О.Є., Шепітько К.В., Гольцев А.Н.

Тривала центральна депривація синтезу тестостерону може призвести до біохімічним і морфологічних змін в яєчках. Вплив тривалого дефіциту тестостерону на вироблення активних форм азоту і кисню, морфологічні зміни в інтерстиційних ендокриноцитів та суспендоцитів ще повністю не вивчені. Кількість інтерстиційних ендокриноцитів знижена в порівнянні з контрольною групою, між звивистими каналцями є інтерстиційні простори з повною відсутністю інтерстиційних ендокриноцитів. Інтерстиційні ендокриноцити зменшені в розмірах, їх ядра гетерохромні. При вивченні структурної організації суспендоцитів щурів експериментальної групи в порівнянні з контрольною групою, ми виявили, що гіперплазія елементів гладкої ендоплазматичної сітки спостерігалася в цитоплазмі суспендоцитів. Кількість мітохондрій в цитоплазмі суспендоцитів зменшилася, електронна щільність мітохондріального матриксу була знижена, білкові структури були присутні або всередині вакуолей, або незалежно розташовувалися в цитоплазмі клітини. Біохімічні дослідження виявили збільшення продукції NO з індукційною NO-синтазою і розвиток окисного стресу. Експериментальна центральна депривація синтезу тестостерону з Дифереліном на 180-й день експерименту призводить до зрушення синтезу NO з конститутивних NO-синтази до індукційної NO-синтази і посилення окисного стресу за рахунок збільшення продукції супероксид-аніон-радикалів і зниження антиоксидантного захисту.

Ключові слова: сім'яники, інтерстиціальні ендокриноцити, суспендоцити, NO-синтаза, iNOS, cNOS, L-аргінін, супероксиддисмутаза, щури.

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СТРУКТУРНАЯ ОРГАНИЗАЦИЯ СТРОМАЛЬНЫХ И ПАРЕНХИМАТОЗНЫХ КОМПОНЕНТОВ СЕМЕННИКОВ КРЫС ПРИ ЦЕНТРАЛЬНОЙ ДЕПРИВАЦИИ СИНТЕЗА ТЕСТОСТЕРОНА НА 180 ДЕНЬ ЭКСПЕРИМЕНТА

Стецюк Е.В., Акимов О.Е., Шепитько К.В., Гольцев А.Н.

Длительная центральная депривация синтеза тестостерона может привести к биохимическим и морфологическим изменениям в яичках. Влияние длительного дефицита тестостерона на выработку активных форм азота и кислорода, морфологические изменения в интерстициальных эндокриноцитах и суспендоцитах еще полностью не изучены. Установлено, что количество интерстициальных эндокриноцитов снижено по сравнению с контрольной группой, между извитыми семенными каналцами имеются интерстициальные пространства с полным отсутствием интерстициальных эндокриноцитов. Интерстициальные эндокриноциты уменьшены в размерах, их ядра гетерохромны. При изучении структурной организации суспендоцитов крыс из экспериментальной группы по сравнению с контрольной группой, мы обнаружили, что гиперплазия элементов гладкой эндоплазматической сети наблюдалась в цитоплазме суспендоцитов. Количество митохондрий в цитоплазме суспендоцитов уменьшилось, электронная плотность митохондриального матрикса была снижена, белковые структуры присутствовали либо внутри вакуолей, либо независимо располагались в цитоплазме клетки. Биохимические исследования выявили увеличение продукции NO из индуцибельной NO-синтазы и развитие окислительного стресса. Экспериментальная центральная депривация синтеза тестостерона с диферелином на 180-й день эксперимента приводит к сдвигу синтеза NO из конститутивных NO-синтаз в индуцибельную NO-синтазу и усилению окислительного стресса за счет увеличения продукции супероксид-анион-радикалов и снижения антиоксидантной защиты.

Ключевые слова: семенники, интерстициальные эндокриноциты, суспендоциты, NO-синтаза, iNOS, cNOS, L-аргинин, супероксиддисмутаза, крысы.

Рецензент Шепітько В.І.

L.O. Stechenko, Y.B. Chaikovsky, O.I. Kryvosheyeva, S.M. Chuhrai, V.A. Pastuhova¹, S.V. Irkha²
Bogomolets National Medical University, Kyiv
¹National University of Ukraine on Physical Education and Sport, Kyiv
²PHEE "Kyiv Medical University", Kyiv

FEATURES OF THE RIGHT ATRIUM STRUCTURE IN EXPERIMENTAL DIABETES MELLITUS AND USE OF ANTIOXIDANTS

e-mail: lostechenko@gmail.com

Right atrium cardiomyocytes were studied in conditions of streptozotocin-induced type 1 diabetes mellitus and with the use of N-acetylcysteine as an antioxidant. The study showed that potential damage of fine mechanisms of synthesis and secretion of atrial natriuretic peptide may be the cause of cardiovascular pathology in diabetes. Use of antioxidant drugs has revealed that N-acetylcysteine partially reduces cardiomyocyte swelling, increases the number of atrial granules containing atrial natriuretic peptide and stimulates autophagy. Based on ultrastructural studies of atrial cardiomyocytes in type 1 diabetes it was found that damage to protein synthesis and accumulation and transformation of abnormal proteins happen via their elimination in two ways: through the ubiquitin-proteasomal and autophago-lysosomal systems. Autophagosomes occur both with a double membrane, i.e. the newly formed one, and with a single membrane after contact with lysosomes. These processes take place to maintain homeostasis in cardiomyocytes and in the myocardium as a whole. Impairment of these systems may lead to development of diabetic cardiomyopathy.

Key words: type I diabetes mellitus in rats, right atrium cardiomyocytes, atrial granules, autophagy.

The work is a fragment of the research project "Study of cellular and molecular mechanisms of pharmacological influence on the reprogramming of macrophages functional phenotype in wound regeneration in the presence of hyperglycemia", state registration No. 0119U1011219.

Cardiovascular complications are often the cause of death of patients with diabetes mellitus (DM). Acute hyperglycemia is associated with heart failure and cardiogenic shock [5]. In the study of this issue preference is given to the left ventricle [2]. Currently, given the endocrine function of the heart, which is mainly performed by the right atrium, and possible complications of diabetes the state of atrial cardiomyocytes attracts considerable interest. In recent years, the role of secretory granules, the morphological equivalent of atrial natriuretic peptide (ANP), in the development of chronic heart failure has been actively studied. The role of ANP in diabetes mellitus, and in pathological complications accompanied by hyperglycemia-induced oxidative stress is unknown. The latter leads to the formation of abnormal cellular proteins that are eliminated through the ubiquitin-proteasomal pathway or by autophagy. In violation of these mechanisms, the risk of deterioration of cardiac function increases. Disruption of these mechanisms increases the risk of cardiac function deterioration. It is known that aberrant proteins and destroyed organelles are engulfed by autophagosomes and destroyed in lysosomes [4]. At the molecular level DM was found to initiate apoptosis of cardiomyocytes by reducing cardiac autophagy, which in fact causes the development of diabetic cardiomyopathy [8]. Impairment of these mechanisms increases the risk of cardiac function deterioration. This indicates the key role of oxidative stress in the regulation of autophagy and the possibility of using drugs with antioxidant action to modulate cardioprotective autophagy with the aim of preventing and correcting diabetic cardiomyopathy. [3,4].

The antioxidant drug N-acetylcysteine (NAC) attracts significant attention. In an ischemia/reperfusion experimental model NAC has significantly reduced induced oxidative stress and cardiomyocyte apoptosis thus preventing postischemic autophagy in DM. [9]. In our earlier studies we have found a positive effect of N-acetylcysteine on heart rate, ventricular contractile activity, and signs of hypertrophy in rats in the early stage of diabetic cardiomyopathy in the left ventricle. [2]. Currently the question of whether NAC will demonstrate a cardioprotective effect on ANP and activate or inhibit autophagy and apoptosis in rats in a model of diabetic cardiomyopathy remains unresolved?

The purpose of the study was to investigate the features of the right atrium cardiomyocytes ultrastructure in conditions of streptozotocin-induced type 1 diabetes mellitus and the use of N-acetylcysteine as an antioxidant.

Materials and methods. Type 1 diabetes mellitus (DM) was simulated by administration of 50 mg / kg of streptozotocin (STZ) to rats. *General Ethical Principles for Animal Experiments* approved by the 1st National Congress on Bioethics (Kyiv, 2001) have been observed throughout the study. Experimental animals were divided into 3 groups: 1 - control group (intact rats receiving 0.9% saline); 2 - DM1 (a group of animals with DM1 simulated by streptozotocin administration); 3 - NAC (group of diabetic rats receiving N-acetylcysteine at a dose of 1.5 g/kg per os). Used as the material for electron microscopic examinations were pieces of the right atrium myocardium, which were fixed with 2.5% solution of glutaraldehyde on phosphate buffer with postfixation in 1% solution of osmium tetroxide and

treated according to conventional methods. Sections were made on an ultramicrotome LKB III (Sweden). The preparations were studied and photographed on an electron microscope PEM-125K.

Results of the study and their discussion. The study revealed that under experimental type 1 diabetes mellitus cardiomyocytes in the right atrium myocardium demonstrate both cytoplasmic swelling and hyperosmia, local myofibril hypercontraction, and increased number of agranular tubules of the endoplasmic reticulum in comparison with control. An accumulation of collagen fibers was found in the interstitium. Ultrastructural analysis of atrial cardiomyocytes showed their heteromorphic structure in simulated diabetes mellitus. In some of them cytoplasmic swelling, myocytolysis, disorganization of myofibrils, compaction of intercalated discs and mitochondria and destruction of their cristae were found (fig. 1A). Other cardiomyocytes preserved structural organization of myofibrils and mitochondria, but cardiomyocytes in the pre-apoptotic state also occurred (fig. 1B). Chromatin in the nuclei of such cells was located only near the nuclear envelope, the integrity of which was lost with cytoplasmic contents (lysosomes, destructively altered mitochondria, autophagosomes) found in the center of the nucleus. In the cytoplasm of atrial cardiomyocytes in the context of diabetes, autophagosomes were observed at different stages of formation: with a double membrane (primary), or a single (secondary) one and electron-dense contents (mostly protein), and in contact with lysosomes.

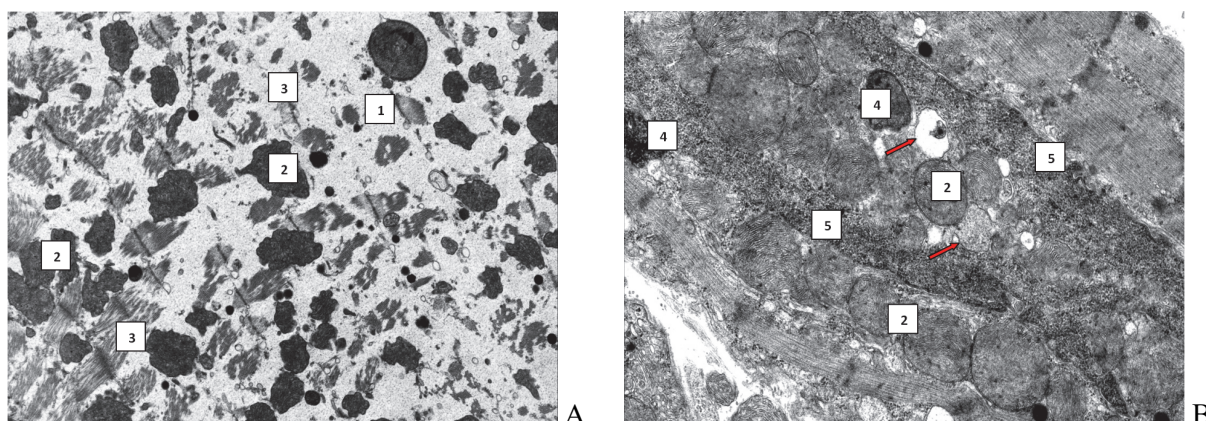


Fig. 1. A - a fragment of an atrial cardiomyocyte in the context of diabetes mellitus: 1 - cytoplasmic swelling, 2 - mitochondria, 3 - myofibrils. Magnification: 10000; B - fragment of an atrial cardiomyocyte: 4 - lysosomes, ↑ - autophagosomes, 5 - nuclear apoptosis. Magnification: 20000

The sarcolemma of such cells is partially lysed, as evidenced by the detection of individual mitochondria in the interstitium.

Autophagosomes were observed in cardiomyocytes in quite a large number. The latter were detected both with a double membrane, i.e. the newly formed (primary) and with a single one (secondary), after contact with lysosomes. The number of autophagosomes increases compared to the control, some of them contain cellular detritus, or individual organelles, such as mitochondria (fig.2 A, B).

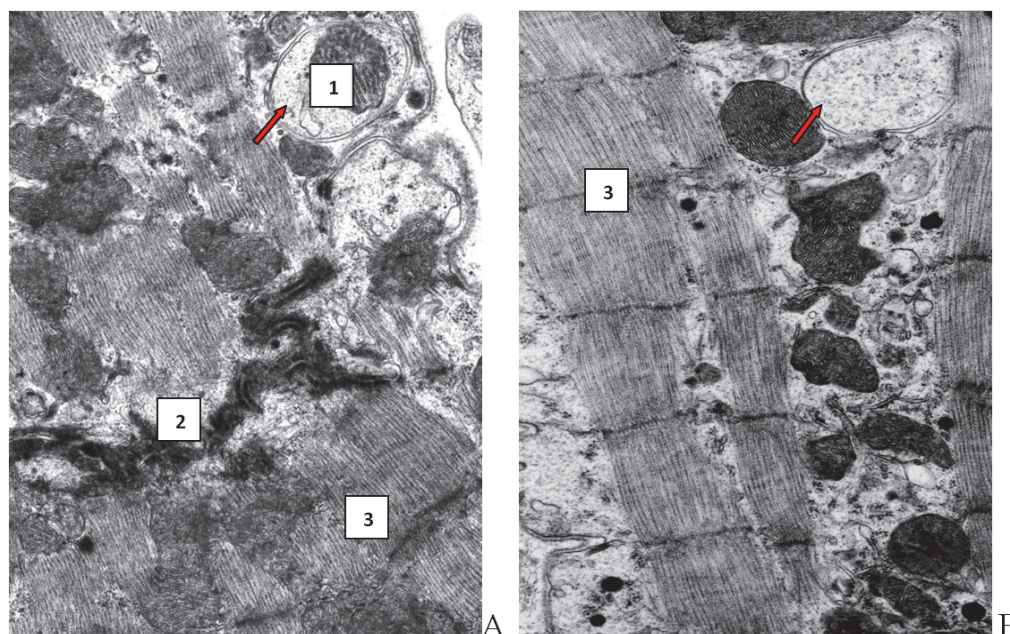


Fig. 2. Fragments of cardiomyocytes of the right atrium in conditions of diabetes mellitus. ↑ - primary autophagosomes, 1 - mitochondria in the autophagosome, 2 - intercalated disc, 3 - myofibrils. Magnification: 18000

The nuclei of some cells had deep invaginations, which revealed cytosigresomes containing cellular detritus, a large number of vacuoles and autophagosomes. (fig.3). Accumulation of abnormal proteins in the cytoplasm of atrial cardiomyocytes in diabetes mellitus is due in part to impaired atrial natriuretic peptide secretion. Concurrently large cytosigresomes including both autophagosomes and elements of the ubiquitin-proteasomal system were observed, which eliminated the damaged (aberrant) intracellular proteins. (fig. 3).

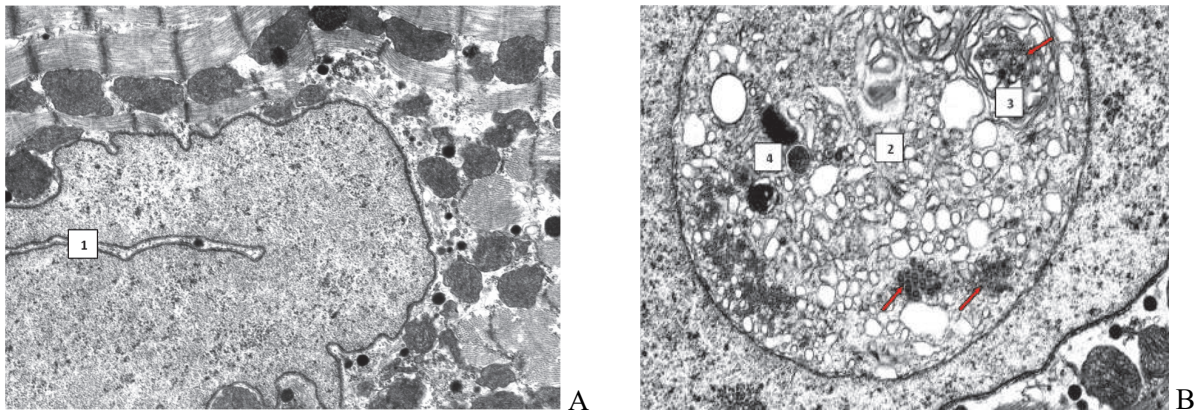


Fig. 3. Fragments of the right atrium cardiomyocytes in conditions of diabetes mellitus. 1 - invagination of the nuclear membrane, 2 - cytosigresome, 3 - autophagosomes, 4 - lysosomes, ↑ - proteasomes. Magnification: A - 10000, B - 20000.

The electron micrograph shows the cytosigresome in the invagination of the nuclear envelope, which contains elements of cellular structures: vacuoles of different sizes, lysosomes, autophagosomes and complexomixes, which seem to be proteasomes equivalents. They include microtubules formed for ubiquitination, after which they break down, while amino acids seem to be used again.

Simulation of diabetes mellitus in the right atrium myocardium revealed a few atrial granules containing ANP, as compared with the control (see fig. 1, 2, 3). In the perinuclear zone, where these granules are formed in the Golgi complex, some swelling and granules of type I too small in size are found. They are newly formed and present in small quantity. Single granules are located between myofibrils. The density of the atrial granules is much higher than in the control, which seems to be due to the condition of the granules themselves. They are mainly type 1 (high density) and are not released into the bloodstream, which may be the result of increased pressure in it. Fewer type 3 granules (diffusing) are found in diabetes mellitus. It is obvious that changes in the synthesis and secretion of such a strong vasodilator as ANP can be a cause of diabetes complications.

The use of antioxidants has shown that N-acetylcysteine partially reduces the swelling of cardiomyocytes. In addition to the typical nuclei of cardiomyocytes, there occur nuclei with invaginations of the nuclear membrane. The number of autophagosomes is increased as compared with animals with simulated diabetes. Most autophagosomes have a double membrane, they are located both in the perinuclear zone and subsarcolemmally and are formed by different membrane structures: endoplasmic reticulum tubules that have lost ribosomes, Golgi cisterns, plasma membrane, and parts of intercalated discs (fig. 4).

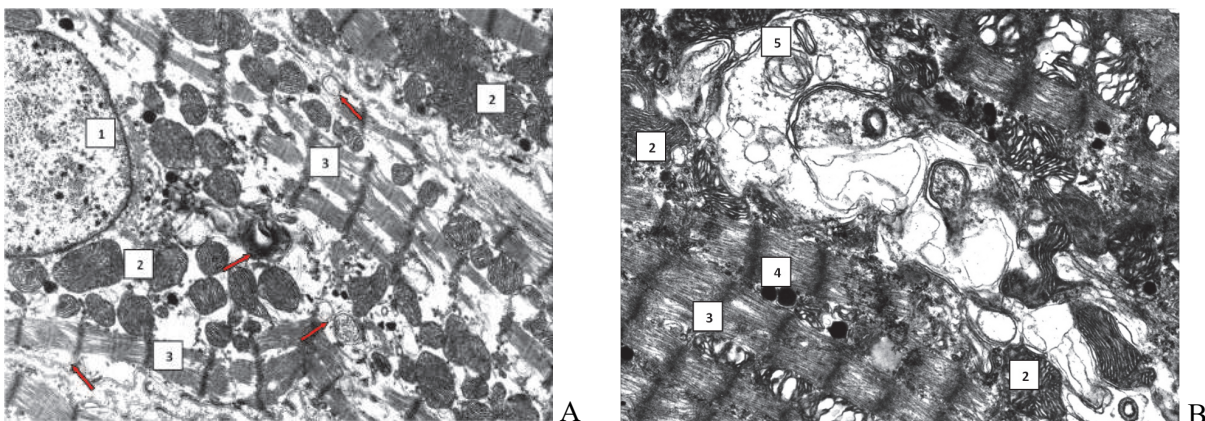


Fig. 4. Fragments of the right atrium cardiomyocytes in conditions of diabetes mellitus during the use of N-acetylcysteine. A: 1 - nucleus, ↑ - autophagosomes, 2 - mitochondria, 3 - myofibrils. B: 4 - atrial granules, 5 - clusters of mitochondria. Magnification: A - 12000, B - 14000.

A special type of autophagosomes - mitosomes are formed by mitochondrial membranes. In the zone of mitosome formation the latter have a hyperosmic matrix, if it is preserved, or a vacuolated

intercrystal space. Atrial granules containing ANP are localized perinuclearly in the Golgi complex area, they are different in size and mainly belong to type 1.

Thus, the conducted study showed that possible damage to the fine mechanisms of synthesis and secretion of atrial natriuretic peptide may be the cause of cardiovascular pathology in diabetes mellitus. The use of antioxidant drugs revealed that N-acetylcysteine partially reduces the swelling of cardiomyocytes, increases the number of atrial granules containing ANP and stimulates autophagy. Based on the conducted ultrastructural studies of atrial cardiomyocytes in type 1 diabetes mellitus and literature data, it can be assumed that damage of protein synthesis and accumulation and cleavage of abnormal proteins occur by their elimination in two ways: through ubiquitin-proteasomal and autophagous-lymphatic systems. [1, 2, 3]. Autophagosomes occur both with a double membrane, i.e. the newly formed ones, and with a single membrane after contact with lysosomes. These processes take place to maintain homeostasis in cardiomyocytes and in the myocardium as a whole. Impairment of these systems may lead to the development of a diabetic cardiomyopathy [7].

The tubular complexomixes found in cytosomes, which are analogs of proteasomes may serve confirmation of these processes. The authors describe them as a radial symmetric protein complex consisting of 26 subunits that form four 7-membered rings packed on top of one another [1]. Hyperglycemia-induced oxidative stress accompanying diabetes leads to the formation of damaged cellular proteins that must be eliminated through the ubiquitin-proteasomal pathway or autophagy. This process - utilization of proteasomes through autophagy is called "proteaphagy". Impairment of these mechanisms increases the risk of cardiac function deterioration [8]. Large areas of mitophagosomes found by us, which are signs of mitochondrial autophagy, indicate the activation of mitophagia as a response to oxidative stress caused by diabetes. According to some authors, mitophagia is responsible for the elimination of damaged mitochondria [6]. This indicates the key role of oxidative stress in the regulation of autophagy and the possibility of using drugs with antioxidant action for prevention and correction of diabetic cardiomyopathy.

Conclusion

The conducted ultrastructural study of atrial cardiomyocytes in type 1 diabetes showed that impairment of protein synthesis as well as accumulation and transformation of abnormal proteins happen via their elimination in two ways: namely, through the ubiquitin-proteasomal and autophago-lysosomal systems. Autophagosomes occur with both a double membrane, i.e. the newly formed ones, and with a single membrane after their contact with lysosomes. These processes take place to maintain homeostasis in cardiomyocytes and in the myocardium as a whole. The antioxidant drug -N-acetylcysteine partially reduces the swelling of cardiomyocytes, increases the number of atrial granules containing ANP and stimulates autophagy and mitophagia.

References

1. Buneeva OA, Medvedev AS. Ubikvitin-nezavisimaya degradatsiya belkov v proteosomakh. Biomedicinskaya khimiya 2018; 64(2):134-48. [in Russian]
2. Sitnik IM, Stechenko LO, Krivosheyeva OI, Natrus LV, Haytovich MV. Vplyv N-acetilsisteyinu ta lozartanu na modulyuvannya tsitoprotekturnoyi autofahiyi v miokardi shchuriv pry eksperimentalnomu tsukrovomu diabeti 1 typu (za danymy elektronnoyi mikroskopiyi). Ukrayinskyi nauko-medychnyi molodizhnyi zhurnal. 2017; 2(101): 25-30. [in Ukrainian]
3. Adams B, Maranga RF, Essop MF. Partial inhibition of the ubiquitin-proteasome system ameliorates cardiac dysfunction following ischemia-reperfusion in the presence of high glucose. Cardiovasc Diabetol. 2015; 14:94-109.
4. Godar RJ, Ma X, Liu H, Murphy JT, Weinheimer CJ, Kovacs A, et al. Repetitive stimulation of autophagy-lysosome machinery by intermittent fasting preconditions the myocardium to ischemia/reperfusion injury. Autophagy. 2015; 11(9):1537-60.
5. Mei Y, Thompson MD, Cohen RA, Tong XY. Autophagy and oxidative stress in cardiovascular diseases. Biochimica et Biophysica Acta 1852. 2015; 2015: 243-51.
6. Moyzis AG, Sadoshima J, Gustafsson AB. Mending a broken heart: the role of mitophagy in cardioprotection. Am J Physiol Heart Circ Physiol. 2015; 308: H183-H192.
7. Zhang L, Ding W, Wang Zh, Tang M, Wang F., Li Y. et al. Early administration of trimetazidine attenuates diabetic cardiomyopathy in rats by alleviating fibrosis, reducing apoptosis and enhancing autophagy. J Transl Med. 2016; 14:109-121.
8. Zhang M, Zhang L, Hu J. MST1 coordinately regulates autophagy and apoptosis in diabetic cardiomyopathy in mice. Diabetologia. 2016. doi:10.1007/s00125016-4070-9.
9. Wang S, Wang C., Yan F. N-acetylcysteine attenuates diabetic myocardial ischemia reperfusion injury through inhibiting excessive autophagy. Mediators of Inflammation. 2017; ID 9257291, 10 p.

Реферати

ОСОБЛИВОСТІ БУДОВИ ПРАВОГО ПЕРЕДСЕРДЯ ПРИ ЕКСПЕРИМЕНТАЛЬНОМУ ЦУКРОВОМУ ДІАБЕТИ ТА ЗА УМОВ ЗАСТОСУВАННЯ АНТИОКСИДАНТІВ

Стеченко Л.О., Чайковський Ю.Б., Кривошеєва О.І., Чухрай С.М., Пастухова В.А., Ірха С.В.

Досліджувались кардіоміоцити правого передсердя за умов стрептозотонин-індукованого цукрового діабету 1

ОСОБЕННОСТИ СТРОЕНИЯ ПРАВОГО ПРЕДСЕРДИЯ ПРИ ЕКСПЕРИМЕНТАЛЬНОМ САХАРНОМ ДИАБЕТЕ И В УСЛОВИЯХ ПРИМЕНЕНИЯ АНТИОКСИДАНТА

Стеченко Л.А., Чайковський Ю.Б., Кривошеєва О.И., Чухрай С.Н., Пастухова В.А., Ирха С.В.

Исследовались кардиомиоциты правого предсердия при стрептозотонин-индуцированом сахарном диабете 1

типу та при застосуванні N-ацетилцистеїну як антиоксиданта. Проведене дослідження показало, що можливе, ушкодження тонких механізмів синтезу та секреції передсердного натрійуретичного пептиду може бути причиною виникнення серцево-судинної патології за умов цукрового діабету. Застосуванням препаратів антиоксидантної дії було встановлено, що N-ацетилцистеїн частково зменшує набряк кардіомиоцитів, підвищує кількість передсердних гранул, що містять передсердний натрійуретичний пептид та стимулює автофагію. Базуючись на проведених ультраструктурних дослідженнях передсердних кардіомиоцитів при цукровому діабеті першого типу, встановлено, що ушкодження білкового синтезу та накопичення і трансформація аномальних білків відбувається елімінацією їх двома шляхами: через убиквітин-протеасомальну та автофаго-лізосомальну системи. Автофагосоми трапляються як з подвійною мембраною тобто новоутворені, так і з одинарною після контакту з лізосомами. Ці процеси здійснюються для підтримки гомеостазу у кардіомиоцитах та у міокарді в цілому. При порушенні цих систем можливий розвиток діабетичної кардіоміопатії.

Ключові слова: кардіомиоцити правого передсердя, цукровий діабет у шурів, автофагія

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типа и в условиях применения N-ацетилцистеина, как антиоксиданта. Проведенное исследование показало, что возможно, повреждение тонких механизмов синтеза и секреции предсердного натрийуретического пептида может быть причиной развития сердечно-сосудистой патологии в условиях сахарного диабета. Применение препарата антиоксидантного действия показало, что N-ацетилцистеин частично уменьшает отек кардиомиоцитов, повышает количество предсердных гранул, содержащих предсердный натрийуретический пептид и стимулирует автофагию. Основываясь на проведенных ультраструктурных исследованиях предсердных кардиомиоцитов при сахарном диабете первого типа, установлено, что повреждение белкового синтеза, накопление и трансформация аномальных белков осуществляется элиминацией их двумя путями: через убиквитин-протеасомальный и автофаго-лизосомальный системы. Автофагосоми обнаруживаются как с двойной мембраной, то есть новообразованные, так и с одинарной после контакта с лизосомами. Эти процессы осуществляются для поддержки гомеостаза у кардиомиоцитах и в миокарде в целом. При нарушении этих систем возможно развитие диабетической кардиомиопатии.

Ключевые слова: сахарный диабет 1 типа у крыс, кардиомиоциты правого предсердия, предсердные гранулы, автофагия.

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V.B. Fik, Ye.V. Paltov, Yu.Ya. Kryvko¹
Danylo Halytsky National Medical University, Lviv
¹Andriy Krupynskyi Lviv Medical Academy, Lviv

SUBMICROSCOPIC CHANGES IN PERIODONTIC TISSUES UNDER EXPERIMENTAL OPIOID ACTION WITHIN TEN WEEKS

e-mail: fikvolodymyr@ukr.net

This paper presents the results of soft periodontal tissues sub-microscopic examination under the experimental effect of an opioid analgesic within ten weeks. The study was carried out on 22 male rats of reproductive age. The animals were administered opioid analgesic in multiple ascending dose from 0.212 mg / kg to 0.283 mg / kg. At the ultrastructural level, it has been established that the prolonged action of opioid for ten weeks leads to marked heterogeneity and reorganization of the periodontal cell components against the background of the chronic inflammatory process development, which is exacerbated by sclerotic changes.

Key words: electron microscopic examination, periodontal tissues, opioid analgesic, rats.

The work is a fragment of the research project "Morpho-functional features of organs in pre- and postnatal periods of ontogeny, under the influence of opioids, nutritional supplements, reconstructive operations and obesity", state registration No 0120U002129.

Opioid analgesics, due to their pronounced analgesic effect, are indispensable medicines in medical practice [2]. Conversely, long-term and not always controlled use of drugs causes formation of tolerance, physical and psychological symptoms of withdrawal, which often leads to overdose and death [7, 12]. The urgency of this issue is determined by the fact that the negative impact of psychoactive substances, in particular, opioids leads to the destruction of almost all organs and systems of the body, especially the mouth, periodontal tissues [3, 5, 8, 10]. However, many issues regarding structural changes in tissues and organs in the use of opioid drugs remain unresolved [11, 13]. It should be noted that comprehensive information on the features of the periodontal components structural organization is extremely important in view of the recent data on formation of a new model of periodontitis pathogenesis [1, 4, 6, 9, 15]. Given the above, we believe that the present study is necessary and relevant in terms of both experimental and practical dentistry and periodontology.

The purpose of the work was to study the depth and dynamics of the of submicroscopic changes growth in the periodontium after ten weeks of opioid exposure.

Materials and methods. The study was carried out on 22 white male rats of reproductive age, Wistar line, weighing 160 - 255 g, 4.5 - 7 months of age. The experimental animals were divided into 2

groups. The first group consisted of intact animals (10). In the second group, rats (12) were injected daily with a single intramuscular injection of the nalbuphine opioid analgesic for ten weeks. The starting dose was 0.212 mg / kg. In the second group, the animals were increased the dose up to 0.283 mg / kg over 9 and 10 weeks. According to the drug instructions, initially an average single therapeutic dose was used, which was increased during the experiment, depending on the mean body weight of rats. The animals were weighed once every two weeks. All adult rats were kept under vivarium conditions and the work on maintenance, care, and other manipulations was performed in compliance with provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes". Before sampling of the material, the animal was euthanized by intraperitoneal administration of sodium thiopental (25 mg / 1 kg). For electron microscopic examination, fragments of periodontal soft tissue were used in the area of the gum margin. The tissue pieces were fixed in 2.5% glutaraldehyde solution and in 1% osmium tetroxide solution in the phosphate buffer with pH 7.2-7.4, dehydrated in alcohols and propylene oxide and embedded into a mixture of epoxy resins with araldite. Using UMPT3m ultramicrotome ultrathin sections were made and counterstained with uranyl acetate and lead citrate to be studied with PEM-100-01 electron microscope.

Results of the study and their discussion. Submicroscopically, it was established that the gums epithelium in the intact rats was characterized by the layered location of cells, in the cytoplasm organelles, nuclei with even contours and perinuclear space were visualized. Intercellular contacts were clearly traced. The periodontium consisted of collagen fiber bundles that were restricted by layers of loose connective tissue where fibroblasts, basophils, and lymphocytes were present. The gum hemocapillaries were of the somatic type, their wall was formed by endothelial cells and the basement membrane.

Electron microscopic studies of the animal gums, performed after ten weeks with the use of opioids, revealed pronounced submicroscopic changes in the structural components. In the epithelial plate of the gums' spare part, most cells of the basal layer exhibited karyorexis and nucleus segregation. Intercellular contacts were not clearly structured, having a look of osmophilic lumps, sometimes partially reduced. Plasmolemmas in part of sites were indistinct, intercellular spaces uneven, sometimes expanded, which may indicate the progression of the edema process (fig. 1). In the epitheliocytes' cytoplasm of the spinous layer, tonofilaments were with fuzzy contours, some of them sticking together and forming dense bundles.

The swollen mitochondria were round-shaped, had an electron-lucent matrix, and the cristas in them were significantly damaged. The granular layer epitheliocytes' cytoplasm contained a large number of electron-dense inclusions of keratogialin. In the gum epitheliocytes' nuclei numerous invaginations of karyolema were formed, signs of nucleoli segregation in the presence of electron-lucent karyoplasms were observed. In the cytoplasm of the basal layer cells, organelles were mostly damaged, mitochondria were vacuolated, with reduced cristas, tonofilaments were mostly fragmented. There were signs of acantholysis, where intercellular contacts were predominantly reduced. Intercellular spaces were significantly enlarged, which was an evidence of spongiosis.

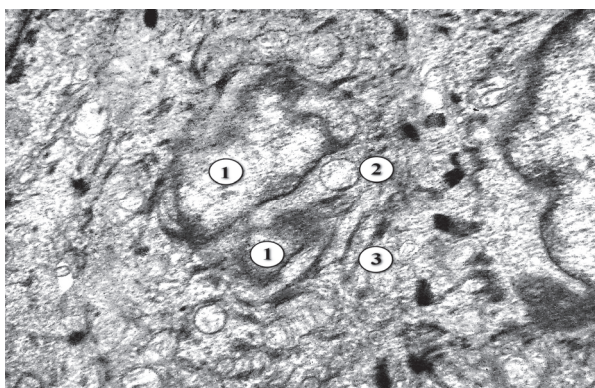


Fig. 1. Epitheliocyte of the basal layer in the spare part of the rat gingiva epithelium ten weeks after opioid administration. 1 - karyorexis, 2 - mitochondria, 3 - bundles of tonofilaments. Electronogram. Approx. 14,000.

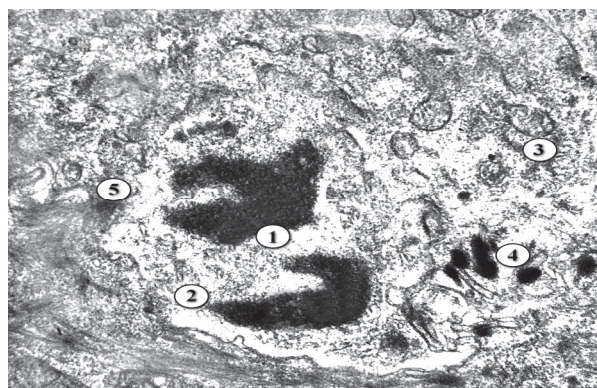


Fig. 2. The epithelium of the attached part of the rat gums after ten weeks with opioid use. 1 - karyorexis, 2 - electron-lucent area of the cytoplasm, 3 - mitochondria, 4 - lysosomes, 5 - lysis of tonofilaments. Electronogram. Approx. 14,000.

In separate epithelium cells of the attached rat gums part, signs of apoptosis, destruction of karyoplasm, karyorexis were revealed, manifested by osmiophilic fragments of the nucleus. In their cytoplasm there were electron-lucent structureless areas, lysosomes. Necrotic processes lead to the destruction of organelles, fragmentation and lysis of tonofilaments (fig. 2).

Submicroscopically, significant changes in its structural components were established in the periodontium. The ultrastructure of fibroblasts was disturbed.

Part of the cells had karyopicosis and karyorexis, deep invasions of karyolema divide the nucleus into fragments. Nuclear membranes were indistinct, perinuclear space was undetermined, karyoplasm was osmiophilic, where heterochromatin predominates. In the cytoplasm, organelles were damaged, vacuole-like structures and lysosomes were observed. Collagen fibers were destructively altered, there was swelling of the intercellular substance (fig. 3).

Electron microscopic studies of the animal gum mucous membrane had established pronounced changes in the vessels of the microcirculatory bed. In the lumen of the blood capillaries, the blood formed elements were visualized; in some areas a sludge-effect was observed. The nuclei of the endothelial cells changed significantly, there were signs of karyopcnosis, due to the deep invaginations of the karyolema, the nuclei had an irregular shape. Heterochromatin occupied a considerable area in their karyoplasm. The endothelial cells cytoplasm had thickened and narrow areas, they lacked organelles and pinocytic vesicles, vacuole-like structures were present. Basal membrane was uneven, fuzzy contoured. In perivascular space, coarse bundles of collagen fibers were observed, indicating the development of sclerotic changes (fig. 4).

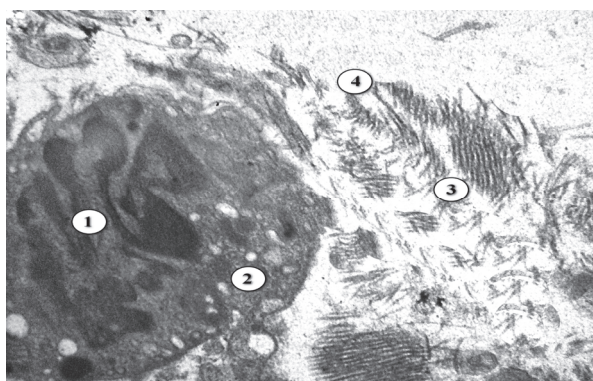


Fig. 3. Rat periodontium ten-weeks after the opioid administration. 1 - the phenomena of karyopcnosis and karyorexis of fibroblast, 2 - vacuolation of the fibroblast cytoplasm, 3 - damaged collagen fibers, 4 - swollen connective tissue. Electronogram. Approx. 12,000.

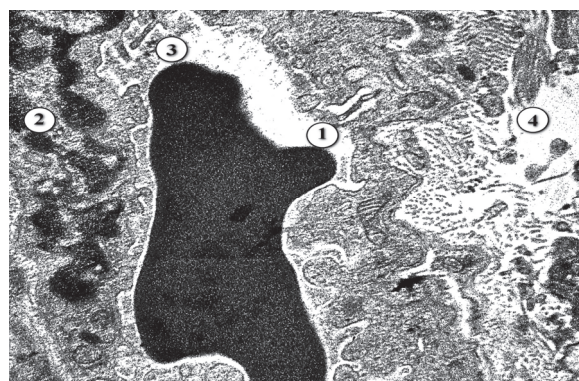


Fig. 4. Rat gums hemocapillary after ten weeks of opioid administration. 1 - lumen with erythrocytes, 2 - karyorexis, 3 - edema of the endotheliocyte cytoplasm, 4 - collagen fibers in the perivascular space. Electronogram. Approx. 12,000.

Ultrastructurally observed significantly expanded, blood-filled lumens of venules, sludge effect was observed. In part of endotheliocytes, nuclei were significantly altered; they had an elongated shape, a wavy karyolema, and an osmiophilic karyoplasm. Destruction of organelles and the cytoplasm edema were noted. Separate areas of the endotheliocytes' adjunctive surface protrude into the lumen of the vessels. Uneven perinuclear space, different sizes vacuoles and electron-dense inclusions were observed in the cytoplasm. The basal membrane was thickened, poorly contoured, perivascular spaces were significantly enlarged.

The obtained data about the ultrastructural reorganization of periodontal tissues under the long-term opioid action permit to compare it to the results of the studies performed in patients with chronic gingivitis and the initial degree of generalized periodontitis. Researchers have found that during the inflammatory process in the periodontium patients developed signs of intracellular reorganization of epitheliocytes, impaired desmosomal contacts, showed intercellular edema [1, 14]. In patients with generalized periodontitis with concomitant arterial hypertension, the authors noted hydropic degeneration of epitheliocytes, foci of cell necrosis and the cytoplasm compaction [6].

In our observations, in addition to these changes, we also noted the reduction of intercellular contacts and the fragmentation or compaction of tonofilaments. In chronic cadmium intoxication, the researchers found pronounced changes in the organelles and nuclear apparatus of epitheliocytes [4]. The above data are compared to the data obtained by us under opioid exposure, where the destruction of organelles, segregation of the nuclei and invagination of the karyolema were observed, which showed irreversible changes in the structure of the nucleus and the cell as a whole.

In patients with gingivitis and periodontitis, the authors noted the obstruction of the microvessels, changes in the of endotheliocyte plasmolemma, the basement membrane integrity disruption [1, 3, 14]. With long-term opioid action, we observed in the endothelial cells thickening of the basement membrane, expansion of perivascular spaces and signs of a sludge effect. Necrotic processes in the endothelium under these conditions led to the destruction of organelles, fragmentation and lysis of tonofilaments, which testified to the signs of hypoxia development.

Conclusion

The ultrastructural study of soft periodontal tissues has established that prolonged opioid action within ten weeks leads to pronounced heterogeneity and reorganization of cellular components against the background of chronic inflammatory process, which is exacerbated by sclerotic changes.

The prospect of further research is to perform an ultrastructural study at later terms of opioid exposure in order to study in depth the dynamics of submicroscopic changes in soft periodontal tissues.

References

1. Hasymov EK, Shadlinskaya RV, Ysrafylova SA. Svetootycheskoe i elektronno-mykroskopicheskoe izuchenie epitelialnogo pokrova svobodnoy chasti desny na razlychnykh stadiyakh khronicheskogo gingivita u patsientov s bolshoy β -talasemiyey. Kazanskiy meditsinskiy zhurnal. 2018; 99 (4): 598–605. [in Russian]
2. Datsiuk NO. Analiz stanu vykorystannya opioidnykh analhetykiv u rehionakh Ukrayiny. Farmatsevtichnyi zhurnal. 2012; 5:16-20. [in Ukrainian]
3. Riznyk YuB. Obruntuvannya korektsii dysfunksii endoteliiu sudyn parodontu v kompleksnomu likuvanni khvorykh na heneralizovanyi parodontyt [dysertatsiya]. Lviv: Lviv. nats. med. un-t imeni Danyla Halytskoho; 2015. 20 s. [in Ukrainian]
4. Tunhushbaeva ZB, Shynybekova ShS. Korrektsiya tagansorbentom morfologicheskikh izmeneniy v ultrastrukturnoy organizatsii desny. Uspekhi sovremennogo yestestvoznaniya. 2014; 3: 200-201. [in Qazaq]
5. Fik VB, Kovalyshyn OA, Paltov YeV, Kryvko YuIa. Ultrastruktura tkany parodonta naprykintsi drugoho tyzhnia eksperymentalnoho opioidnoho vplyvu. World science. 2019; 8(48):49-53. [in Ukrainian]
6. Cherkasova OV. Ultrastruktura yasen u patsientiv z heneralizovanyim parodontytom ta sputnyoyu esentsialnoyu arterialnoyu hipertenziyeyu za umov yikh kompleksnoho likuvannya. Ukrayinskyi morfologichnyi almanakh. 2012; 2 (10):169-174. [in Ukrainian]
7. Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: Evidence and recommendations for everyday practice. Mayo Clin Proc. 2015; 90:828–42.
8. Cury PR, Oliveira MG, de Andrade KM, de Freitas MD, Dos Santos JN. Dental health status in crack/cocaine-addicted men: a cross-sectional study. Environ Sci Pollut Res Int. 2017; 24 (8): 7585-90.
9. Dumitrescu, AL. Editorial: periodontal disease - a public health problem. Front. Public Health. 2015; 3:278.
10. Fan R, Schrott LM, Arnold T, Snelling S, Rao M, Graham D, Cornelius A, Korneeva NL Chronic oxycodone induces axonal degeneration in rat brain. BMC Neurosci. 2018 Mar 23; 19(1):15.
11. Fik VB, Paltov YeV, Kryvko YuYa. Morphofunctional peculiarities of the periodontal tissue under conditions of simulated eight-week opioid effect. Deutscher Wissenschaftscherold German Science Herald. 2018; 1:14-17.
12. Garg RK, Fulton-Kehoe D, Franklin GM. Patterns of opioid use and risk of opioid overdose death among Medicaid patients. Med Care. 2017; 55: 661–668.
13. Janas A, Folwarczna J. Opioid receptor agonist may favorable bone mechanical prosperities in rats with estrogen efficiency induced osteoporosis. Naunyn Schmiedebergs Arch Pharmacol. 2017; 390(2):175–85.
14. Lushnikova EL, Nepomnyashchikh LM, Oskolsky GI, Jurkevich NV. Ultrastructure of gingival epithelium in chronic gingivitis. Bull Exp Biol Med. 2012; 152(5):637-41.
15. Rosier BT, de Jager M, Zaura E, Krom BP. Historical and contemporary hypotheses on the development of oral diseases: are we there yet? Front Cell Infect. Microbiol. 2014; 4:92.

Реферати

**СУБМІКРОСКОПІЧНІ ЗМІНИ
В ТКАНИНАХ ПАРОДОНТА
ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ ДІЇ ОПІОЇДІВ
ПРОТЯГОМ ДЕСЯТИ ТИЖНІВ
Фік В.Б., Пальтов С.В., Кривко Ю.Я.**

В роботі представлено результати ультраструктурного дослідження м'яких тканин пародонту при експериментальному впливі опіоїдного анальгетика протягом десяти тижнів. При дослідженні використано 18 шурів-самців репродуктивного віку. Тваринам вводили опіоїдний анальгетик у зростаючих дозах від 0,212 мг / кг до 0,283 мг / кг. На ультраструктурному рівні було встановлено, що тривалий вплив опіоїдів протягом десяти тижнів призводила до вираженої гетерогенності і реорганізації клітинних компонентів пародонту на тлі розвитку хронічного запального процесу, який поглиблювався склеротичними змінами.

Ключові слова: електронномікроскопічні дослідження, тканини пародонту, опіоїдний анальгетик, шури.

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**СУБМІКРОСКОПІЧЕСКИЕ ИЗМЕНЕНИЯ
В ТКАНЯХ ПАРОДОНТА
ПРИ ЭКСПЕРИМЕНТАЛЬНОМ ВОЗДЕЙСТВИИ
ОПИОИДА В ТЕЧЕНИЕ ДЕСЯТИ НЕДЕЛЬ
Фик В.Б., Пальтов Е.В., Кривко Ю.Я.**

В работе представлены результаты ультраструктурного исследования мягких тканей пародонта при экспериментальном воздействии опиоидного анальгетика в течение десяти недель. При исследовании использовано 18 крыс-самцов репродуктивного возраста. Животным вводили опиоидный анальгетик в возрастающих дозах от 0,212 мг / кг до 0,283 мг / кг. На ультраструктурном уровне установлено, что длительное воздействие опиоида в течение десяти недель предопределяло прогрессирование выраженной гетерогенности и реорганизации клеточных компонентов пародонта на фоне развития хронического воспалительного процесса, который углублялся склеротическими изменениями.

Ключевые слова: электронномікроскопіческие исследования, ткани пародонта, опиоидный анальгетик, крысы.

Рецензент Єрошенко Г.А.

Ye.S. Khilimich, I.I. Starchenko, V.Yu. Davydenko, M.Ya. Nidzelskiy, G.M. Davydenko
Ukrainian Medical Stomatological Academy, Poltava

CONDITION AND STRUCTURAL ORGANIZATION OF THE GLANDULAR AREA MUCOUS MEMBRANE OF ALBINO RAT HARD PALATE UNDER THE 30-DAY-LONG EFFECT OF ACRYLIC MONOMER

e-mail: davydenko.a24@gmail.com

Currently, the problem of the impact of removable laminar denture frames, including residual monomer, on the condition of the minor salivary glands, which play an important role in maintaining the balance in the oral cavity, remains poorly understood. Therefore, the paper was aimed at the experimental study of the effect of the monomer of the base acrylic resin "Ftoraks" on the condition and structural organization of the salivary glands of hard palate of albino rats. The findings of the study show that the monomer disrupts homeostasis of the oral cavity and causes irritation of the mucous membrane, manifested by dystrophy of the epithelial plate on day 30 of the experiment, as well as thickening of the corneal layer due to hypertrophy, which indicates the presence of hyperkeratosis. On day 30 of the experiment, thickening of the entire epithelial layer and the phenomena of hyper- and diskarotosis was detected in the experimental group; the phenomena of plethora, high lymphocyte, neutrophilic and eosinophilic leukocyte count were noted in the lamina propria of the mucous membrane and growing of relative amount of connective tissue can be regarded as the manifestation of a compensatory-adaptive reaction in response to the action of the monomer. 30-day-long experimental studies have shown insignificant effect of the monomer of the base acrylic resin "Ftoraks" on the cumulative size of the salivary glands in the submucous layer of the hard palate. Since the average recommended period of use of full removable laminar dentures is 3-5 years, it was considered necessary to continue the experiment and investigate the effect of the monomer of the base acrylic resin "Ftoraks" on the condition and structural organization of salivary glands of the hard palate of albino rats after 3, 6 and 9 months to further extrapolate the findings of the study to the human body.

Key words: salivary glands, hard palate, mucous membrane, monomer of the acrylic resin.

The work is a fragment of the research project "The effect of dental constructs and material on the prosthetic bed and adaptive abilities of the body", state registration No. 0116U004188.

The main type of masticatory efficiency restoration in edentulous patients is prosthetics with complete removable dentures, which in 90% of cases are made of acrylic resin [3, 7].

The advantages and disadvantages of the above dentures are quite convincingly stated in the publications. Particular attention is paid to the effect of residual monomer of the basic acrylic resins on the condition of the tissues of the oral cavity, prosthetic bed, homeostasis and the body as a whole [3, 4, 5]. The effect of the monomer on the condition of the salivary glands is of particular importance [9, 11]. However, the issue of the impact of removable laminar dentures, including residual monomer, on the condition of minor salivary glands, which play an important role in maintaining balance in the oral cavity, remains poorly understood to date.

The purpose of the work was to perform an experimental study of the effect of the "Ftoraks" base acrylic resin monomer on the condition and structural organization of the salivary glands in albino rat hard palate.

Materials and methods. The total of 12 laboratory Wistar rats, aged 1 to 1.5 years, were involved into the experimental morphological study. The control group involved 5 animals. Lingual mucosa of the rest 7 animals was smeared with 2% aqueous solution of the monomer of the "Ftoraks" base acrylic resin twice a day in the morning and evening to simulate the contact. The animals underwent euthanasia on day 30 of the experiment.

All studies were conducted in compliance with the rules of humane treatment of animals according to the requirements of the Tokyo Declaration of the World Medical Association and the general ethical principles of working with experimental animals, which were approved by the first National Bioethics Congress [8].

After euthanasia, each animal underwent removal of the hard palate, followed by division of the latter into two parts along the midline. One of the obtained fragments of the hard palate, together with the bone base, after fixation for one day in neutral 10% formalin was decalcified for 2-4 weeks, after which it was possible to obtain histological sections from the objects that contained bone tissue [5, 6, 10].

In the second fragment, the mucosa with the submucous layer was separated from the bone tissue using the lid scalpel under the control of a binocular magnifier. Soft tissue fragments were fixed in an upright state in 10% neutral formalin for 1-2 days.

The obtained samples, after conventional dehydration were embedded into liquid paraffin using the "Microm" station for paraffin blocks embedding. Sections of 5 µm thick were obtained from the paraffin blocks on the "Leica" rotary microtome and stained with haematoxylin-eosin by conventional methods [5, 6, 10].

Visualization and imaging of the microspecimens was made by Olympus BX-41 microscope equipped with digital microphoto attachment and licensed software package [1].

Results of the study and their discussion. Marked changes of the outer (covering) layer of the epithelium of the mucous membrane of the glandular area of the hard palate of laboratory animals, caused by the effect of the acrylic monomer were observed for 30 days. First of all, a significant increase in the thickness of the latter, compared to the control group, was noteworthy. At the same time, no significant changes in the thickness of the basal layer were observed; the cells of the latter, similar to control group, were arranged mainly in single layer.

Notably, an increase in the number of sites with 2-3 layers of basal epitheliocytes, which indicated increased proliferative activity of the latter, was noted (fig. 1).

This fact is confirmed by the morphometric studies that showed significant increase of the mitotic index in the basal layer, compared to the control group.

In the spinous layer of the covering epithelium insignificant increase in the number of cellular layers up to 8-10 at some sites was noted. Some observations showed indistinct boundaries between cellular layers, demonstrating a certain polymorphism among the epithelial cells of this layer. In the spinous layer of the epithelium of the mucous membrane we noted the formation of keratin cysts. These structures were orbicular, almost homogeneous eosinophilic formations, which, by their tinctorial properties, resembled the squamae of the corneal layer, which on the periphery were surrounded by the granular epitheliocytes arranged in 3-4 layers, characterized by the presence of fine grains of keratohyalinum in the cytoplasm (fig. 2).

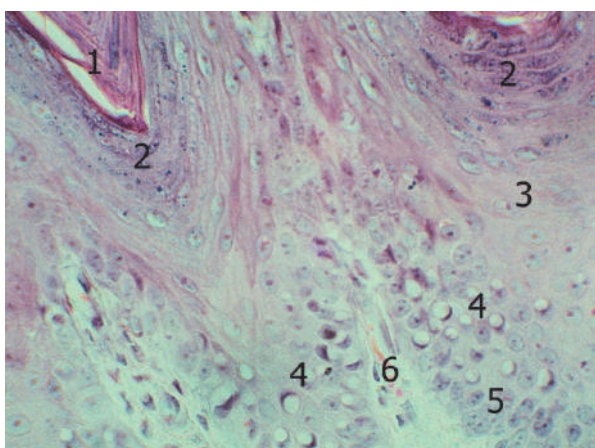


Fig. 1. Mucous membrane of the glandular area of the hard palate (experimental Group I). H&E stain. Lens: 40×magnification, ocular lens: 10×magnification. 1 – corneal layer; 2 – glandular layer; 3 – spinous layer; 4 – epitheliocytes with the phenomena of hydropic dystrophy in the spinous layer; 5 – epitheliocytes of the basal layer; 6 – plethoric vessels of the papillary layer of the lamina propria of the mucous membrane.

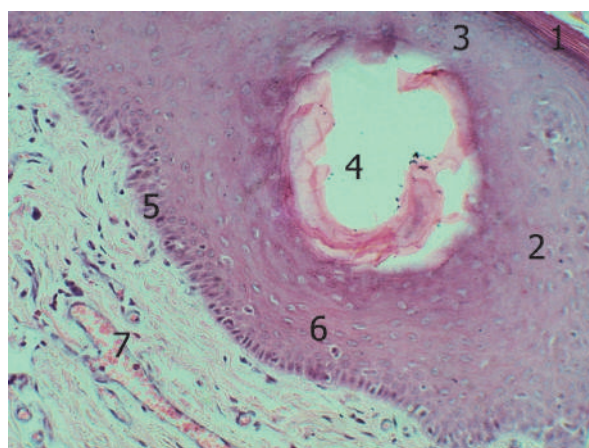


Fig. 2. Mucous membrane of the glandular area of the hard palate (experimental Group I). H&E stain. Lens: 10×magnification, ocular lens: 10×magnification. 1 – corneal layer; 2 – glandular layer; 3 – spinous layer; 4 – cavity of the keratin cyst; 5 – epitheliocytes of the basal layer; 6 – intraepithelial leukocytes; 7 – plethora of vessels of lamina propria of the mucous membrane.

The presence of keratin cysts can be regarded as manifestation of the pathological process, namely, corneal dystrophy (dyskeratosis), associated primarily with impaired differentiation of epitheliocytes and the formation of keratohyalinum.

In the basal and spinous layers, the number of intraepithelial lymphocytes markedly increased, compared to the control group, indirectly indicating the presence of inflammatory process in the underlying connective tissue. Moreover, a significant increase in the number of epitheliocytes with the phenomena of hydropic dystrophy, mainly in the lower parabasal layers of spinous cells was noted (fig. 1, 2).

However, no significant changes in the granular layer, compared to the control group, were found. Notably, insignificant increase in the number of cellular layers was noted in some areas, as well as more pronounced numerous grains of keratohyalinum, which were found in the cytoplasm of the epitheliocytes of the granular layer.

In all observations, a significant thickening of the corneal layer of the epithelium was detected. Significant hypertrophy of the corneal layer indicated the activation of the process of keratohyalinum formation, namely, hyperkeratosis (fig. 1). The latter, in this case, in conjunction with thickening of the entire epithelial layer, can be regarded as the manifestation of compensatory-adaptive (protective) reaction in response to prolonged exposure to monomer that is an external pathogen, resulting in the formation of so-called “corneal shield” along with penetration of the pathogenic chemical agent into the lamina propria of the mucous membrane.

In the granular layer sporadic small areas were detected, in which, along with horny scales (dead keratinocytes conjoined by interdigitations of their cytolemma), a large number of squamous cell with rod-shaped pyknotic nuclei were found.

Noteworthy, in such cases thinning of the granular layer of epitheliocytes, arranged in 2-3 layers, was also noted. In the publications this phenomenon has been called “parakeratosis”, known as the specific type of keratinization. It is believed that the presence of such process in the epithelium of the hard palate,

in contrast to the skin epidermis, is a physiological process. In our studies, the phenomena of parakeratosis were noted more common in the mucous membrane of the hard palate of animals of the control group.

The latter circumstance may indirectly indicate stimulation of keratinization (orthokeratosis), caused by the modeled effect of the monomer, which can also be regarded as the formation of one of the links of the host defense of the mucous membrane to the effect of adverse exogenous agent.

Significant changes were detected in the lamina propria of the mucous membrane, too. Thus, in the papillary layer, a pronounced plethora of vessels, edema was noted overall; in the perivascular spaces a marked increase in lymphocytes and plasma cells was detected (fig. 1). Quite often mast cells were found at the blood vessels, in many of which the phenomena of degranulation were observed. Sporadic large areas of cellular infiltrates were found, which spread beyond the papillary layer into the depth of the lamina propria of the mucous membrane, and were represented mainly by eosinophilic leukocytes (fig. 3). This cellular composition of inflammatory infiltrates indicates the presence of an allergic component in the inflammatory process.

In addition to the areas of eosinophilic infiltrate, in the reticular layer of the lamina propria of the mucous membrane a marked plethora of small vessels, edema events were noted overall, which more were pronounced in the perivascular spaces.

In the reticular layer much more number of cellular elements of hematogenous origin, compared to the control group, were found, among which the most common were cells of monocytic-macrophage series, lymphocytes, plasma cells. Neutrophilic and eosinophilic leukocytes were sporadic. At the same time, no significant difference in the number of cellular elements of the fibroblastic series in the reticular layer, compared to the controls, was found.

Generally, no significant differences in the salivary glands were detected compared to controls. However, a more detailed study of their structural organization and morphometric studies revealed some changes that relate primarily to the stromal component.

Thus, in the stroma of the palatine salivary glands a pronounced plethora of the microvessels, the events of edema were detected. Significant increase in the number of cellular elements of hematogenous origin, which were located both diffusely and in aggregations mainly at the blood microvessels, was noted (fig. 4).

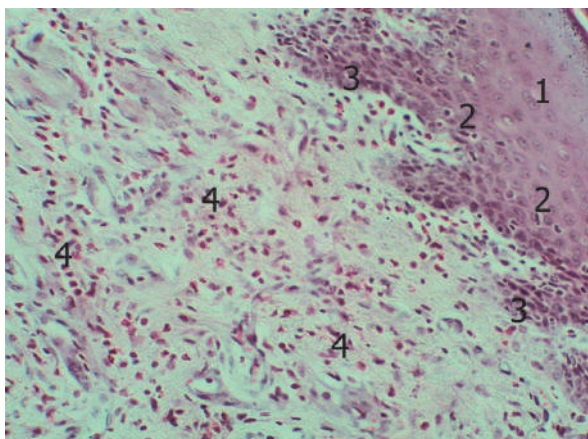


Fig.3. Mucous membrane of the glandular area of the hard palate (experimental Group I). H&E stain. Lens: 10×magnification, ocular lens: 10×magnification. 1 – spinous layer of the covering epithelium; 2 – intraepithelial leukocytes in the spinous layer; 3 – cells of the basal layer of the covering epithelium; 4 – eosinophilic infiltration in the lamina propria of the mucous membrane.

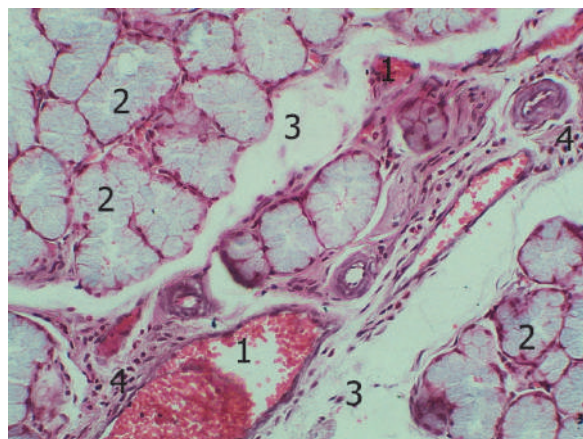


Fig. 4. Palatine salivary gland (experimental Group I) H&E stain. Lens: 10×magnification, ocular lens: 10×magnification. 1 – blood vessels with the events of plethora; 2 – secretory parts; 3 – areas with the events of edema; 4 – inflammatory infiltration in the connective tissue stroma.

Similar to the connective tissue of the lamina propria of the mucous membrane, phagocytes of various degrees of maturity, lymphocytes, plasma cells dominated in the cellular infiltrates. Sporadic neutrophilic and eosinophilic leukocytes were detected. Quite often in the connective tissue, stroma changes that indicated the presence of edema were noted.

However, no significant changes were noted in the acini of the salivary glands, only in isolated observations there was a slight deformation of secretory epitheliocytes and some change in their tinctorial properties. The findings of the morphometric study have shown that inside each minor palatine salivary gland, the relative amount of connective tissue increased slightly and the relative volume of the secretory parenchyma decreased accordingly, compared to the control group.

Notably, publications report that scientists are still debating the negative (toxic and allergic) effect of the basic acrylic monomer on the mucous membrane of the hard palate and minorsalivary glands in particular. The resulting data indicate that the monomer affects the homeostasis of the oral cavity and causes irritation of the mucous membrane, which on day 30 has signs of epithelial plate dystrophy, characterized by the thickening of the corneal layer due to hypertrophy, indicating hyperkeratosis. The data

are confirmed by the findings of other researchers who found that contact of the mucous membrane of the hard palate with 1% methacrylate causes irritation and disorder of the process of epithelial differentiation in the form of increased keratinization with the signs of dystrophy [12, 13].

The findings of the study revealed thickening of the entire epithelial layer, the events of hyper- and dyskeratosis on day 30 in the experimental group, as well as the events of plethora, high lymphocytes, neutrophils and eosinophils count in the lamina propria of the mucous membrane and increased amount of connective tissue, which can be regarded as a manifestation of the compensatory-adaptive response to the action of the monomer. This is fully consistent with the authors [13, 14], who proved that the structural support of the host defence of the glandular mucosa of the hard palate in the epithelial plate is represented by the intraepithelial lymphocytes and antigen-presenting Langerhans cells, and methacrylate causes changes in the number and ratio of immunocompetent cells.

Conclusion

The 30-day long experimental studies showed that the effect of the monomer of the base acrylic resin "Ftoraks" causes the events of dystrophy, hyper- and dyskeratosis in the mucous membrane of the hard palate, and the increase in the intraepithelial lymphocytes and the presence of cellular infiltrates in connective tissue indicate inflammatory process in the connective tissue. However, in the submucous layer of the hard palate, no significant difference in the cumulative size of the salivary glands, compared to similar value in the intact group, was found.

Prospects of further research are as follows. Since the average recommended period of use of full removable laminar dentures is 3-5 years, it was considered necessary to continue the experiment and investigate the effect of the monomer of the base acrylic resin "Ftoraks" on the condition and structural organization of salivary glands of the hard palate of albino rats after 3, 6 and 9 months to further extrapolate the findings of the study to the human body.

References

1. Avtandilov GG. Osnovy kolichestvennoy patologicheskoy anatomii. M.: Meditsina; 2002. 239 s. [in Russian]
2. Bagriy MM, Dibrova VA, Popadinetz OG, Grishchuk MI. Metodyky morfolohichnykh doslidzhen. Vinnytsia: New Book; 2016. 328 s. [in Ukrainian]
3. Bocharov VS, Moskvina YuN, Kim AR. Vliyaniye bazisnykh materialov syemnykh protezov na parametry immunnogo gomeostaza slizistoy obolochki rta. Tikhookeanskiy meditsinskiy zhurnal. 2014; 3:62-64. [in Russian]
4. Bykov IM, Akopova LV, Skorikova LA. Biokhimicheskiye pokazateli gomeostaza i biotsenoza polosti rta u patsiyentov s protezным stomatitom. Mezhdunarodnyy zhurnal prikladnykh i fundamentalnykh issledovaniy. 2015; 3: 217-223. [in Russian]
5. Yeroshenko GA, Tymoshenko YU, Kramarenko DR, Semenova AK, Gerasimenko SB. Vykorystannya metylovoho efiru metakrylovoi kysloty v suchasniy stomatolohiyi. Svit medytsyny ta biolohiyi. 2017; 2(60):179-183. [in Ukrainian]
6. Korzhovsky DE, Gilyarov AB. Osnovy gistologicheskoy tekhniki. SPb: Special Lite; 2010. 95 s. [in Russian]
7. Nidzelsky MYa, Davydenko VY, Davydenko GM, Kuznetsov VV, Sokolovskaya VM. Porivnyalna kharakterystyka rivnyia zalyshkovoho monomeru v bazysakh znimnykh proteziv iz akrylovykh plastmas, vyhotovleny za riznymi tekhnolohiyamy polimeryzatsiyi. Visnyk problem biolohiyi i medytsyny. 2014; 2(108):45-48. [in Ukrainian]
8. Obshchkiye eticheskyye printsipy raboty s eksperimental'nymi zhivotnyimi pri provedenii meditsinskikh biologicheskikh issledovaniy: Natsionalnyy konhress z bioetyky, Kyiv, September 17-20, 2001; G. AMS of Ukraine. 2001; 7(4): 814-816. [in Ukrainian]
9. Romanova YuG, Kilimenchuk OO. Vplyv povnykh znimnykh zubnykh proteziv na funktsionalnu aktyvnist slynykh zaloz u patsiyentiv z hiposalivatsiyeyu. Novyny stomatolohiyi. 2008; 2:68-70. [in Ukrainian]
10. Sarkisov DS, Perov YuL. Mikroskopicheskaya tekhnika: rukovodstvo dlya vrachey i laborantov. Moskva: Meditsina; 1996. 554 s. [in Russian]
11. Stepanenko RS, Afanasyev VV, Polyakova MA. Rol slyunnykh zhelez v gomeostaze organizma. Rossiyskiy stomatologicheskyy zhurnal. 2010; 5:26 - 27. [in Russian]
12. Stechenko LO, Senchakovich SE, Ivleva SE. Reaktsiya potokovoyi systemy pidnebinnykh zaloz shchuriv na vvedennya metakrylatu. Svit medytsyny ta biolohiyi. 2015; 3(52):127-130. [in Ukrainian]
13. Tymoshenko YV. Morfofunktsionalni osoblyvosti slyzovoyi obolonky tverdogo pidnebinnya za umov eksperymentalnoy kserostomiyi [dysertatsiya]. Dnipro, Dnipropetrovska Medychna Academiya MOZ Ukrayiny; 2018. 20 s. [in Ukrainian]
14. Yeroshenko GA, Senchakovich YuV, Yeroshenko AI. Methacrylate-induced changes in metric parameters of rat palatine glands. European International Journal of Science and Technology. 2015. Vol. 4, No. 3:132-135.

Реферати

**СТАН ТА СТРУКТУРНА ОРГАНІЗАЦІЯ
ЗАЛОСИТОЇ ЗОНИ ТВЕРДОГО
ПІДНЕБІННЯ БІЛИХ ЩУРІВ ПІД ВПЛИВОМ
МОНОМЕРУ АКРИЛОВОЇ ПЛАСТМАСИ
ВПРОДОВЖ 30 ДІБ**
Хілінич Є.С., Старченко І.І., Давиденко В.Ю.,
Нідзельський М.Я., Давиденко Г.М.

На сьогодні залишається маловивченою проблема впливу базисів знімних пластинкових протезів, в тому числі і залишкового мономера, на стан малих слинних залоз, які відіграють важливу роль у підтримці балансу в ротовій порожнині. Тому в даній роботі метою стало

**СОСТОЯНИЕ И СТРУКТУРНАЯ ОРГАНИЗАЦИЯ
ЖЕЛЕЗИСТОЙ ЗОНЫ ТВЕРДОГО НЕБА
БЕЛЫХ КРЫС ПОД ВЛИЯНИЕМ МОНОМЕРА
АКРИЛОВОЙ ПЛАСТМАССЫ
В ТЕЧЕНИИ 30 СУТОК**
Хилинич Е.С., Старченко И.И., Давыденко В.Ю.,
Нидзельский М.Я., Давыденко А.Н.

На сегодня остается мало изученной проблема влияния базисов съёмных пластиночных протезов, в том числе и остаточного мономера, на состояние малых слюнных желез, которые играют важную роль в поддержании баланса в ротовой полости. Поэтому целью данной работы было

вивчення в експерименті впливу мономера базисної акрилової пластмаси «Фторакс» на стан та структурну організацію слинних залоз твердого піднебіння білих шурів. Одержані нами в експерименті дані вказують, що мономер порушує гомеостаз порожнини рота та викликає подразнення слизової оболонки, яке на 30-ту добу має ознаки дистрофії епітеліальної пластинки, характеризується збільшенням товщини рогового шару за рахунок гіпертрофії, що свідчить про наявність гіперкератозу. Нами встановлено, що в експериментальній групі на 30-ту добу спостерігається збільшення товщини всього епітеліального пласта, явища гіпер- і дискератозу; у власній пластинці слизової оболонки – явища повнокрів'я, збільшення лімфоцитів, нейтрофілних та еозинофілних лейкоцитів, зростає відносна кількість сполучної тканини, що можна розцінити як прояв компенсаторно-приспосовної реакції у відповідь на дію мономера. Експериментальними дослідженнями впродовж 30 діб встановлено, що внаслідок дії мономера базисної акрилової пластмаси «Фторакс» в підслизовій основі твердого піднебіння сумарний об'єм слинних залоз істотно не відрізняється від аналогічного показника в інтактній групі. Оскільки середній рекомендований термін користування повними знімними пластинковими протезами становить 3-5 років, тому вважали за необхідне продовжити експеримент і дослідити вплив мономера базисної акрилової пластмаси «Фторакс» на стан та структурну організацію слинних залоз твердого піднебіння білих шурів через 3, 6 та 9 місяців, що дасть змогу в подальшому екстраполувати отримані результати на організм людини.

Ключові слова: слинні залози, тверде піднебіння, слизова оболонка, мономер акрилової пластмаси.

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изучить в эксперименте влияние мономера базисной акриловой пластмассы «Фторакс» на состояние и структурную организацию слюнных желез твердого неба белых крыс. Полученные нами в эксперименте данные указывают, что мономер нарушает гомеостаз полости рта и вызывает раздражение слизистой оболочки, которое на 30-е сутки имеет признаки дистрофии эпителиальной пластинки, характеризуется увеличением толщины рогового слоя за счет гипертрофии, что свидетельствует о наличии гиперкератоза. Нами установлено, что в экспериментальной группе на 30-е сутки наблюдается увеличение толщины всего эпителиального пласта, явления гипер- и дискератоза; в собственной пластинке слизистой оболочки – явления полнокровия, увеличение лимфоцитов, нейтрофильных и эозинофильных лейкоцитов, растет относительное количество соединительной ткани, что можно расценить как проявление компенсаторно-приспособительной реакции в ответ на действие мономера. Экспериментальными исследованиями в течении 30 суток встановлено, что всесторонне действие мономера базисной акрилової пластмаси «Фторакс» в подслизистой основе твердого неба суммарный объем слюнных желез существенно не отличается от такого же показателя в интактной группе. Поскольку средний рекомендуемый срок пользования полными съёмными пластинчатыми протезами составляет 3-5 лет, мы считали важным продолжить эксперимент и исследовать влияние мономера базисной акрилової пластмаси «Фторакс» на состояние и структурную организацию слюнных желез твердого неба белых крыс через 3, 6 та 9 месяцев, что позволит в дальнейшем экстраполировать полученные результаты на организм человека.

Ключевые слова: слюнные железы, твердое небо, слизистая оболочка, мономер акрилової пластмассы.

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O.V. Tsyhykalo, I.Yu. Oliinyk, L.A. Andrushchak, I.V. Halysh, D.B. Stolyar
HSEE «Bukovinian State Medical University», Chernivtsi

MORPHOGENESIS FEATURES OF THE URETEROPELVIC JUNCTION IN HUMAN FETUSES AND NEWBORNS

e-mail: tsyhykalo@icloud.com

The purpose of the study was to find out the features of the ureteropelvic junction structure in the fetal period of ontogeny and in newborns, and to determine the critical periods of its morphogenesis. The study was performed on 67 human fetal specimens with 160.0-500.0 mm of parietococcygeal length (PCL) (4th-10th months of prenatal development). A set of morphological study methods was applied, which included anthropometry, morphometry, injection of vessels with their subsequent radiography and preparation, microscopy, graphic and three-dimensional computer reconstruction, statistical analysis. It is established that the size of the ureteropelvic junction in the early period of ontogeny increases asynchronously: during the 4th month its length increases, during the 7th month and in newborns its diameter grows. From the 4th month of intrauterine development up to the newborn period the ureteropelvic junction's diameter increases from 0.95 ± 0.25 mm to 2.2 ± 0.25 mm. At the beginning of the fetal period (4-5 months), the ureteropelvic junctions are determined at the level of the intervertebral interval between II and III lumbar vertebrae. During the second half of the fetal period, its asymmetrical shift occurs: to the left - to level II, and to the right - to level III of the lumbar vertebrae. In the perinatal period of ontogenesis, close anatomical correlations of the ureteropelvic junction with the renal vessels are determined - its anterior surface is crossed by 2-4 branches of the renal artery and 2-3 branches of the renal vein.

Key words: ureteropelvic junction, anatomy, fetus, newborn.

The study is a fragment of the research project "Morphogenesis regularities and structural-functional features of tissues and organs in human ontogenesis", state registration No. 0116U002938.

The incidence of congenital pathology of the urinary system increases annually, which is also explained by the improvement of antenatal diagnosis [3]. In the structure of urological care, special attention is paid to the ureteropelvic segment (UPS) [15]. Pathological changes of the UPS lead to urodynamic disorders, dilatation of the pelvicalyceal system of kidney (PCSK) with the subsequent development of pyelectasia, hydronephrosis, pyelonephritis, nephrolithiasis, vasorenal hypertension. The degree of disturbance of the anatomic permeability of the UPS is determined by changes in the volume and

time characteristics of filling and emptying the renal pelvis [12]. Development of microsurgical technologies in the extrarenal urinary tract and methods of early medical diagnostic imaging requires a detailed analysis of UPS anatomy. Therefore, a comprehensive study of the structural features of UPS in dynamics of prenatal human development is the relevant and timely direction of morphological investigation of age-specific, variant and constitutional anatomy of the upper urinary tract.

The purpose of the study was to find out the structural features of the UPS in the fetal period of ontogenesis and in human newborns, to identify the critical periods of its morphogenesis.

Materials and methods. The study was performed on 67 preparations of human fetuses 160,0-500,0 mm of parietal-coccygeal length (4-10th month of prenatal development). A complex of methods of morphological investigation has been used, which included anthropometry, morphometry, vascular injection followed by radiography and preparation, microscopy, graphics and three-dimensional computer reconstructions, statistical analysis.

The study was conducted following the main bioethics regularities of the European Convention on Human Rights and Biomedicine (04.04.1997), the Declaration of Helsinki developed by the World Medical Association as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data (1964-2008), and the Order of the Ministry of Health of Ukraine № 690 dated 23.09.2009, № 616 dated 03.08.2012 and according to guidelines "The order of removal of biological objects from the dead, the bodies of which are subject to forensic examination and pathoanatomical research, for scientific purposes" [1].

Morphometric data were statistically processed using nonparametric methods of evaluation of the results obtained [8], and by means of the licensed version of "StatPlus 2005 Professional 3.5.3" program (AnalystSoft, Ukraine). The distribution of signs by every obtained variation series, mean values on every sign, standard deviations was assessed. Reliability of differences between independent values was determined by means of Mann-Whitney U-criterion.

Results of the study and their discussion. It is established that at the beginning of the fetal period (4th month of intrauterine development), ureteropelvic junction is a curved segment of the proximal part of the ureter at the border with the funnel-shaped narrowing of the renal pelvis (fig. 1).

Bypassing and repeating the relief of the medial margin of the kidney, the UPS forms a minor medially directed arch. It turns downwards and slightly ventrally at an angle of 80° (to the right) and 85° (to the left).

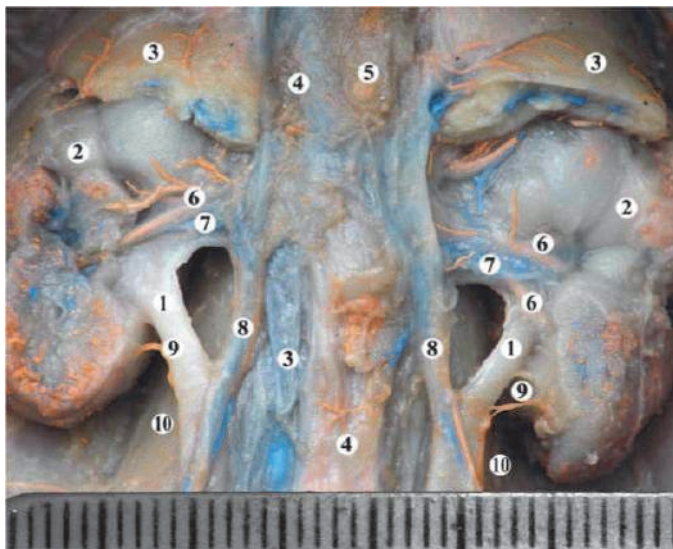


Fig. 1. Organs of the retroperitoneal space of the male fetus 235.0 mm of PCL. The arteries are filled with a mixture of red lead, veins - barium and blue ink. Macrospecimen. Magn. x3: 1 - ureteropelvic segment; 2 - kidney; 3 - adrenal glands; 4 - inferior vena cava; 5 - aorta; 6 - renal arteries; 7 - renal veins; 8 - testicular vessels; 9 - arterial branch to the ureter from the capsular artery; 10 - psoas major muscles.

Features of UPS holotomy are determined by the peculiarities of the structure and topography of the kidneys – its location, variants of the structure of its hilus, renal vessels, etc., so any anatomical variability of the kidneys and vessels of the retroperitoneal space (abnormal renal vessels, nephroptosis) will certainly affect the topography of UPS and can cause birth defects and violations outflow of urine.

The close anatomical relations of the UPS with the abdominal organs are one of the factors that determine its shape. UPS are slightly flattened in the anterior-posterior direction. At an early fetal period, its shape is round, and at the end of the prenatal period of intrauterine development, it becomes oval. The UPS and the abdominal portion of the ureter are located on the psoas major muscles, intersecting them craniocaudally and laterally. The UPS forms an arch

convex to the medial side. The right UPS locates immediate laterally to the inferior vena cava, the left UPS is adjacent to the aorta. Ventral to the UPS at the level of their exit from the medial edge of the kidneys pass the testicular (ovarian) vessels.

Ventral to the intestinal peritoneum, which lays the posterior wall of the abdominal cavity, the loops of the intestine are located. The caecum with the appendix is lateral to the right UPS (at the level of the lower end of the right kidney), the descending colon is lateral to the left UPS and ureter (to the level of

its intersection with the iliac vessels). Due to the fact that the ascending colon is located on the anterior surface of the right kidney and the descending one on the lateral edge of the left kidney, the first one is closer to the right UPS than the second one to the left one. The sigmoid colon crosses the left ureter above or below the point of intersection with the iliac vessels and then rises superiorly medially of it to the lower end of the left kidney. Then it turns down and, continuing into the rectum, passes between the ureter. Loops of the small intestine lie along the ureters, more ventral to them.

In the fetal period of human development, the upper end of the right kidney is located at the level of the 12th thoracic – 1st lumbar vertebrae, the upper end of the left kidney corresponds to the level of the 12th thoracic vertebra. The lower end of both kidneys is determined at the level of 3rd or 4th lumbar vertebrae. The left kidney is above the right one on the height of one vertebra or half of it.

The peculiarities of the temporal dynamics of the morphometric parameters of the kidneys are interrelated with changes in the spatial structure of the renal hilus and, consequently, of the renal vessel's syntopy with the renal pelvis and UPS. We found two variants of the renal hilus shape. Their ratio during the fetal period of intrauterine development is variable - until the 6th month the open form of the kidney hilus is dominated (they are shallow, open, the kidney vessels are evenly distributed in them).

At the end of the 7th – beginning the 8th months (fig. 2), most specimens (67%) determine the compact shape of the kidney hilus (the kidney vessels on all sides are covered by kidney lobes and concentrated in their center). It is probable that close syntopy of the renal pelvis and UPS with the renal vessels in case of the compact form of the renal hilus may be an anatomical precondition for the violation of urodynamics under the conditions of renal vascular branching or the existence of an abnormal vessel in the area of the renal hilus. There is a possibility of compression of the UPS with an additional lower renal artery, which can pass to the kidney among the components of its pedicle. Such cases may be a morphological reason for hydronephrosis, megalocalyx, pyelectasis, vasorenal hypertension, pyelonephritis, nephrolithiasis, or bed sore of the anterior wall of the UPS and renal pelvis.

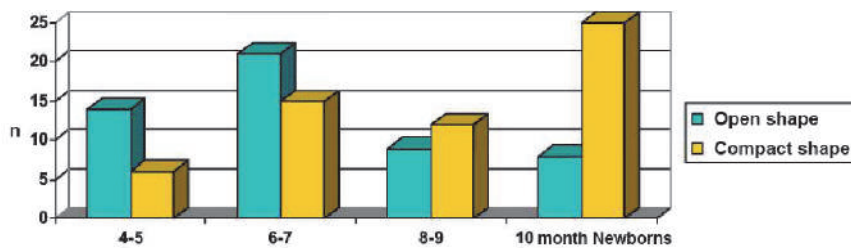


Fig. 2. The ratio of the shape of the kidney hilus in the fetus and newborn.

and are placed on the medial surface of the kidney. Such topographic-anatomical changes give the UPS a slight ventral bend and, in our opinion, are more favorable in view of the functioning of the UPS and PCSK, since they significantly reduce the probability of vasorenal conflicts and their adverse effects on the passage of urine at the level of the proximal cystoid.

The length of UPS increases intensely during the 4th and 6th months and at the end of the prenatal period of intrauterine development. The rates slow down during the 5th and 7-9th months (fig. 3). However, accelerated growth of UPS diameter is observed at 6-7th months of development and in newborns, and deceleration of this measure - at 4th and 8-9th months. Starting from the 4th month of intrauterine development to the period of the newborn period the diameter of the UPS increases from 0.95 ± 0.25 mm to 2.2 ± 0.25 mm.

Thus, the length and diameter of the UPS increase irregularly, which can be explained by the dynamic of intensive processes of its formation at the beginning of the fetal period of ontogenesis, at the

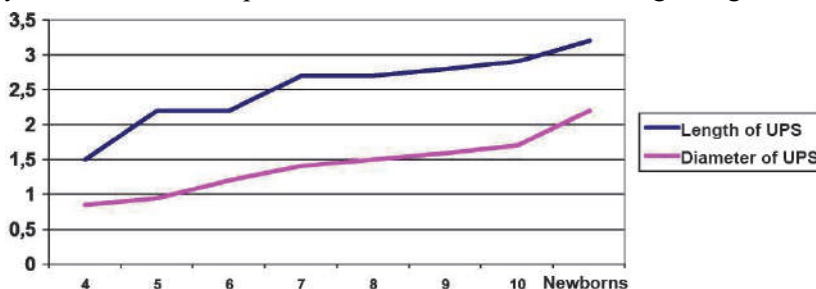


Fig. 3. Dynamics of size (mm) of the UPS in fetuses and newborns.

end of the 6th - at the beginning of the 7th month of intrauterine development, and in newborns. It is worth emphasizing that that in newborns, in contrast to the indicated critical periods in the fetuses, the UPS diameter predominantly increases.

In the specimens of fetuses and newborns, UPS is slightly

compressed in the anteroposterior direction, which makes the shape of their cross-section nearer to the oval.

The study of UPS skeletopy shows that at the beginning of the fetal period of human development (4-5th months) the right and left UPS are located almost at the same level relative to the spine - approximately at the level of the interval between the 2nd and 3rd lumbar vertebrae, but starting from the 6th month, the UPS on the left "rise" to the level of the middle third of the 2nd lumbar vertebra, and the right, on the contrary, "lower" to the middle third of the 3rd lumbar vertebra. Such skeletopy generally remains until the birth.

Syntopy of UPS with renal vessels from right and left is almost the same, during the prenatal ontogenesis does not change significantly. Ventral to the UPS in the posterior direction, the renal artery is divided into 2-4 branches, and then the renal vein is represented by 2-3 vessels. The renal vein is located anterior to the UPS and below the branches of the renal artery. The relative location of the elements of the kidney pedicle outside the kidney hilus is as follows: above is the renal artery, in front of it and slightly below - the vein and behind - the renal pelvis and UPS. There is no such pattern in the kidney hilus: venous vessels after leaving it parenchyma surrounds the corresponding artery on all sides. The vessels pass both in front and behind the renal pelvis, covering it. Identified variants of renal vascular topography and anomalous location of them relative to UPS can lead to congenital renal pathology.

In contrast to the traditional methods of presenting the results of anatomical research, we studied the morphogenesis of UPS comprehensively during the fetal period of human ontogenesis. Such approach takes a possibility to trace in time dynamics how changes in the structure, shape, and size of the UPS affects the syntopy of adjacent organs and structures.

During the fetal period of human ontogenesis, processes of formation of the topography of the urinary system occur. Changes in topography, in particular, skeletal topography and syntopy of UPS with adjacent structures, are treated in much identically by researchers of this issue [7, 13], except for the description of variants and congenital anomalies. We almost always observed an intra-renal type of UPS structure that matches the data of [6], which is surrounded in kidney hilus with cellular tissue, which connects with the renal and continues distally into the periureteral tissue. In our opinion, these cellular spaces play a significant protective and supportive function for upper urinary tract.

Changes in skeletopy of the proximal part of the UPS during intrauterine development result in the establishment of neonatal placement of the right UPS at the level of the upper edge of the I lumbar vertebra, at an angle of 60° to the renal pelvis, the left – at the level of the XII thoracic vertebra at an angle of 40°. These data are broadly consistent with information on the topography of the UPS in fetuses and newborns [4, 9].

Syntopy of UPS with renal vessels in fetuses and newborns is a topical issue of anatomical research focused on the needs of modern surgical technologies [10, 12]. Ventral to the UPS, in the posterior direction, is the renal artery divided into 2-4 branches, and then the renal vein is represented by 2-3 branches. This data does not generally contradict information reported by other researchers [14]. Among the variants of the structure of the UPS, features of their blood supply and the relationship with the renal vessels, we observed in 2 cases an additional right renal artery. Mazengeny P. [11] cites such observations in his work.

The results obtained are not only theoretical but also of practical importance, because knowledge of the patterns of changes in the anatomy of the UPS allows to obtain data about the time and causes of congenital abnormalities [2, 5, 7, 10], which will greatly help in the diagnosis of birth defects and in the development of new methods of their surgical treatment.

Conclusions

1. The sizes of the ureteropelvic segment in the fetal period of ontogenesis increase asynchronously: during the 4th month its length increases more intensively, during the 7th month and in the newborns - the diameter.

2. At the beginning of the fetal period (4-5 months), the ureteropelvic segment are determined at the level of the intervertebral disc between the II and III lumbar vertebrae. During the second half of the fetal period, its asymmetric displacement occurs: to the left of the level II, and to the right to the level III of the lumbar vertebrae.

3. In the perinatal period of ontogenesis, close anatomical relationship between the ureteropelvic segment and the renal vessels is determined - 2-4 branches of the renal artery and 2-3 branches of the renal vein are crossed by its anterior surface.

References

1. Mishalov VD, Voichenko VV, Malysheva TA, Dibrova VA, Kuzyk PV, Yurchenko VT. Poriadok vyluchennia biolohichnykh ob'ektiv vid pomerlykh, tila yakykh pidliahaiut sudovo-medychniy ekspertyzi i patolofoanatomichnomu doslidzhenniu, dlia

- naukovykh tsilei: metodychni rekomendatsii. Osvita Ukrainy: spetsvyпуск hazety. Kyiv: Pedahohichna presa. 2018; 2(62):3–13. [in Ukrainian]
2. Obukhov NS, Voronina EA, Danilyuk SA. Prenatalnaya diagnostika i postnatalnaya verifikatsiya obstruktyvnykh uropatiy u detey pervogo goda zhizni. Vestnik Uralskoy meditsinskoy akademicheskoy nauki. 2016; (2): 24-9. [in Russian]
 3. Pidmurniak OO. Efektyvnist riznykh instrumentalnykh doslidzhen dlia diahnozyky ta prohnozu perebihu urazhen nyrok. Bukovynskiy medychniy visnyk. 2015; 19(2):152-6. [in Ukrainian]
 4. Protsak TV, Byndyu MD. Anomaliyi rozvytku nyrok. Pivdenoukrayinskyy medychnyy naukovyy zhurnal. 2017; 16(16): 77-9. [in Ukrainian]
 5. Spakhi OV, Kokorkin OD, Pakholchuk OP. Analiz osnovnykh chynnykiv ryzyku rozvytku vrodzhenykh vad sechovoyi systemy u ditey. Neonatolohiya, khirurhiya ta perynatalna medytsyna. 2016; 6(1): 38-41. [in Ukrainian]
 6. Stabredov AV. Izmeneniye parametrov stenki pochechnoy lokhanki i plodov y novorozhdennykh cheloveka. Astrakhanskiy meditsinskiy zhurnal. 2011; 6(2): 264-5. [in Russian]
 7. Berendt AM, Wójtowicz-Marzec M. Prenatal diagnosis of urinary track defects. Journal of Education, Health and Sport. 2019; 9(6):275-88.
 8. Indrayan A, Malhotra RK. Medical biostatistics. Chapman and Hall/CRC. 2017. 1032 p.
 8. Johnson KE. Anatomy and embryology of the urinary tract. Clinical Pediatric Nephrology. 2016. 19-32.
 9. Maffi M, Lima M. Congenital Ureteropelvic Junction Obstruction. Neonatal Surgery. Springer; 2019. 515-25.
 10. Mazenganya P. Multiple variations of the renal and testicular vessels: possible embryological basis and clinical importance. Surgical and radiologic Anatomy. 2016; 38(6): 729-33.
 11. Pan P. Micro anatomy of pelvi ureteric junction and its changes in hydronephrosis. International Journal of Current Research. 2017; 9(2):32-8.
 12. Reddy PR. Congenital renal abnormalities in fetuses: a study in a teaching institute Pabbati Raji Reddy. Indian Journal of Clinical Anatomy and Physiology. 2017; 4(4): 465-7.
 13. Rocco F, Cozzi LA, Cozzi G. Study of the renal segmental arterial anatomy with contrast-enhanced multi-detector computed tomography. Surgical and Radiologic Anatomy. 2015; 37(5): 517-26.
 14. Stringer MD, Yassaie S. "Is the pelviureteric junction an anatomical entity?". Journal of pediatric urology. 2013; 9(2):123-8.

Реферати

ОСОБЛИВОСТІ МОРФОГЕНЕЗУ МИСКОВО-СЕЧОВІДНОГО СЕГМЕНТА У ПЛОДІВ ТА НОВОНАРОДЖЕНИХ ЛЮДИНИ

Цигикало О.В., Олійник І.Ю., Андрушак Л.А., Галиш І.В., Столяр Д.Б.

Метою дослідження було з'ясувати особливості будови мисково-сечовідного сегменту у плодovому періоді онтогенезу та в новонароджених людини, визначити критичні періоди його морфогенезу. Дослідження виконано на 67 препаратах плодів людини 160,0-500,0 мм тім'яно-куприкової довжини (ТКД) (4-10-й місяці пренатального розвитку). Застосовано комплекс методів морфологічного дослідження, який включав антропометрію, морфометрію, ін'єкцію судин з наступною рентгенографією та препаруванням, мікроскопію, графічне та тривимірне комп'ютерне реконструювання, статистичний аналіз. Встановлено, що Розміри мисково-сечовідного сегмента в ранньому періоді онтогенезу збільшуються асинхронно: впродовж 4-го місяця інтенсивніше зростає його довжина, впродовж 7-го місяці та в новонароджених – діаметр. Від 4-го місяця внутрішньоутробного розвитку до періоду новонародженості діаметр мисково-сечовідного звуження зростає від $0,95 \pm 0,25$ мм до $2,2 \pm 0,25$ мм. На початку плодovого періоду (4-5 місяці) мисково-сечовідні сегменти визначаються на рівні міжхребцевого проміжку між II і III поперековими хребцями. Упродовж другої половини плодovого періоду відбувається його асиметричне зміщення: зліва – до рівня II, а справа – до рівня III поперекових хребців. У перинатальному періоді онтогенезу визначаються тісні анатомічні взаємовідношення мисково-сечовідного сегмента з нирковими судинами – його передню поверхню перетинають 2-4 гілочки ниркової артерії та 2-3 гілочки ниркової вени.

Ключові слова: мисково-сечовідний сегмент, анатомія, плід, новонароджений.

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ОСОБЕННОСТИ МОРФОГЕНЕЗА ЛОХАНОЧНО-МОЧЕТОЧНИКОВОГО СЕГМЕНТА У ПЛОДОВ И НОВОРОЖДЕННЫХ ЧЕЛОВЕКА

Цигикало А.В., Олійник І.Ю., Андрушак Л.А., Галиш І.В., Столяр Д.Б.

Метою дослідження було з'ясувати особливості будови мисково-сечовідного сегменту у плодovому періоді онтогенезу та в новонароджених людини, визначити критичні періоди його морфогенезу. Дослідження виконано на 67 препаратах плодів людини 160,0-500,0 мм тім'яно-куприкової довжини (ТКД) (4-10-й місяці пренатального розвитку). Застосовано комплекс методів морфологічного дослідження, який включав антропометрію, морфометрію, ін'єкцію судин з наступною рентгенографією та препаруванням, мікроскопію, графічне та тривимірне комп'ютерне реконструювання, статистичний аналіз. Встановлено, що Розміри мисково-сечовідного сегмента в ранньому періоді онтогенезу збільшуються асинхронно: впродовж 4-го місяця інтенсивніше зростає його довжина, впродовж 7-го місяці та в новонароджених – діаметр. Від 4-го місяця внутрішньоутробного розвитку до періоду новонародженості діаметр мисково-сечовідного звуження зростає від $0,95 \pm 0,25$ мм до $2,2 \pm 0,25$ мм. На початку плодovого періоду (4-5 місяці) мисково-сечовідні сегменти визначаються на рівні міжхребцевого проміжку між II і III поперековими хребцями. Упродовж другої половини плодovого періоду відбувається його асиметричне зміщення: зліва – до рівня II, а справа – до рівня III поперекових хребців. У перинатальному періоді онтогенезу визначаються тісні анатомічні взаємовідношення мисково-сечовідного сегмента з нирковими судинами – його передню поверхню перетинають 2-4 гілочки ниркової артерії та 2-3 гілочки ниркової вени.

Ключові слова: мисково-сечовідний сегмент, анатомія, плід, новонароджений.

Рецензент Єрошенко Г.А.

K.V. Shevchenko, G.A. Yeroshenko, A.V. Solod, O.D. Lysachenko, O.S. Yakushko,
N.V. Boruta, D.V. Lichman, D.R. Kramarenko
Ukrainian Medical Stomatological Academy, Poltava

CORRELATION ANALYSIS BETWEEN METRIC PARAMETERS OF PARENCHYMATOUS COMPONENTS OF RAT SUBMANDIBULAR GLANDS UNDER THE EFFECT OF ETHANOL

e-mail: kvshevchenko2017@gmail.com

The effect of ethanol on the salivary glands is manifested by changes in morphometric parameters of both the final departments and excretory ducts. But taking into account that the obtained large number of morphometric indicators is rather complicated, then there is a need for a correlation analysis, where the presence of dependencies between morphometric indicators was determined using the Bravais – Pearson coefficient. It was established that diagnostic criteria for assessing the functional state of rat submandibular glands after ethanol is manifested by the dependence of the outer diameter, lumen diameter and epithelial cell height on day 12 in all parenchymal components, which corresponds to the formation of chronic alcohol dependence in rats.

Key words: submandibular glands, rats, morphometry, correlation analysis.

The work is a fragment of the research project "Experimental morphological study of the effect of cryopreserved cord blood products and embriofetoplacental complex (EFPC), diphereline, ethanol and 1% methacrylate on the morphofunctional condition of certain internal organs", state registration No. 0119U102925.

In the 21st century, the problem of alcohol consumption is one of the most common worldwide, and every year it tends to become large-scaled due to constant stress related to national and territorial cataclysms [5]. Alcohol consumption, as one of the global problems of society, reflects the medical and ethical problems of finding ways to solve the problem, as its consequences directly negatively affect the human body. Thus, being aware of the toxic nature of alcohol, a person does not suspect that the destruction of the body occurs due to chemical reactions catalyzed by ethanol [2]. Awareness of the outcomes of alcohol consumption and its effect on the tissues of the oral cavity and its external organs, involved in maintaining its homeostasis is relevant and important both for preservation of dental health and the entire human body.

The effect of ethanol on the salivary glands is manifested by changes in morphometric parameters of both the acini [8] and excretory ducts [9]. However, given that the resulting big amount of morphometric parameters is quite complex, there is a need for correlation analysis, which can reflect relationship between changes in one parameter with the change of another one [6].

The purpose of the work was determining correlations between the morphometric parameters of the acini, excretory ducts and microvasculature of the normal rat submandibular salivary glands and in chronic ethanol intoxication.

Materials and methods. Morphometry involved study of the separate samples of semi-thin sections obtained from pieces of the submandibular glands of rats, administered which 12 mg/kg of 40° ethanol directly to stomach 4 times a day [3]. The animals were killed under 25 mg/kg thiopental anesthesia overdose on days 5, 9, 12 and 30 of the experiment. Pieces of the submandibular glands were embedded into epon-812 according to standard procedure [1]. Semi-thin sections were stained with methylene blue. The mean values of the outer diameter, the diameter of the lumen of the ducts and the height of the epithelial cells were determined using the Biorex-3 BM-500T microscope equipped with DCM 900 digital microphoto attachment with software, adapted to these studies. Statistical processing of the morphometric data and correlation analysis was performed using the Microsoft Excel software [7] to determine the relationships between morphometric parameters. The presence of correlation between morphometric parameters was determined using the Bravais-Pearson coefficient, where Pearson's r was used to obtain simultaneously information about the direction of correlation (positive +, negative -) and the strength of the relationship (from 0 to 1). If $r = 0$, it is assumed that no correlation exists, the interval of 0-0.3 indicates a weak correlation, the interval of 0.3–0.7 indicates moderate correlation, and the interval from 0.7 to 1.0 is assumed as a strong one. Pearson's method is considered the most accurate for studying the correlation [6].

Results of the study and their discussion. Correlation analysis of the metric parameters of the submandibular glands of rats of the control group has established mainly weak relationship with the mean values of the outer diameter of the acini, except for moderate relationship with the diameter of the lumen of the venules on day 9 and 30 of the experiment ($r = 0.31$ in $p < 0.05$). The diameter of the lumen of the acini of the control group showed weak relationship with all parameters of the submandibular glands, as well as the height of the epithelial cells.

Moderate correlation between the outer diameter on day 5 of the experiment and the diameter of the lumen of arterioles on day 5 ($r = 0.34$) was established, as well as negative moderate relationship with the diameter of the lumen of the venules on day 5 of the experiment ($r = -0.34$). Moderate correlation between the values of the lumen diameter and the values of the diameter of the arterioles on day 5 of the experiment has been established ($r = 0.33$). Moderate correlation between the height of the epitheliocytes of the acini of the submandibular glands on day 5 of the experiment and the diameter of the lumen of the venules on day 9 and 30 of the experiment was established ($r = 0.41$).

Strong correlations between the outer diameter of the acini on day 9 and the values of the outer diameter on day 12 ($r = 1.00$) have been found. Notably, strong positive correlations between the values of the lumen diameter and the similar ones on day 12 ($r = 1.00$) was established. Moderate negative correlations between the values of the height of the epithelial cells and the values of the diameter of the capillary lumen ($r = -0.32$) and strong positive relationship with the values of the height of the epitheliocytes on day 12 ($r = 1.00$) were established.

On day 12 of the experiment weak correlations between the values of the outer diameter and the diameter of the lumen of the rat submandibular glands were established, in contrast to the values of the height of the epithelial cells that showed moderate negative relationship with the values of the diameter of the capillary lumen on day 5 of the experiment ($r = -0.32$).

On day 30, the values showed weak relationships, the most apparent of which were moderate correlations between the outer diameter and the diameter of the acini and the diameter of the lumen of the arterioles, where positive relationship was established with the outer diameter ($r = 0.21$) and weak negative relationship was with the lumen diameter ($r = -0.21$).

Correlation analysis of the metric values of the intercalated ducts of the submandibular glands of rats of control group has shown weak relationships among which the most apparent were weak negative correlations between the diameter of the intercalated ducts and the diameter of lumen diameter ($r = -0.26$) and the diameter of the venule lumen ($r = -0.25$), whereas the diameter of the lumen of intercalated ducts showed weak negative correlations between the diameter of the lumen of arterioles ($r = -0.20$) and the diameter of the capillary lumen ($r = -0.23$) of rats of control group.

Moderate positive correlations ($r = 0,42$) between the value of the outer diameter on day 5 and the values of the diameter of the venule lumen were established in the experimental group and weak relationship with capillary lumen on day 5 ($r = -0.24$) in the same group, with the diameter of the arteriole lumen on day 9 ($r = -0.20$), with the outer diameter of the intercalated ducts ($r = -0.21$), height of the epithelial cells of the intercalated ducts ($r = 0,24$), and negative relationship with the mean values of the diameter of the arteriole lumen ($r = -0,20$) in experimental group on day 30 of the study. Moderate negative correlations ($r = -0.50$) between the values of the diameter of the lumen of intercalated ducts on day 5 of the experiment and the values of the outer diameter of the intercalated ducts on day 9 ($r = 0.54$) and day 12 ($r = 0.54$) were established, as well as values of the diameter of the lumen of the intercalated ducts on day 9 and 12. The comparison of the height of the epithelial cells of the intercalated ducts of the submandibular glands has revealed negative moderate correlations between the outer diameter of the intercalated ducts and values on day 9 and 12 of the experiment ($r = -0.31$). The rest of the morphometric parameters showed weak relationship with the values of the height of epithelial cells on day 5, except for the diameter of the arteriole lumen on day 30 where weak to moderate negative relationship was noted ($r = -0.27, p < 0.05$).

Strong positive correlation between the values of the outer diameter on day 9 and its values on day 12 ($r = 1.00$) was established, as well as moderate negative correlations between the diameter of the lumen of intercalated ducts in its group ($r = -0.40$) and on day 12 of the experiment ($r = -0,40$). Strong positive correlation between the values of the diameter of the lumen of intercalated ducts on day 9 and the diameter of the lumen on day 12 ($r = 1.00$) was established, as well as moderate negative relationship with the values of the outer diameter in its group ($r = -0.40$) and on day 12 of the experiment ($r = -0.40$). Moderate positive relationship with the values of the diameter of the arteriole lumen on day 30 ($r = 0.26$) was established. The comparison of values of the height of the epithelial cells on day 9 showed strong positive relationship with the values of the height of the epithelial cells of the intercalated ducts on day 12 ($r = 1.00$) and moderate positive relationship, compared to values of the arteriole lumen on day 9 and 30 ($r = 0,36$). Weak negative relationship with the values of the diameter of the arteriole lumen on day 5 ($r = -0.25$), and positive relationship ($r = 0.21$) with the values of the lumen of intercalated ducts of its group and experimental group on day 12 was established.

On day 12 of the experiment strong and moderate negative relationships were established that were similar to the above terms, as well as correlation between the outer diameter and values of the diameter of the lumen on day 12 ($r = -0.40$). The analysis of the diameter of the lumen showed weak to moderate relationship with the values of the diameter of the arteriole lumen on day 30 ($r = 0.26$). Moderate positive

correlation between the height of the epithelial cells and values of the diameter of the arteriole lumen on day 30 ($r = 0.36$) was established.

The analysis of the relationships of the intercalated ducts on day 30 revealed strong positive correlations between the outer diameter of the ducts and the lumen diameter of the ducts in its experimental group ($r = 0.75$). Moderate negative correlation between the diameter of the lumen and values of the diameter of the arteriole lumen in control group ($r = -0.32$) was established, as well as weak to moderate positive relationship ($r = 0.20$) with the diameter of the lumen of intercalated ducts in control group. Moderate negative correlations between the height of the epithelial cells and the values of the diameter of the venule lumen in the control group ($r = -0.34$) were established, as well as weak negative relationship with the outer diameter of intercalated ducts in its group ($r = -0.27$).

Correlation analysis of the metric parameters of the striated ducts of the submandibular glands has established weak correlations between the values of the outer diameter of rats of control group and the diameter of the arteriole lumen of its group ($r = 0.22$). Moderate negative correlation ($r = -0.31$) between the lumen diameter and the outer diameter of the striated ducts of control group was established, as well as weak negative relationship ($r = -0.24$) with the diameter of arteriole lumen and positive with the diameter of capillary lumen ($r = 0.27$) of its group. The comparison of the values of the height of the epithelial cells of the striated ducts of control group revealed weak correlations.

Weak correlation between the outer diameter of the striated ducts on day 5 and the values of the diameter of the lumen of the striated ducts ($r = 0.26$) and the height of epithelial cells ($r = 0.25$) of control group and the diameter of the capillary lumen ($r = 0.26$), the diameter of the arteriole lumen of its experimental group ($r = 0.24$) and on day 30 ($r = 0.29$) was established. Moderate positive relationship with the mean values of the diameter of the venule lumen of its group ($r = 0.59$) was established. Moderate negative correlations ($r = 0.25$) between the diameter of the lumen and the values of the height of epithelial cells on day 5 of the experiment were established, as well as weak negative relationship with the diameter of the capillary lumen of its group ($r = -0.24$), the diameter of the arteriole lumen on day 9 ($r = -0.25$) and day 30 ($r = -0.25$) of the experiment. Moderate positive correlations between the mean values of the diameter of the arteriole lumen ($r = 0.32$) and capillary lumen ($r = 0.36$) of its experimental group have been established.

Comparison of the mean values of the outer diameter of the striated ducts on day 9 of chronic ethanol intoxication showed strong positive relationship with its value on day 12 of the experiment ($r = 1.00$) and moderate relationship with the value of the diameter of capillary lumen on day 12 ($r = 0.38$). Strong positive correlation between the diameter of the lumen of striated ducts and their values on day 12 was determined ($r = 1.00$), as well as moderate negative relationship with the values of the diameter of capillary lumen ($r = -0.38$). Strong positive correlation between the values of the height of the epithelial cells and similar parameter on day 12 of the experiment was established ($r = 1.00$).

Weak relationship with the outer diameter on day 12 was determined, except for the mean values of the diameter of capillary lumen of its group where moderate relationship was established ($r = 0.38$). Moderate negative correlations between the diameter of the lumen of striated ducts of the submandibular glands and the value of the diameter of capillary lumen of its experimental group were revealed. Weak relationship with the height of the epithelial cells was established.

The analysis of the correlations between the metric values of the striated ducts on day 30 showed mainly weak relationship, except for positive moderate correlation between the diameter of the lumen and the height of the epithelial cells of its experimental group ($r = 0.43$).

Correlation analysis of the morphometric parameters of the granular ducts of the control group has established weak negative correlations between the outer diameter and the diameter of the capillary lumen of control group ($r = -0.24$). Moderate correlation between the diameter of the lumen of the granular ducts and the values of the capillary lumen of its group ($r = 0.30$) was established, as well as weak positive relationship with the diameter of the capillary lumen on day 5 of the study ($r = 0.24$). Weak positive correlation between the height of the epithelial cells and the values of the venule lumen of the control group ($r = 0.28$) was established.

The findings of the study on day 5 of the experiment showed moderate negative correlations between the mean values of the outer diameter of the granular ducts and the diameter of arteriole lumen ($r = -0.46$) and capillary lumen ($r = -0.54$) of its group. Moderate negative correlations between the diameter of the lumen and values of the diameter of the arteriole lumen on day 9 and 30 ($r = -0.34$) were established. Moderate positive correlations between the height of the ductal epithelial cells and the values of the diameter of the venule lumen on day 5 were determined, as well as weak negative relationship with the values of the capillary lumen on day 30 ($r = -0.26$).

Strong positive correlation between the metric values of the outer diameter on day 9 and the values of the outer diameter on day 12 ($r = 1.00$) was determined, as well as moderate positive relationship with the values of the diameter of arteriole lumen ($r = 0.35$) and capillary lumen ($r = 0.37$). Weak positive relationship ($r = 0.26$) with the diameter of lumen of granular ducts on day 9 and 12 of the experiment was established. Strong positive correlation between the diameter of the lumen of granular ducts and its values on day 12 ($r = 1.00$) was established, as well as weak relationship ($r = 0,28$) with the diameter of the arteriole lumen on day 12. Strong positive correlation between the height of the epithelial cells ($r = 1.00$) and similar parameter on day 12 was established, as well as moderate positive relationship with the values of the diameter of the arteriole lumen on day 12 of the experiment.

Moderate correlations between the values of the outer diameter of the granular ducts on day 12 and the diameter of the arteriole lumen ($r = 0.35$) and capillary lumen ($r = 0.37$) of the experimental group were established. Weak correlation between the diameter of the lumen and the diameter of the arteriole lumen on day 12 ($r = 0.28$) was determined. Moderate positive correlations between the values of the height of the epithelial cells and the values of the diameter of the arteriole lumen of the experimental group ($r = 0,39$) were established.

The findings of our study showed weak relationship with morphometric parameters of the granular ducts of the submandibular glands on day 30.

Other investigators report about significant strong correlations between the morphometric parameters of the epithelial components and elements of the microvasculature of the lobules of rat normal major salivary glands and after stimulation of the peripheral nervous system. Strong correlations were established between the metric parameters of the acini and the parameters of the exchange and capacitive sections of the microvasculature. Strong correlations were determined between the morphometric parameters of the ductal system of the intercalated and intralobular collector ducts of the sublingual gland (in control group of animals) and striated ducts of the submandibular gland, especially after administration of acetylcholine [4].

Conclusion

It has been established that the diagnostic criteria of the evaluation of the functional state of the rat submandibular glands after the effect of ethanol are the correlation between the outer diameter, the diameter of the lumen and the height of the epithelial cells on day 12 in all parenchymatous components that is associated with the development of chronic alcohol dependence in rats.

References

1. Bahriy MM, Dibrova VA, Popadynets OH, Hryshchuk MI. Metodyky morfolohichnykh doslidzen. Bahriy MM, Dibrova VA, redaktory. Vinnytsya: Nova knyha; 2016. 328s. [in Ukrainian]
2. Yefremov AYU, Belkyn VV. Biokhimiya alkoholia i yeye vliyanie na orhanizm. Nauchnye issledovaniya: ot teorii k praktike. 2015; 2(3): 455-56. [in Russian]
3. Yeroshenko GA, Shevchenko KV, Yakushko OS. Morfometrychna kharakterystyka yemnisnoyi lanky hemomikrotsyrkuliatornoho rusla slynyykh zaloz shchuriv v normi ta pry khronichniy intoksykatsiyi etanolom. Svit medytsyny ta biolohii 2018; 3 (65): 149-152. [in Ukrainian]
4. Yeroshenko GA, Kostylenko YuP, Skrypnikov MS, Kryveha LH. Koreliatsiyni zvyazky mizh morfometrychnymy pokaznykamy velykykh slynyykh zaloz shchuriv v normi i pislia stymuliatsiyi peryferychnoyi nervovoyi systemy. Svit medytsyny ta biolohiyi. 2009; 3(1): 64-69. [in Ukrainian]
5. Konkova AV. Vlyaniye alkoholia na podrostkovii orhanyzm. Integrativnye tendentsii v meditsine i obrazovanii. 2019; 2: 42-5. [in Russian]
6. Lanh TA, Sesy M. Kak opisyvat statystyku v meditsine. Annotirovannoe rukovodstvo dlia avtorov, redaktorov i retsenzentov. per. s angl. Leonov VP, redactor. Prakticheskaia medytsyna. 2011; 480 s. [in Russian]
7. Lapach SN, Chubenko AV, Babych PN. Statisticheskiye metody v mediko-biologicheskikh issledovaniyakh s ispolzovaniyem Excel. Kiev: Morion; 2000. 320 s. [in Russian]
8. Shevchenko KV, Garets VI, Fedonyuk LYa, Volkov KS, Nesteruk CO. Histophysiology of submandibular salivary glands end pieces in rats with chronic ethanol intoxication. Word of medicine and biology. 2018; 4 (66): 231-234.
9. Shevchenko KV, Yeroshenko GA, Vilkhova OV, Kramarenko DR, Yakushko OS, Yachmin AI. Remodeling of the duct system of the rat submandibular salivary glands in chronic ethanol intoxication. Wiadomości Lekarskie. 2020; 73(1): 128-133.

Реферати

КОРЕЛЯЦІЙНИЙ АНАЛІЗ МІЖ МЕТРИЧНИМИ ПОКАЗНИКАМИ ПАРЕНХІМАТОЗНИХ КОМПОНЕНТІВ ПІДНИЖНЬОЩЕЛІПНИХ ЗАЛОЗ ЩУРІВ ПІСЛЯ ДІЇ ЕТАНОЛУ

Шевченко К. В., Єрошенко Г. А., Солод А. В., Лисаченко О. Д., Якушко О. С., Борута Н. В., Лічман Д. В., Крамаренко Д. Р.

Вплив етанолу на слинні залози проявляється змінами морфометричних показників як кінцевих відділів так і вивідних проток. Але з огляду на те, що отримана велика кількість морфометричних

КОРРЕЛЯЦИОННЫЙ АНАЛИЗ МЕТРИЧЕСКИХ ПОКАЗАТЕЛЕЙ ПАРЕНХИМАТОЗНЫХ КОМПОНЕНТОВ ПОДНИЖНЕЧЕЛЮСТНЫХ ЖЕЛЕЗ КРЫС ПОСЛЕ ДЕЙСТВИЯ ЭТАНОЛА

Шевченко К. В., Ерошенко Г. А., Солод А. В., Лисаченко О. Д., Якушко, О. С., Борута Н. В., Личман Д. В., Крамаренко Д. Р.

Влияние этанола на слюнные железы проявляется изменениями морфометрических показателей как конечных отделов так и выводных протоков. Но учитывая то, что полученное большое количество морфометрических

показників є досить складною, то виникає необхідність проведення кореляційного аналізу, де наявність залежностей між морфометричними показниками визначали за допомогою коефіцієнту Браве- Пирсона. Встановлено що діагностичними критеріями для оцінки функціонального стану піднижньощелепних залоз щурів після дії етанолу є залежність зовнішнього діаметру, діаметру просвіту та висоти епітеліоцитів на 12 добу у всіх паренхіматозних компонентах що відповідає формуванню хронічної алкогольної залежності у щурів.

Ключові слова: піднижньощелепні залози, щури, морфометрія, кореляційний аналіз.

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показателей есть достаточно сложным, то возникает необходимость проведения корреляционного анализа, где наличие зависимостей между морфометрическими показателям определяли с помощью коэффициента Браве – Пирсона. Установлено что диагностическими критериями для оценки функционального состояния поднижнечелюстных желез крыс после действия этанола проявляется зависимостью внешнего диаметра, диаметра просвета и высоты эпителиоцитов на 12 сутки во всех паренхиматозных компонентах, что соответствует формированию хронической алкогольной зависимости у крыс.

Ключевые слова: поднижнечелюстные железы, крысы, морфометрия, корреляционный анализ.

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V.S. Shkolnikov, S.O. Prykhodko, S.S. Polishchuk, O.V. Kryvoviaz, G.M. Galunko
National Pirogov Memorial Medical University, Ximnytsya

THE MORPHOLOGY OF RADIAL GLIAL SPINAL CORD OF EMBRYOS AND HUMAN FETUSES

e-mail: v.shkolnikov@gmail.com

The study of radial glia morphology and processes of targeted migration of neural stem cells in humans remains far from being resolved. The purpose of this study is to establish the morphological aspects of radial glia of spinal cord of human in prenatal period. Morphological examination of the spinal cord of human embryos and fetuses of 6-7 weeks up to 39-40 weeks was performed. Using anatomical, histological, immunohistochemical, and morphometric morphological aspects of the radial glia of the spinal cord were established. The results showed that strong expression of vimentin and CDX-2 radial glia fibers was observed up to 8-9 weeks. From 11-12 weeks, radial glia fibers retain a radial direction only in the middle part of the segments, which, in our view, is associated with the gradual involution of radial glia, which correlates with the formation of nuclear-neural complexes of gray matter. Until the moment of birth, vimentin-positive structures of radial glia gradually disappear and can be traced only in the neuroepithelium of segments.

Key words: prenatal period, spinal cord, radial glia, neuroepithelium, immunohistochemical markers.

The study is a fragment of the research project "Determination of morphological changes of the central nervous system in the prenatal ontogeny (macroscopic, histological, morphometric and immunohistochemical study)" state registration No. 0118U001043.

Neurogenic fetal brain cells generate major cell types of the nervous system during the prenatal ontogeny, which lasts from fertilization to birth. Such neurogenic cells include neural stem cells (NSC), neural progenitor cells (NPC), and linear-specific progenitors and precursors [2]. NSC are known to be multipotent cells, which are characterized by the proliferation and formation of several cell pools simultaneously: neuroblasts or glioblasts [4, 10, 15]. To date, there is no doubt that the presence of permanent neurogenesis of some areas of the brain performs due to colonies of NSC [9, 14]. Rybachuk O.A. and Pivneva T.A. (2013) emphasize that during the embryonic ontogeny period NSC cranial nerve tubes showed greater proliferative activity than neural cells of the caudal compartments [3]. Thus, it can be predicted that the above processes are inherent in the spinal cord, which precede the formation of neuronal complexes, which in turn requires further study and refinement.

It should also be noted that the identification of NSC in vivo is traditionally based on the analysis of the morphology of these cells, their mitotic activity, and the expression of certain genes and protein synthesis. The most commonly identified NSC markers are Nestin, Sox2, Msashi 1, 2, Oct 4, Nanog, etc., but none can be used as the sole criterion for NSC identification [11].

The next step is to study the mechanisms of migration of differentiated unipotent neural cells that have just formed in the paraventricular zone.

It has been established that the most extensive migration of neural cells occurs during the process of laying the cerebral cortex [5]. At the same time, Tsymbaluk V. I. and Medvedev V. V. (2010) indicate that radial glial (RG) plays a key role in ensuring nerve cell migration during the development of other neural tube compartments and cell migration. The authors have shown that immature neurons migrate along the processes of RG cells in the centripetal direction [5].

Over time, RG cells lose the ability to express nestin and vimentin [8]. However, the authors do not specify a term when such a property is lost. In contrast, Kirik O. V. and Korzhevskii D. E. (2012) indicate that the RG cell population is heterogeneous: some cells contain neural markers (they subsequently

become neuroblasts) and some glial (become glial cells). In the early stages of the development of the spinal cord, the protein of intermediate filaments – vimentin is expressed by cells of the neuroepithelium (subpendicular zone), as well as in RG cells [1].

At present, it is impossible to consider the issues of genealogical relationships between populations of neurogenic cells of the ventricular and subventricular zones and cells of radial glia completely solved [5]. In addition, according to Ostrem B. et al. (2014) study of RG morphology and processes of targeted NSC migration in humans remains relevant and has not been fully resolved to date [13].

The purpose of the study was to establish the morphological aspects of radial glia segments of the spinal cord of human embryos and fetuses using specific immunohistochemical markers.

Materials and methods. The study was performed at the Department of Human Anatomy of the National Pirogov Memorial Medical University, Vinnytsya and the Research Laboratory of Functional Morphology and Genetics of Development of the National Pirogov Memorial Medical University, Vinnytsya (certificate of accreditation: CDL No. 050/15, 03/02/2015 – 01/03/2020).

According to the 2017 Agreement on Joint Scientific and Practical Activities between National Pirogov Memorial Medical University, Vinnytsya and Vinnitsa Regional Anatomical Pathology Bureau, the material was examined directly by the Vinnitsa Regional Anatomical Pathology Bureau, and protocols of pathoanatomical examination were drawn up in accordance with Form No. 013-2/o approved by the order of the Ministry of Health of Ukraine of 14.08.2004 No. 417. According to the opinion of the Commission on Biomedical Ethics of National Pirogov Memorial Medical University, Vinnytsya (protocol No. 10 of 06.12.2018), the work was done in compliance with the basic provisions of the GCP (1996), Council of Europe Convention on Human Rights and Biomedicine (1997) and the study materials do not contradict the basic bioethical standards of the Declaration of Helsinki on the ethical principles of scientific and medical research with the participation of a person adopted by the 59th General Assembly of the World Medical Association in 2008.

This study was performed on 127 human embryos and fetuses between 6-7 and 39-40 weeks of prenatal development in the uterus in the absence of overtly harmful external and internal environmental factors. Serial sections of preparations of human embryos were made entirely (histologic "tomography"), since the extraction of the spinal cord from embryos is difficult and there is a risk of not maintaining its integrity. The method of micropreparation – under the control of binocular magnifier or by the method of thin preparation (in the fetus), the spinal cord was removed together with the membranes. During the removal of the spinal cord in the pre-fetus was used our own technique (Innovative proposal № 17 from 25.04.2002). Examination preparations of the spinal cord were stained with hematoxylin and eosin, toluidine blue (in the Nissl modification), by Van Gieson, and impregnated with silver according to Bilshovskyy.

Immunohistochemical study – «DacoCytomation» (Denmark) diagnostic monoclonal antibodies were used: vimentin, CDX-2, Ki-67 and synaptophysin. We used Vimentin and CDX-2 to investigate the morphology of radial glia, Ki-67 to evaluate the proliferative activity of NSC in the neuroepithelial layer, and synaptophysin – to determine the development of synaptic ligaments and to evaluate myelination of the fibers of the leading pathways. Photo M 1.21 (computer histometry) was used in the morphometric study of a series of sections of spinal cord segments. We studied indices of neuroepithelium values, length and thickness of radial glial fiber, area and linear dimensions of neural stem cells of neuroepithelium, neuroblasts and glioblasts.

Statistical processing of the obtained morphometric parameters was carried out using the standard software package "Statistica 6.1" by StatSoft (license No. BXXR901E246022FA) using parametric and non-parametric criteria for evaluating the obtained results. The differences between the samples were determined using the Mana-Whitney U-test and the Student's t-test, and the mean values for each trait and their standard deviations were determined.

Results of the study and their discussion. The data on the course of NSC proliferation processes in human embryos 6-7 weeks which was obtained indicate that they occur more intensively in the dorsal part of the neuroepithelium than in the ventral (fig. 1).

The intensity of Ki-67 expression in the dorsal part of the neuroepithelium of segments along the spinal cord of human embryos of 6-7 weeks can be estimated as strong, since cell staining was 92 %. In the ventral part, 12 % of cells reacted. However, this pattern is characteristic of all segments of the spinal cord. Due to the high proliferative activity of cells of the dorsal part of the neuroepithelium, a higher density of neuro- and glioblasts locations within the posterior horns was observed.

From the neuroepithelium, NSC migrate along the RG fibers into the mantle layer, where further differentiation of neuroblasts and proliferation of glioblasts is carried out. Neuroblast proliferation in the

mantle layer has not been established. RG fibers that express vimentin protein penetrate into the boundary layer. We also found that, in addition to vimentin, in this gestational term, RG fibers express the CDX-2 protein (fig. 1). NSC, which are located in the mantle layer have an elliptical or spherical shape. The morphology and size of these cells are virtually identical in all parts of the spinal cord. There are larger cells with light cytoplasm that already have axonal tubercles – these are neuroblasts. Their average area was $46.7 \pm 1.4 \mu\text{m}^2$. The area of the nuclei of the neuroblasts was $22.6 \pm 1.2 \mu\text{m}^2$. Smaller cells with dark cytoplasm and accompanying neuroblasts are glioblasts. The area of this cell averaged $31.5 \pm 1.5 \mu\text{m}^2$ and the area of the nucleus of glioblasts was $10.8 \pm 1.0 \mu\text{m}^2$.

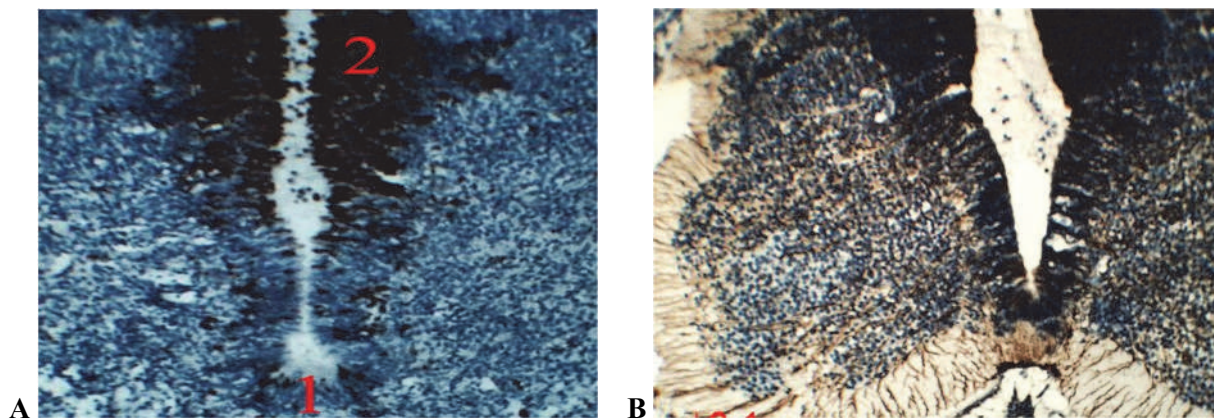


Fig. 1. Spinal cord of human embryo 6-7 weeks. A – neuroepithelium: 1 – ventral part; 2 – dorsal part. Ki-67; $\times 100$. B – expression of CDX-2 in segments. CDX-2; $\times 100$.

The structural basis of the boundary layer is RG fibers (see Fig. 1). Preferably, in the cervical and lumbar segments, the concentration of RG fibers involved in the formation of the anterior roots is noted (fig. 1). Such fibers start from the basement membrane of the neuroepithelium and penetrate the marginal layer. In the course of the study we found that the intensity of synaptophysin expression in segments of spinal cord of embryos of 6-7 weeks was determined in the boundary layer and within the anterior and posterior spinal commissure, which can obviously be associated with the establishment of synaptic connections and the initiation of myelination of the leading pathways. In the mantle layer, synaptophysin expression is mediocre. Thus argue that the first stage of differentiation of post-mitotic cells occurs during their migration, after which maturation continues and ends with the establishment of a synaptic linkage network. Fedorkovskaya B. O. (2013) adheres to the idea that when myelination of nerve fibers begins, then synapses begin to form. According to the chronology, the author attributes this process to the 5th month of intrauterine period [6].

In the ventral part of the neuroepithelium of human fetuses 8-9 weeks. there are 5-6 (4 %) mitotic or post-mitotic NSC. In the dorsal part of such cells – 10-11 (10 %). In general, expression of Ki-67 in the neuroepithelial segments can be assessed as in the ventral and dorsal part as weak.

After mitosis, NSC along the RG fibers migrate into the mantle layer, which extend in the radial direction, starting from the basal membrane of the neuroepithelium, penetrating the mantle layer and ending at the marginal (fig. 2). In the middle part of the mantle layer, the RG fibers sharply change their direction and extend back to the horn region. Short fibers are contained mainly within the neuroepithelium and make up its thickness (fig. 2).

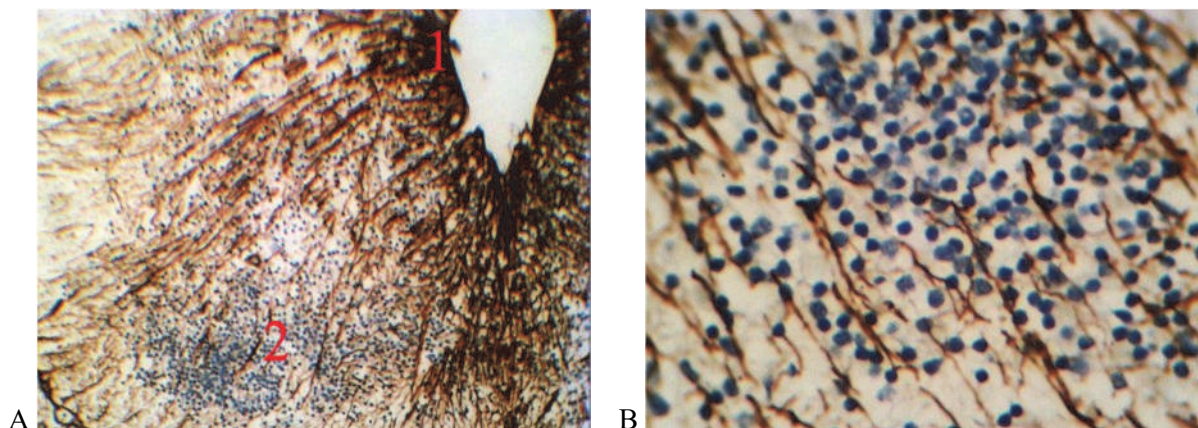


Fig. 2. Spinal cord of human fetus 8-9 weeks. A – RG fiber architectonics in segments: 1 – neuroepithelium; 2 – posterior horns. Vimentin; $\times 100$. B – NSC migration along radial glial fibers. Vimentin; $\times 400$.

The average minimum fiber length was $179.7 \pm 7.1 \mu\text{m}$. The average maximum fiber length of the RG was $688.2 \pm 21.4 \mu\text{m}$. Strong expression of vimentin was observed in the RG fibers of the neuroepithelium and along the anterior and posterior median septa (fig. 2). In other segments of segments, the expression of vimentin is mediocre. Cells with relatively large nuclei migrate along the RG fibers, these are neuroblasts and cells with small nuclei, these are glioblasts (fig. 2). The nuclei of the neuroblasts have a spherical shape and the nuclei of the glioblasts are elliptical. The average area of the nucleus of the neuroblast was $66.1 \pm 3.2 \mu\text{m}^2$, and the average area of the nucleus of the glioblast was $38.9 \pm 1.9 \mu\text{m}^2$.

Medium expression in the anterior and posterior median septa of the segments and poor expression in the posterior cords were observed with the use of CDX-2.

In fetus of 11-12 weeks NSC proliferation processes occur relatively more intensely in the ventral part of the neuroepithelium than in the dorsal one (fig. 3). This trend persists in all segments of the spinal cord. In the ventral part of the neuroepithelium there are 11-12 (13 %) mitotic or post-mitotic NSC, in the dorsal part – 6-7 (7 %) cells. In the ventral and dorsal parts, Ki-67 expression is weak.

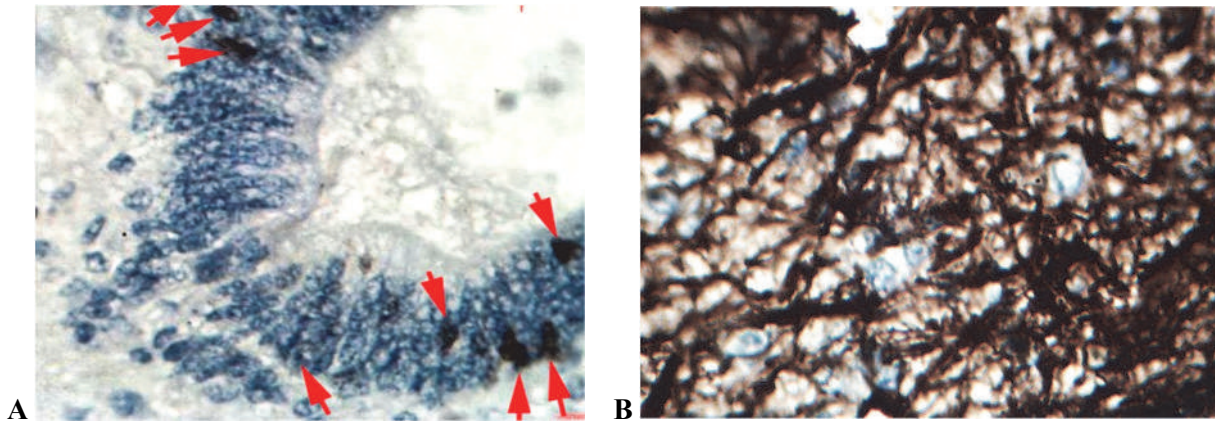


Fig. 3. Spinal cord of human fetus 11-12 weeks. A – nature of NSC proliferation in neuroepithelium (indicated by arrows). Ki-67; $\times 400$. B – formation of RG mesh structures within neural complexes. Vimentin; $\times 400$.

RG fibers retain their intrinsic direction only in the middle part of the segments, between the anterior and posterior horns. The average maximum fiber length of the RG was $963.9 \pm 28.7 \mu\text{m}$. The average minimum fiber length is $104.0 \pm 4.4 \mu\text{m}$. Relatively strong expression of vimentin was observed in the RG fibers around the neuroepithelium and along the anterior and posterior median septa. In other segments of the segment, the expression of vimentin is mediocre. Within the neural complexes, RG fibers form reticulated structures (fig. 3). We will associate this phenomenon with the formation of the neural complexes themselves. The expression of CDX-2 in segmental structures was absent at this age.

The nuclei of migrating neuroblasts have a spherical shape and the nuclei of the glioblasts are elliptical. The average area of the nucleus of the neuroblast was $71.6 \pm 2.9 \mu\text{m}^2$, and the average area of the nucleus of the glioblast was $44.1 \pm 2.6 \mu\text{m}^2$.

Synaptophysin expression in segments along the spinal cord was observed to be relatively strong in the mantle layer. However, the expression of synaptophysin in the neuroepithelium itself is absent.

In human fetus of 17-18 weeks in the ventral part of the neuroepithelium of segments there are 8-9 (10 %) mitotic or post-mitotic cells, and in the dorsal part – 5-6 (5 %) of cells.

RG fibers stored radial direction only in the middle part of the segments and around the neuroepithelium. In the mantle layer, the RG fibers are intermittent and are stored mainly near the vessels. The average minimum fiber length was $59.5 \pm 4.6 \mu\text{m}$. The average maximum fiber length of the RG was $633.3 \pm 33.0 \mu\text{m}$. Strong expression of vimentin was observed in the RG fibers of the neuroepithelium and along the anterior and posterior median septa. In other segments of the segments, the expression of vimentin is weak. The average nuclei area of migrating neuroblasts was $73.9 \pm 2.7 \mu\text{m}^2$, and the average nuclei area of glioblasts was $48.2 \pm 2.8 \mu\text{m}^2$.

In the ventral part of the neuroepithelium segments of the spinal cord of human fetus 22-23 weeks there are 7-8 (9 %) mitotic or post-mitotic NSC and 5-6 (5 %) similar cells in the dorsal part. Ki-67 expression in neuroepithelia is generally weak.

After mitosis, NSC from the neuroepithelium migrate into the mantle layer along the RG fibers, which does not retain radial direction even in the middle part of the segments around the neuroepithelium. The average minimum fiber length is $51.1 \pm 3.7 \mu\text{m}$. The relatively long RG fibers extend away from the basement membrane of the dorsal part of the neuroepithelium and extend along the posterior median septum. The average maximum fiber length of the RG was $346.7 \pm 11.5 \mu\text{m}$. Relatively strong expression

of vimentin was observed in the neuroepithelium and in the middle part of the segments at some distance from the neuroepithelium itself. In the mantle layer, the expression of vimentin was weak and persisted mainly along the vessels and at the site of spinal cord formation, that is, it had a focal character. Also, relatively weak expression of vimentin persisted within the boundary layer. The nuclei of migrating neuroblasts have a spherical shape and the nuclei of the glioblasts are elliptical. The average area of the nucleus of the neuroblast was $84.0 \pm 2.9 \mu\text{m}^2$. The average nuclei area of the glioblast was $55.4 \pm 1.6 \mu\text{m}^2$.

A relatively strong expression of synaptophysin in the spinal cord segments was observed within the mantle layer. Medium expression of synaptophysin occurred within the posterior horns and in fasciculus gracilis, weak - in the anterior and lateral cords.

The processes of proliferation of NSC neuroepithelium of segments of the spinal cord in fetuses 35-36 weeks occur relatively more intensely in the ventral part than in the dorsal one. We found that in the ventral part of the neuroepithelium of segments there are 4-5 (5 %) mitotic or post-mitotic NSC. In contrast, in the dorsal part there are 2-3 (3 %) such cells.

Remains of RG fibers retain radial direction only within the neuroepithelium. The average minimum fiber length was $35.8 \pm 1.5 \mu\text{m}$. The relatively long RG fibers extend away from the basement membrane of the dorsal part of the neuroepithelium and extend along the posterior median septum. The average maximum fiber length of the RG is $122.1 \pm 2.2 \mu\text{m}$. Relatively strong expression of vimentin was observed in the fibers of the RG of the neuroepithelial layer and along the posterior median septum. In the mantle layer, the expression of vimentin was weak and persisted mainly along vessels and at the site of spinal cord formation.

The nuclei of the neuroblasts have a spherical shape and the nuclei of the glioblasts are elliptical. The average area of the nucleus of the neuroblast was $90.0 \pm 2.4 \mu\text{m}^2$. The average nuclei area of the glioblast was $58.3 \pm 1.7 \mu\text{m}^2$.

Relatively strong synaptophysin expression in spinal cord segments was noted in the mantle layer.

In previous research, Barry D. et al. (2013) reported that in embryonic spinal cord, radial glial cells are defined as conductors for migrating neurons. The density of radial glial cells is maintained during development in the dorsal, lateral and ventral parts of the neuroepithelium [7]. We consider the characteristic of the neuroepithelium given by the author to be incomplete, as not only does the relative density of radial glial cells in individual parts of the neuroepithelial segments remain during the prenatal period of ontogeny, but also changes its thickness and the intensity of the mitotic activity of the cells of the neuroepithelium in the in the ventral and dorsal parts. Up to 11-12 weeks the thickness and intensity of cell mitoses are greater in the dorsal part of the neuroepithelial segments than in the ventral. In this case, the relative density of the cells of the posterior horn dominates as such in the anterior horns. After 11-12 weeks the above indicators are already prevalent in the ventral part of the neuroepithelium and this tendency persists until birth. Thus, in our opinion, this phenomenon is connected with the fact that at first a person develops sensitivity and only after that motor functions are established.

Nowakowski T. et al. (2016), by developing a hypothesis for the role of RG in neurogenesis and describing its morphology in mammals, indicates that architectonically radial glia forms a "framework" of continuous fibers covering the thickness of any CNS formation. The difference between people is that the author believes that RG fibers have a discontinuous course [12]. Our research proved the fact that up to 8-9 weeks in human fetus, RG fibers have a radial direction from the central canal and permeate the entire thickness of the nerve tube and also participate in the formation of the spinal cord. By integrating the findings from the research on the expression of vimentin and RG architectonics in segmental structures, we conclude that a decrease in the intensity of vimentin expression before the birth of a child is associated with its gradual involution. In our opinion, the statements of Nowakowski T. et al. (2016) should be supplemented by the fact that, in the early fetus period, RG fibers form reticulated structures, which is a prerequisite for the "terminal stop" of neurons and the structuring of neural complexes.

In future studies, it is promising to use immunohistochemical markers to elucidate the role of radial glia in the formation of nuclear neural complexes of the spinal cord during the prenatal period of human ontogeny and to study the morphology of neural stem cells; as well as comparing the results with similar results in malformations.

Conclusion

The results showed that by 8-9 weeks there was a strong expression of radial glial fibers of both vimentin and CDX-2, which penetrated all layers of the spinal cord. In 8-9 weeks CDX-2 is poorly expressed only in the anterior and posterior median septa of the segments. At 11-12 weeks, radial glia fibers retain radial direction in the middle part of the segments and around the neuroepithelium. In the mantle

layer, the radial glial fibers are intermittent and are predominantly located near the vessels. By birth, the vimentin-positive structures of radial glia gradually disappear and are only observed in the neuroepithelial of segments.

References

1. Kirik OV, Korzhhevskii DE. Vimentin v kletkah ependimy I subventricularnoy proliferativnoy zony konechnogo mozga. Kletochnyye tehnologii v biologii i meditsine. 2012; 4:210-4. [in Russian]
2. Lubyh LD, Lisyani MI. Immunobiologichni vlastyivosti neurohennykh klityn fetalnoho mozku. Fiziologichnyi Zhurnal. 2017; 63(6):118-35. [in Ukrainian]
3. Rybachuk OA, Pivneva TA. Rol neiralnykh stovburovykh klityn v rehenertsii tsentralnoyi nervovoyi systemy. Fiziologichnyi Zhurnal. 2013; 59(2):111-121. [in Ukrainian]
4. Shkolnikov VS. Osoblyvosti histohenesu matrychnoho sharu spynnoho mozku embrioniv ta plodiv lyudyny. Lvivskiy medychniy chasopys. 2015; 1:29-34. [in Ukrainian]
5. Tsymbaluk VI, Medvedev VV. Spinnoy mozg. Elegiya nadezhdy. Vinnitsa: Nova knyga; 2010. 944 s. [in Russian]
6. Fedorkovskaya BO. Morfofunkcionalnyye osobennosti razvitiya notsitseptivnoy systemy u novorozhdennykh. Meditsina neotlozhnykh sostoyaniy. 2013; 3:4-7. [in Russian]
7. Barry DS, Pakan JM, O'Keefe GW, McDermott KW. The spatial and temporal arrangement of the radial glial scaffold suggests a role in axon tract formation in the developing spinal cord. Journal of Anatomy. 2013; 222(2):203-13.
8. Barry DS, Pakan JM, McDermott KW. Radial glial cells: key organizers in CNS development. The International Journal of Biochemistry & Cell Biology. 2014; 46:76-9.
9. Costa V, Lugert S, Jagasia R. Role of adult hippocampal neurogenesis in cognition in physiology and disease: pharmacological targets and biomarkers. Handbook of Experimental Pharmacology. 2015; 228:99-155.
10. Harris L, Zalucki O, Piper M, Heng JI. Insights into the Biology and Therapeutic Applications of Neural Stem Cells. Stem Cells Int [serial on the Internet]. 2016 Mar [cited 2017 Sep 8]; 2016: 9745315 [18p.].
11. Montalban-Loro R, Domingo-Muelas A, Bizy A. Epigenetic regulation of stemness maintenance in the neurogenic niches. World Journal Stem Cells. 2015; 7(4):700-10.
12. Nowakowski T, Pollen A, Sandoval-Espinosa C, Kriegstein A. Transformation of the radial glia scaffold demarcates two stages of human cerebral cortex development. Neuron. 2016; 91(6):1219-27.
13. Ostrem B, Lui J, Gertz C, Kriegstein A. Control of outer radial glial stem cell mitosis in the human brain. Cell Report. 2014; 8(3):656-64.
14. Rueger MA, Schroeter M. In vivo imaging of endogenous neural stem cells in the adult brain. World Journal Stem Cells. 2015; 7(1):75-83.
15. Vishwakarma SK, Bardia A, Tiwari SC, Paspala SA, Khan AA. Current concept in neural regeneration research: NSCs isolation, characterization and transplantacion, in various neurodegenerative diseases and stroke: A review. Journal of Advanced Research. 2014; 5(3):277-94.

Реферат

МОРФОЛОГІЯ РАДІАЛЬНОЇ ГЛІЇ СПИННОГО МОЗКУ ЕМБРІОНІВ ТА ПЛОДІВ ЛЮДИНИ

Школьников В.С., Приходько С.О., Полищук С.С., Кривов'яз О.В., Галушко Г.М.

Вивчення морфології радіальної глії та процесів адресної міграції нейральних стовбурових клітин у людини лишається далеко не вирішеним до кінця питанням. Метою дослідження є встановлення морфологічних аспектів радіальної глії спинного мозку людини у пренатальному періоді. Проведене морфологічне дослідження спинного мозку ембріонів та плодів людини від 6-7 тиж. до 39-40 тиж. При використанні анатомічних, гістологічних, імуногістохімічних, морфометричних методик були встановлені морфологічні аспекти радіальної глії спинного мозку. Отримані результати показали, що сильна експресія виментину та CDX-2 волокон радіальної глії спостерігалась до 8-9 тижня. З 11-12 тижня волокна радіальної глії зберігають радіальний напрямок тільки у середній частині сегментів, що на наш погляд пов'язано з поступовою інволюцією радіальної глії, яка корелює із формуванням ядерно-нейронних комплексів. До народження виментин-позитивні структури радіальної глії поступово зникають і простежуються тільки у нейроепітелії сегментів.

Ключові слова: пренатальний період, спинний мозок, радіальна глія, нероепітелій, імуногістохімічні маркери.

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МОРФОЛОГИЯ РАДИАЛЬНОЙ ГЛИИ СПИННОГО МОЗГА ЭМБРИОНОВ И ПЛОДОВ ЧЕЛОВЕКА

Школьников В.С., Приходько С.А., Полищук С.С., Кривовяз Е.В., Галушко А.М.

Изучение морфологии радиальной глии и процессов адресной миграции нейральных стволовых клеток у человека остается далеко не решенным до конца вопросом. Целью данного исследования является установление морфологических аспектов радиальной глии спинного мозга человека в пренатальном периоде. Проведенное морфологическое исследование спинного мозга эмбрионов и плодов человека от 6-7 нед. до 39-40 нед. При использовании анатомических, гистологических, иммуногистохимических, морфометрических были установлены морфологические аспекты радиальной глии спинного мозга. Полученные результаты показали, что сильная экспрессия виментина и CDX-2 волокон радиальной глии наблюдалась до 8-9 недели. С 11-12 недели волокна радиальной глии сохраняют радиальное направление только в средней части сегментов, что на наш взгляд связано с постепенной инволюцией радиальной глии, которая коррелирует с формированием ядерно-нейронных комплексов. До момента рождения виментин-позитивные структуры радиальной глии постепенно исчезают и прослеживаются только в нейроэпителии сегментов.

Ключевые слова: пренатальный период, спинной мозг, радиальная глия, нейроэпителий, иммуногистохимические маркеры.

Рецензент Єрошенко Г.А.

A.I. Yachmin, O.V. Vilkhova, N.V. Boruta, S.M. Bilash, G.A. Yeroshenko, T.A. Skotareno,
V.P. Bilash, D.R. Kramarenko
Ukrainian Medical Stomatological Academy, Poltava

SPECIFIC STRUCTURE OF THE NORMAL RAT GASTRIC FUNDUS WALL

e-mail: gala_umsa@ukr.net

As a result of a comprehensive study, it was determined that the wall of the fundus of the stomach of rats according to the basic principles of structural organization corresponds to humans and can be used as an experimental model to study the effects of exogenous factors. By means of morphometric research the basic metric indicators of a wall of fundal department of a rats' stomach and histotopographic features of own glands are established.

Key words: fundus of the stomach, wall, own glands, morphometry.

The paper has been written within the research scientific work "Patterns of morphogenesis of organs, tissues and neurovascular formations in normal condition, pathology and under the influence of exogenous factors", carried out at the Ukrainian Medical Stomatological Academy of the MOH of Ukraine (State registration No. 0118U004457).

In Ukraine, diseases of the digestive system rank third among all diseases of the internal organs [4, 11]. Currently, changes in the nature of food consumption do not meet the nutritional, energy and water needs of the human body. This can increase the number of diseases of the digestive system [8, 14].

Data on the influence of the nature of food [9], beverages [12, 15], diseases [2, 6], stress and harmful working conditions on the stomach are becoming more and more common in the literature.

Publications report that about 50% of the adult population of Ukraine suffers from diseases of the gastrointestinal tract, caused by the use of food additives [10], which is accompanied by behavioral disorders [13]. Specific structure and nutrition habits make the rats the most appropriate experimental model for studying the effect of harmful factors on humans; therefore, awareness of features of the structural organization of the normal rat gastric wall is relevant to date.

The purpose of the work was at the establishing the structural features of the normal rat gastric fundus wall.

Material and Methods. 10 outbred mature male albino rats were involved into the study. After animals euthanasia, fragments of the gastric fundus wall were fixed in 10% neutral formalin for three days.

Subsequently, pieces of the gastric fundus wall, fixed in formalin, were embedded into paraffin according to conventional technique [1].

Sections of 5-10 μm thick were made by the sledge micritome and put onto the slides using the stencil technique.

After staining with hematoxylin and eosin the sections were put into polystyrene and studied in the light microscope.

Microimaging and morphometric study of the specimens was carried out using the microscope equipped with the DCM 900 digital microphoto attachment and the software adapted for these studies. Morphometric data were statistically processed using the *Excel* software [5].

Animal housing and experiments on them have been carried out in compliance with the requirements of international principles of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" and general ethical principles of experiments on animals [7].

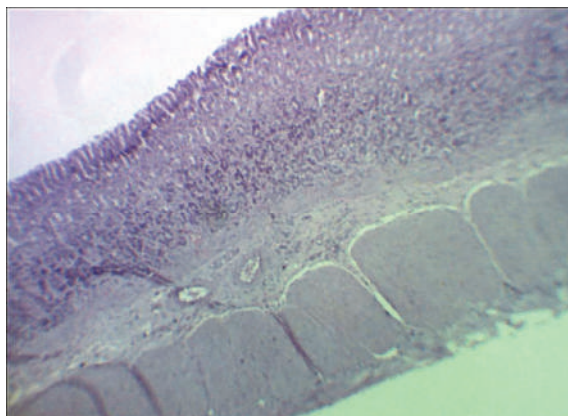


Fig. 1. Gastric fundus wall of rat of the control group. Microimage. H&E stain. 100 \times magnification.

Results of the study and their Discussion.

The gastric wall of rats of the control group had a regular structure and consisted of a mucous membrane with submucous layer, muscular and serous layers (Fig. 1).

The mucous membrane of the gastric fundus of rats of the control group was covered with a single layer columnar epithelium formed by superficial mucocytes. The lamina propria consisted of loose unformed connective tissue in which the vessels of the blood microvascular system were located. The muscular plate of the mucous membrane separated the latter from the submucous layer and was formed by smooth muscle tissue

that formed folds taking part in the formation of the surface topography of the stomach. Large vessels and nerve conductors were found in the submucous layer. Morphometric study has established the basic metric values of the gastric fundus wall of rats of control group (Table 1).

Table 1

Morphometric description of the gastric fundus wall of rats of control group (μm)

Parameters	Total thickness of the wall	Thickness of the mucous membrane	Thickness of the submucous layer	Thickness of the muscular layer	Thickness of the serous layer
Control group	1259,0 \pm 15,47	673,28 \pm 6,18	127,78 \pm 8,19	454,24 \pm 3,13	9,51 \pm 0,67

Superficial mucocytes were cylindrical; mucus granules were localized in the apical part; in the basal part the nucleus and endoplasmic reticulum was visualized (Fig. 2a).

The lamina propria was detected beneath the epithelium, containing the proper gastric glands. They were simple, weakly branched, tubular, and consisted of the isthmus, neck and head (Fig. 1). Proper glands of the gastric fundus contained cervical, basal and parietal exocrinocytes, stem cells and endocrinocytes. Cervical exocrinocytes were found only in the neck of the glands and were similar in structure to superficial mucocytes, had an irregularly shaped nucleus, secretory granules were localized in the apical parts of cells. Stem cells were also detected only in the neck by the cervical exocrinocytes and were a source of regeneration of both the superficial epithelium of the gastric fundus and the cells of the proper glands. Their nuclei had a basal localization (Fig. 1a).

The basal exocrinocytes made up the vast majority of the main part of the gland. Their cytoplasm was stained basophilic, the nucleus was detected in the basal part of the cells, the apical part contained secretory granules (Fig. 2b). Parietal exocrinocytes were detected from the outside of the main cells, were adjacent to their basal ends and were localized mainly in the upper half of their proper glands and scattered ones were found at the bottom. Their cytoplasm was stained oxyphilic (Fig. 2b).

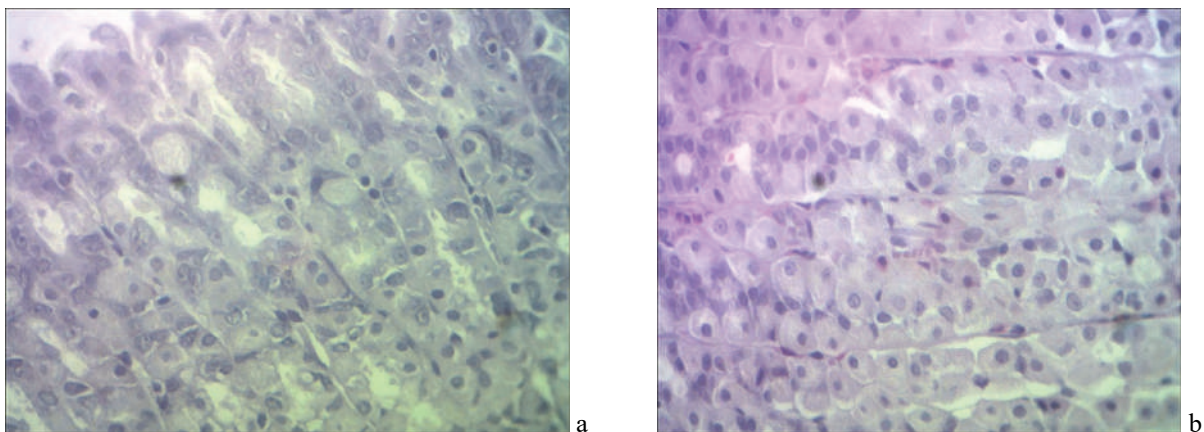


Fig. 2. Necks (a) and bodies (b) of the fundal glands of rat of the control group. Microimage. H&E stain. 400 \times magnification.

Endocrinocytes of the proper gastric glands were detected in the deep parts. The sections, stained with hematoxylin-eosin, had an optically light eosinophilic cytoplasm, apical parts were not conjoined with the lumen, granules were accumulated in the basal parts (Fig. 3a).

Vessels of the blood microvascular system, namely, arterioles and venules, were detected in the lamina propria; capillaries were localized in the connective tissue between the glands (Fig. 3a).

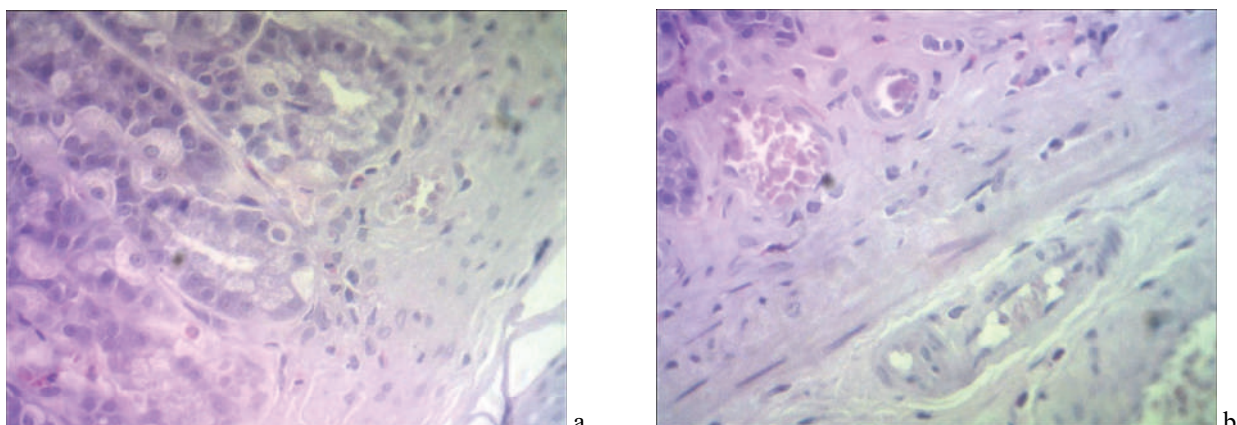


Fig. 3. The bottom of the fundal gastric glands (a) and microvasculature of the lamina propria (b) of rats of the control group. Microimage. H&E stain. 400 \times magnification.

The muscular plate of the mucous membrane was formed by several rows of smooth myocytes. Arteries and veins were visualized in the loose connective tissue of the submucous layer (Fig. 3b).

The local protective barrier in the mucous membrane of the gastric fundus of rats of the control group was represented by intraepithelial lymphocytes (Fig. 4a). Lymphocytes, macrophages and plasma cells were detected perivascularly in the lamina propria (Fig. 4b).

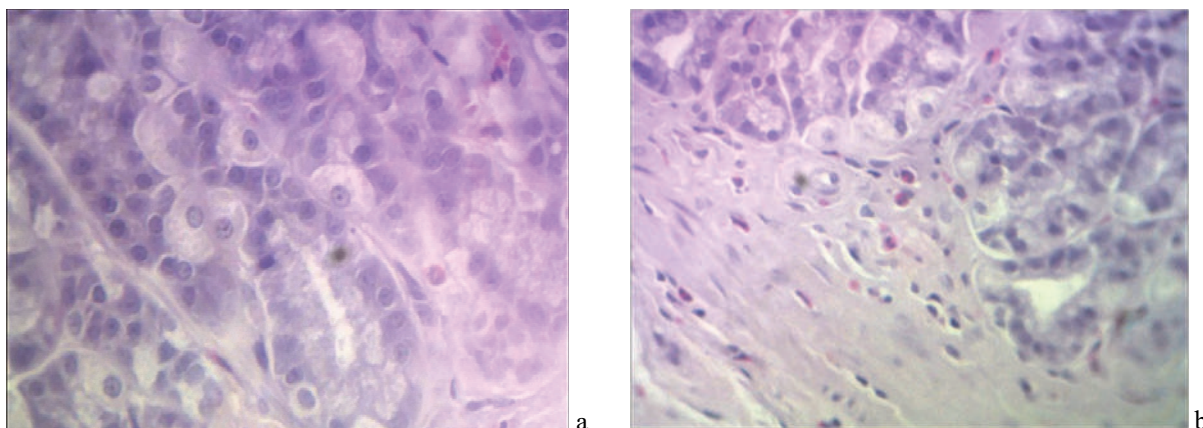


Fig. 4. Intraepithelial lymphocytes at the bottom of the gastric fundal glands (a) and leukocytes in the lamina propria (b) of the gastric wall of rat of the control group. Microimage. H&E stain. 400 × magnification.

At the neck of the gland in the group of intact animals, the outer diameter was $34.17 \pm 1.13 \mu\text{m}$; the diameter of the lumen was $10.63 \pm 0.74 \mu\text{m}$; the height of the epitheliocytes was $12.14 \pm 0.40 \mu\text{m}$.

At the body of the glands, the outer diameter was $32.81 \pm 1.26 \mu\text{m}$; the diameter of the lumen was $7.47 \pm 0.39 \mu\text{m}$; the height of the epitheliocytes was $11.09 \pm 0.55 \mu\text{m}$.

At the bottom of the gland the outer diameter was $43.68 \pm 1.43 \mu\text{m}$; the diameter of the lumen was $7.72 \pm 0.29 \mu\text{m}$; the height of the epitheliocytes was $14.47 \pm 0.47 \mu\text{m}$.

Thus, the results of histological examination suggest that the wall of the fundus of the rats' stomach according to the basic principles of structural organization corresponds to human and can be used as an experimental model to study the effects of exogenous factors.

The determined metrics data showed that the largest indicator of the outer diameter and height of the epitheliocytes of the rats' gastric glands of the control group was in the bottom, the average diameter of the lumen - in the body of the glands. The established values of the average wall thickness are consistent with the data of other researchers [2, 3].

Conclusions

As a result of a comprehensive study, it was determined that the wall of the fundus of the stomach of rats according to the basic principles of structural organization corresponds to humans and can be used as an experimental model to study the effects of exogenous factors. By means of morphometric research the basic metric indicators of a wall of fundal department of a rats' stomach and histotopographic features of own glands are established.

References

1. Bagrij MM, Dibrova VA, Popadinec' OG, Grishchuk MI. Metodiki gistologichnih doslidzen' monografiya; za red. Bagriya MM, Dibrovi A. Vinnicya: Nova kniga. 2016; 328 s.
2. Bilash SM, Shepit'ko VI, Yeroshenko GA. Strukturno-funkcional'ni osoblivosti elementiv difuznoi endokrinnoi sistemi shlunku pri vvedenni kriokonservovanoi placenti na tli zapal'nogo procesu. Svit medicini ta biologii. 2013; 2(38):16–8.
3. Bilash SM, Yeroshenko GA, Pirog-Zakaznikova AV. Morfofunkcional'ni zmini ekzokrinocitiv fundal'nih zaloz shlunku pri gostromu eksperimental'nomu gastriti ta korekciya ih vvedennyam preparatu «Plateks-placentarnij». Visnik problem biologii i medicini. 2013; 1(101):184–7.
4. Dudnik SV, Koshelya II. Tendencii stanu zdorov'ya naseleण्या Ukraїni. Ukraїna. Zdorov'ya naciї. 2016; 4: 67–77.
5. Lapach SN, CHubenko AV, Babich PN. Statisticheskie metody v mediko-biologicheskikh issledovaniyah s ispol'zovaniem Exel. Kiev: Morion. 2000; 320 s.
6. Mihaleva LM, Barhina TG, Shchegoleva NN, Gracheva NA, Golovanova VE. Strukturnye izmeneniya kapillyarov slizistoj obolochki zheludka i dvenadcatiperstnoj kishki pri bronhial'noj astme. Arh. patologii. 2014; 76(1):37–41.
7. Normativnij dokument Ministerstva osviti, nauki, molodi ta sportu Ukraїni. Nakaz vid 01.03.2012 № 249. Poryadok provedennya naukovimi ustanovami doslidiv, eksperimentiv na tvarinah. Oficijnij visnik Ukraїni. Ofic. V id. 2012;24. s. 82.
8. Romanenko EG. Strukturnye izmeneniya v slizistyh obolochkah verhnih otdelov pishchevaritel'nogo trakta pri eksperimental'nom gastroduodenite. Morfologiya. 2013; 7(1): 73–7.
9. Semenova MA, Cyganova NA, Drozhdina EP, Saenko YUV, Glushchenko ES, Antonova AV. i dr. Nekotorye morfologicheskije i fiziologicheskije harakteristiki postnatal'nogo ontogeneza belyh kryv v usloviyah dlitel'nogo pitaniya dispergirovannoj pishchej. Fundamental'nye issledovaniya. 2013; 4(5):1144–48.

10. Falaleeva TM, Kuhars'kij VM, Beregova TV. Vpliv trivalogo vvedennya glutamatu natriyu na strukturno-funkcional'nij stan shlunka ta masu tila shchuriv. Fiziologichnij zhurnal. 2010; 56(4): 102-10.
11. Shchorichna dopovid' pro stan zdorov'ya naseleння, sanitarno-epidemichnu situaciyu ta rezul'tati diyal'nosti sistemi ohoroni zdorov'ya Ukraїni. 2016 rik. MOZ, DU UISD MOZ Ukraїni. Kiiv, 2017:516.
12. Shtanova LYa, Govoruha TM, Vovkun TV. Efekti korvritinu na slizovu obolonku shlunka shchura, urazhenu 80 % etanolom, za riznih doz preparatu. Fitoterapiya. CHasopis. 2013; 3: 23–30.
13. Yachmin' A.I., Kononov B.S., Yeroshenko G.A., Bilash S.M., Bilash V.P. Vznachennya vplivu kompleksu harchovih dobavok na adaptivni reakcii shchuriv. Svit medicini ta biologii. 2020; 1(71):245-248.
14. Al-Qudah MM. The Histological Effect of Hunger Stress on the Stomach in Male Albino Rats: A Study of Light Microscope. Res. J. Biol. Sci. 2011; 6(11): 569–74.
15. Ayuob N, ElBeshbeishy R. Impact of an Energy Drink on the Structure of Stomach and Pancreas of Albino Rat: Can Omega-3 Provide a Protection? J. PLoS ONE. 2016; 11(2): DOI: 0.1371/journal.pone.0149191.S001.

Реферати

**СТРУКТУРНІ ОСОБЛИВОСТІ СТІНКИ
ФУНДАЛЬНОГО ВІДДІЛУ ШЛУНКУ ЩУРІВ
У НОРМІ**

**Ячмінь А.І., Вільхова О.В., Борута Н.В.,
Білаш С.М., Єрошенко Г.А., Скотаренко Т.А.,
Білаш В.П., Крамаренко Д.Р.**

У результаті проведеного комплексного дослідження визначено, що стінка фундальної частини шлунку щурів за основними принципами структурної організації відповідає людині і може бути використана в якості експериментальної моделі для вивчення дії екзогенних чинників. За допомогою морфометричного дослідження встановлені основні метричні показники стінки фундального відділу шлунку щурів та гістолопографічні особливості власних залоз.

Ключові слова: фундальна частина шлунку, стінка, власні залози, морфометрія.

Стаття надійшла 12.05.2019 р.

**СТРУКТУРНЫЕ ОСОБЕННОСТИ СТЕНКИ
ФУНДАЛЬНЫЙ ОТДЕЛ ЖЕЛУДКА КРЫС
В НОРМЕ**

**Ячминь А.И., Вильховая А.В., Борута Н.В.,
Билаш С.М., Ерошенко Г.А., Скотаренко Т.А.,
Билаш В.П., Крамаренко Д.Р.**

В результате проведенного комплексного исследования определено, что стенка фундальной части желудка крыс основными принципами структурной организации соответствует человеку и может быть использована в качестве экспериментальной модели для изучения действия экзогенных факторов. С помощью морфометрического исследования установлены основные метрические показатели стенки фундального отдела желудка крыс и гистолопографические особенности собственных желез.

Ключевые слова: фундальная часть желудка, стенка, собственные железы, морфометрия.

Рецензент Старченко І.І.

ШАНОВНІ КОЛЕГИ!

Матеріали для опублікування приймаються від спеціалістів у галузі теоретичної, профілактичної, клінічної медицини, суміжних дисциплін, а також досліджень в галузі біологічних наук (Наказ МОН України № 612 від 07.05.2019 р.). Мова публікацій – українська, англійська, російська.

Публікація повинна відбивати сучасний стан розробки досліджуваної проблеми, містити нові результати на основі проведеного дослідження, **перспективи подальших розробок у даному напрямку**. Висновки мають бути аргументованими відповідним ілюстративним матеріалом.

До друку приймаються наукові статті, які містять такі необхідні елементи: шифр УДК; назва статті; ініціали авторів та прізвища (кількість авторів однієї статті не повинна перевищувати п'яти осіб); назва установи та місто; дані про **зв'язок публікації з плановими науково-дослідними роботами** (з наведенням номеру держреєстрації)

Вступ: постановка проблеми у загальному вигляді; аналіз останніх (за останні 10 років) досліджень та публікацій, в яких започатковано розв'язання даної проблеми і на які спирається автор; визначення невирішених раніше частин загальної проблеми;

Мету

Матеріал та методи дослідження

Результати дослідження та їх обговорення

Висновки або підсумки

Перспективи подальших розробок у даному напрямку

Список літератури за Ванкуверським стилем спочатку кирилицею, потім – латиницею.

Реферати російською, українською і англійською мовами обсягом не більше 0,5 стор. У випадку наведення статті українською, або російською мовами додаткове резюме англійською мовою – 1,5-2 сторінки англійською мовою, англійською мовою – розширене резюме українською мовою.

Таблиці – не більше 4. Графіки (**не більше 4**) повинні мати чіткі калібрування по осям. Якщо наводяться декілька кривих, безпосередньо на рисунку необхідно вказати їх порядкові номери. Рисунки, крім діаграм, в електронному варіанті бажано надавати в розширенні РСХ, фото (**не більше 4**) – в JPEG.

Список літератури оформлюється без скорочень. Автори подаються за абеткою, спочатку кирилицею, потім латиницею. Посилання в тексті зазначаються цифрами у квадратних дужках.

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За додатковою інформацією звертайтеся до відповідального секретаря – професора Єрошенко Галини Анатоліївни.

Адреса редакції: 36024, м. Полтава, вул. Шевченка, 23, кафедра гістології, цитології та ембріології. Тел. (служ.) (05322) 60-84-44. E-mail: womab.ed@gmail.com

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