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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

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ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

НАУКА

ANALYSIS OF POLYMORPHISM OF MATRIX METALLOPROTEINASE-2 ($C^{-1306} \rightarrow T$) AND TISSUE INHIBITORS OF METALLOPROTEINASE-2 ($G^{303} \rightarrow A$) GENES IN PATIENTS WITH ANASTOMOTIC LEAK IN HOLLOW DIGESTIVE ORGANS

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Despite the improvement of existing techniques and the development of new surgical technologies, the anastomotic leak in the hollow digestive organs is one of the most difficult complications in abdominal surgery. The incidence of such complications, according to various authors, ranges from 2-8.1% in small bowel anastomosis to 3.8-14.6% in operations on the colon [1,2]. Anastomotic leak is accompanied by mortality rate of 14-21.7% [3]; with the development of disseminated peritonitis, abdominal sepsis mortality increases up to 43-82.9% [1,4]. So far, there is no single point of view in the surgical community regarding the causes of anastomotic leak development and surgical tactics in the development of these complications. According to the literature on the subject, among the risk factors for the development of an anastomotic leak are microcirculation disruption in the anastomosis area, tissue regeneration failure, infection, increased intra-intestinal pressure, changes in the rheological properties of blood, homeostatic imbalances, etc. [1]. A separate group of risk factors includes tactical and technical errors in the formation of anastomosis [5].

Although there is no doubt about the role of regenerative processes in the formation of intestinal anastomosis [6,7], scientific publications and research at the current methodological level on this topic are not enough. An in-depth study of the mechanisms of reparative regeneration in the area of the anastomosis and possibilities of regenerative processes stimulation, adequate restoration of morpho-functional characteristics of digestive organs that have been anastomosed is necessary. In domestic and foreign sources, there are almost no publications about the role of undifferentiated dysplasia of the connective tissue (UDCT) in the development of anastomotic leak in hollow digestive organs.

Anastomosis formation is a complex molecular- and cell-mediated process aimed at restoring of the continuity of the hollow digestive organs [7]. It involves both classical processes of inflammation: alteration, exudation, proliferation, and specific reparative processes due to suture technique, suture material, the presence of infection, and other factors [8].

Given the almost unexplored role of genetic predisposition in the development of postoperative complications, namely the failure of anastomotic sutures, we set a goal to study the polymorphism of genes encoding matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of matrix metalloproteinase-2 (TIMP-2). The choice of these genes was not accidental - we were guided by the main known pathophysiological mechanisms involved in the formation of the intestinal anastomosis [7].

Matrix metalloproteinases (MMPs) are a group of enzymes represented by cysteine, serine, aspartyl, and metal-dependent proteinases. They belong to Zn^{2+} - and Ca^{2+}-dependent endopeptidases, which are involved in the remodeling of connective tissue due to the destruction of its organic components at normal pH values. MMPs play a major role in the metabolism of connective tissue proteins. These enzymes are also involved in many physiological (embryonic development, morphogenesis, migration, adhesion, angiogenesis, involution, and tissue remodeling) and pathological (inflammation, malignancy, cardiovascular, pulmonary diseases, arthritis) processes. They are also able to model the activity of growth factors, cytokines, and their receptors. Enzymes from the MMPs group (MMPs -2, -3, -9) affect vascular wall permeability and angiogenesis by regulating the catabolism of extracellular matrix components and cell-matrix interactions [9]. Currently, approximately 30 different MMPs are known, which are divided into 5 groups based on substrate specificity: collagenases; gelatinases; stromelysins; membrane-bound; other matrixins not included in the above groups. The gelatinase subfamily includes 2 enzymes - gelatinase A (MMP-2) and gelatinase B (MMP-9). MMP-2,9 show a high affinity for type IV collagen, so they are sometimes called type IV collagenases. MMP-2 occupy a central position in the regulating of the balance between the processes of synthesis and proteolysis in the extracellular matrix, affect the implementation of physiological processes and pathological changes in the body [9].

The main regulators of matrix metalloproteinases are tissue inhibitors of metalloproteinases - TIMPs (TIMP-1, TIMP-2, TIMP-3, TIMP-4). All 4 groups of TIMPs can inhibit the proteolysis of latent forms of MMP and inhibit the active forms of MMP, but TIMP-1 is more active against MMP-9, and TIMP-2 shows specificity for MMP-2 [10].

Recently these enzymes, namely their expression, polymorphism of the genes that encode them, have been actively studied as diagnostic and prognostic factors in oncological diseases [11,12,13], cardiovascular pathology [14,15], ophthalmology [16], etc.

At the same time, information on the role of MMPs in the development of anastomotic leak in hollow digestive organs is almost absent. During the analysis of the literature, we found a small number of publications on the study of MMP expression in the colorectal anastomoses leak [17-19], postoperative peritonitis [20,21].

However, we have not found publications on the study of genetic polymorphism of matrix metalloproteinases and their regulators in terms of the development of anastomotic leak.

The aim - to analyze the frequency of polymorphic variants of genes MMP-2 ($C^{-1306} \rightarrow T$) and TIMP-2 ($G^{303} \rightarrow A$) in patients with anastomotic leak in hollow digestive organs.

Material and methods. A retro- and prospective trial was based on data on 61 patients, who were treated at the Shalimov National Institute of Surgery and Transplantology. 17 of 61 patients (experimental group 2) suffered anastomotic leak in hollow digestive organs, 44 of 61 patients (experimental group 1) had phenotypic signs of UDCT. For the assessment of genetic polymorphism in the population, 80 practically healthy people

have been examined (control group), who were matched by gender and age with experimental groups. Of the special laboratory tests, we have measured serum procalcitonin and C-reactive protein. For the assessment of connective tissue, we analyzed free hydroxyproline in the serum and urinary glycosaminoglycans. UDCT has been diagnosed with a proven technique (Ukrainian patent for utility model №120158 UA). The stage of dysplasia was evaluated using the original clinical screening scale, which was based on the table of the severity criteria of connective tissue dysplasia made by T.Y. Smolnova (2003) [22].

Genetic studies were performed in the laboratory of the Department of General and Molecular Pathophysiology at the Bogomoletz Institute of Physiology NAS of Ukraine. The collection of the buccal epithelium was performed using buccal brushes with the upcoming freezing of the samples at the temperature of -20 ° C. DNA for the genotyping was extracted from the samples using Diatom™ Prep 200 (Isogen Laboratory, RF) following the manufacturer's protocol.

The following polymorphisms were studied by real-time PCR: $C^{-1306} \rightarrow T$ (MMP2), rs243865 and $G^{303} \rightarrow A$ (TIMP2), rs9900972. Amplification reactions were performed using the Fast Real-time PCR System (Applied Biosystems, USA) in a final reaction volume of 20 µl containing 2X TaqMan Universal Master Mix (Applied Biosystems, USA), assay C_1792560_10 and template DNA. Amplification of gene fragments consisted of a denaturation step at 95° C for 20 s, followed by 40 cycles of amplification at 95° C for 3 s and 60° C for 30 sec. Data analysis was performed with 7500 Fast Real-Time PCR Software (Applied Biosystems, Foster City, USA).

The main part of the statistical analysis was performed using the program «Statistica 7.0» (SPSS) and Excel 2000. Nominal data were presented in the form of quantitative and percentage values. The significance of differences in mean values in groups with different genotypes was determined using the method of one-way analysis of variance (URL: http://www.dgmp.kyiv.ua/index.php/snip-ka). The correspondence of genotype distribution was checked using the Hardy-Weinberg test. Pearson's $\chi 2$ test was used to compare the distribution of genotypes in the experimental and control groups.

Results and discussion. To identify the possible association of polymorphic variants of the MMP-2 ($C^{-1306} \rightarrow T$) and TIMP2 ($G^{303} \rightarrow A$) genes with the risk of anastomotic leak, we performed a one-way analysis of variance of the frequency of genotypes in the studied groups of patients (Table 1).

In the analysis of models of inheritance of the MMP2 gene ($C^{-1306} \rightarrow T$), namely codominant, dominant, recessive, supradominant and additive in the control group (n = 80) and the experimental group 1 with phenotypic signs of UDCT (n = 44), it was found that the distribution of genotypes corresponds to the Hardy-Weinberg law (p> 0.05). Using the $\chi 2$ test with 2 degrees of freedom, we were not able to detect statistically significant differences in the distribution of genotypes in the group of sick people and the group of practically healthy people (p>0.05).

Having analyzed all inheritance models, we selected the best model with the lowest Akaike Information Criterion. Such a model turned out to be a recessive model, for which the table shows the values of the odds ratio, statistical significance, as well as the Akaike Information Criterion (AIC) (Table 2).

Table 1. The distribution of polymorphic variants of genes MMP-2 ($C^{-1306} \rightarrow T$), rs243865 and TIMP-2 ($G^{303} \rightarrow A$), rs9900972 in the studied groups

The studied gene		Control group n=80 (%)	Experimental group 1 (with phenotypic signs of UDCT) n=44 (%)	Experimental group 2 (with anastomotic leak) n=17 (%)
MMP2 ($C^{-1306} \rightarrow T$)	CC	38 (47,5%)	26 (59,1%)	11 (64,7%)
	CT	34 (42,5%)	16 (36,4%)	5 (29,4%)
	TT	8 (10%)	2 (4,5%)	1 (5,9%)
Hardy-Weinberg test (χ^2, p)		χ^2=0,01, p>0,05	χ^2=0,05, p>0,05	χ^2=0,17, p>0,05
TIMP2 ($G^{303} \rightarrow A$)	GG	50 (50%)	24 (54,5%)	14 (82,4%)
	GA	32 (40%)	15 (34,1%)	3 (17,6%)
	AA	8 (10%)	5 (11,4%)	0 (%)
Hardy-Weinberg test (χ^2, p)		χ^2=0,18, p>0,05	χ^2=1,15, p<0,05	χ^2=0,15, p<0,05

Table 2. The odds ratio for a recessive model of inheritance of patients with phenotypic signs of UDCT. Odds ratio with 95% confidence interval

Genotype	Control group n=80 (%)	Experimental group 1 (with phenotypical signs of UDCT)n=44 (%)	Odds ratio	p-value	AIC
CC+CT	72 (90%)	42 (95.5%)	1.00		
TT	8 (10%)	2 (4.5%)	0.43 (0.06 - 1.81)	0.3	16.12

Table 3. The odds ratio for the recessive model of inheritance in patients with failure of anastomotic sutures. Odds ratio with 95% confidence interval

Genotype	Control group n=80 (%)	Experimental group 2 (with anastomotic leak) n=17 (%)	Odds ratio	p-value	AIC
CC+CT	72 (90%)	16 (94.1%)	1.00		
TT	8 (10%)	1 (5.9%)	0.56 (0.03 - 3.39)	0.6	14.62

Analysis of the multiplicative model of inheritance of the MMP-2 gene ($C^{-1306} \rightarrow T$), comparing the control group (n=80) and experimental group 2 with anastomotic leak (n=17) showed compliance with the distribution of genotypes to Hardy-Weinberg's law (p>0,05), which was tested in the control group using the test $\chi 2$ with 1 degree of freedom, without Yates correction. Using the test $\chi 2$ with 2 degrees of freedom, we did not find statistically significant differences in the distribution of genotypes in the group of sick people and the group of practically healthy people (p>0.05). After analyzing all models of inheritance, we chose the best model with the lowest AIC (Table 3).

It is noteworthy that in experimental groups 1 and 2 there were half as many carriers of the homozygous TT genotype as compared with the control: 4.4% and 5.9% versus 10% (p<0.05), respectively. However, carriers of the SS genotype dominant in all groups were greater in the group with suture failure (research 2): 64.7% versus 47.5% (p<0.05) in the control (Fig. 1).

In the analysis of TIMP-2 inheritance models ($G^{303} \rightarrow A$), in the control group (n = 80) and experimental group 1 with phenotypic signs of connective tissue pathology (n = 44), we could not find statistically significant differences in the distribution of genotypes in the group of patients and the group of almost healthy people (p>0.05). The conformity of the genotype distribution to Hardy-Weinberg's law in the control group was checked using the $\chi 2$ test with 1 degree of freedom, without the use of Yates correction. It was found that the distribution of genotypes in the control group corresponds to Hardy-Weinberg's law (p>0.05).

We were able to find statistically significant differences in the distribution of genotypes (p<0.05) in the analysis of TIMP-2 inheritance models ($G^{303} \rightarrow A$), in the control group (n=80) and experimental group 2 with anastomotic leak (n=17). The conformity of the genotype distribution to Hardy-Weinberg's law in the control group was checked using the $\chi 2$ test with 1 degree of freedom, without the use of Yates correction. After analyzing all models of inheritance, we chose the best model with the lowest AIC (Table 4).

In the examined population in the control group and experimental group 1, the distribution of carriers of GG, GA, and AA genotypes was significantly similar. However, in the group of patients with anastomotic leak (experimental group 2), the distribution of genotype carriers was significantly different. Thus, the dominant GG variant almost twice significantly exceeded the indicators of control and experimental group 1 (82.4% vs. 50% and 54.4%, respectively, p<0.05). Heterozygous GA genotype in the second experimental group was more than twice as rare as in the control (17.6% vs. 40%). Carriers of homozygous AA genotype in the group with anastomotic leak were not detected, while a similar variant in control and experimental group 1 was found in 10% and 11.4% of cases (Fig. 2).

In examined patients with anastomotic leak of the hollow digestive organs, signs of UDCT were found in 13 (76.47%) patients. The following phenotypic pathologies of UDCT were most commonly encountered: visceral pathology (76.47%), vascular pathology (70.58%), arrhythmias (52.9%).

The study of phenotypic signs of UDCT in the group of patients with anastomotic leak showed that 3 patients (17.6%) had a mild UDCT, 6 patients (35.3%) had moderate, and 4 patients (23.6%) had a severe degree of UDCT. In 4 patients (23.5%), signs of the pathology of the connective tissue were not detected.

The level of serum hydroxyproline in the group of patients without phenotypic signs of connective tissue dysplasia was 36.9±1.6 μmol/L, which is almost twice as high as in the control group (21.2±0.8 μmol/L). When studying the dynamics of changes in serum hydroxyproline levels, it was found that an increase in the collagenolytic activity of glycosaminoglycans and free hydroxyproline levels had a direct correlation with the severity of UDCT. With a mild degree of UDCT, the level of serum hydroxyproline was (46.9±2.8) μmol/L, moderate (75.2±3.2) μmol/L and severe (122.1±3.6) μmol/l, which is almost 6 times higher than in the control group and 3 times higher than in patients with anastomotic leak without clinical signs of connective tissue dysplasia.

When studying the dynamics of changes in urinary glycosaminoglycans levels, a direct correlation with the severity of UDCT was also revealed. With a mild degree of UDCT, the level of glycosaminoglycans was 80.94±2.8 μmol/L, which is highly reliable, twice as many as in the control group (44.68±1.8). With an average degree of 105.12±3.5 μmol/L and a severe degree of 127.54±3.4 μmol/L, which was almost 3 times higher than the control group and 2 times higher than patients with anastomotic leak without clinical signs of connective tissue dysplasia.

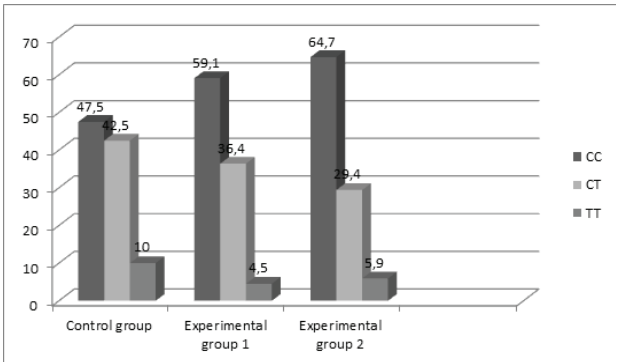

Fig. 1. Frequency distribution of allelic polymorphism (%) of the promoter ($C^{-1306} \rightarrow T$) MMP2 gene

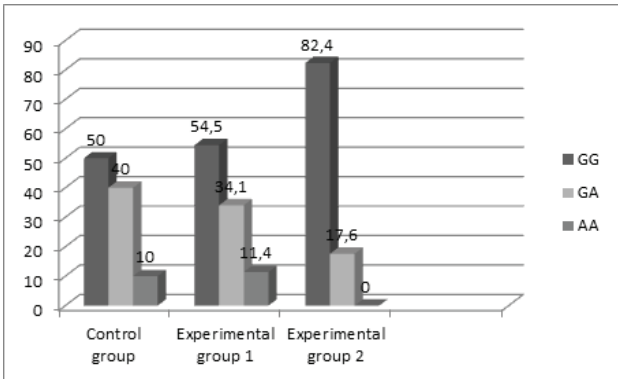

Fig. 2. Frequency distribution of allelic polymorphism (%) of the promoter ($G^{303} \rightarrow A$) of the TIMP2 gene

Table 4. The odds ratio for recessive inheritance model in patients with anastomotic leak. Odds ratio with 95% confidence interval

Genotype	Control group n=80 (%)	Experimental group 2 (with anastomotic leak) n=17 (%)	Odds ratio	p-value	AIC
GG+GA	72 (90%)	17 (100%)	1.00		
AA	8 (10%)	0 (0%)	0 (NA-1.479e+266)	1	15.62

Our data on the study of polymorphic variants of the MMP2 ($C^{-1306} \rightarrow T$) and TIMP2 ($G^{303} \rightarrow A$) genes in the Ukrainian population (n = 80) generally correspond to populations of Europe and the USA [23,24].

The closest genotypic variations in the studied genes were populations of Austria [25] and the Netherlands [26]. Moreover, we found significant differences when compared with the African and Asian populations [27,28]. Interestingly, in these populations, the frequency of the main C allele of the MMP-2 gene (rs243865) was 93.7% (Africa) and 90% (Asia), which significantly exceeds the indices of our control group (76%) and the European population (75,5%). Whereas, the minor T allele was found in 24% of the control group, and 10% (Asia) and 6.7% (Africa), respectively [23].

As a result of genetic and statistical analysis of the polymorphism of the MMP-2 ($C^{-1306} \rightarrow T$) and TIMP-2 ($G^{303} \rightarrow A$) genes, variants of genotypes associated with the risk of development of anastomotic leak of the hollow digestive organs were determined.

Thus, in the experimental group with anastomotic leak, carriers of the homozygous SS genotype of the MMP2 gene were found to be 1.36 times more often than in the control group. At the same time, the minor TT homozygotes in the group of patients with anastomotic leak were almost half that in the control (5.9% versus 10% ($p < 0.05$)).

In the analysis of carriers of TIMP-2 genotypes, we obtained statically reliable data: in the group of patients with anastomotic leak, GG variant was 82.4%, which is 1.6 times higher than in the control group (82.4% vs. 54.4%, $p<0.05$). Carriers of minor homozygotes of AA genotype in the group of patients with anastomotic leak were not detected, while a similar genotype in the control group was found in 10%.

Given the role of matrix metalloproteinases and their inhibitors in the processes of synthesis and proteolysis, connective tissue remodeling, connective tissue protein metabolism, the ability to affect vascular permeability and angiogenesis, [8] the relevance of their study in the context of the pathogenesis of anastomotic leak of the hollow digestive organs is undoubted.

There are several publications in the literature on the detection of changes in the ratio of type I/III collagen, increased expression of MMP-1 and MMP-2 in the mucosa and MMP-2 and MMP-9 in the submucosal layer of the colon in patients with the leakage of colorectal anastomosis [17-19].

The correlation between the level of biochemical markers of collagen biodegradation and the severity of UDST revealed, which is diagnosed on the basis of phenotypic, visceral manifestations, and instrumental examinations. This could serve as an informative diagnostic criterion of UDST and could be used to predict the development and course of complications in patients with anastomotic leak in the hollow digestive organs. Such changes are apparently due to increased proteolytic activity in patients with anastomotic leak. This confirms the data of some authors that the anastomotic leak and development of peritonitis leads to a pronounced and persistent mismatch in the proteinase system - inhibitors of blood proteinases. It is the hyperactivation of proteolytic systems of the body against the background of reduction of inhibitory potential that is regarded as one of the key pathogenetic links of endogenous intoxication.

Understanding the pathogenetic processes underlying the formation of the anastomosis and possible «weaknesses» is no less important than the surgical technique.

In our view, the focus of future research on the pathogenetic factors of abdominal postoperative complications should be shifted to a more cellular and molecular level. Thus, a better understanding of the mechanisms of the formation of intestinal anastomosis will contribute to the development of new diagnostic, prognostic, and therapeutic techniques.

The differences we have identified in allelic variants of the studied genes in the groups with anastomotic leak are the basis for further study and research for molecular genetic markers that encode the main links in the pathogenesis of anastomotic leak and other postoperative complications.

Conclusions.

1. Anastomotic leak in hollow digestive organs is 1.36 times more common in carriers of homozygous CC genotype of the MMP-2 gene, and twice less common in minor homozygotes of TT (5.9% vs. 10%, $p>0,05$).

2. In the group of patients with anastomotic leak in hollow digestive organs, it is statistically significant, the GG variant of the TIMP-2 gene was detected 1.6 times more often. Carriers of minor homozygotes of AA genotype in the group with anastomotic leak were not detected, while a similar genotype in the control group was found in 10% ($p<0,05$).

3. Molecular genetic research can be a new promising area for the development of modern personalized diagnostic criteria and models for predicting the development and course of postoperative abdominal complications, including the anastomotic leak of the hollow digestive organs.

4. The presence of connective tissue dysplasia in patients with anastomotic leak in the hollow digestive organs is an aggravating comorbid factor, which must be considered when choosing adequate surgical tactics and complex pathogenetically substantiated treatment.

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SUMMARY

ANALYSIS OF POLYMORPHISM OF MATRIX METALLOPROTEINASE-2 ($C^{-1306} \rightarrow T$) AND TISSUE INHIBITORS OF METALLOPROTEINASE-2 ($G^{303} \rightarrow A$) GENES IN PATIENTS WITH ANASTOMOTIC LEAK IN HOLLOW DIGESTIVE ORGANS

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The aim. To analyze the frequency of polymorphic variants of MMP-2 ($C^{-1306} \rightarrow T$) and TIMP-2 ($G^{303} \rightarrow A$) genes in patients with anastomotic leak in hollow digestive organs.

The object of the study comprises 61 patients with anastomotic leak and connective tissue pathology, all treated at the Shalimov National Institute of Surgery and Transplantology during 2016-2019. Laboratory, genetic, histological studies and statistical analysis were performed.

As a result of genetic and statistical analysis of the MMP-2 ($C^{-1306} \rightarrow T$) and TIMP-2 ($G^{303} \rightarrow A$) gene polymorphisms, genotype variants have been identified that are associated with the risk of anastomotic leak in hollow digestive organs. Significant differences in the distribution of genotypes in the studied groups were revealed. Analysis of the multiplicative model of inheritance of MMP-2 and TIMP-2 genes showed compliance of genotype distribution with Hardy-Weinberg's law. All models of inheritance were analyzed and the best model with the lowest Akaike Information Criterion, which turned out to be a recessive model, has been determined.

Anastomotic leak in hollow digestive organs is 1.36 times more common in carriers of homozygous CC genotype of the MMP-2 gene and twice less common in minor homozygotes of TT (5.9% vs. 10%, $p>0.05$). It is statistically significant that in the group of patients with anastomotic leak in hollow digestive organs the GG variant of the TIMP-2 gene was detected 1.6 times more often. Carriers of minor homozygotes of AA genotype in the group with suture failure were not detected, while a similar genotype in the control group was found in 10% ($p<0.05$).

Keywords: Anastomotic leak, MMP-2, TIMR-2, gene polymorphism.

РЕЗЮМЕ

АНАЛИЗ ПОЛИМОРФИЗМА ГЕНОВ МАТРИКСНОЙ МЕТАЛЛОПРОТЕИНАЗЫ - 2 (C^{-1306}→T) И ТКАНЕВОГО ИНГИБИТОРА МАТРИКСНОЙ МЕТАЛЛОПРОТЕИНАЗЫ - 2 (G^{303}→A) У БОЛЬНЫХ С НЕСОСТОЯТЕЛЬНОСТЬЮ ШВОВ АНАСТОМОЗОВ ПОЛЫХ ОРГАНОВ ПИЩЕВАРЕНИЯ

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Цель исследования - анализ частоты полиморфных вариантов генов матриксной металлопротеиназы – 2 (C^{-1306}→T) и тканевого ингибитора матриксной металлопротеиназы - 2 (G^{303}→A) у больных с несостоятельностью швов анастомозов полых органов пищеварения.

Обследован 61 пациент с несостоятельностью швов анастомозов (n=17) и патологией соединительной ткани (n=44), которые лечились в Национальном институте хирургии и трансплантологии им. А.А. Шалимова. Проведены лабораторные, генетические, гистологические и статистические исследования.

В результате генетического и статистического анализа полиморфизма генов матриксной металлопротеиназы – 2 (C^{-1306}→T) и тканевого ингибитора матриксной металлопротеиназы – 2 (G^{303}→A) определены варианты генотипов, ассоциированных с риском развития несостоятельности швов анастомозов полых органов пищеварения. Выявлены достоверные различия распределения генотипов в изучаемых группах. Анализ мультипликативной модели наследования генов матриксной металлопротеиназы – 2 (C^{-1306}→T) и тканевого ингибитора матриксной металлопротеиназы – 2 (G^{303}→A) показал соответствие распределения генотипов с законом Харди-Вайнберга. Проанализированы все наследственные модели, лучшей среди них с наиболее низким информационным критерием Акаики оказалась рецессивная модель.

Несостоятельность швов анастомозов полых органов пищеварения в 1,36 раза чаще встречается у носителей гомозиготного СС генотипа гена матриксной металлопротеиназы – 2 (C^{-1306}→T) и вдвое реже - в минорных гомозиготах ТТ (5,9% против 10%, p<0,05). В группе пациентов с несостоятельностью швов анастомозов полых органов пищеварения, статистически достоверно, в 1,6 раза чаще выявлены носители гомозиготного GG варианта гена тканевого ингибитора матриксной металлопротеиназы – 2 (G^{303}→A). Носителей минорных гомозигот АА генотипа в группе с несостоятельностью швов не обнаружено, аналогичный генотип в контрольной группе встречался в 10% (p<0,05).

რეზიუმე

მატრიქსული მეტალოპროტეინაზა-2-ის და მატრიქსული მეტალოპროტეინაზა-2-ის ქსოვილური ინჰიბიტორის გენების პოლიმორფიზმი პაციენტებში საჭმლის მომნელებელი ღრუ ორგანოების ანასტომოზების ნაკერების უკმარისობით

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კვლევის მიზანს წარმოადგენდა მატრიქსული მეტალოპროტეინაზა-2-ის (C^{-1306}→T) და მატრიქსული მეტალოპროტეინაზა-2-ის ქსოვილური ინჰიბიტორის (G^{303}→A) გენების პოლიმორფული ვარიანტების სიხშირის ანალიზი პაციენტებში საჭმლის მომნელებელი ღრუ ორგანოების ანასტომოზების ნაკერების უკმარისობით. გამოკვლეულია 61 პაციენტი ანასტომოზების ნაკერების უკმარისობით (n=17) და შემაერთებელი ქსოვილის პათოლოგიით (n=44), რომლებიც მკურნალობდნენ ა. შალიმოვის სახ. ქირურგიისა და ტრანსპლანტოლოგიის ეროვნულ ინსტიტუტში. ჩატარებულია ლაბორატორიული, გენეტიკური, ჰისტოლოგიური და სტატისტიკური კვლევები. მატრიქსული მეტალოპროტეინაზა-2-ის (C^{-1306}→T) და მატრიქსული მეტალოპროტეინაზა-2-ის ქსოვილური ინჰიბიტორის (G^{303}→A) გენების პოლიმორფიზმის გენეტიკური და სტატისტიკური ანალიზის საფუძველზე განსაზღვრულია გენოტიპების ვარიანტები,დაკავშირებული საჭმლის მომნელებელი ღრუ ორგანოების ანასტომოზების ნაკერების უკმარისობის განვითარების რისკთან. გამოვლენილია გენოტიპების განაწილების სარწმუნო განსხვავება შესწავლილ ჯგუფებს შორის. მატრიქსული მეტალოპროტეინაზა-2-ის (C^{-1306}→T) და მატრიქსული მეტა-ლოპროტეინაზა-2-ის ქსოვილური ინჰიბიტორის (G^{303}→A) გენების დამემკვიდრების მულტიპლიკაციური მოდელის ანალიზმა აჩვენა გენოტიპების განაწილების შესაბამისობა ჰარდი-ვაინბერგის კანონთან. გაანალიზებულია დამემკვიდრების ყველა მოდელი; მათ შორის ყველაზე კარგი, აკაიკის ყველაზე დაბალი ინფორმაციული კრიტერიუმით, აღმოჩნდა რეცესიული მოდელი. საჭმლის მომნელებელი ორგანოების ანასტომოზების ნაკერების უკმარისობა 1,36-ჯერ უფრო ხშირია მატრიქსული მეტალოპროტეინაზა-2-ის (C^{-1306}→T) გენის ჰომოზიგოტური СС გენოტიპის მტარებლებში და ორჯერ უფრო იშვიათი - ТТ მინორულ ჰომოზიგოტებში (5,9% *vs* 10%, p<0,05). საჭმლის მომნელებელი ღრუ ორგანოების ანასტომოზების ნაკერების უკმარისობის მქონე პაციენტების ჯგუფში სტატისტიკურად სარწმუნოდ 1,6-ჯერ უფრო ხშირია მატრიქსული მეტალოპროტეინაზა-2-ის (G^{303}→A) გენის ჰომოზიგოტური GG ვარიანტის მტარებლები. АА გენოტიპის მინორული ჰომოზიგოტების მტარებლები ნაკერების უკმარისობის მქონეთა ჯგუფში არ გამოვლენილა; საკონტროლო ჯგუფში ანალოგიური გენოტიპის სიხშირემ შეადგინა 10% (p<0,05).

EFFECTS OF NUTRITIONAL TREATMENT ON THE QUALITY OF LIFE IN THE PATIENTS AFTER RADICAL SURGERY FOR COLON CANCER

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According to the latest data from International Agency for Research on cancer colorectal cancer is a common cancer disease. There are estimated to be 10.2% newly diagnosed and 9.2% deaths from this disease in the world [1]. Despite the common term "colorectal cancer," the colon and rectum have a different anatomical structure, respectively, colon and rectal cancer require different treatment approaches [2,3]. Today, a radical method of treating colorectal cancer is surgery [4-8]. Despite advances in surgical treatment of colorectal cancer, questions of postoperative consequences and survival remain open. Changes in colorectal anatomy following cancer resection may lead to various functional complications that are important in the distant future [9]. The consequences of surgical treatment of colorectal cancer are well investigated. These consequences are associated with urogenital and sexual disfunction [10-12]. Functional complications after surgical treatment of colon cancer are associated with malabsorption[13] and nutritional deficiency [14]. Malnutrition is one of the functional abnormalities following surgical resection of the colon. Malnutrition is known to be one of the most important problems in oncology and can be caused by both the course of the disease and the consequence of treatment [15]. Certainly, the development of malnutrition has an adverse effect on the prognosis and is one of the causes of death in a cancer patient [16-21].

We were interested in assessing the nutritional status of patients, the impact of nutritional support on quality of life of a patient, and comparing the efficacy of special nutritional support and a high-calorie therapeutic diet to the nutritional status of patients after radical surgical treatment of colon cancer.

Material and methods. The research work was carried out on the basis of the Nur-Sultan City Oncology Center (Republic of Kazakhstan) in the period from 2016-2020. The structure of the research work meets modern ethical norms and requirements. The research protocol was approved by the ethics committee. Before performing the research work, the informed consent of each participant of the research was obtained after explaining the goals and methods of its implementation. Criterion for inclusion: patients with verified diagnosis of colon cancer of stages I-III, signing of informed consent. Criterion of exclusion: patients with verified diagnosis of colon cancer of stage IV, refusal to sign informed consent. 1 month after the surgical treatment in all patients was evaluated the prognostic nutritional index (PNI) according to the formula 10*albumin (g/L)+0,005+ number of lymphocytes was determined. Distribution of PNI was normal. The median was 44,5 (range:30,81-58,25). According to the schedule of ROC-curve (receiver operating characteristic), the threshold value of PNI was 45,0 (sensitivity – 91,8%, specificity – 87,7%). Taking into account the threshold level of PNI, the patients were divided into 3 groups by randomization computer program. G1 - patients with low PNI (68 patients), who were treated with the nutritive correction by enteral feeding courses of 15 days every 3 months, were offered enteral feeding as a supplement to a regular diet. The supplement of choice is specialized enteral mixtures ready to use for cancer patients. Enteral feeding used throughout the study was one brand. The daily amount of consumed cans is 2 pieces (400 ml - 600 kcal, 24 gr of protein), the drink as well is enriched with minerals and vitamins (potassium, calcium, magnesium, phosphorus, vitamins A, B1, B2, B6, B12 C, etc.). G2-patients with low PNI (64), who were prescribed a high-calorie diet. In order to prescribe the diet we individually calculated the calorie of diet taking into account all factors, such as digestive function and absorption capacity of the gastrointestinal tract, psychological state of patients. A diet diary was kept. A therapeutic high-calorie diet (number, type and frequency of meals) was chosen individually with regard to the patient's taste preferences and limitations. G3 - patients with high PNI (88 people), they maintained their ad libitum intake and were dynamically monitored. In the rehabilitation period of 1,3,6,9 and 12 months after surgical treatment clinical and laboratory examination of nutritional status of patients in all groups was conducted.

By prescribing two different types of nutritional status support (high-calorie diet and enteral nutrition), the goal was to provide patients with the necessary amount of protein and energy. Parameters and study measures are described in Table 1.

To assess the nutritional status, the BMI was calculated using the formula (Table 2): $BMI=m/h^2$, where m – is weight, h – is height.

Table 1. Data collection, patient visit schedule

Characteristics	Visit schedule (after surgery)				
	1 month	3 month	6 month	9 month	12 month
Demographic data	+				
Anamnesis vitae	+				
Informed consent	+				
Randomization	+				
BMI, weight	+	+	+	+	+
Nutritional Risk Screening NRS-2002	+	+	+	+	+
Laboratory analysis (albumin, total protein, lymphocytes)	+	+	+	+	+
Food diary	+	+	+	+	+
Calculation of energy intake of the diet	+	+	+	+	+

Abbreviations: BMI- body mass index, NRS- Nutritional Risk Screening

Table 2. BMI indicators

BMI	Stage of body weight loss
21-25 kg/m^2	Normal
up to 20 kg/m^2	Distinct body weight loss
up to 17 kg/m^2	Significant body weight loss
up to 16 kg/m^2	Ultimate body weight loss

Table 3. Nutritional Risk Screening (NRS-2002)

Stage 1		
BMI >20.5	Yes	No
Weight loss in 3 months	Yes	No
Inadequate nutrition over the past week	Yes	No
The patient's condition is serious (or is in the Intensive Care Unit)	Yes	No
A negative answer to all questions indicates that there is no malnutrition. If you give a positive answer at least to one question, you must proceed to Stage 2.		
Stage 2		
Nutritional status		
Weight loss by more than 5% for the last 3 months or eating i n the volume of 50-75% of the previous week's food intake		1 point
Weight loss by more than 5% for the last 2 months or BMI of 18.5-20.5 and poor health or eating in the volume of 25-60% of the volume of previous week's food intake		2 points
Weight loss by more than 5% for the last 1 month (more than 15% for 3 months) or Body Mass Index less than 18,5 and poor health or eating in the volume of 0-25 % of the volume of previous week's food intake		3 points
Disease severity		
Cancer, femoral neck fracture, cirrhosis of the liver, chronic hemodialysis, diabetes.		1 point
Radical abdominal surgery, stroke, severe pneumonia, haemoblastosis		2 points
Cerebral injury, bone marrow transplantation, intensive care (APACHE-II > 10)		3 points

For the purpose of calculating the deviation of body weight, the following formula was used:

Mass deviation = (normal body weight-actual body weight) ÷normal body weight*100%

In the research work we used the NRS - 2002 recommended by Kondrup J et al. [22] (Table 3).

If the sum of points on the NRS-2002 scale exceeded more than 3 points, additional laboratory diagnostics of protein metabolism indicators was performed. We studied: the content of total protein (reference values 66-87 g/L), serum albumin (reference values 35-52 g/L) and number of lymphocytes (mL^3). To obtain accurate and reliable data from a single analyzer, all patients were sent to one and the same clinical laboratory.

Actually, in order to estimate total energy expenditure it is necessary to measure resting energy expenditure and energy related to physical activity by indirect calorimetry-the gold standard. However, according to the ESPEN recommendations, if it is not possible to individually determine the total energy expenditure, it is necessary to calculate the daily energy requirement at the rate of 25-30 kcal /kg/ day [23].

Quality of life was assessed using the European Organization for Research and Treatment of Cancer EORTC QLQ C 30 questionnaire version 3.0. The questionnaire consists of 30 questions, including functional scales: physical, role, emotional, cognitive, social, general health; symptomatic scales (fatigue, pain, nausea/vomiting); 6 items that evaluate individual symptoms and a scale of financial well-being. High scores on functional scales indicate better functioning of the body, while high scores on symptomatic scales have an unfavorable value. The scores were linearly converted to get quality scores from 0 to 100 [24].

Statistical analysis was performed using the SPSS 22 program. Information on incidence, prevalence or frequency is expressed in numbers and percentages (stage of cancer, number of cases of malnutrition etc.) Age, anthropometric data, BMI, blood counts and quality of life indicators were expressed as an average value with a standard deviation. The Wilcoxon test was used to compare continuous indicators. A correlation analysis and Mann-Whitney test was also performed. A statistical significance was established for a P value of less than 0.05.

Results and discussions. The number of patients is 220, including 139 (63%) male and 81 (37%) female. The average age was 62.5±2.3 years. By stages of colon cancer, patients were distributed as follows: Stage I ($T_1N_0M_0$; $T_2N_0M_0$) - 33 (15%) people, Stage II ($T_3N_0M_0$; $T_{4a}N_0M_0$; $T_{4b}N_0M_0$) -108 (49%) people, Stage III ($T_{1,2}N_{1,2a}M0$; $T_{2,3}N_{2a}M0$) - 79 (36%) people. In 40 patients, the tumor was localized in the transverse colon, in 108 - in the descending part of the colon, and in 60 - in the ascending part of the colon. In 12 - in the hepatic flexure of the colon. According to histological classification, adenocarcinoma was detected in 85% of cases, and undifferentiated carcinoma in 15%. Depending on the location and stage of the tumor process, the patients underwent surgery: right hemicolectomy, left hemicolectomy, transverse colon resection (Table 4).

Table 4. Clinical characteristics of patients

Number of patients		**n=220**
Age		62,5±2,3
Sex	Male	139 (63%)
	Female	81 (37%)
Stages of colorectal cancer	Stage I (T1N0M0; T2N0M0)	33 (15%)
	Stage II (T3N0M0; T4aN0M0; T4bN0M0)	108 (49%)
	Stage III (T1,2N1,2aM0; T2,3N2aM0)	79 (36%)
Tumor localization	Transverse colon	40 (18%)
	Descending colon	108(49%)
	Ascending colon	60 (27%)
	Right colic flexure	12 (6%)
Type of operation	Transverse colon resection	40 (18%)
	Right hemicolectomy	72 (33%)
	Left hemicolectomy	108 (49%)

We compared the clinical and laboratory indicators of the nutritional status of patients of the G1 who received special enteral nutrition according to the scheme and the G2 who were prescribed a therapeutic high-calorie diet. In G1 significant changes were made in the indicators of weight, BMI, albumin and total protein, except for the number of lymphocytes. There is an improvement in anthropometric indicators: an increase in body weight by an average of 11.8 kg over 12 months (<0.05) and the achievement of a BMI of 19 kg/m^2, which is an indicator of the patient's transition from the state of "significant body weight loss" to "distinct body weight loss" (<0.03) (Fig. 1,2). Relative to laboratory data, an increase in albumin values from 28±2.3 g/L to 41±2.5 g/L (<0.01) and total protein from 56.2±5.2 g/L to 72±5.5 g/L (<0.01) was registered, with the exception of the number of lymphocytes that did not undergo significant changes from the initial low level (<0.6) (Fig. 3,4). All parameters of nutritional status in patients of G2 remained unchanged.

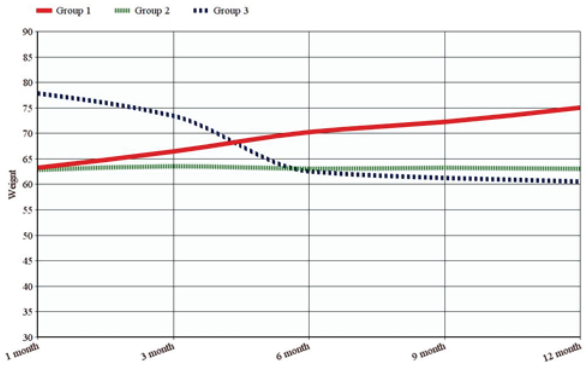

Fig.1. Dynamics of weight of group1,2,3 (kg)

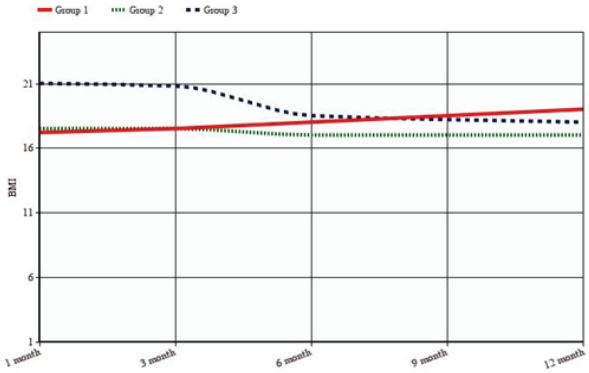

Fig.2. Dynamics of BMI of group1,2,3 (kg/m^2)

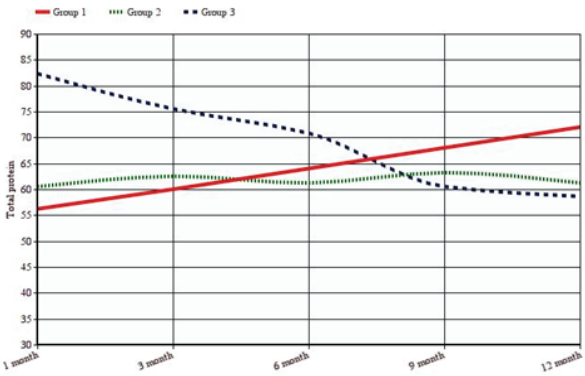

Fig.3.Dynamics of total protein of group1,2,3 (g/L)

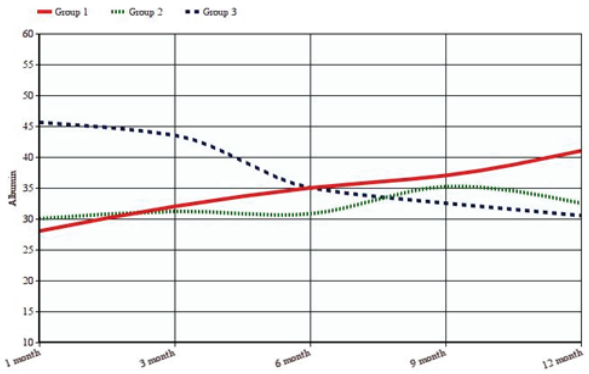

Fig.4.Dynamics of albumin of group1,2,3 (g/L)

Table 5. Quality of life indicators (EORTC QLQ C 30)

Scales	Group 1				Group 2				Group 3			
	Before operation	After 3 mon.	After 6 mon.	After 12 mon.	Before operation	After 3 mon.	After 6 mon.	After 12 mon.	Before operation	After 3 mon.	After 6 mon.	After 12 mon.
Functional												
General health	49	65	78	85	48	50	55	68	50	38	35	28
Physical function	50	64	79	87	49	55	60	62	45	28	25	25
Role-playing function	49	58	65	78	52	65	68	68	40	40	37	35
Emotional function	50	68	75	86	52	58	52	53	50	42	38	35
Social function	51	75	78	85	52	48	50	55	48	35	22	20
Cognitive function	65	68	68	65	68	68	65	67	48	45	45	38
Symptomatic scales												
Fatigue	35	58	46	35	38	48	45	50	48	65	68	75
Pain	28	20	12	12	25	30	28	28	30	32	38	35
Nausea/vomiting	16	15	8	8	15	20	28	20	15	20	15	18
Symptom, individual items												
Dyspnea	7	8	5	3	8	10	13	10	11	12	18	15
Insomnia	16	15	16	15	18	18	17	18	16	18	20	18
Decreased appetite	20	25	20	18	25	45	48	48	15	18	20	22
Constipation	45	58	56	58	48	48	50	58	45	48	45	47
Diarrhea	39	40	35	35	40	45	42	45	38	38	20	28
Financial prosperity	38	38	38	38	45	45	45	45	65	65	65	65

By the 12th month of observation, when comparing the indicators of the nutritional status of G1 and G2, we determined the following changes: increase in body weight (75±12,8kg vs 63,0±10,2 kg) and BMI (19±1,4 kg/m^2 vs 17,0±2,0 kg/m^2); increased protein counts like total protein (72±5,5g/L vs 61,2±5,4g/L) and albumin (41,0±2,5 g/L vs 32,5±2,8 g/L).

According to NRS-2002 assessment and BMI malnutrition developed in 3-6 months in G3. The prevalence of malnutrition was observed in stage II and III by TNM classification. The number of patients who suffer from malnutrition throughout the rehabilitation period was 60 (68%) out of 88 with high PNI at baseline NRS-2002 identified 48 malnourished patients, while BMI identified 12 malnourished patients. Management of patients with initially high PNI in the postoperative period was standard, without special nutritional support. In patients with initially high PNI the following changes were observed: weight loss from 3 months after the operation, the average body weight loss was 17.5 kg during 12 months; BMI from the normal values (21 kg/m^2) decreased to the state of "distinct body weight loss" (18 kg/m^2) (Fig.1,2); from the laboratory parameters the albumin (45±2,2 g/L vs30,5±2,6 g/L) and total protein (85±4,1 g/L vs58,6±2,5 g/L) were significantly changed (<0.01). The number of lymphocytes remained stable (<0,5) (Fig. 3,4). So, According to the results of the NRS-2002, BMI and laboratory results patients of the G3 who had malnutrition did not improve their nutritional status until the end of the follow-up period .

Improvement of functional scales (General health, Physical, Emotional, Role and Social functioning) of quality of life of the patients of the G1 were noted from the 3rd month (p<0,002), having reached a considerably high level by the 12th month of the study (p<0,05). These changes have a positive correlation with the nutritional status of patients (p< 0,05). Symptomatic and other scales did not differ significantly from the initial level. In G2, changes towards improvement were noted in three functional scales, such as General health, Physical and Role functioning, but the changes were not so significant in comparison with changes in functional scales of G1. Of the symptomatic scales, "fatigue" worsened compared to the baseline (p<0,002). The scale of "Decreased appetite" did not change/decreased significantly (p<0,05). The rest of the functional and symptomatic scales have not changed significantly. In the G3, with a baseline high PNI and without nutritional deficiencies in the preoperative period, during the dynamic observation worsened all indicators of functional scales (p<0,03), these changes were closely related to the development of malnutririon (p<0,002). There is also a worsening of the "fatigue" scale, which is associated with the development of nutritional insufficiency in patients during observation (p<0,05).

Correction of nutritional insufficiency is of particular importance in the rehabilitation of patients after surgical treatment of cancer of the gastrointestinal tract as a consequence of malabsorption syndrome. Today, a large number of studies have been

conducted on the nutritional status of patients with esophageal and stomach cancer after special (surgical/chemotherapeutic) treatment. However, there are few studies that focus on the status of patients after surgical treatment of colorectal cancer. According to the results of our research, malnutrition in patients after surgical treatment of colon cancer develops in 68% of cases by the 3rd month of the rehabilitation period, despite high PNI and absence of malnutrition in the preoperative stage (G3). Patients with initially low PNI and presence of mild/middle malnutrition in the preoperative period, who underwent course therapy with enteric nutrition, successfully got out of the state of malnutriotion (G 1). This group of patients had better indicators of nutritional status and quality of life in comparison with patients who were prescribed a high-calorie therapeutic diet (G2) (Table 5).

During the rehabilitation period, special enteral nutrition had a more pronounced positive effect on the nutritional status of patients and indicators of quality of life than a high-calorie diet. Also, despite the initial high PNI and the lack of malnutrition in the preoperative period, the majority of patients 1 year after surgery are subject to the development of malnutrition. Thus, most patients after surgical treatment of colon cancer develop malnutrition by the 3rd month of the rehabilitation period. This requires clinical and laboratory monitoring of nutritional status every 3 months. Also, in order to prevent malnutrition and improve the quality of life of this category of patients, it is necessary to prescribe enteral feeding courses throughout the rehabilitation period.

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SUMMARY

EFFECTS OF NUTRITIONAL TREATMENT ON THE QUALITY OF LIFE IN THE PATIENTS AFTER RADICAL SURGERY FOR COLON CANCER

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Malnutrition is one of the complications following surgical resection of the colon. Aim - to study the impact of enteral nutri-

tional supplements and high-calorie diet on to nutritional status and quality of life within 12 months after surgical treatment.

220 patients after surgery of the colon cancer are divided into 3 groups: group 1 (G1 n=68) - enteral nutrition, group 2 (G2 n=64) - high-calorie diet, group 3 (G3 n=88) - patients with baseline high PNI, follow-up. Nutritional status, NRS-2002 and EORTC QLQ C 30 questionnaire were analyzed.

In G1 there was an increase in body weight, BMI and improvement of laboratory parameters compared with G2, where body weight, BMI and laboratory parameters remained unchanged ($p<0.03$). In G3 there was a decrease in body weight, BMI and a deterioration in blood counts ($p>0.06$). In G1, functional indicators of quality of life were improved ($p<0.002$), which had a positive correlation with nutrition indicators ($p<0.05$). In G2, an improvement in 3 functional scales ($p<0.003$), but not as significant as in G1. In G3 deterioration of all functional and symptomatic scales that had a close correlation with malnutrition ($p<0.05$).

Special enteral nutrition had a more positive effect on the nutritional status and quality of life than a high-calorie diet. Also, despite the initial high PNI and the lack of malnutrition in the preoperative period, the majority of patients 1 year after surgery are subject to the development of malnutrition.

Keywords: colon cancer, malnutrition, quality of life, Republic of Kazakhstan.

РЕЗЮМЕ

ВЛИЯНИЕ НУТРИТИВНОГО ПИТАНИЯ НА КАЧЕСТВО ЖИЗНИ БОЛЬНЫХ ПОСЛЕ РАДИКАЛЬНОГО ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ РАКА ОБОДОЧНОЙ КИШКИ

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Нутритивная недостаточность является одним из осложнений после хирургической резекции толстой кишки. Целью исследования явилось изучение влияния энтерального питания и высококалорийной диеты на нутритивный статус и качество жизни больных после резекции толстой кишки спустя 12 месяцев после хирургического лечения.

220 пациентов после операции по поводу рака толстой кишки разделены на 3 группы: I группа (n=68) - энтеральное питание, II группа (n=64) - высококалорийная диета, III группа (n=88) - пациенты с исходным высоким прогностическим индексом питания (ПНИ). Нутритивный статус проанализирован с применением опросников NRS-2002 и EORTC QLQ C 30.

В I группе выявлено увеличение массы тела, индекса массы тела (ИМТ) и улучшение лабораторных показателей в сравнении со II группой, где масса тела, ИМТ и лабораторные параметры оставались неизменными ($p=0,03$). В III группе наблюдалось снижение массы тела, ИМТ и ухудшение показателей крови ($p=0,06$). В I группе улучшились функциональные показатели качества жизни ($p=0,002$), что находилось в положительной корреляции с показателями, характеризующими статус питания ($p=0,05$). Во II группе отмечалосьулучшение по 3 функциональным шкалам (±0,003), однако не такое значительное, как в I группе, в III группе - ухудшение всех функциональных и симптоматических шкал, что находилось в тесной связи с нутритивной недостаточностью ($p<0,05$).

Специальное энтеральное питание оказало более положительное, чем высококалорийная диета, влияние на состояние больного и качество его жизни. Несмотря на исходно высокий ПНИ и отсутствие нутритивной недостаточности в предоперационном периоде, большинство пациентов спустя 1 год после операции подвержены развитию нутритивной недостаточности.

რეზიუმე

საკვები რაციონის გავლენა პაციენტთა სიცოცხლის ხარისხზე მსხვილი ნაწლავის კიბოს რადიკალური ქირურგიული მკურნალობის შემდეგ

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მსხვილი ნაწლავის ქირურგიული რეზექციის შემდეგ ერთ-ერთ გართულებას წარმოადგენს ნუტრიციული უკმარისობა.

სტატიის მიზანს წარმოადგენდა ენტერული კვებისა და მაღალკალორიული დიეტის ზეგავლენის შესწავლა ნუტრიციულ სტატუსსა და ცხოვრების ხარისხზე ქირურგიული მკურნალობიდან 12 თვის განმავლობაში.

გამოკვლეულია 220 პაციენტი ნაწლავის კიბოს ოპე-რაციის შემდგომ. პაციენტები გაიყო 3 ჯგუფად დაიყო: I ჯგუფი (n=68) - ენტერული კვება, II ჯგუფი (n=64) - მაღალკალორიული დიეტა, III ჯგუფი (n=88) - პაციენტები მაღალი საწყისი პროგნოზული ნუტრიციული ინდექსით. ნუტრიციული სტატუსი გაანალიზებული იყო NRS-2002 და EORTC QLQ C 30 კითხვარის მეშვეობით.

I ჯგუფში აღინიშნა სხეულის მასის მატება და ლაბორატორიული მაჩვენებლების გაუმჯობესება II ჯგუფთან შედარებით, სადაც სხეულის მასა და ლაბორატორიული მაჩვენებლები დარჩა უცვლელი ($p=0.03$). III ჯგუფში აღინიშნებოდა სხეულის მასის კლება და სისხლის ლაბორატორიული მაჩვენებლების გაუარესება ($p=0.06$). I ჯგუფში გაუმჯობესდა ცხოვრების ხარისხის ფუნქციური მაჩვენებლები ($p=0.002$), რომლებიც დადებით კორელაციაში იყო კვების მაჩვენებლებთან ($p=0.05$). II ჯგუფში 3 ფუნქციური სკალის (±0,003) მიხედვით აღინიშნა გაუმჯობესება, მაგრამ არც ისე მნიშვნელოვანი, როგორც I ჯგუფში. III ჯგუფში აღინიშნა ყველა ფუნქციური და სიმპტომური სკალის გაუარესება, რაც მჭიდრო კავშირში იყო ნუტრიციულ უკმარისობასთან ($p<0.05$).

სპეციალურმა ენტერულმა კვებამ უფრო დადებითი გავლენა იქონია კვების მდგომარეობასა და ცხოვრების ხარისხზე, ვიდრე მაღალკალორიულმა დიეტამ. ასევე, მიუხედავად წინასაოპერაციო პერიოდში საწყისი მაღალი პროგნოზული ნუტრიციული ინდექსის და ნუტრიციული უკმარისობის არარსებობისა, ოპერაციიდან 1 წლის შემდეგ პაციენტთა უმრავლესობა მგრძნობიარე იყო ნუტრიციული უკმარისობის მიმართ.

CURRENT TREATMENT STANDARDS OF COMPLEX, LARGE SIZED INCISIONAL HERNIAS

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The term ventral hernia is quite frequently misused by Georgian surgeons and even in some English-speaking literature. The term derives from Latin "venter" and means abdomen. Therefore, it would be correct to use this term more broadly referring all hernias issuing from the abdomen. In our opinion, the term "incisional" reflects the essence of the matter more closely, describing all hernias occurring after incision. Incisional hernias are a common late complication of abdominal surgery, with recent data reporting a prevalence after 1 year at 5.2% and 2 years of approximately 25%.

Recurrences after incisional hernia surgery are an unsolved problem to date. The reports in the literature range from 1% to 50%. The recurrence rate correlates to the follow-up time and there are only a few high-quality studies with a long-term follow-up.

High-quality prospective randomized trials on the broad subject of incisional hernias are rare in the scientific literature as well. A challenge for surgeons and multidisciplinary team is complex, large hernias with Loss of Domain (LD). In spite of the fact that the term complex hernia is quite broadly utilized there is yet no accepted consensus regarding the definition. The following features are characteristic for complex hernias: relatively big-sized (more than 10 cm) eccentric defects, complex anatomic peculiarities and/or a risk of infection. Usually, there are several concomitant risk factors [1,2]. Frequently, these are recurrent hernias and the patients have a history of complications. In addition, there is a risk of complications from the treatment of the hernias. Post-operatively impaired wound healing and recurrences also occur frequently.

Risk factors for incisional hernias might be distributed to the following two groups:

Major risk factors - obesity, COPD, smoking, diabetes, steroids, malnutrition, jaundice, abdominal trauma, bleeding, abdominal sepsis, wound infection, chemo or radiotherapy, connective tissue diseases, disturbances of the collagen metabolism, enhanced abdominal wall tension, re-laparotomies within 1-month, surgeon dependent factors, - incorrect lap and open abdominal closure.

Minor risk factors - anemia, malignancies, renal failure, more than 2 laparotomies through the same incision a year, postoperative: ventilation, coughing, vomiting, straining during defecation, heavy physical efforts.

This article highlights practical issues regarding useful classification, treatment modalities, and multidisciplinary decision-making. There is yet no generally accepted incisional hernia classification. We suggest that the classification should be simple, convenient and broadly accepted. It should facilitate preoperative, intra and postoperative planning; estimation of the expected complexity of minimally invasive treatment methods. It should help to estimate the cost-effectiveness of the treatment.

We summarized many existing classifications [1,2]. Here aere the most useful in practical sense the following criteria for incisional hernias: size, location, symptoms, reducibility, stability of the anterior abdominal wall, how far the gap edges are "escaped", number of the gaps, abdominal wall surface/defect surface ratio, patients body constitution, hernia content, scars, skin infections, risk of obstruction, differentiation "primary" or recurrent incisional hernia.

Treatment of the large incisional hernias is a challenge [3,4]. It needs meticulous planning in preoperative period. Especially if we should deal with giant defects with Loss of Domain (LD). This term is used as more than 25 % of viscera is dislocated out of the genuine abdominal cavity creating a secondary abdomen. In a supine position, those displaced organs are irreducible. There are several reports in the literature that the volume of displaced organs exceeded 50%. In our experience, the greatest volume was 40 %. For more a precise evaluation of LD we used hernia sac/abdominal cavity volume ratio. Ratio ≥0.5 confirms LD. The volume is measured via the sagittal and axial reconstruction of the CT scan: V = 0.52 x L x H x W).

For massive ventral hernia with LD we perform the following preoperative procedures:

1. Progressive Preoperative Pneumoperitoneum recommended by Carbonell et al [5].
2. Botulin toxin (Botox) injection according to the Thomas Ibarra-Hurtado method [7].
3. Preoperative optimization for postoperative respiratory risk factors.

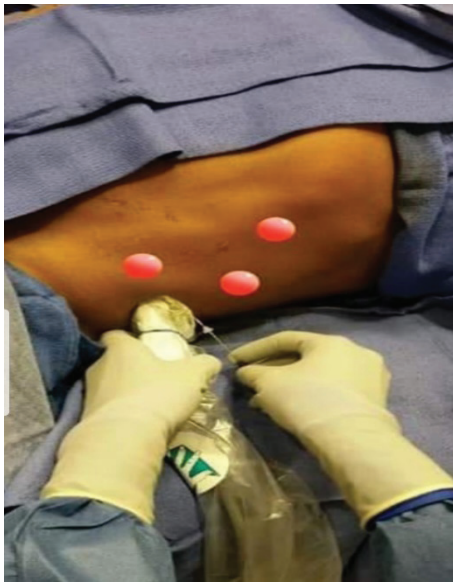
For the Progressive Preoperative Pneumoperitoneum the following steps are performed:

a. Percutaneous vena cava filter is placed and anti-thrombotic medication started because of high risk for thromboembolic complications.
b. explorative laparoscopy and placement of the insufflation catheter
c. full liquid diet with protein supplementation
d. the patient is instructed to utilize incentive spirometry and ambulate daily
e. Beginning of Progressive Preoperative Pneumoperitoneum (from air hose at patient's bedside).
f. daily moisturizing of the skin because of dryness and cracking

If the patient will begin to complain of abdominal tightness and mild flank discomfort, insufflation is stopped. Once the patient begins to experience some shortness of breath or mild anxiety (there is no specific volume of air that should be insufflated nor the intra-abdominal pressure measured, the endpoint of insufflation will always be the patient's level of discomfort) if at any point the patient becomes hemodynamically unstable or the urine output decreases, the pneumoperitoneum can be evacuated).

After 7 days of PPP, a CT scan is repeated to determine the suitability of the abdominal wall repair (if the bowel has not fallen back and the volume of the abdomen does not look to have increased significantly, the PPP should continue for more than 4 to 5 days and CT scan is repeated).

Botulin toxin (Botox-BT) injection starts approximately one month before planned incisional hernia repair. We perform BT injection under sterile technique using ultrasound guidance. The planned tract is anesthetized with 1% lidocaine. BT solution is prepared by diluting 100-150 units of Botox ® into 100 units of sterile saline. Three locations are chosen along the lateral abdominal wall utilizing ultrasound guidance to identify all 3 muscle layers. Using a 21 gause 7 cm needle attached to the BT/saline solution, the 3 layers of the muscles are traversed. Care is taken not to violate peritoneum Injection is started in the transversus (Pic.).



Pic.Botox injection spots in case of incisional hernia

Preoperative optimization for postoperative respiratory risk factors includes: a number of peri-operative relevant factors should be optimized as best as possible prior to complex abdominal wall reconstruction: optimal drug treatment of COPD. Smokers should abstain from nicotine. A pre-existing diabetes mellitus should be treated optimally (HbA1c<7%). Obese patients should aim for a weight reduction pre-operatively. Bariatric procedures (gastric balloon/endobarrier or even surgery) may be recommended to morbidly obese patients to support weight loss. If ulcers or impetigo are present, these have to be treated pre-operatively. In cases of fistulas or mesh infections, antibiotics must be administered targeting the causative agent(s). As the wound areas are often rather large, any medication with anticoagulant properties should be reduced to the necessary minimum in order to avoid postoperative hematomas or hemorrhage. On the other side, consequent drug and mechanical prophylaxis against thrombosis are necessary because of the increased risk from increased intra-abdominal pressure/ decreased venous return.

Surgery for giant incisional hernias has undergone major changes in the last two decades and patients can now be treated with high success rates. With the use of prosthetic mesh becoming the standard of care in the management of incisional hernias, the subsequent rate of recurrence has been lowered to 8–24% from 33 to 44%, but it has not been eliminated, however the question of debate now is the positioning of mesh; on the rectus sheath or under rectus sheath.

Our acknowledgments to prof. A.N. Kingsnorth (UK) who with our team introduced Lichtenstein hernia repair, Rives-Stoppa procedure and component separation technique first time not only in Georgia but also in many post-soviet countries at the beginning of the 21st century. Also our US colleague prof. E. Nicolo, who with us utilize Chevrell onlay technique for the first time in Georgia. After these beginnings, 15 years passed and we gained huge experience, which is shared here, in the article.

The Technique of mesh placement is still at the surgeon's discretion. In Kokerling's meta- analysis the author [9] compared the onlay vs. sublay technique in open incisional hernia repair and identified better outcomes for the sublay operation. Nonetheless, an Expert Consensus Guided by Systematic Review found the onlay mesh location useful in certain settings. Therefore, all studies on the onlay technique were once again collated and analyzed.

Based on the available literature the onlay compared with the sublay technique in incisional hernia repair is associated with markedly more wound complications and seroma rates and with a comparable recurrence rate. Therefore, in the onlay technique the occurrence of wound complications and seroma formation must be prevented through selective indications, surgical experience, careful dissection in the abdominal wall, and prophylactic measures such as drainage, abdominal binders, fibrin sealant. Furthermore, those settings in which the onlay technique has advantages must be better defined [9].

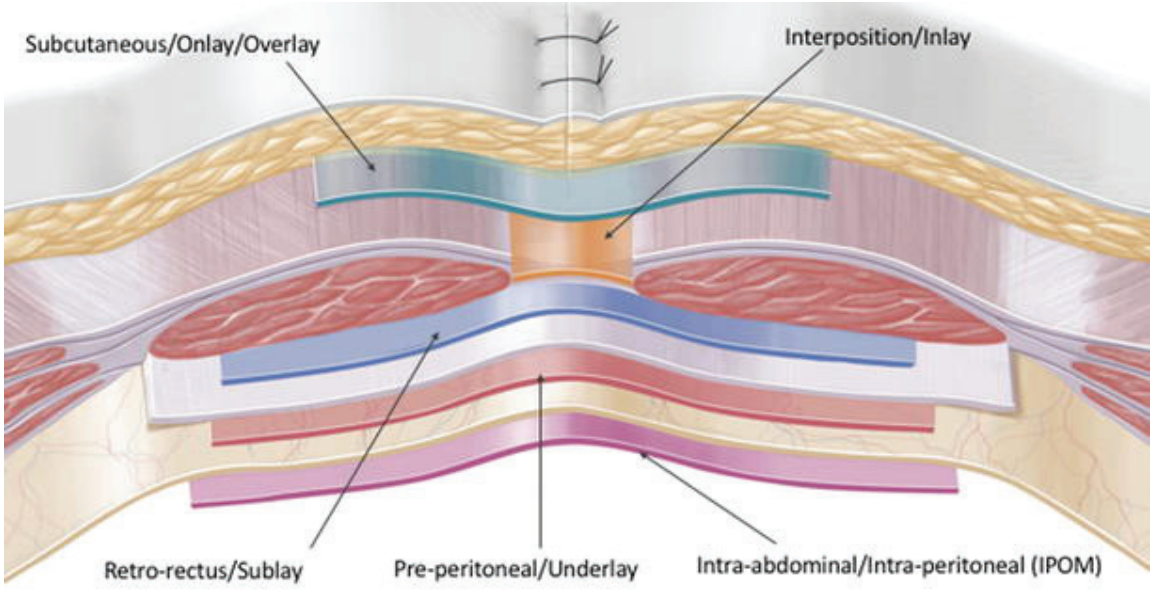


Fig. 1. Anatomy of anterior abdominal wall and mesh placement spaces

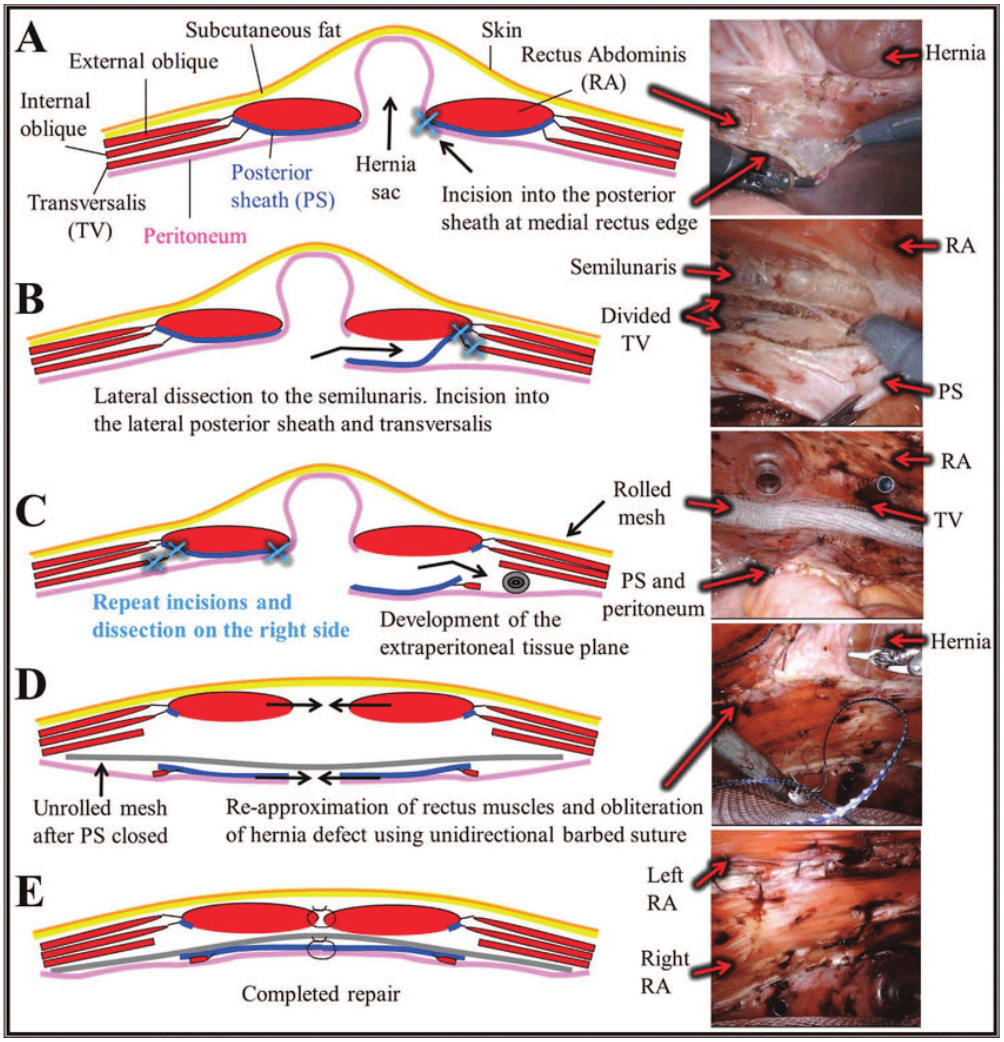


Fig. 2. TAR schematic drawing

In sublay technique, the rectus sheath is opened on both sides and the posterior layer is sutured at the midline. The synthetic mesh is then placed over the posterior layer of the rectus sheath, behind the rectus abdominis muscle, and fixed with a few sutures or fibrin glue. Evolution of sublay repair with the introduction by Rives and Stoppa, followed by Ramirez proposing the anterior component separation at around the same time when Wantz introduced the retromuscular prefascial repair to the United States. Subsequent improvements in component separation techniques including the open anterior perforator-preserving technique, the laparoscopic technique, posterior component separation, and TAR are also shown in Fig. 2. As illustrated in the aforementioned timeline, approximately 25 years passed between the description of the sublay repair and the adjunctive procedure that made it possible to implement appropriately. It then took another two decades for the true scope and applicability of myofascial releases to be described. With substantially decreased surgical site infections (SSIs) and recurrence rates, combining component separation techniques with a sublay mesh repair allows patients with previously "inoperable" hernias to not only have an operation but also one that is durable with decreased recurrence rates.

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SUMMARY

CURRENT TREATMENT STANDARDS OF COMPLEX, LARGE SIZED INCISIONAL HERNIAS

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There is yet no generally accepted incisional hernia classification.This article highlights practical issues of classification, treatment modalities, and multidisciplinary decision-making. We summarized many existing classifications of hernia and suggested the classification that facilitates pre-operative, intra and postoperative planning. Progressive Preoperative Pneumoperitoneum effectively helps to overcome postoperative respiratory complications. For big defects, we use Botox injections in according to Thomas Ibarra-Hurtado method one month prior to surgery. Rives-Stoppa procedure is a golden standard in incisional hernia repair. Component Separation (anterior and posterior) gives good results as well. It maintains flexibility of anterior abdominal wall. We prefer to cover relaxing incisions after CS on newly formed midline with triple sheet of mesh. It prevents recurrences in the mentioned areas. Treatment of giant hernias needs surgeons high experience in the field and multidisciplinary approach. Management of this kind of hernias should be done in specialized Hernia Centers.

Keywords: incisional hernias, Chevrell onlay method, Rives-Stoppa procedure.

РЕЗЮМЕ

СОВРЕМЕННЫЕ СТАНДАРТЫ ЛЕЧЕНИЯ БОЛЬШИХ ИНЦИЗИОННЫХ ПОСТОПЕРАЦИОННЫХ ГРЫЖ

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В статье освещаются вопросы, касающиеся классификации, методов лечения послеоперационных грыж. Предложенная классификация облегчает оценку ожидаемой сложности.

Проанализована научная литература по вопросу хирургического лечения инцизионных грыж; отмечено, что мало научных работ, основанных на рандомизированных проспективных исследованиях высокого качества. Следовательно, нет достоверных рекомендаций, в том числе – по вопросу хирургического лечения больших, сложных (комплексных) грыж с потерей обычного месторасположения.

Хирургическое лечение крупных послеоперационных грыж является вызовом для многопрофильной команды врачей. Особое внимание уделяется предоперационной подготовке пациента, что подразумевает стабилизацию дыхательных, гемодинамических, метаболических параметров, устранение кожных инфекций, формирование прогрессирующего пневмоперитонеума и, в большинстве случаев, инъекции ботокса по периметру т.н. «бегающих» мышечных краёв по методу Ibarra-Hurtado.

Из хирургических методов лечения процедура Rives-Stoppa считается «золотым стандартом» в лечении послеоперационных грыж. В случае больших дефектов его можно легко расширить до процедуры освобождения поперечных мышц живота, т.е. до TAR (Transversus Abdominis Release), что определяет хорошие результаты и, что наиболее важно, поддерживает и/или восстанавливает гибкость мышц передней брюшной стенки.

Как показали исследования, метод Chevrell onlay характеризуется значительно более высокими показателями осложнений послеоперационной раны и образования серомы, чем процедура Rives-Stoppa.

Лечение крупных инцизионных грыж требует определённого опыта в этой области и мультидисциплинарного подхода; лечение же следует проводить в специализированных медицинских центрах.

რეზიუმე

პოსტოპერაციული დიდი ინციზიური თიაქრების მკურნალობის თანამედროვე სტანდარტები

გ.გიორგობიანი, ა.კვაშილავა

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი; ავერსის კლინიკა, საქართველო

სტატიაში განხილულია საკითხები პოსტოპერაციული თიაქრების კლასიფიკაციის და მკურნალობის მეთოდების შესახებ. შემოთავაზებული კლასიფიკაცია აიოლებს მოსალოდნელი გართულებების შეფასებას.

გაანალიზებულია სამეცნიერო ლიტერატურა ინციზიური თიაქრების ქირურგიული მკურნალობის საკითხის შესახებ; აღნიშნულია, რომ მაღალი ხარისხის რანდომიზებულ პროსპექტულ კვლევებზე დაფუძნებული სამეცნიერო ნაშრომების რაოდენობა მცირეა. აქედან გამომდინარე, არ არსებობს სარწმუნო რეკომენდაციები, მათ შორის – დიდი, რთული (კომპლექსური) თიაქრების ქირურგიული მკურნალობის შესახებ ჩვეული ადგილმდებარების დაკარგვით. პოსტოპერაციული დიდი თიაქრების ქირურგიული მკურნალობა გამოწვევას წარმოადგენს ექიმთა მრავალპროფილური გუნდისათვის. განსაკუთრებული ყურადღება ექცევა პაციენტის ოპერაციამდელ მომზადებას, რაც გულისხმობს სუნთქვის, ჰემოდინამიკური და მეტაბოლური პარამეტრების სტაბილიზებას, კანის ინფექციების ალაგებას, პროგრესირებადი პნევმოპერიტონეუმის ფორმირებას და, უმეტეს შემთხვევაში, ბოტოქსის ინიექციას Ibarra-Hurtado-ს მეთოდით კუნთების ე.წ. მორბენალი ნაპირების პერიმეტრზე.

მკურნალობის ქირურგიული მეთოდებიდან პროცედურა Rives-Stoppa ითვლება პოსტოპერაციული თიაქრების მკურნალობის “ოქროს სტანდარტად”. დიდი დეფექტების შემთხვევაში შესაძლებელია მისი გაფართოება მუცლის განივი კუნთების განთავისუფლების პროცედურამდე, ე.ი. TAR-მდე (Transversus Abdominis Release), რაც განსაზღვრავს კარგ შედეგებს

და, რაც ძალიან მნიშვნელოვანია, ინარჩუნებს და/ან აღადგენს მუცლის წინა კედლის კუნთების მოქნილობას.

როგორც კვლევებითაა ნაჩვენები, Chevrell onlay მეთოდი ხასიათდება პოსტოპერაციული ჭრილობის გართულების ბევრად უფრო მაღალი მაჩვენებლით და სერომის წარმოქმნით, ვიდრე პროცედურა Rives-Stoppa. დიდი ინციზიური თიაქრების მკურნალობა მოითხოვს გარკვეულ გამოცდილებას ამ სფეროში და მულტიდისციპლინურ მიდგომას; მიზანშეწონილია, რომ მკურნალობა ჩატარდეს სპეციალიზებულ სამედიცინო ცენტრებში.

OVARIAN CANCER TREATMENT OPTIMIZATION: THE COMPLEX ANALYSIS OF THE RESULTS OF CYTOREDUCTIVE SURGERY, MICROSCOPIC MALIGNANCY AND T-LYMPHOCYTIC INFILTRATION OF THE TUMOR

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Ovarian cancer ranks 7th among the most common cancers in the world and 8th among the causes of death [1-3].

The high mortality rate is due to the absence of effective screening methods and the indolent course of the disease. About 70-80% of the cases of ovarian cancer are diagnosed on the advanced stages (III or IV) of the disease, and the recurrence rate is 75%, while the five-year disease-free survival period is observed in only 35% of patients [4].

Today, the complete cytoreduction of the tumor - the "debulking" surgery – has established itself as a leading choice in the treatment of ovarian cancer.

The main point of cytoreductive surgery is the complete elimination of the macroscopic tumor, which often requires intervention on several organs of the abdominal cavity (resection of the peritoneum, diaphragm (stripping), liver, pancreas, intestine (especially rectosigmoid, which is required in 30-50% of cases of disseminated ovarian cancer), splenectomy, cholecystectomy, appendectomy, omentectomy, salpingo-oophorectomy, hysterectomy) [5-7].

It is important that the complications, associated with the debulking surgery do not increase the mortality rate [8,9].

It is known that the prognosis of ovarian carcinomas is significantly determined by their histological types and the grade of microscopical malignancy. Besides, according to the data of recent years, the clinical outcome and prognosis of ovarian cancer are closely correlated with the presence of tumor-infiltrating lymphocytes (TILs) in the microenvironment of the tumor.

The importance of TILs has been already established in melanomas, non-small-cell lung cancers, "triple-negative" forms of breast cancer, while in cases of the prostate, kidney, esophagus and colorectal carcinomas TILs are being actively studied and the obtained results are being used for choosing a course of immunotherapy [10-12]. The study of TILs has been started in ovarian tumors as well. However, their diagnostic value is not thoroughly clear. Data on their importance in ovarian tumors of various morphological forms are particularly poor [13-15].

The study aimed to investigate the association of accumulation of Infiltrating T-lymphocytes and their subtypes with histology of ovarian cancer tissue excised during debulking surgeries considering the microscopic malignancy grade and the clinical stage.

Material and methods. The present multicenter, retrospective-prospective study involves 64 ovarian cancer patients. It is noteworthy that in advanced cases of ovarian cancer, generally the treatment was started with neoadjuvant chemotherapy, and subsequent surgical treatment prevalently included a total hysterectomy and omentectomy. Since 2016, we have started the treatment recognized as the gold standard: debulking surgery with adjuvant platinum-taxane-based chemotherapy. The patients were selected on the basis of anamnesis and clinical and instrumental examinations, considering the age and comorbidities.

Patients' including criteria were the following: diagnosis of ovarian cancer, adult age, performed treatment (total hysterectomy, omentectomy, debulking surgery with adjuvant chemotherapy [primary cytoreduction] or neoadjuvant chemotherapy with subsequent debulking surgery and adjuvant chemotherapy [interval cytoreduction] or secondary cytoreduction in case of recurrent tumor. Patients' excluding criteria were the following: age 80 years and older, acute hypoalbuminemia and hypoproteinemia, a severe rise of the liver enzymes, the presence of radiologically confirmed distant methastasis. All patients had signed the informed consent form. The patients were divided according to age, clinical diagnosis and scale of surgery, stage of the disease, microscopic malignancy of the tumor, location, histology and lymphocyte infiltration.

Material obtained from 64 surgeries of the ovarian cancer was examined by standard histological (H&E) and immunohistochemical (IHC) technique. Initially, the tumor tissue was fixed in 10% buffer formalin for 6-12 hours. This time is perfect for retaining the antigen in the tissue and preventing the false-negative results of IHC. After fixation, the material was proceeded in the «Leica Bond Max» device and embedded into paraffin. Paraffin blocks were cut into 3 μm thick slices for standard histology and IHC. Shimizu/Silverberg systems as well as "two-tier" grading systems were used to determine the tumor differentiation grade in serous carcinomas. The malignancy grade was determined by the application of an immunohistochemical study technique using the oncoprotein p53 marker. Each specimen was analyzed by two morphologists independently. In the case of two different interpretations of the results, a joint discussion was held until a consensus was reached.

TILs were detected by applying immunohistochemistry using "Novocastra" antibodies: CD2, CD3, CD4, CD8. The markers' expression was studied separately in the stromal and parenchymal components. The percentage of $CD2^+$, $CD3^+$, $CD4^+$, $CD8^+$ lymphocytes in the tumor tissue was calculated by the "ImageJ" software.

All scices were studied be means of the light microscope - Leica DM 750.

The survival of patients with ovarian cancer was examined by using the Kaplan-Meier curves and calculations of Cox Hazard Ratio (HR). Quantitative parameters were presented as average ± standard deviation; Comparative analysis of such data of each group was performed by using Student's t-test, while qualitative parameters were statistically analyzed by using the $\chi 2$ test. Correlations were studied by using the Pearson coefficient (r). Multiple regression analyses of factors influencing surgical intervention was performed by a logarithmic regression method. This method excluded the most unreliable factors step-by-step. Finally, when all the factors in the set of factors showed a reliable correlation, the method ended the analysis. Statistical processing of the results was performed by the statistical software IBM SPSS Statistics V22.0. As a difference reliability criterion there was used (to reject the null hypothesis) $p<0.05$.

Results and discussion. Of all 64 incidents, there were 42 cases of the serous carcinoma, 6 cases of the endometrioid carcinoma, 6 cases of clear cell carcinoma, 6 cases of the mucinous carcinoma. Three patients were diagnosed with a primary peritoneal tumor, and one patient was diagnosed with malignant Struma Ovarii (papillary thyroid carcinoma in Struma Ovarii).

41 out of 64 patients were undergone the primary cytoreduction with the following adjuvant platinum-based chemotherapy, and 19 - underwent neoadjuvant chemotherapy. Secondary cytoreduction was performed in 10 cases out of 64. The patient, diagnosed with malignant Struma Ovarii underwent the total hysterectomy, bilateral adnexectomy, omentectomy; later the total thyroidectomy, followed by radioactive iodine therapy.

The detailed charasteristcs of the included in study patients according to age, clinical diagnosis and scale of surgery, stage of disease, microscopic malignancy of the tumor, location, histology and lymphocyte infiltration is provided in Table 1.

The grade of differentiation along with the histological type was determined in all 64 cases of ovarian cancer. Serous carcinoma was diagnosed in 42 cases (66%), 30 patients (71%) from them had high-grade form, 5 patients (12%) had highly differentiated (low-grade) form, and 7 (17%) patients had moderately differentiated form of serous carcinoma.

Out of the 42 invasive ovarian carcinomas, studied by us with Shimizu/Silverberg grading system, there was observed a poorly differentiated option of the serous carcinoma (G3) in 30 cases, a moderately differentiated –(G2) - in 7 cases and a highly differentiated(G1) - in 5 cases. By a "two-tier" system, 37 cases of high-grade and 5 cases of low-grade malignancy of serous invasive cancer were observed.

As it is known, a tissue of the carcinoma is generally characterized by histological diversity, where different histostructural and differentiation sites interchange; however, it is noteworthy, that in none of the cases of the serous carcinoma of high-grade malignancy, studied by us, was observed the coexistence of sites with borderline malignant and/or low-grade serous carcinoma.

Thus, research has focused on various theories of cancer carcinogenesis. According to one of the theories, the development of serous ovarian cancer is a gradual process: the borderline tumor progresses to low- grade and then high-grade serous carcinoma [16,17]. Upon this theory, low- and high-grade serous carcinomas have a single origin. A markedly different approach to the mentioned is a dualistic theory, arguing that the histogenesis of high-grade and low-grade serous carcinomas are significantly different and their development is resulted by two completely different geneses [18].

The results of the multiple morphological examinations, obtained by us, suggest that the histogenesis of high-grade malignancies of the ovary and low-grade malignancy potential tumors is different. We couldn't find any transformation of low-grade malignancies into high-grade malignancies. Therefore, if there are two interdependent ways of formation of the serous ovarian cancer, we suggest that the "two-tier system" for grading the microscopic malignancy of ovarian serous carcinomas more accurately reflects the biology of the tumor and the mechanism of its formation. Besides, in some cases assigning the moderate malignancy grade (Grade 2) according to the "three-tier" system, may complicate the clinical approach and explicit treatment strategy planning.

The grade of tumor differentiation was determined by the application of the IHC. Oncoprotein p53 expression (monoclonal, Novocastra). was analyzed immunohistochemically according to the tumor differentiation grade."Wild" type p53 is a product of the mutated suppressor gene and is accumulated in most tumor cells as an oncoprotein (oncoprotein p53). It also represents certain molecular features of tumor anaplasia [19].

In those seven cases, in which the «universal» grading system provided by Shimizu/Silverberg diagnosed moderately differentiated serous carcinoma, the tumor differentiation grading was determined immunohistochemically by using oncoprotein p53. It should be noted that even in 30 cases of high-grade serous carcinomas, the marker expression accounted for 90%; nuclear expression of oncoprotein p53 is sharp, in addition, it allows outlining incorrect nuclear contours, which is one of the features of poorly-differentiated carcinomas.

In seven cases, which were classified as moderately differentiated forms (according to the Shimizu/Silverberg scheme), the percentage of marker expression varied in the range of 49.2 -58.0%, while the sharpness in the case of p53 involvement ranged from moderate to strong expression.

As for 5 cases of a highly differentiated serous carcinoma (G1), the expression intensity of oncoprotein p53 was from poor to moderate. Their involvement varied from 22.9 to 41.2%. We made an effort to provide insight into the microscopic malignancy grading of the tumors and evaluate it in terms of tumor cell carcinogenesis. According to one of the hypotheses - "dualistic concept" - the formation of serous carcinoma malignancies with low-grade and high-grade differentiation is by different mechanisms.

In our study, we analyzed to what extent the formation mechanisms of highly differentiated serous and poorly differentiated serous carcinomas differ.

According to our data, none of the cases of high-grade malignancy (poorly differentiated) serous carcinomas were associated with highly differentiated carcinoma structures. The coexistence of the histostructure of a borderline malignant tumor with a serous cancer with a high-grade malignancy was not revealed.

Therefore, we might conclude that the theory on the different histogenesis of low-grade and high-grade malignancies of serous carcinomas is right. We believe that their formation is possible in two different ways. Serous carcinomas with low malignant potential are associated with a relatively better prognosis. They are characterized by indolent disease progression. In many cases, we face all three morphologies simultaneously: benign, borderline malignant tumor and highly differentiated serous carcinoma.

Table 1. Data of the patients included in the study

Age group	**< 60 Yrs.**		**60-65 Yrs.**		**> 65 Yrs.**	
n	28		18		18	
	Medium±SD		Medium±SD		Medium±SD	
Age	49,14±8,42		62,94±1,95		70,89±3,89	
	n	**%**	**n**	**%**	**n**	**%**
Conducted treatment						
First chemotherapy / then surgery	5	17,9	6	33,3	8	44,4
First surgery / then chemotherapy	23	82,1	12	66,7	10	55,6
	Chi2=3.8698 (p=0.1444, NS)					
Morphological type:						
High-grade serous carcinoma- HGSOC	11	39,3	13	72,2	16	83,3
Low-grade serous carcinoma- LGSOC	2	7,1	1	5,6	2	11,1
Mucinous carcinoma – MOC	5	17,9	0	0,0	1	5,6
Endometrioid carcinoma – ENOC	5	21,4	1	5,6	0	0,0
Clear cell carcinoma – CCOC	3	10,7	3	16,7	0	0,0
	Chi2=7.0054 (p=0.0301)					
The degree of tumor malignancy: G1	2	10,7	1	5,6	2	11,1
G2	7	25,0	4	22,2	2	11,1
G3	18	64,3	13	72,2	14	77,8
	Chi2 = 1.7737 (p = 0.7773, NS)					
Stage: 1	6	21,4	0	0,0	2	11,1
2	2	7,1	1	5,6	2	11,1
3	20	71,4	15	83,3	14	77,8
4	0	0,0	2	11,1	0	0,0
	Chi2 = 3.718 (p = 0.7148, NS)					
Lethal Outcome: Dead	3	10,7	7	38,9	3	16,7
Alive	25	89,3	11	61,1	15	83,3
	Chi2 = 5.579 (p = 0.0614, NS)					
Lymphocyte infiltration: Low	17	60,7	5	27,8	3	16,7
High	11	39,3	13	72,2	15	83,3
	Chi2 = 10.2702 (p = 0.0059)					
Metastases / Invasion:						
Metastases	10	35,7	6	33,3	4	22,2
Invasion of nearby organs	6	21,4	5	27,8	8	44,4
Metastases / without invasion	12	42,9	7	38,9	6	33,3
	Chi2 = 2.9134 (p = 0.5724, NS)					
Operations performed due to recurrence						
Yes	5	17,9	4	22,2	1	5,6
	Chi2 = 2.0844 (p = 0.3527, NS)					

According to our data, low-malignant serous carcinomas are predominantly associated with serous cystadenoma and cystadenofibroma, and in the case of low-malignant serous carcinomas, the borderline malignant tumor foci almost always are observed.

As mentioned previously, based on our data, low-malignant serous invasive carcinomas are predominantly associated with cystadenoma and borderline serous malignant processes. In terms of immunohistochemistry, the intensity of oncoprotein p53 expression is poor or moderate in highly differentiated serous cancer, whereas it is weakly positive in serous cystadenoma; the intensity and percentage of marker involvement in cystadenofibroma is increased. It is noteworthy that in some cases routine morphological examination makes it difficult to differentiate the benign processes - serous cystadenoma or serous cystadenofi-

broma - from serous malignant formations with the borderline malignancy, especially when the slice is tangential. Therefore, we assume it would be important to separate these two biologically different processes with additional immunohistochemical analysis by using oncoprotein p53 in serous carcinomas with borderline malignancy.

The expression of $CD2^+$, $CD3^+$, $CD4^+$, $CD8^+$ T-lymphocytes in the tissue of ovarian cancer, as well as in metastases in the omentum, peritoneum and other organs was analyzed.

Tumor-infiltrating T cells ($CD2^+$, $CD3^+$, $CD4^+$, $CD8^+$) are almost absent in the parenchyma of endometrioid carcinoma formed at the background of ovarian endometriosis. In addition, CD3 expression in stroma is detected in less than 1% of lymphocytes. CD4/CD8 positive cells are present in equal amounts (0.9/1%); CD2 expression is not observed.

The expression of CD2, CD3, CD4, and CD8 in ovarian endometrioid carcinomas did not differ according to tumor differentiation grading. A statistically significant difference between bilateral ovarian endometrioid carcinomas and unilateral forms also was not revealed. This suggests that the antineoplastic role of tumor-infiltrating T-lymphocytes is minimal in case of the indolent progression of ovarian cancer. It may be assumed that the indolent tumors «exhaust» the local immunity.

Expression of CD2, CD3, CD4, and CD8 markers in both primary serous ovarian carcinomas and metastatic lesions in the case of highly differentiated forms, is almost absent in the parenchyma of tumor cells, while in the stroma the T-cells involvement is ranging from 0.8 to 6.2%.

In the case of high-grade serous carcinomas, the expression of CD2, CD4, and CD8 markers was equal in the stromal component of the tumor. In contrast to the low-grade forms of serous carcinomas (where, in the parenchyma of the cancer, TILs were either absent or in low amounts), the percentage of TILs distribution in the high-grade forms ranges from 36.4% to 37.5% in the parenchyma and from 9.5 to -12.4% - in the stroma.

It should be noted that there was observed a significant difference between CD4+/CD8+ lymphocytic infiltrations in high-grade serous carcinoma.

The involvement of TILs in serous carcinoma metastases is not significantly different from their quantitative-qualitative distribution in the primary tumor tissue. In addition, the percentage of expression of CD4/CD8 markers is more or less equal.

It is interesting that, in the case of clear cell carcinomas and mucinous carcinomas, an only a single occurrence of CD3, CD4, and CD8 positive TILs are detected in the tumor stroma while they are not observed in the tumor parenchyma. It should be mentioned that the quantitative-qualitative rate of TILs in parenchyma and stroma of ovarian endometrioid, mucinous and clear cell carcinomas does not exceed 1%.

Statistical analysis. A) Influence of morphological type on the outcome of ovarian cancer treatment.

The 3-year survival rate in patients with high-grade serous adenocarcinomas is 41.5% lower than in patients with other morphological types of ovarian cancer, i.e. the probability of a lethal outcome in patients with high-grade serous adenocarcinomas is 41.5% 3 years after surgery. This is higher compared to the mortality of patients with other morphological types of ovarian cancer (Diagram 1, Table 2).

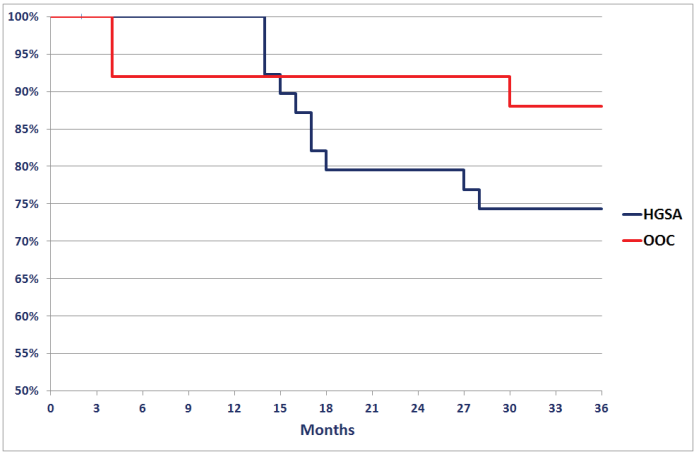

Diagram 1. Kaplan-Meyer curves obtained by survival analysis for the following groups: Group 1 - High-grade serous carcinoma (HGSOC) (dark blue line); Group 2 - Other morphological types of ovarian cancer (OOC) (red line)

Table 2. Comparative analysis of Kaplan-Meyer curve results for groups: Group 1 - High-grade serous carcinoma (HGSOC); Group 2 - Other morphological types of ovarian cancer (OOC)

Survival rate 3 years after surgery	
Group 1 – HGSOC	74.4%
Group 2 – OOC	88.0%
Cox Hazard Ratio (**HR**)	**1.710**
95% confidence intervals for HR (Confidense intervals – 95%CI)	**[1.277, 2.290]**
Chi2-test	**11.401**
P-value	**0.0007**

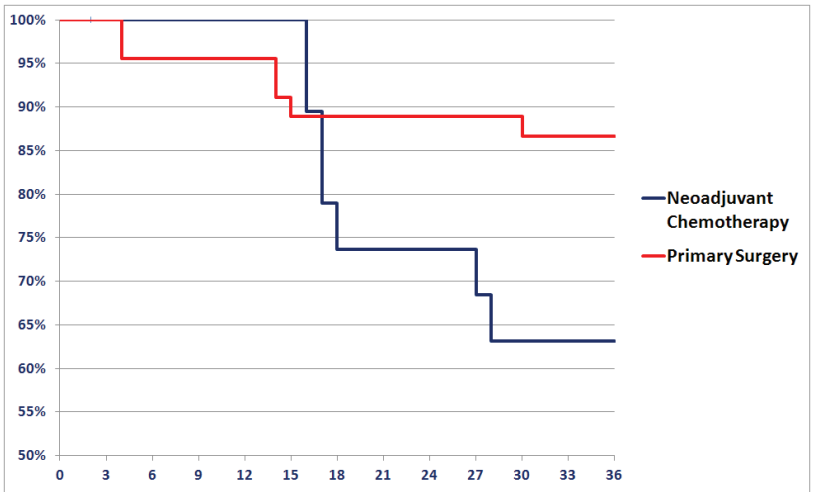

Diagram 2. Kaplan-Meyer curves obtained by survival analysis for the following groups: Group 1 - neoadjuvant chemotherapy (dark blue line); Group 2 – Primary Surgery (red line)

Table 3. Comparative analysis of results obtained by Kaplan-Meyer curves for groups: Group 1 - neoadjuvant chemotherapy; Group 2 - Primary Surgery

Survival rate 3 years after surgery	
Group 1 - Neoadjuvant chemotherapy	63.2%
Group 2 - Primary Surgery	86.7%
Cox Hazard Ratio (**HR**)	**2.064**
95% confidence intervals for HR (Confidense intervals – 95%CI)	**[1.492, 2.854]**
Chi2-test	**25.206**
P-value	**0.0001**

B) The impact of treatment tactics on the treatment outcome of ovarian cancer.

The 3-year survival rate in patients who underwent chemotherapy first and then surgery, was lower by 51.6% than in patients for whom surgical treatment was selected as the primary treatment method; i.e. the probability of a lethal outcome in patients of the initial neoadjuvant chemotherapy group within 3 years after surgery is 51.6% higher than in patients of the primary surgery group (Diagram 2, Table 3).

Multiple regression analysis was performed for the following risk factors (variables) affecting the effectiveness of ovarian cancer surgical treatment (assessed by the lethal outcome).

Pearson correlation coefficient r = 0.3758 (p=0.009).

Therefore, based on the obtained results, it can be concluded that from the combination of risk factors defining the effectiveness of ovarian cancer surgical treatment (lethal outcome) the presence of chemotherapy prior to surgery (neoadjuvant chemotherapy) and high-grade (G3) have a significant impact.

Conclusion. According to the obtained data, the carcinogenesis of high-grade and low-grade serous ovarian carcinoma is different. Low-grade forms are always preceded by serous cystadenoma and/or serous cystadenofibroma, which progresses to borderline serous carcinomas and then to low-grade invasive carcinoma. High-grade serous carcinomas are not developed from the progression of low-grade invasive carcinomas and are the product of the de novo formation.

Based on our study, there was not revealed a statistically significant difference between the universal system, provided by Shimizu/Silverberg and the "two-tier" system - in grading the microscopic malignancy of serous ovarian carcinomas.

Besides, the involvement of oncoprotein p53 in poorly differentiated serous carcinomas of the ovary is more intense compared to highly differentiated serous carcinomas and it is advisable to use it as an additional molecular-biological feature for specifying the grade of microscopic malignancy of the tumor.

The antineoplastic and/or prognostic role of the tumor-infiltrating T lymphocytes is not fully evident and needs further investigation.

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SUMMARY

OVARIAN CANCER TREATMENT OPTIMIZATION: THE COMPLEX ANALYSIS OF THE RESULTS OF CYTOREDUCTIVE SURGERY, MICROSCOPIC MALIGNANCY AND T-LYMPHOCYTIC INFILTRATION OF THE TUMOR

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The paper discusses 64 cases of ovarian cancer (observed in 2016-2019). Patients underwent cytoreductive surgery. Both Shimizu/Silverberg system and the "Two-tier" system were used to grade the tumor differentiation of serous carcinomas. The grade of the differentiation was specified by expression of oncoprotein p53.

The tumor infiltrating lymphocytes (TILs) labeled with immunohistochemical markers - CD2, CD3, CD4, CD8 - were evaluated for the intensity of expression in both - the ovarian tumor parenchyma and stroma. Quantitative assessment of expression was performed by a computer program ImageJ.

The survival of patients with ovarian cancer was examined by using the Kaplan-Meier curves and calculations of Cox Hazard Ratio (HR). Multiple regression analyses of factors influencing surgical intervention was performed by a logarithmic regression method.

According to the obtained data, the carcinogenesis of high-grade and low-grade serous ovarian carcinoma is different: low-grade forms are always preceded by serous cystadenoma and/or serous cystadenofibroma, which progresses to borderline serous carcinomas and then to low-grade invasive carcinoma; high-grade serous carcinomas are not developed from the progression of low-grade invasive carcinomas and are the product of the de novo formation.

p53 may be used as an additional molecular-biological feature for specifying the grade of microscopic malignancy of the tumor in the cases, when the moderate differentiation is established by Shimizu/Silverberg system.

The antineoplastic and/or prognostic role of the tumor-infiltrating T lymphocytes is not fully evident and needs further investigation.

High-grade (G3) of ovarian carcinoma and the neoadjuvant chemotherapy are the factors having a significant impact in defining the effectiveness of the surgical treatment of ovarian cancer.

Keywords: epithelial ovarian cancer, cytoreduction, grading system. TILs.

РЕЗЮМЕ

ОПТИМИЗАЦИЯ ЛЕЧЕНИЯ РАКА ЯИЧНИКОВ: КОМПЛЕКСНЫЙ АНАЛИЗ РЕЗУЛЬТАТОВ ЦИТОРЕДУКЦИИ, МИКРОСКОПИЧЕСКОЙ ЗЛОКАЧЕСТВЕННОСТИ И ИНФИЛЬТРАЦИИ ОПУХОЛИ Т-ЛИМФОЦИТАМИ

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В статье рассматриваются 64 случая рака яичников (наблюдавшихся в 2016-2019 гг.). Пациентам проведена циторедуктивная операция. Как система Симидзу/Сильверберга, так и двухуровневая система использовались для гистологической классификации серозных карцином. Степень дифференцировки дополнительно уточнялась экспрессией онкопротеина p53.

Интенсивность экспрессии инфильтрирующих опухоль лимфоцитов (ОИЛ) как в паренхиме, так и в строме опухоли яичника оценивали с помощью иммуногистохимического исследования. Количественную оценку выполняли с помощью компьютерной программы ImageJ.

Выживаемость пациенток с раком яичников оценивалась с использованием кривых Каплана-Мейера и расчетов коэффициента риска Кокса (HR). Множественный регрессионный анализ факторов, влияющих на хирургическое вмешательство, проводился методом логарифмической регрессии.

Согласно полученным данным, канцерогенез серозной карциномы яичников высокой и низкой степени злокачественности различен: низкостепенным формам всегда предшествует серозная цистаденома и/или серозная цистаденофиброма, которая прогрессирует до пограничной, а затем до инвазивной серозной карциномы низкой степени злокачественности; серозные карциномы высокой степени злокачественности не развиваются в результате прогрессирования инвазивных карцином низкой степени злокачественности и являются продуктом образования de novo.

p53 может быть использован как дополнительный молекулярно-биологический маркер для определения степени микроскопической злокачественности опухоли в тех случаях, когда по системе Симидзу/Сильверберга установлена умеренная дифференцировка.

Противоопухолевая и/или прогностическая роль ОИЛ не полностью очевидна и требует дальнейшего изучения.

Высокая степень (G3) карциномы яичников и неоадъювантная химиотерапия являются факторами, оказывающими значительное влияние на эффективность хирургического лечения рака яичников.

რეზიუმე

საკვერცხის კიბოს მკურნალობის ოპტიმიზაცია: ციტორედუქციის შედეგების, მიკროსკოპიული ავთვისებიანობის და სიმსივნის T-ლიმფოციტებით ინფილტრაციის კომპლექსური ანალიზი

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ნაშრომში განხილულია საკვერცხის კიბოს 64 შემთხვევა (პაციენტებზე დაკვირვება ხდებოდა 2016-2019 წლებში). პაციენტებს უტარდებოდათ ციტორედუქციული ოპერაციები. სიმსივნის დიფერენციაციის ხარისხის განსაზღვრის მიზნით სეროზულ კარცინომებში, გამოყენებული იყო როგორც Shimizu/Silverberg-ის, ასევე „Two tier" სისტემა, ხოლო დიფერენციაციის ხარისხის დაზუსტება ხდებოდა ონკოპროტეინ p53 ექსპრესიის მეშვეობით.

სიმსივნის მაინფილტრირებელი ლიმფოციტების (TILs) ექსპრესიის ინტენსივობის შეფასება ხდებოდა როგორც საკვერცხის სიმსივნის პარენქიმაში, ასევე სიმსივნური ქსოვილის სტრომაში - იმუნოჰისტოქიმიური კვლევის მეთოდით. რაოდენობრივი შეფასება ხორციელდებოდა კომპიუტერული პროგრამით ImageJ.

გადარჩენადობის ანალიზი ჩატარდა კაპლან-მეიერის მრუდების გამოყენებით და კოქსის საფრთხეთა ფარდობის (Hazard Ratio - HR) გამოთვლებით. ქირურგიულ ჩარევაზე გავლენის მქონე ფაქტორების მრავლობითი რეგრესიული ანალიზი ჩატარდა ლოგარითმული რეგრესიის მეთოდით.

კვლევის საფუძველზე დადგინდა, რომ:

-საკვერცხის დაბალდიფერენცირებული და მაღალდიფერენცირებული სეროზული კარცინომების კარცინოგენეზი განსხვავებულია. დაბალი ავთვისებიანობის (low-grade) ფორმებს ყოველთვის წინ უძღვის სეროზული ცისტადენომა და/ან სეროზული ცისტადენოფიბრომა, რომლებმაც შეიძლება ტრანსფორმაცია განიცადოს მოსაზღვრე ავთვისებიან სეროზულ კარცინომად და შემდეგ low-grade ინვაზიურ კარცინომად. ამასთანავე, მაღალი ავთვისებიანობის (high-grade) სეროზული კარცინომები არ წარმოიქმნება low-grade ინვაზიურ კარცინომებისაგან და de novo განითარების შედეგია.

საკვერცხის დაბალდიფერენცირებულ სეროზულ კარცინომებში ონკოპროტეინ p53 ჩართვა ინტენსიური იყო მაღალდიფერენცირებულ სეროზულ კარცინომებთან შედარებით. აღნიშნულის გამო, p53 შეიძლება გამოყენებულ იქნას როგორც დამატებითი მოლეკულურ-ბიოლოგიური მახასიათებელი სიმსივნის მიკროსკოპული ავთვისებიანობის ხარისხის დასაზუსტებლად იმ შემთხვევებში, როდესაც Shimizu/Silverberg სისტემის მიხედვით დგინდება სიმსივნის ზომიერად დიფერენცირებული ფორმა.

- საჭიროა სიმსივნის მაინფილტრირებელი T-ლიმფოციტების ანტინეოპლაზიური და/ან პროგნოზული როლის შემდგომი შესწავლა.
- საკვერცხეების სიმსივნის ოპერაციული მკურნალობის ეფექტურობაზე (ლეტალურ გამოსავალზე) გავლენის მქონე სარწმუნო ფაქტორებად გვევლინებიან ნეოადიუვანტური ქიმიოთერაპია და სიმსივნის დიფერენციაციის დაბალი ხარისხი.

ЯТРОГЕННЫЕ ПОВРЕЖДЕНИЯ ПРИ ВЫПОЛНЕНИИ ПРЕДОПЕРАЦИОННОЙ МАРКИРОВКИ НЕПАЛЬПИРУЕМЫХ ПАТОЛОГИЧЕСКИХ УЧАСТКОВ МОЛОЧНЫХ ЖЕЛЕЗ

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На протяжении длительного времени заболеваемость и смертность от рака молочной железы у женщин в развитых странах мира и на территории РФ не уступают свои лидирующие позиции среди всей онкологической патологии [2,5,6,8,10,11,13,15]. Выживаемость при раке молочной железы и дальнейшее качество жизни пациентов во многом зависят от стадии, на которой выявлено и пролечено заболевание [12]. Именно поэтому принципиальной задачей лучевой диагностики и онкологии остается выявление злокачественного процесса в молочных железах на доклинических стадиях развития болезни [1,7,9]. Для постановки корректного диагноза, при наличии узлового образования в молочной железе категории BI-RADS 4 и 5, помимо стандартных исследований (рентгеновская маммография и ультразвуковое сканирование) в обязательном порядке проводится морфологическая верификация выявленных патологических участков вне зависимости от их размеров. Минимальные (непальпируемые) изменения в тканях молочной железы, подозрительные в отношении злокачественного процесса, требуют перед началом хирургического лечения предоперационной маркировки [17,19]. Для этого используются такие способы навигационной разметки, как проводниковые, ультразвуковые, радионуклидные. Несмотря на наличие выбора, на практике с целью разметки непальпируемых участков молочных желез чаще всего применяются проволочные иглы, устанавливающиеся под рентгенологическим стереотаксическим контролем [14,18]. Однако вне зависимости от развития научно-технического прогресса и появления новых методов и методик, а также подходов к диагностике и лечению, человеческий фактор способен косвенно или напрямую влиять на количественный показатель ятрогений [4]. Основа принципа улучшения качества диагностики гласит, что не возможно исправить то, что не измеряется. Именно поэтому все мероприятия по минимизации диагностических ошибок должны состоять из трех этапов: выявления, анализа и устранения [3,16].

Цель исследования - выявить характер, частоту и виды ошибок врачей-рентгенологов, совершаемых при выполнении предоперационной разметки непальпируемых патологических участков молочных желез.

Материал и методы. Проанализировано 60 клинических наблюдений пациенток в возрастной группе от 40 до 85 лет с выявленными непальпируемыми патологическими участками в тканях молочных желез. Всем больным до начала хирургического лечения выполнено комплексное лучевое обследование молочных желез, включающее в себя проведение обзорной цифровой маммографии в двух стандартных проекциях, ультразвуковое исследование в В-режиме, а также в режиме цветового допплеровского картирования, и морфологическую верификацию посредством трепанобиопсии, преимущественно, под рентгенологическим контролем. Распределение нозологических форм патологических процессов в молочных железах в зависимости от результатов морфологического исследования биоптатов, полученных в процессе проведения трепанобиопсии на догоспитальном этапе, представлено на рис. 1.

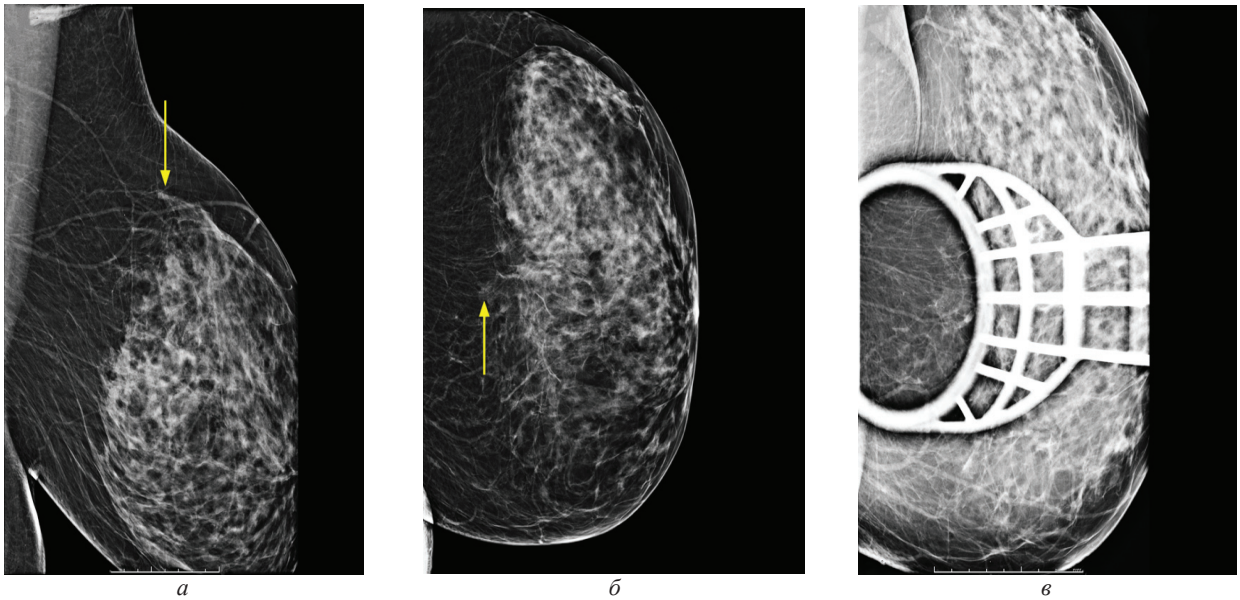
Рис. 1. Распределение нозологических форм непальпируемых патологических участков молочных желез после проведения трепанобиопсии (n=60)

Таким образом, на амбулаторном этапе до начала хирургического лечения рак молочной железы морфологически подтвержден у 10 (16,7%) женщин. В 18 (30%) наблюдениях по данным гистологии имела место пролиферативная форма узловой фиброзно-кистозной мастопатии. У 32 (53,3%) обследуемых выявленные при лучевом обследовании подозрительные в отношении рака молочной железы изменения (участки микрокальцинатов, тяжистые перестройки структуры ткани) не имели морфологически доказанных признаков злокачественности.

Всем 60 пациенткам на первом этапе выполнена секторальная резекция молочной железы с проведением внутритканевой маркировки патологического новообразования иглой-проводником «гарпунного» типа под рентгенологическим контро-

Таблица 1. Распределение ошибок врачей-рентгенологов при выполнении предоперационной маркировки непальпируемых новообразований молочных желез (n=8)

Ошибки предоперационной маркировки непальпируемых образований МЖ	Реоперация						Всего	
	Нет		Перезекция в процессе операции		Отсроченная операция			
	Абс	%	Абс	%	Абс	%	Абс	%
Синтопия на дооперационном этапе, потребовавшая установки дополнительной иглы	4	50,0	-	-			4	50,0
Синтопия, выявленная после иссечения сектора МЖ с установленной иглой-проводником	-	-	2	25,0	1	12,5	3	37,5
Маркировка другого образования	-	-	-	-	1	12,5	1	12,5
Итого	4	50,0	2	25,0	2	25,0	8	100,0



а *б* *в*

Рис. 2. Обзорные маммограммы в двух стандартных проекциях и прицельный снимок с прямым увеличением изображения левой молочной железы пациентки Т., 62 г.: а, б – обзорные маммограммы левой молочной железы в косой и прямой проекциях; в – прицельный снимок левой молочной железы, выполненный с прямым увеличением изображения; определяется В тип рентгенологической плотности ткани молочной железы, на границе верхних квадрантов визуализируется участок скопления плеоморфных кальцинатов - категория BI-RADS 4c (стрелки)

лем с последующей интраоперационной секторографией удаленного участка. В 10 случаях у больных с подтвержденным в амбулаторных условиях раком молочной железы дополнительно проведена лимфодиссекция акисллярных лимфатических узлов со стороны поражения уровня D1-2. В исследование не включены больные, прошедшие неоадъювантную терапию.

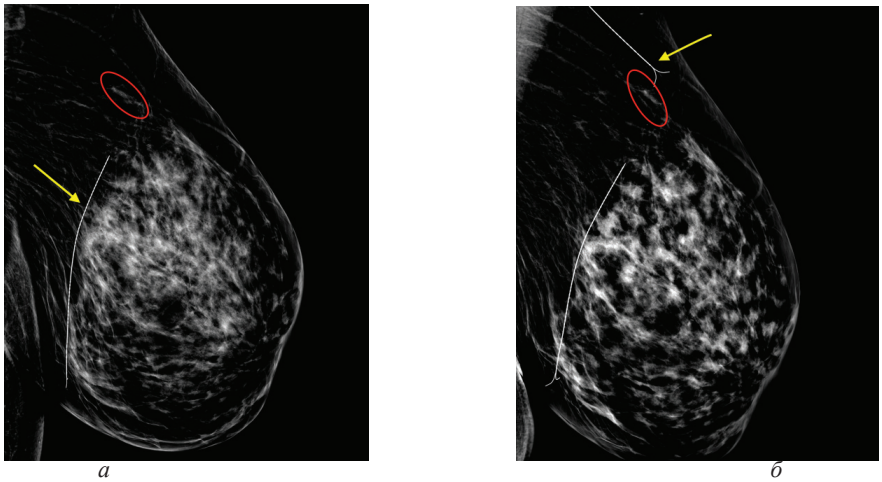
Результаты и обсуждение. По данным анализа качества выполнения врачом-рентгенологом предоперационной разметки непальпируемых образований молочных желез под стереотаксическим рентгенологическим контролем с использованием иглы-проводника количество врачебных ошибок в проведенном исследовании составило 8 (13,3%) от общего числа промаркированных патологических участков. Распределение дефектов предоперационной маркировки в порядке убывания приведено в таблице 1.

В половине клинических наблюдений (4 пациентки) зафиксированы случаи ошибок вследствие неправильной установки маркировочной иглы, которые были определены непосредственно оператором (врачом-рентгенологом) в процессе проведения контрольных маммографических снимков. Такие ситуации требовали имплантации дополнительных меток и были сопряжены с повышением эффективной дозовой нагрузки на пациенток, поскольку приходилось вновь выполнять сначала обзорные, а затем и контрольные маммограммы. Следующая по встречаемости ошибка предоперационной маркировки патологических новообразований молочных желез под рентгенологическим стереотаксическим контролем была синтопия иглы-проводника, которая выявлена у 3 (37,5%) больных после иссечения врачом-хирургом участка ткани с установленной меткой. В таких случаях при проведении секторографии патологические участки не визуализировались, а время пребывания больной в наркозе увеличивалось в 2-3 раза. В 100% таких синтопий пациенткам в нашем исследовании проводились реоперации. В одном клиническом наблюдении выполнена повторная операция, в двух других проведены перезекции. Реже выявлены случаи, когда врач-рентгенолог в процессе проведения предоперационной маркировки устанавливал иглу-проводник рядом с другим, имеющимся у больной узловым образованием, не требующим хирургического лечения.

Приводим клиническое наблюдение, демонстрирующее пример диагностической ятрогении, совершенной врачом-рентгенологом на этапе предоперационной маркировки непальпируемого образования левой молочной железы.

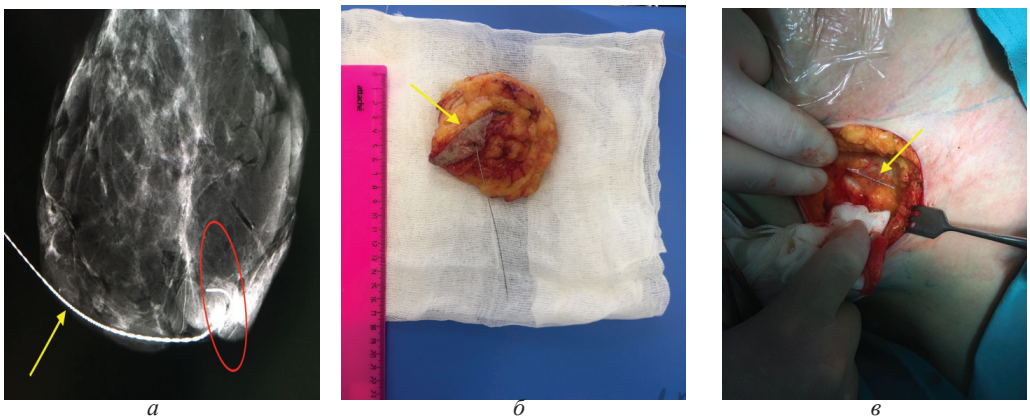
Пациентка Т., 62 г. направлена на хирургическое лечение с подозрением на рак молочной железы. На догоспитальном этапе больной выполнена комплексная клинико-инструментальная диагностика молочных желез. По данным рентгеновской маммографии, в левой молочной железе, в ее задней части, в проекции границы верхних квадрантов выявлен участок скопления плеоморфных кальцинатов (BI-RADS 4c), сохраняющийся на прицельном снимке с прямым увеличением изображения (рис. 2).

При проведении ультразвукового исследования молочных желез и зон регионарного лимфооттока патологические изменения не визуализировались (BI-RADS 1). Выполнена трепанобиопсия участка скопления плеоморфных кальцинатов под рентгенологическим наведением. По данным морфологического исследования, полученного при биопсии биологического материала, выявленные изменения соответствовали дисплазии 2-3 степени. Убедительных данных о злокачественном процессе не получено. На основании заключения клинико-инструментального обследования принято решение о выполнении эксцизионной биопсии патологического участка левой молочной железы со срочным гистологическим исследованием операционного материала. Поскольку выявленные при обзорной и прицельной маммографии изменения в левой молочной железе не пальпировались, пациентке было показано проведение предоперационной маркировки зоны интереса иглой-проводником «гарпунного» типа под стереотаксическим рентгенологическим контролем. При выполнении интервенционной методики разметки непальпируемого новообразования, ввиду неправильного выбора врачом-рентгенологом проекционной точки введения маркера и траектории его имплантации (нарушение методологии процедуры), произошло тотальное погружение иглы-проводника в ткань молочной железы (дистальная часть маркера не выступала над кожей) (рис. 3а). В результате сложившейся ситуации потребовалось выполнение повторной предоперационной разметки (установка дополнительного тканевого маркера) (рис 3б).



а б

Рис. 3. Маммограммы левой молочной железы в медиолатеральной проекции; а – рентгенологическое изображение левой молочной железы в косой проекции после постановки первого маркера: визуализируется игла-проводник «грапунного» типа, полностью погруженная в ткань молочной железы (стрелка), находящаяся в другой проекционной плоскости от участка плеоморфных кальцинатов (овал); б – рентгенологическое изображение левой молочной железы в косой проекции после постановки второго маркера: дополнительно установленная маркировочная игла (стрелка) лоцируется вблизи от участка скопления плеоморфных микрокальцинатов (овал)



а б в

Рис. 4. Интраоперационный материал: а – секторография удаленной ткани левой молочной железы с установленной иглой-проводником (стрелка), «якорная» часть которой расположена вблизи от участка скопления микрокальцинатов (овал); б – внешний вид удаленного участка молочной железы размером 8х8 см: виден маркер, выходящий из кожи (стрелка); в – в ложе послеоперационной раны обнаружена первоначально установленная игла-проводник (стрелка)

Выполнена секторальная резекция левой молочной железы. Удален участок ткани с установленной иглой-проводником «гарпунного» типа (рис. 4а, б).

После выполнения секторальной резекции при ревизии операционной раны в ложе удаленного участка левой молочной железы субфасциально, над большой грудной мышцей обнаружен первоначально неправильно установленный врачом-рентгенологом тканевой маркер, который был сразу удален (рис. 4в).

Данные срочного и планового патоморфологического исследования: опухолевый узел имел строение инфильтративного рака неспецифического типа с участками микрокальцинатов. На основании данных гистологического заключения пациентке установлен диагноз: рак левой молочной железы pT1bN0M0 I стадия.

Все без исключения случаи ошибочной предоперационной маркировки непальпируемых новообразований молочных желез нами расценены как диагностические ятрогении, которые сопровождались повышением эффективной эквивалентной дозы, получаемой женщиной, и длительностью ее пребывания в наркозе. Необходимость повторных оперативных вмешательств закономерно приводила к увеличению уровня стресса у больных. Таким образом, для минимизации количества ятрогенных повреждений молочных желез, совершаемых при проведении предоперационной разметки, врач-рентгенолог должен обладать пространственным мышлением, а также достаточными знаниями и опытом проведения интервенционных манипуляций на молочной железе.

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SUMMARY

IATROGENIC INJURIES DURING PREOPERATIVE MARKING OF NON-PALPABLE PATHOLOGICAL AREAS OF THE MAMMARY GLANDS

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The purpose of the study is to identify the types and frequency of medical mistakes made during preoperative marking of non – palpable pathological areas of the breast.

We analyzed 60 clinical observations of patients with

non-palpable, morphologically verified pathological areas in breast tissues, who underwent surgical intervention at the first stage of treatment with mandatory preoperative marking with a guide needle.

The obtained data indicates that the error rate of radiologists when installing a tissue marker in a non-palpable breast neoplasm is 13.3% and is most often manifested by syntopia of the guide needle, which is detected at the beginning of the operation and requires implantation of additional tags.

All clinical observations were accompanied by an increase in both the equivalent dose received by the patient and duration of the anesthesia. To improve the quality of interventional techniques performed on the breast, also to minimize the number of iatrogenic injuries, the radiologist must have spatial thinking, a sufficient amount of theoretical knowledge and practical skills.

Keywords: iatrogenia, breast cancer, non-palpable formation, preoperative marking.

РЕЗЮМЕ.

ЯТРОГЕННЫЕ ПОВРЕЖДЕНИЯ ПРИ ВЫПОЛНЕНИИ ПРЕДОПЕРАЦИОННОЙ МАРКИРОВКИ НЕПАЛЬПИРУЕМЫХ ПАТОЛОГИЧЕСКИХ УЧАСТКОВ МОЛОЧНЫХ ЖЕЛЕЗ

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Цель исследования – выявить виды и частоту врачебных ошибок, совершаемых при проведении предоперационной разметки непальпируемых патологических участков молочных желез.

Проанализировано 60 клинических наблюдений пациенток с непальпируемыми, морфологически верифицированными патологическими участками в тканях молочных желез, которым на первом этапе лечения проводилось хирургическое вмешательство с обязательной предоперационной маркировкой проводниковой иглой.

Полученные данные свидетельствуют, что частота ошибок врачей-рентгенологов при установке тканевого маркера в непальпируемое новообразование молочной железы составляет 13,3% и проявляется чаще всего синтопией проводниковой иглы, выявляющейся в начале операции и требующей имплантации дополнительных меток.

Все клинические наблюдения сопровождались увеличением как полученной пациенткой эквивалентной дозы, так и времени пребывания пациенток в наркозе. Для улучшения качества проводимых интервенционных методик на молочной железе, а также минимизации числа ятрогенных повреждений врач-рентгенолог должен обладать пространственным мышлением, достаточным объемом теоретических знаний и практических умений.

რეზიუმე

იატროგენული დაზიანებები სარძევე ჯირკვლების არაპალპირებადი პათოლოგიური უბნების ოპერაციამდელი მარკირების ჩატარების დროს

[1,2]ა.ვასილიევი, [1,3]ტ.პავლოვა

[1]სხივური დიაგნოსტიკის ცენტრალური სამეცნიერო-კვლევითი ინსტიტუტი; [2]მოსკოვის ა.ევდოკიმოვის სახ. სახელმწიფო სამედიცინო-სტომატოლოგიური უნივერსიტეტი; [3]ვ.ბუიანოვის სახ. საქალაქო კლინიკური საავადმყოფო, მოსკოვი, რუსეთის ფედერაცია

კვლევის მიზანს წარმოადგენდა სარძევე ჯირკვლების არაპალპირებადი პათოლოგიური უბნების ოპერაციამდელი მონიშვნის დროს დაშვებული საექიმო შეცდომების სახეების და სიხშირის გამოვლენა.

გაანალიზებულია 60 პაციენტის კლინიკური დაკვირვება სარძევე ჯირკვლების არაპალპირებადი, მორფოლოგიურად ვერიფიცირებული პათოლოგიური უბნებით, რომელთაც მკურნალობის პირველ ეტაპზე ჩაუტარდა ქირურგიული ჩარევა აუცილებელი ოპერაციამდელი მარკირებით გამტარი ნემსით.

მიღებული მონაცემები მიუთითებს, რომ ექიმი-რენტგენოლოგების შეცდომების სიხშირე ქსოვილური მარკერის ჩაყენებისას სარძევე ჯირკვლის არაპალპირებად ახალწარმონაქმნში შეადგენს 13,3%-ს და ყველაზე ხშირად გამოიხატება გამტარი ნემსის სინტოპიით, რაც ვლინდება ოპერაციის დასაწყისში და საჭიროებს დამატებითი ნიშნულების იმპლანტაციას.

ყველა კლინიკურ დაკვირვებას თან ახლდა პაციენტის მიერ მიღებული ეკვივალენტური დოზის და ნარკოზის ქვეშ პაციენტის ყოფნის დროის გაზრდა. სარძევე ჯირკვალზე ჩატარებული ინტერვენციული მეთოდიკების ხარისხის გაუმჯობესების მიზნით, ასევე, იატროგენული დაზიანებების რაოდენობის მინიმიზებისათვის ექიმი-რენტგენოლოგი უნდა ფლობდეს განზოგადებული აზროვნების უნარს, თეორიული ცოდნის და პრაქტიკული უნარების საკმარის მოცულობას.

EFFECTS OF DIFFERENT TREATMENT OPTIONS ON THE LEVEL OF SERUM CYTOKINES IN PATIENTS WITH LIVER CANCER

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Liver cancer is a highly lethal tumor. Interaction between cancerous, stromal, immune cells and extracellular matrix proteins form immune suppressive tumor microenvironment. Local microenvironment and systemic immunosuppression allow tumor to escape immune surveillance [1].

Balance of pro- and anti-inflammatory cytokines, different expression of cytokines' receptors on responder cells and the activation state of surrounding cells not only regulate anti-tumoral response, but may have influence on transformations and malignancy of cells in the pathogenesis [2].

Several studies reported that an increased level of IL-10 characterizes different types of cancer. The positive correlation between serum IL-10 levels and tumor progression indicates a key role of IL-10 in the suppression of anti-tumor immune response and establishment of tumor environment. Its pro-tumorigenic effects depend on upregulation of Bcl-2 and downregulation of apoptosis [3].

TGF-β has a dual role in cell proliferation and cell death. Initially, it acts as a tumor suppressor, since it induces apoptosis and inhibits the growth of cells, but at later stages of tumor progression, it is tumor promoter - stimulates angiogenesis, induces T regulatory cells development, inhibits anti-tumor immune response and affects differentiation of epithelial and endothelial cells. It also reduces the amount of antigen presentation by dendritic cells [4]. TGF-β can promote self- renewal of cancer stem cells, or induces their differentiation. Increased levels of TGF-β have been shown to contribute to metastatic spread of tumor cells, via the epithelial/mesenchymal transition.

Pro-inflammatory cytokine, such as IL-17, also has dual effects on tumor immune surveillance (either promotes tumor growth via stimulating angiogenesis or inhibits tumor growth via stimulating cytotoxic T-cell response) [5]. IL-17 pro-tumorigenic role depends on its effect on fibroblasts and endothelial cells in the tumor microenvironment. IL-17 stimulates vascular endothelial cell migration, cord formation of vascular endothelial cells and regulates the production of a variety of pro-angiogenic factors. IL-17 induces vascular endothelial growth factor (VEGF), IL-1β, IL-6, PGE2, enhances ICAM-1 expression in fibroblasts and stimulates IL-8 production. All of these molecules are key factors in angiogenesis and tumor invasion. On the other hand, IL-17 stimulation can induce IL-12 production from macrophages [6]. Both IL-6 and IL-12 have been associated with tumor-specific cytotoxic T lymphocytes (CTL) induction.

IFN-γ is an important factor in the induction of CTL differentiation. IFN-g shows, cytotoxic and proapoptotic (By inducing of specific genes) effects [7], it upregulates MHC expression on tumor cells, inhibits angiogenesis (inhibition of tumor-derived angiogenesis is well-accepted mechanism to limit tumor growth), antagonizes suppression by tumor-derived TGF-β [8]. However, in contrast of these effects, the prolonged presence of IFN-γ promotes changes in tumor phenotype by survival of more aggressive clones of malignant cells, epigenomic or transcriptogenomic changes caused by IFN-γ in tumor cells favor escape from immune surveillance [9,10].

Surgery has always been considered as a gold standard for treatment of liver cancer, in recent years, patients with liver cancer are often managed by non-surgical locoregional treatment approaches, for example, radiofrequency thermal ablation (RFA). It represents minimally invasive treatment option and demonstrates good survival rate over the others with surgical resection when the tumor size is <3 cm [11-14]. RFA results in a higher rate of tumor necrosis (tumor size, number and sites are of importance). Additionally, many studies report that RFA provides adjuvant/"danger" signals to the immune cells, as a consequence stimulates CD4+ T helpers and causes a drastically increase of antigen-specific CD8+ T cells within the tumor microenvironment and tumor-draining lymph node [15-17].

We aimed to study changes in serum cytokines levels due to local disturbance of tumor microenvironment after radiofrequency thermal ablation procedure compare to liver resection in patients with primary and metastatic liver cancer.

Material and methods. We conducted a single center prospective pilot study at Tbilisi State Medical University hospital in accordance with the Declaration of Helsinki from 2014 to 2017. The study was approved by the Ethic Committee of the Tbilisi State Medical University and informed consent obtained from each recruited patient, with primary or secondary liver cancer. The primary endpoint of study was to assess the immunomodulatory changes in cytokines (IL-10, IFN-γ, IL-17, TGF-β) following RFA or liver resection in the liver cancer patients.

A total of 17 patients with primary (HCC and Cholangiocarcinoma) and secondary (metastasis from colorectal cancer) liver cancer were enrolled in this prospective study. Out of 17 patients, 7 were referred to RFA procedure and another 10 underwent surgical liver resection using non-RF based devices. All decisions regarding procedures were tabled by MDT (Multidisciplinary Team). 3 patients underwent anatomic segmental hepatectomy and non-anatomical resection was done in 7 patients. All liver resections were accomplished by using non-RF based liver resection devices. Healthy age-matched 14 volunteers without history of cancer, recent acute or chronic infectious disease, or autoimmune disease, were used as controls for the comparison.

The inclusion criteria for the RFA patients selection were as follows: a) extensive liver disease or medical co-morbidities associated with tumor vascular invasion and thromboses, b) fewer than three nodules without extrahepatic metastasis, c) largest tumor size of 3-4 cm in diameter, d) visualization of the nodule during the planning of RFA by ultrasonography (US). The exclusion criteria included treatment by chemotherapy or TACE, RFA or LR within previous one month.

Radiofrequency thermal ablation (RFA). An image guided RFA was performed by senior interventional radiologist at our centre. The tumor was localized and RF antenna introduced into the target tissue under US guidance. RF processing increases temperature into the target tissue up to 102^0C leading to the irreversible damage by coagulative necrosis. Abdominal contrast computer tomography (CT) was performed to document completeness of the procedure. A peripheral blood samples were obtained one month before and after the procedure.

Liver resection (LR). Surgical resection, anatomic segmental hepatectomy and non-anatomical liver resection was carried out under the general anesthesia using an upper middle incision, using non-RF based liver resection devices.

Blood samples were collected from each patient before and after 1 and 3 months of treatment. The following serum cytokines: IL-10, IL-17, INF-γ, TGF-β were assayed by ELISA (ebiosciences, USA).

None of the patient had received chemotherapy or any other treatment a month before or 3 months after the LR and RFA procedure.

All data were entered into a Microsoft Excel™ database and analyzed using Graph Pad Prizm software. The Student's t-test was used to compare data between RFA and surgical resection group. Furthermore, both study groups were compared with healthy control subjects. *P* values less than 0.05 were considered as statistically significant.

Results and discussion. A total of 17 patients with liver cancer were included in the study. Patients' demographic characteristics of each group has been listed and compared in Table 1. The mean age of patients in RFA and LR group was 55.1±11.2 years and 58.6±8.1 years respectively (p>0.05). There were 3 women (43%) and 4 men (57%) in the RFA cohort whilst, 5 women (50%) and 5 (50%) men in the LR group. Along with that, we didn't observe any significant differences between groups regarding number of tumors, primary or secondary, tumor size, tumor stage, HBsAg, Anti-HCV positive.

The present study showed increased level of IL-10 in patients who underwent RFA procedure compare to healthy age-matched volunteers without history of cancer (p<0.05). 1 month after RFA procedure serum level of IL-10 declined (P<0.01) and was comparable with control. 3 months after RFA procedure serum level of IL-10 continued to reduce (p=0.03). In the patients before liver resection serum level of IL-10 was comparable with indices in healthy volunteers. 1 month after liver resection (LR) serum level of IL-10 increased (p<0.01) and continued to enhance at the point of 3 months after LR (P=0.006) (Fig. 1).

Serum levels of IL-17 were higher in patients, compare to control group and did not change 1 and 3 months after RFA and LR (p>0.05) (Fig. 2).

Serum levels of IFN-γ, were higher in RFA group compare to LR group. 1 and 3 months after treatment it showed decline approximately to control level (P>0.05) (Fig. 3).

Pre-procedural serum level of TGF-β was high, compare to healthy age-matched volunteers. It decreased 1 month after RFA and LR. Noteworthy, in our study at the point of 3 months after RFA procedure it continued to decrease, while at this point TGF-β remained the same in LR group (P>0.05) (Fig. 4).

Cytokines are the main mediators for the growth, invasion and metastasis of cancer. They are produced by cancer cells as well as immune and stromal cells in the affected area and are responsible for further uncontrolled proliferation of malignant cells, remodeling of tumor microenvironment, triggering of intrinsic inflammation, recruiting cells, angiogenesis and cancer cells spread [18].

Clinicopathological factors: higher AFP, tumor size, metastases, lower grade of differentiation are important predictors of the outcome of disease [19]. It is shown, that pre-treatment serum level of cytokines also widely varies in patients with liver cancer and highly determines the prognosis of diseases. Higher pre-therapy serum level of IL-17 and lower IL-10 level predicted poor prognosis (early recurrence of tumor) after surgery in patients with HCC. Other cytokines: IL-23, IL-8, IL-1b, IL-6, IL-1a and TNF-α were not associated with recurrence time of disease [20]. It was supposed, that IL-17 and IL-10 along with other factors form cancerogenic environment responsible for tumor recurrence.

As is consistent with the literature, our study showed that compared with the baseline serum cytokine levels (IFN-γ and TGF-β) there were no significant changes in serum levels of these markers one month after curative treatments (RFA and resection) [21].

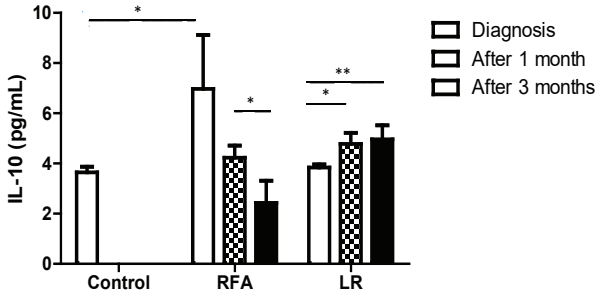

Fig 1. Serum IL-10 levels in patients with liver cancer before and after 1 and 3 months of RFA and liver resection
LR group - diagnosis vs. after 1 month – P<0.01; Diagnosis vs. after 3 months- P=0.006; RFA group- diagnosis vs. after 1 month- P< 0.01; After 1 month vs. after 3 months- P=0.03

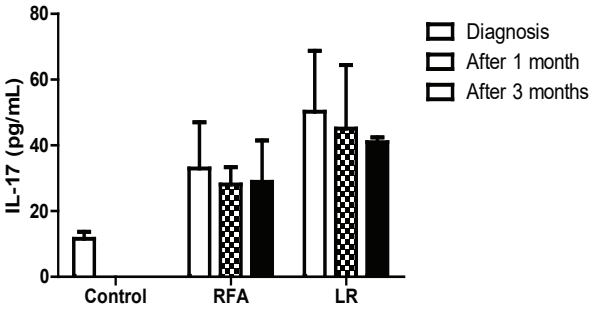

Fig 2. Serum IL-17 levels in patients with liver cancer before and after 1 and 3 months of RFA and liver resection

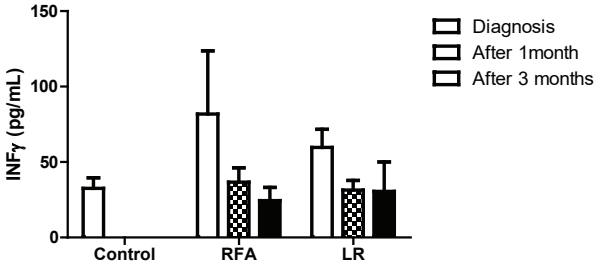

Fig 3. Serum INFγ levels in patients with liver cancer before and after 1 and 3 months of RFA and Liver resection

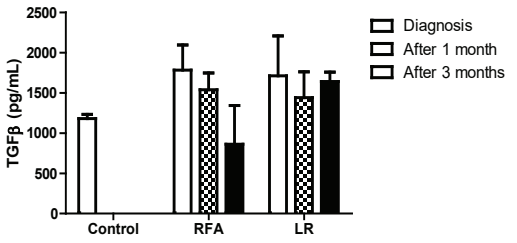

Fig. 4. Serum TGFβ levels in patients with liver cancer before and after 1 and 3 months of RFA and Liver resection

We showed that serum level of IFN-γ in patients had tendency to increase compared to healthy donors as it was observed by A. M. Attallah et al. [22] and in contrary by L. Ji et al. [23]. L. Ji reported that changes of IFN-γ under the influence of the RFA treatment was depended on the AFP level of patients with liver cancer: in patients with reduced AFP levels Th1 cytokines increased, whereas Th2 cytokines decreased after 1 month of treatment. However, in few patients with increased AFP level after RFA treatment IL-2, TNF-α, IFN-γ serum levels significantly declined and IL-4, IL-6 and IL-10 serum levels markedly enhanced ($p<0.05$).

Our study showed an enhanced level of TGF-β in patients with liver cancer in comparison with healthy donors, which insignificantly decreased by both treatment options. It continued to reduce at the point of 3 months after RFA therapy and remained unchanged in the LR group. The newest studies explained the dual role of TGF-β in liver cancer development [24]. This cytokine performs cytostatic and apoptotic function and is considered as tumor suppressor at early stages of tumor development. However, accumulation of suppressor cells: Tregs, MDSC and tumor cells by themselves produce high amount of TGF-β, which inhibits Th1, TCL, NK at advanced stage and promotes tumor escape from immune surveillance. TGF-β presents one of the key cytokines associated with angiogenesis and fibrogenesis. Some studies provided evidence about TGF-β inhibitors in patients with advanced HCC. Tendency of continuous reduction of TGF-β after RFA treatment in our study highlights the beneficial effect of such treatment.

Th-2 cells, B cells, tumor cells and macrophage produce one of the most important immunosuppressive mediator IL-10 - a potent inhibitor of pro-inflammatory cytokines (including IL-1β, TNF-α and IL-6). IL-10, together with TNF-a, autocrinally stimulates the expression of negative costimulatory molecule B7-H1(PDL-1) on macrophage surface - impairs $CD8^+$ T cell activity and supports tumor immune escape [25]. Our results revealed that, radiofrequency ablation and hepatic resection showed the opposite effects on serum IL-10 level in patients with liver cancer: RFA procedure significantly decreased serum level of IL-10, inconsistent with LR, which significantly increased this indicator.

We suppose that important differences in immune responses evoked after two different treatment approaches can be explained by the destruction of tumor microenvironment by RFA and healthy tissue injury during resection.

Local immune responses to surgery lead to systemic proinflammatory and immunosuppressive phases: production of a variety of cytokines leading to a general inflammation: stress, activation of the hypothalamic-pituitary-adrenal axis, release of steroids, such as cortisol, facilitates to the healing of injured tissues. Immunosuppressive phase avoids autoreactivity but on the other hand, it can inhibit antitumor Th1 immune response, provokes development of postoperative immune suppression and stimulates tumor cells growth.

Others and our previous studies reported that destruction of tumor microenvironment by RFA favors the increase of expression of heat shock proteins and release of a wide spectrum of tumor antigens from necrotic cells. Natural adjuvants loaded by antigens are easily uptaken by dendritic cells and effector specific antitumor CD4+ Th1 cells as well as CD8+ T cytotoxic cells are recruited to the tumor microenvironment [26]. We suppose, that Th1 cytokine milieu can establish antitumor environment and inhibits production of IL-10 by Th2, TAM and other cells. These events account for the immunotherapeutic effect of RFA.

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SUMMARY

EFFECTS OF DIFFERENT TREATMENT OPTIONS ON THE LEVEL OF SERUM CYTOKINES IN PATIENTS WITH LIVER CANCER

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Liver cancer is a highly lethal cancer, in which local tumor microenvironment and systemic immune suppression allow tumor to escape immune surveillance. Intervening in tumor microenvironment by locoregional treatment options can be beneficial for patients.

We aimed to study changes in serum cytokines levels due to local disturbance of tumor microenvironment after radiofrequency thermal ablation procedure compare to liver resection in patients with primary and metastatic liver cancer.

A total of 17 patients with primary (HCC and Cholangiocarcinoma) and secondary (metastatic) liver cancer were enrolled in this prospective study. Out of 17 patients, 7 were referred to RFA procedure and another 10 underwent surgical liver resection using non-RF based devices.

Blood samples were collected from each patient before and after 1 and 3 months of treatment. The following serum cytokines: IL-10, IL-17, INF-γ, TGF-β were assayed by ELISA (ebiosciences, USA).

RFA procedure unlike liver resection decreased serum level of IL-10 in patients with liver cancer. No significant changes in the level of the studied cytokines were revealed.

Keywords: proinflammatory, anti-inflammatory cytokines, IL-10, radiofrequency ablation, liver resection, liver cancer.

РЕЗЮМЕ

ВЛИЯНИЕ РАЗЛИЧНЫХ МЕТОДОВ ЛЕЧЕНИЯ НА УРОВЕНЬ СЫВОРОТОЧНЫХ ЦИТОКИНОВ У ПАЦИЕНТОВ С РАКОМ ПЕЧЕНИ

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Рак печени в большинстве случаев завершается летальным исходом. Воздействие местного микроокружения опухоли на иммунную систему позволяет опухоли избежать иммунологического надзора. Следовательно, разрушение микросреды опухоли местными методами лечения может оказаться эффективным для пациентов.

Целью исследования явилось изучение изменений уровня цитокинов, вызванных деструкцией опухолевой ткани в результате применения современного малоинвазивного метода радиочастотной термальной абляции и после резекции печени, у пациентов с первичным и метастатическим раком печени.

В проспективное исследование включены 17 пациентов с первичным (гепатоцеллюлярная карцинома и холангиокарцинома) и вторичным (метастатическим) раком печени. 7 пациентов из 17 подверглись радиочастотной термальной абляции (РЧА), 10 пациентам проведена резекция печени.

Забор крови проводили до лечения и спустя 1 и 3 месяца после лечения. Для измерения концентрации цитокинов (IL-10, IL-17, INF-γ, TGF-β) в сыворотке крови использовали метод иммуноферментного анализа - ELISA (Ebiosciences, США).

РЧА, в отличие от резекции печени, выявила снижение уровня IL-10 у пациентов с раком печени. Существенных изменений в уровнях остальных исследованных цитокинов не выявлено.

რეზიუმე

მკურნალობის სხვადასხვა მეთოდის გავლენა ღვიძლის კიბოთი დაავადებული პაციენტების შრატში ციტოკინების დონეზე

ნ. ქიქოძე, მ. იობაძე, ი. ფანცულაია, მ. მიზანდარი, ნ. ჯანიკაშვილი, თ. ჩიქოვანი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

ღვიძლის კიბო, ძირითადად, ლეტალური გამოსავლით სრულდება. სიმსივნის ლოკალური მიკროგარემოს ზემოქმედება იმუნურ სისტემაზე საშუალებას აძლევს სიმსივნეს თავი დააღწიოს იმუნოლოგიურ ზედამხედველობას. ამიტომ, სიმსივნის მიკროგარემოს დესტრუქცია, მკურნალობის ლოკალური მეთოდების გამოყენებით, შეიძლება სასარგებლო იყოს პაციენტისთვის.

კვლევის მიზანს წარმოადგენდა ღვიძლის კიბოთი დაავადებული პაციენტების მკურნალობის ორი განსხვავებული სტრატეგიის - რადიოსიხშირული თერმული აბლაციისა და ღვიძლის რეზექციის გავლენის შესწავლა პაციენტთა პერიფერიულ სისხლში ციტოკინების დონეზე.

პროსპექტიულ კვლევაში ჩართული იყო ღვიძლის პირველადი (ჰეპატოცელური კიბო და ქოლანგიოკარცინომა) და მეორადი (მეტასტაზური) კიბოთი დაავადებული 17 პაციენტი, მათგან 7-ს ჩაუტარდა რადიოსიხშირული თერმული აბლაცია (რსა), ხოლო დანარჩენ 10 პაციენტს - ღვიძლის რეზექცია.

თითოეული პაციენტისაგან სისხლის ნიმუშის აღება ხდებოდა მკურნალობამდე და მკურნალობის დაწყებიდან 1 და 3 თვის შემდეგ. პერიფერიული სისხლის შრატში ციტოკინების - IL-10, IL-17, INF-γ, TGF-β, განსაზღვრისთვის გამოყენებული იყო იმუნოფერმენტული ანალიზის მეთოდი ELISA (Ebiosciences, აშშ).

რსა-ის გამოყენებამ ღვიძლის კიბოთი დაავადებულ პაციენტებში, ღვიძლის რეზექციისაგან განსხვავებით, გამოიწვია შრატში IL-10–ის შემცირება. სხვა გამოკვლეული ციტოკინების დონის მნიშვნელოვანი ცვლილება არ გამოვლენილა.

СРАВНЕНИЕ РЕЗУЛЬТАТОВ ВОССТАНОВЛЕНИЯ ПОВРЕЖДЕНИЙ АКРОМИАЛЬНО-КЛЮЧИЧНОГО СОЧЛЕНЕНИЯ КРЮЧКОВИДНОЙ ПЛАСТИНОЙ И ПУГОВЧАТОЙ ФИКСАЦИЕЙ TIGHTROPE

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Повреждение акромиально-ключичного сочленения - частая травма в области плеча, относящаяся к спортивной медицине и ортопедии [1,2]. Количество таких повреждений значительно увеличилось в результате роста объема дорожно-транспортных происшествий и вовлеченности в любительский спорт. Выделяются 6 степеней повреждения акромиально-ключичного сочленения в классификации по Rockwood [2,3]. Оперативное лечение показано при степенях повреждений III-VI по Rockwood. Однако, лечение III степени повреждения по Rockwood в научном мире носит дискуссионный характер, так как одни авторы говорят о необходимости консервативного лечения данного повреждения, другие склоняются к оперативному. При этом все авторы сходятся в одном, что оперативное лечение рекомендуется молодым пациентам, спортсменам, лицам, занимающимся физическим трудом. Оперативное лечение при свежих повреждениях акромиально-ключичного сочленения приводит к лучшим результатам [3-7].

Лечение акромиально-ключичного повреждения можно выполнять различными оперативными техниками. Обычно используют метод с установкой крючковидной пластины или артроскопическую технику TightRope, при применении которых добиваются хороших клинических результатов.

Установка крючковидной пластины может повлечь за собой некоторые проблемы, такие как акромиальный остеолиз, миграция металлофиксаторов, тендинит [8]. Помимо этого, после установки пластины пациенты часто испытывают боль в области сухожилия надостной мышцы оперируемого плеча и ограничение движения в нем. С учетом совокупности вышеотраженных возможных осложнений при установке данной металлоконструкции рекомендуется удалять крючковидную пластину по истечении определенного времени [9].

В качестве альтернативы существует метод артроскопической техники с использованием пуговчатого фиксатора (TightRope). У данного метода есть преимущества в виде малотравматичности и анатомичности при восстановлении нормального положения сустава, что невозможно при установке крючковидной пластины. При использовании данного метода нет необходимости удалять фиксатор [10].

Целью исследования явилось сравнение двух представленных методов при лечении акромиально-ключичного сочленения с установкой крючковидной пластины и при помощи пуговчатой фиксации TightRope.

Материал и методы. В период с 2015 по 2019 гг. 60 пациентам проведено оперативное лечение свежих повреждений акромиально-ключичного сочленения III–VI типа по Rockwood. Согласно оперативным методам, пациенты разделены на две группы пациенты первой группы (n=30) прооперированы с использованием крючковидной пластины, второй группы (n=30) – с применением техники TightRope. Соотношение пациентов по гендерному признаку - 48 (80%) мужчин и 12 (20%) женщин. Возраст пациентов варьировал в пределах от 23 до 54 лет, средний возраст - 35.2±8.2 г.

Все пациенты получали лечение в течение 3 недель с момента травмы. 30 пациентам первой группы фиксация вы-

полнена крючковидной пластиной. 29 (96,6%) пациентам первой группы крючковидную пластину удалили спустя 6-8 месяцев после операции. 1 (3,4%) пациент от повторной операции отказался. 6 (20%) пациентов первой группы получили травму в результате занятия любительским спортом. 24 (80%) пациента обратились за лечением в результате получения бытовой травмы.

Хирургическая техника открытой репозиции и фиксации с помощью крючковидной пластины. Операция проводилась под эндотрахеальным наркозом в положении «пляжное кресло». Выполнялся разрез кожи от конца акромиона длиной 6-7 см в медиальную сторону (рис. 1), обнажался акромиально-ключичный сустав, что позволяло поставить крючковидную пластину в данное пространство. Репозиция достигалась при надавливании пластины на ключицу, а акромион использовался как рычаг. Перед введением винтов акромион и ключица устанавливали в правильной позиции, более того, для подтверждения правильности действий использовали ЭОП-контроль, затем вводили винты, и пластина фиксировалась окончательно (рис. 2) [11].

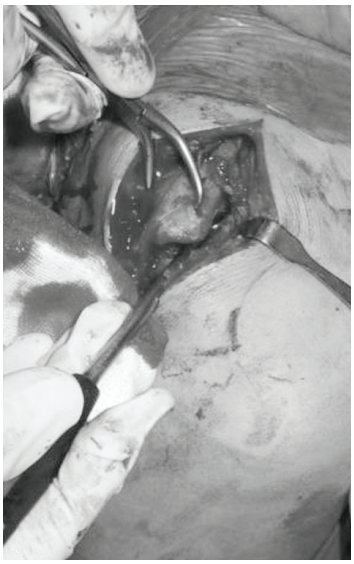


Рис. 1 Первый этап операции фиксации акромиально-ключичного сочленения с помощью крючковидной пластины: разрез от конца акромиона в медиальную сторону

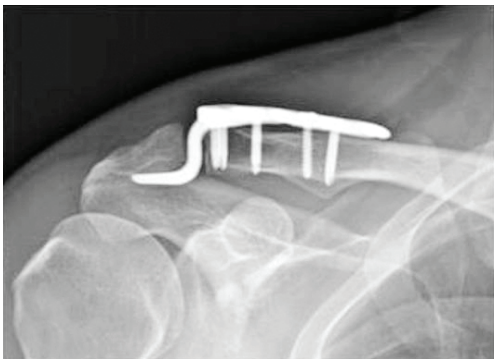


Рис. 2. Финальная рентгенограмма после операции фиксации акромиально-ключичного сочленения с помощью крючковидной пластины

После операции пациентам рекомендовано ношение косыночной повязки до 3-4 недель, разрешалось выполнять пассивные движения оперируемой конечностью. Активные сгибание и разгибание, а также отведение руки на 90° противопоказаны до момента удаления крючковидной пластины, которые выполнялось спустя 6-8 месяцев после установки имплантата. Данные рекомендации призваны снизить болевой синдром и предотвратить травматизацию вращательной манжеты. Активно заниматься спортом разрешалось лишь спустя 6 месяцев после удаления имплантата.

30 пациентов второй группы прооперированы артроскопической техникой с использованием пуговчатого фиксатора с помощью двух металлических пуговиц и шовного материала. 12 (40%) пациентами травма получена в процессе занятий спортом (прямой удар в область плечевого сустава, падение на область плечевого сустава, падение на выпрямленную руку), 18 (60%) пациентов - повреждения в результате бытовой травмы.

Хирургическая техника артроскопической фиксации с помощью пуговчатого фиксатора. Оперативное вмешательство выполнялось в положении «пляжное кресло». Для исключения травмы шейного отдела позвоночника и плечевого сплетения использовался воротник «Филадельфия». Перед началом операции определялись костные выступы в области плечевого сустава, ориентиры портов для проведения артроскопической операции обозначались маркером. Артроскопия производилась на водной среде (физиологический раствор) с применением артроскопической помпы под давлением 60-70 мм.рт.ст. и стандартного набора артроскопических инструментов. Задний артроскопический порт устанавливали примерно на 2-3 см ниже и 1-2 см медиальнее заднелатерального угла акромиального отростка. Передне-верхний и передне-нижний инструментальные порты устанавлись в интервале ротаторов, первый из них – впереди сухожилия длинной головки двуглавой мышцы, второй – возле края сухожилия подлопаточной мышцы (рис. 3). Предварительно выполнялось «расчищение» ротаторного интервала, при этом визуализировался клювовидный отросток. Затем производилась визуализация нижней поверхности клювовидного отростка, после чего устанавливался направитель, при помощи спицы просверливали канал сквозь ключицу и клювовидный отросток. После формирования канала сверлом в 4 мм проводился фиксатор TightRope. После репозиции и фиксации проводился Rg-контроль (рис. 4) [12].

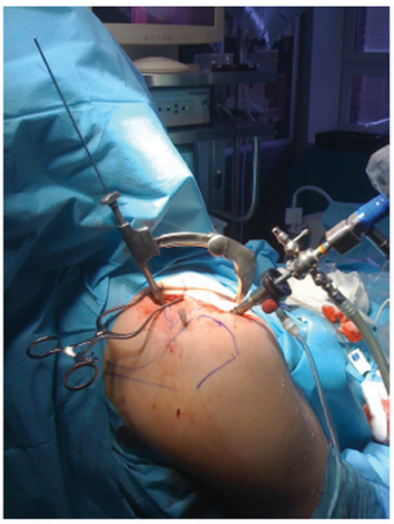


Рис. 3 Третий этап операции с применением техники «TightRope»: установление артроскопических инструментов в порты

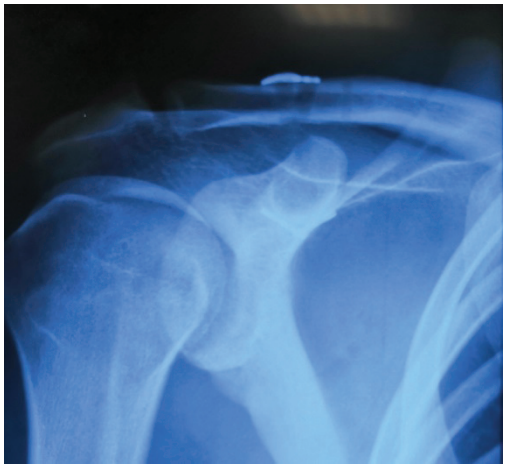
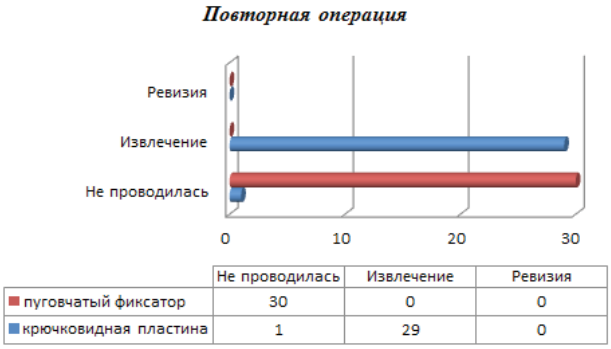


Рис. 4 Финальная рентгенограмма после артроскопической операции с применением техникой «TightRope»

После оперативного вмешательства рекомендовали ношение косыночной повязки от 1 до 4 недель в зависимости от выраженности болевого синдрома. Активные сгибания и разгибания, а также отведение руки на 90^0 разрешалось выполнять спустя 4-6 недель, активно заниматься спортом - спустя 3 месяца после проведенной операции.



	Не проводилась	Извлечение	Ревизия
пуговчатый фиксатор	30	0	0
крючковидная пластина	1	29	0

Диаграмма 1. Оперативная характеристика исследуемых пациентов. Повторная операция

После операции всем пациентам выполнены рентгенограммы оперируемых конечностей и Rg-контроль спустя 3, 6, 12 месяцев после проведения операции. Клинические и рентгенографические оценки проводились, в среднем, спустя 11.5±2.4 месяцев после операций.

Результаты и обсуждение. Все пациенты прооперированы в течение 3 недель после получения травмы. Клинические и рентгенографические оценки получены, в среднем, спустя 11.5±2.4 месяцев после операции (от 6 до 15 месяцев). Средний период оценки пациентов первой группы (с крючковидной пластиной) составил 11,7±1,6 месяцев, пациентов второй группы (TightRope) – 11,3±2,6 месяцев. Различия между группами пациентов наблюдались при оценке интенсивности болевых ощущений в области прооперированной конечности, таким образом, 24 (80%) пациента первой группы (с крючковидной пластиной) отмечали периодическую и невысокую степень болевых ощущений, аналогичный уровень ощущений отмечали 2 (7,7%) пациента второй группы (TightRope). 29 (96,6%) пациентов первой группы впоследствии были прооперированы для удаления крючковидной пластины, 1 (3,4%) пациент отказался от повторной операции. Пациентам второй группы (TightRope) повторных операций не потребовалось. В 2 (7,7%) случаях у пациентов первой группы (с крючковидной пластиной) спустя 1 год на рентгенограмме зафиксирован остеолиз (диаграммы 1,2).

	Отсутствуют	Инфекция	Остеолиз
пуговчатый фиксатор	30	0	0
крючковидная пластина	28	0	2

Диаграмма 2. Оперативная характеристика исследуемых пациентов. Осложнения

Результаты операций представлены на диаграммах 1 и 2. Незначительные различия между пациентами касались неприятных ощущений в оперированной конечности. К активному образу жизни в течение 4-6 недель вернулись большинство пациентов (70%) второй группы (TightRope) и только 40% пациентов первой группы (с крючковидной пластиной). 50% пациентов второй группы и 30% пациентов первой группы смогли активно сгибать оперированную конечность более чем на 150° уже на 4 неделе после операции.

Вывих акромиально-ключичного сочленения - частая травма в области плеча, составляет 20% от всех повреждений плечевого сустава, подразделяется на 6 степеней по Rockwood в соответствии с объемом и вектором смещения ключицы по отношению к акромиону [13].

При раннем оперативном вмешательстве на поврежденной конечности результаты получаются значительно лучше и быстрее приводят к нормализации активности [5-7]. Существуют некоторые дискуссионные моменты по лечению III степени повреждения по Rockwood, однако оперативное вмешательство почти всегда восстанавливает правильность акромиально-ключичного сустава [6,14].

В данном исследовании пациенты, прооперированные с установкой крючковидной пластины показали хорошие результаты относительно силы мышц в оперируемой конечности и удовлетворенности результатом. Периодические и невысокие по уровню интенсивности боли в оперируемой конечности испытывали 24 (80%) пациента. Невысокие ограничения в функционировании оперируемой конечности наблюдались у 20 (66,6%) пациентов (диаграммы 3,4).

Крючковидная пластина является легкой и эффективной технологией для фиксации акромиально-ключичного сочленения. После установки крючковидной пластины встречаются осложнения в виде остеоартроза акромиально-ключичного сочленения и остеолиза, что ухудшает функции плечевого сустава [15].

В проведенном исследовании в 2 случаях у пациентов первой группы (крючковидная пластина) спустя 1 год на рентгенограмме зафиксирован остеолиз.

Диаграмма 3. Характеристика результатов пациентов первой группы

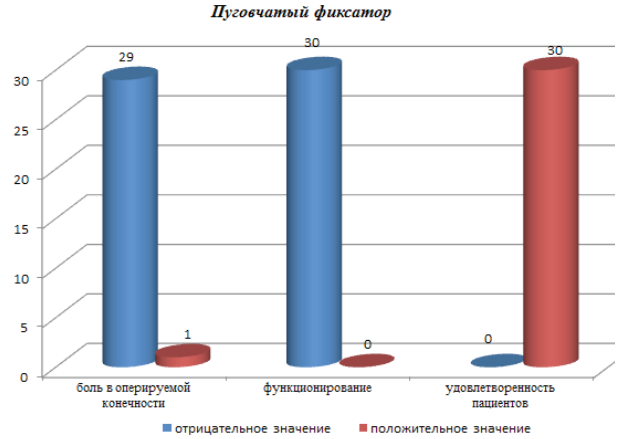


Диаграмма 4. Характеристика результатов пациентов второй группы

В противовес результатам установки данной металоконструкции, все 30 (100%) пациентов второй группы (TightRope), прооперированных артроскопической методикой с установкой 2-х систем TightRope, которая восстанавливает анатомическое соотношение клювовидно-ключичных связок и не нуждается в удалении имплантата. Только у 1 (3,4%) пациента этой группы отмечались периодические и невысокие по уровню интенсивности боли в оперируемой конечности. Отмечались 100% удовлетворенность пациентов и отличный общий результат (диаграмма 4).

Оценивая результаты сравнения операционных методик по стабилизации акромиально-ключичного сочленения (установка крючковидной пластины и техника TightRope), следует отметить хорошие результаты восстановления пациентов после операции и подтвердить эффективность данных методик. Фиксация техникой TightRope позволяет достичь отличных результатов в минимальные сроки с максимальным косметическим эффектом без повторной операции по удалению данной конструкции.

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SUMMARY

A COMPARISON OF RESULTS BETWEEN HOOK PLATE AND TIGHTROPE FOR ACUTE ACROMIOCLAVICULAR JOINT DISLOCATION

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Purpose the study - despite of this fact that there are different surgical techniques to treat acromioclavicular dislocation and also the surgery remains controversial, the purpose of our study is to compare the results of surgery treatment to acromioclavicu-

lar joint dislocation on the condition of surgical method: Hook Plate versus TightRope.

Between 2015 and 2019, 30 patients were with acute Rockwood type III-VI acromioclavicular dislocation at the age of 23-54. Patients were divided into 2 groups according to the surgical methods (Hook plate: n=15; TightRope: n=15)to compare the functional outcome after using either Hook plate and TightRope stabilization. Patients were evaluated using Constant Score and radiography.

Comparing the functional results, were observed some differences between the two groups. According to Constant Score the results were: Hook plate – 78.5, TightRope – 81.4. 14 patients in the hook plate group were reoperated to remove the device, except 1 patient who refused to be reoperated. There was insignificant difference between both groups regarding severity pain. The majority of tightrope group (70%) regained their normal functional activities, whereas only 40% of the hook plate patients did (p<0.001)/ About half (50%) of the tightrope group in comparison with 30% of hook plate group had active forward flexion more than 150° (p<0.01). Both groups showed no significant differences regarding degree of muscle strength, patients' satisfaction, and total outcome.

Both operative methods are effective techniques and could be recommended to treat an acute acromioclavicular joint dislocation. Between the two groups are no significant differences. However, TightRope fixation provides a low rate of failure and complications and avoids the need for second surgery to remove the implant.

Keywords: acromioclavicular joint, acute acromioclavicular joint dislocation, Hook plate, TightRope.

РЕЗЮМЕ

СРАВНЕНИЕ РЕЗУЛЬТАТОВ ВОССТАНОВЛЕНИЯ ПОВРЕЖДЕНИЙ АКРОМИАЛЬНО-КЛЮЧИЧНОГО СОЧЛЕНЕНИЯ КРЮЧКОВИДНОЙ ПЛАСТИНОЙ И ПУГОВЧАТОЙ ФИКСАЦИЕЙ TIGHTROPE

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Целью исследования явилось сравнение результатов двух методов оперативного лечения пациентов с закрытым вывихом акромиального конца ключицы - с установкой крючковидной пластины и пуговчатой фиксацей TightRope.

В период с 2015 по 2019 гг. прооперировано 60 пациентов в возрасте от 23 до 54 лет со свежим повреждением акромиально-ключичного сочленения III–VI типа по Rockwood. Пациенты были разделены на две группы с учетом оперативных методов: пациенты первой группы (n=30) прооперированы с использованием крючковидной пластины, второй группы (n=30) – с применением техники TightRope. Для оценки результатов лечения использованы шкала Constant Score и данные лучевого исследования.

По шкале Constant Score получены следующее результаты: бальная оценка пациентов первой группы ±78.9, второй группе ± 81.4.

29 (96,6%) пациентов первой группы впоследствии прооперированы для удаления крючковидной пластины. 1 (3,4%) пациент от повторной операции отказался. Различия между группами пациентов наблюдались при оценке интенстивности болевых ощущений в области прооперированной конечности. 21 (70%) пациент второй группы (TightRope) вернулись к активному образу жизни в течение 4-6 недель с момента проведения операции и лишь 12 (40%) из первой группы (с крючковидной пластиной) смогли это сделать в аналогичный период времени. Следует отметить, что 15 (50%) пациентов второй группы (TightRope) смогли активно отводить оперированную конечность в плечевом суставе более чем на 150° уже на 4 неделе после операции, в сравнении с 9 (30%) пациентами первой группы (с крючковидной пластиной).

Существенных различий в показателях силы мышц, удовлетворенности лечением и общем результатом среди пациенты обеих групп не выявлено.

Рассмотренные оперативные техники оказались эффективными и могут быть рекомендованы к устранению вывиха акромиально-ключичного сочленения.

Различием между техниками является необходимость повторной операции в случае использования крючковидной пластины (для удаления имплантата), тогда как фиксация повреждения акромиально-ключичного сочленения техникой TightRope не нуждается в повторном оперативном вмешательстве и более анатомична, так как является пластикой клювовидно-ключичных связок.

რეზიუმე

ლავიწ-აკრომიული შესახსრების დაზიანებათა აღდგენის შედეგები კაუჭისმაგვარი ფირფიტით და ღილაკოვანი ფიქსაციით TIGHTROPE

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ვ.ბუიანოვის სახ. საქალაქო კლინიკური საავადმყოფო, მოსკოვი; რუსეთის ხალხთა მეგობრობის უნივერსიტეტი, მოსკოვი, რუსეთის ფედერაცია

კვლევის მიზანს წარმოადგენდა ოპერაციული მკურნალობის ორი მეთოდის შედეგების შედარება პაციენტებში ლავიწის აკრომიული ბოლოს დახურული ამოვარდნილობით – კაუჭისმაგვარი ფირფიტის ჩადგმით და ღილაკოვანი ფიქსაციით TightRope.

2015-2019 წწ. პერიოდში ოპერაცია ჩაუტარდა 23-54 წლის ასაკის 60 პაციენტს ლავიწ-აკრომიული შესახსრების ახალი,III-IV ტიპის (Rockwood-ით) დაზიანებით. ოპერაციული მკურნალობის მეთოდების მიხედვით, პაციენტები დაიყო ორ ჯგუფად: I (n=30) – ოპერაცია კაუჭისმაგვარი ფირფიტის ჩადგმით, II (n=30) – ოპერაცია TightRope-ტექნიკის გამოყენებით. მკურნალობის შედეგების შეფასებისათვის გამოყენებული იყო Constant Score-სკალა და სხივური კვლევის შედეგები.

Constant Score-სკალის მიხედვით მიღებულია ასეთი შედეგები: I ჯგუფის პაციენტების ქულობრივი შეფასება - ±78.9, II ჯგუფისა - ± 81.4.

29 (96,6%) პაციენტს I ჯგუფიდან მოგვიანებით ჩაუტარდა კაუჭისმაგვარი ფირფიტის ამოღების ოპერაცია; 1 (3,4%) პაციენტმა განმეორებით ოპერაციაზე უარი განაცხადა.

პაციენტთა ჯგუფებს შორის განსხვავება აღინიშნა ინტენსიური მტკივნეული შეგრძნებების შეფასებისას ნაოპერაციებ კიდურზე. 21 (70%) პაციენტი II ჯგუფიდან (TightRope) აქტიური ცხოვრების წესს დაუბრუნდა

ოპერაციის ჩატარებიდან 4-6 კვირას; I ჯგუფიდან კი დროის ანალოგიურ პერიოდში ეს შეძლო მხოლოდ 12 (40%) პაციენტმა. უნდა აღინიშნოს, რომ 15 (50%) პაციენტმა II ჯგუფიდან (TightRope) ნაოპერაციები კიდურის 150°-ზე მეტით განზიდვა მხრის სახსარში შეძლო ოპერაციიდან უკვე მეოთხე კვირას, I ჯგუფის 9 (30%) პაციენტთან შედარებით.

არსებითი განსხვავება კუნთების ძალის, მკურნალობით კმაყოფილების ხარისხის და ზოგადი შედეგების მიხედვით პაციენტების ორ ჯგუფს შორის არ გამოვლინდა.

განხილული ორივე ოპერაციული ტექნიკა ეფექტური აღმოჩნდა და შესაძლოა რეკომენდებულ იქნას ლავიწ-აკრომიული შესახსრების ამოვარდნილობის კორექციისათვის. განსხვავება ორ ტექნიკას შორის გამოიხატება განმეორებითი ოპერაციის აუცილებლობაში კაუჭისმაგვარი ფირფიტის გამოყენების დროს (იმპლანტანტის ამოღებისათვის); ლავიწ-აკრომიული შესახსრების დაზიანების ფიქსაცია TightRope-ტექნიკის გამოყენებით განმეორებით ოპერაციულ ჩარევას არ საჭიროებს და უფრო ანატომიურია, წარმოადგენს რა ლავიწის მყესების პლასტიკას.

ОПЫТ АРТРОСКОПИЧЕСКОГО ЛЕЧЕНИЯ ПАЦИЕНТОВ С ДЕФОРМАЦИЕЙ ХАГЛУНДА

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Болезнь Хаглунда – это одна из основных причин боли в области пятки. Впервые описана Хаглундом в 1928 году. Болезнь возникает в результате механически вызванного воспаления ретрокальканеальной и супракальканеальной бурсы и выпуклости в верхне-латеральной части пяточной кости [2]. Болезнь, синдром или деформация Хаглунда, также известная как болезненная деформация по задней поверхности пятки, определяется как комплекс симптомов, включающих костный остеофит в верхне-латеральной части пяточной кости, задний пяточный бурсит и тендинит ахиллова сухожилия [3]. При синдроме Хаглунда боль, как правило, возникает при ходьбе в пятке, в области крепления ахиллова сухожилия, также может возникать при сдавливании увеличенной сумки в медиолатеральном направлении спереди ахиллова сухожилия. Деформация Хаглунда, наряду с бурситом ахиллова сухожилия и ревматоидным артритом, является одной из наиболее распространенных причин заднепяточной боли [1]. Консервативное лечение, такое как ношение нетесной обуви, изменение активности, нестероидные противовоспалительные препараты, физиотерапия; использование ортопедических изделий для обуви, местных кортикостероидных инъекций в заднюю пяточную область обычно рекомендуются на первом этапе лечения [4]. Успешность консервативного лечения - 85-95% случаев [5,6]. Оперативное лечение рекомендуется в случае, когда консервативная терапия ~~оказется~~ неэффективна [7]. Для лечения болезни Хаглунда описаны две различные оперативные методики: открытое хирургическое вмешательство и задняя артроскопия голеностопного сустава. Показаниями для проведения открытого вмешательства являются резекция задневерхней части пяточной области и воспаленной сумки с использованием заднелатерального и заднемедиального подходов. Клиновидная остеотомия пяточной кости предлагалась также другими авторами [8-10]. Однако по причине большого процента осложнений и длительного возврата к дооперационному уровню активности после открытого вмешательства артроскопический метод завоевывает все больше популярности [11].

Целью данного исследования явилась оценка результатов трехлетних наблюдений и надежности артроскопического метода в лечении заднего пяточного бурсита и болезни Хаглунда.

Материал и методы. Исследованы 28 пациентов, (18 мужчин, 10 женщин; средний возраст 37 лет, от 19 до 64 лет), которым выполнено 30 операций. Все операции выполнены в период с 2015 по 2019 годы. Пять пациентов были профессиональными спортсменами. Показанием к операции была боль по задней поверхности пятки в результате бурсита и деформации Хаглунда, которая не устранялась после проведения консервативной терапии.

У всех пациентов отмечалась припухлость мягких тканей с боковой стороны или на срединной поверхности ахиллова сухожилия, а также болезненное растяжение сухожилия. Пальпация причиняла боль по задневерхней поверхности пятки сбоку и/или посередине. Диагноз был подтвержден снимками МРТ и рентгеновскими снимками (Рис. 1 и 2).

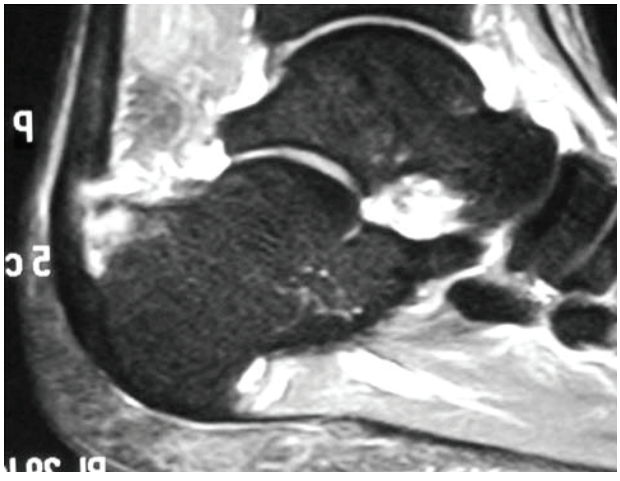

Рис. 1. МР-картина до операции

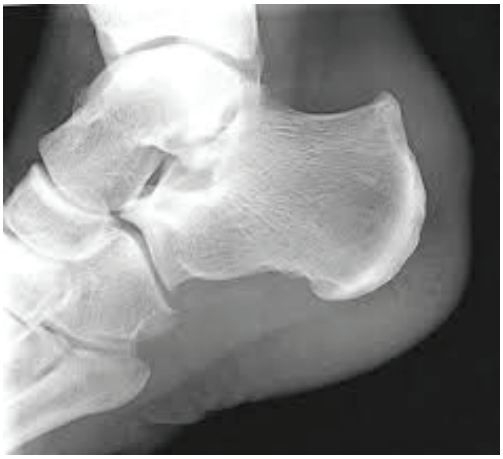

Рис. 2. Рентгеновский снимок пяточной кости в боковой проекции до операции.

Все пациенты получали консервативное лечение (использование ортопедических изделий, специальных вкладок или подпяточников, обуви с открытой пяткой, применение нестероидных противовоспалительных препаратов, покой, лед, изменение активности и упражнения на растяжку) минимум в течение полугода. Пяти пациентам предварительно вводили инъекции стероидов в различных медицинских центрах. Местные инъекции стероидов нами не применялись по причине риска разрыва сухожилия. Помимо этого, пятеро спортсменов использовали PRP-терапию (плазма, обогащенная тромбоцитами) в виде инъекций.

Двум пациентам мужского пола (один с ревматоидным спондилитом, другой – с псориатическим артритом) с отрицательным результатом анализа на артропатию выполнены операции на обоих стопах. Другие пациенты не имели никаких сопутствующих ревматоидных заболеваний.

Операция проводилась с применением спинномозговой анестезии (СМА), назначен 1 грамм цефазолина натрия внутривенно для профилактики. При проведении операции пациент находился в положении лежа на животе, стопы свисали с края стола (рис. 3).

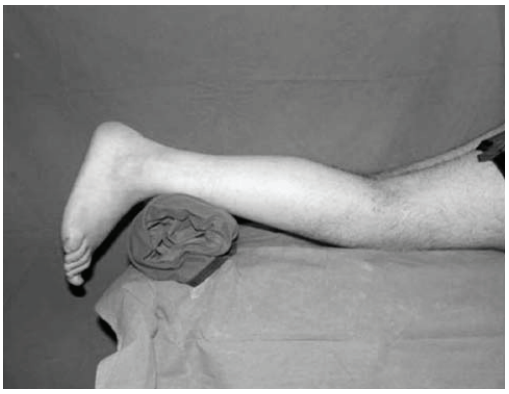

Рис. 3. Укладка пациента

Под голеностопный сустав подкладывали небольшой валик. На нижнюю треть бедра или верхнюю треть голени, после использования резинового отжимного жгута, накладывали пневматический турникет. Сначала установлен латеральный порт над верхним отделом пяточной кости сбоку от ахиллова сухожилия. В условиях непосредственной визуализации средней части в верхний отдел пяточной кости вводили иглу для спинномозговой анестезии, и устанавливали медиальный порт. Через медальный порт вводили инструмент для удаления воспаленной сумки и остеофита пяточной кости (рис. 4).

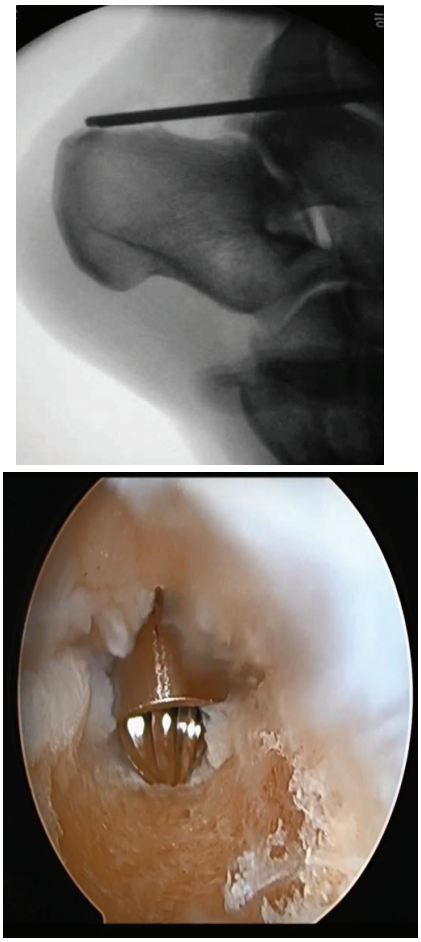

Рис. 4. Удаление деформации Хаглунда с помощью шейверного бура. Рентгенографическая и артроскопическая картины

Резекция кости выполнялась до устранения контакта в области ахиллова сухожилия в положении дорсифлексии стопы. Ахиллово сухожилие защищено посредством того, что режущие поверхности шейвера и бура держались на удалении от него. При необходимости может быть использован ретгеноскопический контроль для определения необходимого уровня резекции кости. Дренаж не использовался. Раны ушивались, использовалось компрессионное белье. Среднее время наложения турникета составило 35 минут (от 20 до 90 минут). Для предотвращения образования гематомы в течение 2 суток после операции местно использовали холод.

Все пациенты были выписаны на следующий день после операции. Пациентам было разрешено выполнять ряд двигательных упражнений в первый день после операции и ходьба на костылях с нагрузкой на ногу по мере переносимости после обследования на третий день после проведения операции. Полная нагрузка на ногу разрешалась на второй неделе после операции.

Контрольные осмотры пациентов проводились спустя 6 недель, 12, 24 и более месяцев. Пациенты прошли по-

вторное обследование, в среднем, спустя 58,4 месяцев (в пределах от 24 до 75 месяцев) наблюдения [12]. До и после операции оценены баллы по шкале AOFAS, ВАШ, произведена оценка боли по 100-бальной шкале, функционального результата, максимальной дистанции, которую можно пройти без проблем, стабильности, поверхности и амплитуды движений. Пациенты во время последнего контрольного посещения врача опрошены на предмет удовлетворенности результатами хирургического вмешательства и состоянием послеоперационных швов. Непараметрические данные ~~были~~ проанализированы при помощи критерия Манна-Уитни и считались статистически достоверными при $p<0,005$.

Результаты и обсуждение. Средний период наблюдения составил 58,4 месяцев (от 24 до 75), средний балл по шкале AOFAS до операции - 52.6 (от 24 до 75), а при последнем контрольном обследовании – 98,6 (от 90 до 100). Данное улучшение показателей было статистически значимым ($p<0,005$). Все пациенты были удовлетворены результатами операции. Для пяти спортсменов командные тренировки были разрешены на 6-й неделе, а полное возвращение к спортивной активности на 3-й месяц. Все пациенты также были довольны миниинвазивными доступами, которые обычно остаются после артроскопических операций. Интраоперационные и послеоперационные осложнения не выявлены.

Визуально-аналоговая шкала (ВАШ) предназначена для измерения интенсивности боли. Она представляет собой непрерывную шкалу в виде горизонтальной или вертикальной линии длинной 10 см (100 мм) и расположенными на ней двумя крайними точками: «отсутствие боли» и «сильнейшая боль» Более высокий балл указывает на большую интенсивность боли (рис. 5).

Рис. 5. Визуально-аналоговая шкала

Средний балл по шкале ВАШ до операции был 4-6 баллов. При последнем контрольном обследовании составил 0-1 балл.

Консервативное лечение, в том числе использование НПВП, силиконовых подпяточников, комплекса упражнений на растяжку и укрепление икроножной и камбаловидной мышц, изменение уровня активности и избегание тесной обуви рекомендуются для лечения болезни Хаглунда [13]. Большинство случаев болезненности задней поверхности пятки могут эффективно лечиться консервативными методами. Инъекции стероидов применяются, в случаях консервативные методы не дают эффекта, при этом многократное их применение может спровоцировать разрыв ахиллова сухожилия [14]. По этой причине нами не применялись инъекции стероидов по отношению к нашим пациентам. Майерсон М. и Клеман Д. [5,6] сообщают об успешном консервативном лечении в 85-95% случаев. З. Лейтце [9] с соавторами указывают на то, что около 10% их пациентов продолжали испытывать симптоматику после консервативного лечения, и была необходимость оперативного вмешательства. В свою очередь, Саммарко и Тейлор сообщают о неэффективности консервативного лечения в течение приблизительно 62 недель (от 4 до 260 недель в отдельных случаях) в 39 (65%) случаях [10].

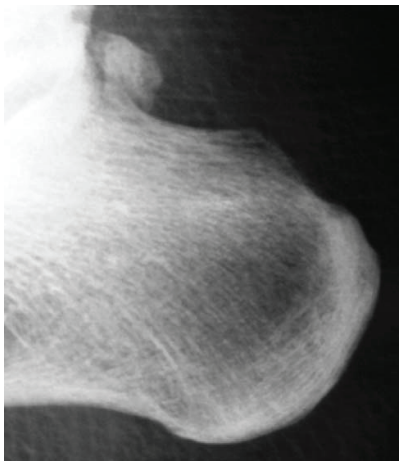

Рис. 6. Рентгеновской снимок пяточной кости в боковой проекции после операции

В случаях неэффективности консервативного лечения следует проводить оперативное вмешательство. В литературе, в основном, представлены описания и результаты открытого хирургического вмешательства, включая остеотомию пяточной кости и резекцию заднепяточной слизистой сумки. Авторы [9,10] сообщали о положительном исходе операций по открытой остеотомии или резекции у 50-100% пациентов. Некоторые осложнения, такие как потеря прочности кости после удаления значительной части задневерхней поверхности пяточной кости, рецидивирующая боль, рубцовые изменения или болезненные ощущения в области рубцов, разрыв ахиллова сухожилия, его ригидность и изменение чувствительности в области пятки выявлены после проведения открытых операций [10,15-18].

В исследовании П. Ангерманна [17], проведенном на 40 пациентах (40 пяток), которые подверглись резекции задневерхней части пяточной кости с использованием заднелатерального разреза, в 37 случаях сразу же разрешена нагрузка на ногу, у 60% пациентов наступило излечение, у 30% - улучшение и у 10% - ухудшение состояния, в среднем, по прошествии 6 лет (от 1 до 12). Осложнения были следующими: один случай поверхностной пяточной инфекции, одна гематома и два случая медленного заживления ран. Аналогичным образом Х. Хубер и М. Валдис [7] сообщили о результатах лечения путем резекции выпирающей задневерхней поверхности пяточной кости у 32 пациентов. Проблемы с мягкими тканями, включая избыточное рубцевание и сохраняющуюся припухлость, наблюдались в 14 случаях. Спустя 18,6 лет среднего периода наблюдения у 73% пациентов были хорошие результаты и у 20% - удовлетворительные.

В 2000 г. Ван Дейк и соавт. [11] описали использование ретрокальканеальной эндоскопии для лечения болезни Хаглунда и заднего пяточного бурсита [11]. В литературе встречаются еще несколько статей по данной теме [18,19].

Артроскопическая хирургия по сей день считается альтернативой открытым хирургическим вмешательствам. Йерош и Насеф [20] в своем исследовании 10 пациентов, подвергшихся эндоскопической кальканеопластике, сообщили о 7 отличных и 3 хороших результатах по Огилви-Харрису после наблюдения за пациентами, в среднем, в течение 5,2 месяцев. Осложнения в ходе операции и послеоперационные осложнения отсутствовали.

Лейтце и соавт. сравнили результаты 33 эндоскопических

декомпрессий в заднепяточной области с 17 открытыми операциями [9]. В обеих группах наблюдались улучшения по шкале AOFAS (в группе с эндоскопической операцией в пределах от 61,8 до 87,5, p<0,001; в группе с открытой операцией в пределах от 58,1 до 79,3, p=0,006), при этом различия были существенны (p=0,115). Показатели осложнений несколько отличались (инфекция: 3% и 12%; изменение чувствительности: 10% и 18%; болезненные рубцы: 7% и 18%). Одна операция была изменена с эндоскопической на открытую по причине неисправности оборудования.

Аналогичным образом в своем исследовании 39 случаев эндоскопической кальканеопластики с последующим периодом наблюдения 4,5 года Шольтен и ван Дейк сообщили о 2 пациентах, которые не поддались лечению, и 30 пациентах с хорошими и отличными результатами по шкале Огилви-Харриса [18]. У одного из пациентов присутствовал неэстетичный вид над пяточной областью; других операционных осложнений или послеоперационных инфекций, равно как и безобразных рубцов не наблюдалось. Дж. Йерош и соавторы выполнили артроскопическую кальканеопластику у 81 пациента в период между 1999 и 2005 годами [19]. Средний период последующего наблюдения составил 35,3 (от 12 до 72) месяцев. У тридцати четырех пациентов был хороший, у 41 – отличный, у 3 – удовлетворительный и у 3 –плохой результат.

Сроки возвращения к спортивной деятельности очень важны для профессиональных спортсменов, указывались следующие сроки: до 9 месяцев для открытого вмешательства и, в среднем, 12 (от 6 до 24) недель - для эндоскопических операций [13]. В нашей выборке для 5 профессиональных спортсменов командные тренировки разрешались на 6-й неделе и полное возвращение в спорт – на 3-й месяц после операции.

Обеспокоенность вызывает время проведения операции. З. Лейтце и Дж. Йерош [9,20] отмечают, что несмотря на то, что еще многое предстоит освоить при выполнении такого рода операций, время проведения уменьшилось до 35 минут со среднего значения 46 минут в выборке Дж. Йероша, а З. Лейтце сообщил, что при наличии опыта время уменьшается с двух часов до среднего показателя в 30 минут [9,20]. Данные показатели сопоставимы с другими результатами исследований, подтверждающими, что артроскопическая кальканеопластика не требует больших временных затрат и может быть проведена намного быстрее, чем традиционные открытые операции.

Как показывает результат анализа в статье классификация синдрома Хаглунда Середа А.П., Белякова А.М. [21] множество случаев синдрома Хаглунда предложили клинико-морфологические классификации синдрома Хаглунда, которые помогают выбрать оптимальную тактику лечения. по клинической форме деформация Хаглунда может быть обычной, атипичной и «скрытой». Особой клинической разновидностью является косметическая форма. В зависимости от морфологических характеристик было предложено различать верхний, верхнебоковой, «дугообразный», тотальный типы и атипичные варианты. При верхнем типе деформации и, реже, при верхнебоковом, предпочтительнее эндоскопическая техника или малоинвазивная хирургическая коррекция. Для более обширных вариантов единственным выходом должна быть открытая процедура.

Выводы: эндоскопия задней поверхности пяточной кости может стать предпочтительным способом лечения болезни Хаглунда, с учетом ее преимуществ в виде непосредственной визуализации ахиллова сухожилия, удаления ретрокальканеальной сумки на задней поверхности пятки под визуальным контролем, определения оптимального уровня резекции кости и ускоренной функциональной реабилитации. Это особенно важно для профессиональных спортсменов, поскольку эндоскопический метод лечения позволяет скорее вернуться к спортивной активности. Недостатками данной технологии является ее сложность и более высокий риск повреждения ахиллова сухожилия, при отсутствии данного опыта [21].

Боковую нестабильность голеностопного сустава, которое при отсутствии лечения может привести к дегенеративному артрозу. Острые травмы связок следует лечить в первую очередь безоперационным путем с помощью курса физиотерапии и функциональной фиксации [22].

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SUMMARY

EXPERIENCE IN ARTHROSCOPIC TREATMENT OF PATIENTS WITH HAGLUND'S DEFORMATION

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The goal of this study was to evaluate the results of arthroscopic calcaneoplasty for the treatment of posterior calcaneal bursitis and Haglund's disease.

The study involved 28 patients who underwent 30 arthroscopic surgeries for Haglund's disease from 2015 to 2019.

Retrocalcanealneoplasty and supracalcaneoplasty were performed using a shaver, an ablator; with the help of a drill, the bone was resected until the contact in the Achilles tendon was eliminated in the position of dorsiflexion of the foot. All patients were discharged the next day and allowed full leg load in the second week after surgery. The AOFAS (American Orthopedic Society for Foot and Ankle Surgery) and VAS scores were calculated, and the patient's condition was estimated.

Results: The average follow-up was 58.4 months. The AOFAS scores significantly improved from the average 52.6 to 98.6 at the final estimation ($p<0.005$). All patients were satisfied with the result of the surgery. VAS scores were low.

Conclusion: Arthroscopic calcaneoplasty has proven to be a safe and effective surgical method for the treatment of posterior calcaneal bursitis and Haglund's disease.

Keywords: calcaneoplasty; haglund's disease; posterior calcaneal bursitis.

РЕЗЮМЕ

ОПЫТ АРТРОСКОПИЧЕСКОГО ЛЕЧЕНИЯ ПАЦИЕНТОВ С ДЕФОРМАЦИЕЙ ХАГЛУНДА

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Целью исследования явилась оценка результатов артроскопической ретрокальканеопластики для лечения заднего пяточного бурсита и болезни Хаглунда.

Исследованы 28 пациентов, которым с 2015 по 2019 гг. выполнено 30 артроскопических операций по поводу болезни Хаглунда. 22 пациента были женщины и 6 - мужчины. Средний возраст пациентов составил 38,6 лет (22-55 лет). Супракальканеопластика выполнялась при помощи шейвера, аблятора, с применением бура проводилась резекция кости до устранения контакта в области ахиллова сухожилия в положении дорсифлексии стопы. Все пациенты выписаны на следующий день, и им разрешена полная нагрузка на ногу на второй неделе после операции. Произведена оценка баллов по шкале Американское ортопедическое общество хирургии стопы и голеностопного сустава (AOFAS) и Визульно-аналоговой шкалы (ВАШ), предназначенной для измерения интенсивности боли, затем оценено состояние пациента.

Средний период наблюдения составил 58,4 месяцев (от 24 до 75), средний балл по шкале AOFAS до операции – 52,6 (от 24 до 75), а при последнем контрольном обследовании – 98,6 (от 90 до 100), $p<0,005$. Все пациенты удовлетворены результатом операции. Баллы по шкале ВАШ, в среднем, составили 4-6 баллов.

В результате проведенного исследования авторами сделан вывод, что артроскопическая кальканеопластика является безопасным и эффективным хирургическим методом лечения заднего пяточного бурсита и болезни Хаглунда.

რეზიუმე

ხაგლუნდის დეფორმაციის მქონე პაციენტების ართროსკოპიული მკურნალობის გამოცდილება

ვ.მენშიკოვი, ფ.ლაზკო, ა.პრიზოვი, ე.ბელიაკი, ა.ზალიანი

რუსეთის ხალხთა მეგობრობის უნივერსიტეტი;
ვ.ბუიანოვის სახ. საქალაქო კლინიკური საავადმყოფო, მოსკოვი, რუსეთის ფედერაცია

კვლევის მიზანს წარმოადგენდა ართროსკოპიული პლასტიკის შედეგების შეფასება ქუსლის უკანა ბურსიტის და ხაგლუნდის დაავადების დროს.

გამოკვლეულია 28 პაციენტი (22 ქალი, 6 მამაკაცი), რომელთაც 2015-2019 წწ. ჩაუტარდა 30 ართროსკოპიული ოპერაცია ხაგლუნდის დაავადების გამო. პაციენტების საშუალო ასაკი – 38,6 წელი (22-55 წელი). პლასტიკა შესრულდა აბლატორის საშუალებით; ბურის გამოყენებით ჩატარდა ძვლის რეზექცია აქილევსის მყესის მიდამოში კონტაქტის მოცილებამდე

ტერფის დორსიფლექსიის მდგომარეობაში. ყველა პაციენტი ბინაზე გაეწერა ოპერაციიდან მეორე დღეს; ოპერაციიდან მეორე კვირას მათ ნებადართული ჰქონდათ ფეხის სრული დატვირთვა.

ქულობრივი შეფასება განხორციელდა ტერფის და კოჭ-წვივის სახსრის ქირურგიის ამერიკული ორთოპედიული საზოგადოების (AOFAS) და ვიზუალურ-ანალოგური სკალების მიხედვით, რომელიც განკუთვნილია ტკივილის ინტენსიურობის განსაზღვრისათვის; შემდგომ შეფასებულ იქნა პაციენტის მდგომარეობა.

დაკვირვების საშუალო პერიოდმა შეადგინა 58,4 თვე (24-75 თვე); საშუალო ქულა AOFAS-ის მიხედვით ოპერაციამდე იყო 52,6 (24-დან 75-მდე), ბოლო საკონტროლო გამოკვლევის დროს კი - 98,6 (90-დან 100-მდე) $p<0,005$. ყველა პაციენტი ოპერაციის შედეგებით იყო კმაყოფილი. ვიზუალურ-ანალოგური შკალის მიხედვით, მაჩვენებელმა შეადგინა, საშუალოდ, 4-6 ქულა.

ჩატარებული კვლევის საფუძველზე ავტორები დაასკვნიან, რომ ართროსკოპიული ნეოპლასტიკა წარმოადგენს ქუსლის უკანა ბურსიტის და ხაგლუნდის დაავადების მკურნალობის უსაფრთხო და ეფექტურ ქირურგიულ მეთოდს.

COMBINED TREATMENT WITH FOCUSED LOW-INTENSITY SHOCK-WAVE THERAPY AND ANDROGEN-STIMULATION THERAPY IN MEN WITH CORPORAL VENO-OCCLUSIVE ERECTILE DYSFUNCTION ON THE BACKGROUND OF HYPOGONADOTROPIC HYPOGONADISM

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Hypogonadism in male population have intensive negative impact on physical and mental health as well as life quality and sexual function. Despite traditional opinion, now there are strong evidence of associations between low androgen levels and corporal veno-oclusive erectile dysfunction.

Low androgen levels have negative impact on penile tissues structural integrity – low testosterone level have negative impact on fibroblast activity that leads to pathological penile connective tissue remodeling associated with poor quality of collagen, elastin and hyaluronic acid that correlates with decreased density of penile connective tissue, low cavernous tissues regeneration and proliferation and increased venous leakage due to decrease of biomechanical characteristics of venous valves [4,10].

The other side of low androgens is related with behavioral and psychological consequences – decrease in sexual drive, sexual behavior and decrease of psychological stress resistance what leads to high anxiety that actually involves in clinics of organic erectile dysfunction massive psychological component [1].

This approach to understanding of association mechanisms of low androgen levels and corporal veno-oclusive erectile dysfunction makes it necessary to use combined therapy models where one component aimed on androgen level correction and other – on penile tissue regeneration and hemodynamic enhancement. First component could be achieved by such techniques as replacement therapy or indirect hormonal stimulation, while second – by novel device-assisted regenerative methods like focused low-intensity shock-wave therapy (LISWT) [4,7,8].

Studies of LISWT biological effects at histological and biochemical levels demonstrated penile tissue regeneration due to the biomechanical activation of multipotent mesenchymal stem cells (MSCs); increases production of signaling proteins – vascular endothelial growth factor (VEGF), what stimulates angiogenesis; increases expression of the components of the nitric oxide system – endothelial NO synthase (eNOS) and neuronal NO synthase (nNOS); which altogether leads to local tissue regeneration and normalization of penile hemodynamic [2,3,6-8].

Thus combination of androgen stimulation and LISWT is beneficial due to complimentary mechanisms of action that could bring more pronounced and rapid remodeling and regeneration of penile connective tissue and combined positive influence on penile hemodynamic – by its stimulation and solving the venous leakage.

Among the pharmacotherapeutic agents that promising to be complement to mentioned above mechanisms, we should highlight Ikariin (ICA), the flavonoid of Epimedium brevicornum, with a spectrum of effects that biological activity similar to PDE-5, stimulation of production of nitric oxide (NO), affinity to androgen receptors, as well as antioxidant activity [9].

Aim – to evaluate efficacy of focused low-intensity shock-wave therapy and androgen-stimulation therapy combination in men with corporal veno-oclusive erectile dysfunction on the background of hypogonadotropic hypogonadism.

Material and methods. A prospective clinical study was conducted on a contingent of 42 patients of "Man's Health Clinic" (Kiev, Ukraine) with diagnosis of corporal veno-oclusive erectile dysfunction (ICD-10: N48.4) on the background of hypogonadotropic hypogonadism (ICD-10: E23). Mean age was 51±2,6 years.

Inclusion criteria:

– biological male sex;

– age 45-60;

– "International index of erectile function" score lover than 17;

– sonographic evidences on corporal veno-oclusive erectile dysfunction;

– "Aging Male Symptoms" score more than 37;

– serum testosterone level lower than 320 ng/dL;

– serum luteinizing hormone level lower than 0,8 UI/ml.

– positive chorionic gonadotropin test (major increase of serum testosterone level after injection of 3000 UI of chorionic gonadotropin) [11].

Exclusion criteria:

– oncologic pathology;

– primary hypogonadism;

– benign prostatic hyperplasia;

– acute inflammatory pathology of prostatic gland;

– condition after prostatectomy;

– endocrine pathology besides hypogonadotropic hypogonadism;

– autoimmune and system pathology;

The following methods were used in the study:

– clinical: a standard set of clinical examinations along with 2 clinical rating scales: International index of erectile function (IIEF-5) and Aging Male Symptoms (AMS) [3];

– serological: evaluations of serum testosterone and luteinizing hormone levels;

– sonographic: pharmacodopplerography of penis with videoerotic stimulation, ultrasound examination of the prostate gland (to exclude inflammatory pathology of prostatic gland, benign prostatic hyperplasia and its oncologic pathology);

– statistical: chi-square test, Students t-test;

Following treatment methods were used:

– recombinant chorionic gonadotropin (ChG) subcutaneous injections in dosage 5000 UI in 1 session weekly;

– extract of Epimedium Breviconum (ICA) oral intake in dosage 50 mg/day (for stimulation of physiological nighttime erections);

– Focused LISWT: 3000 strikes, frequency 3 Hz, total power up to 0,35 mJ/mm2 on standard penile areas by Storz Medical Duolith SD1 device.

Results and discussion. Initial examination data for total study contingent shown in Table 1.

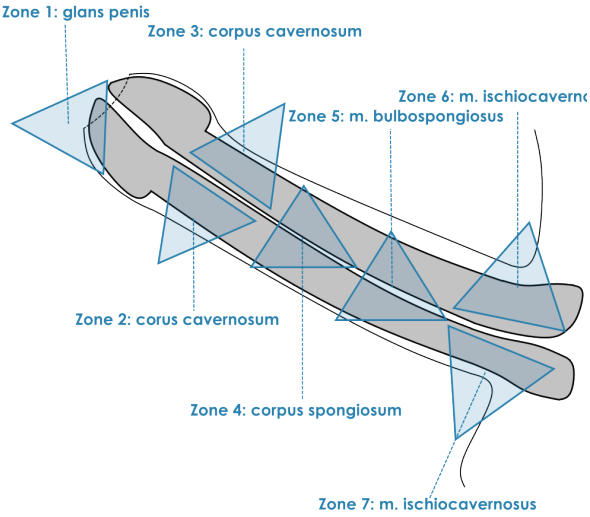

Fig. Scheme of low-intensity shock wave therapy application zones on penile structures: glans penis, corpus cavernosum (bilateral), corpus spongeosum, m. bulbospongeosus, m. ischiocavernosus (bilateral)

Study contingent was openly randomized on two symmetrical groups. Main group (MG) – 22 patients who underwent 3-com-

Table 1. Initial examination data for total study contingent

Criterion	Data
IIEF-5 (qualitative data)	
Mild (21-17 points)	0
Mild-moderate (16-12 points)	7
Moderate (11-8 points)	12
Severe (< 7 points)	23
AMS (qualitative data)	
No significant symptoms (< 26 points)	0
Mild symptoms (27-37 points)	0
Moderate symptoms (38-49 points)	17
Severe symptoms (>50 points)	25
Pharmacodoppler-sonography (quantitative data)	
Mean PSV in stimulation (cm/s)	48.23±5.6
Mean EDV in stimulation (cm/s)	10.9±2.1
Serological data (quantitative data)	
Mean serum testosterone level (ng/dL)	192.94±37.6

Table 2. Treatment models in MG and CG

Week	6 weeks			12 weeks			24 weeks		
MG									
ChG (5000 UI per week)	+	+	+	+	+	+	+	+	+
LISWT (2 sessions per week)	+	+	+	-	-	-	-	-	-
ICA (50 mg daily)	+	+	+	+	+	+	-	-	-
CG									
ChG (5000 UI per week)	+	+	+	+	+	+	+	+	+
LISWT (2 sessions per week)	-	-	-	-	-	-	-	-	-
ICA (50 mg daily)	+	+	+	+	+	+	-	-	-

Table 3. Follow-up examination data for study groups

Criteria	MG n=22	CG N=20	p-value
IIEF-5 (qualitative data, chi-square test)			
Mild (21-17 points)	17	12	0,226
Mild-moderate (16-12 points)	5	4	0,829
Moderate (11-8 points)	0	4	**0,027**
Severe (< 7 points)	0	0	–
AMS (qualitative data, chi-square test)			
No significant symptoms (< 26 points)	16	13	0,862
Mild symptoms (27-37 points)	5	5	0,493
Moderate symptoms (38-49 points)	1	2	0,588
Severe symptoms (>50 points)	0	0	–
Pharmacodoppler-sonography (quantitative data, Students t-test)			
Mean PSV in stimulation (cm/s)	54.10±6.4	49.62±6.7	0,631
Mean EDV in stimulation (cm/s)	2.8±0.6	5.2±0.8	**0,021**
Serological data (quantitative data, Students t-test)			
Mean serum testosterone level (ng/dL)	532.41±47.2	576.92±61.6	0,569

ponent therapy model: 5000 IU of ChG once per week during 24-week treatment course and focused LISWT (3000 strikes, frequency 3 Hz, total power up to 0,35 mJ/mm2 on standard penile areas that shown in Fig.) twice per week during 6-week treatment course (12 sessions total), pharmacotherapy with Icariin (ICA) orally, 50 mg/day in 1 reception (evening), during 12-week treatment course) Control group (CG) – 20 patients who underwent CG and ICA treatment (same as MG) but without LISWT. Treatment models in MG and CG are showed in Table 2.

Follow-up examination was performed in 6 month after treatment course beginning. Clinical efficacy was evaluated by difference between initial and follow up data. Significant differences was found in IIEF-5 and AMS results distribution both in MG and CG (p≤0,01). For pharmacodoppler-sonography data significant difference was found only for EDV in MG (p≤0,05). For serum testosterone levels difference is also significant in both groups (p≤0,01). Data comparison between study groups results showed in Table 3.

Analysis of differences in follow-up qualitative data between groups of study showed better results in MG that presented in IIEF-5 data with lower level of moderate ED cases (p≤0,05). By quantitative data analysis it was found that EDV in MG is significantly lower than in CG (p≤0,05). EDV normalization (<5,0 cm/s) was observed in 65% (13 of 20) cases in CG and in 100% (22 out 22) cases in MG.

Thus, addition of focused LISWT into therapeutic model for corporal veno-oclusive erectile dysfunction on the background of hypogonadotropic hypogonadism is absolutely beneficial due to more effective correction of venous leakage.

Conclusion. Treatment model that combines focused low-intensity shock-wave therapy and androgen-stimulation therapy in men with corporal veno-oclusive erectile dysfunction on the background of hypogonadotropic hypogonadism had shown its efficacy in 6 month follow-up study according to IIEF-5 and AMS data (p≤0,01), pharmacodoppler-sonography data – mean EDV (p≤0,05) in stimulation and serum testosterone levels correction (p≤0,01). Addition of focused low-intensity shock-wave therapy showed better results for erectile dysfunction correction in decreasing number of moderate erectile dysfunction cases (p≤0,05) and EDV decrease (p≤0,05).

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SUMMARY

COMBINED TREATMENT WITH FOCUSED LOW-INTENSITY SHOCK-WAVE THERAPY AND ANDROGEN-STIMULATION THERAPY IN MEN WITH CORPORAL VENO-OCCLUSIVE ERECTILE DYSFUNCTION ON THE BACKGROUND OF HYPOGONADOTROPIC HYPOGONADISM

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Aim – to evaluate efficacy of focused low-intensity shock-wave therapy and androgen-stimulation therapy combination in men with corporal veno-oclusive erectile dysfunction on the background of hypogonadotropic hypogonadism.

A prospective clinical study was conducted on a contingent of 42 patients of "Man's Health Clinic" (Kiev, Ukraine) suffering from moderate corporal veno-oclusive erectile dysfunction on the background of hypogonadotropic hypogonadism. Study contingent was randomized on two groups. MG – 22 patients who underwent 2 component therapy model: ChG, focused LISWT and ICA . CG – 20 patients who underwent CG and ICA treatment (same as MG) but without LISWT. Clinical efficacy was evaluated by difference between initial and follow up data. Significant differences was found in IIEF-5and AMS results distribution both in MG and CG ($p \leq 0,01$). For pharmacodoppler-sonography data significant difference was found only for EDV in MG ($p \leq 0,05$). For serum testosterone levels difference is also significant in both groups ($p \leq 0,01$).

By quantitative data analysis it was found that EDV in MG is significantly lower than in CG ($p \leq 0,05$). Thus, addition of focused LISWT into therapeutic model for corporal veno-oclusive erectile dysfunction on the background of hypogonadotropic hypogonadism is absolutely beneficial due to more effective correction of venous leakage. Treatment model that combines focused low-intensity shock-wave therapy and androgen-stimulation therapy in men with corporal veno-oclusive erectile dysfunction on the background of hypogonadotropic hypogonadism had shown its efficacy in 6 month follow-up study according to IIEF-5 and AMS data ($p \leq 0,01$), pharmacodoppler-sonography data – mean EDV ($p \leq 0,05$) in stimulation and serum testosterone levels correction ($p \leq 0,01$). Addition of focused low-intensity shock-wave therapy showed better results for erectile dysfunction correction in decreasing number of moderate erectile dysfunction cases ($p \leq 0,05$) and EDV decrease ($p \leq 0,05$).

Keywords: focused low-intensity shock-wave therapy, androgen-stimulation therapy, corporal veno-oclusive erectile dysfunction, hypogonadotropic hypogonadism.

РЕЗЮМЕ

ФОКУСНАЯ НИЗКОИНТЕНСИВНАЯ УДАРНО-ВОЛНОВАЯ ТЕРАПИЯ И АНДРОГЕННО-СТИМУЛИРУЮЩАЯ ТЕРАПИЯ В ЛЕЧЕНИИ МУЖЧИН С КОРПОРАЛЬНОЙ ВЕНООККЛЮЗИОННОЙ ЭРЕКТИЛЬНОЙ ДИСФУНКЦИЕЙ НА ФОНЕ ГИПОГОНАДОТРОПНОГО ГИПОГОНАДИЗМА

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Цель исследования - оценка эффективности сочетанной низкоинтенсивной ударно-волновой терапии и андрогеностимулирующей терапии у мужчин с корпоральной веноокклюзивной эректильной дисфункцией на фоне гипогонадотропного гипогонадизма.

Исследованы 42 пациента «Клиники мужского здоровья», страдающих корпоральной веноокклюзивной эректильной дисфункцией на фоне гипогонадотропного гипогонадизма.

Пациенты рандомизировано разделены на две группы: основная группа (n=22) получала 2-компонентную модель терапии - инъекции хорионического гонадотропина, низкоинтенсивную ударно-волновую терапию и препарат икариин. Группу сравнения (контроль) составили пациенты (n=20), которые прошли лечение по модели сочетания инъекций хорионического гонадотропина и приёма икариина, без низкоинтенсивной ударно-волновой терапии.

Клиническую эффективность оценивали по разнице между исходными и последующими данными. Существенные различия обнаружены в распределении результатов шкалы «Международного индекса эректильной фунции» и шкалы «Симптомов мужского старения» ($p \leq 0,01$). Данные фармакодоплер-сонографии выявили достоверное различие только для конечно-диастолической скорости кровотока в основной группе ($p \leq 0,05$). Разница в показателях сывороточного уровня тестостерона также была значимой в обеих группах ($p \leq 0,01$). Количественный анализ данных выявил, что конечно-диастолическая скорость кровотока в основной группе значительно ниже, чем в контрольной ($p \leq 0,05$). Включение фокусной низкоинтенсивной ударно-волновой терапии в комплексное лечение корпоральной веноокклюзивной эректильной дисфункции на фоне гипогонадотропного гипогонадизма способствует более эффективной коррекции венозной утечки.

Таким образом, модель лечения, которая сочетает в себе сфокусированную низкоинтенсивную ударно-волновую и андрогеностимулирующую терапию у мужчин с корпоральной веноокклюзивной эректильной дисфункцией на фоне гипогонадотропного гипогонадизма, выявило свою эффективность в соответствии со шкалами «Международного индекса эректильной фунции», «Симптомов мужского старения» ($p \leq 0,01$) и показателями конечно-диастолической скорости кровотока ($p \leq 0,05$) и уровня тестостерона в сыворотке ($p \leq 0,01$) на протяжении 6 месяцев. Добавление низкоинтенсивной ударно-волновой терапии показало лучшие результаты для коррекции эректильной дисфункции при уменьшении числа случаев умеренной эректильной дисфункции ($p \leq 0,05$) и снижении конечно-диастолической скорости кровотока ($p \leq 0,05$).

რეზიუმე

დაბალი ინტენსივობის შეჯიდული დარტყმით-ბგერითი თერაპია და ანდროგენ-მასტიმულირებელი თერაპიის კომბინაცია კორპორული ვენურ-ოკლუზიური ერექციული დისფუნქციის მქონე მამაკაცებში ჰიპოგონადოტროპული ჰიპოგონადიზმის ფონზე

ი.ზასედა
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ანდროგენების დაბალი დონის თანხვედრა კორპორულ ვენურ-ოკლუზიურ ერექციულ დისფუნქციასთან წარმოშობს თერაპიის კომბინირებული მეთოდების გამოყენების აუცილებლობას, სადაც ერთი კომპონენტი მიმართულია ანდროგენების დონის კორექციაზე, მეორე კი – სასქესო ასოს ქსოვილების რეგენერაციასა და მისი ლოკალური ჰემოდინამიკის გაუმჯობესებაზე.

კვლევის მიზანს წარმოადგენდა შერეული დაბალინტენსიური დარტყმით-ბგერითი თერაპიის და ანდროგენ-მასტიმულირებელი თერაპიის ეფექტურობის შეფასება მამაკაცებში კორპორული ვენურ-ოკლუზიური დისფუნქციით ჰიპოგონადოტროპული ჰიპოგონადიზმის ფონზე.

გამოკვლეულია კლინიკა "მამაკაცური ჯანმრთელობის" 42 პაციენტი კორპორული ვენურ-ოკლუზიური დისფუნქციით ჰიპოგონადოტროპული ჰიპოგონადიზმის ფონზე.

პაციენტები რანდომულად დაიყო ორ ჯგუფად: ძირითად ჯგუფს (n=22) ჩაუტარდა ორკომპონენტიანი თერაპიის მოდელი – ქორიონული გონადოტროპინის ინიექცია, დაბალინტენსიური დარტყმით-ბგერითი თერაპია და პრეპარატი იკარიინი. შედარების (საკონტროლო) ჯგუფი (n=20) შეადგინა პაციენტებმა, რომლებსაც ჩაუტარდა მკურნალობა ქორიონული გონადოტროპინის ინიექციით და პრეპარატი იკარიინით, დაბალინტენსიური დარტყმით-ბგერითი თერაპიის გარეშე.

კლინიკური ეფექტურობა შეფასდა განსხვავებით საწყის და შემდგომ მონაცემებს შორის. არსებითი სხვაობა აღინიშნა შედეგების განაწილებაში სკალების "ერექციული ფუნქციის საერთაშორისო ინდექსის" და "მამაკაცური დაბერების სიმპტომების" მიხედვით (p≤0,01). ფარმაკოდოპლერ-სონოგრაფიის მონაცემებით სარწმუნო განსხვავება ძირითად ჯგუფში გამოვლინდა მხოლოდ სისხლის ნაკადის საბოლოო დიასტოლური სიჩქარის მაჩვენებლებში (p≤0,05). განსხვავება ტესტოსტერონის დონეში სისხლის შრატში მნიშვნელოვანი იყო ორივე ჯგუფში (p≤0,01). მონაცემების რაოდენობრივი ანალიზით გამოვლინდა,რომ სისხლის ნაკადის საბოლოო დიასტოლური სიჩქარე ძირითად ჯგუფში ნაკლებია, ვიდრე საკონტროლოში (p≤0,05). ფოკუსური დაბალინტენსიური დარტყმით-ბგერითი თერაპიის ჩართვა კორპორული ვენურ-ოკლუზიური დისფუნქციის მკურნალობაში ჰიპოგონადოტროპული ჰიპოგონადიზმის ფონზე ხელს უწყობს ვენური გადინების უფრო ეფექტურ კორექციას.

ამრიგად, კორპორული ვენურ-ოკლუზიური დისფუნქციის მკურნალობის მოდელი ჰიპოგონადოტროპული ჰიპოგონადიზმის ფონზე,რომელიც მოიცავს დაბალინტენსიურ დარტყმით-ბგერით და ანდროგენ-მასტიმულირებელ თერაპიას, "ერექციული ფუნქციის საერთაშორისო ინდექსის" და "მამაკაცური დაბერების სიმპტომების" სკალების მიხედვით (p≤0,01), საბოლოო დიასტოლური სიჩქარის მაჩვენებლით (p≤0,05) და ტესტოსტერონის დონით სისხლის შრატში (p≤0,01) ეფექტურობას ავლენს 6 თვის განმავლობაში. დაბალინტენსიური დარტყმით-ბგერითი თერაპიის დამატება აჩვენებს უკეთეს შედეგებს ერექციული დისფუნქციის მკურნალობისათვის, რაც გამოიხატება ზომიერი ერექციული დისფუნქციის შემთხვევების რაოდენობის (p≤0,05) და სისხლის ნაკადის საბოლოო დიასტოლური სიჩქარის შემცირებაში (p≤0,05).

RESULTS OF EXTRACORPOREAL NEPHRON-SPARING SURGERY FOR RENAL CELL CARCINOMA WITH AUTOTRANSPLANTATION

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Bilateral renal tumors and neoplasms of a solitary kidney represent one of the most complex clinical situations in urologic oncology [1,2]. The treatment tactics for this condition may include one of the following options: radical nephrectomy followed by the chronic hemodialysis, in-situ nephron-sparing surgery, or ex-vivo partial nephrectomy in combination with renal autotransplantation. In addition to patient-related factors, the treatment selection is influenced by the tumor parameters such as stage, size and location. In the vast majority of cases, these neoplasms are multifocal, having a large size, accompanied by local invasion involving the venous system, pelvicalyceal system, perirenal or renal sinus fat, and mostly located inside the kidney, deforming the elements of the renal sinus [3]. All these factors make the nephron-sparing surgery for bilateral renal neoplasms and solitary kidney tumors extremely difficult. Besides, the warm renal ischemia time, which should not exceed 20 minutes, is of primary importance. In most cases, partial nephrectomies with imperative indications require longer time due to the need for careful preservation of intrarenal anatomical structures, as well as reconstruction of the collecting system and renal vessels. Therefore, in these patients, the use of anti-ischemic kidney protection techniques is vital for the entire operation.

Among the renal hypothermia techniques, perfusion-mediated cooling with cardioplegia solution plays the leading role and can be performed both intracorporeally and extracorporeally. Due to high complexity and likelihood of vascular complications, these operations are rarely used and mainly in specialized centers. These operations require a complex and challenging surgical approach, it should be performed by experienced kidney transplant surgeons. We present our experi-

ence of extracorporeal nephron-sparing surgeries in patients with renal cell carcinoma (RCC).

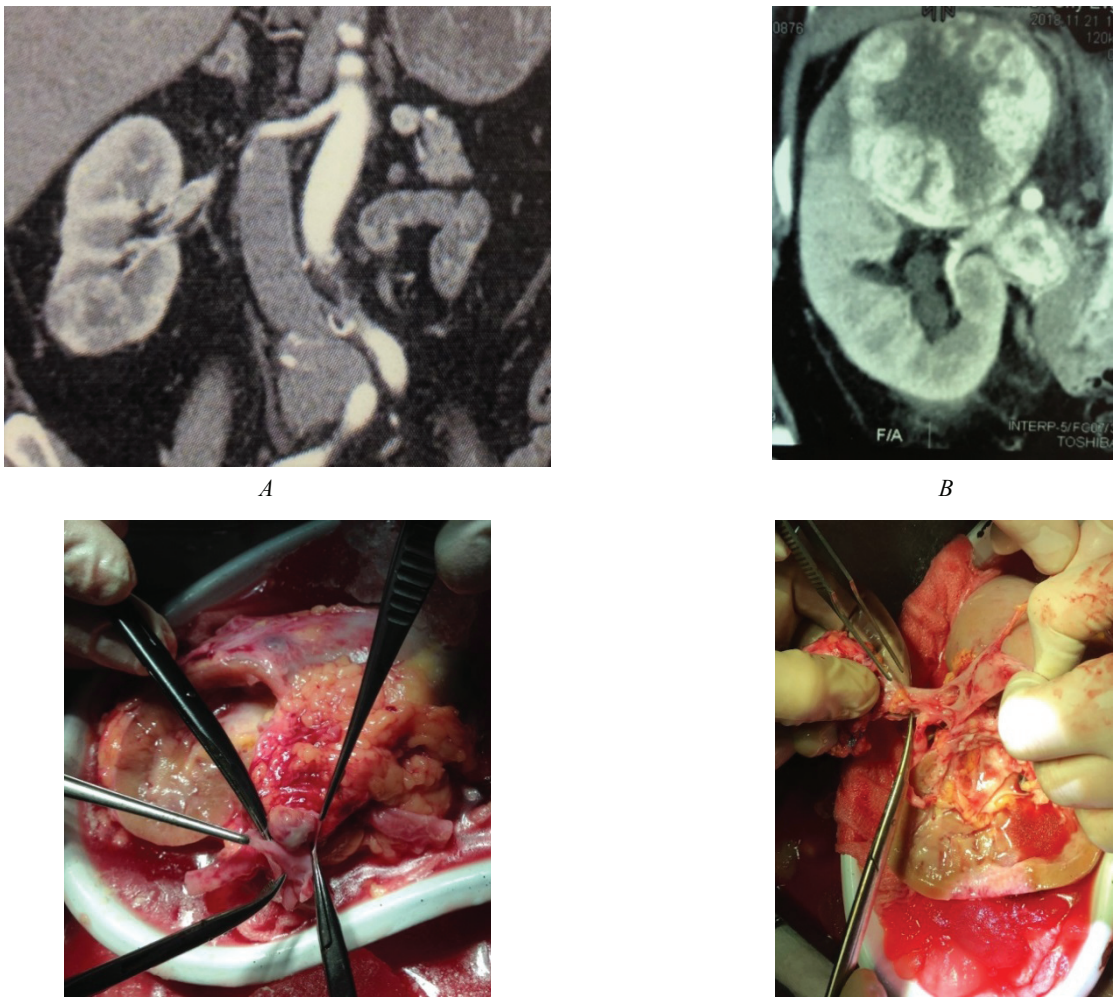
Material and methods. The study included 12 patients with renal cell carcinoma who underwent extracorporeal nephron-sparing surgery followed by autotransplantation of the kidney to the iliac region. The average age of 9 males and 3femaleswas 58.3±12.3years. Their overall condition was assessed as good in 3 (25%) cases (ECOG=0), relatively satisfactory in 6 (50%) cases (ECOG=1), and 3 (25%) patients had significant limitation performing any work activities (ECOG=2). The glomerular filtration rate (GFR) in these patients varied from 30.0 to 92.0 ml/min (on average 51.5±16.8 ml/min), the blood creatinine level was from 86.4 to 280.0 μmol/L (on average 157.9±58.2 μmol/L), and the body mass index (BMI) from 21.8 to 39.4 kg/m^2 (on average 27.7±4.9 kg/m^2).

The left-sided tumors were found in 3 cases, while the right-sided tumors were revealed in 9 cases. The solitary kidney was detected in 7 patients, bilateral tumors in 2 patients, and significant functional impairment of the contralateral kidney was diagnosed in another 2 patients. Thus, absolute imperative indications for nephron-sparing surgery were recorded in 11 out of 12 (91.7%) patients. One patient had imperative indications for this type of treatment due to renal artery stenosis of the contralateral kidney and diabetes mellitus. The average size of tumors in the entire group reached 5.6±1.8 cm (3 to 9 cm). T1 stage was registered in 6 cases, T3a was diagnosed in another 6 cases. Moreover, invasion into the renal vein was detected in 4 patients (2 tumor thrombi of the renal vein segmental branches, 2 tumor thrombi of the renal vein main trunk), into the perirenal or renal sinus fat in another 4 patients, and into the pelvicalyceal system in yet another 4 patients (Fig. 1).

Entirely intraparenchymal tumors were found in 5 (41.7%) patients, while mostly intraparenchymal neoplasms were defined in 6 (50%) patients (Fig. 2).

Multifocality of the neoplastic process was recorded in 1 (8.3%) case. The histological structure of tumors in all cases was represented by clear cell renal cell carcinoma. No distant metastases were detected preoperatively in any patient.

Surgical techniques. In 11 cases, the kidney tissue collection was performed through the thoraco-lumbo-sacral approach via the X or XI intercostal space. After careful mobilization of the kidney, the main renal artery was exposed until the junction with the aorta on the left side and until the retrocaval section on the right side. Accordingly, the left renal vein was exposed until the level of its intersection with the aorta, and the right renal vein until the level of the cavorenal junction. In one case of a solitary right kidney tumor extending to the inferior vena cava, chevron approach was used, and the access to the right renal artery was carried out through the interaortocaval area after transection of the left renal vein and stump formation.



A *B*

C *D*

Fig. 1. MDCT frontal plane reconstructions and intraoperative images demonstrating the solitary kidney tumors extending into the main renal vein

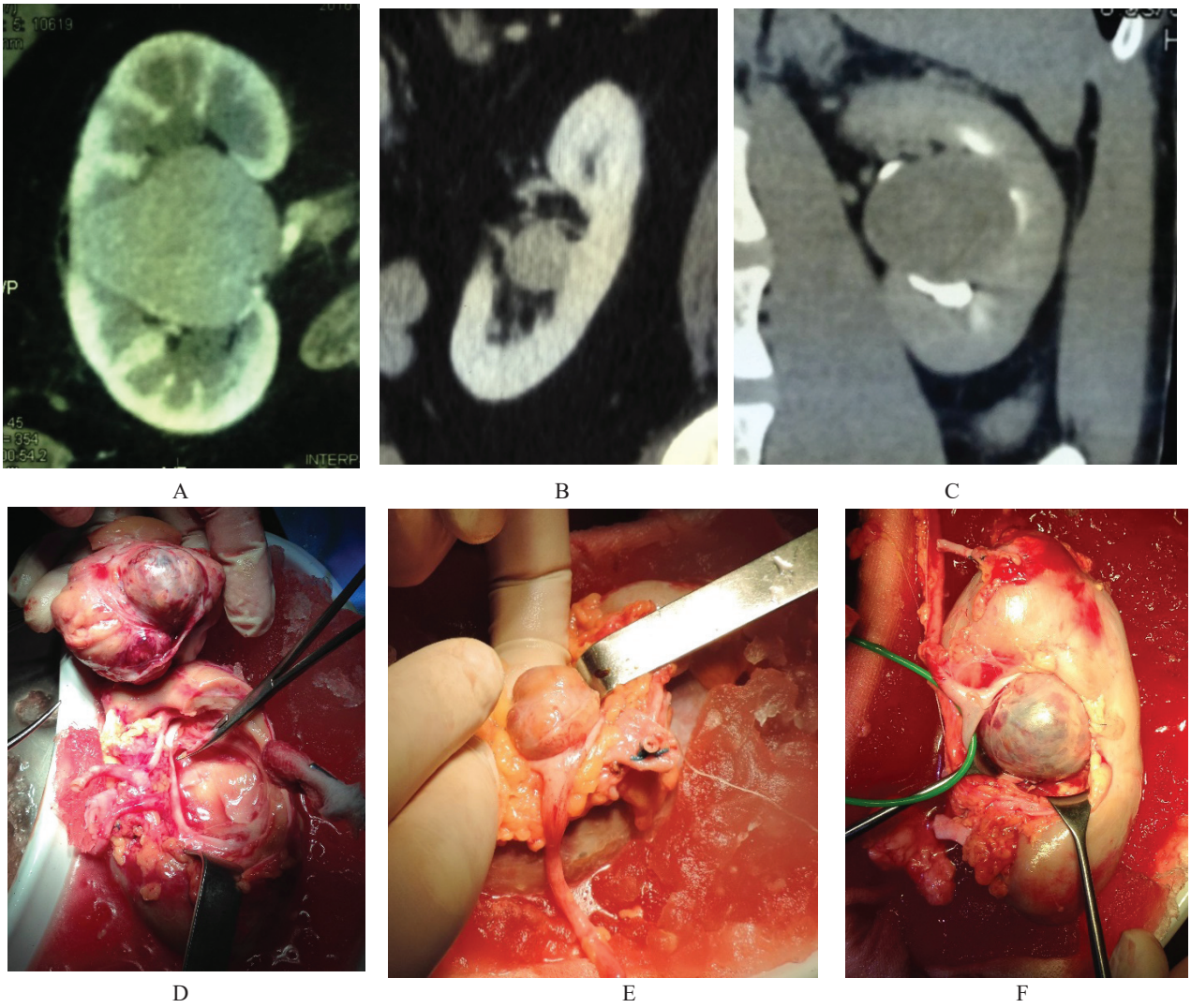


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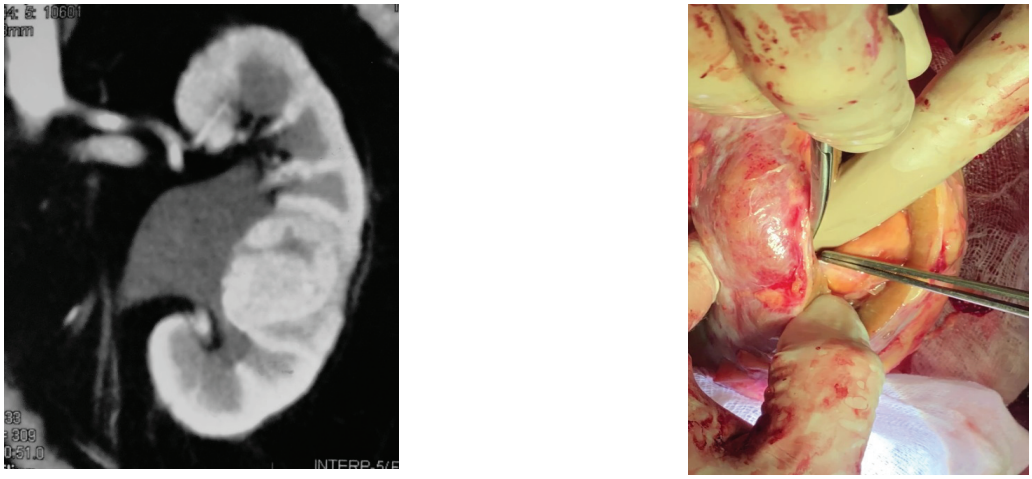
Fig. 2. MDCT reconstructions and intraoperative images of intrarenal tumors



A B

Fig. 3. A - frontal MDCT reconstruction of completely intrarenal tumor in a solitary kidney; B - intraoperative photo of the tumor node enucleation

The renal artery was transected as close as possible to the aorta, and in cases of the right-sided tumors, the vein was dissected off along with a portion of the inferior vena cava. The ureter was transected at the level of its middle third.

The kidney was transferred to a separate table, flushed with cooled Custodiol HTK solution and surrounded with chipped ice afterwords. One surgical team started extracorporeal removal of the tumor, while the other one proceeded to suture the thoraco-

lumbotomy or laparotomy wound and initiated the access to the iliac region for autotransplantation. In 4 cases, autotransplantation of the kidney was performed to the contralateral iliac fossa, while in 8 cases the ipsilateral approach was used.

On examination of the kidney surface and palpation of the renal parenchyma, the size and location of tumor nodes were defined. In the case of completely intraparenchymal tumors, ultrasound was used for their perioperative detection. In 6 patients, the method of enucleoresection was employed for tumor removal. Along the renal parenchyma borderline the incision continued 3-5 mm away from the tumor node, and along the sinus structures borderline the tumor was bluntly separated from them. In the remaining 6 cases, enucleation of the tumor nodes was performed (Fig. 3).

In patients with invasive RCC, the tumor was removed within healthy tissue limits with the renal calyx and renal sinus fat along. In 2 patients (in cases of segmental renal vein tumor thrombi), an intrarenal thrombectomy was utilized to remove neoplasms with intravenous extension, and in another 2 patients (in cases of the tumor invading the main renal vein), an extrarenal thrombectomy was performed. Intrarenal thrombectomy included removal of a thrombus out of the vein lumen from the side of the renal resection area, while in the case of extrarenal thrombectomy an additional opening of the lumen of the main renal vein or of the IVC was used.

Defects of the renal hollow system and intrarenal vessels were carefully sutured. The effectiveness of hemostasis and hermeticity of the hollow system was examined by infusion of Custodiol HTK solution into the renal artery and the ureter. The resection zone was covered with a large TachoComb patch. The parenchymal defect was closed with horizontal mattress and running Vicryl sutures.

The final stage was autotransplantation of the kidney to the iliac region. To do this step, the external iliac artery and vein were mobilized. An anastomosis was applied between the renal and external iliac vein. In 8 patients, arterial anastomoses were performed between the renal artery and internal iliac artery with the end-to-end method, and in 4 patients, between the renal artery and the external iliac artery with the end-to-side method. In 3 patients, anastomosis was performed between the ureter and the bladder placing a 6 Fr/Ch ureteral stent. In one of these patients, a Boari tubular bladder flap was used for vesicoureteral anastomosis. In the remaining 9 cases, uretero-ureteroanastomosis was performed between the middle and the lower third of the ureter.

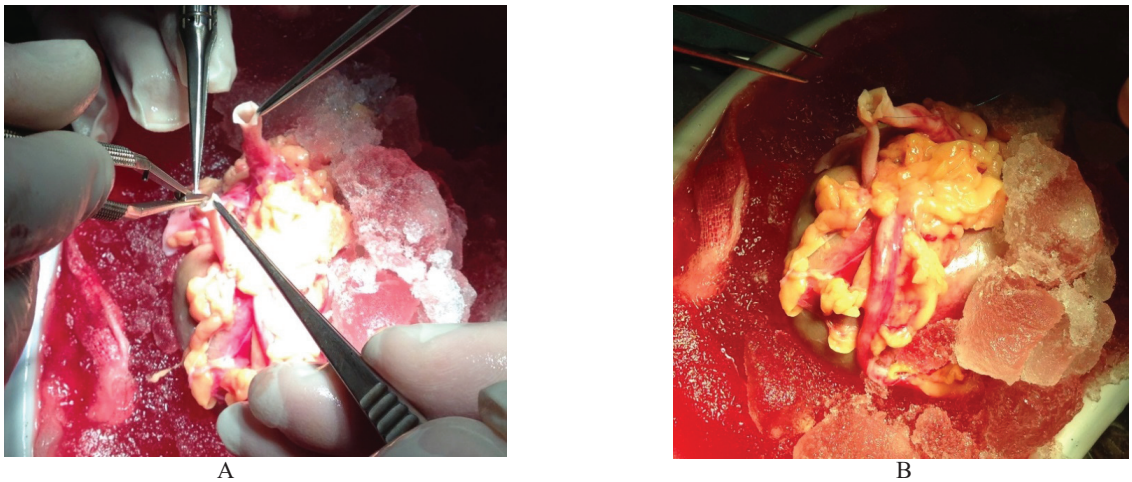
The follow-up period varied from 15 to 84 months and averaged 42.1±18.4 months. The follow-up protocol included ultrasound, serum creatinine and GFR every 3 months. MDCT of the lungs and abdominal area was performed every 6 months. Statistical analysis was carried out based on standard methods of descriptive statistics using “Statistica 8.0” software.

Results and discussion. Different types of vascular reconstruction were required in 4 (30%) of 12 patients. In one case, two renal arteries were combined into one (Fig. 4). In one of the patients, the main trunk of the renal vein was reconstructed using three flaps from the large saphenous vein. In another case, the thrombosis of arterial anastomosis between the renal and external iliac arteries was detected intraoperatively. After evacuation of the thrombus, a massive arterial wall defect appeared, which required prosthetic repair of the external iliac artery and performing a new anastomosis between the renal and internal iliac arteries. In yet another case, an extended defect of the renal vein main trunk of a solitary kidney was sutured after removal of a tumor thrombus reaching the IVC. Besides, four defects of the large intrarenal branches of the renal artery were sutured.

The main characteristics of surgical interventions and complications are presented in Table 1.

The average time of surgical interventions reached 4.5 hours and varied from 240 to 320 minutes. The cold ischemia time during extracorporeal kidney resection on average exceeded 40 minutes, and in 4 patients it lasted longer than 50 minutes (maximum 62 minutes). The average overall time frame of vascular anastomosis was 56.4±6.4 minutes. The blood loss volume ranged from 400 to 700 ml (558.3±99.6 ml on average).

Postoperative complications Grade III-IV by Clavien-Dindo classification were recorded in 5 (41.7%) patients. In 2 cases, bleeding occurred 4 and 8 hours after autotransplantation, respectively (1 from the area of kidney resection, and 1 from the area of venous anastomosis), which required re-operation. In one of these cases, transplant nephrectomy had to be performed. Oligoanuria in the postoperative period occurred in 4 patients, but hemodialysis was necessary only in two of them. Postoperative mortality was observed in two (16.7%) cases. In one of them, a patient died of multiple organ failure after re-operation for bleeding from the venous anastomosis zone 8 hours after the primary surgical intervention. In another case, a female patient with a history of a stroke, while postoperative oligoanuria resolved, demonstrated signs of cerebral edema and heart failure 7 days after surgery.



A B

Fig. 4. Intraoperative images of renal artery reconstruction in a patient with two renal arteries. A - prior to reconstruction; B - after suturing the distal parts of both vessels, a common arterial mouth was formed

Table 1.Characteristics of surgical interventions and complications

	n	%
Average operation time, min	270.8±25.0	
Average warm ischemia time, min	1.9±0.7	
Average cold ischemia time for partial nephrectomy, min.	47.8±7.8	
Average cold ischemia time for vascular anastomoses, min	56.4 ±6.4	
Blood loss, ml	558.3±99.6	
Thrombosis of the arterial anastomosis	1	8.3
Postoperative hemorrhage	2	16.7
Re-operation	3	25
Transplant nephrectomy	2	16.7
Oligoanuria	4	30
Need for hemodialysis	2	16.7
Perioperative mortality	2	16.7
Chronic urinary fistula	1	8.3

A chronic urinary fistula due to ureter necrosis developed in one patient. This complication required the nephrectomy 3 months after the operation. Thus, the rate of graft loss was 16.7% (n=2). Both nephrectomies were performed in patients with the second kidney having reduced function.

Long-term results were observed in all 10 patients. Currently none of the patients requires chronic hemodialysis. The average creatinine level after surgery in the entire group was 139.3±46.1 μmol/L (from 102.4 to 260 μmol/L). Δ creatinine varied from 4.0 to 60.0 μmol/L (on average, 25.3±17.6 μmol/L). GFR averaged 38.7±14.4 ml/min. The difference between the average level of this value before and after surgery did not exceed -9.3±8.6 ml/min.

With an average follow-up period of 42 months, no locoregional RCC recurrences were detected in any of the cases. Metachronous metastases to the lungs were found in one patient 2 years after surgery. The patient is receiving targeted therapy with pazopanib.

Despite significant improvement of the partial nephrectomy techniques, over the past two decades, performing organ-preserving interventions in patients with imperative indications for this type of treatment (tumor of a solitary kidney or the only functioning kidney, bilateral kidney tumors) has been a serious technical challenge. In this setting, nephrectomy can be considered as a more radical and an easy to perform solution, but in clinical practice, nephron-sparing surgeries are undoubtedly preferred. This trend is associated with active attempts to avoid the renoprival condition and chronic hemodialysis.

Although dialysis technologies have been significantly improved over the period of their existence, transferring the patient to a renoprival state is considered by most patients and doctors as an extremely undesirable outcome. This is due to the high cost of chronic hemodialysis, low quality of life and a significant number of complications.

The mortality in dialysis patients exceeds very significantly the rate observed in the general population, even exceeding the figures occurring in neoplastic disease. These features are evidenced by 46% rate of the 5-year survival in non-diabetic dialysis patients. [4]. The high risk of tumors of various origin in the dialysis patients also should be considered. This was clearly presented in the paper by Lin M. Y. et al., Taiwan, who found that the risk of cancer development in these patients was seven times higher than in the general population [5].

Allotransplantation of the kidney in cancer patients is an extremely limited therapeutic option, since immunosuppression can lead to rapid progression of the remnant tumor cells. According to Farrugia et al. in the general population with kidney transplants, the risk of neoplastic process is ten times higher than in healthy people of the corresponding age and gender [6]. Cancer is the second most common cause of mortality and morbidity in kidney transplant recipients after cardiovascular disease. Kidney transplant recipients have at least a twofold higher risk of developing or dying from cancer than the general population [7]. Interestingly, the most common tumor in these clinical settings was renal cell carcinoma of the native kidneys.

All the above stated suggest that the current priority treatment for this group of patients are surgical technologies involving preservation of the kidney. However, surgery in situ does not always permit a maximal radicality and safety of surgical treatment. This is due to the inconvenient manipulation in the narrow lumbotomic wound, limited mobility of the kidney, large size and difficult location of these tumors. Enucleation or enucleoresection of large intrarenal tumors quite often causes extensive damage to the renal hollow system and major intrarenal vessels. Careful reconstruction of these structures may be accompanied by a prolonged warm ischemia time and significant deterioration of the renal function.

An alternative to in situ surgery is extracorporeal removal of the tumor followed by autotransplantation. This approach is one of the most complex treatment methods in modern urologic oncology. It combines not only oncological and reconstructive technologies, but also transplant techniques, which require specialized training of the operating team.

The main advantages of extracorporeal surgery are:

- ability to freely manipulate the kidney in any plane with any angle;
- ability to engage surgical assistants more effectively when performing the most delicate stages of the reconstruction;
- good visibility in the area of interest and, as a result, high radicality of intervention
- effective anti-ischemic protection during several hours.

The disadvantages of this method are the technical complexity, the large volume and duration of the operation, as well as the likelihood of complications of ureteral and vascular anastomoses, which can lead to the loss of the kidney.

For the first time, autotransplantation of the kidney was performed in 1963 by D. Hardy [8]. The surgery was performed for ureteral injury. Later, the concept of surgical correction of pathological changes of the kidney outside the body, was worked out, i.e. «workbench surgery» (operation performed on the table). In 1975, Husberg et al. performed the first ex vivo partial nephrectomy for cancer followed by autotransplantation [9]. At the same time, Putnam C. W. et al. used an extracorporeal technique to remove a kidney coral stone [10]. The main technical aspects of extracorporeal tumor removal were described by Novick A. C. et al. in 1980 [111]. In 1989, Pereverzev A. S. and Shcherbak A. Yu. presented the technical features and results of renal autotransplantation in the monograph «Autotransplantation of the kidney in clinical urology», including the patients with kidney tumors [12]. Despite the active evolution of extracorporeal surgery technology, the literature on the renal autotransplantation usually presents assessment of only selected aspects of this therapeutic approach and include a small number of patients.

The role of autotransplantation in the modern medicine is clearly demonstrated in the study by Moghadamyeghaneh Z. et al., which included analysis of the US national database from 2002 to 2012 [13]. During this period, the kidney autotransplantation was performed in 817 patients. The most frequent indications for surgery were the renal artery disorders (22.7%) and ureteral conditions (17%). Malignant tumors of the kidneys or neighboring structures occurred in 122 (14.9%) patients. The mortality rate was 1.3% with a complication rate of 46.2%. The main postoperative problems were insufficiency of the transplanted kidney (10.7%) and hemorrhagic complications (9.7%). The main prognostic factors for the development of complications were obesity, disorders of water and electrolyte metabolism, and the presence of chronic kidney disease prior to surgery. In cases where autotransplantation was performed to correct the consequences of other operations, the highest mortality and complication rates were observed (7.8% and 92%, respectively). Among patients with malignant neoplasms of the kidneys and surrounding structures, complications were detected in almost half of the cases (47.5%). In this group, the highest incidence of renal graft failure was registered (12.3%), which the authors attribute to the complexity of these surgical interventions.

The results of renal autotransplantation in non-oncological patients were presented in detail in the work by Cowan N. G. et al., which included 51 patients with different indications for this operation [14]. Early complications Grade ≥ III by Clavien system occurred in 14.8% of cases, while the late postoperative complications of any grade were observed in 12.9% of cases.

Table 2. Results of extracorporeal nephron-sparing surgery with autotransplantation

№	Authors	N of all patients	N of patients with kidney tumor	Cold ischemia time,min	Complications	Graft loss	Survival rate
1	Novic A.C. et al. [15]	108	14			14%	5-year OS 70%
2	Morgan W.R. et al. [16]	14	14				5-year CSS 54.9%
3	Tran G. et al. [17]	52	7		Clavien ≥ III 8% early, and 12% late	5 (9.7%)	50% disease recurrence
4	Janssen MWW [18]	12	12	195 [160-280]	Clavien>II 6 (50%)	0	median follow-up 83.5±40.7 months. 6 pts died (50%): 5 from recurrence disease. 5 pts (41.6%) are alive, without evidence of tumor relapse
5	Gritskevich A. A. et al. [19]	37	37	151.4	Intraoperative complications 3 (8,1%) Postoperative complications Clavien ≥ III 10 (27.0%)	3 (8.1%)	21,4 months disease-free survival
6	Mickisch G.H.J. [20]	36	36		Clavien ≥ III 3 (8.3%)	1 (2.8%)	Progression in 2 pts over 2.8 years
7	Komyakov B. K. [21]	9	9	112.6	Clavien ≥ III 4 (44.4%)	0	No progression
8	Kulisa M. [22]	11	11		Clavien ≥ III 8 (72.7%)	2 (18.2%)	After 37.8 months in 2 (18.2%) pts with local recurrence and 5 (45.4%) patients with mts with 2 deaths (18.2%)
9	Stormont TJ [23]	20	20			4 (20%)	35 мес у 4 (25%) лок. рецидив; 37,5% пациентов были свободны от опухоли и гемодиализа

OV – overall survival; CSS – cancer-specific survival

Graft loss was recorded in 2 (3.9%) patients. The authors reported that the complication rate was objectively affected by the duration of cold ischemia.

By now, several dozens of reports on the outcomes of «workbench surgery» and renal autotransplantation for kidney tumors have been published in the world literature presenting a general positive assessment of this technique [15-23]. Regarding the complications, it is considered that their percentage is higher in ex vivo surgery than in in situ interventions. This is due to the imperative indications for such operations and the complex characteristics of the tumors being removed. We analyzed the available data from the largest studies evaluating the results of extracorporeal surgery for renal cell carcinoma. This review included 160 patients whose treatment results were compared with the results of our own study (Table 2).

The average cold ischemia time varied from 112.6 to 195.0 minutes and averaged 152.9 minutes. In our work, the average cold ischemia time for the extracorporeal stage of the operation was 47.8 minutes, and the average time from the beginning to the end of vascular anastomoses procedure was 56.4 minutes (104.2 minutes in total).

Intraoperative challenges associated with the need to perform various types of vascular reconstruction were encountered in 30% of patients in our study. A significant intraoperative complication: thrombosis of arterial anastomosis, was registered only in one (8.3%) case. Similar figures are reported by Gritskevich A. A. et al.: 8.1% of intraoperative complications [19]. However, in the work by Janssen et al. this value reached 50% in 12 patients [18].

Postoperative complications Grade ≥ III by Clavien-Dindo system, according to various researchers, vary from 8.3% to 72.0% and average 25.5% (37 out of 145 patients, based on the results of 5 studies) [17, 19-22]. In our work, this value reached 41.7%, which was associated with the large percentage of completely intraparenchymal tumors and neoplasms with intravenous extension. The level of the graft loss also differed significantly in the presented papers from 0% to 20% (on average, 10.5%; 30 out of 285 according to 8 studies) [15, 17-23]. The most common causes of nephrectomy were vascular complications, in particular, thrombosis of arterial anastomosis. We had to remove the graft in 2 patients (16.7%) due to postoperative bleeding and chronic urinary fistula.

Postoperative mortality in two studies was 2.7% and 2.8%, while in the work by Komyakov B. K. et al. it was reported as 11.1% [19-21]. In our study, this parameter was 16.7%, which was associated with severe condition after a previous stroke in one of the patients and with massive bleeding from the area of venous anastomosis in the other patient.

Cancer outcomes in patients undergoing extracorporeal surgery varied significantly in different studies. Thus, Gritskevich A. et al., Janssen M. W. W. et al., and Komyakov B. K. et al. reported no tumor progression in the operated patients [18, 19, 21]. The latter authors report a recurrence-free disease-specific survival rate for 48 months. We also discovered distant metachronous metastases only in one patient during the follow-up period of 42 months. At the same time, there were no signs of local recurrence of RCC. However, other authors demonstrate much worse oncological results for this treatment approach. Thus, Stormont T. J. et al., with an average follow-up period of 35 months, discovered a local recurrence of the tumor in 4 (25%) patients, while only 6 (37.5%) of 16 patients were free of the tumor and hemodialysis [23]. Similarly, Kulisa M. et al. detected a local tumor recurrence after an average of 37.8 months in 18.2% of patients and distant metachronous metastases in 45.4% of 11 patients [22].

Conclusion. Extracorporeal removal of the kidney tumor with renal autotransplantation is an effective method of nephron-sparing surgery in patients with imperative indications for kidney preservation. However, this technique is accompanied by a high rate of complications Grade ≥ III-IV by Clavien-Dindo classification, which should be taken into account when determining the indications for its application. The undoubted advantages of this surgical approach include the possibility of placing the kidney in any plane, good visibility of the resection area, and the absence of a time barrier associated with warm ischemia. All the above-mentioned makes the surgical intervention as radical as possible. The oncological results of extracorporeal RCC surgery require further study.

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SUMMARY

RESULTS OF EXTRACORPOREAL NEPHRON-SPARING SURGERY FOR RENAL CELL CARCINOMA WITH AUTOTRANSPLANTATION

[1]Lesovoy V., [1]Shchukin D., [1]Khareba G., [2]Antonyan I., [1]Lisova G., [1]Demchenko V., [2]Olkhovska V.

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The study included 12 patients who underwent extracorporeal nephron-sparing surgery followed by autotransplantation of the kidney to the iliac region. A solitary kidney occurred in 7 (58.3%) cases, bilateral tumors in 2 (16.7%) cases, a significant decrease in the function of the contralateral kidney in 2 (16.7%) cases, and relative imperative indications in 1 (8.3%) patient. The ECOG status 0, 1 and 2, respectively, was recorded in 3 (25%), 6 (50%) and 3 (25%) cases. The glomerular filtration rate in patients (GFR) averaged 51.5±16.8 ml/min, the blood creatinine level was 157.9±58.2 μmol/L, and the body mass index (BMI) was 27.7±4.9 kg/m^2. The average size of tumors in the entire group reached 5.6±1.8 cm (3 to 9 cm). T1 stage was registered in 6 cases, T3a was diagnosed in another 6 cases. Besides, invasion into the renal vein was detected in 4 patients, into the pararenal or renal sinus fat in another 4 patients, into the pelvicalyceal system lumen in yet another 4 patients. Intrarenal tumors were found in 11 (91.7%) patients.

Different types of vascular reconstruction were required in 4 (30%) out of 12 patients. The average time of surgical interventions reached 270.8±25.0 minutes. The average cold ischemia time during extracorporeal partial nephrectomy was 47.8±7.8 minutes. The average overall time frame of vascular anastomosis was 56.4±6.4 minutes. The volume of blood loss varied from 400 to 700 ml (on average 558.3±99.6 ml). Postoperative complications Grade III-IV by Clavien-Dindo classification were recorded in 5 (41.7%) patients. Oligoanuria in the postoperative period occurred in 4 (33.3%) patients, but hemodialysis was necessary only in two of them. Postoperative mortality was observed in two (16.7%) cases. The graft loss rate was 16.7% (bleeding and chronic urinary fistula).

Long-term results were evaluated in all 10 patients. Currently none of the patients requires chronic hemodialysis. The average creatinine level after surgery in the entire group was 139.3±46.1 μmol/L (from 102.4 to 260 μmol/L). Δ serum creatinine varied from 4.0 to 60.0 μmol/L (on average 25.3±17.6 μmol/L). Δ GFR on average did not exceed -9.3±8.6 ml/min. With an average follow-up period of 42 months, no locoregional RCC recurrences were detected in any of the cases. Metachronous metastases to the lungs were found in one patient 2 years after surgery.

Extracorporeal removal of a kidney tumor with renal autotransplantation is an effective method of nephron-sparing surgery in patients with imperative indications for kidney preservation. However, this technique is accompanied by a high rate of complications Grade ≥ III-IV by Clavien-Dindo system, which must be taken into account while defining the indications for its use.

Keywords: renal hypothermia techniques, perfusion-mediated cooling, nephron-sparing surgery, renal cell carcinoma.

РЕЗЮМЕ

РЕЗУЛЬТАТЫ ЭКСТРАКОРПОРАЛЬНОЙ ОРГАНОСОХРАНЯЮЩЕЙ ХИРУРГИИ ПОЧЕЧНО-КЛЕТОЧНОГО РАКА С АУТОТРАНСПЛАНТАЦИЕЙ ПОЧКИ

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В связи с высокой сложностью и вероятностью сосудистых осложнений экстракорпоральные резекции почки по поводу почечно-клеточного рака (ПКР) выполняются редко и преимущественно в специализированных центрах. Представлен опыт проведения этих операций.

В исследование включены 12 пациентов, которым выполнялась экстракорпоральная органосохраняющая хирургия с последующей аутотрансплантацией почки в подвздошную область. Единственная почка была у 7 (58,3%) пациентов, двусторонние опухоли – у 2 (16,7%), существенное снижение функции контралатеральной почки – у 2 (16,7%), относительные императивные показания - у 1(8,3%) больного. Оценка статуса больного по шкале ECOG 0, 1 и 2 зафиксирована в 3 (25%), 6 (50%) и 3 (25%) наблюдениях, соответственно. Скорость клубочковой фильтрации у пациентов, в среднем, составила 51,5±16,8 мл/мин, уровень креатинина крови - 157,9±58,2 мкмоль/л, индекс массы тела – 27,7±4,9 кг/м^2. Средние размеры опухолей достигали 5,6±1,8 см (от 3

до 9 см). Стадия T1 зафиксирована в 6 случаях, T3a – также в 6 наблюдениях. Инвазия в почечную вену отмечалась у 4 больных, в паранефральный или синусный жир – у 4, в просвет чашечно-лоханочной системы – у 4. Интраренальные опухоли обнаружены у 11 (91,7%) пациентов.

Различные виды сосудистой реконструкции были необходимы 4 (30%) из 12 пациентов. Среднее время хирургических вмешательств достигало 270,8±25,0 минут. Время холодовой ишемии при экстракорпоральной резекции почки, в среднем, составило 47,8±7,8 минут. Средний период от начала до конца наложения сосудистых анастомозов составил 56,4±6,4 минуты. Объем кровопотери варьировал в пределах от 400 до 700 мл, в среднем, 558,3±99,6 мл. Послеоперационные осложнения градации 3-4 по Clavien-Dindo зафиксированы у 5 (41,7%) пациентов. Олигоанурия в послеоперационном периоде имела место у 4 (33,3%) больных, однако гемодиализ был необходим только двум из них. Послеоперационная летальность отмечена в 2 (16,7%) случаях. Уровень потери трансплантата составил 16,7% (кровотечение и хронический мочевой свищ).

Отдаленные результаты оценены у 10 пациентов. Ни один из них не нуждался в хроническом гемодиализе. Средний уровень креатинина после операции составил 139,3±46,1 мкмоль/л (от 102,4 до 260 мкмоль/л). Δ креатинина крови варьировала в пределах от 4,0 до 60,0 мкмоль/л, в среднем, 25,3±17,6 мкмоль/л. Δ скорости клубочковой фильтрации, в среднем, не превышала 9,3±8,6 мл/мин. При среднем периоде наблюдения 42 месяца локорегиональных рецидивов ПКР ни в одном случае не выявлено. Метастазы в легкие обнаружены у одного больного спустя 2 года после операции.

Экстракорпоральное удаление опухоли почки с почечной аутотрансплантацией является эффективным способом органосохраняющей хирургии у пациентов с императивными показаниями к сохранению почки. Однако, эта методика сопровождается высоким уровнем осложнений градации ≥3-4 по Clavien-Dindo, что необходимо учитывать при определении показаний к ее использованию.

რეზიუმე

თირკმლის უჯრედული კიბოს ექსტრაკორპორული ორგანოშემანარჩუნებელი ქირურგიის შედეგები თირკმლის აუტოტრანსპლანტაციით

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სისხლძარღვოვანი გართულებების განვითარების სიმძიმისა და ალბათობის გათვალისწინებით, თირკმლის ექსტრაკორპორული რეზექცია თირკმლის უჯრედული კიბოს დროს ტარდება იშიათად და, უმეტესწილად, სპეციალიზებულ სამედიცინო ცენტრებში. სტატიაში წარმოდგენილია ასეთი ოპერაციების გამოცდილება.

კვლევაში ჩართული იყო 12 პაციენტი, რომელთაც ჩაუტარდათ ექსტრაკორპორული ორგანოშემანარჩუნებელი ქირურგიული ჩარევა, შემდგომში თირკმლის აუტოტრანსპლანტაციით მლივი ნაწლავის შესაბამის მიდამოში. ერთი თირკმელი ჰქონდა 7 (58,3%) პაციენტს, ორმხრივი სიმსივნე – 2 (16,7%), კონტრალატერალური თირკმლის ფუნქციის მნიშვნელოვანი დაქვეითება – 2 (16,7%), შეფარდებითი იმპერატიული ჩვენებები – 1 (8,3%). ECOG-სკალით პაციენტის სტატუსი 0, 1 და 2 დაფიქსირდა, შესაბამისად, 3 (25%), 6 (50%) და 3 (25%) შემთხვევაში. გორგლოვანი ფილტრაციის სიჩქარემ პაციენტებში შეადგინა, საშუალოდ, 51,5±16,8 მლ/წთ, კრეატინის დონემ სისხლში - 157,9±58,2 მკმოლ/ლ, სხეულის მასის ინდექსმა - 27,7±4,9კგ/მ². სიმსივნის საშუალო ზომა აღწევდა 5,6±1,8 სმ (3-დან 9 სმ-მდე). სტადია T1 დაფიქსირდა 6 შემთხვევაში, T3a – ასევე 6 შემთხვევაში. ინვაზია თირკმლის ვენაში აღინიშნა 4 პაციენტთან, პარანეფრულ ან სინუსურ ცხიმში – 4 პაციენტთან, ფიალების სისტემაში – 4 პაციენტთან. ინტრარენული სიმსივნე აღენიშნა 11 (91,7%) პაციენტს. სხვადასხვა ტიპის სისხლძარღვოვანი რეკონსტრუქცია აუცილებელი გახდა 4 (30%) პაციენტის შემთხვევაში (12-დან). სისხლის დანაკარგი ვარირებდა 400-700 მლ-ის ფარგლებში, საშუალოდ, 558,3±99,6 მლ. ოპერაციისშემდგომი გართულებები Clavien-Dindo მიხედვით გრადაციით 3-4 დაფიქსირდა 5 (41,7%) პაციენტთან. ოლიგოანურია ოპერაციისშემდგომ პერიოდში ჰქონდა 4 (33,3%) პაციენტს, თუმცა, ჰემოდიალიზი მათგან მხოლოდ ორს დასჭირდა. ოპერაციისშემდგომი ლეტალობა აღინიშნა 2 (16,7%) შემთხვევაში. ტრანსპლანტანტის დანაკარგის დონემ შეადგინა 16,7% (სისხლდენა და შარდის ქრონიკული ფისტულა).

შორეული შედეგები განისაზღვრა 10 პაციენტის შემთხვევაში. არც ერთ მათგანს არ დასჭირდა ქრონიკული დიალიზი. კრეატინინის საშუალო დონემ ოპერაციის შემდეგ შეადგენდა 139,3±46,1 მკმოლ/ლ (102,4-დან 260 მკმოლი/ლ-მდე). სისხლში კრეატინინის Δ ვარირებდა 4,0-დან 6,0 მკმოლ/ლ-ის ფარგლებში, საშუალოდ, 25,3±17,6 მკმოლ/ლ. გორგლოვანი ფილტრაციის სიჩქარის Δ, საშუალოდ, არ აღემატებოდა 9,3±8,6 მლ/წთ. დაკვირვების საშუალოდ 42-თვიან პერიოდში თირკმელ-უჯრედული კიბოს ლოკორეგიონული რეციდივის არც ერთი შემთხვევა არ გამოვლენილა. მეტასტაზები ფილტვში ოპერაციიდან 2 წლის შემდეგ აღმოაჩნდა ერთ ავადმყოფს.

თირკმლის სიმსივნის ექსტრაკორპორული მოცილება თირკმლის აუტოტრანსპლანტაციით წარმოადგენს ორგანოშემანარჩუნებელი ქირურგიის ეფექტურ საშუალებას პაციენტებში თირკმლის შენარჩუნების იმპერატიული ჩვენებით. თუმცა, ამ მეთოდიკას თან ახლავს გართულებათა მაღალი დონე, გრადაციით ≥3-4 Clavien-Dindo-ს მიხედვით, რაც აუცილებლად გასათვალისწინებელია ჩვენებების განსაზღვრისას ამ მეთოდის გამოყენებასთან დაკავშირებით.

КЛИНИКО-ПАТОЛОГОАНАТОМИЧЕСКИЙ АНАЛИЗ СЛУЧАЯ СИНДРОМА ЛЕВОСТОРОННЕЙ ГИПОПЛАЗИИ СЕРДЦА У ОДНОГО ИЗ БЛИЗНЕЦОВ ПРИ БЕРЕМЕННОСТИ, НАСТУПИВШЕЙ С ПРИМЕНЕНИЕМ ЭКСТРАКОРПОРАЛЬНОГО ОПЛОДОТВОРЕНИЯ. СОБСТВЕННОЕ НАБЛЮДЕНИЕ

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По данным Всемирной организации здравоохранения (ВОЗ), в последние десятилетия отмечается увеличение частоты бесплодных браков до 12-20%. Решение проблемы бесплодия удается с применением вспомогательных репродуктивных технологий (ВРТ). Однако, беременность, наступившая в результате ВРТ, имеет более высокий риск преждевременных родов, многоводия, формирования пороков развития плода, плацентарной недостаточности [12].

Целью исследования явился клинико-патологоанатомический анализ случая доношенной беременности с синдромом левосторонней гипоплазии сердца у одного из близнецов, наступившей с применением экстракорпорального оплодотворения.

Материал и методы. Исследовались мертвый мацерированный плод и бихориальная биамниотическая плацента. Анамнестические данные: женщина В., 29 лет, беременность III (I беременность закончилась физиологическими родами, II беременность — замершая на 7-8 неделе), двойня, экстракорпоральное оплодотворение (ЭКО) в связи с вторичным бесплодием. Во время планового ультразвукового (УЗ) исследования на 19 неделе беременности у одного из плодов был обнаружен врожденный порок развития: синдром левосторонней гипоплазии сердца (СЛГС) с атрезией клапана аорты и гипоплазией восходящей части и дуги аорты, с недостаточностью и дисплазией митрального клапана. С согласия женщины на 20 неделе беременности проведен селективный фетоцид плода с врожденными пороками развития путем введения хлорида калия в полость сердца [11]. После внутриутробной гибели плода с СЛГС и прогрессирования данной беременности, на 40 неделе естественным путем родился живой ребенок, второй из двойни, с массой 3200 г, по шкале APGAR 9 баллов. Мертвый плод и плацента были направлены на патологоанатомическое исследование.

Результаты и обсуждение. Макроскопическое исследование. Плод массой 200 г, с выраженной мацерацией кожных покровов, трупным аутолизом внутренних органов. Отмечались крыловидные складки кожи между левым плечом и боковой поверхностью туловища, между ипсилатеральными конечностями слева. Выраженные аутолитические изменения в сердце плода не позволяли подтвердить порок развития сердца, выявленный при УЗ исследовании (рис. 1).

При проведении патологоанатомического исследования необходимо тщательно описать существующие пороки развития для медико-генетического консультирования родителей в будущем. Исследуя сердце при СЛГС важно не только подтвердить диагноз гипоплазии левого желудочка (ЛЖ), но и установить тип его строения (I — щелевидно-гипопластический, II — щелевидно-гипертрофический, III — цилиндрический, IV — лакунарный, V — лакунарно-цилиндрический) [1,4,7]. Это необходимо для прогнозирования результатов лечения, поскольку при щелевидно-гипопластическом типе целесообразно применять процедуру Норвуда в периоде новорожденности, а при щелевидно-гипертрофическом в пренатальном периоде — фетальную аортальную вальвулопластику. Другие три типа считаются неблагоприятными для любого вида хирургической коррекции [1,7].

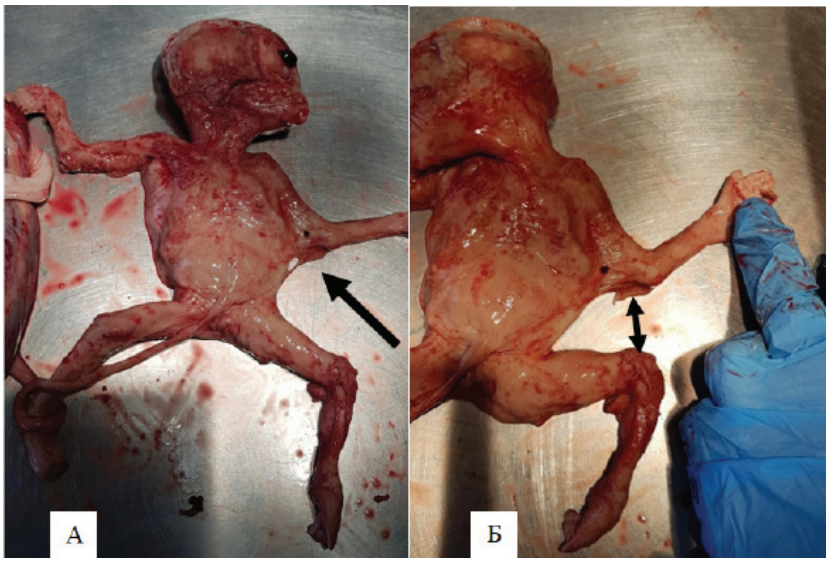

Рис. 1. Макрофото. Мацерированный плод с пороками развития. Синдром множественных птеригиумов в сочетании с СЛГС. А — крыловидная складка кожи между плечом и туловищем (стрелка), Б — разорванная складка кожи между верхней и нижней левыми конечностями (стрелка)

Таким образом, в нашем случае для установления типа строения гипоплазированого ЛЖ патологоанатомом, который занимался изучением типов строения ЛЖ при СЛГС на секционном материале, совместно с врачом ультразвуковой диагностики, проведены дополнительные измерения структур сердца плода с пороком на архивных видеоматериалах, что позволило ретроспективно установить и количественно подтвердить тип строения ЛЖ при СЛГС (рис. 2).

Толщина свободной стенки ЛЖ (Тст) — 0,55 см, при этом, преобладает толщина компактного слоя миокарда (Мк), которая составляет 0,33 см, толщина трабекулярного слоя (Мт) — 0,22 см. Вычислен индекс толщины слоев (ИТС), который является соотношением линейных размеров Мт/Мк [6, 7, 10]. ИТС составил 0,66 ед. Также на продольных срезах возможно измерить ширину полости (Шп) — расстояние от межжелудочковой перегородки до свободной стенки ЛЖ, и длину полости ЛЖ (Дп) с последующим вычислением их соотношения — индекс формы полости фронтальный (ИФПф) = Шп/Дп [8]. В нашем случае он имел значение 0,49 ед. Также возможно вычислить полостно-миокардиальный индекс (ПМИ) = Шп/Тст, который в нашем случае составил 0,75 ед.

Макроскопическое исследование плаценты. Плацента бихориальная биамниотическая массой 450 г, масса плаценты живого плода 330 г, размер — 13×11×2 см, пуповина длиной 22 см прикреплена эксцентрично, имеет три сосуда; на разрезе ткань плаценты синюшно-красного цвета, губчатая, на материнской поверхности сгустки крови; масса плаценты плода после селективного фетоцида — 120 г, размер 7×8×0,5 см, желтоватого цвета, плотной консистенции, пуповина прикреплена эксцентрично, длиной 19 см, дряблая, с тремя сосудами (рис. 3). Амниотические оболочки серые, тусклые.

Микроскопическое исследование плаценты. Плацента живого плода (рис.4). Оболочки с явлениями очаговой лимфоцитарной инфильтрации. Преобладают стволовые ворсины с фиброзированной стромой и расширенными малочисленными сосудами, расположенными в центре ворсин. Вокруг стволовых ворсин наблюдаются ворсины удлиненной формы с небольшим количеством капилляров. Терминальные ворсины в небольшом количестве, содержат по 3-4 центрально расположенных капилляра. Межворсинчатое пространство расширено, с небольшим количеством эритроцитов. Увеличено количество синцитиальных почек. Базальная пластинка с увеличенным количеством фибриноида, эритроцитами, очаговой лимфоцитарной инфильтрацией. Патоморфологический диагноз: гипоплазия терминальных ворсин.

При микроскопическом исследовании плаценты плода после селективного фетоцида выявлены преимущественно стволовые и промежуточные ворсины-тени, лишенные сосудов. Строма ворсин частично замещена фибриноидом, в межворсинчатом пространстве обнаружен фибрин в большом количестве и очаговое отложение кальция (рис. 5.А), со стороны базальной пластинки среди большого количества фибриноида дистрофически измененые децидуальные клетки и очаговая лимфоцитарная инфильтрация (рис. 5.Б).

При патологоанатомическом исследовании мертвого плода необходимо подробно описать все выявленные пороки развития, подтвердить клинический диагноз СЛГС с установлением типа строения ЛЖ. Хотя следует отметить, что наибольшую ценность имеет пренатальное определение типа строения гипоплазированного ЛЖ, для решения вопросов лечебной тактики: прерывать беременность при неблагоприятных типах ЛЖ, рекомендовать операцию Норвуда в периоде новорожденности при I типе или проводить фетальную аортальную вальвулопластику, которая внедряется в ведущих клиниках мира и целесообразна только при II типе ЛЖ [1].

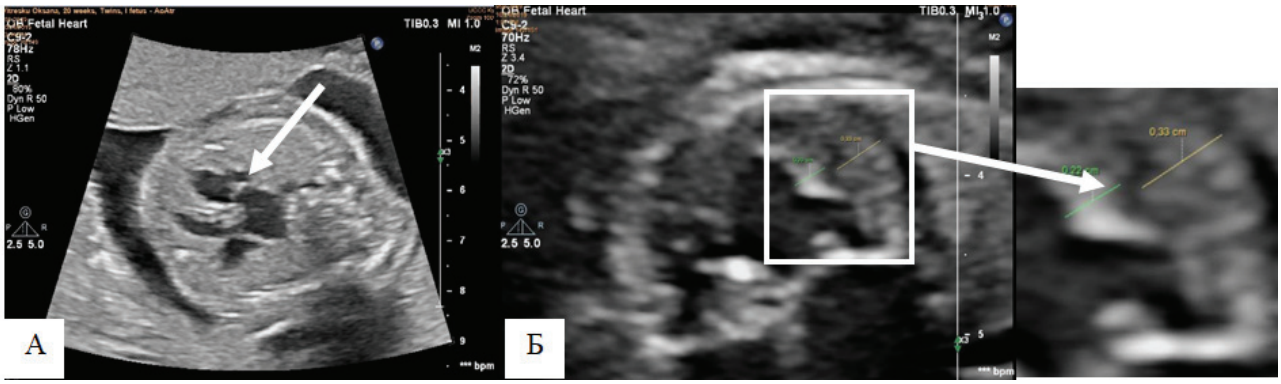

Рис. 2. Случай В. Продольные срезы сердца плода с СЛГС. А — ЛЖ цилиндрического типа строения (стрелка) Б — показано измерение толщин трабекулярного и компактного слоев миокарда (стрелка)

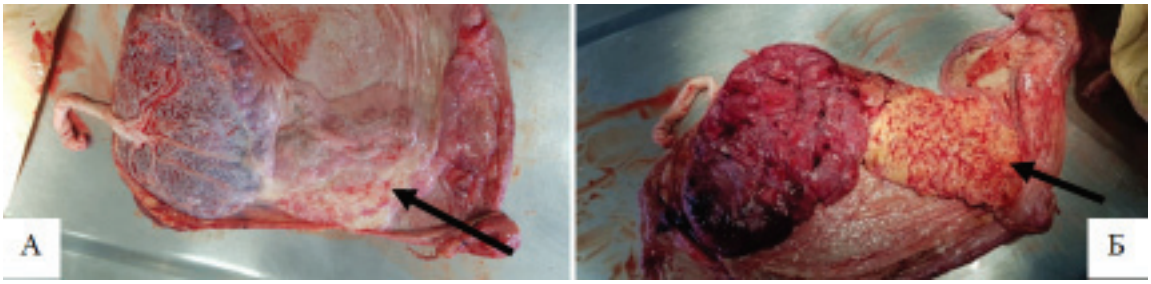

Рис. 3. Макропрепараты. Плацента бихориальная биамниотическая. А — плодовая поверхность; Б — материнская поверхность. Стрелкой обозначена плацента плода после фетоцида

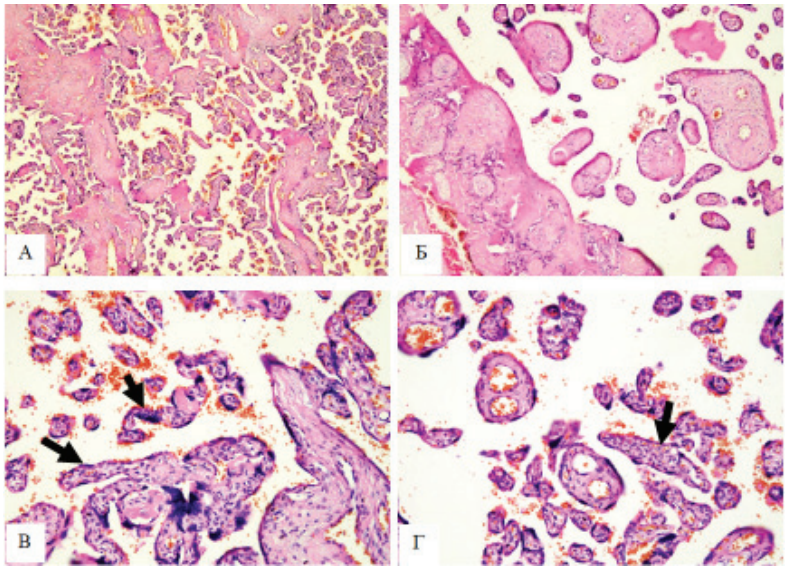

Рис. 4. Микропрепарат. Плацента живого плода. А — общий вид, преобладают стволовые ворсины, ×40; Б — базальная пластинка: фибриноид, эритроциты, ×100; В, Г — расширенное межворсинчатое пространство, ворсины удлиненной формы (стрелка) с небольшим количеством эритроцитов, увеличено количество синцитиальный почек, окраска гематоксилином и эозином, ×200

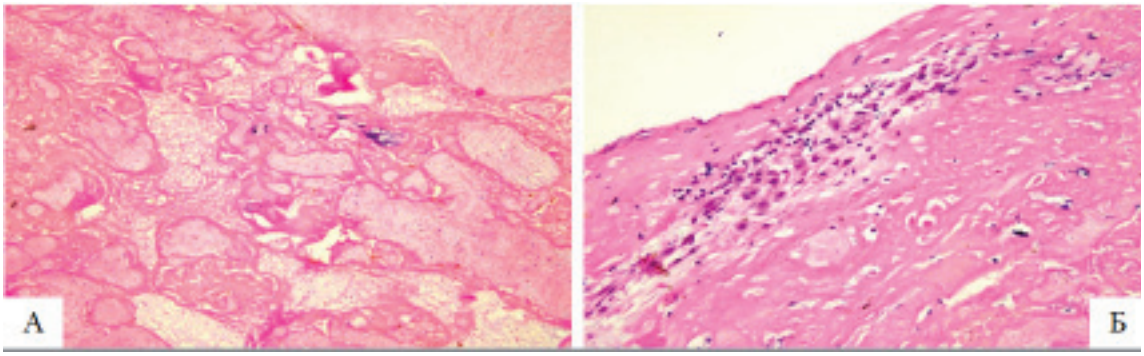

Рис. 5. Микропрепарат. Плацента плода после фетоцида. А — общий вид, ворсины-тени, фибриноид в межворсинчатом пространстве, отложения кальция, × 100; Б — базальная пластинка: лимфоцитарная инфильтрация, фибриноид, окраска гематоксилином и эозином, ×200

Таблица 1. Зависимость типа строения ЛЖ и сочетания пороков аортального и митрального клапанов

	АА	**АС**
МА	I	II
МС	II, III, IV, V	II, III, V

примечания: АА — аортальная атрезия, АС — аортальный стеноз, МА — митральная атрезия, МС — митральний стеноз

В нашем случае бихориальной биамниотической двойни после установления диагноза СЛГС у одного из плодов на 19 неделе был проведен селективный фетоцид плода с пороками. Мертвый мацерированный плод родился через 20 недель после его антенатальной гибели, поэтому выраженные аутолитические изменения не позволяли подтвердить диагноз порока сердца. Было решено провести измерения структур сердца ЛЖ на архивных видеоматериалах УЗ диагностики данного наблюдения с вычислением индексов, являющихся диагностическими для различных типов ЛЖ при СЛГС. На архивных видеоматериалах УЗ диагностики выявлена атрезия клапана аорты и дисплазия с гипоплазией митрального клапана. По данным литературы [1,8] при сочетании митрального стеноза и аортальной атрезии могут формироваться II, III, IV и V типы ЛЖ (таблица 1).

В правых отделах сердца атрезия клапана легочной артерии приводит к формированию изменений в правом желудочке (ПЖ), подобных изменениям в ЛЖ при атрезии аортального клапана, а при дополнительной дисплазии миокарда ПЖ (аномалия Уля) — к дилатации камер (предсердия и желудочка) [9]. В нашем случае обнаружен фиброэластоз эндокарда ЛЖ. При I и II типах строения фиброэластоз ЛЖ никогда не встречался, поэтому нам необходимо было дифференцировать между типами с фиброэластозом: III, IV или V (рис. 6).

Согласно литературным данным [1,8] IV (лакунарный) тип, характеризует небольшой размер ЛЖ с многочисленными лакунарными полостями, оконтурированными фиброэластозом, и тонкий слой компактного миокарда (рис. 6А), что и определялось на архивных видеоматериалах УЗ диагностики других случаев лакунарных типов ЛЖ (рис. 7).

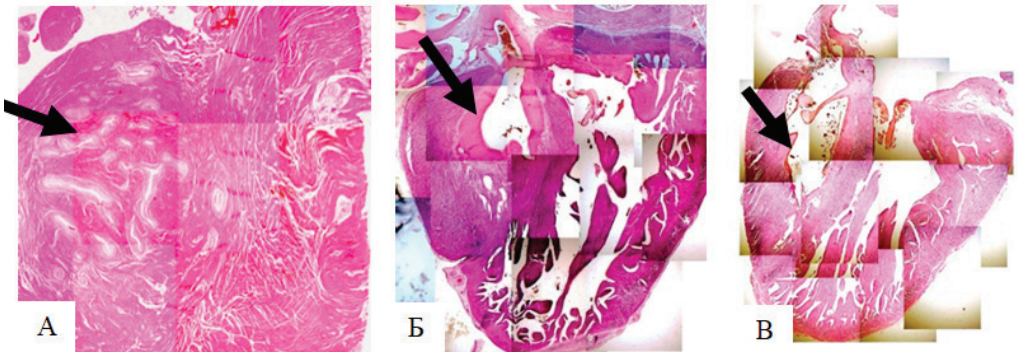

Рис. 6. Типы ЛЖ с фиброэластозом эндокарда при СЛГС: А — лакунарный (поперечный срез), Б — лакунарно-цилиндрический (продольный срез) В — цилиндрический (продольный срез). Стрелками обозначены ЛЖ. Компьютерная реконструкция. ГЭ

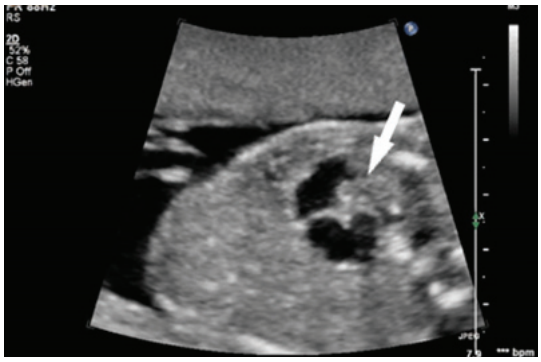

Рис 7. Лакунарный (IV) Тип ЛЖ (стрелка) при СЛГС

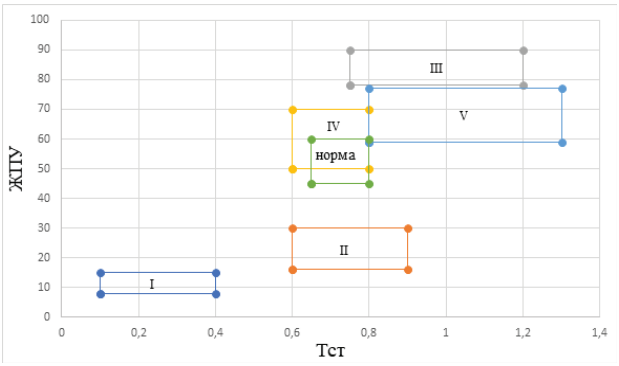

Рис. 8. Распределение ЛЖ по значениям толщины стенки и желудочково-перегородочного угла

В нашем случае была выявлена одна полость ЛЖ, поэтому необходимо было дифференцировать между III и V типами ЛЖ (рис. 6Б, 6В). Оба типа сопровождаются гипертрофией стенки ЛЖ, которая более выражена при V типе [3, 5, 7, 8]. III тип характеризовала большая Дп.

Однако, следует заметить, что наибольшую информативность для установления типа строения ЛЖ имеет показатель, выявляемый только на поперечных срезах сердца — желудочково-перегородочный угол (ЖПУ) (рис. 8) [4]. Из рис. 8 видно, что желудочки лакунарного и лакунарно-цилиндрического типов могут иметь значение толщины стенки и ЖПУ, которые находятся в пределах нормы, но наличие фиброэластоза и различия по другим морфометрическими показателями предоставляют возможность установить диагноз СЛГС. Желудочки I, II и III типов независимо от наличия (III) или отсутствия фиброэластоза (I и II) могут быть достоверно идентифицированы по данным показателям. Это важно учитывать при проведении УЗ исследования.

На продольных срезах можно было вычислить Тст, Шп, Дп. Вычисленные значения (ИТС = 0,66 ед; ИФПф = 0,49 ед; ПМИ = 0,75 ед) согласно схеме (рис. 9) [8] относились к III (цилиндрический) типу ЛЖ, который является неблагоприятным для любого вида хирургического вмешательства, поэтому тактика относительно селективного фетоцида была вполне оправданной.

Кроме того, считается, что на морфогенез СЛГС, а именно типов ЛЖ с фиброэластозом, влияет инфекционный фактор. В нашем случае порок развития сердца в комплексе с синдромом множественных птеригиумов возник лишь у одного из близнецов, что свидетельствует в пользу других генетических факторов [1].

Живой плод из этой двойни родился естественным путем на 40 неделе с высокими баллами по шкале APGAR, массой 3200 г. Но несмотря на это, исследования плаценты живого плода выявило нарушения ее созревания. На развитие данной патологии влияют инфекционные заболевания матери, сахарный диабет, ожирение. Нарушение процессов созревания ворсин хориона может проявится задержкой роста плода и риском самопроизвольных абортов [2]. Выявленные при микроскопии единичные терминальные ворсины, преобладание стволовых ворсин и ворсин удлиненной формы с расширением межворсинчатого пространства, позволило установить диагноз гипоплазии терминальных ворсин. Диагноз подтверждается и небольшой массой плаценты (330 г), которая обычно сопровождает данную патологию. Следует отметить, что в нашем случае изменения в плаценте были компенсированы, что гистологически проявлялось увеличением количества синцитиальных почек, а клинически — удовлетворительным состоянием новорожденного.

Изменения плаценты плода после селективного фетоцида возникли вторично, после гибели плода с СЛГС. Преобладание в гистологическом препарате плаценты ворсин-теней стволового и промежуточного типа не может свидетельствовать в пользу задержки развития плаценты к фетоциду, так как в сроке 19 недель преобладают ворсины эмбрионального типа. Такие изменения в плаценте как фибриноидная дезорганизация стромы ворсин с облитерацией просвета сосудов могут быть вызваны и другими состояниями, например, при патологии пуповины (обвитие, амниотические перетяжки). Этот факт важно учитывать, исследуя плаценты с первичной плацентарной недостаточностью.

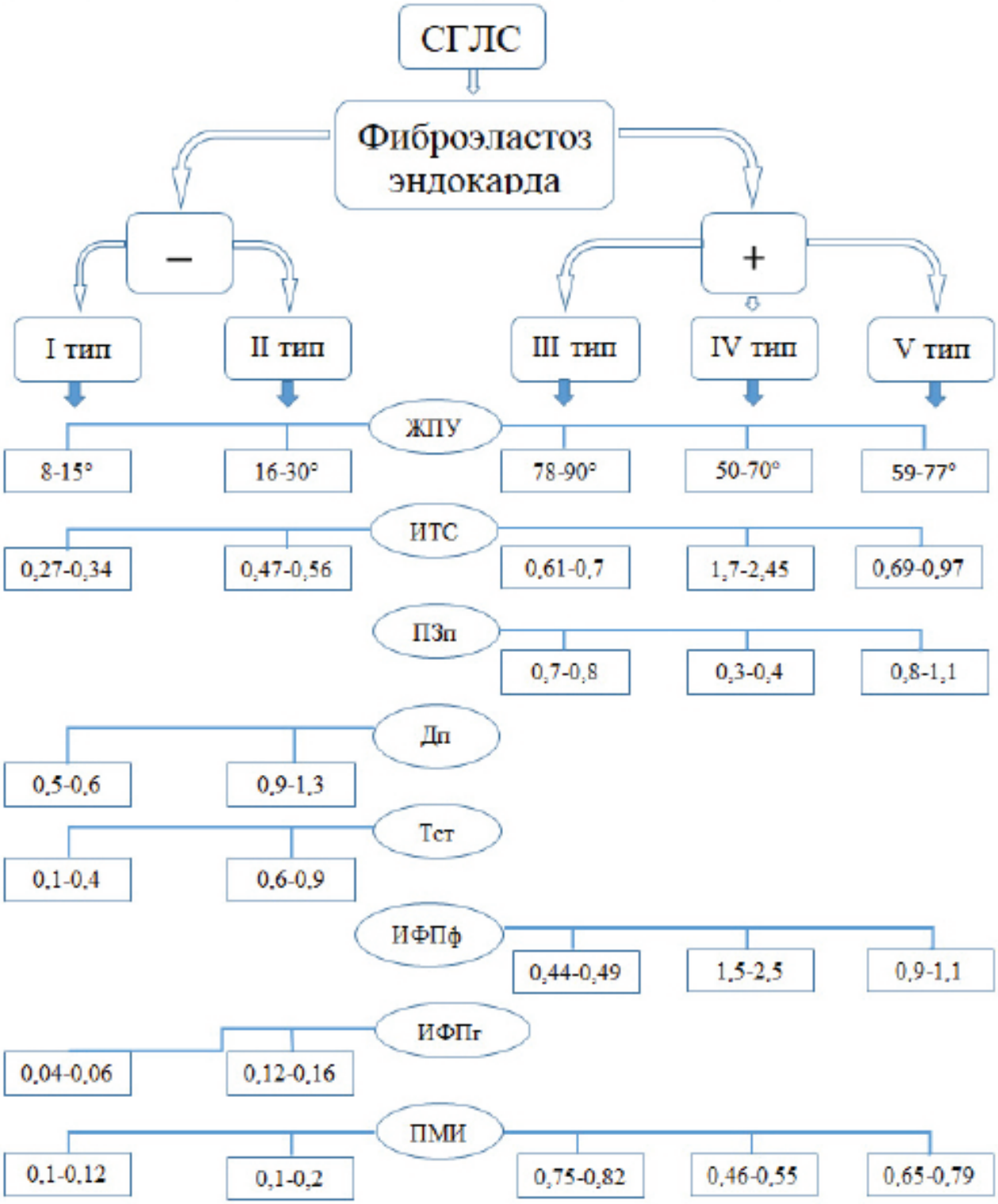

Рис. 9. Схема дифференциальной диагностики типов ЛЖ при СЛГС по морфометрическими показателям.
Дп и Тст — показатели, рассчитанные у новорожденных.
Примечания: ЖПУ — желудочково-перегородочный угол; ПЗп — передне-задний размер полости (см);
Дп — длина полости (см); Тст — толщина стенки (см); ИФПф — индекс формы полости во фронтальной плоскости (ед); ИФПг — индекс формы полости в горизонтальной плоскости (ед); ПМИ — полостно-миокардиальный индекс (ед)

Заключение. В описанном нами случае бихориальной биамниотической двойни после селективного фетоцида на 20 неделе одного плода из двойни с СЛГС имело место прогрессирование данной беременности с рождением живого плода, второго из двойни. Ретроспективно на архивных видеоматериалах ультразвуковой диагно-

стики был установлен цилиндрический тип строения ЛЖ при СЛГС у мертворожденного плода путем измерения структур сердца. Выявленное нами нарушение созревания плаценты (гипоплазия терминальных ворсин) живого плода подтверждает, что беременности, полученные с использованием ВРТ, являются группой повышенного риска нарушения развития как плода, так и плаценты, и требуют тщательного обследования во время всего периода беременности.

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SUMMARY

CLINICAL AND PATHOLOGICAL ANALYSIS OF THE HYPOPLASTIC LEFT HEART SYNDROME IN ONE OF THE TWINS IN PREGNANCY WHICH OCCURRED USING IN VITRO FERTILIZATION. OWN OBSERVATION

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The article represents clinical and pathoanatomical analysis of a case of full-term pregnancy with hypoplastic left heart syndrome (HLHS) in one of the twins, which occurred using in vitro fertilization (IVF). The dead macerated fetus with malformations after selective feticide at the 20th week of pregnancy and dichorial diamniotic placenta were studied. In connection with the expressive autolytic changes in the internal organs of the fetus, which do not allow to confirm the diagnosis of left ventricular hypoplasia at autopsy and establish its type of structure, additional measurements of the heart structures of the fetus with HLHS on archived video materials of ultrasound diagnostics were performed. After calculating the diagnostic indices: the index of myocardial layer thickness (ratio of the thicknesses of the trabecular and compact myocardium), the index of cavity shape of the heart in frontal axis (ratio of width to cavity length), cavity-myocardial index (ratio of wall thickness to cavity width), the cylindrical LV structure was retrospectively determined, which is prognostically unfavorable any kind of surgical correction, which justified selective feticide. The article presents the values of diagnostic indices for identifying the types of structure of hypoplastic LV. Prenatal determination of LV type determines treatment tactics: terminate pregnancy in case of adverse LV types, recommend Norwood procedure in the neonatal period with type I or perform fetal aortic valvuloplasty with type II of LV. The maturation disorders (distal villous hypoplasia) that we found in the placenta of a living fetus confirms that, despite the relatively satisfactory condition of the newborn, pregnancies that occur with the use of IVF are high risk group of developmental disability both the fetus and placenta.

Keywords: hypoplastic left heart syndrome, type of ventricle structure, distal villous hypoplasia of placenta, selective feticide.

РЕЗЮМЕ

КЛИНИКО-ПАТОЛОГОАНАТОМИЧЕСКИЙ АНАЛИЗ СЛУЧАЯ СИНДРОМА ЛЕВОСТОРОННЕЙ ГИПОПЛАЗИИ СЕРДЦА У ОДНОГО ИЗ БЛИЗНЕЦОВ ПРИ БЕРЕМЕННОСТИ, НАСТУПИВШЕЙ С ПРИМЕНЕНИЕМ ЭКСТРАКОРПОРАЛЬНОГО ОПЛОДОТВОРЕНИЯ. СОБСТВЕННОЕ НАБЛЮДЕНИЕ

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В статье представлен клинико-патологоанатомический анализ случая доношенной беременности с синдромом ле-

восторонней гипоплазии сердца (СЛГС) у одного из близнецов, наступившей с применением экстракорпорального оплодотворения (ЭКО). Исследованы мертвый плод с пороками развития после селективного фетоцида на 20 неделе беременности и бихориальная биамниотическая плацента. В связи с выраженными аутолитическими изменениями внутренних органов плода, не позволяющими подтвердить на вскрытии выявленный при ультразвуковом исследовании диагноз гипоплазии левого желудочка (ЛЖ) и установить тип его строения, проведены дополнительные измерения структур ЛЖ сердца плода с СЛГС на архивных видеоматериалах ультразвуковой диагностики. После вычисления диагностических индексов: толщины слоев (отношение толщин трабекулярного и компактного миокарда), формы полости (отношение ширины к длине полости) и полостно-миокардиального (отношение толщины стенки к ширине полости) ретроспективно определен цилиндрический тип строения ЛЖ, являющийся прогностически неблагоприятным для любого вида хирургической коррекции, что обосновывало селективный фетоцид. В статье приведены значения диагностических индексов для идентификации типов строения гипоплазированного ЛЖ. Пренатальное установление типа ЛЖ определяет лечебную тактику: прерывать беременность при неблагоприятных типах ЛЖ, рекомендовать операцию Норвуда в периоде новорожденности при I типе или проводить фетальную аортальную вальвулопластику при II типе ЛЖ. Обнаруженное нарушение созревания плаценты (гипоплазия терминальных ворсин) живого плода подтверждает, что несмотря на относительно удовлетворительное состояние второго доношенного плода, беременности, наступившие с использованием ЭКО, являются группой повышенного риска нарушения развития как плода, так и плаценты.

რეზიუმე

ექსტრაკორპორალური განაყოფიერების გზით დამდგარი ორსულობის დროს ტყუპებისაგან ერთ-ერთის გულის მარცხენამხრივი ჰიპოპლაზიის სინდრომის კლინიკურ-პათოლოგოანატომიური ანალიზი. საკუთარი დაკვირვება

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ა. ბოგომოლცის სახ. ეროვნული სამედიცინო უნივერსიტეტი, [1]პათოლოგიური ანატომიის კათედრა №2; [2]ფიზიოლოგიის კათედრა; [3]სახელმწიფო დაწესებულება "უკრაინის ჯანდაცვის სამინისტროს ბავშთა კარდიოლოგიისა და კარდიოქირურგიის სამეცნიერო-პრაქტიკული სამედიცინო ცენტრი", კიევი, უკრაინა

ნაშრომში წარმოადგენილია ექსტრაკორპორალური განაყოფიერების (ეკო) გზით დამდგარი სრულვადიანი ორსულობის დროს ტყუპებისაგან ერთ-ერთის გულის მარცხენამხრივი ჰიპოპლაზიის სინდრომის შემთხვევის კლინიკურ-პათოლოგოანატომიური ანალიზი. გამოკვლეულია ორსულობის მე-20 კვირაში ჩატარებული სელექციური ფეტოციდის შემდეგ წარმოშობილი განვითარების პათოლოგიის მქონე მკვდარი ნაყოფი და ბიხორული ბიამნიოტიკური პლაცენტა. ნაყოფის შინაგან ორგანოებში გამოხატული აუტოლიტური ცვლილებების შესწავლასთან დაკავშირებით, რაც გაკვეთის დროს არ იძლევა ულტრაბგერითი გამოკვლევისას აღმოჩენილი მარცხენა პარკუჭის ჰიპოპლაზიის დიაგნოზის დადასტურების და მისი სტრუქტურის ტიპის დადგენის საშუალებას, დამატებით იყო ჩატარებული ულტრაბგერითი დიაგნოსტიკის დაარქივებულ ვიდეო მასალებში არსებული ნაყოფის მარცხენამხრივი ჰიპოპლაზიის სინდრომის მქონე გულის მარცხენა პარკუჭის სტრუქტურების გაზომვები. სადიაგნოსტიკო ინდექსების გაანგარიშების შემდეგ: შრეების სისქე (ტრაბეკულური და კომპაქტური მიოკარდიუმის სისქეების თანაფარდობა), ღრუს ფორმის (ღრუს სიგანისა და სიგრძის თანაფარდობა), ღრუს -მიოკარდიუმის (კედლის სისქის და ღრუს სიგანის თანაფარდობა) რეტროსპექტულად განისაზღვრა მარცხენა პარკუჭის აგებულების ცილინდრული ტიპი, რაც პროგნოზულად არახელსაყრელია სელექციური ფეტოციდის გასამართლებელი ნებისმიერი სახის ქირურგიული კორექციისათვის. სტატიაში მოცემულია ჰიპოპლაზური მარცხენა პარკუჭის აგებულების ტიპების იდენტიფიკაციის სადიაგნოსტიკო ინდექსების მნიშვნელობები. მარცხენა პარკუჭის ტიპის პრენატალური დადგენა განსაზღვრავს მკურნალობის ტაქტიკას: ორსულობის შეწყვეტა მარცხენა პარკუჭის არახელსაყრელი ტიპების შემთხვევაში, ნორვუდის ოპერაციის ჩატარების რეკომენდაცია ახალშობილობის პერიოდში მარცხენა პარკუჭის I ტიპის შემთხვევაში ან ფეტალური აორტალური ვალვულოპლასტიკის ჩატარების რეკომენდაცია მარცხენა პარკუჭის II ტიპის შემთხვევაში. ავტორების მიერ აღმოჩენილი ცოცხალი ნაყოფის პლაცენტის მომწიფების (ტერმინალური ბუსუსების ჰიპოპლაზია) დარღვევა ადასტურებს, რომ, მიუხედავად მეორე სრულვადიანი ნაყოფის შედარებით დამაკმაყოფილებელი მდგომარეობისა, ეკო-ს გზით დამდგარი ორსულობა წარმოადგენს როგორც ნაყოფის, ასევე პლაცენტის დაქვეითებული განვითარების მაღალი რისკის ჯგუფს.

FEATURES OF AUTOAGGRESSIVE BEHAVIOR IN MENTAL DISORDERS: SELF- PERFORATION OF EYE IN PATIENTS WITH SCHIZOPHRENIA (CLINICAL CASE)

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Over the past half century, during which auto-aggressive behavior (self-harm, self-harm) has become one of the urgent problems of psychiatry, the specific forms of auto-aggressive activity, its manifestations and socio-psychological predictors, as well as clinical and psychopathological disorders combined with self-destructive behavior have substantially changed. Self-harming behavior is comorbid with respect to a wide range of other disorders [4], including: affective disorders [11], attention deficit hyperactivity disorder [9], post-traumatic stress disorder, eating disorders, autism spectrum disorders [13], borderline personality disorder, schizophrenia. The study of the features of auto aggressive behavior in the context of a psychotic episode deserves special attention, since auto aggressive behavior is one of the leading causes of death for the mentally ill - studying the predictors of its formation at an early stage of the disease will allow timely identification of persons at high risk of suicide, to carry out their treatment and prevention of auto aggressive manifestations [2,3,10].

Autoaggression as a form of self-harm has a variety of manifestations. The complexity of the phenomenon of autoaggression is due to its interdisciplinary nature. The problem of studying autoaggressive behavior is in the sphere of interests of such sciences as psychiatry, psychology, sociology, pedagogy, philosophy, law. Each of them uses the terminology and understanding of the essence of auto aggression in solving the stated problems [8].

An analysis of psychiatric literature indicates that there are a number of terms that reflect the process of self-harm: "self-destructive behavior", "auto-aggressive behavior", "suicidal behavior", "parasuicide", "suicidal and non-suicidal equivalents", "direct and indirect self-destruction", " self-destructive behavior "," self-mutilation "," avital activity "and many others that are used as synonyms, however, their semantic load is different. American "Diagnostic and Statistical Manual of Mental Disorders of the fifth review» (DSM-5) has placed "suicidal behavior" and "non-suicidal self-harm" in a new section of conditions requiring further research.

The relevance of the study of self-harming behavior is due to the need for a theoretical generalization of domestic and insufficiently represented in the scientific literature foreign studies on the problems of this phenomenon in normative and impaired mental development; insufficiency and fragmentation of empirical studies of risk factors; the need for scientific justification of assistance and prevention programs. The study of this problem is carried out in different directions: biological, clinical, psychological, social: experimental studies of psychophysiological and neurobiological correlates are carried out; the influence of adverse environmental conditions, deprivation, mental trauma on the formation of auto-aggressive behavior is investigated; body modifications are studied as its socially sanctioned forms. Broad structural and phenomenological variability makes the introduction of many researchers such clarifying concepts as parasuicide, suicidal fantasy, autoaggression, non-suicidal self-injurious behavior or phenomena of self-harm are considered narrow in nosologically homogeneous groups, such as, for example, the mentally ill patients. In the analysis of the group with a suicidal fantasizing it was revealed the predominance among them individuals with affective disorders (depression, BAR) - 60.0% and schizophrenia - 27.0% [6].

A. Favazza and R. Rosenthal (1993) identified three different types of self-harming behavior in patients with mental disorders: superficial or moderate self-harm is observed in people with personality disorders; stereotypical self-harming behavior is often observed in mentally retarded people, as well as in autists; serious injuries are most often associated with severe psychopathology (psychotic conditions, schizophrenia).

Modern authors interpret auto-aggressive behavior as actions aimed at causing any damage to their physical or mental health. Non-suicidal self-harm is a type of auto-aggression [7]. This is a complex concept that combines suicidal behavior, unconscious life-threatening actions, defamatory blackmailing attempts, as well as deliberate self-destructive acts. Non-suicidal self-harm is clinically psychopathologically very different from other types of auto-aggression, which makes it justified to study them as a separate phenomenon.

In terms of severity, all observed non-suicidal self-harm can be divided into three groups: mild, moderate and severe. According to the research, light self-injuries (not dangerous for life and do not cause severe damage to health) prevail in patients with personality disorders, and moderate self-harm (lead to moderate anatomical and physiological damage) in patients with schizophrenic spectrum diseases ($p < 0,001$) [7]. It is noted [7] that in patients with schizophrenic spectrum diseases, self-destruction is more sophisticated, artsy and more traumatic (exposure to the teeth with teeth, head blows to large stationary objects, etc.), as well as combined destruction (use simultaneously or sequentially for one self-destructive episode of several methods of self-harm). Patients with diseases of the schizophrenic spectrum cause excoriation both with the help of nails, and with the help of knives, forks, pencils, parts of fountain pens, fragments of plastic dishes. Exclusively in this group of patients, bites of the hands and forearms, tears of the skin of the genitals, auricles, interdigital spaces were noted, as well as extensive injuries of moderate severity through the teeth and nail [7].

Self-harm in schizophrenia is the most severe form of self-injuries behavior. Accurate numbers of the prevalence of self-harm associated with schizophrenia throughout life are difficult to establish, because much of the evidence is based on studies of completed suicides. However, one study of a group of young people aged 14-17 suffering from schizophrenia revealed that the overall prevalence of self-harm was 48%.

Patients who have a history of self-harm have significantly more pronounced symptoms of depression, suicidal thoughts, an increase in the number of hospitalizations and a longer duration of the disease compared to patients without a history of self-harm. The development of self-damaging behavior in schizophrenia is characterized by serious bodily harm, up to the self-removal of a part of the body. Research data allow us to conclude that self-harm is carried out by patients within the framework of the symptoms of the schizophrenic process, ac-

companied by the corresponding judgments or the content of hallucinations [4]. It is known that patients with schizophrenia are trying to harm themselves due to peremptory hallucinations, catatonic agitation, or because of comorbid depression. In one study indicates self-castration of male genitals young man with schizophrenia, which confirms the fact that in schizophrenia marked the highest severity of self-injuries. In this regard, K. Meninger (1938) raised the question, what is considered insanity: an unreasonably large sacrifice or the absurdity of the act itself? In relation to patients suffering from schizophrenia and having committed self-castration, the author indicates that, despite their quiet and correct behavior at first (as in the described clinical case), over time, their subconscious aggressiveness progresses, and, in the end extrapolated to self. In patients of this category, which undoubtedly confirms the clinical illustration, the sexual component often remains completely unrealized, this kind of "inferiority" is probably felt by them and concentrates their auto aggression on the genitals, and not on any other part of the body. Due to the fact that sexuality is always associated with genitals, and mentally ill people are not able to hide their motives, they get rid of the "guilty" organ in the most direct way, becoming a victim of a conflict of instinct with its suppression. Particularly noteworthy here is the fact that a mentally ill man, saving himself from his own genitals, turns into a person without primary sexual characteristics, kills his "self" in order to preserve himself as a biological object.

The clinical features of patients with schizophrenia who are self-harming compared to patients who are not self-harming include: self-harm in the past before the manifestation of schizophrenia, experienced depression, substance abuse and past psychiatric hospital admissions. These symptoms are mainly associated with the fact that before the onset of schizophrenia, a person already had impaired functioning, such as dependence on a psychoactive substance and depression. A study by S. Harvey (2008) indicates that men with schizophrenia are more prone to developing self-destructive behavior.

Specific mental disorders and the motivation for self-harming actions with them are described in a number of publications, including observations and their analysis in the framework of various diseases [1]: in personality disorders, non-suicidal self-harm can be inflicted from blackmail-demonstrative (pseudo-suicidal behavior in hysterical individuals), as well as masochistic (epileptoid psychopaths) considerations; with depersonalization syndrome, self-destructive attempts can be made to "feel yourself again"; in adolescents, especially women, self-harm, comorbid hyperactivity disorder and attention deficit disorder with affective disorders and dependence on psychoactive substances are described [9]; elf-harm is often found in delusional disorders: dermatozoic delirium (patients try to extract a non-existent parasite from under the skin) [1], a delirium of self-accusation (by self-destruction, patients punish themselves - cause cuts, hit themselves on the head, etc.). Self-mutilating behavior is also possible with imperative "voices", for example, autocastration, autoenucleation, penile removal [1]. Establishing the motivation for self-harm presents certain difficulties in connection with their unpredictability and impulsivity, especially in patients with schizophrenia. In addition, patients usually hide their intentions from others, which also creates difficulties to prevent such actions [1].

The insufficient attention of psychiatrists to the problem of self-harm in mentally ill patients is apparently due to the fact that such patients do not always end up in a psychiatric hospital after being assisted by internists, so far there is no comprehensive description of the phenomenology of self-harm, their options have not been highlighted, the analysis of the motivation and comorbidity of self-destructive acts was carried out, risk factors and measures to prevent repeated self-injuring actions were not identified.

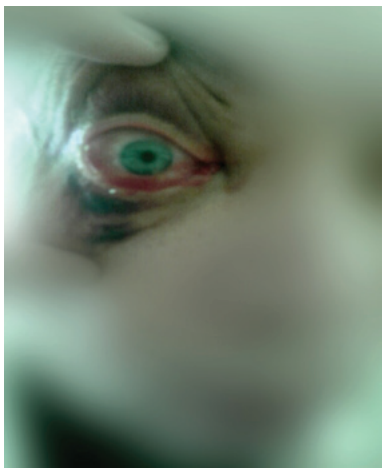
The purpose of the study was to inform clinicians, including ophthalmologists and psychiatrists, about the self-perforation of the eye in patients with mental disorders based on a clinical case.

Material and methods. As an illustration, we present a clinical observation of a young patient with schizophrenia with penetrating damage to the right eye. In research were used an overview, biomicroscopy of the ocular surface, ophthalmoscopy examination, ocular X-ray examination, MRI, general-clinical studies, consultation with psychiatrist and anesthesiologist and content analysis of professional literature on the problem.

Results and discussion. A detailed clinical and psychopathological analysis of the medical history and mental state made it possible to diagnose auditory hallucinations in the context of schizophrenia as the cause of self-destructive behavior. The motivation for the crippling action was the execution of peremptory hallucinatory orders to "tear out the eye," as a result of which the patient suffered pain, bleeding, without going to a doctor.

Clinical case. A patient – 47 years old man came with his mother in Ophthalmology department, the patient was catatonic and no cooperative, so no history could be obtained. Mother of the patient has noticed bloody discharge on pillow and in lower eyelid of the right eye.

External examination O.D: no changes in the eyelid, in the conjunctiva of the lower arch in the internal third there was noticed a limited hemorrhage, trauma of conjunctiva, the mobility of the eyeballs was not disturbed, the bottom part of the face was unchanged (Pic. 1).



Pic. 1. External examination O.D

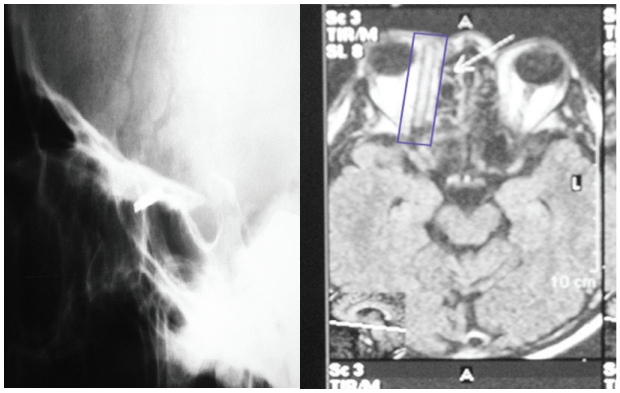
Antibacterial and anti-inflammatory drops were prescribed (Signicef, Clodifen).

On second day O.D: hematoma of the eyelid, chemosis of the conjunctiva, limitation of the eyeball movements, lack of the of the pupil reaction to the light, pallor optic disc, blindness.

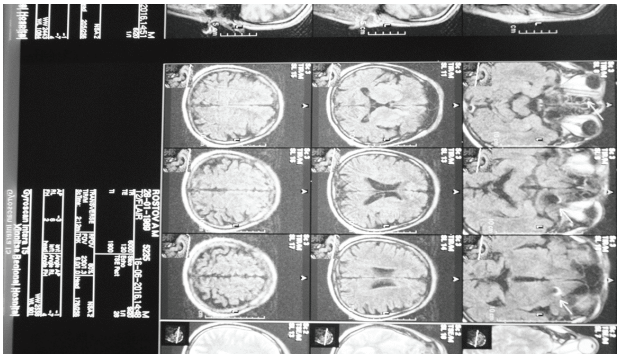
Under the skin in the projection of superior medial of orbit was palpated a foreign body with diameter 5mm.

O.S: hematoma of lower and upper eyelids and blindness.

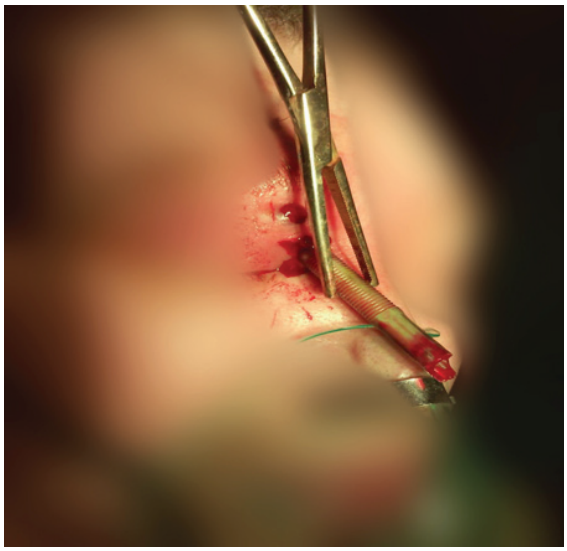
X-RAY examination of the orbit (Pic. 2, 3): was noticed a foreign body measuring 4 by 2 mm which was localized in projection of the left orbit.



Pic. 2, 3. X-RAY examination of the orbit



Pic. 4. Results of the MRI research



Pic. 5, 6. Half of the plastic pen which was removed from the right orbit during the surgery

MRI (Pic. 4): was noticed the shadow of foreign body on the right orbit 4.5 by 0.5 mm which was localized near the inner wall of the orbit and reached its top, as a result damage 2/3rd of the right optic nerve. To the left of the orbit was determined the shadow of foreign body that intersects with the optic nerve.

During the surgery half of the plastic pen was removed from the right orbit (Pic. 5, 6). On the left orbit was present the end of the pen ball (the other half of the pen) but was decided not to remove it.

Total damage of the optic nerve of the right eye and damage of the rods on the left eye.

The psychiatrist found out that the patient had auditory hallucinations which ordered him to scratch his eyes, which he did by the pen.

The case presented by us indicates that self-harming behavior is a common phenomenon, and indicates the presence of experiences and / or mental disorders that can lead to suicide. This behavior requires further study, research, as well as the creation of diagnostic techniques and methods of correctional work.

Authors, which despite the existence of many definitions of auto-aggressive actions, agree that they have their own dynamics and, at times, combine [6]. At one time, the relationship between self-harming and suicidal behavior was tragically demonstrated by Vincent van Gogh, who cut off his earlobe in 1888 two years before a shot in the heart [6]. Due to the fact that self-harm in history and suicide are often combined, most modern authors pay attention to factors that contribute to the transformation of auto-aggressive behavior [5,12,14].

Conclusions. Patients with mental disorders are able to self-attack and resulting in loss of the vision. In the absence of the contact the collection of anamnesis and diagnosis the problem it is complicated. In patients suspected of injuries it is recommended to be used all the methods of examinations so not to lose time.

It can be assumed that self-damaging behavior is a wide continuum of behavioral strategies that in some cases contribute to a kind of maturation of emotional-regulatory mechanisms, allowing a dangerous period of exacerbation of the disease to pass without significant losses, and in some patients, they are fixed as the main form of avoiding difficulties, later transforming into various forms of self-destructive behavior with the addition of various addictions and/or suicidal tendencies.

From our point of view, dynamic observation of a patient from the moment the first signs of self-injurious behavior are manifested makes it possible to differentially use various therapeutic strategies related both to pharmacotherapy aimed at eliminating symptoms of mental disorder and to choosing a psychotherapeutic focus on work aimed at normalizing interpersonal relationships that is problem-solving behaviors and characteristics of emotional regulation.

Thus, our observation demonstrates the importance of the correct nosologically qualification of such mental disorders, as well as determining the motivation for self-harming actions to provide adequate and effective care to patients.

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SUMMARY

FEATURES OF AUTOAGGRESSIVE BEHAVIOR IN MENTAL DISORDERS: SELF- PERFORATION OF EYE IN PATIENTS WITH SCHIZOPHRENIA (CLINICAL CASE)

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Autoaggression as a form of self-harm has many manifestations. Self-harming behavior accompanies a wide range of mental disorders, including schizophrenia.

The aim of our study is to inform clinicians, including ophthalmologists and psychiatrists, about their own perforation of the eye in patients with mental disorders based on a clinical case. We present a clinical observation of a young patient with schizophrenia with penetrating damage to the right eye. The studies used specific methods of clinical ophthalmic surgery, consultations with a psychiatrist and a content analysis of professional literature on this issue. The case presented by us indicates that self-harming behavior is a frequent occurrence and indicates the presence of experiences and/or mental disorders that may lead to suicide in the future. Such behavior requires further study, research, as well as the creation of diagnostic techniques and methods of correctional work.

Keywords: non-suicidal self-harm; autoaggression; autodegradation; self-mutilation; mental disorders; schizophrenia.

РЕЗЮМЕ

ОСОБЕННОСТИ АУТОАГРЕССИВНОГО ПОВЕДЕНИЯ ПРИ ПСИХИЧЕСКИХ РАССТРОЙСТВАХ: САМОПОВРЕЖДЕНИЕ ГЛАЗА ПАЦИЕНТОМ С ШИЗОФРЕНИЕЙ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Аутоагрессия как форма самоповреждения имеет множество проявлений. Самоповреждение сопутствует широкому кругу психических расстройств, включая шизофрению.

Целью исследования явилось описание клинического случая повреждения глаза пациентом с психическим расстройством, в частности, шизофренией.

Описано клиническое наблюдение молодого пациента с шизофренией с проникающим повреждением правого глаза.

В исследованиях использованы конкретные методы клинической офтальмологической хирургии, консультации с психиатром и контент-анализ профессиональной литературы по данной проблеме. Представленный случай указывает, что поведение, наносящее себе вред, встречается часто и указывает на наличие переживаний и/или психических расстройств, которые могут привести в дальнейшем к самоубийству. Динамическое наблюдение за пациентом с момента появления первых признаков самоповреждающего поведения позволяет дифференцированно использовать различные терапевтические стратегии, связанные как с фармакотерапией, направленной на устранение симптомов психического расстройства, так и с выбором психотерапевтического направления. Поведение самоповреждения требует дальнейшего изучения, исследования, а также создания диагностических приемов и методов коррекционной работы.

რეზიუმე

აუტოაგრესიული ქცევის თავისებურებანი ფსიქიკური დარღვევების დროს:
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“ვინიცას ნ.პიროგოვის სახელობის საოლქო კლინიკური საავადმყოფო”

კვლევის მიზანს წარმოადგენდა თვალის თვითდაზიანების კლინიკური შემთხვევის აღწერა ფსიქიკური დარღვევის მქონე პაციენტის მიერ.

აღწერილია კლინიკური დაკვირვება შიზოფრენიის მქონე ახალგაზრდა პაციენტზე მარჯვენა თვალის გამჭოლი დაზიანებით. გამოყენებულია კლინიკური ქირურგიული ოფთალმოლოგიის კონკრეტული მეთოდები, კონსულტაციები ფსიქიატრთან და პროფესიული ლიტერატურის კონტენტ-ანალიზი ამ პრობლემასთან დაკავშირებით. წარმოდგენილი შემთხვევა მიუთითებს, რომ თვითდაზიანებითი ქცევა ხშირია და აჩვენებს განცდების და/ან ფსიქიკური დარღვევების არსებობაზე, რაც, შესაძლოა, მომავალში სუიციდამდე მივიდეს. თვითდაზიანებითი ქცევის პირველი ნიშნების გაჩენისთანავე პაციენტზე დინამიკაში დაკვირვება იძლევა სხვადასხვა თერაპიული სტრატეგიის დიფერენცირებულად გამოყენების საშუალებას – როგორც ფსიქიკური დარღვევების ალაგებაზე მიმართული ფარმაკოთერაპიული საშუალებების, ასევე, ფსიქოთერაპიული მიმართულების შერჩევის მხრივ. თვითდაზიანებითი ქცევა მოითხოვს შემდგომ კვლევას და ასევე, კორექციული მუშაობის სადიაგნოსტიკო საშუალებებისა და მეთოდების შექმნას.

ИЗУЧЕНИЕ ПРОТИВОВИРУСНОГО И ИММУНОКОРРИГИРУЮЩЕГО ДЕЙСТВИЯ ЛАЗОЛЕКСА У ПАЦИЕНТОВ С РЕЦИДИВИРУЮЩИМ ГЕРПЕТИЧЕСКИМ СТОМАТИТОМ

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Заболевания, вызванные вирусом простого герпеса (ВПГ), занимают заметное место в вирусной патологии слизистых оболочек человека, в частности – ротовой полости. В развитии хронического рецидивирущего герпетического стоматита основная роль принадлежит ВПГ-I типа, единственным резервуаром которого являются инфицированные люди (в последние годы в качестве этиологического фактора зафиксирован генитальныйааа герпес, т.е. ВПГ-II типа). Попав в организм, вирус сохраняется в нем на протяжении всей жизни, периодически вызывая болезни различной тяжести [16,19,21]. Рецидивы заболевания наступают в результате периодически возникающего иммунодефицита у практически здоровых лиц под влиянием провоцирующих факторов [15].

Для хронического герпетического стоматита характерными являются частые рецидивы повреждений на слизистой поверхности, губах и коже, сопровождающиеся нарушением целостности эпителия, местной воспалительной реакцией и выраженным болевым симптомом. В этом плане, достаточно значимым считается мониторинг местной и системной терапии указанного заболевания [10,11,18]. Среди имеющихся средств лечения, большинство не удовлетворяет основным требованиям лечения: быстрая, безболезненная и эффективная эпителизация слизистой оболочки ротовой полости, красной каемки губ и прилегающих участков кожи.

В последние годы в практике лечения герпеса, наряду с антивирусной терапией (из группы зовиракса), все активнее используются иммунокорригирующие средства как при обострении, так и при ремиссии [5,12-14]. Означенный момент должен особо учитываться, поскольку в период ремиссии, из-за нейрогумарольного барьера и инкорпорации в геном нейроцитов, вирус становится недоступным для зовиракса [20].

В настоящее время в нашей стране продолжаются интенсивные исследования по изысканию и внедрению в практику новых натуральных лечебных препаратов, приготовленных из экологически чистых эндемических растений Грузии по рецептам народной медицины с использованием новейших подходов биотехнологии. Примером подобных исследований в компании Иверия-фарма является отечественный лекарственный препарат лазолекс (экстракт перикарпиума незрелого грецкого ореха), который прошел необходимые доклинические испытания и успешно применяется в клинике в качестве противовирусного средства [4,9]. Впервые его клинические эффекты изучены у пациентов с герпетическими повреждениями слезистой полости рта [1,2].

В испытаниях in vitro в клеточных культурах, а также на лабораторных животных, экстракт для производства лазолекса проявил защитные свойства против вируса простого герпеса. Кроме того, в тех же условиях эксперимента, а также на здоровых добровольцах обнаружены положительные иммунотропные эффекты лазолекса [4]. Поэтому, целью данного исследования явилось изучение особенностей противовирусного эффекта препарата и его иммуномодулирующих свойств в клинических условиях, конкретно – при хроническом герпетическом стоматите.

Материал и методы. Хорошо известен факт о серьезном дисбалансе иммунных параметров при различных воспалительных заболеваниях ротовой полости. Для оценки иммуного статуса организма нами использовались следующие адекватно реагирующие показатели: система Т- и В-лимфоцитов, фагоцитоз, интерферон в крови, в слюне секреторные иммуноглобулины А и лизоцим (всего, около 15 параметров). Поскольку, некоторые из их отличались монотонностью, т.е. их колебания находились в узком диапазоне и были сравнительно менее информативными, в нашем обсуждении мы остановились на 6 параметрах, которые были максимально динамичными, информативными и достоверными. Прежде всего, это – система интерферона (ИФНа и ИФНg), 8=45:A 8<<C=>@53C;OF88, D03>F8B0@=K9 8=45:A, 0 B0:65 <5AB=K5 D0:B>@K 70I8BK sIgA и лизоцим в слюне [7,8].

Иммунный статус по указанным 6 параметрам изучен у 54 пациентов с хроническим рецидивирущим герпетическим стоматитом. Пациенты распределены на две группы: 1) условно названная, «традиционное лечение», где дополнительно назначалась 5%-ная мазь зовиракса (контроль, 27 пациентов); 2) вместо зовиракса использовали 5%-ный гель лазолекса (27 пациентов, основная группа). Аппликации мази производились на поврежденные участки губ и слизистой ротовой полости, ежедневно в течение 10 дней. В зависимости от тяжести процесса, каждая группа была разделена на 3 подгруппы – легкая форма (А), средней тяжести (В) и тяжелая форма (С). Состояние иммунного гомеостаза пациентов оценивали в динамике, т.е. при первом обращении в клинику, а также на 10-13 день лечения. В таблице 1 (первое посещение) объединены данные всех 54 пациентов с учетом тяжести герпетического стоматита. В таблице 2 – по-отдельности и в комплексе оценены иммунологические аспекты двух лечебных подходов (зовиракс и/или лазолекс), в зависимости от тяжести герпеса и результатов лечения, а также сделан обобщающий анализ полученных данных.

Обработка результатов проводилась методом вариационной статистики, с вычислением t-критерия значимости различия Стьюдента.

Результаты и обсуждение. Обследование пациентов с хроническим герпетическим стоматитом выявило заметные изменения в системе иммунитета, причем в сторону угнетения, затрагивающие все его факторы, которые во-многом зависели от тяжести процесса, т.е. наиболее сильная иммунодепрессия зафиксирована у больных тяжелой формой стоматита.

Из таблицы явствует, что легкий пародонтит протекал на фоне компенсаторной реакции организма за счет гуморального звена. Значимым является достоверное усиление переваривающей способности лейкоцитов крови (4,7) и повышение в слюне концентрации секреторного IgA (0,37г/л) и лизоцима (40,6%), важнейших факторов местной защиты ротовой полости. Особенно чувствительной оказалась система интерферона (снижение, а-ИФ до 28,0ед/мл, g-ИФ до 17,4ед/мл). Однако, при ухудшении клинического состояния пациентов происходило истощение компенсаторных возможностей и каскадное угнетение почти всех изучаемых факторов.

При средней тяжести хронического пародонтита почти все параметры претерпевают дальнейшее угнетение: фагоцитарный индекс – 3,8; аИФН – 26,8 ед/мл; gИФН – 13,4 ед/мл. Следует особо подчеркнуть, что при этой форме стоматита достоверно снизилось в слюне содержание лизоцима – 34,4%, и чуть ниже нормы – количество SIgA (0,26г/л). Иными словами, при средней степени нельзя судить о компенсаторных механизмах со стороны иммунной системы, что характерно для стоматита легкой степени.

Серьезное иммунодефицитное состояние формируется при тяжелой степени: все изучаемые параметры оказались заметно ниже нормы. Таким образом, эти исследования, которые носили как-бы предварительный характер, указывают на серьезное иммуно-патологическое состояние организма, которое сопровождает средние и тяжелые формы герпетического стоматита.

Таблица 1. Иммунологические показатели у пациентов с хроническим рецидивирущим герпетическим стоматитом (поступление в клинику)

Показатели	Тяжесть герпетического стоматита (А – легкая; В – средняя; С – тяжелая)				Контроль (n=30)
	Пациенты (n=54)	A (n=21)	B (n=22)	C (n=11)	
aIFN (U/мл)	*25.1	*28.0	*26.8	*20.3	41.3
gIFN (U/мл)	*13.2	*17.4	*13.4	*8.7	28.6
Ii	*1.72	2.05	*1.76	*1.36	2.28
PhI	*3.9	4.7	*3.8	*3.1	4.9
sIgA (г/л)	0.26	*0.37	0.26	*0.12	0.28
Lyz (%)	*33.5	40.6	34.4	*25.7	41.9

Примечание: знаком (*) показана достоверная разница с контролем

Таблица 2. Иммунологические показатели у больных герпетическим стоматитом в зависимости от тяжести заболевания и результатов лечения (10-13 сутки после лечения)

Форма	А. Легкая			**В.** Средняя			**С. Тяжелая**			До лечения	Конт- роль
	Традиционное лечение + зовиракс (мазь, ежедневно, 10 дней)										
Эффективность	A[I] n=5	[II] n=6	[III] 0	[I] 0	[II] n=9	[III] n=2	[I] 0	[II] 0	[III] n=5	**n=27**	**n=30**
aIFN	35.0	*30.1	–	–	*25.5	*16.0	–	–	*12.0	*24.6	**41.3**
gIFN	20.4	*18.8	–	–	*15.3	*12.0	–	–	*8.0	*13.5	**28.6**
Ii	2.25	2.09	–	–	*1.65	*1.50	–	–	*1.30	*1.67	**2.28**
PhI	4.8	4.5	–	–	*4.3	*4.1	–	–	*3.8	*3.9	**4.9**
sIgA	*0.40	0.31	–	–	0.27	0.20	–	–	*0.14	0.28	**0.28**
Lyz	39.8	36.3	–	–	*34.4	*33.2	–	–	*27.7	*33.3	**41.9**
	Традиционное лечение + лазолекс (гель, ежедневно, 10 дней)										
Эффект	A[I] n=10	[II] 0	[III] 0	[I] n=9	[II] n=2	[III] 0	[I] 0	[II] n=4	[III] n=2	**n=27**	**n=30**
aIFN	37.0	–	–	*31.5	*27.4	–	–	*16.0	*16.0	*25.5	**41.3**
gIFN	24.5	–	–	*19.9	*17.6	–	–	*9.6	*10.0	*12.8	**28.6**
Ii	2.31	–	–	*1.95	*1.70	–	–	*1.24	*1.06	*1.77	**2.28**
PhI	5.2	–	–	*4.8	*4.4	–	–	*4.4	*3.9	*3.9	**4.9**
sIgA	*0.42	–	–	*0.37	0.31	–	–	*0.17	*0.10	0.26	**0.28**
Lyz	43.3	–	–	38.7	36.0	–	–	*27.7	*23.6	*33.8	**41.9**

Примечание: в графе «эффективность», в квадратных скобках отмечены критерии лечения и количество пациентов в подгруппе; знаком (*) показана достоверная разница с контролем

Поэтому, полученный факт явился достаточным обоснованием для использования в качестве адъювантной терапии иммуномодулирующих средств, в конкретном случае – лазолекса. Сразу же отметим, что этот препарат существенно повышает эффективность традиционного лечения, а с иммунологических позиций можем обоснованно утверждать, что он способствует иммунореабилитации больных (таблица 2, иммунограмма).

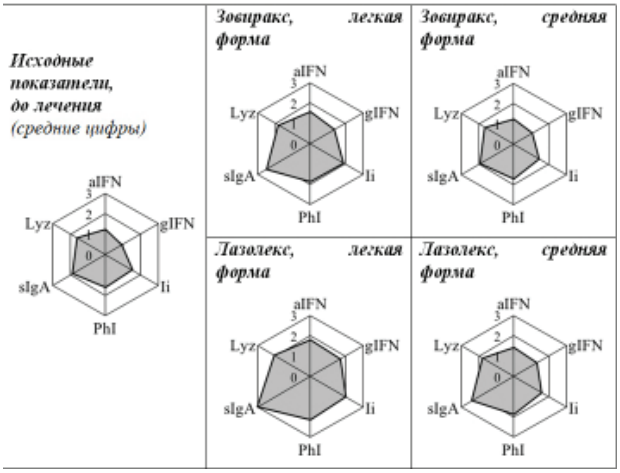
Клиническую эффективность оценивали по следующим критериям: 1) значительное улучшение: уменьшалась продолжительность обострения, в 2 раза и больше повышались сроки ремиссии); 2) улучшение: продолжительность ремиссии повышалась не менее чем в 1,5 раза; 3) отсутствие эффекта: местные и общие явления не менялись. В первых двух случаях результаты лечения считались успешными.

Результаты исследования 27 пациентов показали, что применение лазолекса сопровождалось значительным улучшением у 19 (70,3%) больных легкой и средней формой, улучшением – у 6 (22,2%) больных средней и тяжелой формы, без эффекта – у 2 (7,5%) пациентов с тяжелой формой. Аналогичные исследования, с применением зовиракса (n=27) зафиксировали следующие результаты: у 5 (18,4%) пациентов с легкой формой герпеса – значительное улучшение; у 15 (55,4%) пациентов с легкой и средней формой – улучшение, у 7 (26,2%) пациентов со средней и тяжелой формой – без эффекта.

При проведении сравнительных параллелей между этими статистическими данными, критериями клинической эффективности препаратов и показателями иммунного статуса указанных пациентов выявлена дополнительная интересная информация об участии иммунных факторов в этиологии, патогенезе и исходе герпетической инфекции ротовой полости (таблица 2).

Представленные в таблице 2 результаты полностью подтвердили отмеченную выше корреляцию между клинической тяжестью герпеса и показателями иммунокомпетентности организма больных. Подобная зависимость сохранялась на протяжении обострения заболевания и в процессе выздоровления (а также в период ремиссии и повторного обострения – собственные данные). У 19 пациентов из подгруппы I (критерий – «значительное улучшение»), терапия лазолексом характеризовалась быстрой нормализацией иммунологических параметров, особенно при легкой форме герпеса, и менее интенсивно – при средней форме, Следует отметить, что результаты лечения 11 больных зовираксом также оказались «значительно лучше» только у 5 больных. Как следует из таблицы, при средней и, особенно, тяжелой формах стоматита состояние иммунного статуса пациентов достоверно «отставало» от нормального уровня. Заслуживает внимания факт сравнительно лучших результатов (тяжесть болезни, критерий выздоровления и иммунная активности) среди пациентов, получавших лазолекс.

Для лучшего восприятия этих данных, мы воспользовались иммунограммами, в которых контрольная информация представлена в виде правильного 6-угольника. Заштрихованный (неправильный) многоугольник отражает динамику иммунологических показателей из различных групп (например, разная тяжесть заболевания, результаты лечения, различные другие факторы и единицы измерения).



Иммунограмма статуса пациентов с герпетическим стоматитом после лечения зовираксом и лазолексом (сравнение с контролем – линия 2)

Таким образом, определение состояния разных звеньев иммунитета у пациентов с хроническим рецидивирущим герпетическим стоматитом имеет важное практическое значение, поскольку позволяет прогнозировать течение и исход вирусной (герпетической) инфекции ротовой полости. Известно, что своевременная и патогенетически обоснованная терапия позволяет добиться практически полной компенсации нарушений гомеостатических механизмов [5,12,14]. При нерациональном лечении пациентов, показатели иммунокомпетентности организма длительное время могут оставаться измененными, что увеличивает вероятность торпидного течения заболевания и возникновения осложнений в результате активации других патогенных факторов. Поэтому, наряду со специфическим лечением (зовиракс или лазолекс), решающее значение приобретает комплексная терапия, включающая средства, направленные на восстановление иммунного гомеостаза (лазолекс).

Конкретно говоря о лазолексе, впервые использованном при герпетическом стоматите в качестве адъювантного средства, можно судить о двойном действии препарата: он существенно повышает эффективность прямого противовирусного лечения, а с иммунологических позиций – способствует иммунореабилитации больных. Такое мнение основывается на факте четкой корреляции между клиническим состоянием больных, накоплением вируса в крови и динамикой иммунологических показателей [3,6,17]. Особенно эффективно препарат проявляет свои иммуномодулирующие свойства при легкой форме заболевания, когда почти все параметры приближаются к контрольному уровню (особенно при успешных результатах лечения больных). Достаточно надежным является действие лазолекса при средней форме стоматита.

Таким образом, проведенное исследование убедительно показало, что лазолекс может с успехом использоваться для избирательной нейтрализации иммуносупрессивного воздействия вируса герпеса. Рассуждая о различных механизмах указанных способностей препарата, наиболее приемлемыми представляются следующие: при герпесе в организме формируется гормональный дисбаланс, развивается общая и клеточная гипоксия, деструктивные процессы приводят к интоксикации. Все эти явления протекают либо на фоне уже существующей иммунопатологии, либо ведут к ней, т.е. при герпесе, как минимум присутствуют все четыре указанных фактора – гормональный дисбаланс, гипоксия, интоксикация, иммунопатология, со взаимо-усиливающим эффектами. Эти эффекты, на наш взгляд, реализуются за счет физиологически активных веществ, содержащихся в экстракте (антибиотик Юглон и флавоноиды; микроэлементы; комплекс витаминов С, Е, РР), которые способствуют усилению функциональной активности иммунокомпетентных клеток [9].

Испытанный нами растительный экстракт Юглон, для производства препарата лазолекс можно отнести к активным натуральным средствам, которые можно использовать для профилактики и лечения вирусных и бактериальных инфекций, гнойно-воспалительных заболеваний, а также других патологических состояний, требующих улучшения обменных и адаптационных процессов. Таким образом, проведенные клинико-лабораторные и иммунологические исследования позволяют рекомендовать лазолекс к активному использованию для патогенетического лечения больных хроническим рецидивирущим герпетическим стоматитом.

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SUMMARY

STUDY OF ANTIVIRAL AND IMMUNECORRECTIVE EFFECTS OF LAZOLEX IN PATIENTS WITH RECURRENT HERPETIC STOMATITIS

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At present, our country continues intensive research to find and introduce into practice new natural medicinal preparations made from ecologically clean endemic plants of Georgia. An example of such studies in the Iveria-Pharma company is the domestic drug Lazolex (extract of the pericarpium of an unripe walnut), which has passed the necessary preclinical tests and began to be used in the clinic as an antiherpetic agent. On healthy volunteers, we found positive immunotropic effects of Lazolex. Therefore, we considered it necessary to study the antiviral effect of the drug and its immunomodulatory properties in a clinical setting, specifically in chronic herpetic stomatitis.

First of all, it was shown that the state of the patients' immune system was in a clear correlation with the severity of the herpes process, i.e. the most severe immunosuppression was recorded in patients with severe stomatitis. The double effect of the drug is to significantly increase the results of antiviral treatment and immunorehabilitation of patients.

As a result of a parallel study of Zovirax and Lazolex, a high clinical activity of both drugs was recorded. However, the presence of pronounced immuno-corrective properties in Lazolex manifested itself in an improvement in the quality of patient treatment: active tissue regeneration and a significant decrease in the timing of exacerbation of local herpetic lesions, an increase in the duration of remission. Conducted clinical, laboratory and immunological studies allow us to recommend Lazolex for active use in dental practice for viral diseases.

Keywords: herpetic stomatitis, zovirax, lazolex, antiviral and immunocorrective effect.

РЕЗЮМЕ

ИЗУЧЕНИЕ ПРОТИВОВИРУСНОГО И ИММУНОКОРРИГИРУЮЩЕГО ДЕЙСТВИЯ ЛАЗОЛЕКСА У ПАЦИЕНТОВ С РЕЦИДИВИРУЮЩИМ ГЕРПЕТИЧЕСКИМ СТОМАТИТОМ

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В настоящее время в нашей стране продолжаются интенсивные исследования по изысканию и внедрению в практику новых натуральных лечебных препаратов, приготовленных из экологически чистых эндемических растений Грузии. Примером подобных исследований в компании Иверия-Фарма является отечественный лекарственный препарат Лазолекс (экстракт перикарпиума незрелого грецкого ореха), который прошел необходимые доклинические испытания и применятся в клинике в качестве противогерпетического средства.

На здоровых добровольцах нами были обнаружены положительные иммунотропные эффекты Лазолекса. Целью исследования явилось изучить противовирусный эффект препарата и его иммуномодулирующие свойства в клинических условиях, конкретно – при хроническом герпетическом стоматите.

Показано, что состояние иммунной системы пациентов находилось в четкой корреляции с тяжестью герпетического процесса, т.е. наиболее сильная иммунодепрессия была зафиксирована у больных с тяжелой формой стоматита. Двойное действие препарата заключается в существенном повышении результатов противовирусного лечения и иммунореабилитации больных.

В результате параллельного изучения зовиракса и лазолекса, зафиксирована высокая клиническая активность обоих препаратов. Наличие у лазолекса выраженных иммунокорригирующих свойств, проявилось в улучшении качества лечения пациентов: активная регенерация тканей, достоверное снижение сроков обострения местных герпетических поражений и увеличение продолжительности ремиссии.

Проведенные клинико-лабораторные и иммунологические исследования позволяют рекомендовать лазолекс к активному использованию в стоматологической практике при вирусных заболеваниях.

რეზიუმე

ლაზოლექსის ანტივირუსული და იმუნომაკორიგებელი მოქმედების შესწავლა პაციენტებში ქრონიკული მორეციდივე ჰერპესული სტომატიტით

მ.გოგოტიშვილი, ნ.აბაშიძე, ბ.კორსანტია

თსსუ-ის პაროდონტისა და პირის ღრუს ლორწოვანის დაავადებათა დეპარტამენტი; ქართულ-გერმანული იმპლანტაციის ცენტრი Hbi-DentImplant-ი; სტომატოლოგიური კლინიკა Davident-ი; თსსუ-ის ელ.ბახუტაშვილის სახ. სამედიცინო ბიოტექნოლოგიის ინსტიტუტი; თბილისი; შოთა რუსთაველის ბათუმის სახელმწიფო უნივერსიტეტის საუნივერსიტეტო კლინიკა BSU DENT-ი, საქართველო

სადღეისოდ ჩვენს ქვეყანაში გრძელდება ინტენსიური კვლევები ეკოლოგიურად სუფთა ენდემური მცენარეებისგან დამზადებული ახალი ნატურალური სამკურნალო პრეპარატების მოძიებისა და დანერგვის კუთხით. კომპანია "ივერია-ფარმაში" იკვლევენ სამამულო პრეპარატ "ლაზოლექს" (ნედლი კაკლის პერიკარპიუმის ექსტრაქტი), რომელმაც უკვე გაიარა კლინიკამდელი კვლევები და დაწყებულია კლინიკაში მისი, როგორც ანტიჰერპესული საშუალების, გამოყენება.

ჯანმრთელ მოხალისეებზე ჩატარებულმა ცდებმა აჩვენა ლაზოლექსის დადებითი იმუნოტროპული ეფექტი, აქედან გამომდინარე, კვლევის მიზანს წარმოადგენს პრეპარატის ანტივირუსული მოქედების ეფექტის და მისი იმუნომოდულირებადი თვისებების შესწავლა კლინიკის პირობებში, კერძოდ, ქრონიკული მორეციდივე ჰერპესული სტომატიტის დროს.
აღმოჩნდა, რომ პაციენტის იმუნური სისტემა დაკავშირებული იყო ჰერპესული პროცესის სიმძიმესთან, ანუ – უფრო ძლიერი იმუნოსუპრესია ფიქსირდებოდა გართულებული (მძიმე) ფორმის პაციენტებთან. პრეპარატმა გამოავლინა მისი ორმაგი მოქმედების ეფექტურობა პაციენტებში, როგორც ანტივირუსული თვისებით, ასევე იმუნოტროპულობით. ზოვირაქსისა და ლაზოლექსის პარალელური კვლევების შედეგად დაფიქსირდა ორივე პრეპარატის მაღალი აქტივობა. თუმცა, გამოვლინდა, რომ ლაზოლექსის აღნიშნული თვისებები უფრო მეტად აუმჯობესებს პაციენტის მკურნალობის ხარისხს: ადგილობრივად ქსოვილის აქტიური რეგენერაცია, დაავადების გამწვავების პერიოდის შემცირება, რემისიის გახანგრძლივება.
ჩატარებული კლინიკურ-ლაბორატიული კვლევების საფუძველზე რეკომენდებულია ლაზოლექსის, როგორც ანტივირუსული და იმუნომამოდულერებელი პრეპარატის აქტიური გამოყენება სტომატოლოგიურ პრაქტიკაში.

EXPERIENCE OF CLINICAL APPLICATION OF SURFACE ELECTROMYOGRAPHY AND LIGHT-CURING HYDROSTATIC SPLINT EASY BITE® IN ORTHODONTIC TREATMENT

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Degenerative diseases of the temporomandibular joint (DD TMJ) are the most common concomitant diseases of the dentofacial anomalies (DFA) [6, 10].

In recent decades, there has been a persistent upward trend of DD TMJ [1,2]. This pathology complicates orthodontic treatment of not only adult patients, but also children and adolescents [4,9]. The leading direction of pathogenetic therapy of DFA in patients with DD TMJ is not so much the normalization of the shape of the dentition as the determination and fixation of the therapeutic position of the lower jaw (TP LJ) with the obligatory correction of the tone of the masticatory muscles, restoration of their balance with the subsequent reconstruction of the occlusal plane with orthodontic and orthopedic ways [5].

At present, there are many ways to determine and register the central ratio of the jaws and TP LJ [7,8]. To this end, surface electromyography (s EMG) is actively used to analyze occlusal contacts and muscle balance [3].

The aim of this study is to increase the effectiveness of the treatment of dento-alveolar anomalies in patients suffering from degenerative diseases of the temporomandibular joint by improving the algorithm for determining the therapeutic position of the lower jaw under the control of surface electromyography using light-curing hydrostatic splint Easy Bite®.

Easy bite® is an elastic shell in the form of a bite fork filled with liquid light-curing polymer that controls its height (Fig. 1).

If Easy bite® is used for the analysis of dental contacts and muscle balance in combination with surface electromyography, the clinical protocol presents the following algorithm: 1. Complete examination using clinical and additional methods. 2. Obtaining two complete two-layer anatomical impressions from the upper and lower dental arches with C - silicone impression mass and the manufacturing of two pairs of gypsum combined models. 3. Fixation of wireless electrodes in the region of both temporal and both masticatory muscles (Fig. 2). 4. Determination of the initial muscle balance by surface electromyography using a BTS TMJOINT or Teethan™ apparatus from BTS Bioengineering (Italy): a cotton roll bite test and maximum closure in the habitual occlusion (clench). 5. Analysis of baseline muscle balance using the Dental Contact Analyzer software package.

To analyze the mutual influence of 4 chewing muscles on occlusal contacts, six main indices are used (Fig. 3):

Fig. 1. Easy bite® device kit for muscle relaxation (MR) of the masticatory muscles and registration of central ratio (CR): 1) a syringe with a fluid light-curing material - 4 syringes of 5 g each in a set, filling (2) an elastic shell - 12 pieces in a set, 3) a cannula for a syringe - 12 pieces in a set and (4) caps for the shell - 12 pieces, 5) clamp

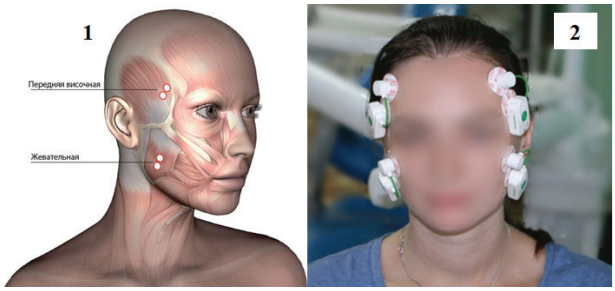


Fig. 2. Fixation of the electrodes on the anterior bundles of the temporal and proper chewing muscles for recording their biological activity: 1) diagram; 2) in patient

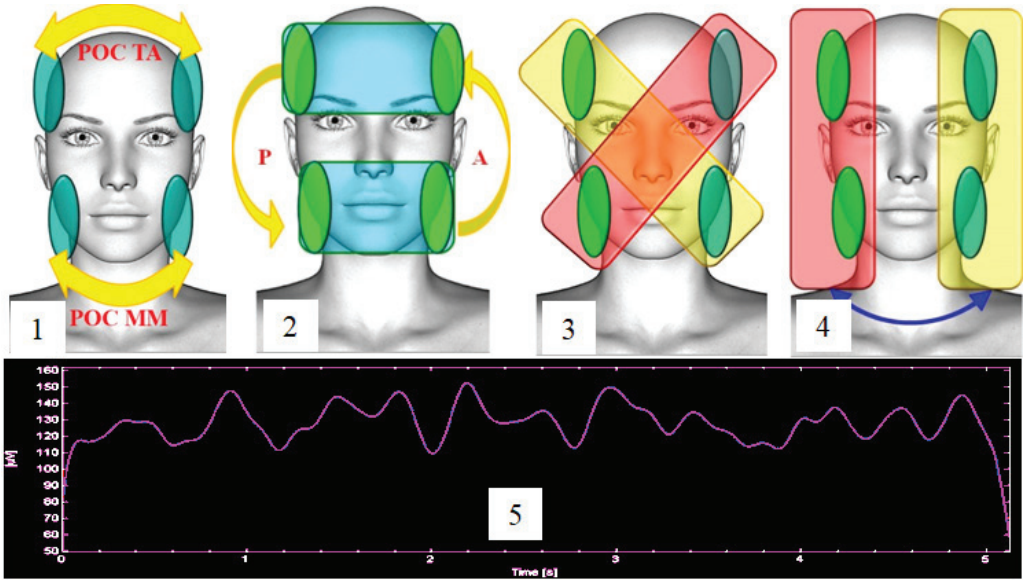


Fig. 3. Schematic designation of the indices used in the analysis of muscle balance program Dental Contact Analyzer: 1) POC TA u POC MM; 2) BAR; 3) TORS; 4) ASSIM; 5) IMPACT. Sh.

POC Index: Percentage Overlay - Comparison of the activity of the temporal POC TA (temporalis anterior) and the proper chewing muscles of the POC MM (musculus masseter) in the corresponding pair. The index indicates the dominance of activity of the right (R) or left (L) temporal or proper masticatory muscles, respectively.

So in Figure 4, with normative POC TA values from 85 to 100%, the index is 62.67 with a predominance of temporal muscle activity on the right side. And POC MM with the same regulatory values of 81.54 with a predominance of the same right side, which corresponds to the predominance of the right chewing muscle proper.

BAR index: Location of the occlusal mass inertial center is an index that assesses the prevalence of temporal muscle activity over the masticatory (A) - anterial displacement of the mass inertial center during the temporal type of chewing or chewing over the temporal (P) - posterior displacement of the mass - inertial center. So in Figure 4, at standard values, the index value is from 90 to 100% and the patient's BAR index is 54, that is, it reflects a significant posterior displacement, i.e., a pronounced masseteric type of chewing.

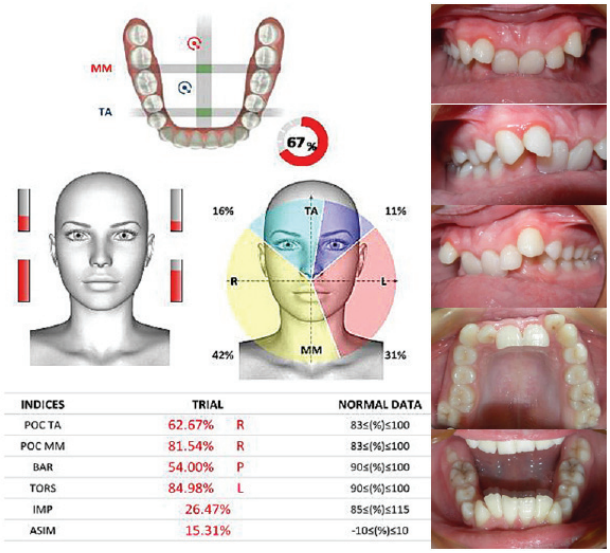
TORS index: lower jaw torque is an index giving a quantitative characteristic of the lateral and anterior - posterior displacement of the lower jaw from the moment of first contact to the moment of maximum intercuspension. In patient D., twisting of the lower jaw to the left is noticeable.

ASSIM index: lower jaw torque is an index that quantifies the neuromuscular balance between the temporal and proper chewing muscles of the left and right sides in relation to the horizontal plane. A positive value of 15.31 with normative from -10 to + 10 confirms the sharp predominance of activity of the muscles of the right side (right temporal 16% and chewing 42% against 11% of the left temporal and 31% chewing).

IMPACT Index: generated energy is an index that measures the work performed by muscles, expressed graphically as the area of a curve that reflects the development of muscle electrical activity over time.The greater the number of occlusal contacts and the larger their area, the better muscle activity will be. Values exceeding the norm are associated with the type of jaw growth of the patient, the presence of parafunctions, gritting of teeth, bruxism.

Values lower than normal may indicate acute proprioceptive or nociceptive inhibition (presence of pain in TMJ, aggravation of periodontitis, contact of teeth with mucous membranes).

As can be seen from Figure 4, in patient D., as a result of horizontal jaw growth, a deep traumatic bite was developed, complicated by anomalies of class 2, subclass 2 according to Engle. Such contact with the mucosa of the palate and the mucosa of the transitional fold due to sharp pain makes it impossible to close the teeth. Therefore, at a rate of 85 to 100%, the IMPACT index is only 26.47% (Fig. 4).



INDICES	TRIAL		NORMAL DATA
POC TA	62.67%	R	83≤(%)≤100
POC MM	81.54%	R	83≤(%)≤100
BAR	54.00%	P	90≤(%)≤100
TORS	84.98%	L	90≤(%)≤100
IMP	26.47%		85≤(%)≤115
ASIM	15.31%		-10≤(%)≤10

Fig. 4. Schematic representation of the visualization of the analysis report of patient D. and the type of occlusion (frontal, right, left), view of the upper and lower dental arch (explanation in the text)

6. Filling the hydrostatic splint with a light-curing polymer. Correction of the height of the splint according to the subjective sensations of the patient (either removing the clamp and releasing excess material through the tip of the shell, or pumping an additional portion of the polymer from the syringe through the cannula). 7. Biting the splint for 15 minutes. 8. Pre-polymerization of the splint in the oral cavity. The final polymerization of the splint outside the oral cavity (Fig. 5). 9. Determination of muscle balance when compressing teeth on a solid splint. 10. Correction of the splint (Fig. 6, 2).

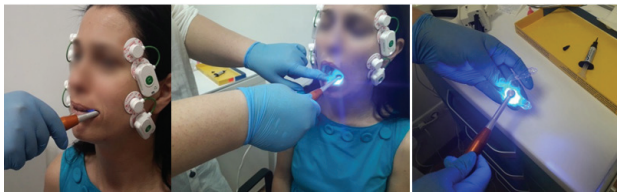


Fig. 5. Steps of sequential polymerization of the Easy bite® hydrostatic splint filled with a light curing composite during registration of the therapeutic position of the lower jaw of patient C

The final definition of muscle balance. 11. Registration of the therapeutic position of the lower jaw with a balanced muscle condition A - silicone material (Fig. 6.3). 12. Determining the location of the upper jaw in the skull using the facial arch and the bite fork. 13. Plaster casting of models into the articulator according to the registered therapeutic position.

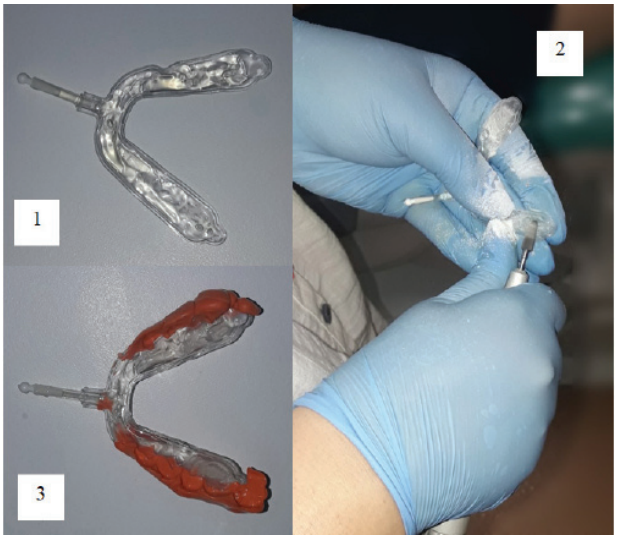


Fig. 6. The final stages of determining and registering the therapeutic position of the lower jaw using the light-curing hydrostatic Easy bite® splint under the control of EMG: 1) type of polymerized splint, 2) correction of the splint, 3) splint with bite registration (A - silicone)

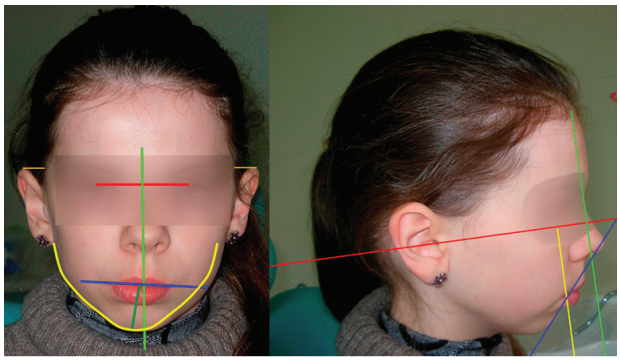


Fig. 7. Photometry in the direct and lateral projections of patient R., 12 years old

As an illustration, we provide an extract from the outpatient card of patient R., 12 years old, with complaints of incorrect tooth position and aesthetic disorders. The external examination: the physique is proportional, the constitutional type is asthenic, the Staffel posture is round-concave back, the scoliotic posture, the shape of the head is dolichocephalic. Hypermobility of the knee and elbow joints, interphalangeal joints of the fingers. Extraoral examination in full face: the forehead is beveled, the face is asymmetrical, elongated, disproportionate, the middle third of the face is visually reduced, the lower one is enlarged, the zygomatic region is not expressed, the chin is shifted to the right, the eyes are deep-set, the skin around the eyes is dark, the nasolabial folds are smoothed, asymmetrical, the lips come together with tension, the red border of the lips is dry, chapped, the corners of the mouth are asymmetrical.

Extraoral examination in profile: convex type of profile, increased angle between the cheek line and the back of the nose, the positive position of the lips to the aesthetic line of Ricketts, the chin is sloping posteriorly. The angle of the lower jaw is deployed. Opening the mouth with deviation of the lower jaw.

Intraoral examination: the vestibule of the oral cavity is shallow, 4 mm.

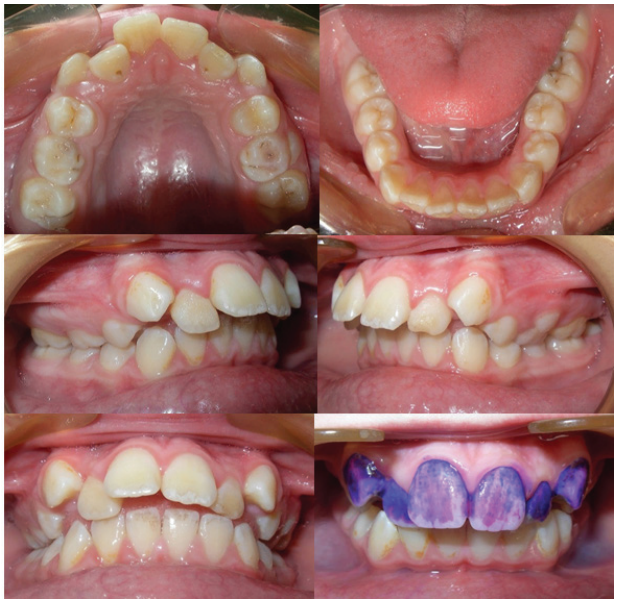


Fig. 8. View of the oral cavity of the patient R., 12 years old

The gingiva is pale, the interdental papillae are triangular in shape, their height is sharply reduced, the tips are rounded. The recession of the gingiva is determined in the area of the teeth 43, 42, 41, 31, 32, 33. The frenulum of the upper and lower lips have the correct shape, size, the correct place of attachment and coincide with the middle line of the face.

There is an abundant amount of dental deposits on oral and vestibular surface of all teeth and pigmented plaque on teeth 23, 26, 36, 35.

Lateral teeth of the upper and lower jaw have an oral position, teeth 13, 11, 21 and 23 have a vestibular position.

										15		
16	55	14	13	12	11	21	22	23	24	65	26	
46	45	44	43	42	41	31	32	33	34	35	36	37

The upper dental arch is V - shaped, narrowed and elongated. The lower dental arch is trapezoidal, narrowed and shortened.

Dento-alveolar shortening in the frontal area of the upper dentition, dento-alveolar elongation in the lateral areas of both dentitions.

The medial-buccal tubercle of the first permanent molar of the upper jaw on both sides is in contact with the same hillock of the same antagonist.

In the transversal plane, the buccal tubercles of the upper posterior teeth contact end-to-end with the buccal tubercles of the lower posterior teeth.

The tearing tubercle of the canine of the upper jaw is projected on both sides onto the tearing tubercle of the canine of the lower jaw.

The cutting edges of the upper incisors are projected at the level of the cutting edges of the lower incisors. The middle line of the lower dentition is shifted to the right by 1 mm. Overjet is 8 mm.

The tongue tie has the correct form and size. The tongue is lowered to the bottom of the oral cavity, the tone of the tongue is reduced. The mucous membrane of the oral cavity is normal in color, moist, without pathological changes. The pharynx is clear, tonsils do not protrude due to palatine arches, the mucous membrane of the posterior pharyngeal wall is normal, the palate is normal. The palate is high.

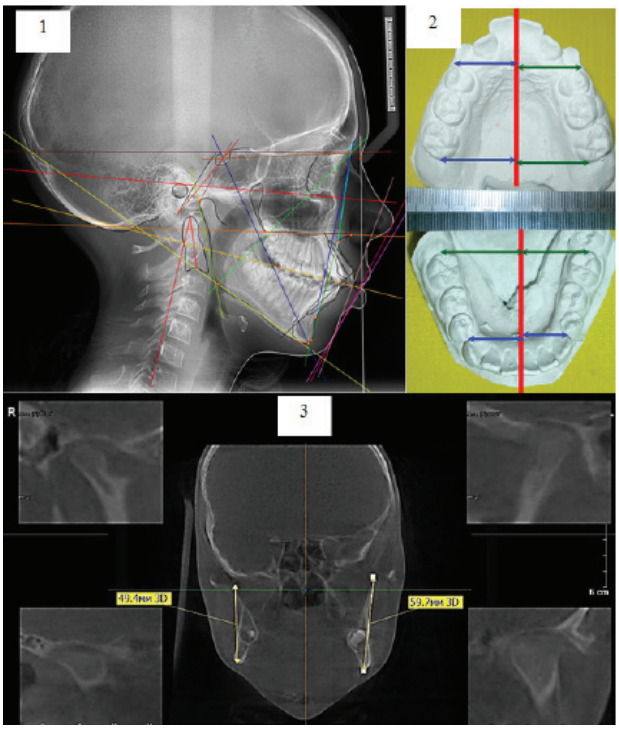


Fig. 9. Visualization of the results of additional methods of examination of patient R., 12 years old: 1) lateral cephalometry, 2) control diagnostic models analysis, 3) analysis of CBCT of the bones of the skull

The Quigley i Hein Oral Hygiene Index is unsatisfactory – 2.9. PMA in the modification of Parma is 39%.

Conducting of functional tests: the Ashler - Bitner test is positive-negative (morphological changes in both jaws); a colloquial test: anterior interdental sigmatism, non-closure of the lips when counting, a symptom of a thimble.

Palpation of the masticatory muscles: soreness in the atlanto-occipital joint on the right, both temporal muscles (mainly on the right), sharp pain in the lateral and medial pterygoid muscles (mainly on the left), chin-hyoid and mylohyoid muscles.

A manual functional study of the TMJ: a slight restriction of mouth opening to 43 mm, a click in both joints when opening by 30 mm, pain on palpation of the anteroposterior synovial space in the right TMJ and lateral pole of the mandible head in statics and dynamics, pain on palpation both lateral ligaments and soreness retrodiscal tissue of the right TMJ during the test - provocation with load.

Examination plan: 1. referral to a pediatric surgeon dentist to remove 55 and 65 teeth; 2. consultation of a cardiorematologist regarding confirmation of undifferentiated connective tissue dysplasia.

Consultation of a periodontist regarding the thin phenotype of periodontal tissues, the small vestibule of the oral cavity and recessions of the lower anterior teeth. Consultation of a kinesiologist regarding impaired posture, forced front position of the head and cranio-cervical dysfunction. Consultation of an ENT doctor regarding abstructive sleep apnea, oral breathing and glossoptosis. Consultation of a speech therapist for myofunctional correction of infantile swallowing, oral breathing, temporal chewing, impaired pronunciation of sounds; 3. anthropometric study of diagnostic models; CBCT and cephalometry in the lateral projection; analysis of photographs of the face in direct and lateral projection.

During the analysis of TRG (Fig. 9, 1) in the lateral projection, it was found: micrognathia of the lower jaw (- 7 mm), reduction of branches l / j (- 5 mm), macrognathia of the upper jaw (+ 3 mm), retroposition of the upper jaw (∠F = 82º), retroclination of the occlusal plane, ∠ Pn-OSP = 75º, retroclination of the lower jaw ∠ Pn-MP = 54º, protrusion of the dentoalveolar complex, ∠ii = 103º, vestibular inclination of the upper incisors ∠i = 58 º, vestibular inclination of the lower incisor ∠ī = 78º, the vestibular inclination of the lower incisor to the dentoalveolar complex ī - APg = 7, the vertical type of growth (5 qualitative and 8 of 13 quantitative signs), the distal position of the chin to the upper jaw ∠ MM = 76º, the skin chin is sloping posteriorly ∠T = 21º, the positive position of the upper lip to the Ricketts aesthetic line (+1), the positive position of the lower lip to the Ricketts aesthetic line (+5), smoothed cervical lordosis axis angle = 17º.

When analyzing the control diagnostic models (Fig. 9, 2) using the Pont method, in the Linder-Hart modification, narrowing of the upper dental arch (- 5.35 mm) and lower dental arch (- 4.34) was established in the area of the first premolars, narrowing of the upper (- 5.12) and the lower (- 2.7) dental arch in the area of the first permanent molars; using the Korghouse method in the sagittal plane, it was found: lengthening of the anterior portion of the upper dental arch (+ 2.18 mm) and shortening of the inferior dental arch in the anterior portion (- 0.5 mm); using the Nance method, it was established: the general lengthening of the upper dental arch (+ 5.68) and the shortening of the lower dental arch (- 1.5 mm).

When analyzing the data of cone-beam computed tomography (Fig. 9, 3), a description of the radiologist has been obtained: the left TMJ. The head of the articular process of the left branch of the lower jaw is somewhat flattened. Adjacent locking plates in the anterior-medial section of the joint space are fuzzy. The structure of a locking plate of the articular head In the central part is broken. In habitual occlusion, the articular head is located not deep in the articular fossa, displaced anteriorly and medially.

The width of the joint space of the left TMJ in the anterior part is 0.9 mm, in the posterior part is 2.1 mm, in the central part is 1.2 mm, in the medial part is 0.8 mm, in the lateral part is 2.5 mm. The articular tubercle is smoothed and has heterogeneous structure.

The right TMJ. The head is deformed, its upper medial quadrant is fragmented. In the subchondral part of the head, at this level, a section of aseptic necrosis is determined with dimensions up to 2.4 × 2.0 mm. The connecting plate of the articular cavity is deformed and sclerosed, the subchondral part is unevenly sclerotic. In habitual occlusion, the articular head is located shallowly in the articular fossa, displaced posteriorly and medially.

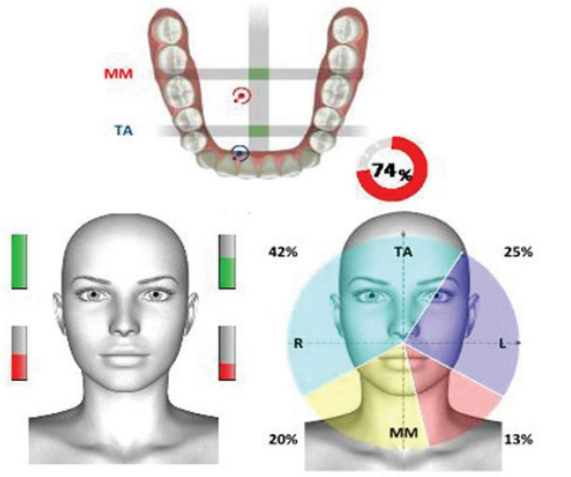
The width of the joint space is uneven and amounts to 4.0 mm in the anterior section, 2.6 mm in the central section, 2.0 mm in the posterior section, 1.3 mm in the medial section, and 3.4 mm in the lateral section. In the posterior-medial section, the joint space is not differentiated. The articular tubercle is smoothed, unevenly sclerotic.

Conclusion: CT signs of aseptic necrosis and fragmentation of the articular head of the right TMJ, arthritis-arthrosis of the left TMJ against the background of dysplasia of both TMJ.

Orthodontic diagnosis: underlying disease: skeletal class 2, vertical type of jaw growth, skeletal reduction of the branch of the lower jaw on the right by 10 mm, anomaly of the 2nd class, 1st subclass according to Engle of moderate severity, complicated by an anterior open bite of mild severity, complicated by a double-sided buccal crossbite with a shift of the lower jaw to the right, of a slight degree, narrowing and lengthening of the upper dental arch, narrowing and shortening of the lower dental arch, dentoalveolar elongation in the lateral areas, dentoalveolar shortening in the front portion of the upper dental arch, thin biotype periodontal tissue, small vestibule of the oral cavity, chewing unbalanced temporal type, infantile swallowing, mouth breathing, front interdental lisping, glossoptozis.

Concomitant diseases: a round-concave back according to Staffel, scoliotic posture, undifferentiated connective tissue dysplasia, aseptic necrosis and fragmentation of the joint head of the right TMJ, arthritis of the left TMJ against the background of both TMJ dysplasia.

At the first stage of orthodontic treatment, the patient was scheduled for occlusal shinotherapy. For this, the initial occlusal contacts and the state of muscle balance were analyzed (Fig. 10) using the BTS TMJoint apparatus (Bioengeeniring, Italy).



INDICES	TRIAL		NORMAL DATA
POC TA	73.46%	R	83≤(%)≤100
POC MM	76.15%	R	83≤(%)≤100
BAR	67.93%	A	90≤(%)≤100
TORS	86.61%	R	90≤(%)≤100
IMP	74.76%		85≤(%)≤115
ASIM	23.81%		-10≤(%)≤10

Fig. 10. Visualization of the results of the initial analysis of occlusal contacts and muscle balance of the patient R., 12 years old (explanation in the text)

As can be seen from the figure, the formation of such a compression in the right temporomandibular joint is due to the excessively pronounced hypertonicity of the right temporal muscle (42%) compared with the activity of the left temporal muscle 25%. POC TA 73.46% emphasizes the dominance of the temporal muscle of the right side. The chewing muscles are in a hypotonic state of 20% of the right and 13% of the left muscle, respectively.

POC MM 76.15% characterizes the dominance of the right among the masticatory muscles. The BAR index of 67.93% (A) confirms a significant displacement of the mass inertial center anterially, that is, a lack of occlusal support (dental contacts) in the frontal region. This explains the pronounced temporal type of chewing of the patient.

The TORS 86.61% index indicates twisting of the lower jaw from the moment of initial contact to maximum intercuspidation (central occlusion) to the right. The 74.76% IMP index empha-

sizes a general decrease in muscle activity, and ASIM - a sharp dominance of muscle activity on the right side.

Thus, to normalize muscle balance, it is necessary to add the height of the contacts to the area of the dentition, the closure of which is carried out by muscles with less activity.

After 15 minutes of using a light-curing hydrostatic splint with a height comfortable for the patient, it was polymerized. The output analysis of muscle balance and occlusal contacts was repeated with a solid splint (Fig. 11).

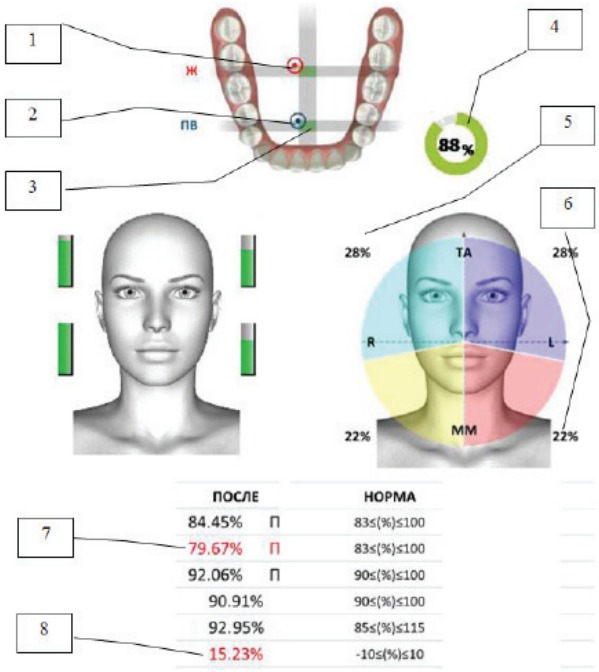


Fig. 11. Visualization of the results of the output analysis of occlusal contacts and muscle balance of the patient R., 12 years old (explanation in the text)

As can be seen from Figure 11, the use of a hydrostatic splint allowed balancing occlusal contacts and muscle activity. So the overall index of harmony of occlusion was 85% (Fig. 11, 4). In the upper part of the figure, a diagram of the normal arrangement of the mass-inertial centers (Fig. 11, 3), marked with green rectangles, is projected onto the dental arch. The blue target, "target," is the projection of the balance of the anterior temporal muscles (Fig. 11, 2).

It should be noted that the balance point of these muscles is not only as close as possible to the "ideal position", but, unlike the initial state, does not have a twisting vector and is represented by a point.

Compared with the initial analysis, the right anterior temporal muscle is active by 28% instead of 42%, and the left has increased its activity to 28% instead of the original 25, (Fig. 11, 5).

It must be recalled that with physiological occlusion and preserved muscle balance, all four muscles participating in the study should be 25% active, and their activity diagram projected onto a schematic face should resemble a BMW car brand sign - proportional quarters.

Similarly, the balance of the masticatory muscles of the right and left sides was restored (Fig. 11, 1) - a red target with a point (without twisting). In the initial analysis, the right proper chewing muscle was active at 20% and the left at 13%. After correction of the occlusal contacts by the hardened splint, the muscle activity was normalized to 22% on both sides (Fig. 11, 6).

However, out of all 6 analyzed indices marked in black (that is, corresponding to the norm), there are two indices highlighted in red. These are BAR (Fig. 11, 7) and ASIM (Fig. 11, 8).

In the output analysis of occlusion, BAR is almost 80%, that is, 3% is not enough to normal. This deviation can be neglected, especially since a long-term orthodontic treatment is planned and at the final stages it will be performed remodeling of the occlusal plane, including using micro prosthetics.

The ASIM index confirms the remaining dominance of muscle activity on the right side, however, for the decompression of the right head of the lower jaw at the stage of initiating occlusal splint therapy, this condition may be acceptable.

After the correction of the occlusal splint by the method of fractional disocclusion, the occlusal contacts of the right and left sides were normalized. Five months later, a second CBCT examination of both jaws and temporomandibular joints was performed.

The following conclusion was obtained by the radiologist: the right TMJ. The shape of the head of the articular process of the right branch of the lower jaw is round, the neck is somewhat shortened. The connecting plate of the head in the anterior part of the joint space is fuzzy. The subchondral departments of the articular head and articular cavity are not changed. In habitual occlusion, the articular head is not located deep in the articular fossa. The joint gap of the right TMJ is uneven. The width of the joint space in the medial section is 1.3 mm, in the central section is 1.2 mm, in the anterior section is 1.2 mm, in the posterior section is 2.4 mm, in the lateral section is 1.6 mm. The articular tubercle is flattened, its posterior slope is oblique, and the cortical plate is fuzzy in the apex region.

The left TMJ. The central section of the head of the articular process of the left branch of the lower jaw is somewhat flattened. The connecting plate of the anterolateral part of the articular surface of the head for up to 3 x 6 mm is fuzzy. The connecting plate of the articular cavity is without features. The subchondral departments of the articular head and articular cavity are not changed. In habitual occlusion, the articular head is usually located in the articular fossa. The joint gap of the left TMJ is unevenly narrowed in the medial and anterior sections. The width of the joint space in the medial section is 1.3 mm, in the central section 2.4 mm, in the anterior section 1.9 mm, in the posterior section 2.2 mm. The articular tubercle is not changed.

Conclusion: CT signs of dysplastic atrito-arthrosis in the right TMJ. CT signs of the initial manifestations of dysplastic arthritis-arthrosis.

Thus, the processes of restorative remodeling of tissues of the right TMJ are observed. The patient completes the active period of orthodontic treatment.

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SUMMARY

EXPERIENCE OF CLINICAL APPLICATION OF SURFACE ELECTROMYOGRAPHY AND LIGHT-CURING HYDROSTATIC SPLINT EASY BITE® IN ORTHODONTIC TREATMENT

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This study describes the clinical experience with the use of Easy Bite® light-curing hydrostatic splint for initiating muscle relaxation and determining the therapeutic position of the lower jaw under the control of surface electromyography at the stage of occlusal splinting prior to orthodontic treatment.

Surface electromyography was performed using a BTS TMJOINT apparatus from BTS Bioengineering (Italy) and the Dental Contact Analyzer software package. The article describes the interpretation of the six indices, such as POC TA, POC MM, BAR, TORS, IMP, ASIM, for the analysis of occlusion and muscle balance in a clinical example with illustrations.

The developed algorithm for determining the therapeutic position of the lower jaw is described and the results of 5 months of occlusal splint therapy of a 12-year-old patient with skeletal grade 2, a vertical type of jaw growth, a skeletal reduction of the lower jaw branch on the right, aseptic necrosis and fragmentation of the articular head of the right TMJ, arthritis-arthrosis of the left TMJ, dysplasia of both TMJs on the background of undifferentiated connective tissue dysplasia are presented.

Keywords: hydrostatic splint, surface electromyography, occlusal splinting, therapeutic position of the lower jaw.

РЕЗЮМЕ

ОПЫТ КЛИНИЧЕСКОГО ПРИМЕНЕНИЯ ПОВЕРХНОСТНОЙ ЭЛЕКТРОМИОГРАФИИ И СВЕТООТВЕРЖДАЕМОЙ ГИДРОСТАТИЧЕСКОЙ ШИНЫ EASY BITE® НА ЭТАПАХ ОРТОДОНТИЧЕСКОГО ЛЕЧЕНИЯ

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В исследовании описан клинический опыт применения светоотверждаемой гидростатической шины Easy Bite® для инициирующей миорелаксации и определения терапевтического положения нижней челюсти под контролем поверхностной электромиографии на этапе окклюзионной шинотерапии перед ортодонтическим лечением.

Поверхностная электромиография осуществлялась с использованием аппарата BTS TMJOINT фирмы BTS Bioengineering (Италия) и пакета программного обеспечения Dental Contact Analyzer. В материале статьи описана интерпретация шести индексов POC TA, POC MM, BAR, TORS, IMP, ASIM для анализа окклюзии и мышечного баланса на клиническом примере с иллюстрациями.

Описан разработанный алгоритм определения терапевтического положения нижней челюсти и приведены результаты 5 месяцев окклюзионной шинотерапии пациентки 12 лет с со скелетным 2 классом, вертикальным типом челюстного роста, скелетным уменьшением ветви нижней челюсти справа, асептическим некрозом и фрагментацией суставной головки правого височно-нижнечелюстного сустава (ВНЧС), артрито-артрозом левого ВНЧС, дисплазией обоих ВНЧС на фоне недифференцированной дисплазии соединительной ткани.

რეზიუმე

ზედაპირული ელექტრომიოგრაფიის და სხივით გამყარებადი ჰიდროსტატიკური არტაშანის EASY BITE® კლინიკური გამოყენების გამოცდილება ორთოდონტიული მკურნალობის ეტაპზე

ა.ლიუბჩენკო, ი.ტკაჩენკო

ხარკოვის დიპლომისშემდგომი განათლების სამედიცინო აკადემია, უკრაინა

სტატიაში აღწერილია სხივით გამყარებადი ჰიდროსტატიკური არტაშანის EASY BITE® გამოყენების კლინიკური გამოცდილება მაინიცირებელი მიორელაქსაციისა და ქვედა ყბის თერაპიული მდგომარეობის განსაზღვრისათვის ზედაპირული ელექტრომიოგრაფიის კონტროლის ქვეშ ოკლუზიური არტაშანოთერაპიის ეტაპზე ორთოდონტიული მკურნალობის დაწყებამდე.

ზედაპირული ელექტრომიოგრაფია განხორციელდა ფირმა BTS Bioengineering-ის (იტალია) აპარატით BTS TMJOINT და პროგრამული უზრუნველყოფის Den-

tal Contact Analyzer-პაკეტის გამოყენებით. სტატიაში ოკლუზიისა და კუნთოვანი ბალანსის ანალიზისათვის კლინიკურ მაგალითზე და ილუსტრაციებით აღწერილია ექვსი ინდექსის (POC TA, POC MM, BAR, TORS, IMP, ASIM) ინტერპრეტაცია.

ქვედა ყბის თერაპიული მდგომარეობის განსაზღვრისათვის აღწერილია შემუშავებული ალგორითმი და 12 წლის ასაკის პაციენტი-გოგონას 5-თვიანი ოკლუზიური არტაშანოთერაპიის შედეგები, ყბის ზრდის ვერტიკალური ტიპით, ქვედა ყბის ჩონჩხოვანი შემცირებით მარჯვენა მხარეს, ასეპტიკური ნეკროზით, მარჯვენა საფეთქელ-ქვედა ყბის სასახსრე თავის ფრაგმენტაციით, მარცხენა საფეთქელ-ქვედა ყბის სახსრის ართრიტ-ართროზით, ორივე საფეთქელ-ქვედა ყბის სახსრის დისპლაზიით შემაერთებელი ქსოვილის არადიფერენცირებული დისპლაზიის ფონზე.

ЭФФЕКТИВНОСТЬ РАДИОЛОГИЧЕСКИХ МЕТОДОВ ДИАГНОСТИКИ ЗАБОЛЕВАНИЙ БЕДРЕННО-ПОДКОЛЕННО-БЕРЦОВОГО СЕГМЕНТА

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Атеросклероз - главная причина периферических окклюзирующих заболеваний сосудов. С возрастом риск заболевания увеличивается - окклюзирующие заболевания периферических артерий проявляются у 3-10% населения, а у лиц старше 60 лет - в 15-20% случаев. Атеросклеротические стенозы в артериях нижних конечностей могут вызвать перемежающую хромоту или критическую ишемию нижних конечностей у 19,8% мужчин и 16,8% женщин в возрасте старше 65 лет [4,6,11].

Окклюзия поверхностной бедренной артерии является общей особенностью при заболеваниях периферических сосудов, поэтому глубокая артерия бедра (ГАБ) является решающим коллатеральным путем для перфузии нижней конечности [4,15]. Ее значение в обеспечении жизнеспособности нижней конечности при хронической ишемии ранее было задокументировано Leeds и Gilfillan, а также Morris и др. в 60-х годах [9,14].

Однако, в настоящее время отсутствует строгий алгоритм, который определяет возможность использования ГАБ для полноценной реваскуляризации нижней конечности. Кроме того, нет строгих дифференциально-диагностических критериев выбора того или иного способа выполнения профундопластики в каждом конкретном случае.

Успех реконструктивных сосудистых операций в большинстве случаев связан с усовершенствованием прогрессивных методов диагностики, которые позволяют верифицировать поражения, определять оптимальную хирургическую тактику и избегать ошибок [2,3,7], что возможно при современных диагностических методах, включающих функциональную и морфологическую оценку состояния сосудов. Адекватная дооперационная оценка состояния магистральных артерий является значимым фактором в определении оптимального объема реконструктивной операции и места расположения как проксимального, так и дистального анастомозов [2,7,8,11]. На сегодняшний день в арсенале врачей для эффективной диагностики доступны ультразвуковое исследование магистральных артерий (УЗИ), ультразвуковое дуплексное сканирование (УДС), рентгенконтрастная ангиография (РКАГ) и мультиспиральная компьютерная томография (МСКТ).

Целью исследования явилось определение эффективности современных методов радиологической диагностики для улучшения результатов лечения больных дистальными окклюзионно-стенотическими заболеваниями бедренно-подколенно-берцового сегмента атеросклеротического генеза.

Материал и методы. Проведен анализ обследований и лечения 150 пациентов с дистальным атеросклерозом, находившихся в отделении сосудистой хирургии Закарпатской областной клинической больницы им. А. Новака. Пациентам проведены следующее исследования: УЗИ и УЗДС магистральных артерий 150 пациентам; рентгенконтрастная ангиография 87 пациентам; МСКТ - 110 пациентам.

Надежность и обоснованность (т.е. адекватность) способов диагностики определялись следующими общедоступными классическими показателями [2,4]: диагностическая специфичность, чувствительность и эффективность метода диагностики.

Семантика показателей определялась в соответствии с матрицей ретроспективно верифицированных на основании данных историй болезни пациентов, диагностических выводов (таблица 1).

Диагностическая чувствительность (ДЧ) - процентное выражение частоты истинно положительных результатов теста у больных на эту болезнь. Чувствительность показывает способность метода правильно выявить больных с проходимостью исследуемого сосуда среди группы лиц, в рамках теории вероятности (вероятность ИП результата у больного) [3,4]:

Таблица 1. Семантика показателей

По результатам применения метода у больного	**Верифицировано**	
	Наличие проходимости сосудов	**Отсутствие проходимости сосудов**
Наличие проходимости сосудов	ИП	ЛП
Отсутствие проходимости сосудов	ЛО	ИО

примечание: ИП - истинно положительное заключение; ИО - истинно отрицательное заключение; ЛП- ложно положительное заключение; ЛО - ложно отрицательное заключение

$$ДЧ = \frac{ИП}{ИП + ЛО} x100\%$$

Чувствительность метода диагностики характеризуется его вероятностью выявить заболевание у здоровых лиц.

Диагностическая специфичность (ДС) является процентным выражением частоты истинно отрицательных результатов теста у лиц, нестрадающих этой болезнью [3,4]:

$$ДС = \frac{ИО}{ИО + ЛП} x100\%$$

Диагностическая эффективность теста (ДЭ) выражается процентным отношением истинных результатов теста к общему числу полученных результатов [2]:

$$ДЭ = \frac{ИП}{ИП + ИО + ЛП + ЛО} x100\%$$

Прогнозируемость - способность метода предсказать развитие положительного результата/патологии, если результаты исследования являются положительными (в рамках теории вероятности - вероятность развития положительного результата/патологии, если результаты теста ИП) [3]:

$$П = \frac{ИП}{ИП + ЛП} x100\%$$

Точность - доля настоящих выводов в общем количестве исследований [3]:

$$Т = \frac{ИП + ИО}{ИП + ИО + ЛП + ЛО} x100\%$$

Результаты и обсуждение. Результаты анализа эффективности методов радиологического исследования представлены в таблице 2.

При диагностике бедренно-подколенно-берцового сегмента ложноотрицательный и ложноположительный результат при ультразвуковом исследовании наблюдались, соответственно, у 11 и 3 пациентов. При дуплексном сканировании ложноотрицательный результат наблюдался у 5 пациентов, ложноположительный у двух пациентов, при рентгенконтрастной ангиографии, соответственно, у 14 и 5 пациентов, при МСКТ - у 3 и 2 больных. При исследовании ГАБ наибольшее число ложноположительных и ложноотрицательных результатов наблюдалось при ультразвуковом исследовании 12 и 5 больных и рентгенконтрастной ангиографии 18 и 12 пациентов, соответственно.

При этом прогнозируемость метода исследования для диагностики артерий бедренно-подколенно-берцового сегмента составляла для УЗИ – 97,7%, УЗДС - 97,1%, для РКАГ – 91,1%, для МСКТ – 98% при точности соответственно 90,7%, 95,3% 78,2%, 95,5%. Для ГАБ прогнозируемость УЗИ составила 95,9%, УЗДС – 96,9%, РКАГ – 58,6%, МСКТ – 99% при точности соответственно 88,7%, 93,3%, 66,5%, 97,3%.

Чувствительность УЗИ метода для магистральных артерий составила 92%, специфичность 76,9% при эффективности 84%, а для ГАБ - чувствительность составила 90,6%, специфичность – 77,3% при эффективности 77,3%.

В протокол УЗИ магистральных артерий включали визуализацию окклюзии сегментов артерий, измерение диаметра проходимости артерий, расчета пиковой систолической скорости кровотока, максимальной конечной диастолической скорости кровотока, средней по времени максимальной скорости кровотока, индекса периферического сопротивления, индекса пульсации, объемной скорости кровотока (рис. 1).

Таблица 2. Эффективность лучевых методов в дооперационной диагностике артерий нижней конечности

Сегмент	Характеристики методик	Методы диагностики			
		УЗИ магистральных артерий	УЗДС	РКАГ	МСКТ
Бедренно-подколенно-берцовой сегмент	Чувствительность, %	92	96,4	78,5	97,1
	Специфичность, %	76,9	83,3	77,3	77,8
	Эффективность, %	84	88,7	58,6	89,1
	Прогнозируемость,%	97,7	97,1	91,1	98
	Точность,%	90,7	95,3	78,2	95,5
	Ложно (-) результат	11	5	14	3
	Ложно (+) результат	3	2	5	2
Глубокая артерия бедра	Чувствительность, %	90,6	95,3	48,6	98
	Специфичность, %	77,3	81	76,9	88,9
	Эффективность, %	77,3	82	19,5	90
	Прогнозируемость,%	95,9	96,9	58,6	99
	Точность,%	88,7	93,3	66,5	97,3
	Ложно (-) результат	12	6	18	1
	Ложно (+) результат	5	4	12	2

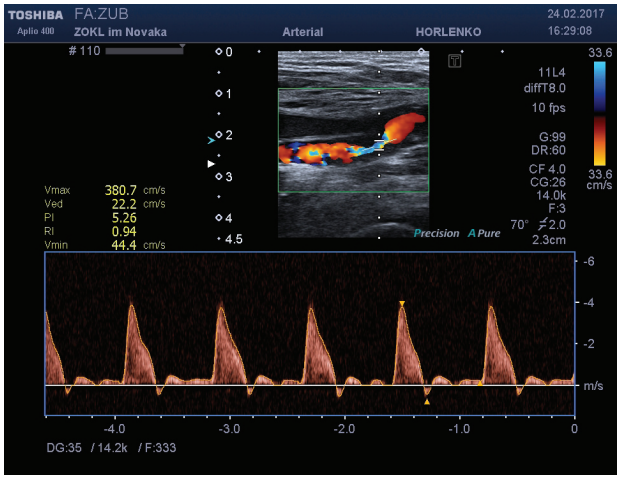

Рис. 1. Ультразвуковое исследование глубокой артерии бедра. Спектральный анализ: увеличение пиковой систолической скорости кровотока (более 380 см/с), стеноз ГАБ более 70% протяжённостью более 1,5 см

При выполнении обследования изучали: гемодинамические параметры; толщину сосудистой стенки; наличие атеросклеротических бляшек, стенозов и окклюзий; ход артерий; плече-лодыжечный индекс (ПЛИ); глубокобедренно-подколенный индекс (ГБПИ); пиковую систолическую скорость (ПСС) кровотока (таблица 3).

Ультразвуковое дуплексное сканирование магистральных артерий. Первые успехи ультразвуковых допплеровских исследований артерий конечностей, полученные при выявлении окклюзий бедренно-подколенного сегмента, P.G. Clifford и соавт. [2] доказали информативность дуплексного сканирования, оценивая проходимость бедренно-подколенного сегмента и способность бедренно-подколенных шунтов. В последнее время дуплексное ультразвуковое сканирование быстро превратилось в неотъемлемую часть сосудистой диагностики [8,15], хотя в начале своего развития исследования периферических артерий с помощью ДС характеризовалось сдержанным энтузиазмом.

Чувствительность метода для бедренно-подколенно-берцового сегмента составила 96,4%, специфичность - 83,3%, эффективность - 88,7%, а для ГАБ чувствительность составила 95,3%, специфичность - 81%, эффективность - 82%.

Благодаря возможности изменять плоскость исследования при дуплексном сканировании удается избежать наложения начальных сегментов поверхностной бедренной и глубокой артерий бедра и диагностировать поражение устья последней, что не всегда возможно провести при ангиографии [4]. С артерий, берущих начало от ГАБ, при УЗДС чаще всего удается локализовать латеральную огибающую артерию (рис. 2). Кроме того, иногда появляется возможность различить разные варианты отхождения ГАБ и ее ветвей от общей бедренной артерии.

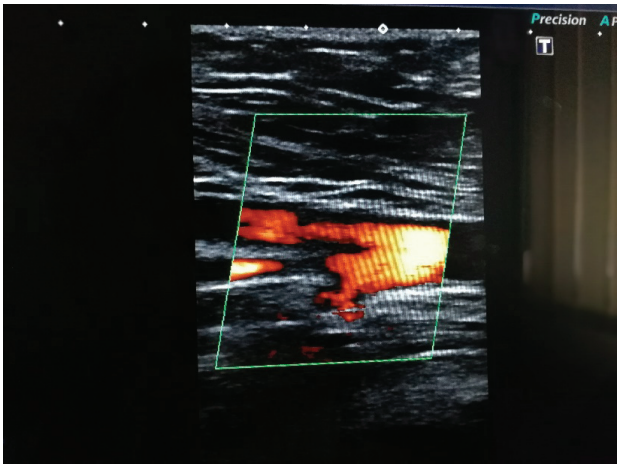

Рис. 2. Визуализация ГАБ в режиме цветовое допплеровское картирование. Визуализируется латеральная огибающая артерия ГБА

Преимуществами ДС являются возможность одновременной эхолокации сосудов с изучением состояния гемодинамики по количественным параметрам кровотока и получение цветной картограммы потока в режиме реального времени. Значимым преимуществом ДС является возможность определения бляшки по критерию гомогенности - однородность ее структуры (эхогенность). При наличии мягкой бляшки (гипо- или анэхогенное образование) можно планировать выполнение эндартерэктомии в ходе аортобедренных реконструкций или профундопластики. Твердая бляшка содержит гиперэхогенные включения. Весьма часто (81,9%) определялись гетерогенные бляшки, которые имели смешанную структуру и сливались с гипо-, гипер- и анэхогенных участков. Такие бляшки чаще выявлялись при «больших» стенозах артерий, а при «малых» стенозах наблюдались гомогенные бляшки. Айриян П.Е. [1], не без оснований считает, что с помощью ДС возможно оценивать адекватность коллатерального русла. Важным, по мнению Соколовича А.Г. [2,5], - является возможность изучения сосудов с любой скоростью кровотоком. То есть, оценка проходимости артерий со слабым коллатеральным кровотоком, а также у выявления критического стеноза поверхностной бедренной артерии при развитом коллатеральном кровотока. Применение энергетического допплеровского картирования также позволяет диагностировать стеноз артерий, особенно с редукцией просвета менее 50%, не розпи-известные при ангиографии [5]. Несомненным преимуществом ДС перед рентгенконтрастным исследованием является физиологичность (неинвазивность) и возможность его многократного

Таблица 3. Ультразвуковые показатели дистального атеросклероза

Норма	При атеросклеротическом поражении сосудов
- контур стенок сосудов четкий, ровный; - просвет эхо отрицательный; -ход магистральных артерий прямолинейный; - пристеночные образования и цветной поток соответствует настоящему диаметру сосуда	- стенки уплотнены; - имеют повышенную эхогенность; - неровный внутренний контур; - УЗДС кровоток в зоне окклюзии не определяется; - уменьшение ПЛИ и увеличение ГБПИ >0,35; - ПСС >200 см/с

использования для динамического контроля за состоянием сосудов и шунтов [2]. Значительным преимуществом является также возможность определения характера бляшки, что имеет большое практическое значение в плане выбора тактики оперативного вмешательства.

Недостатками ДС являются технические трудности при абдоминальном доступе у пациентов с ожирением и метеоризмом и невозможность демонстрации всего «артериального дерева», т.е. небольшая зона анатомического охвата. К недостаткам относятся также частые артефакты при ДС, отсутствие костных ориентиров, менее стандартизированные результаты исследования и зависимость разрешения от квалификации специалиста [2,7].

Итак, УДС магистральных артерий является, в первую очередь, неинвазивным, безопасным, достаточно точным, относительно дешевым, эффективным методом исследования артерий нижних конечностей различного калибра, который в некоторых случаях превосходит по точности рентгенконтрастную ангиографию и может многократно применяться для контроля.

Рентгенконтрастная ангиография (РКАГ). Результаты исследований некоторых авторов свидетельствуют [1], что ангиография более информативна когда критические стенозы принимались за окклюзии, сегментарные окклюзии принимались за стеноз, а также при атипичном размещении сосудов

По данным РКАГ возможно оценивать степень развития коллатеральной системы между ветвями ГАБ и подколенной артерии. Данный метод обеспечивает только анатомическую информацию о сосудах и не позволяет при этом получить данные о функциональном состоянии артериального русла, в первую очередь - о состоянии коллатерального кровообращения.

По наблюдениям некоторых авторов [2,7], косое направление, множественность изгибов артерий, их грубая атеросклеротическая деформация и локализация бляшек на задней стенке обусловливают малоинформативность ангиографического исследования в одной проекции и требуют проведения полипроэкционного УЗИ артерий. Малая информативность ангиографии в оценке состояния бедренных артерий обусловлена тем, что на снимках, проведенных в передне-задней проекции, начальные сегменты глубокой и поверхностной бедренной артерий перекрывают друг друга, поэтому невозможно оценить поражения начальных сегментов ГАБ (рис. 3). К недостаткам рентгенконтрастной ангиографии следует отнести также плохое качество контрастирования изображения при низкой скорости коллатерального кровотока [7]. По данным РКАГ невозможно делать выводы об истинных размерах просвета сосуда.

С развитием технического обеспечения и накоплением опыта ультразвуковой диагностики появляется все больше исследований, указывающих, что дуплексное сканирование мало уступает ангиографии в выявлении стенозов (50-99%) или окклюзий бедренно-подколенно-берцовой зоны [2].

Чувствительность рентгенконтрастной ангиографии для бедренно-подколенно-берцового сегмента составляет 78,5%, специфичность - 77,3%, эффективность - 58,6%. Для ГАБ чувствительность ангиографии составила только 48,6%, при специфичности 76,9% и эффективности 19,5%.

Интраоперационная ревизия у 10 пациентов выявила сохранение проходимости подколенной артерии или артерий голени, которая не визуализировалась при ангиографическом обследовании, однако наблюдалась при УЗДС.

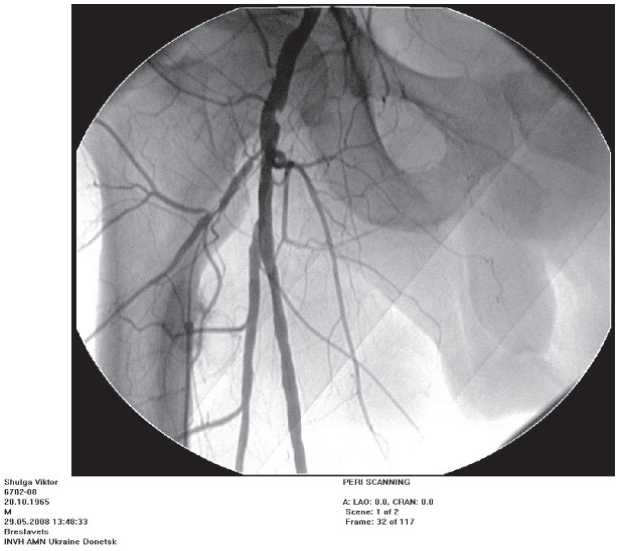

Рис. 3. Отхождение ГАБ от задней стенки общей бедренной артерии. Устье ГАБ перекрывается начальным сегментом поверхностной артерии бедра

Мультиспиральная компьютерная томография (МСКТ). На современном этапе МСКТ занимает значимое место в диагностике сосудистой хирургии. Чувствительность метода для бедренно-подколенно-берцового сегмента составила 97%, специфичность - 77,8% при эффективности 89,1%, для ГАБ чувствительность составила 98%, специфичность - 88,9% при эффективности 90%.

Особенностью метода является получение изображения сосудистого бассейна на всем протяжении, возможность определить выраженность стеноза соответствующего русла, оценить риски кровопотери благодаря визуализации близко расположенных вен на поперечных срезах и мест отхождения ветвей магистральных артерий в 3D-режиме (рис. 4) [10].

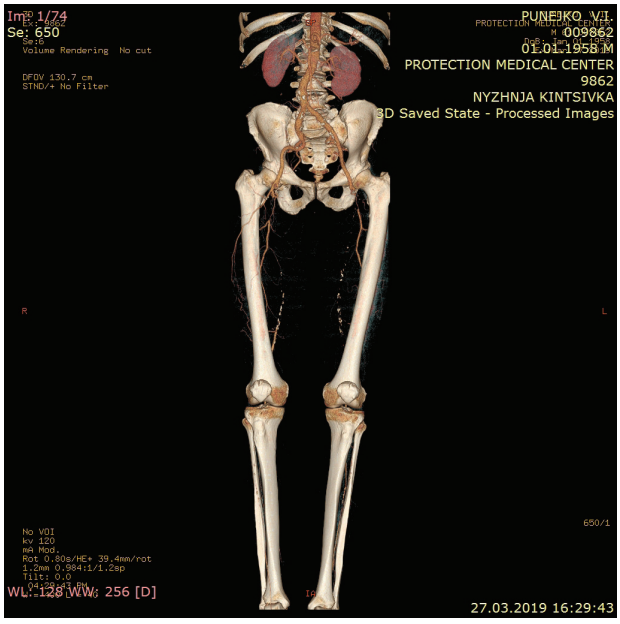

Рис. 4. МСКТ аорты и артерий нижних конечностей. Бедренный сегмент: окклюзия устья ГАБ и поверхностной бедренной артерии с обеих сторон на всем протяжении. Коллатеральная система ГАБ хорошо развита

Получение 3D-изображений позволяет проводить лучшую предоперационную подготовку, включающую оценку анатомических и топографических особенностей; позволяет предварительно продумать тактику оперативного вмешательства, определить зоны создания анастомозов.

Недостатками МСКТ являются возникновение аллергических реакций на йод, ограниченное использование при почечной недостаточности, невозможность пациентом выполнить задержку дыхания на 15-20 сек., что особенно актуально в случаях острой нарастающей ишемии.

Сравнение представленных методов диагностики, несмотря на некоторые расхождения в результатах, позволяет сделать вывод, что дуплексное сканирование является высокоинформативным методом исследования артерий нижних конечностей различного калибра, равным рентгенконтрастной ангиографии, а иногда превосходящим ее по точности. Метод безопасен, безвреден и может многократно использоваться в динамике.

С точки зрения [4,10], полноценное использование УЗДС ведет к уменьшению числа пункций, которые сопровождают артериографию, использования катетеров, сокращению продолжительности процедуры и понижению стоимости лечения.

УЗДС имеет преимущество перед МСКТ, обеспечивая гемодинамическими данными проксимальней, дистальней и в месте обструкции, то есть наличие или отсутствие кровотока, позволяет диагностировать ступень и протяжение обструкции, получение спектрального анализу кровотока. Ограничивающим фактором для допплерографии является зависимость исследования от квалификации оператора. Еще одним недостатком УЗДС является отсутствие возможностей артериальной визуализации, присущей МСКТ, которые необходимы хирургу для предоперационного планирования. Данные УЗДС позволяют лишь документировать небольшой артериальный сегмент на каждом изображении, поэтому в большинстве случаев целесообразно заменить ультразвуковое дуплексное сканирование МСКТ. Недостатками, препятствующими широкому использованию МСКТ, являются ограниченное количество мультиспиральных КТ-аппаратов и ограниченный опытный персонал, который может выполнить такое обследование. Обязательна интерпретация изображений рентгенологом, имеющим опыт визуализации сосудов. Ограничивающим фактором также является высокая стоимость обследования.

Выводы.

1. При сравнении радиологических методов диагностики артерий бедренно-подколенно-берцового сегмента и глубокой артерии бедра наиболее эффективными оказались методы МСКТ (89,1% и 90%, соответственно) и УДС (88,7% 82% соответственно).
2. Прогнозируемость исследования для диагностики артерий бедренно-подколенно-берцового сегмента метода УЗИ составила 97,7%, для УЗДС – 97,1%, для РКАГ – 91,1%, для МСКТ – 98% при точности 90,7%, 95,3%, 78,2%, 95,5%, соответственно. Для ГАБ прогнозируемость УЗИ составила 95,9%, УДС – 96,9%, РКАГ – 58,6%, МСКТ – 99% при точности 88,7%, 93,3%, 66,5%, 97,3%, соответственно.

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SUMMARY

EFFICIENCY OF RADIOLOGICAL METHODS FOR DIAGNOSING THE ARTERIES OF THE FEMORO-POPKLITE-TIBAL SEGMENT

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Objective - to determine the effectiveness of modern methods of radiological diagnostics for improving the results of treatment of patients with distal occlusive-stenotic diseases of the femoral-popliteal-tibial segment of atherosclerotic genesis.

The analysis of examinations and treatment of 150 patients with distal atherosclerosis, who were in the Department of Vascular Surgery of the Regional Clinical Hospita A. Novaka.

On ultrasound examination of the arteries of the femoral-popliteal-tibial segment, false negative and false positive results were observed in 11 and 3 patients, respectively. On duplex scanning, a false negative was observed in 5 patients, a false positive in two patients. On X-ray contrast angiography, respectively, in 14 and 5 patients, with MDCT - in 3 and 2 patients. To study of the deep femoral artery, the largest number of false positive and false negative results were observed during ultrasound examination of 12 and 5 patients and X-ray contrast angiography in 18 and 12 patients, respectively.

Have compared the radiological methods for diagnosing the arteries of the femoral-popliteal-tibial segment and the deep femoral artery, the most effective were MDCT (89.1% and 90%, respectively) and ultrasound duplex scanning (88.7% 82%, respectively). The predictability of the research method for diagnosing the arteries of the femoral-popliteal-tibial segment for ultrasound was 97.7%, for ultrasound - 97.1%, for RCAH - 91.1%, for MSCT - 98% with an accuracy of 90.7%, 95 , 3%, 78.2%, 95.5%. For the deep femoral artery, the predictability of ultrasound was 95.9%, ultrasound - 96.9%, RCAH - 58.6%, MSCT - 99% with an accuracy of 88.7%, 93.3%, 66.5%, 97.3%, respectively.

Keywords: deep femoral artery, ultrasound, duplex ultrasonography, X-ray contrast angiography, MDCTA, obliteration atherosclerosis of the lower extremities vessels.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ РАДИОЛОГИЧЕСКИХ МЕТОДОВ ДИАГНОСТИКИ ЗАБОЛЕВАНИЙ БЕДРЕННО-ПОДКОЛЕННО-БЕРЦОВОГО СЕГМЕНТА

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Цель исследования - определить эффективность современных методов радиологической диагностики для улучшения результатов лечения больных дистальными окклюзионно-стенотическими заболеваниями бедренно-подколенно-берцового сегмента атеросклеротического генеза.

Проведен анализ обследований и лечения 150 пациентов с дистальным атеросклерозом, находившихся в отделении сосудистой хирургии Закарпатской областной клинической больницы им. А. Новака.

При ультразвуковом исследовании артерий бедренно-подколенно-берцового сегмента ложно-отрицательный и ложно-положительный результат наблюдались у 11 и 3 пациентов, соответственно. При дуплексном сканировании ложно-отрицательный результат наблюдался у 5 пациентов, ложно-положительный - у 2 пациентов, при рентгенконтрастной ангиографии (РКАГ) у 14 и 5 пациентов, при мультиспиральная компьютерная томография (МСКТ) - у 3 и 2 пациентов, соответственно. При исследовании глубокой артерии бедра (ГАБ) наибольшее число ложно-положительных и ложно-отрицательных результатов наблюдалось при ультразвуковом исследовании - 12 и 5 больных и рентгенконтрастной ангиографии - 18 и 12 пациентов, соответственно.

При сравнении радиологических методов диагностики артерий бедренно-подколенно-берцового сегмента и глубокой артерии бедра наиболее эффективными оказались МСКТ (89,1% и 90%, соответственно) и ультразвуковое дуплексное сканирование (88,7% и 82%, соответственно). Прогнозируемость метода исследования для диагностики артерий бедренно-подколенно-берцового сегмента для ультразвуковое исследования (УЗИ) составила 97,7%, для ультразвуковое дуплексного сканирования (УЗДС) – 97,1%, для рентгенконтрастной ангиографии (РКАГ) – 91,1%, для МСКТ – 98% при точности 90,7%, 95,3%, 78,2%, 95,5%, соответственно. Для ГАБ прогнозируемость УЗИ составила 95,9%, УЗДС – 96,9%, РКАГ – 58,6%, МСКТ – 99% при точности 88,7%, 93,3%, 66,5%, 97,3%, соответственно.

რეზიუმე

ბარძაყ-მუხლქვეშა-წვივის სეგმენტის არტერიების დაავადებათა დიაგნოსტიკის რადიოლოგიური მეთოდების ეფექტურობა

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კვლევის მიზანს წარმოადგენდა რადიოლოგიური დიაგნოსტიკის თანამედროვე მეთოდების ეფექტურობის განსაზღვრა ბარძაყ-მუხლქვეშა-წვივის სეგმენტის დისტალური ოკლუზიურ-სტენოზური ათეროსკლეროზული გენეზის დაავადებათა მკურნალობის შედეგების გაუმჯობესების თვალსაზრისით.

ჩატარებულია დისტალური ათეროსკლეროზის მქონე 150 პაციენტის გამოკვლევისა და მკურნალობის ანალიზი ზაკარპატიეს ა.ნოვაკის სახელობის საოლქო კლინიკური საავადმყოფოს სისხლძარღვთა ქირურგიის განყოფილებაში.

ბარძაყ-მუხლქვეშა-წვივის სეგმენტის არტერიების ულტრაბგერითი კვლევის შედეგად ცრუ-უარყოფითი და ცრუ-დადებითი შედეგი აღინიშნა 11 და 3 პაციენტთან, შესაბამისად. ულტრაბგერითი დუპლექსკანირებით ცრუ-უარყოფითი შედეგი აღინიშნა 5 პაციენტთან, ცრუ-დადებითი – 2 პაციენტთან, რენტგენოკონტრასტული ანგიოგრაფიით – შესაბამისად, 14 და 5 პაციენტთან, მულტისპირალური კომპიუტერული

ტომოგრაფიით – შესაბამისად, 3 და 2 პაციენტთან. ბარძაყის ღრმა არტერიების გამოკვლევისას ცრუდადებითი და ცრუ-უარყოფითი შედეგების ყველაზე დიდი რაოდენობა აღინიშნა ულტრაბგერითი კვლევის დროს, შესაბამისად, 12 და 5 პაციენტი, რენტგენოკონტრასტული ანგიოგრაფიის დროს, შესაბამისად, 18 და 12 პაციენტი.

ბარძაყ-მუხლქვეშა-წვივის სეგმენტის არტერიების და ბარძაყის ღრმა არტერიების დიაგნოსტიკის რადიოლოგიური მეთოდების შედარებისას ყველაზე ეფექტური აღმოჩნდა მულტისპირალური კომპიუტერული ტომოგრაფია (89,1% და 90%, შესაბამისად) და ულტრაბგერითი დუპლექს-სკანირება (88,7% და 82%, შესაბამისად).

ბარძაყ-მუხლქვეშა-წვივის სეგმენტის არტერიების დიაგნოსტიკისათვის კვლევის მეთოდის პროგნოზულობამ ულტრაბგერითი კვლევისათვის შეადგინა 97,7%, ულტრაბგერითი დუპლექს-სკანირებისათვის - 97,1%, რენტგენოკონტრასტული ანგიოგრაფიისათვის- 91,1%, მულტისპირალური კომპიუტერული ტომოგრაფიისათვის – 98% სიზუსტის მაჩვენებლებით, შესაბამისად, 90,7%, 95,3%, 78,2%, 95,5%. ბარძაყის ღრმა არტერიებისათვის ულტრაბგერითი კვლევის პროგნოზულობამ შეადგინა 95,9%, ულტრაბგერითი დუპლექს-სკანირებისა - 96,9%, რენტგენოკონტრასტული ანგიოგრაფიისათვის – 58,6%, მულტისპირალური კომპიუტერული ტომოგრაფიისათვის-99% სიზუსტის მაჩვენებლებით, შესაბამისად, 88,7%, 93,3%, 66,5%, 97,3%.

HYPERSENSITIVITY REACTIONS TO FOOD ADDITIVES IN PEDIATRIC PRACTICE: TWO CLINICAL CASES

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In the past, a list of foods, which humans consumed, was rather short. Meat, fish, milk, different vegetables were given by nature, some foods were „invented" by humans – bread, dairy products, sugar, wine. At present, we live in the era of scientific and technical progress, which significantly violated this idyll. It is simpler and cheaper to synthesize desirable taste, color and odor of food than to achieve it by improving the quality of food. Thus, currently we have to pay off for such „acceleration" [4,6]. Products from a „test-tube" possess many exceptional properties. For example, they do not spoil for months, even being exposed to the sun, preserve marketable condition for a long time. Often, appealing package has tiny writing on a label, which completely contradicts its content [2].

There are international standards for food products, which are united in unified nomenclature system "Codex Alimentarius". Thus, safety and quality of food products are regulated: consumers can be aware of the quality and safety of the products they buy, and importers – that food products, ordered by them, will meet their specifications [5,6].

In this sphere of legislative regulation, Law of Ukraine „On introduction of amendments to some legislative acts of Ukraine on food products" is in action (dated 22.07.2014 № 1602-VII) [5]. European integration law was approved by Verkhovna Rada (Supreme Council) of Ukraine to harmonize legislation of Ukraine with legislation of the European Union in the domain of safety and quality of food products.

Food additives are substances of natural and artificial origin, purposefully added to food products to achieve certain technological effects (color, resistance to spoiling, preservation of structure and appearance). Biological additives should be biologically inert for the body, because they are present in almost all food products and even in the so-called "ecological products". Use of food additives is under constant control of national and international organizations, which provide safety of food products. Presence of food additives in products is indicated on food labels [1,3].

Food additives are assessed and approved by The European Food Safety Authority; besides, each country makes decision concerning their permission within its territory. A list of approved food additives for manufacture of food products is constantly reviewed and renewed due to the last scientific data about their properties [4]. Nowadays, it includes several hundreds of substances. Among them approximately half are natural, the rest are synthetic. In different countries of the world about 500 food additives are currently used [11].

European council adopted a unified digital system for classification of food additives. All studied and checked additives by this classification received an index "E" (from the word "Europe") and three-digit code. Thus, the letter "E" became warranty of the study of food additive. It does not mean that any substance, which has "E" index, is allowed to be used and its influence on the human body has been studied [1,4].

Food additives can be added to products at different stages of their manufacture, storage and transportation to improve and ease manufacturing process, to increase resistance of the product to different kinds of spoiling, to preserve structure and appearance of the product. Different additives can remain in products completely, partially or as substances, which are formed as a result of chemical interaction with the components of food products [3,10].

Most food products, as a rule, do not have nutritional features and are biologically inert for the body. However, it is known that any chemical substance in certain conditions can be toxic. Thus, strict requirements are made in relation to food additives. They are considered safe, when acute and chronic toxicity, mutagenic, teratogenic and gonadotropic properties are absent.

Not only harmful and rather dangerous chemical substances are hidden under the labeling "E", but also harmless and even useful substances. There is no need to be afraid of all food additives. Many substances acting as additives are common extracts of natural products and plants. For example, an ordinary apple contains many substances, which are labeled with a letter E. For instance, ascorbic acid (E 300), citric acid (E 330), pectin (E

440), riboflavin (E 101), acetic acid (E 260). In addition to positive consequences of using food additives, negative side effects are also observed while being used by humans [1,3,5].

We have analyzed a list of products, which most often contain "harmful" food additives. Basic functional classes of food additives and their correlation with allergic reactions are presented in Table 1 [7,8].

Thus, dyes can be present in any products and are the most common cause of development of severe allergic reaction among food additives. Their amount is especially high in confectionery, sausages, pate, and beverages.

Preservatives are present in large amount in sauces, mayonnaise, beverages, meat, dairy products and confectionery.

Stabilizers and thickening agents by technological requirements are added to jams, marmalade, jelly, desserts, sauces, cheese and dry milk.

Emulsifiers, disintegrators can be a part of desserts, ice cream, dairy products, beverages, sauces, sausages, soups, broths.

Antioxidants are present in animal fats, oil for products with heat processing, soups, sauces, spices, canned products, dry breakfasts, chewing gum [3,4].

It should be taken into account that safe level is established for each additive, considering accessible daily dose. Such dose is calculated per kilogram of body weight. Thus, it is important for parents to understand that food, which contains food additives, should be given in certain amount to children. Daily accessible doses of synthetic dyes are presented in Table 2 [7].

Mean amount of tartrazine in food products:

- Yellow chewing gum – 74 – 160 mg/kg, orange – less 24 mg/kg, green – 28 – 86 mg/kg.
- Yellow pudding – 70 – 1223 mg/kg.
- Yellow jelly candies – 24 – 96 mg/kg, orange – less 14 mg/kg.
- Yellow beverages – 12 – 134 mg/kg, orange – less 118 mg/kg, green – less 21 mg/kg [4,7].

Table 1. Functional classes of food additives and their correlation with allergic reactions

<table>
<tr><td colspan="2">E 100 – E 181 – food additives and dyes</td><td>E 200 – E 299 – preservatives (promote preservation of products)</td></tr>
<tr><td colspan="2">E 100 – E 109 – yellow</td><td>E 200 – E 209 – sorbate</td></tr>
<tr><td colspan="2">E 110 – E 119 – orange</td><td>E 210 – E 219 – benzoate (urticaria, dermatitis, asthma)</td></tr>
<tr><td colspan="2">E 120 – E 129 – red</td><td>E 220 – E 229 – sulfite (asthma, urticaria, anaphylaxis)</td></tr>
<tr><td colspan="2">E 130 – E 139 – blue</td><td>E 230 – E 239 – phenols and formiates (methanoate)</td></tr>
<tr><td colspan="2">E 140 – E 149 – green</td><td>E 240 – E 259 – nitrate</td></tr>
<tr><td colspan="2">E 150 – E 159 – black, brown</td><td>E 260 – E 269 – acetate (ethanoate)</td></tr>
<tr><td colspan="2">E 160 – E 199 – other</td><td>E 270 – E 279 – lactate</td></tr>
<tr><td colspan="2">Threatening as to development of allergic reactions (dermatitis, urticaria)</td><td>E 280 – E 289 – propionate (propanoate)</td></tr>
<tr><td>E102 - tartrazine</td><td>E103 – alkaline</td><td rowspan="5">E 290 – E 299 – other</td></tr>
<tr><td>E104 – yellow quinoline</td><td>E105 – yellow transparent</td></tr>
<tr><td>E110 – yellow "sunset"</td><td>E111 – orange alpha-naphthol</td></tr>
<tr><td>E122 – carmuazine</td><td>E123 – amaranth</td></tr>
<tr><td>E124 – ponso 4R</td><td>E126 – ponso 6R</td></tr>
<tr><td colspan="2">E 300 – E 399 – antioxidants (slow down oxidation)</td><td>E 400 – E 481 – stabilizers (preserve consistency)</td></tr>
<tr><td colspan="2">E 500 – E 575 – emulsifiers (form homogenous mixture of products), disintegrators (maintain structure of a product)</td><td>E 631 – E 637 – fragrants</td></tr>
<tr><td colspan="2">E 900 – E 999 – anti-foaming agents (substances to decrease foaming)</td><td>E 1100 – E 1105 – enzymes, biological catalyzers</td></tr>
<tr><td colspan="2">E 1400 – E 1450 – modified starches (for the formation of necessary consistency)</td><td>E 1510 – E 1520 – solvents</td></tr>
</table>

Table 2. Daily accessible doses of synthetic dyes

Code of synthetic dye	Name of synthetic dye	Daily accessible dose, mg/kg of weight
E102	tartrazine	7.5
E104	yellow quinoline	0.5
E120	carmine	5.0
E122	carmuazine	1.25
E123	amaranth	1.25
E127	erytrozine	2.5
E131	blue patented V	2.5
E132	indigo carmine	5.0
E142	green S	5.0
E180	black S	1.0

In our practice, we faced possible harmful influence of food additives on a child's body. Our experience is given below as two clinical cases.

Clinical case №1. Patient S., 11 years old (weight 32 kg), consumed three liters of sparkling non-alcoholic beverage with multivitamin taste throughout a day. The symptoms developed in summer, it was hot and the boy was eating only bread and drinking the beverage all day.

Signs of severe allergic reaction were in the form of generalized urticarial rashes on the body, swelling of the eyelids and lips were observed (Fig. 1).

Family anamnesis was not burdened.

A doctor related the development of the disease to consumed beverage, since other causative and trigger factors could not be revealed.

Orange beverages contain 118 mg/kg of tartrazine. We calculated amount of consumed tartrazine E 102 by the patient: 118 x 3 kg (3 L) = 354 mg.

Accessible daily dose of E 102 is the following: 7.5 x 32 = 240 mg.

Thus, the boy consumed excessive amount of tartrazine E 102 in the beverage (dye, which gives intensive yellow and orange color), which, most likely, was the cause of severe urticaria and Quincke's edema.

Inpatient treatment lasting four days was conducted (hypoallergenic diet, dexamethasone, clemastine, sorbent) with further outpatient treatment (loratadine for 14 days). On the second day, swelling disappeared, on the fifth day, rash regressed completely.

Throughout 6-month monitoring, no allergic manifestations recurred in the child.

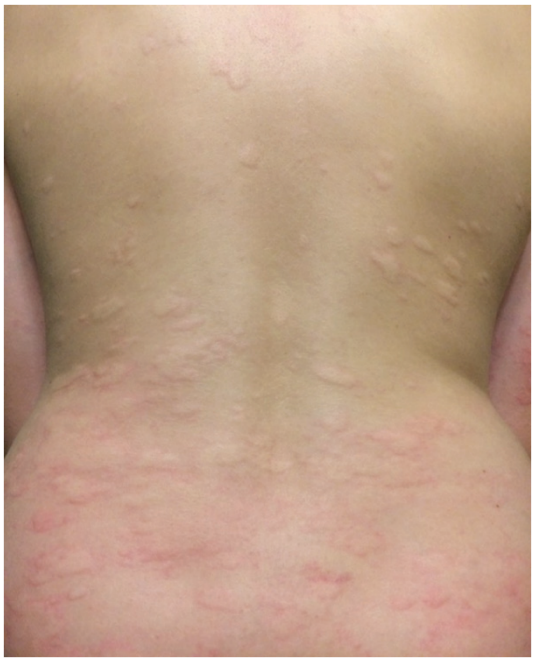

Fig. 1. Skin changes after consumption of sparkling non-alcoholic beverage with multivitamin taste

Clinical case №2. Patient K., 3 years old. On admission to inpatient department, there were complaints about rash on the body of spotty papular nature, generalized, in some places – merged, marked itching and restlessness (Fig. 2). Rash appeared in five hours after consumption of a colorful lollipop. Anamnesis: an episode of severe urticaria 10 months before (the child was cured in three days on an outpatient basis, was not examined).

Family anamnesis: not burdened.

Treatment was conducted on an outpatient basis for one day: diphenhydramine, sorbent. During the night the child was restless, cried and had marked itching.

Peculiarities of anamnesis: the child does not attend kindergarten, is constantly under mother's control. The day before, they had visited an entertaining center. The boy had dinner at home; in the center, he only drank fruit stew and ate a lollipop.

Ten months before, the patient experienced acute respiratory infection. During treatment of the infection, he received paracetamol 0.17 in suppositories (it was also used at age 6-7 months for fever during eruption of teeth) and cough syrup (carbocisteine) – liquid of orange color.

Having related two episodes of urticaria, we studied the composition of a lollipop and syrup.

Composition of a lollipop: glucose syrup, citric acid, corn syrup, glycerin, artificial dye (E 110).

Composition of cough syrup: carbocisteine, glycerol – 5 g, sucrose – 70 g, dye E 110 – 1 mg, filtered water.

Thus, the cause of severe urticaria in the patient was revealed – consumption of a lollipop and syrup, which contain a common type of dye – E 110 (yellow "sunset").

Administered treatment (hypoallergenic diet, intravenous administration of dexamethasone and chloropyramine hydrochloride, sorbent) enabled to stabilize the child's health condition within three days. Recommendations were given to follow diet and take cetirizine for 10 days. Throughout an 8-month monitoring of the child, no allergic manifestations were observed.

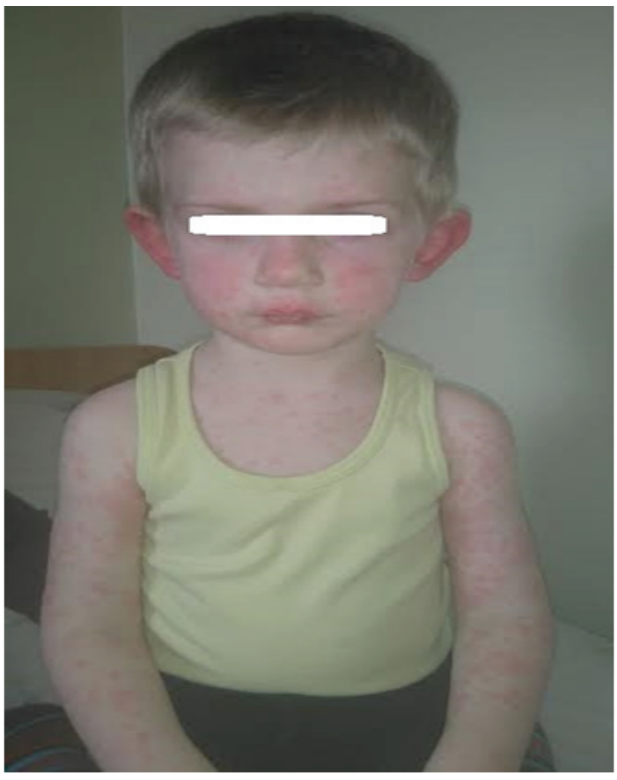

Fig. 2. Skin changes after consumption of a colorful lollipop

Thus, when buying or consuming a product, it is necessary not only to look at integrity of packaging, to read shelf life, but also its composition, including food additives. Do not be cheated with labels: "ecological product" or "it does not contain artificial dyes", because this product can contain ingredients, for

manufacture of which artificial or genetically modified elements were used [2,4]. The longer a list with the composition of product on the package, the more likelihood exists that it contains suspicious ingredients. Proper reading and analyzing of information on the label can be warranty of a child's and family members' health.

Conclusions. 1. Food additives are widely spread in the children's diet.

2. Brightly colored food products, goods with intensive odor and long shelf life are often the source of "harmful" food additives.

3. „Harmful" food additives are most commonly present in meat and dairy products, confectionery, beverages, sauces, canned products, spices.

4. It is necessary to instruct patients or their parents to read and properly interpret information on the package about composition of products and drugs.

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SUMMARY

HYPERSENSITIVITY REACTIONS TO FOOD ADDITIVES IN PEDIATRIC PRACTICE: TWO CLINICAL CASES

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The article presents analysis of causes of occurence and own diagnostic search for hypersensitivity to food additives in children.

Food additives are substances of natural and artificial origin, purposefully added to food products for certain technological effects (color, resistance to spoiling, maintenance of the structure and appearance). It has been shown in the article that most frequently „harmful" food additives are present in meat, dairy and confectionery products, beverages, sauces, canned products, spices. The most threatening as to the development of allergic reactions in children (dermatitis, urticaria) are the following additives: E 102 - tartrazine, E 103 - alkaline, E 104 - yellow quinoline, E 105 - transparent yellow, E 110 - yellow "sunset", E 111 - orange alpha-naphthol, E 122 - carmoazine, E 123 - amaranth, E 124 - ponso 4R, E 126 - ponso 6R. Regarding the preservatives, the most commonly spread triggers of allergic reactions are benzoates (E 210-219) and sulfites (E 220-229), which can cause urticaria, dermatitis, bronchial asthma exacerbations, and anaphylaxis.

Taking two clinical cases as the example, the observation of the development of severe allergic reactions associated with the harmful effects of certain nutritional additives (E 102 - tartrazine and E 110 - yellow „sunset") could be conducted.

It is necessary to instruct patients to read and correctly interpret the information on the packaging of the products. Brightly colored foods, products with intense smell and long shelf life are often the source of "harmful" food additives. The longer is the list of the ingredients of the product on the packaging, the higher is the likelihood that it contains doubtful ingredients.

Keywords: food additives, children, hypersensitivity.

РЕЗЮМЕ

РЕАКЦИИ ГИПЕРЧУВСТВИТЕЛЬНОСТИ К ПИЩЕВЫМ ДОБАВКАМ В ДЕТСКОЙ ПРАКТИКЕ (СЛУЧАИ ИЗ ПРАКТИКИ)

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В статье представлены анализ причин возникновения и собственный диагностический поиск гиперчувствительности к пищевым добавкам у детей.

Пищевые добавки – это вещества природного или искусственного происхождения, специально внесенные в пищевые продукты для достижения определенных технологических эффектов (цвет, стойкость, сохранение структуры и внешнего вида). В статье показано, что чаще всего «вредные» пищевые добавки находятся в мясной, молочной и кондитерской продукциях, напитках, соусах, консервах, специях. Угрожающими по развитию аллергических реакций у детей (дерматит, крапивница) среди красителей являются: Е 102 - тартразин, Е 103 - алканин, Е 104 - желтый хинолин, Е 105 - желтый прозрачный, Е 110 - желтый «закат», Е 111 - оранжевый альфа-нафтол, Е 122 - кармуазин, Е 123 - амарант, Е 124 - понсо 4R, Е 126 - понсо 6R. Среди консервантов триггерами чаще всего выступают бензоаты (Е 210-219) и сульфиты (Е 220-229), которые могут вызвать развитие крапивницы, дерматита, обострение бронхиальной астмы, анафилаксии.

На примере двух клинических случаев показано наблюдение за детьми с развитием тяжелых аллергических реакций,

связанных с вредным воздействием некоторых пищевых добавок (Е 102 - тартразин и Е 110 - желтый «закат»).

Необходимо развивать у пациентов навыки читать и правильно трактовать информацию на упаковке о составе пищевых продуктов. Ярко окрашенные продукты, с интенсивным запахом и долгим сроком хранения часто содержат «вредные» пищевые добавки. Чем длиннее список с составом продукта на упаковке, тем больше вероятность того, что в нем содержатся сомнительные ингредиенты.

რეზიუმე

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სტატიაში მოცემულია ბავშვებში საკვების დანამატებისადმი ჰიპერმგრძნობელობის აღმოცენების მიზეზების ანალიზი და საკუთარი დიაგნოსტიკური ძიება.

საკვები დანამატები ბუნებრივი ან ხელოვნური წარმოშობის ნივთიერებებია, სპეციალურად შეტანილი საკვებ პროდუქტებში გარკვეული ტექნოლოგიური ეფექტების (ფერი, სიმყარე, სტრუქტურისა და გარეგანი სახის შენარჩუნება) მიღწევისათვის. სტატიაში ნაჩვენებია, რომ "მავნე" საკვები დანამატები უფრო ხშირად არის ხორცის,რძის და საკონდიტრო პროდუქციაში, სასმელებში, სოუსებში, კონსერვებში, სპეციებში. ბავშვებში ალერგიული რეაქციების (დერმატიტი, ჭინჭრის ციება) განვითარების საფრთხის თვალსაზრისით საღებავებს შორის არის: Е 102 – ტარტრაზინი, Е 103 – ალკანინი, Е 104 – ყვითელი ქინოლინი, Е 105– ყვითელი გამჭვირვალე, Е 110– ყვითელი "დაისი", Е 111 – ნარინჯისფერი ალფა-ნაფტოლი, Е 122 – კარმუაზინი, Е 123 – ამარანტი, Е 124 – პონსო 4R, Е 126 – პონსო 6R. კონსერვანტებს შორის ტრიგერს ყველაზე ხშირად წარმოადგენს ბენზოატები (Е 210-219) და სულფიტები (Е 220-229), რომლებმაც შეიძლება გამოიწვიონ ჭინჭრის ციება, დერმატიტი, ბრონქული ასთმის გამწვავება, ანაფილაქსიური რეაქცია.

ორი კლინიკური შემთხვევის მაგალითზე ნაჩვენებია დაკვირვება ბავშვებზე მძიმე ალერგიული რეაქციით, რომელიც დაკავშირებული იყო ზოგიერთი საკვები დანამატის (Е 102 – ტარტრაზინი და Е 110– ყვითელი "დაისი") მავნე მოქმედებასთან.

პაციენტებისათვის აუცილებელია საკვები პროდუქტების შესახებ შეფუთვაზე დატანილი ინფორმაციის წაკითხვა და სწორად გააზრება. მკვეთრი შეფერადების პროდუქტები, ინტენსიური სუნით და შენახვის ხანგრძლივი ვადით, ხშირად შეიცავს "მავნე" საკვებ დანამატებს. რაც უფრო ხანგრძლივი შენახვის ვადაა მითითებული პროდუქტის შეფუთვაზე, მით მეტია ალბათობა, რომ იგი შეიცავს საეჭვო ინგრედიენტებს.

LYME BORRELIOSIS - ENDEMIC DISEASE IN CHILDREN OF TERNOPIL REGION

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Lyme borreliosis (LB) is an endemic multisystemic disease caused by the *Borrelia burgdorferi sensu lato spirochete (sl)*, which is transmitted to humans by ticks. Ixodes ricinus are carriers of the pathogenic Lyme borreliosis species in Europe [38].

There has been a sharp increase in number of episodes of LB in recent decades in Canada [8], Western Europe [57], especially in its northern region [55]. Incidence of LB in Ukraine is also steadily increasing. For example according to the data from the Center for Public Health of the Ministry of Health of Ukraine [5], only 58 cases of LB were registered in 2000 (0.12 per 100 000 of the population), and in 2018 there were already 5418 cases (12.78 per 100 000 of the population) (Figure 1). Therefore, during this period, the incidence of LB increased 93.4 times [31]. Slight decrease in number of cases was observed in 2019 with 4482 cases (10.6 per 100,000 population).

The incidences of Lyme disease in different areas depends on the frequency of borrelia-infected ticks (0 to 40%) and the lifestyle of the population [18,40]. As children are the most dynamic group of society, they are in a highest risk group of tick bite and therefore, of Lyme borreliosis. Often, ixodic ticks are concurrently infected with several pathogens of human infectious diseases [26,39,42].

Despite high incidence, it is difficult to detect *B. burgdorferi s.l* [32] because it affects multiple organs and systems [18]. Nonspecific symptoms of LB and lack of specific and sensitive laboratory diagnostics of neuroborelliosis complicate verification and classification of LB. Diagnostic criteria of Lyme disease (including Lyme disease of CNS in polyneuropathy) are recommended by European Federation of Neurological Societies: (EFNS). The following 3 criteria are named for diagnosis of late CNS Lyme disease with polyneuropathy: Clinical diagnosis of Peripheral neuropathy, CSF pleocytosis and presence of B. *burgdorferi* - specific antibodies in serum [37]. CNS Lyme disease diagnosis requires 2 of the 3 criteria to be met. In cases when a third criterion is missing, a repeat test is done in 6 weeks and it needs to be positive. Therefore, if the child has only nonspecific symptoms that can be caused by many other illnesses, misdiagnosing is possible. Additionally, the sensitivity of serological testing for LB may be low at an early stage but it increases to about 95% 8 weeks after the onset of the disease [22]. That's why we prescribe Routine two-stage test [53].

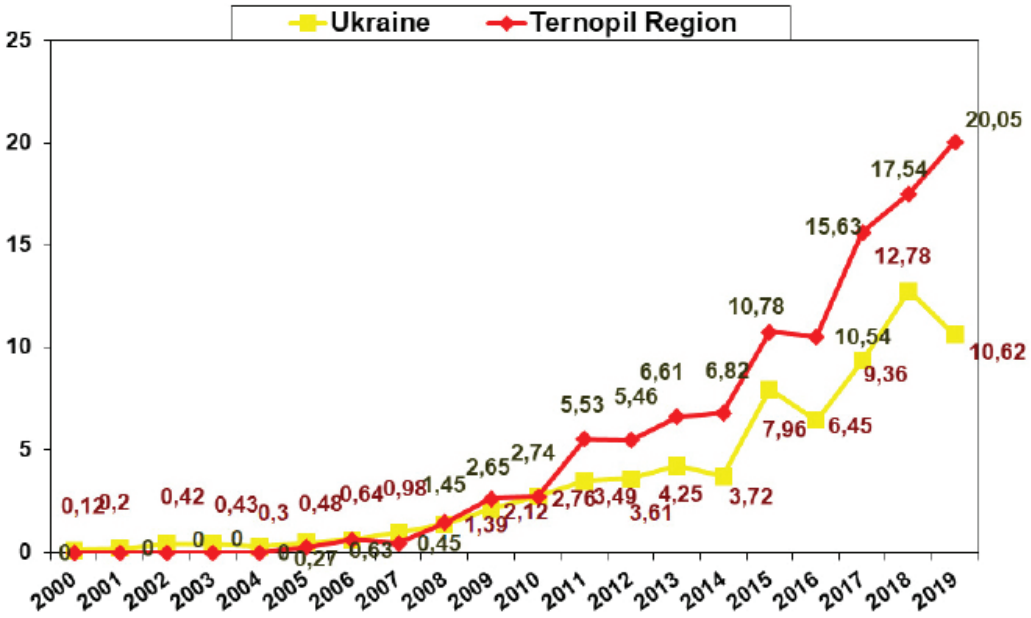

Fig.1. Incidence of LB cases per 100,000 population during 2000-2019 in Ukraine and Ternopil Region

It is very important to characterize the etiologic agents and their role in the pathogenesis and clinical manifestation of LB for two main reasons. First, endemicity' of Lyme disease in an area is an important factor that influences correct diagnosis. Second, the types of pathogens effect Lyme borreliosis symptoms and the timely diagnosis. Knowledge about these two factors helps medical doctors to estimate a patient's exposure and to start timely treatment **[**18,40**].**

Differences in the prevailing clinical picture depend on the genome of Borellia. About 18 genotypes of the complex Borrelia *burgdorferi sensu lato* are detected and studied, of which the pathogenic agents are B. *afzelii*, B. *garini*i, B. *burgdorferi sensu stricto*, B. *bavariensis* and B. *spielmanii* [9]. *B. afzelii* is more associated with skin infections, *B. garinii* – with neurological symptoms, and lesions caused by *B. burgdorferi sensu stricto* – with arthritis [53]. All three causative agents (*Borrelia burgdorferi s.l., Borrelia miyamotoi* and *A. phagocytophilum)* cause erythema migrans (ME). Several genotypes of the pathogen are also possible in one vector, which causes a polymorphic clinical picture [33].

The largest diversity of *B. burgdorferi sensu stricto* genotypes has been described in Europe and Asia [41]. Long-term observations have revealed that in Europe the disease is in most cases is caused by *B. afzelii* and *B. garinii*, [17] whereas in the US – by *B.burgdorferi* [8]. In Russia, the dominant spirochetes are *B. garinii* and B. *afzelii*. [26,34,52]. *B. burgdorferi* is the only cause of infection in the US, and is the most arthritogenic.

Aim of this study is to estimate the percentage of LB-infected ticks and to evaluate LB pathogen's genotype in children with clinical suspicion of Lyme borreliosis in the Ternopil region, Ukraine. A clinical and epidemiological connection between the tick bite and the development of clinical symptoms is explored.

Material and methods. Our study was conducted, in Ternopil region (Western Ukraine) and consists of two parts: during the first study we conducted a survey and in the second study we performed laboratory examination of collected ticks and blood samples.

Study 1. Our survey aimed at determination of complains and clinical features of the children with tick bite, that were admitted to Ternopil Regional Children's Hospital. Altogether 795 children who had clinical suspicion of Lyme borreliosis were enrolled in our survey. Survey was conducted by doctors of Ternopil Region Hospital. All participants completed a questionnaire that consisted of 20 questions. Questionnaire was filled out either by patients or by caregivers in those cases when the child was too young. Survey included questions about geographical location of tick bite, area of tick bite (upper limb, lower limb, neck, chest, shoulders, head, abdomen), time between tick bite and it's removal, method of tick removal, symptoms that occurred after the tick bite, presence of erythema migrans, treatment method of LB and other chronic diseases, having a pet and whether pet has been bitten by a tick. (Survey was done in 2018-2020 years).

Study 2. During the second study, we did laboratory analysis of the collected ticks and blood samples in order to determine the percentage of LB-infected ticks and to evaluate genotype of LB pathogen. This study was conducted in 2017 - 2019. 795 ticks and 109 blood samples were examined.

Ticks were used to detect infectious pathogens with following evaluation of pathogen's genotype. 70.0% of the ticks were extracted and the locus of bite was acepticized using anti-infective agent in Ternopil Children's Hospital. The rest of ticks were extracted by other methods. Examination was carried out in Laboratory of the Center for the study of Lyme borreliosis and other ticks infections of I. Horbachevsky Ternopil National medical university.

In order to detect infected ticks and to evaluate pathogen's genotype we conducted real-time Polymerase Chain Reaction (PCR) using [4]. Presense of the deoxyribonucleoside (DNK) of the following ticks pathogens was evaluated: B.*burgdorferi* s.l. (B. *afzelii*, B. *burgdorferi sensu stricto* and B. *garinii*), A. *phagocytophilum*, B.*miyamotoi*. We also evaluated pathogens in the mixed infections: B.*burgdorferi* s.l. and A.*phagocytophilum*, B. *burgdorferi* s.l. and B.*miyamotoi* and A. *Phagocytophilum*, B.*miyamotoi* with A. *phagocytophilum*, B.*burgdorferi* s.l.and B. *miyamotoi.*

Percentage of infected ticks was calculated from total number of 795 ticks that we studied. Infected ticks were the ticks that tested positively to Borrelia burgdorferi sensu lato DNK during PCR.

In order to detect species of ixodes that attacked children we conducted microscopia of 795 ticks.

According to the recommendations of the US Centers for Disease Control and Prevention (CDC) [6], routine two stage method (Fig. 2) was used to analyse blood samples in order to confirm LB diagnosis, to determine forms of the lesion, and to identify antigens of pathogens: *B. afzelii*, B. *burgdorferi sensu stricto* and B. *garinii*. [39]. 109 blood samples were taken from those children with tick bite who agreed to participate in the study and were able to donate blood for the confirmation of Lyme disease. The test was performed during the period within one and three month after tick bite. During the first stage, the presence of *B. burgdorferi s.l.* was detected by the method of immunoassay analysis using the Euroimmun AG test systems (Germany). Specific IgM were detected using Anti-Borrelia Burgdorferi ELISA (IgM), and antibodies IgG were detected by Anti-Borrelia plus VLsE ELISA (IgG). According to the manufacturer's recommendations, the result ≥ 22 RU/ml was considered positive, while in the range between 16 and 22 RU/ml it was considered intermediate, and if less than16 RU/ml result was negative [6, 17]. During the second stage, those children, (Fig. 2) who showed positive and intermediate result (63 children) in ELISA underwent immunoblot method (EUROLINE Borrelia RN-AT). IgM antibodies were detected by Anti Borrelia EUROLINE Borrelia RN-AT (IgM), and IgG antibody by using Anti-Borrelia EUROLINE RN-AT (IgG). According to the manufacturer's recommendations, the presence of specific IgM antibodies was considered positive, intermediate or negative, depending on the combinations of OspC antigens of the three species of Borrelia (B. *afzelii*, B. *burgdorferi* s.s. and B. *garinii*), p39 and VLsE Bb. At the same time, the presence of IgG was considered to be positive or negative, depending on the combinations of VLsE antigens of the three species of Borrelia (B. afzelii, B. burgdorferi s.s. and B. garinii) and other specific antigens: p18, p19, p20, p21, p58 , OspC (p25), p39, p83, Lipid Ba, Lipid Bb.

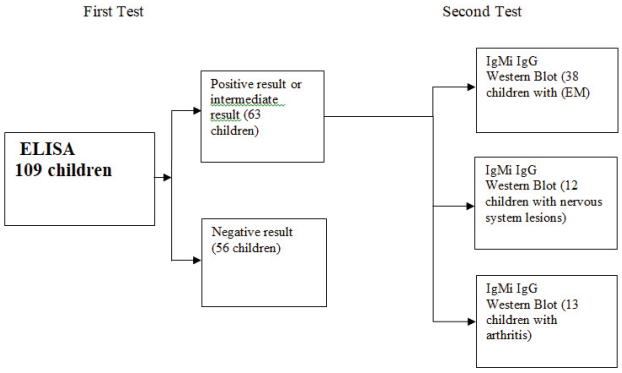

Fig. 2. Two Stage method

Additional examination was carried out in 33 children who had extracutaneus disseminated disease (arthritis=13, neurolyme=20). Out of 20 children with neurolyme 12 children were subject to two-stage test examination. These children did not have examined ticks, as they already developed clinical manifestations of LB. 12 children with neurolyme were subject to obligatory clinical-laboratory examination – CSF (cerebrospinal fuid), PCR, general blood analysis. CSF analyses included cell counts, glucosae, protein [11, 44]. Their CSF was tested by PCR in order to determine acidi nucleinici DNA of the pathogen. 13 children who had arthritis had general clinical examination, acute reumatic test, ultrasound examination of the knee joint.

Results and discussion. In this section we present results of the first study regarding clinical features of the children with tick bite and of the second study that aimed at determination of percentage of LB-infected ticks and genotyping of the infectious pathogens.

Study 1. We found that the average age of children, bitten by tick, was 11.9 years (children were aged from 6 months to 18 years). The gender distribution was 355 (44.6 %) girls, and 440 (55.3%) boys. Children were referred by general practitioners or (mostly general) pediatricians from all over the Ternopil region. Our survey showed that in 30% of tick bite cases 12 hours passed from the moment of the tick bite to tick removal, up to 24 hours – in 34.3%, 24 - 48 hours and more – in 4%, and 31.7% of children did not remember the bite itself.

The most common localizations of the bite are the section of the head 255 (32.%), ear 9%, and lower limbs 180 (22.6%). Torso (trunk front 67 (8,4%), trunk back 69 (8,6%) and abdomen were second most common localizations of the bite in 67 (8.4%) and 57 (7.1%) correspondingly. Neck 76 (9.5%), upper extremities 77 (9.6%) and section of sex organ 14 (1.7 %) are least common localizations.

The average interval between the tick bite and the appearance of clinical symptoms was 12 days. On average, the clinical diagnosis was established 14 days after the bite. Terms for treatment prescription lie within the range of 2 to 31 days.

According to the results of our survey, the leading symptoms of LB were Exanthema – in 83 (10.4 %) children, fever in 17 (2.1%), headache in 14 (1.8%), myalgia – in 15 (1.8%), and enlarged lymph nodes near the tick bite place – in 6 patients (0.75%). 520 (65.4%) respondents didn't report any clinical symptoms. 27 (3.4 %) respondents reported the itching at the bite's place, decreased vision – in 1 patient, pain at the site of bite – 7 (0.9%), infiltration at the bite point – 6 (0.7%), Scleroderma spots originated in 1 child. 11.9% of patients complained of fatigue, myalgias, and cognitive changes were noted in 12 (1.3%) children.

The survey showed that the most common clinical manifestation of LB is a typical skin disorder, known as erythema migrans (ME). EM, a rash spreading slowly from the site of a tick bite that may have been in apparent. Systemic symptoms, including myalgia and arthralgia, can accompany EM, especially in Bb and Bg infections [48]. As noted by G. Stanek (2012) [50], the peculiarities of the clinical manifestations of Lyme disease in children are sometimes similar to those seen in adults, although symptoms may take shorter and the result may be more evident [59]. ME appeared during the period for up to 24 hours in 25 patients (30.1%), 24 to 48 hours in 23 patients (27.7%), more than in 48 hours in 11 patients (13.2%), more than 3 days in 6 patients (7.2%), after several months – in 1 patient (2.3%). 17 people (20.5%) with ME did not remember the bite itself.

Detected ticks were removed with tweezers in 675 (84.9%) children, scratched off with a finger nail in 25 (3.1%), lubricated with fat (e.g. butter, oil) to make it get out - 28 (3.5%), other methods 67 (8.4%). A disinfectant solution was applied only in 701 (88.2%) children.

Our survey determined that the most common geographical location for the tick bite was the city, since 357 (45%) of children were bitten there, while only 143 (18%) reported being bitten in the village. 31 (17.3%) tick bites occurred in the forest, dacha 151(19%), 39 (5%) in the garden, 19 (23%) in the park, and 55 (7%) do not remember being bitten by the tick.

Among the examined group of patients there were detected concomitant diseases. 7 (0.8%) respondents reported Epstein Barr Infection, 23 (3.1%) reported diseases of the upper respiratory tract (bronchitis, adenoid vegetation, pneumonia), changes in the nervous system in 10 (0.8%). Congenital heart defects were reported in 3 cases.

28% of respondents have domestic animals, which lived in families, namely dogs, cats and rabbits. Pets were bitten by a tick in 26% of cases.

Study 2. We found that only 33.5% (267) of children who participated in the study were bitten by infected ticks (Table 1). LB was caused by one or few of the following pathogens: *B.burgdorferi s.l., A.phagocytophilum,* and *B.miyamotoi.* There were 172 tick bites in children registered during 2017 while only 34 (19%) ticks were infected by studied pathogens. *B.burgdorferi s.l.* was detected in 19 (55.9%) ticks*, A. phagocytophilum* – in 12 (35.3%). In 2018, there were 376 registered tick bites in children, and 128 (34%) of the ticks were infected with studied pathogens. Among the 128 infected ticks, removed from children's skin in 2018 *B.burgdorferi s.l.* was detected in 54 (42.3%) ticks, *A. phagocytophilum* – in 53 (41.4%). In 2019, 247 children were affected by ticks, only 105 ticks (42.5%) were infected . B. *burgdorferi* s.l. was detected in 57 (54.3%) of the infected ticks, A. *phagocytophilum* – in 33 (31.4%), B. *miyamotoi* – in 3 (2.8%).

We found that 33 ticks were infected with several pathogens. The DNA of infectious pathogens in mixed infections revealed that B. *burgdorferi* s.l. with A. *phagocytophilum* was found in 24 (8.9%) cases, B. miyamotoi and A. phagocytophilum – in 2 (0.74%), B. burgdorferi s.l., and B. miyamotoi – in 2 (0.74%), B. *burgdorferi* s.l., B. *miyamotoi* and A. *Phagocytophilum* - in 5 (1.8%) ticks (Table 2).

We identified that out of 795 studied ticks, 787 (98.9%) were Ixodes Ricinus and 8 (1.0%) - Dermacentor reticulatus.

Immunological examination of the blood samples, using ELISA method showed that out of 109 children 53 children were seropositive and intermediate and 56 - sero-negative.

In 109 children with lesions the following forms were noted:
- skin - erythema form in 83 (76.1%) cases;
- nervous system in 20 (18.3%) cases;
- arthritis in 13 (11.9%) cases;
- heart in 1 (0.9%) case.

The presence of Erythema migrans is considered the diagnostic criterion of LB disease without confirmation. The biggest group of patients with LB, namely 83 (76.1%) children had Erythema migrans.

Not all parents of the children agreed to participate in study. However, 20 children participated in two-stage study, and 19 respondents participated only in 2nd stage (taking into account that children often refuse injections).

During clinical examination of children with ME lesions of the nervous system with lesions of the neck muscles (1 child) have been identified. EM was pathognomonic syndrome in the beginning of the clinical symptoms in 15 children with disseminated form of LB, arthritis (10 children), and encephalitis (5 children).

20 children were diagnosed with disseminated form of lime borreliosis. Eight patients had a peripheral facial palsy, two patients had acute encephalitis, two had neuromuscular damage that were associated with neuroborreliosis.

We examined blood and spinal fluid in 10 patients and in one boy with nervous system disorder (neuro-lyme) by PCR. A. *Phagocytophilum* of spinal fluid was positive in one patient, B. *burgdorferi* s. was negative. Six patients had a pleocytosis.

Table 3 presents immunoblote results in 38 seropositive cases of erythema migrans, in 12 seropositive cases of neuroborelosis and in 13 seropositive cases of arthritis.

In our laboratory study we determined following indicators: OspC Ba (*B. afzelii),* OspC Bb *(B.burgdorferi)*, OspC Bg (*B. garinii)* to IgM*,* and OspC (*B. afzelii*) to IgG. Imunoblot method revealed, highly specific IgM for OspC B. *afzelii* in 28,57% cases (from 63 seropositive patiens), Ospc B. *burgdorferri in* 14.28% of cases, OspC Bg (B. *garinii*) in 23.8%, P41 in 46.03%. (For intermediate and high indicator).

Antigen VLsE IgG *B. afzelii* in 25.3%, VLsE *B. burgdorferri* 31.7.%, VLsE B. *garinii 23.8* % in patients with erythema migrans in the acute period of the disease P41 – 63.4 % (Table 3).

Table 1. Number and percentage of infected ticks in 2017-2019 and their genotype (PCR method)

Year	Total number of tick bites	Infected ticks		B.burgdorferi s.l.		A.phagocytophilum		B.miyamotoi	
		abc.	%	abc.	%	abc.	%	abc.	%
2017	172	34	19.7	19	55.9	12	35.3		
2018	376	128	34	54	42.3	53	41.4	3	2.3
2019	247	105	42.5	57	54.3	33	31.4	3	2.8
Total	795	267	48.6	130	48.6	98	36.7	6	2.2

Table 2. Number and percentage of different combinations of pathogens in infected ticks

Year	Infected ticks		B.burgdorferi s.l. and A.phagocytophilum		B. burgdorferi s.l., B.miyamotoi and A.Phagocytophilum		B.miyamotoi with A. phagocytophilum		B.burgdorferi s.l., B. miyamotoi	
	abc.	%	abc.	%	abc.	%	abc.	%	abc.	%
2017	34	19.7	3	8.8						
2018	128	34	14	10.9	4	3.1				
2019	105	42.5	7	6.7	1	0.9	2	1.9	2	1.9
Total	267		24	8.9	5	1.8	2	0.7	2	0.7

Table 3. Antigenic categories of borrelias depending on the pathology (immunoblot method)

IgM					IgG						
Indicator (n/%)	**P41 (n-%)**	**OspC Ba (*B. afzelii*) (n-%)**	**OspC Bb *(B.burg-dorferi)***	**OspC Bg (*B. garinii*) (n-%)**	**VLsE (*B. afzelii*) (n-%)**	**VLsE (*B. burgdor-ferri*) (n-%)**	**VLsE (*B. garinii*) (n-%)**	**Lipid Ba (B.*afzelii*)**	**Lipid Bb (B.burg-dorferri)**	**OspC (*B. afzelii*) (n-%)**	**P41**
Arthritis I* (n=3/11.9%)	-	2/ (15.4%)	-	1/ (7.7%)	2/ (15.4%)	2/ (15.4%)	1/(7.7%)		1/(7.7%)	1/(7.7%)	-
Arthritis H (n=13/11.9%)	5/ (38.5%)	2/ (15.4%)	1/ (7.7%)	2/ (15.4%)	3/ (23.1%)	3/ (23.1%)	2/ (15.4%)	1/(7.7%)	1/(7.7%)	6/ (46.2%)	7-53.8%
CNS I* (n=12/11.0%)	3/ (2.7%)	-	-	-	1/ (0.9%)	-	2/(1.8%)	1/(0.9%)	-	-	-
CNS H* (n=12/11.0%)	2/ (1.8%)	4/ (3.7%)	2/ (1.8%)	3/ (2.7%)	-	1/ (0.9%)	-	-	-	3/(2.7%)	6 / (5.4%)
Erythema I* migrans inter-mediate results (N=38/34/9.3.%)	12/ (31.6%)	4/ (10.5%)	3/ (7.9%)	4/ (10.5%)	-	4/ (10.5%)	2/ (5.3%)	-	-	7/ (18.4%)	1/(2.6%)
Erythema migrans high results H* (N=20/13.8%)	7/ (18.4%)	6/ (15.8%)	3/ (7.9%)	5/ (13.2%)	10/ (26.3%)	10/ (26.3%)	8/ (21.1%)	2/(5.3%)	-	8 (21.1%	26/ (69.4%)

*notes: * H –high, I –Intermediate Indicators*

We determined that, in the acute period of the CNS diseases highly specific IgM to OspC *B. afzelii* was found in 3.7% cases, Ospc B. *burgdorferri* in 6.8%, OspC Bg (B. *garinii*) in 2,7%, antigens P41 in 29% and IgG to VLsE B. afzelii 3.7%, Ospc B. *burgdorferri* in 1,8 % of cases VLsE B. *garinii* 1,8%, VLsE *B. burgdorferri 0.9%,* OspC *B. afzelii* in 2 .7%, while P41 in 4.5%.

Our results show that highly specific IgM to OspC B. *afzelii* was detected during the acute period of arthritis in 30.8% of the 13 children. OspC Bg (B. *garinii)* was detected in 23.1% of them, Ospc B. *burgdorferri* in 7.7% of cases and higher rate of positivity of the IgG OspC, VLsE B. *afzelii* - in 38.5% and VLsE (B. *burgdorferri*) in 38.5%, while VLsE (B. *garinii*) in 23.1%, Ospc B. *afzelii in* 53.9%. Lipid Ba (B.*afzelii) 15.4 %.*

Higher rate of positivity of the IgG p58 and OspC Antibodies against OspA, an indicator of later stage infection, occurred more frequently in the refractory group without reaching significant level. Over 85% of IgG - positive serum can only be identified by assessing VlsE antigen of the three species of Borrelia (B. *afzelii*, B. *burgdorferri* s.s. and B. *garinii*) **[9].**

We studied immunological parameters in various forms of LB: antibodies to *B. burgdorferi sensu stricto* was revealed in children with erythema migrans, arthritis and neurolyme; high specificity of IgM to OspC *(B. afzelii)* and *B. garinii* was detected in patients with arthritis and CNS; high levels IgG VLsE (*B. burgdorferri*) and VLsE (B. *burgdorferri*) was found in patients with skin disorders. As a result of immunological testing (immunoblot methods), we estimate organotropism of B. *burgdorfery* to skin lesion (erythema migrans) in 31, 6 %.

We performed survey and laboratory examination of children from a Lyme endemic region.

In our study 787 (98.9%) ticks were Ixodes Ricinus and 8 (1.0%) - Dermacentor reticulatus.

Findings from other studies suggest that in Ukraine are found three species of ticks: I. ricinus, D. reticulatus and R. sanguineus, and I. ricinus dominates [1, 46] This data coincides with findings of scientists from Belgium [29] that the great majority of ticks belonged to *Ixodes ricinus* (99%). Among the 10 species of ticks ixodides found in the Western region of Ukraine, Ixodes ricinus and Dermacentor reticulatus are the most common in the region (Ben, Lozynskyi, 2019) [33]. Prevalence of I. ricinus corresponds to our results, however it contrasts with indicators of infection with I. Ricinus ticks from the Czech Republic (0.8 – 7.2%) [26], Hungary (8.8%) [27], Poland (1.7-14.0%) [58], Slovakia (2.9 – 7.2%) [47].

We found that percentage of Borrelia - infected ticks in children of Ternopil region is 33.5%. This number is relatively higher in contrast to Ukraine in general, where number of infected ticks is 9.7 [5]. Overall, we find that edipemiological situation of LB in Ukraine is understudied, since the retrospective epidemiological analysis of Lyme borreliosis dynamics in the period from 2000 was done only in Sumy, Rivne and Kharkiv regions [31,34,36]. During 2000 – 2018, the incidence of Lyme disease increased 93.4 times in Ukraine. The increase in Sumy region (East of Ukraine) was 75.5 times (Sumy region) [31] and in Ternopil region (Western region) 167 times compared to year 2000 [5].

At the same time, percentage of infected ticks in Poland is 6.2% , in Ukraine - 9.7%, in Belarus - 9.4%, in Lithuania - 11%, in Russia – from 24.5% to 90%, in Latvia – from 18 to 51% [44,47,48]. Therefore our study shows that rate of infected ticks is much higher in Ternopil region than in Ukraine in general and also higher than in other neighbouring countries.

According to our results, the most common localizations of the bite are the section of the head 255 (32.%), ear 9%, lower limbs (22.6%). Our results coincide with other studies of children, that report up to 70% of the infestations take place on the head and its vicinity (behind the ears, on the hair line, neck) [2]. Studies of tick bites in adults report that skin of lower extremities, buttocks, groins and abdomen are the most frequent bite areas [40].

Tick-borne pathogens. Our PCR examination of the bacterial DNA, showed that only 267 (33.5%) ticks of 795 were contaminated by the gene-complex B.*burgdorferi sensu lato*. This finding coincides with the other findings that report number of ticks infected by B. *burgdorferi S. L* range from 0.5 to 85.0% in Europe and 15.3% in Poland [50]. In Germany, the percentage of infected ticks amounted to 11.1% [56]. In Romania and Belgium, the number of infected ticks was – 3.7 and 3.9%, respectively, while the researchers in Italy found a slightly higher rate – 5.7% [10, 29]. In another scientific work from Netherlands B. *burgdorferi* s.l. serologic tests were performed in 310 (95.4%) patients [39] and of these, only 28 children (32.9%) had a diagnosis of LB. Another study from USA reports that 19.2% of ticks are infected with B. *burgdorferi* s. l. [56].

We found B. *Burgdorfery* in 130 (48.6%) infected ticks, A. *phagocytophilum* in 98 (36.7%), and in 6 (2.2 %) – B. *miyamotoi*.

Even though the data on anaplasma infection in Ukraine is scance, according to Morochkovsky, I.I. Ben [36] the presence of A. phagocytophilum was identified by PCR method in 6 patients during the period from 2012 to 2014 in Volyn (Western region). In this research monoinfection (anaplasmosis) was detected in one patient, in other cases it was present an association with Lyme borreliosis. The author indicates that in mix-infection with Lyme disease, the symptoms of Human granulocytic anaplasmosis are weakness and diseases progresses with the prevalence of the clinical picture of borreliosis. Other studies on the structure of tick-borne zoonosis of the region have shown that in the Western Ukraine, the proportion of granulocytic anaplasmosis can be up to 28.6% [3], which is in line with our findings.

Mixed infections. In our study we detected the DNA of combined infections in ticks. We found B. *burgdorferi* s.l. in combination with A. *phagocytophilum* in 24 (8.9%) cases. Our findings correspond to findings of a study of mixed infections that were recorded in four DNA samples, representing the prevalence of B. *burgdorferi* s.l. and Borrelies and A.*phagocytophilum* of ten form combined cells in natural conditions and are able to be transmitted by tick bites as a mix-infection [30].

In our research B. *miyamotoi* and A. *phagocytophilum* was found in 2 (0.74%) cases. B. *burgdorferi* s.l., and B. *miyamotoi* was seen in 2 (0.74%) cases. B. *burgdorferi* s.l., B. *miyamotoi* and A. *Phagocytophilum* was detected in 5 (1.87%) ticks. In general, our findings on tick contamination by several pathogens are in line with the results of studies. However, some of the numbers are lower comparing to findings of other study of mixed infections where tick-borne pathogens, namely spirochetes from B. *burgdorferi* s. l. complex, *A. phagocytophilum*, and Babesia microti, were detected in 11.1% of tested I. ricinus ticks [10]. Other studies also report higher numbers of simultaneously diagnosed DNA of several bacteria – 3.8% [53]. Also in comparison to other study from Canada [15] we see prevalence of Borrelia *miyamotoi* infection, and co-infections with other *Borrelia* s.l. In our study in 2 cases, anaplasmosis was confirmed by IFA in patients' blood while clinically there was migrating erythema present.

These findings are consonant with the results of other studies. In scientific work [40] we found study of coinfection in patients with erythema migrans. In other scientific work B. *afzelii* is the most common genospecies isolated from human skin samples, and is therefore associated with skin manifestations of LB, whereas B. garinii predominates in cerebrospinal fluid specimens from neuroborreliosis patients [**26**]. According to the literature 2.3% - 10% of patients presenting with erythema migrans (acute Lyme disease) are cocomplex [11,17].

In our study genotype of *B. burgdorferi sensu stricto* was revealed in children with erythema migrans, arthritis and neurolyme. High level Ig G VLsE (*B. burgdorferri*) and VLsE (B. *burgdorferri*) was found in skin disorders.

High specificity of Ig M to OspC *(B. afzelii)* and *B. garinii* was presented in patients with arthritis in their blood and CNS (OspC Bg (B. *garinii)* was detected in 15% of them, OspC B. *burgdorferri* in 5% in children with arthritis and IgG OspC, VLsE B. *afzelii* - in 23.1% and VLsE (B. *burgdorferri*) in 38.5%, while VLsE (B. *garinii*) in 23.1%.

We have found antibodies against *B. burgdorferi in 57,7%* child. In the acute period of the CNS diseases highly specific IgM to OspC *B. afzelii* was found in 3.7% cases. specific IgM to OspC B. *afzelii* was detected during the acute period of arthritis in 30.8% of the 13 children. OspC Bg (B. *garinii)* was detected in 23.1% of them, Ospc B. *burgdorferri* in 7.7% of case.Antibodies against *B. burgdorferi* can be detected in 50-90% of patients in stage II of Lyme disease [16,27]. In the early phase of this stage mainly IgM antibodies are present, and in the late phase there are often only IgG antibodies, but the levels of specific IgM can persist for a long time [41].Our data is consonant with the survey of 96 practically healthy donors [38] which had antibodies in various titers to Borrelia burgdorferi s. l., the causative agent of the Lyme boreliosis, identified 11% of cases, to Ehrlichia ch., 4% of cases and 1% of cases to A. *phagocytophilum*., and in 3% of cases it had place of mixed-infection. In our study in one case, Anaplasma was detected by the PCR of spinal fluid. The serologic prevalence ranges from 1.9% to 14% in Germany , while clinically apparent infections of HGE have not been reported [30].

Manifestations of LB. In our study – erythema migrans form was found in 83 (76.1%) cases. This is due to the fact that solitary EM (SEM) is the characteristic sign of early localized LB. At the same time multiple EM (MEM) is one of the main characteristics of early disseminated stage of the disease. Our results coinside with other studies of European continent which report that ME is the most common single manifestation in about 90% of patients in population-based prospective studies [12-14,39] and skin manifestations account for 79–90% of all LB cases in children [33].

We observe 15 children who had out-of-skin forms of lyme borreliosis in the foreplay of the disease had EM. The high rate, early onset, and prolonged duration of risk for spirochetemia are found as possible explanations to why untreated patients with EM are at risk for dissemination of B.*burgdorferi sensu stricto* to anatomic sites beyond the skin lesion site. Differences in the strain of infecting spirochete, as well as host factors, may be important determinants of hematogenous dissemination [2,52].

According to some studies, B. *miyamotoi* is a tick-borne bacterium which has only recently been identified in Europe as a human pathogen causing relapsing fever and little is known about its local impact on human health [8,21,47] while in our study it had asymptomatic progress.

We find that 20 persons had extracutaneus disseminated disease (arthritis = 13, neurolyme = 20). Scientific literature confirm this finding that arthralgia and myalgia can be features of early disseminated disease [38]. Studies report that borreliosis arthritis and carditis are more common in the US, whereas neurological and late cutaneous manifestations are more commonly found in Europe [13,47,48]. According to Klyys [24], 18.3% of cases of LB disease in Ukraine are accompanied by lesions of the musculoskeletal system, while 10.7% by pathology of the cardiovascular system (in our study it is much smaller and only

1%). Klyys also finds that about 40% of lesions are of the nervous system while at our study it is much lower - only 18.3%. In children, the most common manifestations of neuroborreliosis are facial palsy (FP), uncommonly bilateral and meningitis. Some children may present with nonspecific complaints such as malaise, headache, fatigue and neck pain without clear neurological signs at physical examination [44].

In our study we found only two of three diagnostic criteria for CNS Lyme disease, namely clinical diagnosis of Peripheral neuropathy and CSF pleocytosis. Possible CNS Lyme disease requires 2 of the 3 criteria; if a third criterion is missing, a repeat test done 6 weeks later needs to be positive [35].Information on disease endemicity in an geographical area should be regularly provided to clinicians. Type of tick's pathogen and combination of pathogens influence Lyme borreliosis symptoms and course of the disease, therefore clinicians should determine pathogen's genotype to provide timely treatment of Lyme disease. When treating patients who were exposed to a tick in Tenopil region, Ukraine, medical doctors should consider B. *burgdorferi* s.l., B. *Miyamotoi*, A. *Phagocytophilum* pathogens and their combinations as a causative agent of infection.

Conclusions. The types of pathogens influence on Lyme borreliosis clinical symptoms and therefore on the timing of the diagnosing.

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SUMMARY

LYME BORRELIOSIS - ENDEMIC DISEASE IN CHILDREN OF TERNOPIL REGION

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The aim of research is to estimate the number of LB-infected ticks and to evaluate their LB pathogen's genotype in children with clinical suspicion of Lyme borreliosis in the Ternopil region, Ukraine.

In our first part of the study we conducted survey of 795 patients with clinical suspicion of Lyme borreliosis. In our second study we did laboratory analysis of the 795 ticks and 109 blood samples from children that were bitten by a tick. Real-time Polymerase Chain Reaction (PCR) using Vector-Best production test systems were used to detect infected ticks and evaluate pathogen's genotype.

Only 267 (33.5%) children from the total number were bitten by infected ticks. The following forms of the lesion were noted:- skin - erythema form in 83 (76.1%) children, nervous system in 20 (18.3%), arthritis in 13 (11.9%) and heart in 1 (0.9%).

The remaining (59.2.%) of children at the time of the study had no external manifestations and other clinical signs of the disease. LB was caused by one or a combination of the few pathogens: *B.burgdorferi s.l., A.phagocytophilum,* and *B . miyamotoi.* The DNA of several infectious pathogens *B.burgdorferi s.l., A. phagocytophilum, B. Miyamotoi* simultaneously were diagnosed in (12.3%). We identify antibodies to the Borrelia *burgdorferi sensu lato* in 57.7.% of the examined children.

The types of pathogens influence on Lyme borreliosis clinical symptoms and therefore on the timing of the diagnosing.

Keywords: Lyme disease, borreliosis, PCR, erythema migrans, lyme arthritis, neuroborreliosis, co-infection, ELISa, Immunoblot.

РЕЗЮМЕ

ЛАЙМ-БОРРЕЛИОЗ - ЭНДЕМИЧЕСКОЕ ЗАБОЛЕВАНИЕ У ДЕТЕЙ ТЕРНОПОЛЬСКОЙ ОБЛАСТИ

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Лайм-боррелиоз (ЛБ) является эндемическим многосистемным заболеванием, вызванным *Borrelia burgdorferi sensu lato (s.l).* Так как дети являются наиболее динамичной популяцией общества, они находятся в группе высокого риска укуса клещами и, следовательно, развития болезни Лайма.

Целью исследования является определение процента инфицированных лайм-боррелиозом клещей и оценка генотипа ЛБ-патогена у детей с клиническим подозрением на заболевание.

Исследованы 795 детей с клиническим подозрением на Лайм-боррелиоз. Выявлено, что 267 (33,5%) детей из общего числа укушены инфицированными клещами. На момент исследования у 109 детей отмечены следующие формы клинических признаков заболевания: кожа (эритемная форма) – у 83 (76,1%), нервная система - у 12 (11,1%), суставы – у 13 (11,9%), сердце – у 1 (0,9%). У остальных 158 (59.2.%) детей на момент исследования клинических проявлений не выявлено.

С целью выявления инфицированных клещей и оценки генотипа патогена определены Deoxyribonucleoside киназы (DNK) Borrelia burgdorferi sensu lato. системы тестирования vector-Best для в режиме реального времени полимеразной цепной реакции.

В результате исследования выявлено, что ЛБ вызван одним или комбинацией нескольких патогенов: B.*burgdorferi* s.l., A.*phagocytophilum* и B.*miyamotoi.* DNK нескольких инфекционных патогенов B.*burgdorferi* s.l., A. *phagocytophilum*, B. *Miyamotoi* одновременно были диагностированы в 12,3%. Антитела к Borrelia burgdorferi s. l. выявлены у 57,7% обследованных детей.

Типы патогенных микроорганизмов влияют на клинические проявления Лайм бореллиоза и, следовательно, на сроки постановки диагноза.

რეზიუმე

ლაიმ-ბორელიოზი – ენდემური დაავადება ტერნოპოლის ოლქის ბავშვებში

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ტერნოპილის ი. გორბაჩევსკის სახ. ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

ლაიმ-ბორელიოზი წარმოადგენს ენდემურ მრავალსისტემურ დაავადებას, რომელიც გამოწვეულია *Borrelia burgdorferi sensu lato (s.l)*-თი. ვინაიდან ბავშვები საზოგადოების ყველაზე დინამიკური ჯგუფია, ისინი ტკიპების ნაკბენის და, შესაბამისად, ლაიმის დაავადების მაღალი რისკის ჯგუფს მიეკუთვნებიან.

კვლევის მიზანს წარმოადგენდა ლაიმ-ბორელიოზით ინფიცირებული ტკიპების პროცენტის და ლაიმ-ბორელიოზის გამომწვევი გენოტიპის შეფასება ბავშვებში დაავადებაზე ეჭვის არსებობის შემთხვევაში.

გამოკვლეულია 795 ბავშვი ეჭვით ლაიმ-ბორელიოზზე. პოლიმერაზულ-ჯაჭვური რეაქციის (პჯრ) მეთოდით რეალური დროის რეჟიმში Vector-Best საწარმო ტესტური სისტემების გამოყენებით განისაზღვრა Borrelia burgdorferi sensu lato-ს Deoxyribonucleoside-კინაზები (DNK).

2017-2019 წწ. პერიოდში ლაიმ-ბორელიოზის და ტკიპებით გადაცემული სხვა ინფექციების კვლევის ლაბორატორიულ ცენტრში გამოკვლეულია 795 ბავშვი ტკიპების ნაკბენით, მათგან 267 (33,5%) ბავშვი ნაკბენი იყო ინფიცირებული ტკიპებით. დაზიანების ვარიანტის მიხედვით 109 ბავშვს აღენიშნა შემდეგი

ფორმები: კანის (ერითემული ფორმა) – 83-ს (76,1%), ნერვული სისტემის – 12-ს (11,1%), სახსრების – 13-ს (11,9%), გულის – 1 (0,9%).

პჯრ-მეთოდით ჩატარებული ეპიდემიოლოგიური კვლევის შედეგად გამოვლინდა, რომ ბორელიას პათოგენებით ინფიცირებული ტკიპების სიხშირე მერყეობს 34-42%-ის ფარგლებში. ტერნოპილის ოლქის ბავშვების სისხლის ნიმუშებში ერთდროულად დიაგნოსტირებული იყო რამდენიმე ბაქტერიის DNM - B. burgdorferi s.l.-ის, A. phagocytophilum-ის და B. Miyamotoi-ის. გამოკვლეული ბავშვების 57.7%-ს გამოუვლინდა ანტისხეულები Borrelia burgdorferi sensu lato-ს მიმართ. ჩატარებული კვლევის შედეგად დადგენილია, რომ პათოგენური მიკროორგანიზმების ტიპი მოქმედებს ლაიმ-ბორელიოზის დიაგნოსტიკის ვადებსა და მის სიმპტომებზე.

RISK FACTORS AND COMORBIDITY IN DIFFERENT TYPES OF FUNCTIONAL DYSPEPSIA: RETROSPECTIVE COHORT ANALYSIS

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Functional dyspepsia (FD) is one of the most common functional gastrointestinal disorders. Extensive trials demonstrated that FD affects nearly 10-30% of the population worldwide [3, 4, 7]. In global studies it was evaluated that FD was diagnosed in 14-27.5% of European population, 12-28% of USA and Canadian inhabitants, 18-28% of Asian population, up to 45% of men and women in Africa, and 24-39% of Australian inhabitants [2]. In 2012 the Ministry of Health of Ukraine published statistical data for Ukrainian population, according to which the prevalence rate of FD is 30-40%. Experts expect the real level to be significantly higher as around 50% of patients do not visit specialists, and so could not be included in official statistics [1].

According to Rome IV definition (2016) FD is a medical condition that has multifactorial pathophysiological factors [4].

There is a significant data about overlap of FD and irritable bowel syndrome (IBS), however mostly the data is based on the previous diagnostic criteria and do not include other pathologies [6,10].

In the previous researches there were no differential statistical analysis performed for different types of FD – postprandial distress syndrome (PDS) and epigastric pain syndrome (EBS).

Aim of the study - to assess potential risk factors and the prevalence of comorbid conditions associated with FD and to compare their frequency with the same in the group with no dyspeptic complaints and in patients with different types of FD – PDS and EPS.

Material and methods. We performed a retrospective database analysis of the patients with newly set diagnosis of FD on the basis of Gastro center of the Clinic "Oberig" in Kyiv, Ukraine in the period from June 2016 till June 2019. We compared the results of the patients with FD with the control group and in patients with different types of FD – PDS and EPS.

Diagnosis of FD was set if the patients had symptoms according to Rome IV criteria either for postprandial distress syndrome (PDS) (bothersome postprandial fullness or early satiety severe enough to affect daily life or ability to finish a regular-size meal for 3 or more days per week in the past 3 months, with at least a 6-month history) or for epigastric pain syndrome (EPS) (bothersome epigastric pain or epigastric burning 1 or more days per week in the past 3 months, with at least a 6-month history).

Patients with a prior organic upper or lower gastrointestinal diagnosis that might explain their symptoms, such as esophageal, pancreatic or bowel disease, were excluded. Patients with prior cancer, alcoholism or drug dependence recorded within 3 months before the FD was set, as well as pregnant women, were also excluded. Patients with red flag symptoms – onset in the age >45 years, persistent vomiting, signs of bleeding, iron deficiency anemia, family history of upper gastrointestinal cancer, progressive dysphagia and/or odynophagia – were not included into the analysis as well as cases with no details of medical history.
This study was conducted as a cross-sectional study in adult patients with FD and volunteers with no dyspeptic complaints. The 3 study groups were formed:

- Group 1 included 158 patients with PDS;
- Group 2 included 87 patients with EBS;
- Group 3 included 90 volunteers with no dyspeptic complaints.

There were no differences in age, sex, body mass index (BMI) among all study groups, and the duration of symptoms was equal in Group 1 and Group 2. The details are provided in Table 1.

Table 1. Clinical anamnestic characteristics of study participants

Characteristic	Study group			p	
	Group 1 (n=158)	Group 2 (n=87)	Group 3 (n=90)	p_{1-2}	$p_{(1+2)-3}$
Age, years (M±SD)	35.7±7.7	34.2±6.1	33.0±4.5	0.119*	0.007*
Women/men, n	98/60	54/33	58/32	0.948#	0.682#
BMI, kg/m^2 (M±SD)	21.1±1.9	20.9±1.8	21.0±1.8	0.507*	0.671*
Duration of symptoms, months (M±SD)	94.5±11.9	93.6±10.9	-	0.704*	-

** - t-test; # - χ2-test; no statistical significance of differences, p>0.05*

For all the cases the information on demographic (working status, family status) and lifestyle characteristics (BMI, smoking status, and alcohol consumption), and comorbidities were collected from the medical files.

The medical histories for all the patients were analyzed in details. All the participants underwent a complete blood count, glucose level test, TSH test, stool test, and abdominal ultrasound. *Helicobacter pylori* infection was diagnosed via rapid one-step immunochromatographic assay for detection of monoclonal *H. pylori* antigen in stool samples or in PCR for *H. pylori* DNA or using histological methods. Subjects older than 45 had esophagogastroduodenoscopy with proximal jejunoscopy and chromoscopy endoscopy using the Olympus Evis Exera III system with high-resolution functions, zoom up to ×115, narrowband imaging (NBI), followed by a morphological study of biopsy samples. In these cases biopsies from the duodenum and stomach also were obtained. MRI and/or CT of abdominal cavity were performed when necessary.

We statistically analyzed the presence of comorbidity and its frequency in the patients with FD (Group 1 and Group 2) and compared the results with control group (Group 3) and in the groups with different types of FD (Group 1 in comparison with Group 2) according to the generally accepted standards using the statistical program Statistica 6.

Results and discussion. Detailed results of demographic and lifestyle characteristics, and their associations with a FD diagnosis and type of FD are demonstrated in the Table 2.

Analysis of comorbid conditions demonstrated that in both groups there were cases of gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), chronic gastritis and/or duodenitis, anxiety, depression, autoimmune thyroiditis (AIT), arterial hypertension, ischemic heart disease (IHD). Detailed information about amounts of fixed comorbidities is shown in the Table 3.

Table 2. Demographic and lifestyle characteristics of the study groups

Characteristic		Study Group			P (χ^2)	
		Group 1 (n=158)	Group 2 (n=87)	Group 3 (n=90)	$p_{(1+2)-3}$	$p_{(1-2)}$
Smoking	Smokers	80 (50.6%)	39 (44.8%)	43 (47.8%)	p=0.742	p=0.640
	Non-smokers	63 (39.9%)	40 (46%)	36 (40%)		
	Ex-smokers	15 (9.5%)	8 (9.2%)	11 (12.2%)		
Alcohol consumption[1]	Normal	119 (75.3%)	60 (69%)	72 (80%)	p=0.194	p=0.284
	Higher than normal	39 (24.7%)	27 (31%)	18 (20%)		
Sleep disorders	Yes	38 (24.1%)	19 (21.8%)	11 (12.2%)	p=0.026*	p=0.695
Working status	Employed	103 (65.2%)	58 (66.7%)	80 (88.9%)	p<0.001*	p=0.816
	Unemployed	55 (34.8%)	29 (33.3%)	10 (11.1%)		
Family status	Married	78 (49.4%)	45 (51.7%)	49 (54.4%)	p=0.491	p=0.724
	Single	80 (50.6%)	42 (48.3%)	41 (45.6%)		

[1]According to National Institute on Alcohol Abuse and Alcoholism (NIAAA) weekly volume guideline normal alcohol consumption is not to exceed 14 drinks per week for men and 7 drinks per week for women
** statistical significance of differences*

Table 3. Comorbid conditions in the study groups

Comorbidity	Study Group			Odds ratio (OR)	
	Group 1 (n=158)	Group 2 (n=87)	Group 3 (n=90)	$OR_{(1+2)-3}$ (95%CI)	OR_{1-2} (95%CI)
GERD	40 (25.3%)	15 (17.2%)	7 (7.8%)	3.4 (1.50-7.9); **p=0.002***	1.6 (0.84-3.2); p=0.147
IBS	77 (48.7%)	30 (34.5%)	9 (10.0%)	7.0 (3.35-14.5); **p<0.0001***	1.8 (1.05-3.1); **p=0.031***
Chronic gastritis and/or duodenitis	82 (51.9%)	41 (47.1%)	29 (32.2%)	2.1 (1.28-3.5); **p=0.003***	1.2 (0.72-2.0); p=0.475
Anxiety	103 (65.2%)	61 (70.1%)	7 (7.8%)	24.0 (10.6-54.3); **p<0.0001***	0.8 (0.45-1.4); p=0.433
Depression	104 (65.8%)	38 (43.7%)	6 (6.7%)	19.3 (8.1-45.9); **p<0.0001***	2.5 (1.45-4.2); **p=0.001***
AIT	7 (4.4%)	5 (5.7%)	6 (6.7%)	0.7 (0.26-2.0); p=0.525	0.8 (0.23-2.5); p=0.648
Arterial hypertension	4 (2.5%)	2 (2.3%)	2 (2.2%)	1.1 (0.22-5.6); p=0.904	1.1 (0.20-6.2); p=0.910
IHD	5 (3.2%)	2 (2.3%)	3 (3.3%)	0.9 (0.22-3.4); p=0.820	1.4 (0.26-7.3); p=0.697

Statistical analysis demonstrated that smoking, alcohol consumption, and family status were not associated with the risk of FD. However the increased risk of FD was associated within the presence of unemployed ($p<0.001$), and sleep disorders ($p=0.026$).

The comparison of the results in the Group 1 and Group 2 demonstrated that there were no statistical difference in risk factors for the PDS and EPS ($p>0.05$).

We evaluated that GERD, IBS, chronic gastritis and / or duodenitis, anxiety, and depression occur more frequently in the group of patients with FD. At the same time no association between AIT, arterial hypertension and IHD was evaluated ($p>0.05$).

The presence of chronic gastritis and / or duodenitis was increased in the group of FD patients (OD 2.1, 0.95 CI 1.28-3.5). The more measurable overlap of FD with GERD was confirmed in our study if to compare with the Group 3 results (OD 3.4, 0.95 CI 1.50-7.9). The strongest association with FD was demonstrated for the IBS (OD 7.0, 0.95 CI 3.35-14.5), anxiety (OD 24.0, 0.95 CI 10.6-54.3), and depression (OD 19.3, 0.95 CI 8.1-45.9).

The comparison of the results in the Group 1 and Group 2 demonstrated that there was no statistical difference for the frequency of GERD, chronic gastritis and / or duodenitis, anxiety, AIT, arterial hypertension, and IHD ($p > 0.05$). However, IBS was more frequent diagnosed in the patients with PDS (OD 1.8, 0.95 CI 1.05-3.1). Depression also was set a comorbid disease in the group of patients with PDS, than with the EPS (OD 2.5, 0.95 CI 1.45-4.2).

As there is lack of data of the similar studies in Ukraine, we compared the received results with those that were published for European and American populations. In the previous researches there were no differential statistical analysis performed for different types of FD.

Overlap between FD and GERD was demonstrated in numerous studies. Y. Fujiwara and T. Arakawa performed a systematical review of the published studies and confirmed that in over half of the subjects with FD had GERD [5]. The data that was collected in those studies was based on Rome III criteria to set the diagnosis of FD.

According to Rome IV criteria, FD and IBS are distinct functional gastrointestinal disorders; however, overlap of these conditions is common in population-based studies. M. von Wulffen et al. published a huge cohort analysis that included data of 1127 cases of FD. In the study the overlap between FD and IBS was 64% [10]. In our study the frequency of FD / IBS overlap was 46.5%. There was no significant difference in comparison.

The relationship between FD and chronic gastritis has been being an objective of numerous studies, however it is still remains controversial. N. J Talley et al. published data that 50% of patients with functional dyspepsia have co-existent *H. pylori* gastritis [9]. Our findings were consistent with the published literature, however we did not performed any separate analysis for *H. pylori* status in this study.

Psychiatric and psychological comorbidities, including anxiety and depression, have been reported in FD. Overlap is reported consistently in studies from both tertiary referral centers and primary care. A. D. P. Mak et al. demonstrated that the symptoms of anxiety and depression were present in up to 40% of subjects with FD [8]. Our findings were consistent with the published literature.

Conclusions. Smoking, alcohol consumption, and family status were not associated with the risk of FD. However the presence of sleep disorders and being unemployed increased the risk of FD. The comparison of the results of the patients with different types of FD demonstrated that there were no statistical difference in risk factors for the PDS and EPS.

GERD, IBS, chronic gastritis and / or duodenitis, anxiety, and depression occur more frequently in the group of patients with FD. No association between AIT, arterial hypertension and IHD was evaluated. There was no statistical difference for the frequency of GERD, chronic gastritis and / or duodenitis, anxiety, AIT, arterial hypertension, and IHD in the patients with different types of FD. However, it was evaluated that IBS and depression occur more frequently in the group of patients with PDS, than in the patients with EPS.

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SUMMARY

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There is a significant data about overlap of functional dyspepsia (FD) and irritable bowel syndrome (IBS), however mostly

the data is based on the previous diagnostic criteria and do not include other pathologies. In the previous researches there were no differential statistical analysis performed for different types of FD – postprandial distress syndrome (PDS) and epigastric pain syndrome (EBS).

Aim of the study - to assess potential risk factors and the prevalence of comorbid conditions associated with FD and to compare their frequency with the same in the group with no dyspeptic complaints and in patients with different types of FD – PDS and EPS.

This study was conducted as a retrospective database analysis of the patients with newly set diagnosis of FD and control group. For all the cases the information on demographic (working status, family status) and lifestyle characteristics (body mass index, smoking status, and alcohol consumption), and comorbidities were collected from the medical files. We statistically analyzed the presence of risk factors, comorbidity and its frequency in the patients with FD and compared the results with control group and in the groups with different types of FD according to the generally accepted standards.

This study included 158 patients with PDS, 87 patients with EBS, and 90 volunteers with no dyspeptic complaints. Smoking, alcohol consumption, and family status were not associated with the risk of FD. The presence of sleep disorders and being unemployed increased the risk of FD. The comparison of the results of the patients with different types of FD demonstrated that there were no statistical difference in risk factors for the PDS and EPS. Gastroesophageal reflux disease (GERD), IBS, chronic gastritis and/or duodenitis, anxiety, and depression occur more frequently in the group of patients with FD. No association between autoimmune thyroiditis (AIT), arterial hypertension and ischemic heart disease (IHD) was evaluated. There was no statistical difference for the frequency of GERD, chronic gastritis and / or duodenitis, anxiety, AIT, arterial hypertension, and IHD in the patients with different types of FD. However, it was evaluated that IBS and depression occur more frequently in the group of patients with PDS, than in the patients with EPS.

Keywords: functional dyspepsia, postprandial distress syndrome, epigastric pain syndrome, risk factors, comorbidity.

РЕЗЮМЕ

ФАКТОРЫ РИСКА И КОМОРБИДНОСТЬ ПРИ РАЗНЫХ ТИПАХ ФУНКЦИОНАЛЬНОЙ ДИСПЕПСИИ: РЕТРОСПЕКТИВНОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ

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Функциональная диспепсия (ФД) является одним из самых распространенных функциональных гастроинтестинальных расстройств, которая поражает 10-30% мировой популяции. В ранних исследованиях продемонстрирован перекрест между ФД и синдромом раздраженного кишечника (СРК), хотя они базировались на предыдущих диагностических критериях и анализ не включал другие нозологии. Не проводился сравнительный анализ в группах с разными типами ФД – постпрандиальным дистресс-синдромом (ПДС) и эпигастральным болевым синдромом (ЭБС).

Цель исследования - оценка потенциальных факторов риска и распространенности коморбидных состояний при функциональной диспепсии, сравнение их частоты с таковой в группе волонтеров без диспепсических жалоб, а также среди пациентов с разными типами функциональной диспепсии – постпрандиальным дистресс-синдромом и эпигастральным болевым синдромом.

Исследование является ретроспективным анализом базы данных пациентов с недавно установленным диагнозом ФД и контрольной группы. Проанализирована медицинская документация: демографические данные (рабочий статус, семейное положение) и показатели образа жизни (индекс массы тела, курение, потребление алкоголя), а также наличие факторов риска, сопутствующей патологии и ее частота у пациентов с ФД. Результаты сравнены с контрольной и группами с различными типами ФД в соответствии с общепринятыми стандартами. Исследованы 158 пациентов с ПДС, 87 – с ЭБС и 90 волонтеров без диспепсических жалоб. Курение, потребление алкоголя и семейное положение не ассоциированы с повышенным риском формирования ФД. Риск ФД возрастал при нарушении сна и отсутствии работы. Факторы риска ПДС и ЭБС не различались. Гастроэзофагеальная рефлюксная болезнь (ГЭРБ), синдром раздраженного кишечника (СРК), хронический гастрит и/или дуоденит, тревога и депрессия встречались чаще в группах пациентов с ФД. Связи между аутоиммунным тиреоидитом (АИТ), артериальной гипертензией и ишемической болезнью сердца (ИБС) не выявлено. Статистически значимых различий по частоте ГЭРБ, хронического гастрита и/или дуоденита, тревожности, АИТ, артериальной гипертонии и ИБС у пациентов с различными типами ФД не обнаружено. Однако показано, что СРК и депрессия встречаются чаще в группе пациентов с ПДС, чем у пациентов с ЭБС.

რეზიუმე

რისკის ფაქტორები და კომორბიდობა ფუნქციური დისპეპსიის სხვადასხვა ტიპის დროს: რეტროსპექტული კოჰორტული კვლევა

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ფუნქციური დისპეპსია (ფდ) წარმოადგენს ერთ-ერთ ყველაზე გავრცელებულ ფუნქციურ გასტროინტესტინურ დარღვევას, რომელიც აზიანებს მსოფლიო პოპულაციის 10-30%-ს. ადრეულ კვლევებში ნაჩვენებია კავშირი ფდ-სა და გაღიზიანებული ნაწლავის სინდრომს (გნს) შორის, თუმცა, ეს კვლევები ეფუძნება წინა სადიაგნოსტიკო კრიტერიუმებს და ანალიზი არ მოიცავს სხვა ნოზოლოგიებს. ასევე, არ ჩატარებულა შედარებითი ანალიზი ფდ-ის სხვადასხვა ტიპებს შორის – პოსტპრანდიული დისტრეს-სინდრომი (პდს) და ეპიგასტრული ტკივილის სინდრომი (ეტს).

კვლევის მიზანს წარმოადგენდა ფუნქციური დისპეპსიის პოტენციური რისკის ფაქტორებისა და კომორბიდული მდგომარეობების გავრცელების შეფასება, მათი სიხშირის შედარება მოხალისეების ჯგუფის მონაცე-

მებთან დისპეპსიური ჩივილების გარეშე და პაციენტებს შორის ფუნქციური დისპეპსიის სხვადასხვა ტიპით.

კვლევა წარმოადგენს ფდ-ის ახლახან დადგენილი დიაგნოზის მქონე პაციენტების და საკონტროლო ჯგუფის მონაცემების რეტროსპექტულ ანალიზს. გაანალიზებულია სამედიცინო დოკუმენტაცია: დემოგრაფიული მონაცემები (სამუშაო სტატუსი, ოჯახური მდგომარეობა) და მონაცემები ცხოვრების წესის შესახებ (სხეულის მასის ინდექსი, თამბაქოს და ალკოჰოლის მოხმარება), ასევე, რისკის ფაქტორების, თანმხლები პათოლოგიის არსებობა და სიხშირე ფდ-ის მქონე პაციენტებში. საზოგადოდ მიღებული სტანდარტების მიხედვით შედარებულია საკონტროლო ჯგუფის და ფდ-ის სხვადასხვა ტიპის მქონე ჯგუფების მონაცემები. გამოკვლეულია 158 პაციენტი პდს-ით, 87 – ეტს-ით და 90 მოხალისე დისპეპსიური ჩივილების გარეშე. თამბაქოს და ალკოჰოლის მოხმარება და ოჯახური მდგომარეობა არ ასოცირდება ფდ-ის განვითარების მომატებულ რისკთან. ფდ-ის რისკი იზრდება ძილის დარღვევის და სამუშაოს არქონის პირობებში. პდს-ის და ეტს-ის რისკის ფაქტორები არ დიფერენცირ-დება. გასტროეზოფაგური რეფლუქსური დაავადება, გაღიზიანებული ნაწლავის სინდრომი, ქრონიკული გასტრიტი და/ან დუოდენიტი, შფოთვა და დეპრესია უფრო ხშირად აღინიშნებოდა ფდ-ს მქონე პაციენტების ჯგუფში. კავშირი აუტოიმუნურ თირეოიდიტს, არტერიულ ჰიპერტენზიას და გულის იშემიურ და-ავადებას შორის არ გამოვლინდა. გასტროეზოფაგური რეფლუქსური დაავადების, ქრონიკული გასტრიტის და/ან დუოდენიტის, შფოთვის და დეპრესიის, აუტოიმუნური თირეოიდიტის, არტერიულ ჰიპერტენზიის და გულის იშემიური დაავადების სიხშირის გათვალისწინებით ფდ-ის სხვა-დასხვა ტიპის ჯგუფებს შორის სტატისტიკურად მნიშვნელოვანი განსხვავება არ გამოვლინდა. თუმცა, ნაჩვენებია, რომ გაღიზიანებული ნაწლავის სინდრომი და დეპრესია უფრო ხშირია პაციენტებში პდს-ით, ვიდრე პაციენტებში ეტს-ით.

RESULTS AND ADVERSE OUTCOMES AFTER PERCUTANEOUS CORONARY INTERVENTION: HISTORICAL COHORT STUDY

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Coronary artery disease (CAD) is the most common type of heart disease and cause of mortality in the developed countries [14]. Because populations in advanced nations are aging thanks to the progress made in medical science, the number of elderly patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) has been increasing [11,22,25,29].

The mortality rate due to cardiovascular disease in Kazakhstan is two times higher than in European countries. [32] Unfortunately cardiovascular diseases are the main cause of low life expectancy and high mortality rate among people of working age. It constitutes a significant challenge for physicians and patients because of its devastating effect on the relatively active lifestyle of young patients and the substantial economical toll on society due to the cumulative loss of quality adjusted life-years. [10,23,30].

The highest numbers of acute coronary syndrome were recorded in the population of the North Kazakhstan region (137.7 cases per 100 thousand people), East Kazakhstan region (105.9 cases), Akmola (89.9 cases), Karaganda (85.4 cases) and Pavlodar (58.3 cases) regions. [33]. The Government of Kazakhstan has developed and over the past 10-15 years has implemented a targeted State program in the field of healthcare to reduce mortality from a cardiovascular disease, which is constantly being improved by new targets aimed at improving the effectiveness of preventive activities of medical organizations and increasing the commitment of citizens of the country to follow to healthy lifestyle. According to implementation of the State program "Salamatty Kazakhstan for 2011-2015", the population is provided with cardio surgical care. [28] Despite the constant development and improvement of cardio surgical care in Kazakhstan, due to which it was possible to reduce mortality from these diseases, the indicators are still disappointing. Percutaneous coronary intervention (PCI) has dramatically improved the prognosis of patients with coronary artery disease (CAD) [20].

A percutaneous coronary intervention is developed in Kazakhstan very quickly for many years. But there is no information about outcomes of this operation. The goal of this study was to analyze the short-term outcomes after percutaneous coronary interventions in two regions Kazakhstan during 2012-2018 years.

Material and methods. This is a historical cohort study of all patients who underwent percutaneous coronary intervention (PCI) in East Kazakhstan and Pavlodar regions of Kazakhstan. Individual-level mortality data were obtained from the registry. This registry is nationwide, obligatory, and automatically collected. The electronic patient registry – an information system entitled "Electronic In-patient Registry" (EIPR) that comprises health records of all patients hospitalized to healthcare facilities of Kazakhstan. The registry was established within the framework of the Unified National Health System in 2015 and presents a unified and centralized information database that stores all data on the record-by-record basis and enables access to relevant statistical information by provision of analytical reporting at the level of in-patient care. Currently, the Ministry of Healthcare of Kazakhstan obligates all medical doctors at hospitals to report on their hospitalized patients using a specially designed form and in turn, hospital technicians manually transfer the reported data to EIPR. The current study included patients who underwent PCI and were recorded in registry between January 2012 and December 2018. The study was approved by the ethical committee of the Semey Medical University, Kazakhstan (protocol 9 from 13 September 2017). Given that we used anonymized registry data, no consent from individual participants were required.

We use the data from three hospitals of Pavlodar and East Kazakhstan regions: Pavlodar regional cardiology hospital, Hospital of Semey medical university and East Kazakhstan regional hospital; only in these hospitals are made cardiac surgery in these regions.

We use official registry of these three hospitals. Data on age, sex, way of hospitalization, date of admission to the hospital, date of discharge from hospital, date of death, diagnose, treatment outcome were obtained from registry. Unfortunately, this registry does not have information about comorbidity of patients, reason of death, and risk factors.

In order to avoid selection bias, all patients who underwent surgery during the study period were included in the study. We used a standard data collection form to avoid misclassification bias. The study included 11931 patients who underwent PCI. The study included all deaths (320 cases) for the period from 2012 to 2018.

Continuous variables are summarized as means with standard deviation (SD). Discrete variables are described as proportions (frequency/percentage). A multivariate logistic regression analysis was utilized to find the independent predictors for in-hospital mortality. The variables entered into the model included age, gender, residency, way of admission, hospital, year of admission, diagnose. We only had these variables as say before. There was not information about diabetes, hypertension, dyslipidemia, renal failure, previous heart failure, coronary artery disease and MI in the registry. Odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Statistical significance was determined at P-values of <0.05 and all P-values were two sided. The incidence rates were calculated as

Table 1. Patients' characteristics

Characteristics	**N=11931**
Male, n (%)	8349 (70,0%)
Female, n (%)	3582 (30,0%)
Age (yr), mean (SD)	62,7 (10,40)
Male (yr), mean (SD)	60,5 (10,00)
Female (yr), mean (SD)	67,90 (9,41)
Age group, y n (%)	
<29	11 (0,1%)
30-39	158 (1,3%)
40-49	1009 (8,5%)
50-59	3425 (28,7%)
60-69	4279 (35,9%)
≥70	3049 (25,6%)
Residency n (%)	
Urban n (%)	8744 (73,3%)
Rural n (%)	3187 (26,7%)
Sending to hospital n (%)	
Sending by GP n (%)	3559 (29,8 %)
Sending by Consultative diagnostic clinic n (%)	959 (8,0 %)
Emergency ambulance n (%)	4704 (39,4 %)
Sending by other medical Institution n (%)	1479 (12,4 %)
Other n (%)	1230 (10,3 %)
Length of stay (n) mean (SD)	9,73 (4,23)
Way of admission to hospital n (%)	
Planned n (%)	3154 (26,4%)
Unplanned emergency way n (%)	8777 (73,6%)
Outcome n (%)	
Improvement n (%)	11597 (97,2%)
Without changes n (%)	14 (0,1%)
Death n (%)	320 (2,7%)
Diagnose n (%)	
Acute myocardial infarction (I21)	4872 (40,8%)
Chronic Ischemic Heart Disease (I25)& Angina pectoris (I20)	5878 (49,3%)
Subsequent myocardial infarction (I22)	1139 (9,5%)
Cerebral infarction (I63)	11 (0,1%)
Other diseases	31 (0,3%)

GP- general practitioner; SD – standard deviation

the number of cases per 100000 person-years of follow-up and 95% CI. The patient data were analyzed from the database, in which International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes is used to define the corresponding diseases. Statistical analysis was performed with SPSS. IBM SPSS Statistics for Windows, Version 20.0 (SSMU Semey city).

Table 2. Patients' characteristics who died in-hospital period

Characteristics	**N=320**
Male, n (%)	179 (55,9%)
Female, n (%)	141 (44,1%)
Age (yr), mean (SD)	70,5 (9,97)
Male (yr), mean (SD)	67,8 (9,71)
Female (yr), mean (SD)	73,9 (9,26)
Age group, y n (%)	
<29	0 (0,0%)
30-39	1 (0,3%)
40-49	7 (2,2%)
50-59	41 (12,8%)
60-69	98 (30,6%)
≥70	173 (54,1%)
Residency n (%)	
Urban n (%)	254 (79,4%)
Rural n (%)	66 (20,6%)
Mortality rate per 100 000 population	
Male (yr), mean (95% CI)	2144,0 (1841,4-2482,4)
Female (yr), mean (95% CI)	3936,3 (3313,4-4643,1)
Way of admission to hospital n (%)	
Planned n (%)	6 (1,9%)
Unplanned emergency way n (%)	314 (98,1%)
Mortality rate according to way of admission per 100 000 population	
Sending by GP mean (95% CI)	7187,5 (4556,2-10784,8)
Sending by Consultative diagnostic clinic mean (95% CI)	2500,0 (1079,3-4926,0)
Emergency ambulance mean (95% CI)	74375,0 (65225,9-84456,6)
Sending by other medical Institution mean (95% CI)	13750,0 (9990,8-18458,7)
Other mean (95% CI)	312,5 (7,9-1741,1)
Mortality rate according to hospital per 100 000 population	
Pavlodar regional cardiology hospital mean (95% CI)	2201,5 (1675,9-2839,8)
Hospital of Semey medical university mean (95% CI)	4626,9 (3848,3-5517,7)
East Kazakhstan regional hospital mean (95% CI)	2959,0 (2484,2-3498,6)
Diagnose n (%)	
Acute myocardial infarction (I21)	214 (66,9%)
Chronic Ischemic Heart Disease (I25)& Angina pectoris (I20)	7 (2,2%)
Subsequent myocardial infarction (I22)	93 (29,1%)
Cerebral infarction (I63)	5 (1,6%)
Other diseases	1 (0,3%)
Mortality rate according to diagnose per 100 000 population	
Acute myocardial infarction (I21) mean (95% CI)	4392,4 (3823,6-5022,6)
Chronic Ischemic Heart Disease (I25)& Angina pectoris (I20) mean (95% CI)	119,1 (4,79-245,4)
Subsequent myocardial infarction (I22) mean (95% CI)	8165,1 (6590,3-10002,7)
Cerebral infarction (I63) mean (95% CI)	45454,6 (14758,7-106076,2)
Other diseases mean (95% CI)	10000,0 (253,3-55716,3)

Table 3. Predictors of in-hospital mortality in all patients, using multivariate logistic regression analysis

Variable	Odds ratio	95% CI	p-value
Age	8,18	0,43-0,85	0,000
Gender	1,32	1,03-1,69	0,027
Way of hospitalization	14,71	6,48-33,37	0,000
Diagnose	42,31	19,95-89,74	0,000
Urban\rural	0,82	0,61-1,09	0,170
Hospital	1,01	0,91-1,12	0,867
Year of hospitalization	2,57	1,39-4,76	0,106
95% confidence intervals [CI]			

Results and discussion. A total of 11931 subjects who underwent PCI from 2012 to 2018 in Pavlodar regional cardiology hospital, Hospital of Semey medical university and East Kazakhstan regional hospital during the study period. Of these, 8349 (70,0%) were male, 3582 (30,0%) were female. Most of the patients 8744 were urban residents. The main way of hospitalization of patients was Emergency ambulance (8777). Majority of patients (66,9%) had diagnose acute myocardial infarction. A total of 320 patients (2,7%) died after the PCI during in-hospital period (2012-2018). Patients who died in-hospital period were predominantly male (55,9%), mean age 67,8 (9,71) years. Mortality rate was higher in women, and patients who were sent by other medical Institution. Mortality rate was higher in patients with diagnose cerebral infarction. The baseline patients' characteristics are presented in Table 1 and 2. A multivariate logistic regression analysis for the independent predictors of in-hospital mortality is presented in Table 3.

Percutaneous coronary intervention (PCI) is currently indicated for the management of patients presenting with acute coronary syndrome and in individuals with chronic stable angina that is refractory to optimal medical therapy. Advances in devices, stent design, adjunctive technology, development of more potent and effective antiplatelet therapy, and judicious use of PCI are increasing the safety of the procedure. However, major periprocedural complications during PCI still occur [12]. Evidence supports the use of stent implantation for patients with coronary artery disease (CAD) and acute coronary syndrome (ACS) [34].

In this cohort study, we compared patients' characteristics and adverse outcomes of patients underwent PCI from 2012 to 2018 in two regions of Kazakhstan. The main finding of our study is same as in the world. According to many international investigations the average age at presentation of coronary artery disease (CAD) is approximately 55 years for men and 65 years for women. [6, 30] The average age of our patients was 62,7 (10,40) years, while the average age of men was 60,5 (10,00) years, and of women was 67,9 (9,41) years (Table 1).

Despite advancements in the management of ACS, various studies have shown a clear disparity in the clinical outcomes between men and women, with women having worse outcomes. [2,4,5,19,21] There are pathophysiological differences in the causes of ACS with respect to sex. In men, there is typically rupture of a thin-capped atheromatous plaque which triggers thrombosis. Women are more likely to develop thrombosis caused by endothelial erosion. Women are more likely to present with atypical symptoms, have delays in the administration of treatment and therefore have longer ischemic times [24]. There is also evidence to suggest that women with ACS are less likely to receive evidence-based treatments and less likely to undergo cardiac catheterization and revascularization. [1,3,4,7,8,13-15,19,21,26,27].

According to our finding during the study period quantity of women who were underwent of PCI was less than men. (3582 (30,0%) vs 8349 (70,0%) (Table 1).

In contemporary PCI practice, there remains a disparity between the outcomes of women versus men, with women having significantly worse outcomes and a higher mortality. The causes are multifactorial and relate to differences in health-seeking behavior as well as sub-optimal medical therapy. Women are less likely to undergo cardiac catheterization and revascularization; are not treated as quickly as men; and are less likely to receive optimal pharmacotherapy [34].

Our findings also confirm these reports. So for men in hospital mortality rate was 2144,0 per 100 000 population and for women it was 3936,3 per 100 000 population (Table 2). A multivariate logistic regression analysis for the independent predictors in-hospital mortality demonstrated gender (OR=1,32, 95% CI=1,03-1,69, p=0,027), to be associated with higher in-hospital mortality (Table 3).

Coronary artery disease is a leading cause of mortality and morbidity in the elderly. Structural and functional changes in the cardiovascular system with aging and higher comorbidities make them more prone to unfavorable outcome [17]. Because populations in advanced nations are aging thanks to the progress made in medical science, the number of elderly patients with CAD undergoing PCI has been increasing. [11,18,22,29]

Our finding demonstrated that mostly in-hospital mortality was higher in patients aged 70 years and elder (173 (54,1%) (Table 2). A multivariate logistic regression analysis for the independent predictors in-hospital mortality demonstrated age (OR=8,18, 95% CI=0,43-0,85, p=0,000), to be associated with higher in-hospital mortality (Table 3).

Risk factors for death within the first year after the procedure were increasing age, history of heart failure, dyslipidemia and renal failure. Elderly acute myocardial infarction ST elevation (STEMI) patients undergoing PCI are consistently at an elevated risk for both in-hospital and long-term mortality. The higher burden of comorbid conditions [9,35] in the elderly makes age itself an important risk factor beyond other risk factors associated with advanced age [9]. Comorbidities such as hypertension (more frequent) [36], previous heart failure, peripheral arterial disease prior valvular disease and cardiogenic shock are known to increase with advancing age. Unfortunately the EIPR does not have information about comorbidities of patients such as hypertension, previous heart failure, peripheral arterial disease prior valvular disease and cardiogenic shock.

According to our data mainly patients who died during in-hospital period after PCI had diagnose Acute myocardial infarction 214 (66,9%), but mortality rate was higher at patients with diagnose Cerebral infarction (I63) - 45454,6 (14758,7-106076,2) per 100 000 population (Table 2). A multivariate logistic regres-

sion analysis for the independent predictors in-hospital mortality demonstrated diagnose (OR=42,31, 95% CI=19,95-89,74, p=0,000), to be associated with higher in-hospital mortality (Table 3).

We found that majority of patients 8777 (73,6%) were admitted to hospital for operation by unplanned emergency way and the rest of patients were admitted by planned way 3154 (26,4%). (Table 1) It is clear that mortality rate was higher in patients who were admitted by emergency service it was 74375,0 (95%CI:65225,9-84456,6) per 100 000 population, but we found that mortality rate among patients who were sent by other medical Institution was also high it was 13750,0 (95%CI: 9990,8-18458,7) per 100 000 population (Table 2), may be due to many factors, that were unclear we didn't have any information about risk factors of patients, and one of the main factor could be delay for operation. For a patient with angiographically proven coronary artery disease for whom surgical revascularization is planned, a long wait for the surgery may lead to worsening of symptoms, deterioration in the patient's condition and a less favorable clinical outcome. [31]

Pavlodar regional cardiology hospital started to make PCI earlier than other two hospitals. We hypothesized that this factor may affect to mortality outcomes. We compared mortality rate between three medical centers (Table 2). Mortality rate was higher in Hospital of Semey medical university (4626,9 (95%CI:3848,3-5517,7) per 100 000 population (Table 2). A multivariate logistic regression analysis for the independent predictors in-hospital mortality demonstrated that hospital to be not associated with higher in-hospital mortality (OR=1,01, 95%CI=0,91-1,12, p=0,867) (Table 3).

We suppose that year of hospitalization could influence to quality of PCI and worse outcome. But as was shown by multivariate logistic regression analysis that year of hospitalization to be not associated with higher in-hospital mortality (OR=2,57, 95%CI=1,39-4,76, p=0,106) (Table 3).

We compare in-hospital mortality between urban and rural residents, but the multivariate logistic regression analysis for the independent predictors in-hospital mortality demonstrated that residency to be not associated with higher in-hospital mortality (OR=0,82, 95%CI=0,61-1,09, p=0,170) (Table 3).

Study Limitations. This retrospective observational cohort study has some limitations that have to be taken into consideration when interpreting the results. The data are limited by the need to use ICD-10-CM codes for diagnoses, but the use of discharge diagnoses should improve discrimination. Risk adjustment is limited by the inability to determine the extent of disease using ICD-10-CM diagnostic codes. We had no information regarding the main cause of death, the rate of cardiac events and data regarding graft patency during the follow-up period. The lack of information regarding the main cause of death weakens the conclusions of this study. We also were unable to validate deaths that occurred outside the hospital for this study. Also unknown and unmeasured confounders may exist, and the results should be interpreted with caution.

Despite these limitations, it is first study in Kazakhstan where we analyzed adverse outcomes after PCI. The strengths of this study include the ability to collect data on all patients, because reporting is mandatory. Outcome information is secure in that data points are actual hospital admissions.

Conclusion. In summary, our study demonstrated that in-hospital mortality rate was higher in women than in men and in patients aged 70 years and elder. Mortality rate was higher at patients with diagnose Cerebral infarction. Majority of patients were admitted to hospital for operation by unplanned emergency way and mortality was higher in patients who were admitted by emergency service. Independent predictors of in-hospital mortality for patients of East Kazakhstan and Pavlodar regions were age, gender, way of hospitalization, diagnose.

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SUMMARY

RESULTS AND ADVERSE OUTCOMES AFTER PERCUTANEOUS CORONARY INTERVENTION: HISTORICAL COHORT STUDY

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Percutaneous coronary intervention (PCI) is developed in Kazakhstan very quickly for many years. But there is no information about outcomes of PCI. The objective of this study was to analyze the outcomes after percutaneous coronary interventions in two regions Kazakhstan during 2012-2018 years.

This registry-based historical cohort study obtained data on all patients who underwent PCI in East Kazakhstan and Pavlodar regions of Kazakhstan. Data are presented as the means ± standard deviation or as frequencies and percentage. The incidence rates were calculated as the number of cases per 100000 person-years of follow-up and 95% CI. A multivariate logistic regression analysis was utilized to find the independent predictors for in-hospital mortality. A total of 11931 subjects were undergone of PCI. Of these, 8349 (70,0%) were male, 3582 (30,0%) were female. A total of 320 patients (2,7%) died after the PCI during in-hospital period. Patients who died in-hospital period were predominantly male (55,9%), mean age 67,8 (9,71) years. Mortality rate was higher in women, and patients who were sent by other medical Institution and in patients with diagnose cerebral infarction.

In-hospital mortality rate was higher in women than in men and in patients aged 70 years and elder. Independent predictors of in-hospital mortality for patients were age, gender, way of hospitalization, diagnose.

Keywords: Percutaneous coronary intervention (PCI), Coronary artery disease (CAD), Kazakhstan, outcomes, incidence, mortality.

РЕЗЮМЕ

РЕЗУЛЬТАТЫ И НЕБЛАГОПРИЯТНЫЕ ИСХОДЫ ПОСЛЕ ЧРЕСКОЖНОГО КОРОНАРНОГО ВМЕШАТЕЛЬСТВА: РЕТРОСПЕКТИВНОЕ КОГОРТНОЕ ИССЛЕДОВАНИЕ

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Целью исследования явился анализ исходов после чрескожного коронарного вмешательства на примере двух регионов Казахстана (Восточно-Казахстанская и Павлодарская области) за период 2012-2018 гг.

В ретроспективное когортное исследование включены данные о пациентах, перенесших чрескожное коронарное вмешательство (ЧКВ). Данные представлены в виде среднего±стандартного отклонения или частот и процентов. Показатели заболеваемости рассчитывались как количество случаев на 100000 населения с 95%ДИ. Для выявления независимых предикторов внутрибольничной смертности использован многомерный логистический регрессионный анализ. В исследование включен 11931 пациент, перенесший ЧКВ, из них 8349 (70,0%) - мужчин, 3582 (30,0%) - женщины. Внутригоспитальная смертность после ЧКВ составила 320 (2,7%) случаев, в основном, мужчины (55,9%), средний возраст 67,8±9,71 лет. В результате проведенного анализа выявлены высокие показатели смертности у женщин и пациентов в возрасте 70 лет и старше, а также у больных с диагностированным инфарктом головного мозга. Показатели внутрибольничной смертности были выше у женщин, чем у мужчин, а ее независимыми предикторами были возраст и пол.

რეზიუმე

კანგავლითი კორონარული ჩარევის შედეგები და არაკეთილსაიმედო გამოსავალი: რეტროსპექტული კოჰორტული კვლევა

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კვლევის მიზანს წარმოადგენდა კანგავლითი კორონარული ჩარევის გამოსავლის ანალიზი ყაზახეთის ორი რეგიონის მაგალითზე (აღმოსავლეთ ყაზახეთის და პავლოდარის ოლქები) 2012-2018 წწ.

რეტროსპექტულ კოჰორტულ კვლევაში ჩართული იყო მონაცემები პაციენტების შესახებ, რომელთაც ჩაუტარდა კანგავლითი კორონარული ჩარევა. მონაცემები მოტანილია საშუალო სტატისტიკური გადახრის, ან სიხშირისა და პროცენტების სახით. ავადობის მაჩვენებლები გამოითვლილია, როგორც შემთხვევათა რაოდენობა 100000 მოსახლეზე 95%-იანი დაშვების ინდექსით. შიდაჰოსპიტალური სიკვდილობის დამოუკიდებელი პრედიქტორების გამოსავლენად გამოყენებული იყო მრავალფაქტორული ლოგისტიკური რეგრესიული ანალიზი. კვლევაში ჩართული იყო 11931 პაციენტი, რომელთაც ჩაუტარდა კანგავლითი კორონარული ჩარევა, მათგან 8349 (70,0%) – მამაკაცი, 3582 (30,0%) – ქალი. შიდაჰოსპიტალურმა სიკვდილობამ კანგავლიტი კორონარული ჩარევის შემდეგ შეადგინა 320 (2,7%) შემთხვევა, მათგან უმეტესობა - მამაკაცები (55,9%), საშუალო ასაკი – 67,8±9,71 წელი. ჩატარებული ანალიზის შედეგად გამოვლინდა სიკვდილობის მაღალი მაჩვენებელი ქალებში და 70 წლის და მეტი ასაკის პაციენტებში, ასევე, პაციენტებში დიაგნოსტირებული ტვინის ინფარქტით. შიდაჰოსპიტალური სიკვდილობის მაჩვენებლები, ასევე, უფრო მაღალი იყო ქალებში, ვიდრე მამაკაცებში, მის დამოუკიდებელ პრედიქტორებს კი წარმოადგენდა ასაკი და სქესი.

THE MAIN CAUSES OF THE COMPLICATED COURSE OF COVID-19 IN PATIENTS WITH DIABETES MELLITUS AND TREATMENT (REVIEW)

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Coronavirus disease 2019 (COVID-19) has confidently and aggressively marched across the planet since December 2019. Among the main risk factors for the development of a severe course of COVID-19 are old age, arterial hypertension, diabetes mellitus (DM), chronic obstructive pulmonary diseases, cardiovascular and cerebrovascular diseases [1]. Recently, based on the epidemiological data DM is not considered as a risk factor for SARS-CoV-2 infection, but diabetes is associated with a more severe course of COVID-19 [2]. What is the reason for the severe course of COVID-19 in diabetic patients? The need to provide an answer to this question led to this study.

The aim of this study was to determine the main causes of complicated COVID-19 course in diabetic patients.

Material and methods. Literature search was conducted through PubMed and Google Scholar using keywords: COVID-19, diabetes, hyperglycemia, carbohydrate metabolism disorders, complications. 946 publications were initially identified. Articles were published between December 2019 and July 15, 2020.

Results and discussion. In our opinion, there are three groups of factors that can worsen the course of infectious disease in patients with diabetes:

1. Features of DM and the mutual influence of the DM and COVID-19.
2. Influence of separate groups of drugs used in the treatment of both diseases.
3. Shortcomings in the organization of patients treatment and care.

Let's consider all the reasons in sequence.

Features of diabetes mellitus and the mutual influence of diabetes and COVID-19

Currently, there are only a limited number of experimental studies that directly concern the role of hyperglycemia and DM in the pathogenesis and prognosis of viral respiratory diseases [3]. Thus, Morra ME, et al. [4] discovered that elevated blood glucose levels can directly increase the concentration of glucose in respiratory mucosal secretions. Due to the influence of elevated glucose concentrations on lung epithelial cells, virus penetration and replication significantly increase in vitro, which let us suggest that hyperglycemia may increase virus replication in vivo. Elevated glucose levels can also lead to inhibition of the antiviral immune response. These results are similar to those in studies of patients infected with highly pathogenic avian influenza, where hyperglycemia was associated with a fatal outcome. Hyperglycemia can also affect lung function, that is why the respiratory dysfunction induced by the influenza virus is amplified in patients with DM. Diabetes is associated with numerous structural changes in the lungs, in particular with increased vascular permeability and collapse of the alveolar epithelium in animal models [5].

Another reason that complicates the course of coronavirus disease is the features of the autonomic nervous system in patients with DM. The severity of COVID-19 in diabetic patients may be hidden by a milder presentation of viral infection, with fewer patients experiencing fever, chill, chest tightness, and shortness of breath [6]. This phenomenon resembles the "silent" symptoms that are observed in DM. Thus, a disorder of the autonomic innervation of the heart which is described as "cardiac autonomic neuropathy" leads to damage to afferent autonomic fibers which determine the perception of pain during myocardial injury. As a result, diabetic patients often have painless "silent" myocardial infarction [7]. The same situation can be observed in patients with diabetes and COVID-19 who underestimate their symptoms. Thus, adequate treatment is not prescribed in time. As a result, medical help is delayed, complications develop, and treatment results worsen.

The next mechanism that influences the course of coronavirus disease is a pancreatic dysfunction in the background of infection. It is considered that SARS-CoV-2 leads to temporary disorders of the function of pancreatic islet cells [8]. It was found that coronaviruses attach to host cells using dipeptidyl peptidase-4 (DPP-4), which is physiologically involved in modulating the action of insulin, and as an enzyme plays a major role in glucose metabolism, and is responsible for the degradation of incretins such as glucagon-like peptide-1 (GLP-1) [9,10]. Hyperglycemia observed in patients with COVID-19 can be caused by these (or similar) mechanisms [11]. The problem of the need to prescribe DPP-4 inhibitors during the COVID-19 pandemic has been actively discussed in the scientific literature and there is currently no data on the need to cancel treatment with these drugs.

Another phenomenon that is observed in the case of the development of viral infection in patients with DM is the mutual influence of these two diseases. Thus, hyperglycemia itself can negatively affect lungs function and immune response [12], and diabetes is a risk factor influencing on the progression and prognosis of COVID-19. Guo W, et al. (2020) in their study founded that COVID-19 patients who had no other comorbidities except diabetes had a high risk of severe pneumonia, the release of tissue-related enzymes, excessive uncontrolled reactions to inflammation, and hypercoagulation associated with impaired glucose metabolism [13]. In addition, the serum level of inflammation biomarkers, such as interleukin-6 (IL-6), C-reactive protein, serum ferritin, prothrombin index, and D-dimer, were significantly higher ($p<0.01$) in diabetic patients compared to patients without DM, which indicates the development of a broader complex of inflammatory reactions in patients with diabetes, and this, in turn, leads to a rapid worsening of COVID-19 course [13].

In turn, COVID-19 can worsen the course of DM in patients. As Maddaloni E. and Buzzetti R. (2020) emphasize, the interaction between COVID-19 and diabetes can be bi-directional since SARS-CoV-2 can potentially worsen the course of co-existing diabetes or even predisposition to diabetes in individuals who do not suffer from DM [6].

Thus, hyperglycemia and insulin resistance are often registered in seriously ill patients, including COVID-19 patients. This happens due to the release of contrinsular hormones such as glucagon, cortisol, and epinephrine, as well as increased levels of pro-inflammatory cytokines such as IL-6 and TNF-α, which leads to a "cytokine storm" [14]. Their effect on insulin-sensitive tissues leads to a decrease in glucose uptake in muscles, increased lipolysis, and increased glucose synthesis in the liver [15].

COVID-19 can also manifest by dyspeptic symptoms, such as vomiting and diarrhea, leading to dehydration [16]. Research by Li J, et al. (2020) showed that SARS-CoV-2 infection was associated with ketoacidosis in 12% of diabetic patients [17].

It is generally recognized that some viral diseases can cause autoimmune type 1 diabetes in genetically predisposed patients, or even cause rapid development of diabetes from the mass collapse of β-cells [16]. COVID-19 uses the angiotensin-converting enzyme type 2 receptor (ACE-2) as a "gateway" to invade human target cells [18]. This enzyme is expressed by various tissues and cell types, including the lungs, as well as the endocrine part of the pancreas [18]. In a study by Yang JK, et al. (2010) it has been suggested that SARS-CoV-2, which also uses the ACE-2 receptor as an entry receptor, may damage the islets of Langerhans, causing hyperglycemia during the infection course [8]. Drucker DJ. (2020) reported a pancreatic injury characterized by elevated plasma amylase and lipase levels in 17% of patients with COVID-19, among whom 67% had moderately elevated plasma glucose levels [19].

The influence of certain groups of drugs used in the treatment of diabetes mellitus and COVID-19. ACE inhibitors

ACE inhibitors are currently the most controversial group of drugs often used in patients with hypertension and diabetes, including the cases of coronavirus disease. Although well-known angiotensin-converting enzyme 1 (ACE-1) promotes the conversion of angiotensin I to angiotensin II, its homologous analogue, ACE-2, is a membrane-bound enzyme (carboxypeptidase) that usually contributes to the inactivation of angiotensin II, and therefore physiologically contracts the activation of the renin-angiotensin-aldosterone system (RAAS) [18-20].

ACE-2 has many physiological roles, in particular: negative regulation of RAAS and facilitation of amino acid transport. Recently, ACE-2 was identified as a SARS-CoV-2 receptor that provides a critical link between immunity, inflammation, and cardiovascular diseases [21]. ACE-2 also acts as a receptor that

allows coronaviruses (SARS-CoV-2 and SARS-CoV) to enter human cells [22]. SARS-CoV-2, associated with ACE-2, is activated by type II transmembrane protease, serine 2 (TMPRSS2) to promote virus invasion and replication within human target cells, including type II pneumocytes [22]. On the other hand, ACE-2 plays a crucial role in maintaining glucose homeostasis and B-cell functions [19,23].

ACE inhibitors usually suppress ACE-1 but not ACE-2 [24]. However, studies have shown that these drugs enhance the regulation of the ACE-2 receptor, which the SARS-CoV-2 uses to enter host cells [25]. In turn, SARS-CoV-2 entering into human alveolar epithelial cells often leads to acute respiratory distress syndrome (ARDS), a clinical condition with high mortality associated with poor prognosis in patients with COVID–19 [26]. In addition, DM increases the expression of ACE-2, as shown in several experimental models [27,28], and the resulting increase in viral load may also explain the more severe course of COVID-19 in diabetic patients [29]. All this can complicate the course of COVID-19 and worsen the condition of patients taking ACE inhibitors. Some publications suggest replacing ACE inhibitors and angiotensin II receptor blockers in patients with hypertension and diabetes with other groups of drugs, such as calcium channel blockers [30].

However, there are other thoughts. In particular, a group of American and Dutch researchers led by Danser AHJ, et al. (2020) argue that ACE inhibitors do not inhibit ACE-2, since ACE-1 and ACE-2 are different enzymes, and therefore ACE inhibitors cannot contribute to the entry of the virus into the cell [22]. Also, there is no precise evidence to support the statement that ACE inhibitors or angiotensin II type 1 receptor blockers facilitate the entry of SARS-CoV-2 coronavirus by increasing the expression of ACE-2 [22]. Some other researchers agree with this position. Moreover, it is not known whether alternative antihypertensive agents do not have the same risk. Because of the lack of evidence, the European Medical Association (EMA) advises not to stop taking ACE inhibitors during the COVID-19 pandemic [31].

Ibuprofen and other non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are often used to treat hyperthermia in the case of viral infections. However, Day M. (2020) demonstrates four cases in which young patients with COVID-19 who did not have any underlying health problems developed serious symptoms after using NSAIDs at an early stage of the disease [32]. Somewhat earlier Voiriot G, et al. (2019) described cases of severe disease course with increased frequency of empyema, lung cavitation, and prolonged stay in the ICU of patients had used NSAIDs to treat pneumonia [33]. However, today WHO notes the current lack of evidence of severe adverse events and the need for additional medical care (hospitalization, intensive care, oxygen support) in patients with COVID-19 due to the use of NSAIDs [34].

NSAIDs, including ibuprofen, must be used with caution in patients with concomitant diseases of the gastrointestinal tract and cardiovascular system. It is contraindicated to use NSAIDs in the case of renal failure [35]. The NICE review (the UK, 2020) indicates that available evidence suggests that although the anti-inflammatory effect of NSAIDs reduces acute symptoms (e.g. fever), these drugs may either not affect or worsen long-term treatment outcomes, possibly due to masking symptoms of progression of acute respiratory infection. Additional evidence from randomized clinical trials is needed to confirm the effect of NSAIDs on the course of COVID-19 [36].

The use of NSAIDs to treat fever in patients with COVID-19 is still discussed. Until more evidence is found, Surviving Sepsis Campaign (2020) suggests that severely ill adults with COVID-19 should use acetaminophen (paracetamol) to treat fever [37]. It should be noted that the use of NSAIDs in patients with diabetic nephropathy is contraindicated due to the possibility of developing an acute renal injury. Therefore, we recommend to avoid using ibuprofen and other NSAIDs for the treatment of pain or hyperthermia and use paracetamol in patients with DM and COVID-19.

Glucocorticosteroids

Treatment protocols of critically ill patients often include extensive use of glucocorticosteroids (GCS), which significantly worsens infection-related hyperglycemia. A report from the Italian National Institute of Health (ISS, Istituto Superiore di Sanità) indicates that GCS was used in 34% of ICU patients [38]. At the same time, GCS therapy increases glucose levels in 80% of diabetic patients and in many non-diabetic patients, which may increase the risk of mortality in the case of coronavirus infection [39]. It should be remembered that GCS are not recommended to all patients with severe COVID-19. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with COVID-19 recommends using GCS only for patients who have mechanical ventilation due to severe ARDS, as well as for patients with refractory shock [37]. Using of GCS for patients without ARDS and in other routine cases is not recommended [37]. In the case of GCS prescription blood sugar level should be carefully monitored to maintain euglycemia, which contributes to optimal respiratory and immunological functions [37].

Hydroxychloroquine

Hydroxychloroquine and chloroquine are used to prevent and treat malaria and certain autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus. These medications are considered by researchers as one of the potential agents in the fight against COVID-19 [35]. However, hydroxychloroquine and chloroquine can have serious side effects. Thus, cases of cardiomyopathy, which led to the development of heart failure, have been reported, in some cases with a fatal outcome [40]. It is also noted that due to hydroxychloroquine using, QT interval is often prolonged, which can lead to dangerous arrhythmias [41]. It is interesting that in the mentioned study the administration of hydroxychloroquine was stopped prematurely in ten patients due to side effects: overwhelming nausea, hypoglycemia, and one case of ventricular arrhythmia torsades de pointes [41]. Besides, patients with DM may have severe hypoglycemia during treatment with hydroxychloroquine [42].

It is worth remembering that the molecule of hydroxychloroquine has a hypoglycemic effect and is used in India as an alternative means to reduce blood sugar level [43]. The mechanisms underlying this hypoglycemic effect are not well understood; a series of complex molecular effects can improve both insulin sensitivity and insulin secretion [16]. The dosage of hypoglycemic drugs should be adjusted.

However, there are some positive reviews. In particular, Singh AK, et al. (2020) believe that given the minimal risk of use, long-term experience in other diseases, cost-effectiveness and availability, hydroxychloroquine and chloroquine can be considered for clinical use as experimental drugs, even in patients with concomitant DM [43]. Taking into account the literature data, we consider that hydroxychloroquine can be used in patients with DM and COVID-19 only in exceptional cases within the clinical studies, and, of course, only in a hospital, under strict monitoring, and cannot be used by patients themselves.

Azithromycin

Azithromycin is a broad-spectrum macrolide antibiotic that has activity against bacteria and other microorganisms. There

are only insufficient evidence or contradictory evidence about the use of azithromycin together with hydroxychloroquine in COVID-19 patients [35]. In a study by Gautret P, et al. (2020) a positive result was obtained in 6 patients with lower respiratory tract infection due to COVID-19 treated with hydroxychloroquine together with azithromycin [44]. In a study by Rosenberg ES, et al. (2020) azithromycin treatment was performed in 211 patients, including 58 (27.5%) patients with DM, among 1,438 hospitalized patients diagnosed with COVID-19 in New York. However, this treatment did not lead to changes in the mortality rate [45]. If azithromycin is intended to be used for the treatment of COVID-19, it is necessary to check prescriptions and cancel unnecessary medications that may prolong the QT interval. While treating patients with a known hereditary long QT syndrome or a history of drug-induced polymorphic ventricular tachycardia (torsades de pointes) a decision about using these drugs must be made only after consulting a cardiologist [35].

Metformin and other oral hypoglycemic agents

Metformin was approved by the FDA in 1995 as an oral hypoglycemic agent, which has become one of the most commonly prescribed drugs to treat DM worldwide [46]. In recent years, it has been suggested that metformin may inhibit the activity of viruses by increasing insulin sensitivity [47]. In the United States, a retrospective cohort study was conducted from 2002 to 2012 for elderly patients over the age of 65 and with a history of diabetes who were hospitalized with pneumonia. It is interesting that pre-administration of metformin to these patients was associated with significantly lower mortality [48]. According to some authors, it is advisable to add to the indications for metformin using in the official instructions an option "as adjunctive therapy to reduce the risk of mortality from COVID-19 in elderly, obese and diabetic patients due to weight loss and reduced risk of pneumonia" [49]. Also, there are reports of the effectiveness of metformin in concomitant liver diseases and liver functional changes due to SARS-Cov-2 infection [50]. However, most researchers are not sure about the possibility of using metformin in coronavirus disease. Thus, Orioli L, et al. (2020) believe that patients with severe forms of COVID-19 should cancel metformin due to the risk of lactic acidosis [16]. In addition, metformin is contraindicated to patients with acidosis or risk of acidosis, including patients who have hemodynamic instability, hypoxia, and/or severe renal injury [51].

Thus, in severe forms of COVID-19, metformin and SGLT-2 inhibitors should be discontinued, taking into account their own risk of lactic acidosis and ketoacidosis.

There are several important issues to consider when using DPP-4 inhibitors in a hospital. The DPP-4 enzyme has been identified as a co-receptor for Middle East respiratory syndrome coronavirus (MERS-CoV), but not for SARS-CoV or SARS-CoV-2. At present, no data would demonstrate the harmful or beneficial effect of these drugs in patients with COVID-19 [19]. The use of saxagliptin and alogliptin is not recommended due to concerns about increasing the frequency of heart failure. It is important to note that all published trials of DPP-4 inhibitors usage in inpatient settings were conducted in combination with insulin for correction, and several were in combination with basic insulin therapy. Due to the unstable nature of acutely ill patients hospitalized with COVID-19, DPP-4 inhibitors are not generally recommended [52].

Thus, insulin therapy remains the standard of care for hyperglycemia in patients hospitalized with COVID-19. Selective use of DPP-4 inhibitors, sitagliptin and linagliptin may be considered for patients with type 2 diabetes or mild hyperglycemia when they have regular meals and are expected to be discharged home [52]. In the case of severe decompensation of DM and with disorders of consciousness, the transition to insulin as the optimal way to correct disorders of carbohydrate metabolism is mandatory.

Shortcomings in the organization of patients treatment and care

The first shortcomings in the treatment of patients with COVID-19 with concomitant DM have appeared since outpatient stage. It is known that most patients with diabetes cancel regular appointments to the endocrinologist. Many patients develop excessive stress associated with social isolation and lack of exercise, which contributes to the deterioration of glycemic control and further increases the risk of developing COVID-19 in this vulnerable category of patients [3]. Improper organization of outpatient appointments, insufficient and unbalanced nutrition, lack of medicines and diagnostic devices, insufficient communication with an endocrinologist and family doctor, disregard for personal hygiene and social distance – these are not all problems in the organization of treatment and care of patients during COVID-19 pandemic.

There are no fewer problems in the management of patients with DM and COVID-19 at the inpatient stage of treatment too. Thus, experimental data support the important thesis that glycemic control may favourably influence on clinical outcomes in patients with concomitant diabetes and viral respiratory diseases such as COVID-19 [3]. At the same time, most emergency medicine practitioners are not professional endocrinologists and they may not be concerned about the patient's blood glucose level and may have lack of clinical experience in diabetes therapy, which can lead to sharp fluctuations in glycemia and the development of acute disorders of carbohydrate metabolism in diabetic patients as shown by experience in outbreak centers [53]. Therefore, it is very important to raise awareness among doctors who are directly involved in the treatment of COVID-19 patients about the importance of controlling glycemia in these patients and to establish standardized management of glycemia in diabetic patients with COVID-19.

Zhou J. and Tan J. (2020) draw attention to the fact that during a stay in a quarantined hospital, it is impossible to exercise through limited indoor space and reduced respiratory function of the patient. In addition, a diet for COVID-19 patients or a personalized diet is often not available [54], while in a study by Li X, et al. (2020) it is shown that insufficient and improper nutrition is often observed in patients with severe disease [55].

Due to these factors, the optimal treatment of COVID-19 patients with concomitant DM should include a multi-disciplinary team approach involving specialists in emergency medicine, endocrinology, infectious diseases, respiratory support, nutrition and rehabilitation.

Performed analyses suggest that the main factor that is crucial in the management of COVID-19 patients with co-existing DM is the normalization of blood sugar level and carbohydrates metabolism by all possible means.

Conclusions:

1. Existing DM can complicate the course of COVID-19, worsen patients' condition and increase mortality.
2. According to the data analysis, in our opinion, there are three groups of factors that can worsen the course of infectious disease in patients with diabetes:

1) Features of the DM and the mutual influence of diabetes and COVID-19.

2) Influence of separate groups of drugs used in the treatment of both diseases.

3) Shortcomings in the organization of patients' treatment and care.
3. The main factor that is crucial in the management of COVID-19 patients with co-existing DM is the normalization of blood sugar level and carbohydrates metabolism achieved by all possible means.

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SUMMARY

THE MAIN CAUSES OF THE COMPLICATED COURSE OF COVID-19 IN PATIENTS WITH DIABETES MELLITUS AND TREATMENT (REVIEW)

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Among the main risk factors for the development of a severe course of Coronavirus disease 2019 (COVID-19) are old age, arterial hypertension, diabetes mellitus (DM), chronic obstructive pulmonary diseases, cardiovascular and cerebrovascular diseases.

The aim of this study was determinating the main causes of complicated COVID-19 course in diabetic patients.

Publications were searched using PubMed and Google Scholar for keywords: COVID-19, diabetes, hyperglycemia, carbohydrate metabolism disorders, and complications.

The review of scientific literature considers the main causes and pathogenetic mechanisms of COVID-19 complications development in patients with DM. Groups of factors that worsen the disease course were identified. We also proved that modern treatment of COVID-19 in diabetic patients should consider all risk factors and include a multidisciplinary team approach with specialists in emergency medicine, endocrinology, infectious diseases, respiratory support, nutrition and rehabilitation.

The main reasons that worsen the course of COVID-19 in patients with DM are features of DM and mutual influence of DM and COVID-19; the influence of separate medicines groups used in the treatment of both diseases; shortcomings in the organization of patients' treatment and care. The main factor that is crucial in the management of these patients is the normalization of blood sugar level and carbohydrates metabolism achieved by all possible means.

Keywords: COVID-19, diabetes mellitus, hyperglycemia, complications.

РЕЗЮМЕ

ОСНОВНЫЕ ПРИЧИНЫ ОСЛОЖНЕННОГО ТЕЧЕНИЯ COVID-19 У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ (ОБЗОР)

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Факторами риска тяжелого течения новой коронавирусной болезни (COVID-19) являются преклонный возраст, артериальная гипертензия, сахарный диабет (СД), хронические обструктивные заболевания легких, сердечно-сосудистые и цереброваскулярные заболевания.

Целью исследования явилось определение основных причин осложненного течения COVID-19 у больных сахарным диабетом.

Проведен поиск и анализ публикаций в системах PubMed и Google Scholar по ключевым словам: COVID-19, сахарный диабет, гипергликемия, нарушение углеводного обмена и осложнения. В обзоре рассматриваются основные причины и патогенетические механизмы развития осложнений COVID-19 у пациентов с СД. Выявлены группы факторов, ухудшающие течение заболевания.

Продемонстрировано, что при лечении пациентов с COVID-19 и сопутствующим СД основным фактором является нормализация уровня сахара в крови и углеводного обмена, достигаемая всеми возможными способами.

Основными причинами, ухудшающими течение COVID-19 у больных СД, являются: особенности СД и взаимное влияние СД и COVID-19; взаимодействие отдельных групп лекарственных средств, применяемых при лечении обоих заболеваний.

რეზიუმე

COVID-19-ის გართულებული მიმდინარეობის ძირითადი მიზეზები შაქრიანი დიაბეტით ავადმყოფებში (მიმოხილვა)

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პ.შუპიკის სახ. დიპლომისშემდგომი განათლების ეროვნული სამედიცინო აკადემია, კიევი, უკრაინა

ახალი კორონავირუსული დაავადების (COVID-19) მძიმე მიმდინარეობის რისკის ფაქტორებს მიეკუთვნება ხანდაზმული ასაკი, არტერიული ჰიპერტენზია, შაქრიანი დიაბეტი, ფილტვების ქრონიკული ობსტრუქციული დაავადება, გულ-სისხლძარღვთა და ცერებროვასკულური დაავადებები.

კვლევის მიზანს წარმოადგენდა COVID-19-ის გართულებული მიმდინარეობის მიზეზების განსაზღვრა შაქრიანი დიაბეტით ავადმყოფებში.

ნატარებულია პუბლიკაციების ძიება და ანალიზი სისტემებში PubMed და Google Scholar შემდეგი საკვანძო სიტყვებით: COVID-19, შაქრიანი დიაბეტი, ჰიპერგლიკემია, ნახშირწყლოვანი ცვლის დარღვევა და გართულებები.

სტატიაში განხილულია COVID-19-ის გართულებების განვითარების ძირითადი მიზეზები და პათოგენეზური მექანიზმები შაქრიანი დიაბეტით პაციენტებში. გამოვლენილია დაავადების მიმდინარეობის გაუარესების განმაპირობებელი ფაქტორების ჯგუფი.

ნაჩვენებია, რომ COVID-19-ის და თანმხლები შაქრიანი დიაბეტით პაციენტების მკურნალობის დროს ძირითად ფაქტორს წარმოადგენს შაქრის დონის და ნახშირწყლოვანი ცვლის ნორმალიზების მიღწევა ყველა შესაძლო საშუალებით.

შაქრიანი დიაბეტით ავადმყოფებში COVID-19-ის მიმდინარეობის გაუარესების განმაპირობებელი ძირითადი მიზეზებია: შაქრიანი დიაბეტის თავისებურებანი და შაქრიანი დიაბეტის და COVID-19-ის ურთიერთგავლენა; ორივე დაავადების მკურნალობისათვის გამოყენებული სამკურნალწამლო საშუალებების ცალკეული ჯგუფების ურთიერთქმედება.

МАРКЕРЫ ОЖИРЕНИЯ В КЛИНИЧЕСКИХ ИССЛЕДОВАНИЯХ И ПРАКТИЧЕСКОЙ МЕДИЦИНЕ (ОБЗОР)

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Ожирение по сей день является серьезной проблемой общественного здравоохранения. Всемирная организация здравоохранения (ВОЗ) признала ожирение эпидемией XXI века. По прогнозам эпидемиологов предполагается, что к 2025 г. от ожирения будут страдать 40% мужчин и 50% женщин. Глобальная эпидемия ожирения нарастает почти во всех странах мира, и в будущем ожидается дальнейший рост [42]. Ожирение увеличивает риск многих хронических заболеваний и ассоциируется с более низкими показателями продолжительности жизни. Наиболее распространенными заболеваниями, для которых ожирение представляет фактор риска, являются сахарный диабет 2 типа (СД2), сердечно-сосудистая патология, некоторые виды злокачественных новообразований [1,45].

В клинической практике для диагностики ожирения используют количественный параметр - индекс массы тела (ИМТ). Исследования показали, что дополнительно к ИМТ (кг/м 2), индекс талия/бедро (см) и индекс талия/рост (см) как мера распределения жира может улучшить прогнозирование заболевания. Все более сложные лучевые методы количественной оценки жировой ткани не всегда доступны в обычной клинической практике. Измерение биомаркеров, отражающих основные биологические механизмы повышенного риска заболевания является альтернативным подходом для характеристики соответствующего фенотипа ожирения. На современном этапе исследование гормонов и цитокинов, непосредственно секретируемых жировой тканью получило дальнейшее развитие благодаря применению методов, отражающих значимую информацию, связанных с ожирением, и может быть использовано для лучшей характеристики ожирения [39,61].

Антропометрические и лучевые методы оценки диагностики ожирения

ВОЗ определяет ожирение как аномальное или чрезмерное накопление жира, которое может нанести ущерб здоровью [76]. Традиционно ожирение классифицируется согласно индексу массы тела (ИМТ), рассчитанного как вес в килограммах, деленный на квадрат роста в метрах. Согласно ВОЗ и большинству современных руководств для западных стран, ожирение определяется как ИМТ ≥30 кг/м2 [17,76]. Эта классификация основана на более высоком риске смертности при ИМТ равном 30 и больше. В тех же рекомендациях избыточный вес (ИВ) классифицируется как ИМТ от 25,0-29,9 кг/м2, .нормальный вес колеблется при ИМТ от 18,5 до 24,9 кг/м2, а ИМТ ниже 18,5 кг/м2 считается дефицитом массы тела. ИМТ является простой и разумной мерой для диагностики ожирения, поскольку он коррелирует с жировой массой и связан с заболеваемостью и смертностью, как было показано в большом количестве эпидемиологических исследований. Однако хорошо известно, что ИМТ имеет некоторые значимые ограничения в диагностике ожирения на индивидуальном уровне. Прежде всего, несмотря на то, что ИМТ коррелирует с жировой массой, сам показатель не различает жировую и мышечную массу. Таким образом, лица с относительно небольшим количеством жира и более развитой мышечной массой могут иметь относительно высокий ИМТ.

Классификация страдающих ожирением на основе ИМТ различается в разных этнических группах и по возрасту. Например, предложено, чтобы предельные значения ИМТ для определения избыточного веса и ожирения были слишком высокими для азиатских групп населения, что привело к отсутствию диагностики ожирения и избыточного веса в этих группах населения. Предложены этнические ограничения ИМТ для лучшего учета ожирения и риска заболеваний [10], например, для азиатского населения в руководствах для Азиатско-Тихоокеанского региона [49]. Диагностика ожирения в детском возрасте является сложной ввиду быстрого развития, которое приводит к существенным изменениям ИМТ с возрастом. Чаще применяются возрастные референсные кривые, однако нет единого мнения относительно выбора соответствующих пределов для диагностики ожирения у детей референтных групп населения [76]. Другим значимым недостатком ИМТ как показателя ожирения является то, что он не отражает распределение жировой ткани в организме. Что касается связанных с ожирением метаболических последствий и риска заболевания, накопление висцерального жира вызывает особую озабоченность. В то время как подкожная жировая ткань представляет собой наибольшее жировое пространство по массе и размеру, висцеральная жировая ткань метаболический более активна и выделяет цитокины и гормоны, которые при дисбалансе смогут спровоцировать нарушения метаболических процессов, таких как резистентность к инсулину и хроническое воспаление [23].

Окружность талии (ОТ) или отношение талии к бедрам (индекс Т/Б) являются простыми измерениями для оценки распределения жира в организме и более тесно связаны с висцеральной жировой тканью, чем ИМТ [53]. По данным ВОЗ, рекомендуется проводить дополнительные измерения у лиц с ИМТ от 25,0 до 34,9 с целью определения абдоминального ожирения, при этом предлагаемый объем окружности талии составляет 102 см для мужчин и 88 см для женщин, для соотношения талии и бедер 0,95 у мужчин и 0,80 у женщин [17,76]. Однако в последнее время показано, что измерение окружности талии актуально и для более низких категорий ИМТ, поскольку риск заболеваемости и смертности значительно повысился у лиц с низким ИМТ, но с высокой окружностью талии [18,55]. Описанные ограничения классических мер исследований ожирения послужили поводом для применения различных более сложных методов, включая инструменты анализа биоимпедансометрии, ультразвуковое исследование (УЗИ), компьютерную томографию (КТ) и магнитно-резонансную томографию (МРТ). Указанные методы позволяют количественно определить объем и массу различных отделов тела, таких как жировая ткань в подкожном, вис-

церальном и эпикардиальном отделах, и обезжиренные отсеки, такие как костный мозг и ткань скелетной мускулатуры. Сравнения показали, что МРТ наиболее подходит для прямого надежного количественного определения массы жира [35,38,43,63], а алгоритмические усовершенствования позволяют в настоящее время автоматизировать с высокой повторяемостью и воспроизводимостью измерений. Хотя эти результаты свидетельствуют о высокой потенциальной полезности визуальных методов для исследования ожирения, а также клинического использования и стратификации риска, данные меры гораздо сложнее оценить в сравнении с измерением роста, веса, талии и окружности бедер, и они требуют значительных финансовых вложений [81,82]. Кроме того, не разработаны критерии оценки степени ожирения и не определены связи с этнической принадлежностью, возрастом, полом, в связи с чем в настоящее время они все еще имеют ограничения в клинической практике. Для оценки ожирения возможно также использование измерения толщины кожной складки [52]. Однако, существует значительная разница между индивидуумами в отношении толщины подкожной клетчатки и сжимаемости ткани в данном месте исследования [65].

В настоящее время нет единого мнения относительно анатомического участка, где следует измерять ОТ. Тем не менее, в исследовании детей в возрасте 6-9 лет обнаружено, что ОТ, определенный в средней точке между последним ребром и гребнем подвздошной кости, представляет лучшую корреляцию с процентным содержанием телесного жира. Bosy-Westphal et al. отметили, что у детей значения ОТ значительно различались в зависимости от анатомического места измерения. Наименьшее значение выявлено при измерении ниже последнего ребра, и самое высокое значение - над гребнем подвздошной кости, тогда как промежуточное значение было найдено в средней точке между этими участками [6,64].

Таким образом, интерпретация различий в ОТ между исследованиями разных популяций должна проводиться с осторожностью, учитывая, что измерение могло проводиться в разных анатомических участках [4,26,62].

Биологические маркеры, ассоциированные с ожирением

Эндокринная функция жировой ткани, в частности, секретируемые различные цитокины и адипокины висцеральной жировой ткани предложены в качестве биологической связи между ожирением и хроническими заболеваниями. Полученные знания могут быть использованы для расширенного определения ожирения, выходящего за рамки антропометрических измерений. Однако современные знания о специфической роли биомаркеров, связанных с ожирением, в развитии заболевания ограничены, и поэтому измерение биомаркеров ожирения в настоящее время не проводится в контексте диагностики ожирения в клинической медицине, однако в то же время представляют механизмы развития риска заболеваний.

Предполагается, что основными путями, обеспечивающими связь между ожирением и риском заболевания, являются ось инсулин/инсулиноподобный фактор роста (ИФР), хроническое воспаление, исследованы также лептин, адипонектин и другие специфические адипокины.

Инсулинорезистентность и гиперинсулинемия предло-

Таблица. Диагностические маркеры ожирения, их связь с хроническим заболеванием/смертностью и использование в практической медицине

Критерий	**Связь с хроническим заболеванием/смертностью по данным клинических исследований**	**Использование в практической медицине**
ИМТ	Сердечно-сосудистые заболевания [40,66], рак [59]. Смертность (диабет,сердечно-сосудистая патология, новообразования) [76]. Колоректальный рак [29,70], рак поджелудочной железы [8], эндометрия [48].	ИМТ≥30 кг/м^2 (ВОЗ). Стандартная практика для диагностики ожирения.
Коэффициент талия/бедра	Сердечно-сосудистые заболевания, СД 2 [15,12]. Рак [21].	>0,95 см у мужчин и >0,80 см у женщин.
Талия	Сердечно-сосудистые заболевания [15]. Рак [21].	При абдоминальном ожирении 102 см для мужчин и 88 см для женщин, ИМТ 25,0–34,9 кг/м^2 (ВОЗ).
СРБ	Колоректальный рак [44,57,82]. Не подтверждено для коронарной болезни сердца [73].	Использование биомаркера при расширенной диагностике ожирения.
Инсулин/С-пептид	Сердечно-сосудистые заболевания (ИБС, гипертония, без инсульта) [78]. Рак [54].	Использование биомаркера при расширенной диагностике ожирения.
ИФР-1	Колоректальный рак [60]. Рак и сердечно-сосудистая смертность [7].	Использование биомаркера при расширенной диагностике ожирения.
Резистин	Летальный исход среди пациентов с сердечно-сосудистыми заболеваниями или диабетом [19,20].	Использование биомаркера при расширенной диагностике ожирения.
Лептин	Колоректальный рак [31]. Не подтверждено для заболеваний сердечно-сосудистой системы [79].	Использование биомаркера при расширенной диагностике ожирения при ограниченных текущих данных
Адипонектин	Не подтверждено для заболеваний сердечно-сосудистой системы [34]. Нет подтвержденных данных для колоректального рака [46].	Использование биомаркера при расширенной диагностике ожирения при ограниченных текущих данных.

СРБ - С-реактивный белок

жены в качестве связи между ожирением и хроническими заболеваниями, такими как сердечно-сосудистые заболевания и СД 2 типа [32,58]. Показано, что инсулин натощак и С-пептид положительно коррелируют с ИМТ [58,1]. Результаты исследования общего ИФР-1 и ожирения выявили нелинейные или обратные ассоциации с ИМТ [2,13,39,50]. В мета-анализе проспективных когортных исследований более высокие концентрации инсулина натощак связаны с высоким риском гипертонии и ИБС, однако не с инсультом [78]. Показано, что С-пептид предсказывает общую и сердечно-сосудистую смертность у лиц, не страдающих диабетом, лучше, чем другие показатели инсулинорезистентности, включая инсулин натощак и глюкозу крови.

Участие в онкогенезе ИФР-1 подтверждено в многочисленных исследованиях, влияя на дифференцировку, миграцию и выживание клеток не только в здоровых, но и в клетках с генетическим повреждением [22,41].Показано также, что инсулин за счет подавления апоптоза и стимуляции пролиферации клеток, сам по себе влияет на риск развития рака [25,56]. Таким образом, инсулин и ИФР предложены в качестве одного биологического механизма, связывающего ожирение с риском развития рака [61]. Достоверные доказательства того, что метаболизм инсулина играет значимую роль в канцерогенезе, представлены в исследовании [72], в котором из наблюдения, что риск развития некоторых видов рака - поджелудочной железы, матки, ободочной и прямой кишки, молочной железы: выше у диабетиков, чем у лиц без диабета. Высказывается предположение, что гиперинсулинемия специфически связана с раком поджелудочной железы [69,74]. Серологические исследования, связывающие инсулин натощак или С-пептид с риском развития колоректального рака, выявили положительные ассоциации [30,54]. Умеренная положительная связь между концентрациями ИФР-1 и риском развития колоректального рака обнаружена в мета-анализе 11 проспективных исследований. В мета-анализе проспективных исследований, изучающих ИФР-1 и смертность, наблюдалась U-образная связь с более высоким риском смертности при низких и высоких концентрациях ИФР-1 [7].

Биомаркеры воспаления. Ожирение связано с хроническим системным воспалением, которое, предположительно, играет ключевую роль в патогенетических механизмах инсулинорезистентности [33]. Воспаление, вызванное ожирением, опосредуется секрецией провоспалительных адипокинов, таких как лептин и резистин и снижение производства противовоспалительного адипонектина. Благодаря доступности стандартизированных анализов и его временной стабильности [51], С-реактивный белок (СРБ) является наиболее изученным воспалительным биомаркером в отношении риска заболевания. Однако для определения хронического воспаления слабой степени необходимы высокочувствительные анализы, которые способны определить концентрацию СРБ в субклинических диапазонах. Таким образом, несмотря на то, что СРБ связывается с ЛПНП и присутствует в атеросклеротических бляшках, его причинная роль при сосудистых заболеваниях поставлена под сомнение, поскольку точный биологический механизм для СРБ в атерогенезе не известен. Предполагается, что при раке связанное с ожирением хроническое воспаление слабой степени играет роль в канцерогенезе, способствуя пролиферации, выживанию и миграции клеток [11]. Существуют доказательства положительной связи между концентрациями СРБ и риском развития рака [3,27]. В мета-анализе 18 проспективных исследований (все использовали высокочувствительный анализ СРБ) высокие концентрации СРБ связаны с более высоким риском развития колоректального рака [82]. В исследовании EPIC лица, несущие генетические варианты *СРБ,* связанные с его высокими концентрациями в течение всей жизни, подвержены высокому риску развития колоректального рака, подтверждая гипотезу о том, что повышенный уровень СРБ непосредственно вовлечен в колоректальный канцерогенез [44].

Адипокины. Жировая ткань представляет собой активный эндокринный орган, выделяющий различные гормоны адипокины, которые опосредуют метаболические и воспалительные последствия ожирения и представляют собой связь между ожирением и риском заболевания [71]. Наиболее распространенными адипокинами являются лептин и адипонектин. Как адипонектин, так и лептин экспрессируются, в основном, жировой тканью. В отличие от большинства других адипокинов, экспрессия адипонектина в жировой ткани у лиц с ожирением снижается, указывая, что у лиц с ожирением концентрация адипонектина ниже, чем у лиц с нормальной массой тела [9]. Адипонектин играет роль в энергетическом обмене и оказывает противовоспалительное и сенсибилизирующее действие на инсулин [68]. Предложены кардиозащитные и антиатерогенные эффекты адипонектина, однако представленный мета-анализ некоторых проспективных когортных исследований связи между циркулирующим адипонектином и ишемической болезнью сердца или инсультом не выявил [34]. Защитная роль адипонектина в развитии рака, предполагается либо непосредственно через адипонектин-опосредованное ингибирование роста клеток и индукцию апоптоза, либо косвенно через благоприятное действие адипонектина на чувствительность к инсулину и уменьшение воспаления [36].

Резистин обладает провоспалительными свойствами и играет значимую роль в инсулинорезистентности, связанной с ожирением, по крайней мере, на мышиной модели [37]. Показано, что резистин участвует в патологических процессах, приводящих к сердечно-сосудистым заболеваниям, таким как дисфункция эндотелия, тромбоз, ангиогенез [28]. В мета-анализе проспективных исследований, в основном, среди пациентов с сердечно-сосудистыми заболеваниями или диабетом, имеются данные, что более высокие концентрации резистина связаны с более высоким летальным исходом [20].

Основной функцией лептина является регуляция аппетита и энергетического баланса [79]. Лептин является адипокином, который отражает массу жировой ткани, т.е. при ожирении наблюдаются более высокие концентрации лептина, чем у лиц с нормальным весом [67], что свидетельствует о состоянии устойчивости к лептину при ожирении [16]. Высказано предположение, что лептин является медиатором связанного с ожирением более высокого риска сердечно-сосудистых заболеваний, поскольку он считается провоспалительным адипокином [71]. Доказательства связи между циркулирующим лептином и сердечно-сосудистыми заболеваниями неубедительны. Между генетической изменчивостью в гене рецептора лептина (LEPR) и риском сердечно-сосудистых заболеваний выявлена значительная положительная связь для нескольких генетических вариантов LEPR [77]. Описаны действия, способствующие развитию

лептина, такие как усиление пролиферации клеток, снижение апоптоза, а также стимулирование миграции и ангиогенеза [24]. Что касается рака, мета-анализ 6 проспективных исследований показал, что более высокий уровень циркулирующего лептина связан с более высоким риском развития колоректального рака [31], и растворимый рецептор лептина идентифицирован как один из основных циркулирующих биомаркеров, предопределяющий положительную связь между ожирением и риском колоректального рака в исследовании EPIC [1].

Заключение. Данные антропометрических методов оценки диагностики ожирения, такие как ИМТ, окружность талии и бедер, коэффициент объема талии/бедер и биоэмпидансометрия являются первостепенными и более доступными в диагностике ожирения в эпидемиологических исследованиях, а также клиническом контексте. Последовательная доказанная связь ожирения, диагностированного с учетом показателей данных методов с такими болезнями как сахарный диабет 2 типа, сердечно-сосудистые заболевания, патология опорно - двигательной системы и некоторые видов злокачественных новообразований, подчеркивает, что это более доступные инструменты. Применение методов лучевой диагностики (УЗИ, КТ, МРТ) дает достоверную оценку висцерального ожирения для детального исследования роли состава жира в этиопатогенезе заболевания.

Знания биологических маркеров, ассоциированных с ожирением за последние десятилетия существенно расширились, благодаря значительному вкладу клинических исследований, что явилось значимым звеном в определении взаимосвязи между ожирением и риском хронических заболеваний.

Таким образом, мультидисциплинарный подход в клинических исследованиях и практической медицине позволит усовершенствовать тактику диагностики ожирения и своевременно определить риск осложнений.

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SUMMARY

MARKERS OF OBESITY IN CLINICAL RESEARCH AND PRACTICAL MEDICINE (REVIEW)

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The purpose of this article is to describe the state-of-the-art knowledge of risk factors and targetmarkers of obesity needed for personalization of disease prevention. The frequency of diagnosis of obesity depends to a large extent on how it is determined. In the clinical evaluation of a patient with obesity, it is necessary to assess the anthropometric, metabolic and functional status of organs and systems. This review discusses modern tactics for the diagnosis of obesity. Early diagnosis of the pathological conditions associated with obesity is necessary for their timely treatment and prevention of severe complications. Accurate diagnosis of visceral obesity is not an easy task, as most methods have both merits and limitations for their use.

Keywords: obesity, excess body mass, fat tissue valuation, biomarkers of obesity.

РЕЗЮМЕ

МАРКЕРЫ ОЖИРЕНИЯ В КЛИНИЧЕСКИХ ИССЛЕДОВАНИЯХ И ПРАКТИЧЕСКОЙ МЕДИЦИНЕ (ОБЗОР)

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Западно-Казахстанский медицинский университет им. Марата Оспанова, [1]кафедра внутренних болезней №1; [2]отдел научно-аналитической работы; [3]кафедра нормальной и топографической анатомии с оперативной хирургией, Актобе, Казахстан

Целью исследования является анализ современного уровня знаний о факторах риска и целевых маркерах ожирения,

необходимых в персонализированной профилактике заболевания. Частота диагностики случаев ожирения в значительной степени зависит от способов его определения. При клинической характеристике пациента с ожирением необходимо оценить антропометрические показатели, метаболический статус и функциональное состояние органов и систем. В обзоре обсуждаются вопросы современной тактики постановки диагноза ожирения. Необходима ранняя диагностика патологических состояний, ассоциированных с ожирением, для их своевременного лечения и профилактики тяжелых осложнений. Точная диагностика висцерального ожирения является непростой задачей, так как большинство методов имеют как достоинства, так и ограничения для их использования.

Знания биологических маркеров, ассоциированных с ожирением, за последние десятилетия существенно расширились благодаря значительному вкладу эпидемиологических исследований, что явилось значимым звеном для определения взаимосвязи между ожирением и риском хронических заболеваний.

Таким образом, мультидисциплинарный подход в клинических исследованиях и практической медицине позволит усовершенствовать тактику диагностики ожирения и своевременно определить риски осложнений..

რეზიუმე

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კვლევის მიზანს წარმოადგენდა თანამედროვე ცოდნის დონის ანალიზი სიმსუქნის რისკის ფაქტორებისა და სამიზნე მარკერების შესახებ, რაც აუცილებელია დაავადების პერსონალიზებული პროფილაქტიკისათვის. სიმსუქნის დიაგნოსტიკის სიხშირე მნიშვნელოვანწილად დამოკიდებულია მისი განსაზღვრის მეთოდებზე. სიმსუქნის მქონე პაციენტის კლინიკური დახასიათებისათვის აუცილებელია ანთროპომეტრული მახასიათებლების, მეტაბოლური სტატუსის და ორგანოებისა და სისტემების ფუნქციური მდგომარეობის შეფასება.

მიმოხილვაში გაანალიზებულია სიმსუქნის დიაგნოზის დასმის თანამედროვე ტაქტიკის საკითხები. სიმსუქნესთან ასოცირებული პათოლოგიური მდგომარეობების დროული მკურნალობისა და პროფილაქტიკისათვის აუცილებელია მათი ადრეული დიაგნოსტიკა. ვისცერული სიმსუქნის ზუსტი დიაგნოსტიკა მარტივ ამოცანას არ წარმოადგენს, რადგანაც საამისო მეთოდების უმეტესობას აქვს როგორც დირსებები, ასევე, შეზღუდვები. ცოდნა სიმსუქნესთან ასოცირებული ბიოლოგიური მარკერების შესახებ, გამოყენებული ეპიდემიოლოგიური კვლევების მნიშვნელოვანი წვლილის მეოხებით, ბოლო ათწლეულის განმავლობაში არსებითად გაფართოვდა, რაც მნიშვნელოვანი რგოლი აღმოჩნდა ურთიერთკავშირის განსაზღვრისათვის სიმსუქნესა და ქრონიკული დაავადებების რისკებს შორის.

ამრიგად, შესწავლის მულტიდისციპლინურმა მიდგომამ კლინიკურ კვლევებსა და პრაქტიკულ მედიცინაში შესაძლოა ხელი შეუწყოს სიმსუქნის დიაგნოსტიკის ტაქტიკის სრულყოფას და გართულებათა აღმოცენების რისკის დროულ განსაზღვრას.

ОТНОШЕНИЕ БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА К ЗАБОЛЕВАНИЮ

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Известно, что до середины XX века в медицине господствовала концепция «слепого», т.е. неукоснительного соблюдения пациентом предписаний врача [1]. Данный подход был более эффективен в борьбе с инфекционными заболеваниями, но, как показала практика оказался совершенно не рассчитан для лечения хронических состояний. В мировом масштабе от неинфекционных заболеваний сегодня страдает больше людей, чем от инфекционных. Борьба с хроническими заболеваниями – одна из наиболее непростых задач.

Особое место в структуре множественных хронических заболеваний отводится сахарному диабету 2 типа [2,3]. Лечение сахарного диабета 2 типа представляет определенные трудности как для врача, так и медицинских сестер и узких специалистов. Достигнуть цели лечения без общения, создания доверительных отношений между медицинским работником и пациентом невозможно. Прогрессирующее развитие осложнений приводит к ухудшению самочувствия больных и является ведущей причиной их инвалидизации и смерти [4].

В Казахстане для уменьшения бремени хронических неинфекционных заболеваний, в рамках Государственной программы развития здравоохранения «Денсаулық» функционирует Программа управления заболеваниями (ПУЗ) [5], ключевой особенностью которой является стремление

помочь пациентам быть более компетентными в самоконтроле не только своего самочувствия, но и поведения, чувств и эмоций.

В связи со стремительным ростом числа лиц с хроническими заболеваниями следует оказывать не только медицинскую и психологическую помощь, но и развивать у пациента навыки самоуправления психоэмоциональным состоянием в кризисные периоды болезни [6-8].

Наиболее значимыми характеристиками, влияющими на течение хронического заболевания, являются: жизненная ситуация, в которой находится больной, переживание о болезни, поведение, ощущения больного и восприятие болезни в целом.

Целью исследования явилось определить характер отношения пациентов с сахарным диабетом 2 типа к своему заболеванию.

Материал и методы. В исследовании приняли участие 100 человек в возрасте от 21 до 80 лет, 47 мужчин и 53 женщины с диагнозом сахарный диабет 2 типа, которые принимали участие в Программе управления заболеваниями на базе «Городская поликлиника №7» и «Городская поликлиника №9». Для определения типов отношения к болезни и изучения внутренней картины болезни пациентов применяли личностный опросник Бехтеревского института, который является методикой, предназначенной для определения типов отношения больных хроническими неинфекционными заболеваниями к болезни и ее лечению. Опросник включает в себя 12 таблиц-наборов, каждый из которых содержит от 11 до 16 пронумерованных вопросов, касающихся самочувствия пациента, его настроения, сна, аппетита. В опросник включены также вопросы по отношению больного к болезни, лечению, врачам и медицинскому персоналу, родным и близким, к работе/учебе, окружающим, отношение к одиночеству и будущему. В каждой таблице-наборе пациент может выбрать не более 3 утверждений, которые для него больше всего подходят. Если ни одно из определений не подходит, то пациент может выбрать содержащийся в каждой таблице «нулевой вариант». Если же у пациента нет желания отвечать именно на данную тему, таблица остается незаполненной. Однако число выбранных «нулевых вариантов» и незаполненных таблиц в сумме не должны превышать трех. Время заполнения опросника не ограничено, однако не допускается консультация с другими лицами. Данный опросник позволяет определить тип отношения, представленный в таблице.

Таблица 1. Интерпретация типов отношений [13]

Тип отношения	**Интерпретация**
Гармоничный (Г)	Трезвая оценка своего состояния без склонности преувеличивать его тяжесть и без оснований видеть все в мрачном свете, но и без недооценки тяжести болезни. Стремление во всем активно содействовать успеху лечения. Нежелание обременять других тяготами ухода за собой. В случае неблагоприятного прогноза в смысле инвалидизации – переключение интересов на те области жизни, которые останутся доступными больному. При неблагоприятном прогнозе quo ad vitam сосредоточить внимание, заботу, интересы на судьбе близких или своего дела
Тревожный (Т)	Постоянное беспокойство и мнительность в отношении неблагоприятного течения болезни, возможных осложнений, неэффективности и даже опасности лечения. Поиск новых способов лечения, жажда дополнительной информации о болезни, вероятных осложнениях, методах лечения, непрерывный поиск “авторитетов”. В отличие от ипохондрии более интересуют объективные данные о болезни (результат анализов, заключения специалистов), чем собственные ощущения. Поэтому предпочитают больше слушать высказывания других, чем без конца предъявлять свои жалобы. Настроение прежде всего тревожное и угнетенность вследствие этой тревоги.
Ипохондрический (И)	Сосредоточение на субъективных болезненных и иных неприятных ощущениях. Стремление постоянно рассказывать о них окружающим. На их основе преувеличение действительных и выискивание несуществующих болезней и страданий. Преувеличение побочного действия лекарств. Сочетание желания лечиться и неверия в успех, требований тщательного обследования и боязни вреда и болезненности процедур.
Меланхолический (М)	Удрученность болезнью, неверие в выздоровление и возможное улучшение, в эффект от лечения. Активные депрессивные высказывания вплоть до суицидных мыслей. Пессимистический взгляд на все вокруг. Неверие в успех лечения даже при благоприятных объективных данных.
Апатический (А)	Полное безразличие к своей судьбе, к исходу болезни, к результатам лечения. Пассивное подчинение процедурам и лечению при настойчивом побуждении со стороны. Утрата интереса ко всему, что ранее волновало.
Неврастенический (Н)	Поведение по типу “раздражительной слабости”. Вспышки раздражения, особенно при болях, неприятных ощущениях, неудачах лечения, неблагоприятных данных обследования. Раздражение нередко изливается на первого попавшегося и часто завершается раскаянием и слезами. Непереносимость болевых ощущений. Нетерпеливость. Неспособность ждать облегчения. В последующем – раскаяние за беспокойство и несдержанность

Обсессивно-фобический (О)	Тревожная мнительность прежде всего касается опасений не реальных, а маловероятных осложнений болезни, неудач лечения, а также возможных (но малообоснованных) неудач в жизни, работе, семейной ситуации в связи с болезнью. Воображаемые опасности волнуют более, чем реальные. Защитой от тревоги становятся приметы и ритуалы.
Сенситивный (С)	Чрезмерная озабоченность о возможном неблагоприятном впечатлении, которое могут произвести на окружающих сведения о своей болезни. Опасения, что окружающие станут избегать, считать неполноценным, пренебрежительно или с опаской относиться, распускать сплетни или неблагоприятные сведения о причине и природе болезни. Боязнь стать обузой для близких из-за болезни и неблагожелательного отношения с их стороны в связи с этим.
Эгоцентрический (Я)	“Уход в болезнь”. Выставление напоказ близким и окружающим своих страданий и переживаний с целью полностью завладеть их вниманием. Требование исключительной заботы – все должны забыть и бросить всё и заботиться только о больном. Разговоры окружающих быстро переводятся “на себя”. В других людях, также требующих внимания и заботы, видят только “конкурентов” и относятся к ним неприязненно. Постоянное желание показать свое особое положение, свою исключительность в отношении болезни.
Эйфорический (Ф)	Необоснованно повышенное настроение, нередко наигранное. Пренебрежение, легкомысленное отношение к болезни и лечению. Надежда на то, что “само все обойдется”. Желание получать от жизни все, несмотря на болезнь. Легкость нарушений режима, хотя эти нарушения могут неблагоприятно сказываться на течение болезни.
Анозогнозический (З)	Активное отбрасывание мысли о болезни, о возможных ее последствиях. Отрицание очевидного в проявлениях болезни, приписывание их случайным обстоятельствам или другим несерьезным заболеваниям. Отказ от обследования и лечения. Желание “обойтись своими средствами”.
Эргопатический (Р).	“Уход от болезни в работу”. Даже при тяжести болезни и страданиях стараются во что бы то ни стало продолжить работу. Трудятся с ожесточением, с еще большим рвением, чем до болезни, работе отдают все время, стараются лечиться и подвергаться обследованию так, чтобы это оставляло возможность для продолжения работы.
Паранойяльный (П)	Уверенность, что болезнь - результат чьего-то злого умысла. Крайняя подозрительность к лекарствам и процедурам. Стремление приписывать возможные осложнения лечения или побочные действия лекарств халатности или злому умыслу врачей и персонала. Обвинения и требования наказаний в связи с этим. Система отношений, связанных с болезнью, может не укладываться в один из описанных типов. Здесь речь может идти о смешанных типах, особенно близких по картине (тревожно-обсессивный, эйфорически-анозогно-зический, сенситивно-эргопатический). Но система отношений может еще не сложиться в единый паттерн–тогда ни один из перечисленных типов не может быть диагностирован и черты многих или всех типов бывают представлены более или менее одинаково.

Результаты и обсуждение. При оценке ответов всех больных, включенных в исследование, получены следующие результаты: среди опрошенных пациентов у 8,5% мужчин и 9,4% женщин диагностирован ипохондрический тип отношения к заболеванию. Для данного типа характерно преобладание тревоги, которая направлена на собственные тягостные ощущения. Пациенты нередко записывают свои многообразные болезненные и неприятные ощущения для осведомления лечащего врача. Больные могут жаловаться на недоброкачественные лечение и уход, неадекватно относятся даже к незначительному побочному эффекту лечения.

У 6,4% мужчин и 9,4% женщин определен тревожный тип, т.е. этих пациентов постоянно мучает внутренняя тревога, которая касается всего, что имеет отношение к болезни: ее исхода, продолжительности, возникновения осложнений, эффективности лекарств, возможных побочных эффектов, сохранения работоспособности, риска инвалидизации. Для таких пациентов характерна склонность просить повторного проведения лабораторных или инструментальных исследований. Свою тревогу они могут перекладывать на близких. Ухудшение состояния пациентов с тревожным типом или недоброкачественный уход могут привести к развитию у них сильнейшей депрессии.

Сенситивный тип отмечен у 8,5% опрошенных мужчин и 7,5% женщин и характеризуется опасениями об отношении окружающих к пациенту и его болезни. Беспокойство по поводу того, что больного начнут избегать, считать неполноценным, относиться пренебрежительно или распускать слухи о причине болезни.

Основным признаком эргопатического типа является уход от болезни в работу. В нашем случае 10,6% пациентов мужчин и 5,7% женщин болезни старались продолжать работу несмотря на тяжесть заболевания. 13,2% опрошенных женщин и 2,1% мужчин относятся к паранойяльному типу. Пациенты утверждают, что болезнь произошла в результате чей-то злонамеренности («порча» либо «сглаз»). Они с сомнением относятся к каждому вновь назначаемому лекарству или процедуре, много выясняют о возможных последствиях.

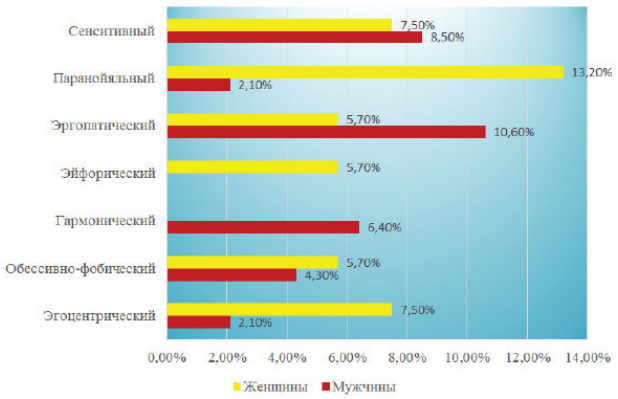

Рис. 1a. Типы отношения пациентов к заболеванию

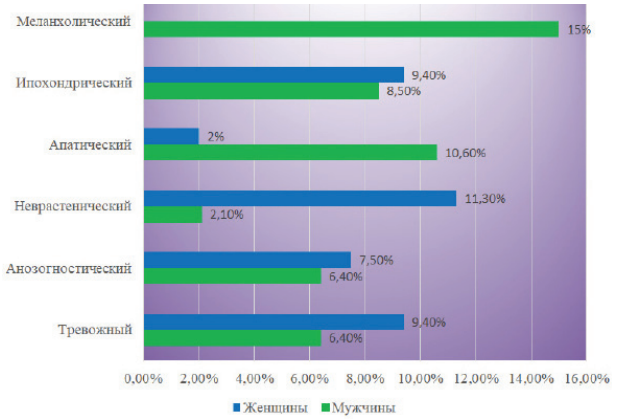

Рис. 1b Типы отношения пациентов к заболеванию

В 15% случаев отмечен меланхолический тип у мужчин. Свойствен пессимистический настрой, даже при положительной динамике в течении заболевания. У таких больных наблюдается склонность к развитию депрессии и склонность к суициду.

Неврастенический тип отмечен у 2,1% у мужчин и 11,3% женщин. Ведущей чертой является «раздражительная слабость». Вспышки раздражения могут возникать по малейшему поводу, затем вспышка гнева сменяется резким утомлением. Характерной особенностью также является нетерпеливость.

Наличие анозогностического типа обнаружено у 7,5% опрошенных женщин и у 6,4% мужчин. Присуще активное отбрасывание мыслей о болезни, отрицание очевидного. Анозогностические пациенты предписывают развитие заболевания случайности и считают его незначительным, что проявляется в отказе от лечения, в предпочтении лечению использование «своих» средств терапии (настойки, отвары, обливания водой, определенные дозы алкоголя), что в дальнейшем вызывает серьезные осложнения.

Апатический тип диагностирован в 10,6% случаев у мужчин и у2% женщин. Большинство проявлений аналогичны с меланхолическим типом. Наблюдается апатия, малоподвижность, безразличие к окружающему. Пропадает интерес к повседневным делам: работа, «хобби», чтение книг, прогулки, походы в кино и театр, просмотр телевизора.

Обсессивно-фобическому типу, выявленному в 4,3% случаев у мужчин и 5,7% женщин, также свойственна тревожная мнительность, однако она направлена на маловероятные осложнения болезни. Реальные опасности волнуют меньше, чем воображаемые. Обсессии – это навязчивые состояния, представляющие собой непроизвольные мысли или представления, которые возникают периодически. Самому избавиться от обсессий пациентам обычно не удается.

Главная особенность пациентов с эгоцентрическим типом отношения к болезни – это стремление поставить себя в центр интересов всех окружающих. В нашем случае это 7,5% женщин и 2,1% мужчин, которым важно завладеть вниманием близких, а также медицинского персонала и выставить свои страдания напоказ.

5,7% опрошенных женщин относятся к эйфорическому типу. У пациентов с этим типом постоянно повышено настроение, пренебрежительно относятся ко всем диагностическим и лечебным процедурам или вовсе игнорируют их. В ситуации болезни они исповедуют принципы: «что будет, то и будет», «пусть все идет, как идет», «что ни делается, все к лучшему».

Согласно результатам, из 100 опрошенных только 6,4% мужчин относятся к гармоническому типу. Основное отличие - реализм, способность трезво оценивать своё состояние. Пациент не придает ни преуменьшенного, ни преувеличенного значения болезни, активно способствует успеху лечения, проявляет нежелание обременять близких уходом за собой. При неблагоприятном прогнозе пациенты стремятся переключиться на те области жизни, которые доступны.

Пациенты, у которых диагностированы сразу несколько типов объеденены в смешанный тип. В результате проведенного исследования у 17% мужчин и 15% женщин выявлен смешанный тип отношения к болезни, проявление которого весьма многообразно.

Осознание наличия неизлечимого заболевания у каждого проявляется по-разному. Так, смеем утверждать, что демонстрация наличия гармонического типа в 6,4% среди опрошенных мужчин ничтожно мало по сравнению с 28,57% случаев среди женщин и 33,34% случаев среди мужчин в аналогичном исследовании, проведенном Петровой М. М. и соавторами. Наличие тревожного типа было подтверждено как среди мужчин, так женщин, в то время как раннее тревожный тип наблюдался только у 10,71% женщин [9]. Примерно равное количество (9% и 10,6%) респондентов имеют ипохондрический тип отношения к болезни. Полученные значения, 5,7% опрошенных женщин с эйфорическим типом, в нашем случае можем считать оптимальными в соотношении со значениями в 11,6%, в исследовании, проведенном Сапожникова И. Е. и соавторами [10]. В аналогичном исследовании, проведенном в 2017 году паранойяльный тип, был интерпретирован у 15% мужчин и женщин. При сравнении с результатами, полученными в нашем исследовании, 13,2% женщин и 2,1% мужчин с паранойяльным типом, различия не ощутимы [11]. Возможность возникновения депрессии среди пациентов с сахарным диабетом в 2,39% случаях подтвердилась только среди женщин, и это значение можно считать допустимым по сравнению с 10,6% пациентов диагностированным меланхолическим типом в исследовании Кравченко А.Я. и соавторами [12].

Несмотря на то, что сахарный диабет 2 типа не является смертельным заболеванием, хроническое течение обязывает пациентов изменить свой привычный образ жизни. В частности, в этот период остро необходима поддержка не только близких и друзей, но и консультации психолога, который входит в мультидисциплинарную команду специалистов в рамках Программы управления заболеваниями. Смешанный или неопределенный тип отношения к болезни подтвердился только в нашем исследовании, что позволяет судить о необходимости использования дозированной

адекватной психологической помощи. Применение психологического воздействия и психотерапевтических методов позволит в условиях длительного течения заболевания выявить скрытые возможности личности, мобилизовать ее внутренние ресурсы, улучшить навыки самоконтроля заболевания в любых жизненных ситуациях.

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SUMMARY

TYPES OF RELATIONSHIPS OF PATIENTS WITH TYPE 2 DIABETES TO THE DISEASE

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The need to study the psychological picture of patients with chronic disease, is determined by the fact that the patient's attitude to their disease affects the course of the disease and success in treatment. A modern feature of the course of chronic diseases is polymorbidity (i.e., the multiplicity of diseases in one patient), therefore, the presence of concomitant diseases, especially the chronic form, lead to the syndrome of mutual aggravation.

The purpose: study the types of attitudes and internal picture of the disease of patients with type 2 diabetes.

Methods. The study involved 100 people aged 21 to 80 years, 47 men and 53 women diagnosed with type 2 diabetes. To determine the types of attitude to the disease and study the internal picture of the disease, we used a personal questionnaire from the Bekhterev Institute (LOBI).

Among the patients we surveyed, 8.5% of men and 9.4% of women were diagnosed with the hypochondriac type. The sensitive type was observed in 8.5% of men and 7.5% of women surveyed. The main feature alopaticos the type of care from illness to work. In our case, this is 10.6% of male patients and 5.7% of women. 13.2% of women and 2.1% of men surveyed are paranoid. In 15% of cases, we noted the melancholic type in men. 5.7% of women surveyed are euphoric. Of all the respondents, only 6.4% of the men surveyed are of the harmonic type. 6.4% of men and 9.4% of women were identified as having an anxiety type.

Conclusion. It is well known that any disease is accompanied by more or less serious changes in the patient's psyche. And it is during this period that patients urgently need the support of their relatives and friends. Therefore, in the process of treating the disease, an important aspect is not only drug therapy, but also the emotional mood of the patient.

Keywords: personality, attitude to the disease, diabetes mellitus, internal picture of the disease.

РЕЗЮМЕ

ОТНОШЕНИЕ БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА К ЗАБОЛЕВАНИЮ

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Целью исследования явилось определить характер отношения больных сахарным диабетом 2 типа к заболеванию.

В исследовании приняли участие 100 больных сахарным диабетом 2 типа в возрасте от 21 до 80 лет, 47 мужчин и 53 женщины. Для определения типов отношения к болезни

применен личностный опросник Бехтеревского института. Среди опрошенных пациентов у 8,5% мужчин и 9,4% женщин диагностирован ипохондрический тип. Сенситивный тип отмечен у 8,5% мужчин и 7,5% женщин. Основной признак эргопатического типа – уход от болезни в работу, в нашем случае - у 10,6% мужчин и 5,7% женщин. 13,2% женщин и 2,1% мужчин относятся к паранойяльному типу. В 15% случаев отмечен меланхолический тип у мужчин, 5,7% женщин относятся к эйфорическому типу. Из всех опрошенных 6,4% относятся к гармоническому типу. У 6,4% мужчин и 9,4% женщин определен тревожный тип.

Любое заболевание сопровождается более или менее серьезными изменениями психики пациента. В частности, в период болезни пациенты особо нуждаются в поддержке родных и близких. Поэтому в процессе лечения заболевания значимым аспектом является не только лекарственная терапия, но и эмоциональный настрой самого пациента.

რეზიუმე

შაქრიანი დიაბეტი ტიპი 2-ით ავადმყოფების დამოკიდებულება დაავადების მიმართ

შ.ბატარბეკოვა, დ.ჟუნუსოვა, გ.დერბისალინა, ჟ.ბეკბერგენოვა, გ.რახიმგალიევა

არასაჯარო სააქციო საზოგადოება "სამედიცინო უნივერსიტეტი ასტანა", ნურ-სულტანი, ყაზახეთი

კვლევის მიზანს წარმოადგენდა შაქრიანი დიაბეტი ტიპი 2-ით ავადმყოფების დაავადების მიმართ დამოკიდებულების განსაზღვრა.

კვლევაში მონაწილეობდა 100 ავადმყოფი შაქრიანი დიაბეტი ტიპი 2-ით, 21-დან 80 წლის ასაკში, 47 მამაკაცი და 53 ქალი. დაავადების მიმართ ავადმყოფების დამოკუდებულების განსაზღვრისათვის გამოყენებული იყო ბეხტერევის ინსტიტუტის პიროვნების კითხვარი. გამოკთხულთა შორის 8,5% მამაკაცს და 9,4% ქალს აღმოაჩნდა იპოქონდრიული ტიპი, 8,5% მამაკაცს და 7,5% ქალს - სენსიტიური ტიპი. ერგოპატიური ტიპი, რაც გულისხმობს ავადმყოფობისთვის თავის არიდებას მუშაობაში ჩართულობით, აღმოაჩნდა 10,6% მამა-კაცს და 5,7% ქალს. პარანოული ტიპი ახასიათებდა 13,2% ქალს და 2,1% მამაკაცს, მელანქოლიური ტიპი - 15% მამაკაცს; 5,7% ქალს აღმოაჩნდა ეიფორიული ტიპი. გამოკითხულთა 6,4% განეკუთვნა ჰარმონიულ ტიპს. 6,4% მამაკაცს და 9,4% ქალს განესაზღვრა შფოთიანი ტიპი.

ნებისმიერი დაავადება იწვევს მეტნალკებად სერიოზულ ცვლილებებს პაციენტის ფსიქიკაში და დაავადების პერიოდში პაციენტებს სჭირდებათ ნათესავებისა და ახლობლების თანადგომა, ამიტომ, მკურნალობის მნიშვნელოვან ასპექტს წარმოადგენს არა მხოლოდ მედიკამენტური თერაპია, არამედ ავადმყოფის ემოციური განწყობა.

DIAGNOSIS OF BLUNT TRAUMA OF KIDNEY INJURY WITH INFRARED THERMOMETER METHOD

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Traumatic injuries account for about 40% of violent deaths and about 26% of all deaths. In the structure of mortality from traumas, the number of traumatic and traumatic brain injuries prevails, the second place is occupied by the combined trauma, and the third place is shared by the injuries of the chest and abdominal organs [1-3]. Among those killed are men of working age - 20-60 years, which underscores the relevance and feasibility of research to develop preventative measures to reduce injuries. Research on kidney damage in medical practice is quite common and is of scientific and practical value for both clinicians and forensics. A number of authors found that kidney damage among the blunt trauma of the abdominal cavity occurs in 6 to 18% of cases [4-6]. According to some authors, when they fall from the height of the kidney, 28.8% of all cases with damage to the abdomen are injured. The rest of the kidney injury in people with closed abdominal trauma was observed in 6.1% of cases, with 60% of cases of kidney injury combined with damage to other abdominal organs [7-9]. Our research has confirmed that the use of infrared histological and thermometry methods for the study of traumatic and intact abdominal cavity and abdominal space is of great importance in the diagnosis of trauma from dull objects [10-13].

The aim of the study. The study of the prescription of injury on the dynamics of changes in temperature indices of the injured kidney tissues in blunt trauma.

Material and methods. The material of the study to date are the tissues of the kidneys of 256 male and female persons, aged 20 to 60 years, who died at a known time of trauma and prescription of death in the were subject to autopsy at the Department forensic examination of the Luhansk region during 2008-2013. In our studies, we studied the temperature of the kidneys at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24 hours after the autopsy. The ambient temperature in the department autopsy the studies was 18ºC. To address the question of the age of occurrence of kidney

damage, we used a modern method of infrared thermometry. The study was performed using a TH 9100 PMVI-WL Thermo Tracker thermal imager, which is a contactless high-sensitivity infrared camera. The work was carried out in accordance with the requirements of the «Instructions on the forensic medical examination» (Order of the Ministry of Health of Ukraine No. 6 of 01/17/1995), in accordance with the requirements and norms, a typical provision on ethics of the Ministry of Health of Ukraine No. 690 of 09/23/2009, «The procedure for the removal of biological objects from the dead, whose bodies are subject to forensic examination and pathological examination, for scientific purposes» (2018).

Results and discussion. When carrying out the thermometry of the kidneys, it should be borne in mind that the location of the kidneys with a pronounced network of blood vessels creates the opportunity for the formation of large hemorrhages in them and disruption of tissue integrity in trauma, as well as that the right kidney is protected more than left; in women, the kidneys are lower than in men. According to our data, a well-anamnesis, knowledge of the mechanism of trauma, laboratory tests of blood and urine (determining the increase in the content of trypsin, amylase, lipase, etc.), conducting laparoscopy of the abdominal cavity and retroperitoneal space, ultrasound of the internal organs helps with the establishment of kidney injury.

The analysis of the obtained kidney thermograms showed that the temperature indices in the area of the injured kidney tissues and intact parts gradually decrease with time after injury and have a certain pattern of decrease. A gradual decrease in temperature is shown in Figures 1-4.

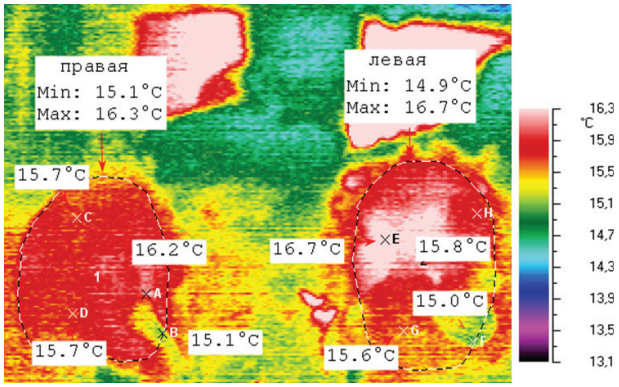


Fig. 1. The temperature of the tissues of the kidneys after 5 minutes after opening. E - is the area of damage of the left kidney A, B, C, D, H - are the areas of intact tissues of the right and left kidneys

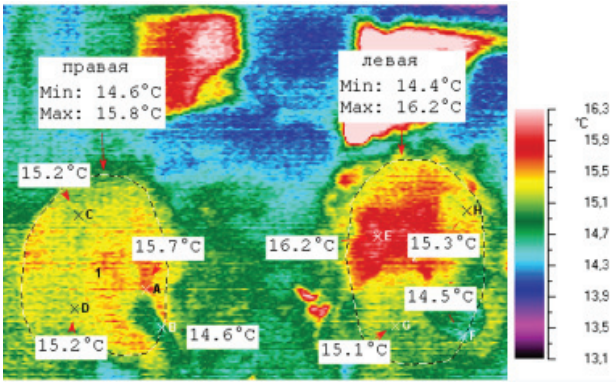


Fig. 2. Temperature of kidney tissues within 1 hour after opening. E - is the area of damage of the left kidney; A, B, C, D, H - are the areas of intact tissues of the right and left kidneys

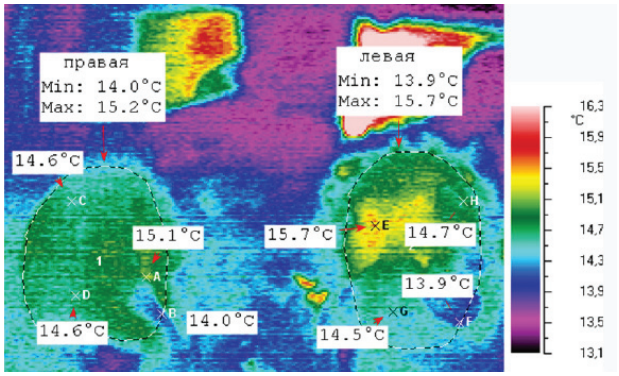


Fig. 3. Temperature of kidney tissues 12 hours after opening. E - is the area of damage of the left kidney; A, B, C, D, H - are the areas of intact tissues of the right and left kidneys

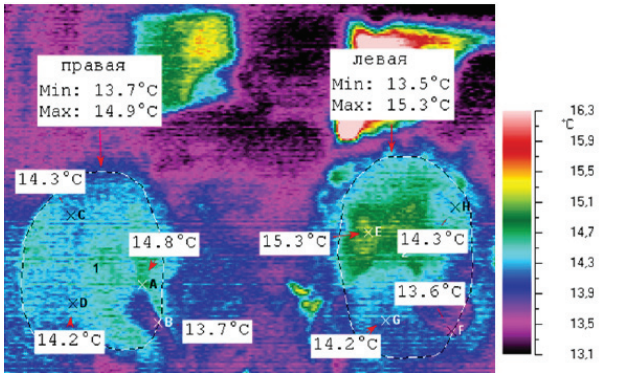


Fig. 4. Temperature of kidney tissues 24 hours after opening. E - is the area of damage of the left kidney; A, B, C, D, H - are the areas of intact tissues of the right and left kidneys

After statistical processing of the obtained temperature indicators of the kidneys from the area of damage and located adjacent to its intact tissues, with obligatory consideration of the temperature indices of the outer skin, we found that there is a significantly statically significant decrease in the temperature indices of the right and left kidneys, as in men and women, depending on the ambient temperature at the time of death and the thickness of the subcutaneous tissue. The aforementioned statistically significant dynamics allowed us to develop mathematical models for the most accurate determination of limitation of the onset of death according to changes in the temperature indices of the left and right kidneys taking into account external and internal factors, such as ambient temperature and biological features of the organism of the dead. In our study, it was found that such a factor as gender, the temperature of both kidneys is not significantly affected.

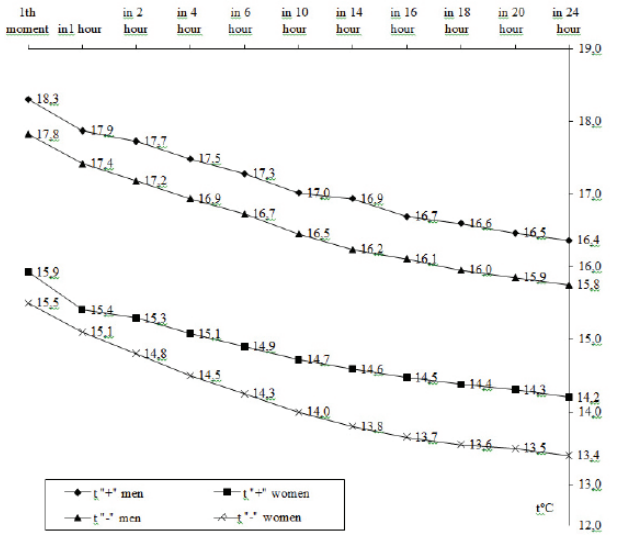
The dynamics of changes in the temperature indicators of the kidneys, depending on the sex and temperature of the environment in the dead after a blunt kidney injury are shown in Tables 1 and 2 and Graphs 1 and 2.

Table 1. Dynamics of changes in the average values of the temperature of the right kidney, depending on sex and ambient temperature, M±m (95% CI)

Terms of study after autopsy	Negative temperature		Level of difference	Positive temperature		Level of difference
	Male, n=76	Female n=32		Male, n=80	Female n=68	
5 minutes	18,31±0,27 (17,77 – 18,84)	17,31±0,42 (16,44 – 18,17)	0,10	17,83±0,20 (17,44 – 18,21)	15,93±0,15 (15,63 – 16,22)	<0,0001
1 hour	17,87±0,28 (17,31 – 18,44)	16,94±0,43 (16,06 – 17,82)	0,21	17,43±0,20 (17,02 – 17,83)	15,41±0,15 (15,10 – 15,71)	<0,0001
2 hour	17,73±0,28 (17,17 – 18,29)	16,69±0,44 (15,79 – 17,59)	0,08	17,19±0,20 (16,79 – 17,58)	15,29±0,16 (14,98 – 15,60)	<0,0001
4 hour	17,49±0,28 (16,92 – 18,05)	16,43±0,45 (15,51 – 17,35)	0,09	16,94±0,20 (16,54 – 17,33)	15,08±0,16 (14,76 – 15,39)	<0,0001
6 hour	17,29±0,29 (16,72 – 17,86)	16,21±0,45 (15,28 – 17,13)	0,056	16,73±0,20 (16,33 – 17,13)	14,90±0,16 (14,58 – 15,21)	<0,0001
10 hour	17,02±0,29 (16,45 – 17,59)	15,95±0,45 (15,02 – 16,88)	0,046	16,45±0,20 (16,06 – 16,85)	14,71±0,16 (14,40 – 15,03)	<0,0001
14 hour	16,94±0,30 (16,34 – 17,53)	15,84±0,48 (14,86 – 16,81)	0,06	16,24±0,20 (15,84 – 16,63)	14,59±0,17 (14,25 – 14,92)	<0,0001
16 hour	16,69±0,30 (16,09 – 17,30)	15,63±0,46 (14,68 – 16,57)	0,17	16,11±0,20 (15,70 – 16,51)	14,47±0,16 (14,15 – 14,79)	<0,0001
18 hour	16,60±0,29 (16,02 – 17,17)	15,51±0,46 (14,57 – 16,45)	0,027	15,95±0,20 (15,55 – 16,35)	14,38±0,16 (14,06 – 14,70)	<0,0001
20 hour	16,47±0,29 (15,90 – 17,03)	15,42±0,45 (14,49 – 16,34)	0,049	15,85±0,20 (15,46 – 16,25)	14,30±0,16 (13,98 – 14,62)	<0,0001
24 hour	16,37±0,29 (15,80 – 16,93)	15,32±0,45 (14,39 – 16,24)	0,049	15,75±0,20 (15,36 – 16,15)	14,20±0,16 (13,88 – 14,52)	<0,0001

Table 2. Dynamics of changes in mean values of left kidney temperature depending on sex and ambient temperature, M ± m (95% CI)

Terms of study after autopsy	Negative temperature		Level of difference	Positive temperature		Level of difference
	Male, n=76	Female n=32		Male, n=80	Female n=32	
5 minutes	18,30±0,25 (17,80 – 18,80)	17,11±0,46 (16,17 – 18,06)	0,001	17,90±0,18 (17,53 – 18,26)	15,74±0,14 (15,47 – 16,01)	<0,0001
1 hour	17,89±0,26 (17,37 – 18,42)	16,75±0,47 (15,79 – 17,71)	0,002	17,35±0,19 (16,97 – 17,72)	15,37±0,14 (15,09 – 15,65)	<0,0001
2 hour	17,73±0,26 (17,20 – 18,25)	16,49±0,48 (15,52 – 17,47)	0,001	17,09±0,19 (16,71 – 17,46)	15,20±0,14 (14,91 – 15,48)	<0,0001
4 hour	17,49±0,27 (16,96 – 18,02)	16,22±0,49 (15,23 – 17,21)	0,002	16,80±0,19 (16,43 – 17,17)	14,96±0,14 (14,68 – 15,25)	<0,0001
6 hour	17,28±0,27 (16,75 – 17,81)	16,00±0,49 (15,00 – 17,00)	0,002	16,61±0,19 (16,23 – 16,98)	14,79±0,14 (14,51 – 15,08)	<0,0001
10 hour	17,01±0,27 (16,47 – 17,54)	15,75±0,49 (14,75 – 16,75)	0,004	16,34±0,18 (15,97 – 16,70)	14,62±0,14 (14,33 – 14,91)	<0,0001
14 hour	16,85±0,27 (16,32 – 17,38)	15,54±0,49 (14,55 – 16,54)	0,002	16,16±0,19 (15,79 – 16,54)	14,49±0,15 (14,19 – 14,78)	<0,0001
16 hour	16,70±0,28 (16,15 – 17,25)	15,44±0,50 (14,42 – 16,46)	0,002	15,97±0,19 (15,59 – 16,35)	14,36±0,15 (14,06 – 14,65)	<0,0001
18 hour	16,59±0,27 (16,05 – 17,13)	15,31±0,49 (14,30 – 16,32)	0,003	15,83±0,19 (15,46 – 16,20)	14,28±0,15 (13,98 – 14,58)	<0,0001
20 hour	16,47±0,27 (15,93 – 17,00)	15,23±0,49 (14,23 – 16,22)	0,003	15,73±0,19 (15,36 – 16,10)	14,20±0,15 (13,91 – 14,49)	<0,0001
24 hour	16,37±0,27 (15,83 – 16,90)	15,12±0,49 (14,13 – 16,12)	0,001	15,62±0,19 (15,25 – 15,99)	14,10±0,15 (13,81 – 14,39)	<0,0001



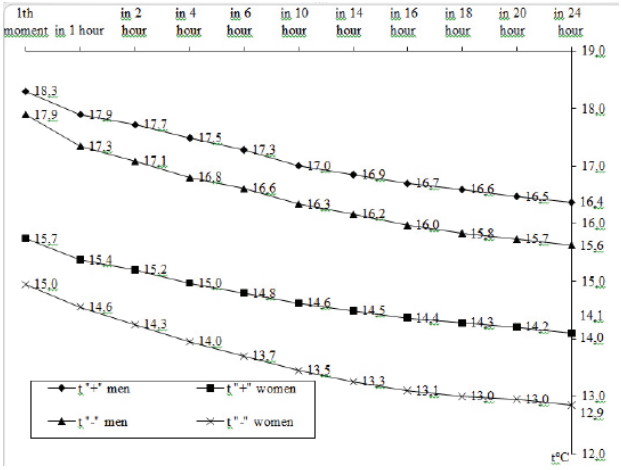
Graph 1. Dynamics of changes in temperature indicators of the right kidney, depending on the sex and temperature of the environment at the time of death.

t "+" pers - temperature indices of the tissues of the right kidney of men at a positive ambient temperature;

t "-" persons are the temperature indices of the tissues of the right kidney of men at a negative ambient temperature;

t "+" women - temperature indices of women's right kidney tissues at positive ambient temperature;

t "-" women - temperature indices of women's right kidney tissues at negative ambient temperature.



Graph 2. Dynamics of changes in temperature indices of the left kidney, depending on sex and ambient temperature at the time of death.

t "+" persons are the temperature indices of the tissues of the left kidney of men at a positive ambient temperature;

t "-" persons - temperature indices of the tissues of the left kidney of men at a negative ambient temperature;

t "+" women - temperature indices of left kidney tissues of women at positive ambient temperature;

t "-" women - temperature indices of women's left kidney tissues at negative ambient temperature.

However, in the area of trauma throughout the period after the autopsy of the dead (24 hours of study), observed higher quantitative temperature compared with non-injured kidney tissues, on average, 2-3 ° C (± 0.28). To take into account the fact that the right kidney is protected more than the left kidney and less vulnerable to body compression, it is not accompanied by a shift in the impact of traumatic objects; at 1.5-2 ° C (± 0.14).

In this way, we came to the gown, who, when injured by blunt objects, are willing to take into account the laws of the organs of the black empty, that they must be injured a long time ago [6, 7]. In our opinion, the use of changes of only one injured organ to establish the limitation period of the caused mechanical damage from blunt trauma is not accurate enough, since pathological changes are observed not only in the area of the injury and one injured organ, but also in the intact internal organs and significantly affect for the course of pathological processes into organisms. Therefore, we believe that determining the limitation of the onset of mechanical trauma by changes in the infrared thermometry performed in the complex, it is appropriate and such that provide a full amount of information about the time of injury and we propose to apply only a comprehensive approach using both modern laboratory methods of investigation - infrared thermometry and traditional histological and histochemical methods.

Conclusions. Thus, as a result of the study, we discovered, first, that in traumatic and intact tissues of the kidneys in the victims of traumas there is a constant dynamics of decrease in temperature, which can be used as one of the criteria in establishing the limitation of the onset of injury; second, that higher quantitative temperature indicators are observed directly in the area of trauma compared to the non-injured kidney tissues and make a difference of an average of 2-3 ° C (± 0.28).

However, it should be remembered that in the diagnosis of renal injury by infrared thermometry it is necessary to take into account the rate of cooling of the corpse, which is also affected by various factors: ambient temperature, humidity, the presence of clothing, the duration of the agonal period, etc. That is, all of the above should be taken into account when assessing the prescription of the onset of death and the prescription of damage on the temperature indicators of the internal organs, in particular the kidneys.

Research relation to the plans, programs and department themes. The study was carried out within the framework of the department research: "Pathogenetic substantiation of correction of pathophysiological disturbances in the human body under the influence of endogenous and exogenous factors", state registration number is 0118U004006

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SUMMARY

DIAGNOSIS OF BLUNT TRAUMA OF KIDNEY INJURY WITH INFRARED THERMOMETER METHOD

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Aim - the study of the prescription of injury on the dynamics of changes in temperature indices of the injured kidney tissues in blunt trauma.

The material of the study to date are the tissues of the kidneys of 256 male and female persons, aged 20 to 60 years, who died at a known time of trauma and prescription of death in the were subject to autopsy. To address the question of the age of occurrence of kidney damage, we used a modern method of infrared thermometry (using a TH 9100 PMVI-WL Thermo Tracker thermal imager, which is a contactless high-sensitivity infrared camera).

In this way, we came to the gown, who, when injured by blunt objects, are willing to take into account the laws of the organs of the black empty. However, in the area of trauma throughout the period after the autopsy of the dead (24 hours of study), observed higher quantitative temperature compared with non-injured kidney tissues, on average, 2-3 ° C (± 0.28). To take into account the fact that the right kidney is protected more than the left kidney and less vulnerable to body compression, it is not accompanied by a shift in the impact of traumatic objects; at 1.5-2 ° C (± 0.14).

We believe that determining the limitation period of the onset of mechanical trauma by changes in the infrared thermometry indices carried out in the complex are appropriate and such that provide the full amount of information about the time of causing the trauma.

Keywords: blunt injury, kidneys, diagnostics, infrared thermometry, injury limitation, pathological changes.

РЕЗЮМЕ

ДИАГНОСТИКА ТУПОЙ ТРАВМЫ ПОЧКИ МЕТОДОМ ИНФРАКРАСНОЙ ТЕРМОМЕТРИИ

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Цель исследования - изучение влияния травмы на динамику изменения температурных показателей поврежденных тканей почек при тупой травме.

Материалом исследования служили ткани почек, забранные во время вскрытия у 256 мужчин и женщин в возрасте от 20 до 60 лет, умерших от травмы, с известным временем давности наступления травмы и смерти. Для решения вопроса о времени повреждения почек применен современный метод инфракрасной термометрии с использованием тепловизора TH 9100 PMVI-WL Thermo Tracker, (NEC Avio infrared Technologies Co. Ltd., Япония), который является бесконтактной высокочувствительной инфракрасной камерой.

В результате проведенного иссследования установлена характерная динамика изменения температурных показателей при травме почек тупым предметом. Однако, в зоне травмы в течение всего периода после вскрытия (24 часа исследования) наблюдались более высокие количественные температурные показатели непосредственно в области травмы почки, в среднем, на 2-3°С (±0,28) в сравнении с неповрежденными тканями почки. Температурные показатели правой почки снижаются медленнее, в среднем, на 1,5-2°С (±0,14) относительно левой, что связано с топографоанатомическими особенностями расположения почек.

Установлено, что при тупой травме в поврежденных и интактных тканях почек наблюдается закономерная динамика уменьшения температурных показателей, что может быть использовано для определения времени наступления травмы с помощью метода инфракрасной термометрии.

რეზიუმე

თირკმლის ბლაგვი ტრავმის დიაგნოსტიკა ინფრაწითელი თერმომეტრიის მეთოდით

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კვლევის მიზანს წარმოადგენდა ბლაგვი ტრავმის გავლენის შეფასება თირკმლის დაზიანებული ქსოვილების ტემპერატურული მაჩვენებლების დინამიკაზე.

კვლევის მასალას წარმოადგენდა თირკმლების ქსოვილი, მიღებული 20-60 წლის ასაკის 256 მამაკაცის და ქალის გაკვეთის შემდგომ, რომელთა სიკვდილი განვითარდა ტრავმის შედეგად; ტრავმის ხანდაზმულობისა და სიკვდილის დადგომის ვადა ცნობილია. თირკმლის დაზიანების დროის დადგენის საკითხის გადაწყვეტისათვის გამოყენებული იყო ინფრაწითელი თერმომეტრიის თანამედროვე მეთოდი თერმოვიზორის TH 9100 PMVI-WL Thermo Tracker (NEC Avio infrared Technologies Co. Ltd., იაპონია) გამოყენებით, რომელიც წარმოადგენს უკონტაქტო მაღალმგრძნობიარე ინფრაწითელ კამერას.

ჩატარებული კვლევის შედეგად დადგენილია ტემპერატურული მაჩვენებლების ცვლილებების დამახასითებელი დინამიკა თირკმლის ბლაგვი საგნით ტრავმირების დროს. ამასთან, გაკვეთის შემდგომ მთელი პერიოდის განმავლობაში (კვლევის 24 საათი) უშუალოდ თირკმლის ტრავმის მიდამოში აღინიშნებოდა, საშუალოდ, 2-3°C-ით (±0,28) უფრო მაღალი ტემპერატურული მაჩვენებლები, თირკმლის დაუზიანებელ ქსოვილებთან შედარებით. მარჯვენა თირკმლის ტემპერატურული მაჩვენებლები, საშუალოდ, 1,5-2°C-ით (±0,14) უფრო ნელა მცირდება მარცხენასთან შედარებით, რაც დაკავშირებულია თირკმლების განლაგების ტოპოგრაფიულ-ანატომიურ თავისებურებებთან.

დადგენილია, რომ ბლაგვი ტრავმის დროს თირკმლების დაზიანებულ და ინტაქტურ ქსოვილებში აღინიშნება ტემპერატურული მაჩვენებლების შემცირების კანონზომიერი დინამიკა, რაც შესაძლოა გამოყენებული იყოს ტრავმის განვითარების დროის განსაზღვრისათვის ინფრაწითელი თერმომეტრიის მეთოდით.

АНАЛИЗ АРХИТЕКТОНИКИ НОЧНОГО СНА У БОЛЬНЫХ РАЗНЫМИ ТИПАМИ РАССЕЯННОГО СКЛЕРОЗА

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Рассеянный склероз (РС) - хроническое, демиелинизирующее заболевание головного и спинного мозга, отличающееся разнообразием неврологических симптомов, развивающееся преимущественно у лиц молодого возраста [1].

На сегодняшний день различают следующие типы течения рассеянного склероза: ремитирующе-рецидивирущий (РРРС), первично-прогрессирующий (ППРС), вторично-прогрессирующий (ВПРС), прогрессирующе-рецидивирующий (ПРРС). Однако, несмотря на то, что основные клинические типы течения определены, биологически существует только 2 формы - рецидивирующая и прогрессирующая.

РРРС - наиболее распространенная форма, затрагивающая около 85% пациентов с РС. Для РРРС характерна манифестация в молодом возрасте, чередование клинических обострений и ремиссий с наличием очаговых неврологических симптомов поражения основных функциональных систем центральной нервной системы (ЦНС).

ППРС начинается с прогрессирования без рецидивов и составляет 10% и выше случаев РС, с характерной манифестацией в более позднем возрасте, резистентностью к проводимой терапии. Вовлечение в процесс спинного мозга чаще встречается при первично-прогрессирующем типе течения РС, иногда при отсутствии очаговых изменений на МРТ головного мозга.

ВПРС развивается у некоторых пациентов с рецидивирующим типом течения. Течение болезни продолжает ухудшаться с периодами стабилизации состояния или сглаживания выраженности симптомов.

ПРРС - редкая форма, поражающая менее 5% пациентов, прогрессирует с самого начала, с периодически возникающими нарастающими симптомами без периодов ремиссии.

В ряде случаев для характеристики клинического течения используются термины «прогрессирующе-ремитирующее» и «ремитирующе-прогрессирующее (РПРС)» в зависимости от преобладания прогрессирования или наличия обострений и ремиссий [1-3].

В основе патогенеза РС лежит развитие процессов демиелинизации, аутоиммунного воспаления. Сочетанное развитие воспалительных и нейродегенеративных процессов в головном и спинном мозге проявляются в виде потенциально обратимых очаговых неврологических симптомов или прогрессирующей необратимой физической и когнитивной инвалидности и, в конечном итоге, приводит к атрофии структур ЦНС [1,4,5].

Совокупность вышеуказанных реакций вызывает нарушение проведения нервных импульсов по проводящим путям ЦНС и обуславливает развитие разнообразных неврологических проявлений РС, таких как пирамидные, мозжечковые, чувствительные нарушения, симптомы поражения ствола головного мозга, развитие ретробульбарного неврита, а также когнитивных и эмоционально-аффективных нарушений, сексуальной дисфункции [6].

Учитывая разнообразие клинических проявлений, вероятность изменения типа течения на прогрессирующий, распознавание, диагностика РС на ранних этапах является одной из трудных задач современной неврологии. При этом необходимо учитывать взаимосвязь различных факторов, в том числе и расстройств цикла сон-бодрствование.

Нарушения сна являются сложной, мультифакторной проблемой современной неврологии, встречающейся приблизительно в 60% случаев РС, в то время как патофизиологические аспекты этих симптомов мало изучены. Расстройства сна у пациентов с РС включают хроническую бессонницу, синдром обструктивного сонного апноэ, расстройство поведения во сне с быстрыми движениями глаз, нарколепсию, синдром беспокойных ног у взрослых и детей [7,8].

Согласно Международной классификации по диагностике нарушений сна (ICSD-3), бессонница является нарушением начала, продолжительности, консолидации, качества сна, возникающая, несмотря на возможность и обстоятельства сна, и приводящая к дневной сонливости. Известно, что, по крайней мере, 30–40% пациентов с РС подвержены повышенному риску развития бессонницы. По данным, приведенным Braley TJ et al. [9], в исследовании 195 пациентов с РС, у 46% обследуемых была выявлена клиническая бессонница от умеренной до тяжелой степени, согласно Индексу тяжести бессонницы (ISI). Кроме того, 85% обследованных подтвердили, по крайней мере, один ночной симптом (боль, спастичность, чувство беспокойства, недержание мочи, невозможность сна из-за подергиваний мышц), что существенно влияет на качество ночного сна, причем 54% пациентов отмечали три или более таких симптомов. Учитывая эти результаты, рекомендуется, чтобы все пациенты с РС, которые предъявляют жалобы на дневную сонливость, расстройства засыпания, наличие ночных пробуждений, должны быть оценены для исключения бессонницы [11,12].

Синдром обструктивного апноэ во сне (СОАВ) характеризуется повторяющимися эпизодами нарушениями дыхания и гипоксией во время сна. Согласно последним исследованиям, 21% пациентов с РС могут иметь данный диагноз. Клинические признаки поражения ствола мозга или наличие очагового поражения ствола мозга на МРТ у больных РС предусматривают необходимость проведения ночного полисомнографического исследования для исключения СОАВ [10,13,14].

Синдром беспокойных ног характеризуется побуждением двигать ногами и часто сопровождаемым неприятным ощущением, которое усугубляется в покое, имеет тенденцию появляться в вечернее время суток, облегчается при движении, встречается примерно в три раза чаще при РС в сравнении с населением земного шара в целом. Исследования радиографических коррелятов синдрома беспокойных ног у пациентов с РС предполагают, что наличие очагового поражения шейного отдела может также быть независимым фактором риска, подчеркивая потенциально значимую взаимосвязь с допаминергическими проекциями спинного мозга [10,12].

Расстройства сна приводят к ухудшению общего состояния больного, включению астенических проявлений в структуру синдромокомплекса основного заболевания и являются декомпенсирующим фактором. Частые экзацербации при РС могут усложнять течение заболевания, приводить к нарастанию неврологического дефицита, что, в свою очередь, ведет к стойкой инвалидизации больного [15].

Своевременная диагностика и лечение нарушений сна, их лучшее понимание у пациентов с РС дает ключевую возможность оптимизировать общее состояние здоровья и повысить качество жизни в этой группе населения, а также знание потенциальных причин расстройств сна при различных типах течения РС позволит уточнить некоторые патогенетические аспекты этого заболевания и разработать новые подходы к терапии.

Цель исследования – определить клинико-неврологические особенности, структуру ночного сна у больных рассеянным склерозом с разными типами течения.

Материал и методы. Исследованы 58 больных РС в возрасте от 22 до 50 лет, 30 женщин и 28 мужчин, предъявляющих жалобы на нарушение ночного сна и 10 практически здоровых добровольцев того же возраста, составивших группу сравнения. Больные разделены на 2 группы в зависимости от типа течения заболевания: I группа – 31 больной РС с ремитирующим типом течения (РТ), II группа - 27 больных РС с прогредиентным типом течения (ПТ), в которую вошли больные с вторично-прогредиентным течением (ВПРС).

У всех пациентов, участвующих в исследовании, диагноз подтвержден в соответствии с критериями McDonald, 2017.

Обследование больных с РТ и ПТ проводилось в стадии ремиссии и стабилизации состояния, учитывая возможное развитие бессонницы – одного из системных побочных эффектов глюкокортикостероидов, применяемых для купирования экзацербаций. Клиническое исследование проводилось с использованием специально разработанных оценочных шкал Kurtzke: шкала неврологического дефицита, «functional system» (FS) и расширенная шкала инвалидизации Expanded Disability Status Scale (EDSS).

В целях выделения клинических вариантов нарушений сна у больных РС с различными типами течения использованы специальные шкалы-опросники, где подробным образом выявлен характер расстройств сна в течение месяца.

Полиграфические исследования ночного сна проводились с использованием компьютерного комплекса «Нейрон-Спектр+». Больным РС запись полиграммы проводилась до назначения базовой терапии. Полиграмма ночного сна включала электроэнцефалограмму (ЭЭГ) - монополярные отведения С3А1, С4А2, О1А1, О2А2 по системе «10-20», электроокулограмму (ЭОГ), электромиограмму (ЭМГ) и электрокардиограмму (ЭКГ). Оценка структуры ночного сна осуществлялась по Международной классификации стадий и фаз сна. При построении гипнограммы и анализе структуры ночного сна использовали эпохи длительностью 30 с. Расчет показателей ночного сна проводился с помощью программного обеспечения «НЕЙРОН-СПЕКТР-ПСГ». Для статистического анализа использованы пакеты Excel и SPSS. Достоверность различий между группами наблюдений оценивалась с использованием непараметрического критерия Манна-Уитни при уровне достоверности $p \leq 0,05$.

Результаты и обсуждение. Выявлено, что динамика развития неврологического дефицита вариабельна и определялась типом течения заболевания (рис. 1).

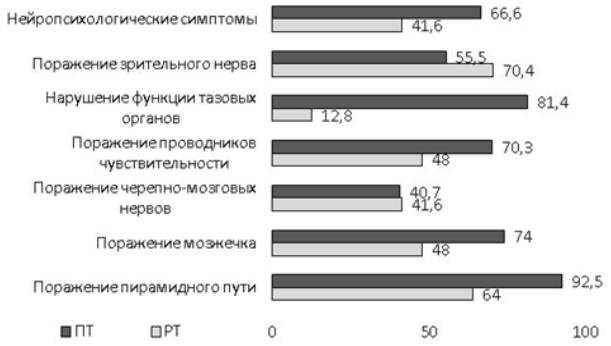

Рис. 1. Структура неврологической симптоматики больных в зависимости от типа течения РС

При ремитирующих формах РС отмечалось исчезновение или значительное уменьшение неврологических нарушений во время полных и неполных ремиссий. При прогрессирующих формах отмечалась стойкость выявленных нарушений, постепенное ухудшение состояния больных, а также появление новых неврологических симптомов.

При сравнительном анализе распределения баллов по расширенной шкале инвалидизации EDSS в исследуемых

группах средний балл EDSS составил: у больных с РТ 3,0±0,2; у больных ППРС это показатель имел самые высокие значения и составил 6,5±0,4 баллов.

В результате анализа субъективной оценки ночного сна установлено, одно из ведущих мест в клинической картине занимали расстройства засыпания. Жалобы на невозможность уснуть в течение 30 минут были более выражены у больных РТ (92,8%), чем у больных ПТ (88,8%), что провоцировало более частое использование снотворных препаратов в этих группах больных.

У всех больных РС отмечались жалобы на ночные пробуждения и ранние в утренние часы. В группе ПТ больные просыпались посреди ночи или рано утром значительно чаще (85,1%) в сравнении с группой РТ (60,8%).

Основными причинами пробуждений являлись посторонний звук, чувство нехватки воздуха, субъективные ощущения изменения окружающей температуры, возникающие вовремя сна боли в конечностях, мышечные спазмы, нарушения мочеиспускания, что и вызывало проблемы со сном у больных РС с различной частотой.

Все обследованные больные жаловались на изменение качества ночного сна. Качество сна оценивалось как «хорошее», «плохое» и «очень плохое». Чаще всего сон оценивался больными как «плохой» или «очень плохой» в группе ПТ (81,4%) в сравнении с группой РТ (41,6%). Следует отметить, что даже при наличии ночных пробуждений, больные могли оценивать качество ночного сна как «хорошее».

44,8% больных РТ оценивали свой сон как «прерывистый». 54,4% больных с ремитирующим течением РС считали свой сон «спокойным». 40,7% больных группы ПТ оценивали сон как «поверхностный», 59,2% как «прерывистый».

Довольно часто больные РС отмечали замедленный переход от сна к бодрствованию и трудность с включением в активную деятельность. Подавляющее число больных в середине дня испытывали общую слабость, сонливость, снижение внимания, отмечали рассеянность, потерю интереса к поддержанию активной деятельности, заторможенность.

В сравнении с группой здоровых (группа контроля) у больных РС как в группе РТ, так и в группе ПТ выявлены достоверные изменения показателей ночного сна.

Общие изменения, характерные для группы РТ и группы ПТ в сравнении с контролем:

- увеличение продолжительности и процентной представленности ночного бодрствования в общей структуре сна за счет увеличения длительности сегментов (эпизодов) бодрствования;
- уменьшение длительности и процентной представленности дельта-сна. В обеих группах сравнения дефицит дельта-сна связан с уменьшением длительности и процентной представленности стадии С3;
- наряду с дельта-сном отмечены негативные изменения в организации и реализации фазы быстрого сна, в частности уменьшение продолжительности и процентной представленности фаз быстрого сна (ФБС) в структуре сна;
- при дефиците-дельта сна отмечается достоверное удлинение эпизодов поверхностного медленноволнового сна (стадия С2), за счет чего общая продолжительность фазы медленноволнового сна, по всей вероятности, не имеет достоверных различий с группой контроля;
- низкий индекс эффективности сна у больных РС связан с увеличением эпизодов ночного бодрствования;
- изменение архитектоники сна и уменьшение числа завершенных циклов.

Специфические различия нарушения сна у больных РС в сравнении со здоровыми представлены в таблицах 1, 2:

- у больных РТ значимо увеличивается латентный период фазы быстрого сна, с чем, возможно, связано и нарушение архитектоники сна. В группе больных ПТ латентный период ФБС достоверно не увеличивается, а нарушение архитектоники сна, очевидно, связано с выраженным возрастанием числа незавершенных циклов сна;
- у больных РТ значимо повышается количество кратковременных ночных пробуждений (менее 3 мин), у больных ПТ значимо повышается количество длительных ночных пробуждений (более 3 минут);
- у больных ПТ в сравнении со здоровыми значимо уменьшается общая продолжительность ночного сна. В группе РТ этот показатель не имеет достоверного различия.

Таблица 1. Достоверные различия показателей ночного сна в группе больных РС РТ и группе контроля

Показатели ночного сна	**Группа РТ n=31**	**Группа контроля n=10**	**P≤0,05**
Латентный период ФБС, мин	132,8±13,8	77,2±6,2	0,05
Длительность бодрствования, мин	74,2±7,5	31,2±3,8	0,05
Длительность С3, мин	47,6±4,4	74,2±7,8	0,05
Длительность ФБС, мин	73,0±6,0	102,0±8,1	0,05
Длительность дельта-сна, мин	106,7±6,1	156,7±14,1	0,04
Представленность бодрствования, %	17,3±2,3	7,2±1,1	0,05
Представленность С3, %	11,1±1,1	16,5±3,6	0,05
Представленность ФБС, %	16,4±1,2	23,1±0,3	0,04
Представленность дельта-сна, %	24,5±1,4	35,0±3,0	0,03
Средняя длительность сегментов бодрствования, мин	5,6±0,8	1,6±0,1	0,01
Средняя длительность сегментов С2, мин	6,2±0,4	3,8±0,3	0,05
Количество пробуждений < 3 мин	10,8±1,4	18,7±3,2	0,05
Индекс эффективности сна, %	76,8±2,5	89,6±2,0	0,05
Число завершенных циклов сна	3,1±0,2	4,7±0,3	0,03

*примечание: * - различие с группой сравнения с достоверностью p≤0,05 по критерию Манна-Уитни*

Сравнение показателей ночного сна в группах больных РТ и ПТ показало, что:
- у больных ПТ в сравнении с больными РТ значимо повышается продолжительность и представленность бодрствования;
- у больных ПТ увеличивается количество кратковременных пробуждений;
- у больных ПТ уменьшается общая продолжительность ночного сна;
- у больных ПТ на фоне низкой продолжительности сна уменьшается длительность как фазы медленноволнового сна, так и фазы быстрого сна;
- несмотря на отсутствие достоверных различий в суммарной длительности стадий дельта-сна выявлено, что у больных ПТ значительно короче длительность эпизодов стадии С4 (наиболее синхронизированной стадии) и длительность эпизодов дельта-сна в целом, что связано с возрастанием ночных пробуждений и повышением фрагментарности, прерывности дельта-сна (страдает плавность переходов стадий);
- у больных ПТ значимо нарушается реализация как всей фазы медленноволнового сна в целом, так и, непосредственно, отдельных ее стадий, в частности стадии С2;
- на фоне выраженного дефицита дельта-сна у больных ПТ отмечается высокая потребность в этом сне, о чем свидетельствуют короткие латентные периоды наступления стадий (стадии С3 и С4) дельта-сна;

Таблица 2. Достоверные различия показателей ночного сна в группе больных РС ПТ и группе контроля

Показатели ночного сна	Группа ПТ n=27	Группа контроля n=10	P≤0,05
Длительность бодрствования, мин	102,2±9,9	31,2±3,8	0,03
Длительность С3, мин	40,6±3,8	74,2±7,8	0,05
Длительность С4, мин	58,8±5,8	82,5±3,8	0,05
Длительность ФБС, мин	58,2±5,4	102,0±8,1	0,01
Длительность дельта-сна, мин	99,5±7,8	156,7±14,1	0,05
Представленность бодрствования, %	24,4±2,8	7,2±1,1	0,02
Представленность С3, %	10,0±1,0	16,5±3,6	0,05
Представленность С4, %	14,4±1,5	18,4±0,6	0,05
Представленность ФБС, %	14,2±1,2	23,1±0,3	0,01
Представленность дельта-сна, %	24,4±1,9	35,0±3,0	0,05
Средняя длительность сегментов бодрствования, мин	6,8±0,9	1,6±0,1	0,01
Средняя длительность сегментов С2, мин	5,7±0,4	3,8±0,3	0,05
Продолжительность сна, мин	311,8±12,1	412,2±39,4	0,03
Количество пробуждений >3 мин	5,0±0,5	3,0±0,1	0,05
Индекс эффективности сна, %	66,9±2,6	89,6±2,0	0,01
Число завершенных циклов сна	3,1±0,2	4,7±0,3	0,02

*примечание: * - различие с группой сравнения с достоверностью p≤0,05 по критерию Манна-Уитни*

Таблица 3. Достоверные различия показателей ночного сна в группах больных РС РТ и РС ПТ

Показатели ночного сна	Группа РТ n=31	Группа ПТ n=27	P≤0,05
Латентный период С3, мин	17,1±1,8	14,1±1,01	0,05
Латентный период С4, мин	47,2±10,6	27,8±6,7	0,05
Длительность бодрствования, мин	74,2±7,5	102,2±9,9	0,04
Длительность С2, мин	158,8±9,8	126,9±7,8	0,02
Длительность ФБС, мин	73,0±6,04	58,2±5,4	0,04
Длительность ФМС, мин	281,9±10,1	244,22±9,70	0,01
Представленность бодрствования, %	17,3±2,3	24,4±2,8	0,04
Представленность С2, %	36,3±2,1	30,9±1,8	0,04
Средняя длительность сегментов С4, мин	12,8±1,7	7,5±0,9	0,05
Средняя длительность сегментов дельта-сна, мин	16,5±1,9	10,3±1,0	0,05
Средняя длительность сегментов ФМС, мин	25,3±2,2	18,5±1,4	0,05
Продолжительность сна, мин	363,0±13,7	311,8±12,1	0,00
Количество пробуждений <3 мин	10,8±1,4	18,1±1,6	0,05
Индекс эффективности сна, %	76,8±2,5	66,9±2,6	0,00

- у больных ПТ индекс эффективности сна меньше, что связано с повышением бодрствования и уменьшением продолжительности сна (таблица 3).

Выводы. Таким образом, проведенное исследование позволило сделать следующие выводы:

1. У больных с ремитирующим и прогредиентным течением РС выявлены структурно-функциональные нарушения взаимодействия процессов бодрствования и сна, проявляющиеся в пространственно-временной несогласованности структуры сна, его цикличности, представленности фаз медленноволнового и быстрого сна, стадий медленноволнового сна, которые свидетельствуют о нарушении механизмов регуляции сна, обусловленных типом течения РС.

2. Отмечены нарушения эффективности сна вследствие сокращения его общей продолжительности, увеличения средней продолжительности эпизодов активного и пассивного бодрствования во время ночного сна, которые отражают активацию десинхронизирующих систем мозга, наиболее выраженную у больных с прогредиентным типом течения РС.

3. Показаны особенности перестройки архитектоники ночного сна у больных с различными типами течения РС в виде нарушения цикличности и снижения числа завершенных циклов сна, что обусловлено лабильностью и истощаемостью механизмов регуляции ритмичности ночного сна.

4. Установлены особенности нарушения механизмов организации и поддержки фазы медленноволнового сна, которые проявляются в увеличении продолжительности сегментов поверхностных стадий на фоне сокращения числа и средней продолжительности сегментов глубоких стадий, дефиците дельта-сна, при относительном сохранении функционирования механизмов инициации глубоких стадий сна с превалированием у больных с прогредиентным типом течения РС.

5. Выявлены особенности нарушения механизмов организации и поддержки фазы быстрого сна, проявляющиеся в удлинении латентного периода, сокращении числа эпизодов фаз быстрого сна, снижении представленности фазы быстрого сна в общей структуре ночного сна с наибольшей выраженностью у больных с прогредиентным типом течения РС.

Полученные результаты необходимо учитывать при прогнозировании типа течения РС, а также при подборе и проведении лечебно-профилактических мероприятий по коррекции нарушений сна у больных РС.

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SUMMARY

ARCHITECTONICS OF THE NIGHT SLEEP BASED ON ITS POLYSOMNOGRAPHIC CHARACTERISTICS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Aim of our study is to establish polysomnographic characteristics of nocturnal sleep in various forms of multiple sclerosis.

Fifty eight patients with different clinical course of multiple sclerosis (MS) were included into the study. Disturbances of sleep architectonics were identified: representation of deep stages of NREM sleep, as well as REM sleep were reduced. Maintenance and continuity of sleep and its architecture were affected, leading to reduced sleep efficacy. Destabilization of sleep phases can be explained by activation of desynchronizing brain systems, leading to poor organization of NREM and REM sleep. These disorders were especially pronounced in patients with progressive course of MS. Thus, abovementioned sleep disorders can have prognostic value for predicting clinical course severity in patients with MS. Management of sleep disorders can improve quality of live in people with MS.

Keywords: multiple sclerosis, sleep-wake cycle, polysomnography, night's sleep architectonics.

РЕЗЮМЕ

АНАЛИЗ АРХИТЕКТОНИКИ НОЧНОГО СНА У БОЛЬНЫХ РАЗНЫМИ ТИПАМИ РАССЕЯННОГО СКЛЕРОЗА

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Цель исследования - определение клинико-неврологических особенностей структуры ночного сна у больных рассеянным склерозом с разными типами течения.

В статье представлены результаты клинико-неврологического, полисомнографического исследования ночного сна у 58 больных рассеянным склерозом (РС) с различными типами течения в фазе ремиссии и стабилизации состояния.

У больных с ремитирующим и прогредиентным течением РС выявлены функциональные нарушения процессов бодрствования и сна, проявляющиеся в нарушении структуры медленноволнового и быстрого сна и его цикличности, что свидетельствует о нарушении механизмов регуляции сна, обусловленных типом течения РС. Выявлены особенности нарушения механизмов организации и поддержания фазы медленноволнового сна, быстрого сна. Нарушения эффективности сна превалируют у больных с прогредиентным типом течения РС.

Полученные результаты необходимо учитывать при оценке и прогнозировании типа течения РС, а также при подборе и проведении лечебно-профилактических мероприятий по коррекции нарушений сна у больных РС.

რეზიუმე

ღამის ძილის არქიტექტონიკა პაციენტებში გაფანტული სკლეროზის სხვადასხვა ტიპით

ნ.ვოლოშინა, ვ.ვასილოვსკი, მ.ჩერნენკო, ვ.სუხორუკოვი, ვ.ვოვკი

უკრაინის მედიცინის მეცნიერებათა ეროვნული აკადემიის ნევროლოგიის, ფსიქიატრიისა და ნარკოლოგიის ინსტიტუტი, ხარკოვი; ხარკოვის ვ. კარაზინის სახ. ეროვნული უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა ღამის ძილის სტრუქტურის კლინიკურ-ნევროლოგიური თავისებურებების განსაზღვრა პაციენტებში გაფანტული სკლეროზის მიმდინარეობის სხვადასხვა ტიპით.

სტატიაში წარმოდგენილია გაფანტული სკლეროზის მიმდინარეობის სხვადასხვა ტიპის მქონე 58 პაციენტის ღამის ძილის კლინიკურ-ნევროლოგიური, პოლისომნოგრაფიული კვლევის შედეგები რემისიის ფაზაში და მდგომარეობის სტაბილიზებისას. პაციენტებში გაფანტული სკლეროზის რემისიული და პროგრედიენტული მიმდინარეობით გამოვლინდა ღვიძილის და ძილის პროცესების ფუნქციური მოშლილობები, გამოხატული ნელტალღოვანი და სწრაფი ძილის სტრუქტურის დარღვევით, რაც მოწმობს ძილის რეგულაციის მექანიზმების დაზიანების შესახებ და პირობადებულია გაფანტული სკლეროზის მიმდინარეობის ტიპით. გამოვლინდა ძილის ნელტალღოვანი და სწრაფი ფაზების ორგანიზების მექანიზმების დარღვევების თავისებურებანი. ძილის ეფექტურობის დარღვევები პრევალირებს პაციენტებში გაფანტული სკლეროზის პროგრედიენტული მიმდინარეობით. მიღებული შედეგების გათვალისწინება აუცილებელია გაფანტული სკლეროზის მიმდინარეობის ტიპის შეფასებისა და პროგნოზირებისას, ასევე, ძილის კორექციის სამკურნალო-პროფილაქტიკური ღონისძიებების ჩატარებისას გაფანტული სკლეროზის მქონე პაციენტებში.

RESEARCH OF PECULIARITIES OF DEVELOPMENT OF TIME PERCEPTION FUNCTION IN 13-15 YEAR-OLD ATHLETES WITH DIFFERENT BLOOD GROUPS

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It is known that achieving high sports results in most sports is not possible without proper development of coordination abilities. The latter to some extent reflect a human motion pattern [12]. It is also known that one of the integral components of coordination abilities is dexterity [15,16,21]. The latter is manifested in the coordination complexity of performing physical exercises of different nature in accordance with the spatio-temporal and spatio-power parameters of motor action [2].

In opinion of Yu.V. Koryagina and others [4,5,7] chronobiological features of time and space perception are one of the leading factors that limit the success of sports activities. According to the above, we find information about the impact of various sports on time management for athletes (own perception of time) as a mental process of reflection in their minds of holistic images, objects, etc. [3,19,20].

However, despite the fact that there is a relatively large arsenal of studies by different authors on the impact of different sports on the development of this function, but, paradoxically, the results (in most cases) remain contradictory. Thus, in one of the works of Yu.V. Koryagina [6] we find that athletes of situational sports are

characterized by a more accurate perception of temporal and spatial parameters compared to representatives of cyclic and acyclic sports. Whereas in another work [5] the authors conclude that the smallest error in the value of an individual unit of time in relation to the astronomical minute is observed in athletes of cyclic sports, whose activities are not limited by space or time, respectively, the largest one is in representatives of acyclic sports. Researchers N.I Moiseeva, N.I. Karaulova, S.V. Panyushkina and others [10] note that the individual perception of time segments in athletes of martial arts (boxing, wrestling) is the closest to the actual countdown. In their opinion, this is due to the fact that the duration of a sports match (for example, a boxing round) is determined by the athlete not by a timer (the latter is under a referee's control), but he relies on his feelings «internal clock». No less interesting, as we think, are the materials of research by R. Soloshenko and D. Nedogonova [14], in which the authors point to the fact of hereditary conditionality of the rate of reproduction of time segments of different duration. However, this evidence, in opinion of the authors, requires additional research.

And finally, in the work of M.F. Khoroshukha [18] are presented the results of research of peculiarities of changes in the time perception function in young athletes aged 13-16 years of specialized sports institutions depending on the direction of their training process. The general conclusion of this work is to establish the fact of specificity of influence of trainings of different orientation (on force, speed and endurance) on the mentioned mental function of teenagers. In particular, it was found that due to influence of training loads of speed-power nature there is an improvement in the time perception function, whereas in contrast some insignificant changes in the indicators of this feature due to influence of loads on endurance are observed. It is known from the materials of research by G. Korobeynikov and other scientists [3] that the time perception function may change due to influence of improving specific sports activities and it depends on the nature of specialization in a greater degree than on gender differences. Nevertheless, the ignorance of human sexual dimorphism in the analysis of chronobiological features of time perception is a scientific error of researchers. So, in the works of Yu.V. Koryagina and others [5,8] we find the following: the system of perception of time periods in girls who do not play sports is more accurate than in boys who are not athletes. Whereas an opposite picture is observed in athletes, namely, the smallest error in the value of an individual unit of time in relation to the astronomical minute is registered in boys compared to girls.

In these recent times, special attention should be paid to the research of scientists that is devoted to the current problem of influence of serological markers of blood groups on the development of certain motor [26, 27, 28] and mental [13,22-24] skills of people of different ages and occupations. The result of such research is to establish the fact of existence of associative relations between blood groups according to the ABO system and the development of basic mental properties in individuals tested, mainly of male sex.

In our previous work [25] the results of influence of serological markers of blood groups on the development of the attention function in adolescent girls specializing in sports of different training orientation are presented. As for the problem of influence of serological markers of blood groups on the development of the time perception function in girls-athletes engaged in various sports, it remains unexplored.

Material and methods. The study involved girls-athletes aged 13-15 years (n= 178) from Brovary Higher School of Physical Culture (experimental group), who according to the classification of sports by A.G. Dembo [1] were divided into two groups: group A (n = 96) - speed and power sports (freestyle wrestling, athletics: sprinting, hurdles, jumping, shot put and discus); group B (n = 82) - endurance sports (skiing, swimming: 200, 400 and 1500 m, athletics: running at 800, 1500, 3000 and 5000 m, speed walking)**.** The control group of participants of study was divided into two subgroups: subgroup 1 - pupils aged 13-15 years from secondary school № 3 of Brovary City (Kyiv region), who did not play sports (n=117); subgroup 2 - students of 1–3 courses, aged 17–20 years (n=115), from M.P. Dragomanov National Pedagogical University (n=61) and Borys Hrinchenko University of Kyiv City (n=54), who did not play sports too.

The research of the time perception function was carried out by method of V.L. Maryshuk et al. [9]. Its essence is expressed in the following: the experimenter beating with pencil on a table starts the countdown, and at the next beat completes a certain (in seconds) time interval; a person tested, in turn, must reproduce the time interval set by the experimenter also by beating with pencil on a table surface, with the help of which the beginning and end of a time interval was determined. The range of time intervals was from 6 to 12s. Each individual was offered to perform the above test consisting of 10 items. The prototype of the above-mentioned method is the method of D. Zakay, R.A. Block [29], which involves determining the error in perception of a period of time by registering the so-called coefficient of subjective estimation of duration, as the ratio of subjective estimation of duration of time to the factual one.

$$T = 100 - \frac{C_2 \times 100}{C_1}$$

where, T – accuracy of time interval, %;

C_1 – amount of time intervals determined by the experimenter.

[*Note.* For all individuals tested, this indicator was the same and amounted to 89s, and the components of this amount (time intervals) were set in the following sequence: 8→11→6→10→7→12→6→9→11 c];

C_2 – amount of errors concerning the individual tested, s.

Taking into account a possible dependence of the results of this kind of study on the emotional state of man [11], testing was conducted in an isolated room in the morning (from 9 to 12 hours, not earlier than 2 hours after a meal). One or two days before testing, the participants of study were asked to reduce the volume and intensity of physical activity by 50%, not to use tonics and sedatives, and on the day of testing - strong tea or coffee.

The blood group data were taken from the medical records of the participants of study. Individuals who did not have data on their blood type were not allowed to be tested.

In the course of testing, the significance of the difference between individuals with different blood groups of the ABO system, who represented the experimental (young athletes) and control (pupils and students) groups was determined using the parametric Student's t-test.

The purpose of the article is to investigate the influence of serological markers of blood groups on the development of the time perception function in adolescent athletes, taking into account sexual dimorphism.

Theoretical analysis and generalization of scientific and methodical literature, pedagogical observation, testing, methods of statistics.

Results and discussion. The data of the associative relation of blood groups with the properties of the time perception function in adolescent girls-athletes without taking into account the specifics of their sports are set forth in table 1. As can be seen from the data in this table, changes in these indices (amount of errors, accuracy of time perception) in young athletes with dif-

ferent blood groups did not have statistically significant differences (P>0,05), but there is a tendency to reduce these indices in girls with B (III) blood group compared to persons having 0 (I), A (II) and AB(IV) blood groups. Thus, the average values of the amount of errors in persons with B (III) blood group were 4,2±0,33 s, while in their age mates with 0 (I) blood group, they were equal to 4,8±0,35 s, and in individuals with A (II) and AB (IV) groups, respectively, - 4,7±0,40 and 4,8±0,39 s. As expected, there were no significant changes in the accuracy of time perception (P>0,05 in all cases) in athletes of different blood groups.

The following two tables (Tables 2 and 3) contain the data of comparative analysis of time perception function in girls-athletes specializing in sports of different training orientation: group A - speed and power sports, group B - endurance sports.

Table 1. Indices of time perception function in young athletes aged 13-15 years (without taking into account the specifics of sports) with different blood groups, X±m, (n=178)

№	Blood group	n	Time perception	
			Amount of errors, s	Accuracy of time perception, %
1	O(I)	60	4,8±0,35	94,6±0,39
2	A(II)	55	4,7±0,40	94,7±0,45
3	B(III)	36	4,2±0,33	95,3±0,29
4	AB(IV)	27	4,8±0,39	94,6±0,35
Significance of difference		P1–P2	>0,05	>0,05
		P1–P3	>0,05	>0,05
		P1–P4	>0,05	>0,05
		P2–P3	>0,05	>0,05
		P2–P4	>0,05	>0,05
		P3–P4	>0,05	>0,05

Table 2. Indices of time perception function in young girls-athletes aged 13-15 years who predominately develop the speed and power properties (group A), with different blood groups, X±m, (n=96)

№	Blood group	n	Time perception	
			Amount of errors, s	Accuracy of time perception, %
1	O(I)	32	4,1±0,38	95,4±0,42
2	A(II)	30	4,2±0,43	95,2±0,48
3	B(III)	19	3,8±0,34	96,0±0,38
4	AB(IV)	15	4,2±0,39	95,2±0,43
Significance of difference		P1–P2	>0,05	>0,05
		P1–P3	>0,05	>0,05
		P1–P4	>0,05	>0,05
		P2–P3	>0,05	>0,05
		P2–P4	>0,05	>0,05
		P3–P4	>0,05	>0,05

Table 3. Indices of time perception function in young girls-athletes aged 13-15 years, who predominantly develop the quality of endurance (group B), with different blood groups, X±m, (n=82)

№	Blood group	n	Time perception	
			Amount of errors, s	Accuracy of time perception, %
1	O(I)	28	5,5±0,43	93,8±0,48
2	A(II)	25	5,2±0,47	94,2±0,53
3	B(III)	17	4,7±0,40	94,6±0,44
4	AB(IV)	12	5,3±0,45	94,1±0,49
Significance of difference		P1–P2	>0,05	>0,05
		P1–P3	>0,05	>0,05
		P1–P4	>0,05	>0,05
		P2–P3	>0,05	>0,05
		P2–P4	>0,05	>0,05
		P3–P4	>0,05	>0,05

From the actual material of the above tables it is also clear that there is no statistically significant difference between the above indicators of the time perception function in young athletes, some of whom mainly develop speed and power qualities, and others - the quality of endurance. However, as in the first case (Table 1), among young girls-athletes of group A (table 2) and their age mates – girls-athletes of group B (Table 3), who have B (III) blood group, there is a tendency to reduce the indicator of amount of errors in time segments. So, the average values of this indicator among the representatives of group A is 3,8±0,34s, and, respectively, group B – 4,7±0,40 s. In view of the foregoing, as we think, it reasonable to assume that young athletes with B (III) blood group have the best associative relation with the time perception function.

The factual material of investigation of the time perception function in pupils aged 13-15 years, who do not go in for sports, is set forth in table 4. It is evident from the data of this table that the individuals with B (III) blood group have made less errors compared to other persons.

Thus, the analysis of changes in the average values of the indicator of the amount of errors points to a statistically significant improvement thereof in pupils with B (III) blood group compared with individuals having 0 (I) and AB (IV) blood groups (P <0,05 in both cases). Notwithstanding that the significant difference in the values of this indicator among girls having B (III) and A (II) blood groups has not been found, however, there is a tendency to improve it in persons with B (III) blood group, namely: in individuals of B (III) blood group, this figure is 4,7±0,38s, and in persons of A (II) group, respectively, - 5,8±0,40 s (t=2,02; P>0,05). As expected, there are the similar changes in the amount of errors in time perception in girls with different blood groups, and the character of changes in the indicator of accuracy of time perception is also noted. This figure remains significantly higher in people with B (III) blood group. No significant differences (P>0,05) were found in the values of the above indicators between persons with 0 (I), A (II) and AB (IV) blood groups.

From our previous research [22-24] it is known that the basic mental functions of a person improve over the years. Therefore, in our case, we can assume that the time perception function is more expressively manifested in late adolescence than in early adolescence. And therefore the materials of psychological research of students aged 17-20 years of higher education institutions are specified in table 5.

As can be seen from the data in this table, students with B (III) blood group in terms of the amount of errors and accuracy of time perception have significantly better values of the time perception function compared to their age mates who had 0 (I), A (II) and AB (IV) blood groups (P <0,05 in all cases). No statistically significant difference was found in all indicators of time perception function between persons with 0 (I), A (II) and AB (IV) blood groups (P>0,05). Therefore, individuals with blood type B (III) can be considered to have the best associative relations with the time perception function. It is probably impossible to determine the worst associative relation among other individuals in this group.

Table 4. Indices of time perception function in pupils aged 13–15 years, who do not go in for sports, with different blood groups, X±m, (n=117)

№	Blood groups	n	Time perception	
			Amount of errors, s	Accuracy of time perception, %
1	O(I)	31	6,2±0,41	93,1±0,44
2	A(II)	34	5,8±0,40	93,5±0,45
3	B(III)	29	4,7±0,38	94,7±0,40
4	AB(IV)	23	5,9±0,38	93,4±0,44
Significance of difference		P1–P2	>0,05	>0,05
		P1–P3	<0,05	<0,05
		P1–P4	>0,05	>0,05
		P2–P3	>0,05	>0,05
		P2–P4	>0,05	>0,05
		P3–P4	<0,05	<0,05

Table 5. Indices of time perception function in students aged 17-20 years, who do not go in for sports, with different blood groups, X±m, (n=115)

№	Blood groups	n	Time perception	
			Amount of errors, s	Accuracy of time perception, %
1	O(I)	37	5,7±0,38	93,4±0,42
2	A(II)	34	5,8±0,35	93,5±0,39
3	B(III)	24	4,5±0,36	94,9±0,40
4	AB(IV)	20	5,8±0,39	93,5±0,45
Significance of difference		P1–P2	>0,05	>0,05
		P1–P3	<0,05	<0,05
		P1–P4	>0,05	>0,05
		P2–P3	<0,05	<0,05
		P2–P4	>0,05	>0,05
		P3–P4	<0,05	<0,05

Table 6. Comparative analysis of average values of development of time perception in young athletes (girls and boys) of specialized sports institutions (without taking into account specifics of sports) with different blood groups, X±m, (n=317)

Indices of memory function	**Statistical values**	**Blood groups**			
		O(I)	A(II)	B(III)	AB(IV)
Girls (1)					
Amount of errors, s	X±m	n=60	n=55	n=36	n=27
		4,8±0,35	4,7±0,40	4,2±0,33	4,8±0,39
Accuracy of time perception, %	X±m	94,6±0,39	94,7±0,45	95,3±0,29	94,6±0,35
Boys (2) [23]					
Amount of errors, s	X±m	n=46	n=43	n=28	n=22
		4,6±0,26	4,3±0,23	3,9±0,27	4,2±0,34
Accuracy of time perception, %	X±m	94,8±0,29	95,1±0,26	95,6±0,30	95,3±0,38
Amount of errors, s	P1–P2	>0,05	>0,05	>0,05	>0,05
Accuracy of time perception, %	P1–P2	>0,05	>0,05	>0,05	>0,05

Table 7. Comparative analyses of average values of development of time perception in girls and boys of general educational institutions, who do not go in for sports, with different blood groups, X±m, (n=223)

Indices of memory function	**Statistical values**	**Blood groups**			
		O(I)	A(II)	B(III)	AB(IV)
Girls (1)					
Amount of errors, s	X±m	n=31	n=34	n=29	n=23
		6,2±0,41	5,8±0,40	4,7±0,38	5,9±0,38
Accuracy of time perception, %	X±m	93,1±0,44	93,5±0,45	94,7±0,40	93,4±0,44
Boys (2) [23]					
Amount of errors, s	X±m	n=28	n=30	n=26	n=22
		5,4±0,32	5,2±0,26	4,2±0,39	5,2±0,30
Accuracy of time perception, %	X±m	94,1±0,35	94,5±0,29	95,6±0,42	94,5±0,33
Amount of errors, s	P1–P2	>0,05	>0,05	>0,05	>0,05
Accuracy of time perception, %	P1–P2	>0,05	>0,05	>0,05	>0,05

Table 8. Comparative analysis of average values of development of time perception in students (girls and boys) of higher educational institutions, who do not go in for sports, with different blood groups, X±m, (n=265)

Indices of memory function	**Statistical values**	**Blood groups**			
		O(I)	A(II)	B(III)	AB(IV)
Girls (1)					
Amount of errors, s	X±m	n=37	n=34	n=24	n=20
		5,7±0,38	5,8±0,35	4,5±0,36	5,8±0,39
Accuracy of time perception, %	X±m	93,4±0,42	93,5±0,39	94,9±0,40	93,5±0,45
Boys (2) [23]					
Amount of errors, s	X±m	n=40	n=49	n=35	n=26
		5,6±0,44	5,7±0,35	3,1±0,30	5,7±0,41
Accuracy of time perception, %	X±m	93,7±0,49	93,6±0,39	96,5±0,34	93,6±0,47
Amount of errors, s	P1–P2	>0,05	>0,05	<0,01	>0,05
Accuracy of time perception, %	1–P2	>0,05	>0,05	<0,01	>0,05

Comparative analysis of gender features of development of time perception function in three groups of study participants (young athletes, pupils and students) having different blood groups according to the ABO system is presented in tables 6, 7 and 8.

From the data of these tables we find the following: the significant differences in average values of time perception function (P>0,05) (Table 6) among the adolescent athletes (girls and boys) have not been established; the statistically significant differences in the nature of changes in the amount of errors and the accuracy of time perception in girls and boys of secondary schools with different blood groups who do not play sports (Table 7) have not been found too; the difference in the values of the above-mentioned indicators of the time perception function among the students (girls and boys) who have B (III) blood group was significant (P<0,01) and it indicates that boys have a more accurate perception of time intervals than in girls with the same blood group, while no significant differences between students of both sexes with 0 (I), A (II) and AB (IV) blood groups were found (P>0,05 in all cases).

Studying the nature of changes in the time perception function (amount of errors, accuracy of time perception) in young athletes aged 13-15 years with different blood groups, we conclude that despite the fact that all indicators of this function did not find significant differences between individuals of 0 (I), A (II), B (III) and AB (IV) blood groups (P>0,05), however, there is a tendency to reduce the amount of errors in the perception of time periods in girls-athletes of different sports who have B (III) blood group, compared with other individuals. The above leads us to believe that the athletes with B (III) blood group have the best associative relation with the properties of time perception. The fact that no significant differences in the indicators of the mentioned mental function (P>0,05) have been found among the girls with different orientation of training process (according to the classification of sports by A.G. Dembo) is an indisputable evidence of the specific impact of training loads of different orientation on the body functions of young athletes [17].

Evidence that all such people with B (III) blood group have the best associative relation with the properties of time perception are the data of research of pupils aged 13-15 years and students 17-20 years who do not go in for sports (control groups). According to the results of research, the best values of time perception function (in most cases) are registered in girls with B (III) blood group compared to their age mates who have other blood groups (P<0,05 in all cases). It should be added to the above that that the properties of time perception are more expressively manifested in students in late adolescence than in pupils in early adolescence.

Finally, a comparative analysis of gender peculiarities of development of time perception function in persons tested, who have different blood groups, shows that sexual dimorphism in most cases (for example, in the case of study of school youth) does not make significant adjustments to the specifics of changes in this function, while the study of student youth, on the contrary, makes significant adjustments thereto. One of such adjustments is a statistically significant (at P<0,01) decrease in the amount of made errors in male students compared to female students. The latter gives good reason to believe that men with B (III) blood group yet still have the best associative relation with the properties of time perception, while the worst associative relation remains not cleared up.

Theoretical and practical relevance of the work. Theoretical basis of many years research are the provisions and conclusions of a number of authors (M.N. Fox, M. Khoroshukha et al., V. Lyshevska, S. Shepoval, L. Serhiynko, E. Strikalenko et al.) concerning the possibility to use serological markers of ABO blood system in the genetic prediction of development of separate somatic diseases, motor and mental skills of people of different ages, genders and occupations. The practical relevance of the work consists in the possibility to use psychophysiological selection of young athletes for going in for those sports, for which the time perception function plays an important role in the growth of sports mastery.

Conclusions. The use of serological markers of blood groups according to the ABO system, in our opinion, is possible in the genetic prediction of the development of time perception in young adolescent athletes (boys and girls), their age mates - pupils who do not go in for sports and students (boys and girls). In general, based on the results of many years research, we conclude that genetic markers of blood groups are more informative in predicting the development of time perception in boys with B (III) blood group than in girls with the same blood group. The worst associative relation remains not cleared up**.**

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SUMMARY

RESEARCH OF PECULIARITIES OF DEVELOPMENT OF TIME PERCEPTION FUNCTION IN 13-15 YEAR-OLD ATHLETES WITH DIFFERENT BLOOD GROUPS

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The aim of the work is to investigate the influence of serological markers of blood groups on the development of the time perception function in adolescent athletes taking into account sexual dimorphism. The study involved girls (n=178) and boys (n=139) from a specialized sports institution, who according to the classification of sports by A.G. Dembo were divided into two groups: group A - speed and power sports, group B - endurance sports. The control group consisted of pupils [girls (n=117), boys (n=106)] aged 13–15 years and students [girls (n=115), boys (n=150)] aged 17–20 years, who did not play sports. The research of the time perception function was carried out according to the method of V.L. Maryshuk et al., the prototype of which is the method of D.Zakay, R.A. Block. The fact of possible use of blood groups in genetic prediction of development of time perception was established. Individuals of male and female sex with blood group B (III) have been found to have the best associative relation with the properties of this function, while the worst relation remains unclear. The properties of time perception are more expressively manifested in students in late adolescence than in pupils in early adolescence. It was found that sexual dimorphism does not make significant adjustments in the specifics of changes in the time perception function, but genetic markers of blood groups are more informative in predicting the development of the abovementioned mental quality in boys with B (III) blood group than in girls with the same blood group.

Keywords: mental functions, perception of time, research, sexual dimorphism, young athletes, pupils, students.

РЕЗЮМЕ

ОСОБЕННОСТИ РАЗВИТИЯ ФУНКЦИИ ВОСПРИЯТИЯ ВРЕМЕНИ У СПОРТСМЕНОВ 13-15 ЛЕТ С РАЗНЫМИ ГРУППАМИ КРОВИ

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Цель исследования - определить влияние серологических маркеров групп крови на развитие функции восприятия времени юных спортсменов подросткового возраста с учетом полового диморфизма. В исследовании приняли участие девушки (n=178) и юноши (n=139) 13-15 лет специализированного спортивного заведения, которые, согласно

классификации видов спорта А.Г. Дембо, разделены на две группы: группа А – скоростно-силовые виды спорта, группа Б – виды спорта на выносливость. Контрольную группу составили ученики: девушки (n=117), юноши (n=106) 13-15 лет и студенты: девушки (n=115), юноши (n=150) 17-20 лет, которые не занимались спортом. Исследование функции восприятия времени проводилось по методике В.Л. Маришука и соавт. Установлен факт возможного использования групп крови в генетическом прогнозировании развития восприятия времени. Выявлено, что лица мужского и женского пола с В(III) группой крови имеют лучшие ассоциативные связи со свойствами данной функции, тогда как худшая связь продолжает оставаться невыясненной. Свойства восприятия времени более выраженно проявляются у студенток юношеского возраста, чем у учениц-подростков. Установлено, что половой диморфизм не вносит существенных изменений в специфику показателей функции восприятия времени, однако генетические маркеры групп крови более информативны в прогнозировании развития данного психического качества у юношей с В(III) группой крови, чем у девушек с такой же группой крови.

რეზიუმე

დროის შეგრძნების ფუნქციის განვითარების თავისებურება
13-15 წლის სპორტსმენებში სისხლის სხვადასხვა ჯგუფით

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კვლევის მიზანს წარმოადგენდა სისხლის ჯგუფის სეროლოგიური მარკერების გავლენის შესწავლა დროის შეგრძნების ფუნქციის განვითარებაზე მოზარდ სპორტსმენებში სასქესო დიმორფიზმის გათვალისწინებით.

კვლევაში მონაწილეობდა სპეციალიზებული სპორტული დაწესებულების 178 ქალიშვილი და 139 ვაჟი, რომლებიც დ.დემბოს სპორტის სახეობების კლასიფიკაციის თანახმად გაყოფილი იყო 2 ჯგუფად: ჯგუფი A - ჩქაროსნულ-ძალოსნური და ჯგუფი B - გამძლეობითი. საკონტროლო ჯგუფი შეადგინა 13-15 წლის მოსწავლეებმა (117 ქალიშვილი და 106 ვაჟი) და 17-20 წლის სტუდენტებმა (115 ქალიშვილი და 150 ვაჟი), რომლებიც არ იყვნენ დაკავებული სპორტით. დროის შეგრძნების ფუნქციის გამოკვლევა ჩატარდა ვ.მარიშუკის და თანაავტ. მეთოდით. დადგენილია დროის შეგრძნების განვითარების გენეტიკურ პროგნოზირებაში სისხლის ჯგუფის შესაძლებელი გამოყენების ფაქტი. გამოვლინდა, რომ B(III) სისხლის ჯგუფის მქონე მამრობოთი და დედრობოთი სქესის პირები ამჟღავნებენ საუკეთესო ასოციაციურ კავშირს აღნიშნულ ფუნქციასთან. დროის შეგრძნების თვისება უფრო გამოხატული აღმოჩნდა სტუდენტებში, ვიდრე მოზარდ-მოსწავლეებში. დადგენილია, რომ სასქესო დიმორფიზმს მნიშვნელოვანი კორექტივები არ შეაქვს დროის შეგრძნების ფუნქციის მაჩვენებლების ცვლილებებში, ხოლო სისხლის ჯგუფის გენეტიკური მარკერები უფრო ინფორმატიულია აღნიშნული ფსიქიკური თვისების განვითარების პროგნოზირებაში B(III) სისხლის ჯგუფის მქონე ვაჟებში, ვიდრე ამავე სისხლის ჯგუფის ქალიშვილებში.

BIOCHEMICAL ASPECTS OF SYMPTOMATIC TREATMENT IN PATIENTS WITH COVID-19 (REVIEW)

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The most urgent problem of the 21st century, which put in crisis not only the health of the population, also the social and economic situation of all countries, is the SARS-CoV-2 virus. SARS-CoV-2 became the newly discovered virus. The first outbreak was identified in China, in Wuhan and it already spread to almost all countries of the world and the number of infected reached nearly several million.

It should be noted, that the transmission of the virus is very quick through airborne droplets. There are data of a long-time vital capacity of the virus on different surfaces, however cultivation time from the same surfaces should be much less, otherwise the outspread of the virus would be wider.

SARS-CoV-2 fastens to the angiotensin-converting enzyme 2 (ACE2) receptor, located on the host cell membrane by S protein, which has a receptor-binding domain (RBD). As a result, the virus crosses the cell membrane and enters the cytosol, where the favorable conditions are created for its multiplication and prevalence of the infection. SARS-CoV-2 has a high ACE2 receptor-binding affinity. ACE2 is synthesized in the kidneys, intestinal and vascular epithelial cells, as well as in heart and brain. It is noteworthy that, ACE2 is abundantly synthesized in the type II alveoli. Consequently, if the virus enters the respiratory tract, a person can be easily infected. Such distribution of ACE2 in the body is the cause of various clinical manifestations

in patients with COVID-19, including acute respiratory distress syndrome, diarrhea, dysgeusia, anosmia, etc. Transmembrane serine protease 2 (TMPRSS2) participates in the entry into the cells along with SARS-CoV-2 which is followed by the breakdown of ACE2 and reduction of its amount. ACE2 protects lung from injury, while angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and angiotensin receptor (AT1R) contribute to lung tissue damage [1, 11].

Recent studies have shown, that ACE2 reduction in mice also worsened the cardiac contractile function. Thus, a large amount of ACE2 improves the result, however, it increases the scale of the infection [16]. Angiotensin 1,7 produced by this membrane enzyme ACE2, has antioxidant, anti-inflammatory, cardioprotective properties, increases endothelial and neuronal NO-synthase activity, generates NO, has an antiarrhythmic effect, and promotes the production of prostacyclin. The fact, that the mortality rate in children and women is low, while high in men and the elderly should be related to the amount of ACE2. The amount of this enzyme is high in children and young people and decreases with age. In young women, ACE2 levels are high because estrogens increase its expression. We suppose, that the severity of the disease is determined not by the number of ACE2 before infection, but by its critical decrease due to the entry of the virus into the cell.

As for Transmembrane serine protease 2 (TMPRSS2), which helps SARS-CoV-2 to enter the cell, an increase in the expression of a gene encoding this protein occurs by androgen hormones, in case of prostate cancer, the exact function of the protein is unknown. This may explain the fact, that cancer patients are at high risk [26].

As the amount of TMPRSS2 is increased under the influence of androgens, supposedly its expression will be low in women because a reduction of ACE2 is related to the bad outcome, TMPRSS2 supports the connection of virus with ACE2 and its reduction. Increasing the expression of TMPRSS2 should lead to a severe form of the disease. The reason for the high mortality rate in men can be caused by the growth of this protein by androgen hormones.

Thus, Camostatmesylate, an inhibitor of serine protease 2 (TMPRSS2) can block entry of the virus in a cell and maintain the amount of ACE2, the research is ongoing in this regard [25]. This medicine is used in Japan to treat pancreatitis. It is also interesting, that heparin inhibits serine proteases, it is not known whether it has a specific effect on TMPRSS2, but the use of heparin, when the risk of thrombosis is increased during COVID-19, may have a double benefit.

According to the recently published study, in patients with failure, a relatively high number of ACE2 were detected in men (the average age of 69) compared with women (the average age of 75). The authors of the study explain the high mortality rate during SARS-CoV-2 infection by this fact. However, the study was not performed in patients infected with SARS-CoV-2, so the increased mortality rate associated with the increased number of ACE2 is incorrect [2, 20]. A decrease in the number of ACE2 in COVID-19 patients will also lead to a decrease in produced angiotensin 1,7, which increases the permeability of the alveolar-capillaries and worsens gas exchange. Due to a decrease in angiotensin 1,7 vasoconstriction will be increased, caused by the action of Ang II on AT1-receptor, vascular permeability, and pulmonary edema. Vasoconstriction in turn will disrupt gas exchange, which will lead to decrease PH of blood. All these worsen the condition, facilitates the release of iron from the transferrin and develop bacterial infections [12].

Angiotensin 1,7 stimulates prostaglandin synthesis, has an antioxidant and anti-inflammatory effect, stimulates endothelial eNO and neuronal nNO synthesis, which eventually produces NO, has an antiarrhythmic effect and promotes the synthesis of prostacyclin. The latter should be the cause of the microvascular thrombosis.

ACE2 produces angiotensin 1,7 from both angiotensin II and angiotensin I. Neprilysin and TOP (Thimet oligopeptidase) both are involved in the synthesis of angiotensin I from angiotensin 1,7. Because angiotensin 1,7 deficiency is one of the causes of the severity of the disease, it should be discontinued from the treatment regimen (Fig.).

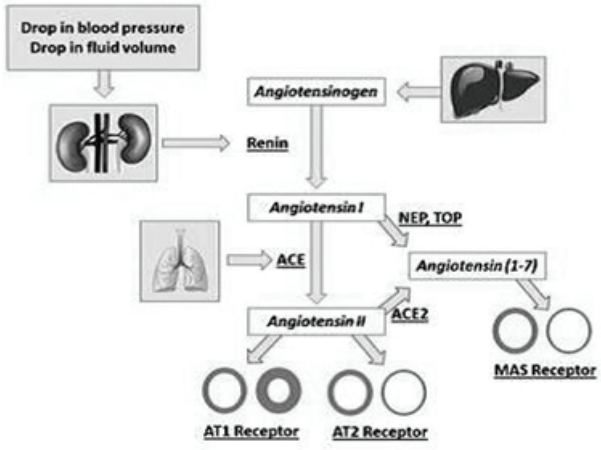

Fig. Renin-Angiotensin System

Angiotensin 1,7 produced by ACE 2, activates NO-synthase and stimulates NO secretion. Consequently, it is like that, NO will no longer be released during ACE2 deficiency caused by the virus. We suppose that decrease of NO should play an important role in the pathogenesis of COVID-19. Decreased NO levels lead to the development of endothelial dysfunction [5]. Hypercholesterolemia, hyperhomocysteinemia, hyperglycemia, hypertension, smoking, and age, characterized by endothelial dysfunction, worsen the COVID-19 infection.

There are 3 forms of NO-synthase: neuronal, endothelial, and inducible. Angiotensin 1,7 activates only endothelial and neuronal forms. Factors causing endothelial dysfunction are diverse and include a reduction of vasodilators, an increase of vasoconstrictors, excessive production of oxygen reactive species, activation of an inflammatory immune response, imbalance between coagulation and fibrinolysis [9].

Endothelin 1 (ET 1) is a peptide with strong vasoconstrictive properties derived from endothelium consisting of 21 amino acids. 0.05 fmol/ml is considered normal. Determination of ET1 would be important to confirm an endothelial dysfunction and its association with severity of disease in patients with SARS-CoV-2 [29].

NO has a diverse role in physiological and pathological processes, in the development of inflammatory reactions and immune response. NO reduces the activity of nuclear

factor-kappa B (Nf-kB), has antithrombotic and antioxidant effects. It enhances the expression of superoxide dismutase, which converts superoxide to hydrogen peroxide and protects tissues from damaging effects of superoxide.

Substances that enhance eNOs signaling pathway and improve endothelial dysfunction can also affect the course and outcome of COVID-19, especially when pathogenetic treatment is not yet known.

These substances are:
1. Estrogen - that's why the disease in women is less lethal. Genistein is a phytoestrogen derived from soybeans, which has an antioxidant effect. Genistein reduces endothelial dysfunction in patients with hypertension and hyperhomocysteinemia. The protective effect is caused by an increase of eNO activity, it's expression and decrease of production of cytokines and ROS. Genistein also increases the number of endothelial-dependent vasodilators in the postmenopausal period in women and reduces the number of ET1. We can assume that other phytoestrogens will also have a positive effect on the course of the disease. Soybean, which is rich with L-arginine, not only enhances eNOs expression but also inhibits NF-kB activity and prevents cytokine storms, thus phytoestrogens should have a positive effect on the course and outcome of the disease [7,20].
2. ACE-inhibitors - these medications are widely used to treat high blood pressure. It is established, that ACE inhibitors can improve endothelial function in patients with heart failure and coronary diseases. This effect is associated with a decrease of angiotensin 2, as well as an increase in the amount of bradykinin. Also, ACE inhibitors increase expression of eNO, which is caused by the effect of bradykinin on B2 receptors. It should be noted, that quinapril can act directly on the eNOs signaling pathway [22,23,28].
3. Bradykinin - is synthesized by the vascular wall, which acts on type B1 and B2 receptors. Activation of B2 by bradykinin enhances eNOs and prostacyclin, protects endothelial cells from the harmful impact of ROS (Reactive Oxygen Species). ACE inhibitors increase the amount of bradykinin that improves endothelial dysfunction [3,17,27].
4. Beta blockers - especially cardioselective beta blockers have a protective effect on the endothelium. For example, nebivolol improves the effect of endothelium-dependent vasodilators in patients with arterial hypertension and in smokers. Non-selective beta blockers, such as carvedilol also improve the endothelium-dependent response in patients with hypertension, as it seems this is associated with their antioxidant properties. A combination of carvedilol with ACE inhibitors shows better effect in patients with arterial hypertension and obese patients [15].
5. Statins - are used to treat hypercholesterolemia, especially to reduce LDL. They improve the endothelial function because LDL and OxLDL reduce the amount of eNOs and increase the level of caveolin-1. Statins also increase the bioavailability of NO. Statins have anti-inflammatory effects, for example, treatment with atorvastatin reduces the amount of cytokines, TNF alpha, IL-1, and IL-6. Therefore, it would be advisable to identify the lipid spectrum in patients with COVID-19 and treat with statins in case of dyslipidemia [6,10,14,19].
6. Calcium channel blockers - some dihydropyridine calcium channel blockers, such as Azelnidipine, Nifedipine, and Amlodipine, have been shown to have anti-inflammatory effects by reducing CRP and IL-6. Nicardipine and Nifedipine protect endothelial cells from damage caused by ROS and reduce glutathione. The combination of amlodipine with renin inhibitors has improved endothelial dysfunction in patients with hypertension associated with NO release and anti-inflammatory effects. Combination therapy of Amlodipine and Statins, compared to their monotherapy causes positive effects on endothelium in patients with diabetes and hypertension [30].
7. PDE-5 inhibitors - PDE-5 is an enzyme that is localized in heart, vascular smooth muscle, placenta, platelets, skeletal muscle, liver, pancreas, and lungs. PDE-5 inhibitors increase eNOs expression and therefore increases NO release, followed by prolonged vasodilator effect. PDE-5 inhibitors improve the function of the endothelium of coronary and peripheral blood vessels and inhibit platelet activation. They also improve endothelium-dependent vasorelaxation in diabetic patients, reduce the concentration of ET1, and improve Raynaud syndrome [4, 24].
8. Metformin - because of AMP-dependent protein kinase causes phosphorylation of serine 1177 and activation of eNOs in the NOs signaling pathway, metformin helps to enhance NO synthesis.
9. Vitamin D - it also enhances cellular immunity, in part by reducing the cytokine storm induced by the innate immune system. The innate immune system generates pro-inflammatory and anti-inflammatory cytokines in response to viral infections, as observed in COVID-19 patients 1,25(OH)2D3 promotes induction of the T regulatory cells, thereby inhibiting inflammatory processes. Serum 25(OH)D concentrations tend to decrease with age, which can explain case-fatality rates increase with age in COVID-19 patients. Reasons include less time spent in the sun and reduced production of vitamin D as a result of lower levels of 7-dehydrocholesterol in the skin. Besides, some pharmaceutical substances reduce serum 25(OH)D concentration by activating the pregnane-X receptor. Such drugs include antibiotics, antiepileptics, antineoplastics, anti-inflammatory agents, antihypertensives, antiretrovirals, and endocrine drugs. Pharmaceutical drug use typically increases with age. Vitamin D supplementation also enhances the expression of genes related to antioxidation. The increased glutathione production spares the use of ascorbic acid (vitamin C), which has antimicrobial activities and has been proposed to prevent and treat COVID-19 [8].
10. Antioxidant agents - especially vitamin C, E, and N-Acetylcysteine have an antioxidant effect. Vitamin C protects the endothelium from the superoxide, platelet and neutrophil activation, as well as inhibits the types of reactive nitrogen produced by peroxidase. Vitamin C can improve endothelial function in smokers, in patients with hypercholesterolemia and diabetes. Vitamin C is notable for helping NO synthesis to maintain the coenzyme tetrahydrobiopterin in the BH4 state, while folic acid provides a strong link between BH4 and NO synthesis, which is a necessary prerequisite for NO synthesis [13]. Vitamin E has a protective effect on the endothelium in smokers and during hypercholesterolemia, although its effects on diabetic patients are arguable. N-acetycysteine is the first-line drug for acute coughs, However, experimental studies have shown that it is a powerful antioxidant, acting on glutathione products that protect the cardiovascular system from the damaging effects of TNF-alpha, that on one's part led to a reduction of the amount of glutathione and an increase of ROS production. N-acetylcysteine also inhibits the aggregation of platelet-dependent Willebrand factor and binding of collagen to glycoprotein receptors. Also important is prostacyclin (PGI2), which is generated by arachidonic acid from COX in endothelial cells, Activation of IP receptors by prostacyclin causes vascular relaxation. However, the synthesis of PGI2 may be inactivated by an increase of cytokines, which once again indicates a decrease in the severity of prostacyclin in patients with COVID-19 and inadequacy of nonsteroidal anti-inflammatory drugs.

As mentioned above, Angiotensin 1,7, produced by ACE 2 stimulates NO production. In addition to its antiarrhythmic and antioxidant effects, NO blocks NF-kB, which determines the main immune response during infections. Its improper regulation is associated with the development of tumors, inflammation and autoimmune diseases, septic shock, viral infections, and excessive immune responses [18]. SARS-CoV-2 reduces

the amount of ACE 2, accordingly decreases the synthesis of angiotensin 1,7 and NO production. In the absence of NO, not only worsens oxygenation-ventilation and endothelial dysfunction but also NF-kB is activated and cytokine storm begins. In such a case it is not allowed to use drugs, that also promote the development of cytokine storms.

Activation of NF-kB leads to an increase in osteoprotegerin, which is associated with an increase in cardiovascular mortality. Its activation may also be related to the development of schizophrenia.

It is known, that ROS-reactive oxygen spices activate NF-kB (therefore, the positive effect of ozone on the course of the disease is doubtful), also TNF, IL-1, Cocaine, and isoproterenol (the use of albuterol inhalers will also help with cytokine storm). The structural analog of isoproterenol is adrenaline, so it would be best to use other medications to stabilize hemodynamic status if there is an alternative. Some substances interfere with the activation of NF-kB, such as the protein SIRTUIN 1, which inhibits the NF-kB factor because of its deacetylation, however, it should be noted that SIRTUIN 1 is inhibited under conditions of hyperglycemia. A high mortality rate could be explained by this fact also. It should be noted that the substance resveratrol (one of the components of red wine) causes an increase in the amount of SIRTUIN 1 protein, which leads to inhibition of NF-kB.

Activation of NF-kB is also caused by hydroxychloroquine (Plaquenil), that is why the positive effect on the course of the disease is doubtful [21]. Methylene blue inhibits NF-kB and also the synthesis of NO, which helps to enhance endothelial dysfunction. As for metformin, it inhibits NF-kB and stimulates NO synthesis, which is why it should have a doubly positive effect in patients with COVID-19, because hydroxychloroquine predominates in the treatment protocols of COVID-19 in many countries, patients treated with metformin before being infected were more likely to be discontinued, because the combination of metformin and hydroxychloroquine is contraindicated. Accordingly, the positive effect of metformin was out of focus.

The medications listed here can theoretically have a positive or negative effect on the course of the disease. Therefore, if there is an alternative, it would be better to use medications that compensate for the changes caused by the decrease in ACE2, the reduction of NO synthesis and the activation of NF-kB.

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SUMMARY

BIOCHEMICAL ASPECTS OF SYMPTOMATIC TREATMENT IN PATIENTS WITH COVID-19 (REVIEW)

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The new Coronavirus has challenged modern medicine. The disease caused by this virus, COVID-19, is characterized by a high rate of lethality, especially in the older age group. There is still no vaccine and no specific treatment, therefore prevention remains the main way to fight the virus. SARS-COV-2 is characterized by high virulence and contagiousness, that's why the main preventive recommendation is social distance.

The article reviews the features of this virus, ways of invading the virus in the body, the possible pathogenesis of the disease and the biochemical and pharmacological aspects of symptomatic treatment. The article also discusses the views of various authors, the results of previous studies and sets new perspectives on fighting the virus. The article discusses the mechanism of action of all drugs and the possible impact on the course and outcome of the disease, which has led to differences of opinion among various groups of scientists since the spread of the virus.

Keywords: SARS-CoV-2 virus, COVID-19, cytokine storm.

РЕЗЮМЕ

БИОХИМИЧЕСКИЕ АСПЕКТЫ СИМПТОМАТИЧЕСКОГО ЛЕЧЕНИЯ ПАЦИЕНТОВ С COVID-19 (ОБЗОР)

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Новый коронавирус бросил вызов современной медицине. Заболевание, вызываемое этим вирусом, COVID-19, характеризуется высокой летальностью, особенно в старшей возрастной группе. По сей день вакцины и специального лечения не существует, поэтому профилактические меры остаются одним из основных средств борьбы. Вирус SARS-COV-2 характеризуется высокой вирулентностью и контагиозностью, поэтому основной профилактической рекомендацией является социальная дистанция.

В статье рассматриваются особенности вируса SARS-COV-2, пути проникновения в организм, возможный патогенез заболевания, а также биохимические и фармакологические аспекты симптоматического лечения. В статье обсуждаются взгляды различных авторов, результаты предыдущих исследований и отражаются новые пути борьбы с вирусом, обсуждаются механизмы действия всех лекарств и возможное влияние на течение и исход заболевания, которые привели к разногласиям среди различных групп ученых с момента распространения вируса.

რეზიუმე

COVID-19-ით დაავადებული პაციენტების სიმპტომური მკურნალობის ბიოქიმიური ასპექტები (მიმოხილვა)

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COVID-19 ხასიათდება ლეტალობის მაღალი მაჩვენებლით, განსაკუთრებით ხანდაზმულ ასაკობრივ კატეგორიაში. ბრძოლის ერთ-ერთ მთავარ საშუალებას წარმოადგენს პრევენციული ღონისძიებები. Sars-Cov-2 ვირუსი ხასიათდება მაღალი ვირულენტობით და კონტაგიოზურობით, რის გამოც მთავარი საპრევენციო რეკომენდაციას სოციალური დისტანცირება წარმოადგენს.

სტატიაში აღწერილია აღნიშნული ვირუსის გავრცელების თავისებურებები, ორგანიზმში შეჭრის გზები, დაავადების შესაძლო პათოგენეზი და სიმპტომური მკურნალობის ბიოქიმიური ასპექტები. განხილულია სხვადასხვა ავტორთა შეხედულებები, აქამდე არსებული კვლევების შედეგები, დასახულია ვირუსთან ბრძოლის გზები და პარსპექტივები, ასევე, მედიკამენტის მოქმედების მექანიზმი და შესაძლო გავლენა დაავადების მიმდინარეობასა და გამოსავალზე.

ANDROGEN INSENSITIVITY SYNDROME, REVIEW OF LITERATURE BASED ON CASE REPORTS

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Congenital conditions with diverse pathophysiology are described as Disorders of sex development (DSD). These disorders can be determined at different development stages of the life-cycle in fetuses or newborns with atypical external genitalia, dysgenetic gonads and internal genitalia. In older children and adolescents it manifests with delayed puberty, unexpected virilization or gynaecomastia, infertility, or gonadal tumors and primary amenorrhea [1]. Based on etiology DSD is divided into five subclasses differentiated by numerical or structural variations in sex chromosomes, disorders in gonadal and/or adrenal steroidogenesis and hormone functions, variations in genes involved in gonadal and/or genital development (bringing to inactivation or activation), endogenous or exogenous maternal factors or endocrine disruptors that possibly can affect genital development [2-5].

The purpose of this article is to describe one of the forms of 46 XY DSD which is related to androgen peripheral actions. There are two disorders related to DSD with preserved testosterone production by the testes, which are Androgen insensitivity syndrome (AIS) and type 5α-reductase deficiency. Although the above-mentioned conditions have similar clinical manifestations, they are initiated by different pathogenetic mechanisms. AIS has X-linked recessive inheritance pattern and is presented by total or partial insensitivity of androgen receptors to male sex hormones.

The androgen receptor (AR) is one of the nuclear receptor superfamily which is responsible for mediating the physiological effects of androgens. Proper functioning of the AR is required for normal male foetal sex development and mutations in the gene encoding the AR may result in a variable degree of resistance to androgens, leading to AIS. The type of AR mutation determines failure of sexual differentiation: either complete (CAIS) or partial (PAIS).

Individuals with CAIS have normal female external genitalia with absence of female internal genitalia. Before puberty masses in the inguinal canal subsequently identified as testes or primary amenorrhea and sparse to absent pubic or axillary hair at puberty may be detected. Breasts and female adiposity develop normally. They typically have female sexual identity and heterosexual orientation [6,7].

PAIS with predominantly female external genitalia manifests similarly to CAIS. However, these individuals have expressions of external genital masculinization which includes posterior labial fusion or clitoromegaly.

Sex of rearing. Determining the sex of rearing may be challenging for children with frank genital ambiguity. The management is defined only for individuals without genital ambiguity for which no management disagreements exist: female with CAIS [8]. Usually these infants are brought up as girls because of female appearance which masks the CAIS. These individuals usually have no expressions of gender dysphoria showing typical female gender development and behavior.

Nonetheless, individuals with CAIS may be unhappy with their primary sex organs, even without apparent signs of gender atypism [9]. Their insecurity may be caused by their body perception due to inconsistency between phenotypic gender and karyotype. In families with PAIS, phenotypic disparity may warrant male sex of rearing in one affected sib and female sex of rearing in another affected sib [10]. Children with PAIS who have predominantly male genitalia are brought up as males. At adolescence all individuals with PAIS develop gynecomastia and impaired spermatogenesis. Typically, they have moderate pubic hair; facial, body, and axillary hair are often scarce [11]. Individuals with PAIS may develop gender dysphoria [12]. Nearly 25% of them develop gender dysphoria regardless of the sex they are brought up [13]. Research of outcomes of gonadectomy and vaginoplasty in females affected by CAIS range from satisfaction with surgery [14,15] to preference for early surgery, to a lack of sexual desire and dyspareunia attributed to these procedures [16,17]. Among the factors contributing to the high dissatisfaction with treatment in this subgroup are the lacks of information provided to the patient about their condition and its management; therefore they hardly can make an informed decision for themselves. It is unclear if improved surgical techniques have resulted in higher patient satisfaction, since age did not influence the satisfaction rates with surgery [18-20].

Material and methods. Four patients with Androgen insensitivity syndrome were selected from the initial cohort of 32 DSD patients with karyotype 46XY. Selection criteria were absence of Mullerian ducts derivatives, as well as preserved testosterone biosynthesis evaluated by basal profile of steroids and/or after stimulation of hCG.

Patients were assessed by experienced paediatric endocrinologists. This study was approved by the Local Ethics Committee.

Table. The summary results of investigation

Patient ID	Age of presentation	Sex of rearing	AR mutation	PAIS/CAIS	External Genitalia	Age of gonadectomy
1	19	F	(AR):c.1822C>T (p. Arg608Ter)		Normal female external genitalia	21
2	18	F	(AR):c.1886-1G>A(rs886041130)		Normal female external genitalia	20
3	19	F	(AR):c.393C>A (p.Cys131Ter)		Normal female external genitalia	19
4	8	M	(AR):G324S		Micropenis, glandular hypospadias and cryptorchidism	-

Case 1. The 19-year-old girl was admitted to an endocrinology clinic for primary amenorrhea. Clinical examination revealed a female phenotype: the breasts were normally developed, however, the labia was small and we notice the absent of axial and pubic hair. Gynecological examination puts in evidence the hymen, a short vagina (2.5cm) and no uterus. Gonadotropins were measured and found normal (FSH 2.28 IU/L (2.0-12.0 IU/L)), LH 17 IU/L (1.0-18.0 IU/L)), the progesterone and estradiol had normal levels for woman (6.59 ng/ml (2.0-20.0 ng/ml) and 93.3 pmol/l (36.7-146.8 pmol/l)), but the testosterone was high for a women (29.27 nmol/l (0.3-2.1 nmol/l)), dihydrotestosterone (DHT) 254 pg/ml (240 and 650 pg/ml)), anti-Müllerian hormone (AMH) was low (less than 0.01ng/ml (0.9-9.5 ng/ml)). The karyotype was mapped and revealed 46XY. Ultrasound investigation revealed intra-abdominal testes and absence of ovaries and uterus, hypoplastic vagina. Mutation c.1822C>T (p.Arg608Ter) in of AR gene was identified in the patient. Then a decision to remove the undescended testes was taken. The patient completely refused any intervention. After 2 years at the age of 21 she came and under general anesthesia the orchiectomy was done. Histopathology identified no signs of testicular cancer. Estrogen substitution therapy was prescribed.

Case 2. The 18 years old girl was referred to an endocrinology clinic. The main complaint was the primary amenorrhea. The patient presented with infantile female genitalia, absence of breast development, and blind end of the vagina, absence of axial and pubic hair. Serum concentrations of luteinizing hormone (11.5 IU/L (1.0-18.0 IU/L)) and follicle-stimulating hormone (11.7 IU/L (2.0-12.0 IU/L)), estradiol (9.5ng/ml 2.0-20.0 ng/ml)) were at the normal range, testosterone was high (18.7 nmol/l (0.3-2.1 nmol/l)), DHT 374 pg/ml (240 and 650 pg/ml), and AMH (0.01ng/ml (0.9-9.5 ng/ml)) was lower than the normal range. The karyotype was 46,XY. Pelvic ultrasonography could not find her ovary and uterus. The mutation c.1886-1G>A(rs886041130) of AR gene was detected in this patient. Gonadectomy was done at the age of 20. After surgery evidence of germ cell neoplasm in situ, the precursor of gonadal germ cell cancer was reported.

Case 3. The patient was a 19-year-old phenotypically female person with 46 XY chromosomal karyotype who presented with a chief complaint of primary amenorrhea. History and physical examination findings showed the patient to be 175 cm in height, with normal breast development, and a lack of pubic or axillary hair. Serum levels of hormones were as follows: testosterone 19.8 nmol/l (0.3-2.1 nmol/l); estradiol, 9.3 ng/ml (2.0-20.0 ng/ml), LH 9.5 IU/L (1.0-18.0 IU/L) and FSH 11.4 IU/L (2.0-12.0 IU/L), DHT 189 pg/ml (240 and 650 pg/ml) and an undetectable level of AMH. The mutation of AR gene (c.393C>A (p.Cys131Ter)) was reported. The diagnosis of CAIS was done. Then patient subsequently underwent surgery and gonadectomy was done. Histological examination of the removed testes revealed a germ cells neoplasm in situ.

Case 4. A 8-year-old boy was referred to our clinic with complaints concerning the external genital organs and undescended testicles. He was raised as a boy. In the examination, the micropenis with glandular hypospadias was seen. Ultrasonography revealed the absence of a uterus and ovaries in the abdomen and found testes in the inguinal canals. Hormone profiles were normal only low basal level of testosterone was established and the level of AMH was 8.7ng/ml (104.1-194.9 ng/ml). Test with hCG was done and after stimulation exaggerated level of testosterone was revealed. Karyotype was determined as 46 XY on chromosomal analysis. Partial androgen insensitivity syndrome was diagnosed. A genetic test of AR gene shown G324S mutation. Then a decision to orchiopexy was taken.

Results and discussion. The median age of the study participants was 16.5±5 years. The patients were allocated into two groups depending on extent of disorder of external genitalia. One group included three patients (75%) who had normal female external genitalia and were raised as girls. Their main complaint was primary amenorrhea. The second group consisted of one patient of pre-pubertal age [8], and the reasons for applying to the doctor were micropenis, glandular hypospadias and cryptorchidism. This patient was raised as a male.

Depending on the patient age the patients underwent hormonal tests. For pre-pubertal age patient examination included basal and stimulated levels of T and DHT (intramuscular hCG 1500 units on three consecutive days). A testosterone and DHT response were labeled as normal (absolute testosterone and DHT concentrations reached twice the baseline values). In patients who have reached puberty levels of LH, FSH, T and AMH were determined. All patients underwent the AR gene test. The summary of investigation is presented in the Table.

These mutations have already reported in the AR Mutation Database (at http://androgendb.mcgill.ca/AR23.pdf). Three patients from the group one already underwent gonadectomy. The average age of gonadectomy was 19±3 years. After surgery evidence of germ cell neoplasm in situ, the precursor of gonadal germ cell cancer, was reported in 2 (67%) out of 3 patients whom pathology results were formally provided. One patient of three with PAIS (23%) had retained gonads. Three patient with CAIS who underwent gonadectomy had dissatisfaction due to a lack of sexual desire/arousal. After gonadectomy estrogen deficiency have been corrected with estrogen replacement therapy.

AIS is an X-linked recessive disorder caused by mutations

of the androgen receptor. The gene responsible for this disorder is located at the proximal long arm of the X chromosome at Xq11-12 [21]. According to the AR mutation database (http://www.mcgill.ca/androgendb), there are more than 1000 different mutations reported so far. The syndrome was first defined by Morris in 1953 as testicular feminization based of the study of 82 patients with the disorder [22]. Later this syndrome was as termed androgen insensitivity syndrome. The prevalence of AIS is estimated to be between 1 and 5 in 100,000 genetic males. Molecular diagnosis for these patients is often problematic considering the large heterogeneity of clinical presentations of these disorders. The degree of impairment of AR activity appears to correlate broadly with the severity of the patient's phenotype.

Karyotyping should be considered for all female infants diagnosed with a bilateral inguinal hernia [22] because the latter is infrequent in normal female infants and associated with CAIS in 1-2% of cases [23,24].

The comparative approach described in this study has its limitations. However, it may prove usefulness of predicting phenotype in patient with PAIS who have management issues relating to sex assignment.

Though it is still common practice to perform the laparoscopic gonadectomy soon after puberty, in the existing literature sources the timing of gonadectomy is now becoming controversial and many women prefer to postpone or decline the surgical procedure. Despite of the fact that gonadal germ cell cancer development is a rare event, gonadectomy after puberty is general recommendation in CAIS patients. For PAIS patients recommendations are more variable. Overall, the existing scientific data reflect the need for evidence-based guidelines on prophylactic gonadectomy in AIS patients.

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SUMMARY

ANDROGEN INSENSITIVITY SYNDROME, REVIEW OF LITERATURE BASED ON CASE REPORTS

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The article describes one of the forms of 46 XY DSD which is related to androgen peripheral actions. There are two disorders related to DSD with preserved testosterone production by the testes, which are Androgen insensitivity syndrome (AIS) and type 5α-reductase deficiency. Although the above-mentioned conditions have similar clinical manifestations, they are initiated by different pathogenetic mechanisms. AIS has X-linked recessive inheritance pattern and is presented by total or partial insensitivity of androgen receptors to male sex hormones.

Keywords: androgen receptor, insensivity, genital ambiguity.

РЕЗЮМЕ

СИНДРОМ РЕЗИСТЕНТНОСТИ К АНДРОГЕНАМ, ОБЗОР ЛИТЕРАТУРЫ НА ОСНОВЕ КЛИНИЧЕСКИХ СЛУЧАЕВ

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Одной из причин, приводящих к нарушению формирования пола у мальчиков (НФП 46XY), является нарушение периферического действия андрогенов. Из 32 исследованных пациентов с НФП 46XY отобрано 4 пациента с нарушением периферического действия андрогенов, критериями которого являлось отсутствие дериватов мюллеровых протоков, а также наличие сохранного биосинтеза тестостерона, оцененного по данным исследования базального профиля стероидов или/и после стимуляции хорионического гонадотропина человека (ХГЧ). В зависимости от возраста, пациентам проводилось гормональное обследование, которое для детей допубертатного возраста включало определение базальных и стимулированных на пробе с ХГЧ уровней тестостерона и дигидротестостерона. У пациентов, достигших половой зрелости, определялись уровни лютеинизирующего и фолликулостимулирующего гормонов и тестостерона. Всем пациентам выполнен анализ гена AR. В исследуемой когорте пациентов мутации в гене AR выявлены во всех случаях. Из 4 пациентов с доказанным дефектом AR 3 были первоначально зарегистрированы в женском поле, а 1 - в мужском поле.

რეზიუმე

ანდროგენების მიმართ რეზისტენტობის სინდრომი, ლიტერატურის მიმოხილვა და კლინიკური შემთხვევების ანალიზი

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მოზარდ ვაჟებში გენდერული ფორმირების დარღვევის (DSD 46XY) ერთ-ერთ მიზეზს წარმოადგენს ანდროგენების პერიფერიული მოქმედების დარღვევა. 32 გამოკვლეულ პაციენტიდან DSD 46XY-თი შერჩეული იყო 4 პაციენტი ანდროგენების პერიფერიული მოქმედების დარღვევით, რაც გამოწვეული იყო მიულერის მილების არარსებობით და ტესტოსტერონის შენარჩუნებული ბიოსინთეზით, რომელიც შეფასებული იყო სტეროიდების ბაზალური პროფილის გამოკვლევით ან/და ადამიანის ქორიონული გონადოტროპინის (აქგ) სტიმულირების შემდეგ.

პაციენტებს, ასაკის გათვალისწინებით, ჩაუტარდა ჰორმონალური გამოკვლევა, რომელიც პუბერტატულ პერიოდამდე ბავშვებში მოიცავს ტესტოსტერონის და დიჰიდროტესტოსტერონის ბაზალურ და აქგ-ს სინჯით სტიმულირებულ დონის განსაზღვრას, ხოლო სქესობრივ მომწიფებას მიღწეულ პაციენტებში - მალუთეინიზირებელი და ფოლიკულ-მასტიმულირებელი ჰორმონების და ტესტოსტერონის დონის. ყველა პაციენტს ჩაუტარდა AR გენის ანალიზი. შესწავლილ პაციენტთა ჯგუფში ყველა შემთხვევაში გამოვლინდა AR გენის მუტაციები. 4 პაციენტიდან დადასტურებული AR დეფექტით 3 დაფიქსირდა ქალებში, ხოლო 1 - ვაჟებში.

ASSESSMENT OF KNOWLEDGE LEVEL AMONG GEORGIAN PARENTS ABOUT VITAMIN D INFLUENCE ON CHILD'S HEALTH. QUESTIONNAIRE SURVEY

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Vitamin D is a group of fat-soluble secosteroids. It has a secosteroid structure in which a bond (C9–C10) in ring B of the steroid structure is broken. Vitamin D_3 and vitamin D_2 are produced by the photochemical reaction of 7-dehydrocholestrol and ergosterol with ultraviolet light B (naturally with sunlight), and subsequent heat isomerization, respectively. These two chemical reactions (not enzymatic reactions) are essential for vitamin D synthesis. In human, these reactions of 7-dehydrocholestrol occur in the skin. They are responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and multiple other biological effects. In humans, the most important compounds in this group are vitamin D_3 (also known as cholecalciferol) and vitamin D_2 (ergocalciferol) [3,8,11].

Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements. Only a few foods, such as the flesh of fatty fish, naturally contain significant amounts of vitamin D. In the U.S. and other countries, cow's milk and plant-derived milk substitutes are fortified with vitamin D, as are many breakfast cereals. Mushrooms exposed to ultraviolet light contribute useful amounts of vitamin D. Dietary recommendations typically assume that all of a person's vitamin D is taken by mouth, as sun exposure in the population is variable and recommendations about the amount of sun exposure that is safe are uncertain in view of the skin cancer risk [5,7,11].

Vitamin D from the diet, or from skin synthesis, is biologically inactive. A protein enzyme must hydroxylate it to convert it to the active form. This is done in the liver and in the kidneys. Cholecalciferol is converted in the liver to calcifediol (25-hydroxycholecalciferol); ergocalciferol is converted to 25-hydroxyergocalciferol. These two vitamin D metabolites (called 25-hydroxyvitamin D or 25(OH)D) are measured in serum to determine a person's vitamin D status. Calcifediol is further hydroxylated by the kidneys to form calcitriol (also known as 1,25-dihydroxycholecalciferol), the biologically active form of vitamin D. Calcitriol circulates as a hormone in the blood, having a major role regulating the concentration of calcium and phosphate, and promoting the healthy growth and remodeling of bone. Calcitriol also has other effects, including some on cell growth, neuromuscular and immune functions, and reduction of inflammation [16,17,25].

The active vitamin D metabolite calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), which is principally located in the nuclei of target cells. The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such as TRPV6 and calbindin), which are involved in calcium absorption in the intestine. The vitamin D receptor belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast. VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content [2,11,15].

As one of the most important roles of vitamin D is to maintain calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels, vitamin D deficiency can result in lower bone mineral density and an increased risk of reduced bone density (osteoporosis) or bone fracture. Vitamin D is also critical for bone remodeling through its role as a potent stimulator of bone resorption [16].

The VDR regulates cell proliferation and differentiation. Vitamin D also affects the immune system, and VDRs are expressed in several white blood cells, including monocytes and activated T and B cells. In vitro, vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells, and affects the synthesis of neurotrophic factors, nitric oxide synthase, and glutathione [15,16].

Vitamin D receptor expression decreases with age and findings suggest that vitamin D is directly related to muscle strength, mass and function. Apart from VDR activation, various alternative mechanisms of action are under study, such as inhibition of signal transduction by hedgehog, a hormone involved in morphogenesis [26].

An estimated one billion people worldwide are either vitamin D insufficient or deficient. Vitamin D deficiency is widespread in the European population [1,5,9,17,20]. European research is assessing vitamin D intake levels in association with disease rates and policies of dietary recommendations, food fortification, vitamin D supplementation, and small amounts of sun exposure [1,3,5,9,11,17]. A diet with insufficient vitamin D in conjunction with inadequate sun exposure causes vitamin D deficiency. Severe vitamin D deficiency in children causes rickets, a softening and weakening of bones, which is a rare disease in the developed world, but common in developing countries. Being deficient in vitamin D can cause intestinal absorption of dietary calcium to fall to 15%. When not deficient, an individual usually absorbs between 60-80%.

Vitamin D functions to activate the innate and dampen the adaptive immune systems. Deficiency has been linked to increased risk or severity of viral infections, including HIV. Low levels of vitamin D appear to be a risk factor for tuberculosis, and historically it was used as a treatment. Supplementation slightly decreases the risk of acute respiratory tract infections and the exacerbation of asthma. Evidence is lacking on whether it does so in children under five years of age [4,6,10,12,16,18,21,25].

Various institutions have proposed different recommendations for the amount of daily intake of vitamin D. These vary according to precise definition, age, pregnancy or lactation, and the extent assumptions are made regarding skin synthesis of vitamin D.A 2014 review concluded that the most advantageous serum levels for 25(OH)D for all outcomes appeared to be close to 30 ng/mL (75 nmol/L). The optimal vitamin D levels are still controversial [7,8,11,13,16,19,23,27].

Supplementation with vitamin D is a reliable method for preventing or treating vit D deficiency. Identifying and treating vitamin D insufficiency or deficiency is important to maintain bone strength and may even improve the health of other body systems, such as the immune, muscular, and cardiovascular systems [11,21]. Success of treatment greatly depends on parental understanding of vit D importance for child health. The present study was aimed to determine the parents' knowledge level about vit D importance for children normal health state, functions of vit D, sources, recommended duration of supple-

mentation. We couldn't find any published data about parental knowledge for vit D.

Material and methods. The questionnaire was utilized as cross-sectional survey to determine the awareness of parents about vit D influence and importance for child health. The questionnaire was designed by the authors. Survey questions covered the topics of parents'/caregivers' information needs; understanding of importance of vit D supplementation, causes of vit D deficiency, duration of supplementation, importance of screening adolescent girlsfor vit D deficiency. The survey was administered to parents/ caregivers of children of age from 1 to 15 years old living in Tbilisi and different regions of Georgia. The data were analyzed using Excel.

Results and discussion. A total 850 individuals participated in the study. Most of them 88,3% (Diagram 1, Column 1) believed vit D to be important for health of a child, but could not explain why the vit D deficiency must be prevented. The participants were asked what they believed to be good dietary sources of vitamin D. 74% (Column 2) of respondents could identify oily fish or eggs. However, 3 (46%) believed dairy products to be a good dietary source of vitamin D. 21,6% (4) - cannot answer. More than 5 (59%) of participants supported their children by vit D drops up to age of 1 year, 6 (40%) by themselves decide to give it only 1-2-months. Only 7 (12%) of mothers continue to support her child by vit D till 24 months and more. On the question about the importance of prevention the vit D deficiency among adolescent girls, as for future mothers, 8 (85,3%) of participants answered they hadn't any information about this.

The questionnaire asked respondents whether general pediatricians have provided education or advice about the importance of maintaining adequate vitamin D levels in children, only 9% (Column 9) of parents said that they had received information from their child's pediatrician. 89% (Column 10) of respondents to the questionnaire wanted more information about vitamin D and vitamin D deficiency.

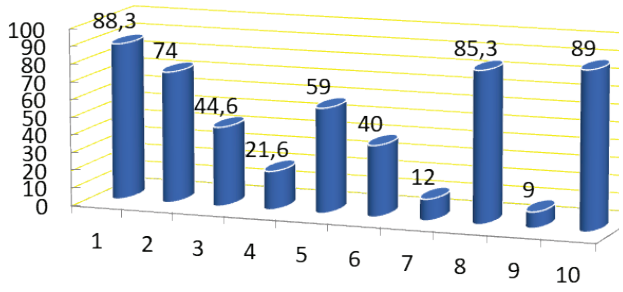

Diagram 1. Parents knowledge level for vit D

Vitamin D deficiency and insufficiency are highly prevalent among children worldwide. Assessment of vitamin D concentrations was included in the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study. The study results indicate that vitamin D deficiency is a highly prevalent condition in European adolescents and should be a matter of concern for public health authorities [5,9,17,20,24]. There are published data from Asian countries with high prevalence of hypovitaminosis D [12,28] mostly in adolescent girls.

According to received data about vitamin D importance for health state in any ages of life, the vitamin D deficiency should be corrected. It is clear, that effectiveness of hypovitaminosis D prevention and treatment highly depends on parental understanding of problem. We couldn't find any published data about parental knowledge for vit D in Georgian population. The present study was performed to determine the level of parental knowledge about vit D importance for children normal health state, functions of vit D, sources, recommended duration of supplementation.

The questionnaire was utilized as cross-sectional survey. Survey questions covered the topics of parents'/caregivers' information needs; understanding of importance of vit D supplementation, causes of vit D deficiency, duration of supplementation, importance of screening adolescent girls for vit D deficiency. Study results revealed the parental/care givers poor awareness and level of knowledge about vit D importance for child normal growth and health state. The level of knowledge was quite not enough for maintaining sufficient level of vit D plasma concentration in children.

As a conclusion we can say, that there is a need for increased level of parental education to ensure children have a better chance of maintaining adequate vitamin D levels. For this it can be recommended to create informational network between parents and medical service providers, support Georgian population with informational booklets, organize TV and other meetings about importance of balanced diet, physical activity outdoor, developmental needs of children. Especially, it is important among adolescent girls. They must be discussed as future mothers and it is confirmed the influence of maternal vit D plasma level during pregnancy on fetus and neonate growth and development [2,4,13,14,19,22,28].

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SUMMARY

ASSESSMENT OF KNOWLEDGE LEVEL AMONG GEORGIAN PARENTS ABOUT VITAMIN D INFLUENCE ON CHILD'S HEALTH. QUESTIONNAIRE SURVEY

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The present study was aimed to determine the parents' knowledge level about vit D importance for children normal health state, functions of vit D, sources, recommended duration of supplementation or treatment.The questionnaire was utilized as cross-sectional survey to determine the awareness of parents about vit D influence and importance for child health. The questionnaire was designed by the author. The survey questions covered the topics of parents'/caregivers' information needs; understanding of importance of vit D supplementation, causes of vit D deficiency, duration of supplementation, importance of screening adolescent girls for vit D deficiency. The survey was administered to parents/ caregivers of children of age from 1 to 15 years old living in Tbilisi and different regions of Georgia. The data were analyzed using Excel.A total 850 individuals participated in the study. Most of them 88,3% believed vit D to be important for health of a child, but could not explain why. 74% of respondents could identify oily fish or eggs as main source of vit D. However, 46% believed dairy products to be a good dietary source of vitamin D. More than 59% of participants supported their children by vit D drops up to age of 1 year, 40% by themselves decide to give it only 1-2-months. Only 12% of mothers continue to support her child by vit D till 24 months and more. About the importance for vit D deficiency prevention among adolescent girls, as for future mothers, 85,3 % of participants answered they have no information about this. According to received results, the parental awareness and level of knowledge about vit D importance for child normal growth and health is poor.Sothere is a need for increased levels of parental education to ensure children have a better chance of maintaining adequate vitamin D levels.

Keywords: vit D supplementation, children, questionnaire, knowledge, survey.

РЕЗЮМЕ

ОЦЕНКА УРОВНЯ ЗНАНИЙ РОДИТЕЛЕЙ ДЕТЕЙ, ПРОЖИВАЮЩИХ В ГРУЗИИ, О ВЛИЯНИИ ВИТАМИНА D НА ЗДОРОВЬЕ ДЕТЕЙ. АНКЕТНЫЙ ОПРОС

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Целью исследования явилось определение уровня знаний родителей о значимости витамина D для состояния здоровья детей, его функциях, источниках, рекомендуемой продол-

жительности профилактики или лечения. Анкета, разработанная авторами, использовалась для определения осведомленности родителей о влиянии витамина D на здоровье детей. Вопросы опроса охватывали темы информационных потребностей родителей/опекунов; понимание значимости приема витамина D, причин его дефицита, продолжительности приема, необходимости обследования девочек-подростков на дефицит витамина D. Опрос проводился среди родителей/опекунов детей в возрасте от 1 до 15 лет, проживающих в Тбилиси и различных регионах Грузии. Данные проанализированы с использованием программы Excel. В исследовании приняли участие 850 человек. Согласно полученным результатам, осведомленность родителей и уровень знаний о значимости витамина D для нормального роста и здоровья ребенка являются низкими и существует необходимость в повышении уровня родительского воспитания с целью обеспечения у детей адекватного уровня витамина D и избежания гиповитаминоза.

რეზიუმე

საქართველოში მცხოვრები ბავშვების მშობლების ცნობადობის დადგენა D ვიტამინის გავლენის შესახებ ჯანმრთელობის მდგომარეობაზე. ანკეტური გამოკითხვა

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, საქართველო

ჩატარებული კვლევების მიხედვით ათეულობით მილიონი ადამიანი ამჟამად მთელს მსოფლიოში განიცდის D ვიტამინის დეფიციტსა და უკმარისობას, განსაკუთრებით ბავშვთა ასაკში. პრობლემის მოგვარების ძირითადი გზას წარმოადგენს შესაბანისი დოზითა და ხანგრძლივობით ბავშვთა პოპულაციის D ვიტამინით უზრუნველყოფა. ბავშვებში D ჰიპოვიტამინოზის წარმატებული პრევენცია და მკურნალობა დამოკიდებულია მშობლების ინფორმირებულობის ხარისხზე.

შრომის მიზანს წარმოადგენდა საქართველოს მოსახლეობის ინფორმირებულობის დადგენა D ვიტამინის მნიშვნელობის შესახებ ადამიანის ჯანმრთელობისათვის. ავტორების მიერ შექმნილი კითხვარით გამოკითხულია საქართველოს სხვადასხვა რეგიონში მცხოვრები 1-დან 15 წლამდე ასაკის ბავშვის 850 მშობელი. კითხვარი მოიცავდა შეკითხვებს: აძლევთ/აძლევდით თუ არა თქვენს შვილს D ვიტამინს და რა ხანგრძლივობით, რომელი საკვებია მდიდარი ამ ვიტამინით, D ჰიპოვიტამინოზის გართულებები, D ვიტამინის გავლენის შესახებ ორგანიზმის სხვადასხვა სისტემების ფუნქციონირებაზე, ჰქონდათ თუ არა ინფორმაცია მოზარდ გოგონებში D ჰიპოვიტამინოზის შორეული შედეგების შესახებ. მიღებული შედეგების საფუძველზე ავტორებს გამოტანილი აქვთ დასკვნა, რომ საქართველოს მოსახლეობის ცნობადობის ხარისხი D ჰიპოვიტამინოზის გავლენის შესახებ ბავშვის ჯანმრთელობის მდგომარეობაზე დაბალია. რეკომენდებულია გაიზარდოს მშობლების ინფორმირებულობის ხარისხი, რაც გააუმჯობესებს ბავშვების D ვიტამინით უზრუნველყოფას და შეამცირებს D ჰიპოვიტამინოზის გართულებებს.

EXPERIMENTAL STUDY OF STRESS EFFECT ON CONNECTIVE TISSUE METABOLISM IN WHITE RATS DURING SUBCUTANEOUS ADRENALINE ADMINISTRATION

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According to the literature, a long-term effect of stress on the body can significantly affect the indices of homeostasis, which are greatly influenced by the liver activity [1]. The researchers studied adrenaline administration effect on the oxidative metabolism of the liver in rats manifested by increased oxidative damage of the mitochondrial apparatus of cells [2]. Structural changes in the liver of rats under chronic stress were also studied. They stated an increase in the number of cells in a state of degeneration and an increase in the area of sinusoidal capillaries. There were reparative processes in the liver parenchyma of rats with high resistance to stress, which were manifested by an increase in the number of dual-core hepatocytes [3].

An assessment of the functional state of the liver in rats after a single administration of adrenaline revealed an increase in the content of medium molecules and lipid peroxidation products in liver homogenates, as well as an increase in the activity of lactate dehydrogenase, ALT, and AST in the blood. The results of histological studies detected blood flow disorders and hepatocyte dystrophy [4]. After intraperitoneal adrenaline administration, glycogen content in the liver of rats with low locomotor activity, was less than in stress resistant animals. Due to the fact that adrenaline can enhance glycolysis, we can state that preliminary training animals helps reduce the liver's response to adrenaline [5]. Adrenaline is also known to be able to influence vasoconstriction in the liver and cause hypertension [6].

Thus, the study of morphofunctional disorders in hepatocytes due to the action of adrenaline and its effect on the metabolism of liver tissues, in particular its stromal component, in experimental rats in order to establish the clinical and pathogenetic value of stress in the development of liver disease can be considered a relevant area of research.

Purpose – to experimentally assess the effect of adrenaline stress on connective tissue metabolism based on morphological studies of white rats' liver and to determine metabolites-markers of connective tissue (common chondroitin sulfates and individual fractions of glycosaminoglycans) in the blood serum of animals.

Material and methods. The studies were conducted in 2018 on white outbred 3-month-old male rats weighing 180-220 grams, which were kept under standard vivarium conditions. The research complied with all bioethical standards for animals in accordance with the "General Principles of Experiments on Animals", approved by the First National Congress on Bioethics (Kyiv, 2001), the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Aims" (Strasbourg, 1987) and Law of Ukraine No. 692 "On the Protection of Animals from Cruelty" (3447 – IV) dated February, 21, 2006.

Animals were divided into 3 groups: the intact group had 5 rats; the control group included 10 animals who were subcutaneously injected with 0.9% NaCl solution daily for 21 days; the experimental group with 10 animals who were administered adrenaline subcutaneously at a dose of 0.5 mg per 100 grams of body weight daily for 21 days. Blood was collected during decapitation under anesthesia in Vacuette vacuum tubes to obtain serum, 5-10 ml. Blood serum was obtained by centrifugation after clot formation at 3000 rpm. within 15 minutes. Blood biochemical studies were performed at the Department of Laboratory Diagnostics and Immunology, Sytenko Institute of Spine and Joint Pathology NAMS of Ukraine" (accreditation certificate № 100-125 / 2012 dated 15.05.2012). Serum glucose content was determined by glucose oxidase method, alanine (ALT) and asparagine (AST) aminotransferase activity – by Reutman & Frankel, γ-glutamyltranspeptidase (GGT) – by kinetic method; the content of total chondroitin sulfates was assessed by Nemeth-Csoka method in the modification of L. I. Slutsky, glycosaminoglycan (GAG) fractions (chondroitin-6, -4- and heparan sulfates) were determined by reaction with resochin [7–9].

Material for histological examination of liver tissue were fixed in 10% aqueous neutral formalin solution. Histological sections of the tissues were performed according to the classical scheme of histopreparation, followed by staining of paraffin sections with Karachi hematoxylin and eosin [10]. Statistical processing of the digital data was performed using the Statistica v.10.0 computer program using the Student's parametric criterion with the mean (M) and its error (m) [11].

Results and discussion. According to the table, the group of rats, administered adrenaline every day for one week, developed an acute stress reaction, which was indicated by a significantly elevated serum glucose level. Due to "adrenaline stress" animals showed a significant increase in the activity of transaminases in this period, which indicated an increase in the cytolysis of hepatocytes. With the "adrenaline stress" white rats had an increase in the activity of ALT and AST by 2.5 times, and GGT – by 1.8 times within one week, which indicated the cytolytic syndrome with cholestasis. We did not detect any change in serum chondroitin sulfate levels during the study period (Table 1).

Table 1. Biochemical parameters of blood serum of white rats during subcutaneous adrenaline administration (M±m)

Indices		Intact group, n=5	Experimental group, n=10		Control group, n=10	
			after 1 week	after 3 weeks	after 1 week	after 3 weeks
ALT, U/L		88.71±1.47	216.78±14.01 ***	94.71±6.00 ♦♦♦	92.05±8.67 ♦♦♦	1.56±6.67
AST, U/L		34.68±2.53	87.38±3.60 ***	40.68±3.34 ♦♦♦	33.35±4.00 ♦♦♦	34.68±4.00
Glucose, mmol / l		5.03±0.23	10.82±1.37**	9.85±1.05 **	5.18±0.80 ♦	7.42±1.56
GGT, U/L		1.48±0.10	2.62±0.16 **	1.67±0.11 ♦♦	1.50±0.11 ♦♦	1.59±0.06
Total chondroitinsulfates, g / l		0.26±0.020	0.35±0.037	0.56±0.025 ***, ♦♦	0.29±0.008	0.30±0.022 ●●●
GAG fractions, U	Chondroitin-6-sulfate	6.62±0.26	14.36±0.84 ***	21.42±1.18 ***,♦	6.16±0.55 ♦♦♦	6.38±0.43 ●●●
	Chondroitin-4-sulfate	9.22±0.35	7.36±0.50	11.66±0.58 *,♦♦	7.26±0.55	6.94±0.27 **, ●●●
	Heparane-sulfate	4.26±0.24	2.50±0.20 **	2.10±0.11 ***	3.64±0.28 ♦	3.32±0.13 *,●●
	Total factions	20.1±0.79	24.22±1.35	35.18±1.50 ***,♦♦	17.06±1.31 ♦	16.64±0.78 *●●●

*notes: * – p≤0.05; ** – p≤0.01; *** – p≤0.001 compared to intact animals;*
♦ – p≤0.05; ♦♦ – p≤0.01; ♦♦♦ – p≤0.001 compared to the index in the experimental animals within one week;
●● – p≤0.01; ●●● – p≤0.001 compared to the experimental animals within three weeks

We observed a decrease in the activity of transaminases and GGT to the level of intact animals ($p \geq 0.05$) in rats who were administered adrenaline for three weeks. This most likely indicates partial adaptation of the liver to the regulation of the experiment. However, serum glucose content remained almost 2 times higher than in control animals, confirming the adrenaline stress effect on white rats within three weeks from the beginning of the experiment.

At the autopsy, we noted that the liver was grey-yellow in color, its edges were rounded, the color was heterogeneous. In the histological sections of the liver, the most affected areas of the particles were periportal and centrolobular ones. They formed different necrosis foci with nuclear cytoplasmic detritus. We observed a large-scale steatosis transforming into fatty degeneration of hepatocytes. The destructive regions of the parenchyma were moderately infiltrated with polynuclear leukocytes and circulatory cells compared with the liver of an intact rat (Fig.).

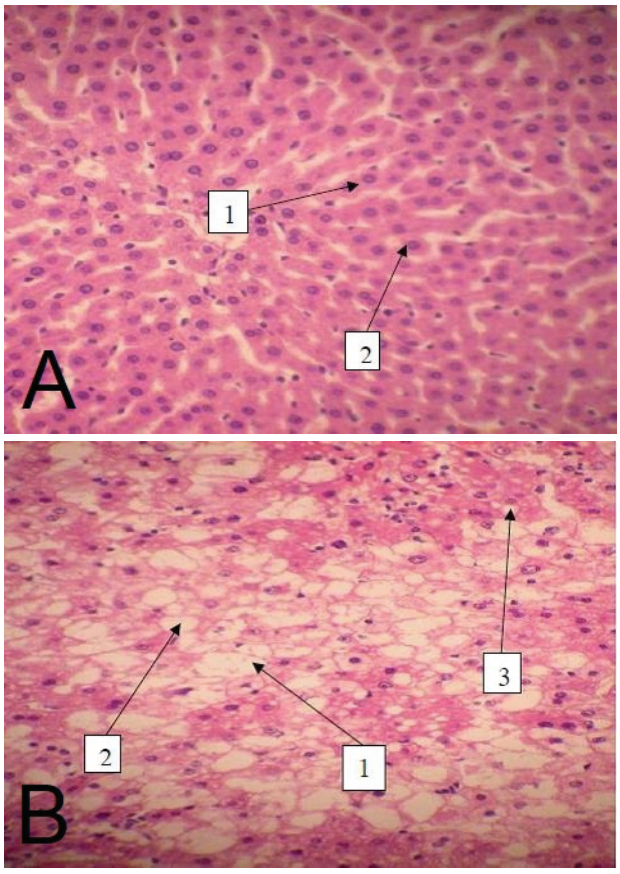

Fig. Results of histological examination of a rat's liver. A is the intact control: normal structure of liver beams (1), hepatocytes without pathological changes (2). B is after 3-week adrenaline injection: massive destruction of the parenchyma (1), coarse-grained steatosis (2), fat vacuoles in hepatocytes (3). Carat hematoxylin staining and eosin. Eye. 10, lens 25

Animals of the control group were subcutaneously administered 0.9% sodium chloride solution daily to account for the effects of emotional and pain stress caused by animal fixation, injection, and other manipulations. However, these procedures did not significantly affect animals, as evidenced by the lack of significant increase in serum glucose content compared to intact animals. This indicates little pathogenicity and rapid adaptation of rats to such a factor. There were no significant changes in the level of other analytes, including indicators of connective tissue status, in control animals.

The chondroitin sulfate content was significantly higher by 2.2 and 1.6 times, respectively, in the serum of rats administered adrenaline for three weeks compared with the serum of intact animals, and the serum of rats administered adrenaline for one week. Apparently, these changes are associated with the development of hepatodystrophy on the background of initial fibrosis, as evidenced by the level of biochemical markers of the state of liver interstitium. It is known that the content of glycosaminoglycans in the blood, in particular hyaluronic acid, can be used as a marker of liver fibrosis [12]. This process is accompanied by the replacement of one type of GAG by another, which indicates the restructuring of connective tissue. The level of chondroitin sulfate in the serum of rats increased during this experiment (3 weeks).

The content of the GAG fractional composition in the serum of white rats during adrenaline stress was the subject to the following changes. We observed a one-week increase in the proportion of chondroitin-6-sulfate by 2.2 times together with a 1.7-fold decrease in heparan sulfate compared with intact animals and control rats. Serum content of chondroitin-4-sulfate tended to decrease compared to the intact animals. Usually, chondroitin-6-sulfate is considered to be more metabolically active than chondroitin-4-sulfate due to the final arrangement of the sulfate group in the molecule. It was a probable reason for increasing its level after one week of adrenaline administration.

There was a probable increase of total GAGs by 1.75 times, and the 1st (by 2.15 times) and the 2nd (by 1.26 times) fractions (chondroitin-6- and chondroitin-4-sulfates) in serum of animals during 3 weeks of stress compared with the intact animals, and the rats administered adrenaline and 0.9% sodium chloride solution for one week. There was a 2-fold decrease in serum heparansulfate levels. Heparansulfate is an integral part of the basal membranes of the liver and kidneys. It is obvious that due to the stress caused by a long-term administration of adrenaline, the content of heparan sulfates in the interstitium of the liver decreased due to their replacement by chondroitin sulfates. It is known that stress is one of the leading pathogenetic factors of liver fibrosis [13,14]. The source for the synthesis of all GAGs is glucose. Its formation is enhanced by gluconeogenesis under the influence of increased concentrations of glucocorticoids, which is usually the result of a stress reaction. Thus, during the "adrenaline stress" there was an increase in the activity of both transaminases and GGT in white rats during one week, indicating the presence of cytolytic syndrome with cholestasis. Administration of adrenaline for three weeks was accompanied by hyperglycemia. But the syndromes of cytolysis and cholestasis did not increase. The three-week adrenaline administration to rats was accompanied by an increase in the serum content of chondroitin-6- and 4-sulfates on the background of decreased heparan sulfate, which is characteristic of liver fibrosis and indicates the high informativeness of these tests.

Thus, the subcutaneous adrenaline administration to white rats daily for 7 and 21 days at a dose of 0.5 mg per 100 grams of body weight led to a stress response, which was confirmed by an increase in serum glucose by 2 or more times. Within three weeks, there appeared necrosis foci in the liver of animals, and fatty degeneration of hepatocytes in the form of coarse-grained steatosis, the so-called fatty hepatodystrophy. The hallmarks of these changes are the GAG fractions along with commonly accepted biochemical tests.

Conclusions. 1. The subcutaneous adrenaline administration to white rats daily for 21 days at a dose of 0.5 mg per 100 g of body weight caused a stress reaction leading to hyperglycemia, fatty hepatodystrophy with the formation of necrosis foci and coarse steatosis on the background of the growth of ALT, AST, and GGT activity by 2.5 and 1.8 times on the 7th day, indicating the cytolytic syndrome with cholestasis.

2. The adrenaline administration to experimental rats for 3 weeks was accompanied by an increase of chondroitin-6 and chondroitin-4-sulfates in the serum content and a decrease in heparan sulfates, which indicated the development of liver fibrosis.

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SUMMARY

EXPERIMENTAL STUDY OF STRESS EFFECT ON CONNECTIVE TISSUE METABOLISM IN WHITE RATS DURING SUBCUTANEOUS ADRENALINE ADMINISTRATION

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Purpose – to experimentally assess the effect of adrenaline stress on connective tissue metabolism based on morphological studies of white rats' liver and to determine metabolites-markers of connective tissue (common chondroitin sulfates and individual fractions of glycosaminoglycans) in the blood serum of animals.

The studies were conducted in 2018 on white outbred 3-month-old male rats weighing 180-220 grams in Sytenko Institute of Spine and Joint Pathology NAMS of Ukraine". Animals were divided into 3 groups: the intact group had 5 rats; the control group included 10 animals who were subcutaneously injected with 0.9% NaCl solution daily for 21 days; the experimental group with 10 animals who were administered adrenaline subcutaneously at a dose of 0.5 mg per 100 grams of body weight daily for 21 days.

The subcutaneous adrenaline administration to white rats daily for 21 days at a dose of 0.5 mg per 100 g of body weight caused a stress reaction leading to hyperglycemia, fatty hepatodystrophy with the formation of necrosis foci and coarse steatosis on the background of the growth of ALT, AST, and GGT activity by 2.5 and 1.8 times on the 7th day, indicating the cytolytic syndrome with cholestasis. The adrenaline administration to experimental rats for 3 weeks was accompanied by an increase of chondroitin-6 and chondroitin-4-sulfates in the serum content and a decrease in heparan sulfates, which indicated the development of liver fibrosis.

Keywords: rats, adrenaline stress, connective tissue, liver, chondroitinsulfates, heparansulfates, fibrosis.

РЕЗЮМЕ

ВЛИЯНИЕ СТРЕССА, ВЫЗВАННОГО ПОДКОЖНЫМ ВВЕДЕНИЕМ АДРЕНАЛИНА, НА МЕТАБОЛИЗМ СОЕДИНИТЕЛЬНОЙ ТКАНИ В ЭКСПЕРИМЕНТЕ

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Целью исследования является установление в эксперименте на белых крысах влияния адреналинового стресса на метаболизм соединительной ткани на основе морфологических исследований печени и определения в сыворотке

крови животных метаболитов-маркеров соединительной ткани – общих хондроитинсульфатов и фракций гликозаминогликанов.

Исследования проведены на белых беспородных крысах-самцах 3-месячного возраста, живая масса - 180-220 грамм, на базе Института патологии позвоночника и суставов им. проф. М.И. Ситенко Национальной академии медицинских наук Украины. Животные распределены на 3 группы: интактные – 5; контрольная группа – 10 крыс, которым ежедневно, в течение 21 суток подкожно вводили 0,9% раствор NaCl, исследуемая – 10 животных, которым ежедневно, в течение 21 суток подкожно вводили адреналин в дозе 0,5 мг на 100 грамм живого веса.

Введение подкожно белым крысам адреналина ежедневно, в течение 21 суток в дозе 0,5 мг на 100 г живой массы тела вызывает стрессовую реакцию, которая приводит к гипергликемии, жировой гепатодистрофии с образованием очагов некроза и крупнокапельного стеатоза на фоне роста на 7 сутки опыта активности аланин-аминотрансферазы, аспартат-аминотрансферазы и гамма-глутамилтрансферазы в 1,8 и 2,5 раза, что свидетельствует о наличии цитолитического синдрома с холестазом. Введение адреналина экспериментальным крысам в течение 3 недель сопровождается повышением содержания в сыворотке крови хондроитин-6 и хондроитин-4-сульфатов и снижением гепарансульфата, что свидетельствует о развитии фиброза печени.

რეზიუმე

ადრენალინის კანქვეშ შეყვანით გამოწვეული სტრესის გავლენა
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კვლევის მიზანს წარმოადგენდა ადრენალინური სტრესის გავლენის დადგენა შემაერთებელი ქსოვილის მეტაბოლიზმზე თეთრ ვირთაგვებში ღვიძლის მორფოლოგიური კვლევის საფუძველზე და ცხოველების სისხლის შრატში შემაერთებელი ქსოვილის ცხოველური მეტაბოლიტი-მარკერების – საერთო ქონდროიტინსულფატების და გლიკოზამინოგლიკანების ფრაქციების, განსაზღვრა.

კვლევა ჩატარდა 3 თვის ასაკის უჯიშო მამრ თეთრ ვირთაგვებზე, ცოცხალი მასით – 180-220 გრ; კვლევა ჩატარდა მ. სიტენკოს სახ. ხერხემლისა და სახსრების პათოლოგიის ინსტიტუტში. ცხოველები განაწილდა სამ ჯგუფად: ინტაქტური – 5, საკონტროლო – 10, რომელთაც ყოველდღიურად, 21 დღის განმავლობაში კანქვეშ უკეთდებოდა NaCl-ის 0,9%-იანი, ხსნარი, საკვლევი – 10, რომელთაც ყოველდღიურად, 21 დღის განმავლობაში კანქვეშ უკეთდებოდა ადრენალინი, დოზით 0,5 მგ ცოცხალი წონის 100 გრ-ზე.

ადრენალის შეყვანა მითითებული დოზით და სქემით განაპირობებს სტრესულ რეაქციას, რომელიც იწვევს ჰიპერგლიკემიას, ცხიმოვან ჰეპატოდისტროფიას ნეკროზის და მსხვილწვეთოვანი სტეატოზის კერების გაჩენით, ექსპერიმენტის მე-7 დღეს ალანინ-ამინოტრანსფერაზას, ასპარტატ-ამინოტრანსფერაზას და გამა-გლუტამილტრანსფერაზას აქტივობის 1,8-ჯერ და 2,5-ჯერ ზრდის ფონზე, რაც მიუთითებს ციტოლიზური სინდრომის არსებობაზე ქოლესტაზით. ექსპერიმენტულ ცხოველებში ადრენალის შეყვანა 3 კვირის განმავლობაში იწვევს სისხლის შრატში ქონდროიტინ-6 და ქონდროიტინ-4-სულფატების შემცველობის მომატებას და ჰეპარანსულფატის შემცირებას, რაც მიუთითებს ღვიძლის ფიბროზის განვითარებაზე.

ХИРУРГИЧЕСКИ ВЫЗВАННАЯ ТРАВМА И РАНОЗАЖИВЛЯЮЩИЕ СВОЙСТВА БЕТУЛИНСОДЕРЖАЩИХ МАЗЕЙ (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

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Чрезвычайные ситуации, связанные с участившимися пожарами в общественных местах (клубы, рестораны) [1], диктуют разработку новых и оптимизацию применения уже известных фармакологических средств, используемых при термических травмах [2,3]. В связи с этим внимание фармакологов в значительной степени привлекает тритерпеноид бетулин, обладающий поливалентным действием. Бетулин впервые был получен путем сублимации из березовой коры в 1788 году Т. Ловицем, как соединение белого цвета, обладающее максимальным лечебным эффектом в лечении ожогов и поверхностных травм. Свое современное название он получил благодаря Мэзону в 1831 году. Ранее уже изучалась противовоспалительная активность бетулина [4] и ранозаживляющая и противоожоговая активность некоторых его производных [5], однако, использовали бетулин в 5 %–й концентрации. Имеются данные об использовании 0,015% эмульсии бетулина [6]. При этом не получено статистически значимой разницы в репарации ран у животных с эмульсией

бетулина и эмульсионной основой. Поэтому представляет интерес изучение бетулина в диапазоне концентраций 0,015 5%.

Цель исследования - изучение противовоспалительных свойств бетулинсодержащих мазей на моделях кожно–плоскостной и ожоговой ран.

Материал и методы. Ранозаживляющие свойства бетулина изучали на 170 беспородных белых крысах обоего пола массой 180–200 г на модели кожно–плоскостной раны (в нашей модификации). В опыте использовали мази с содержанием бетулина 0,2%, 0,5% и 5%. Помимо бетулина в состав мазевых композиций входили: гекторит – 5,0 (для 5% мази – 4,0) и катамин АБ (бензалкония хлорид) 0,1% до 100,0. На выстриженном участке спины размером 9 см^2 у животных под барбамиловым наркозом по трафарету вырезали овальный участок кожи до фасции площадью 400 мм^2.

Животных разделили на 5 групп. Группе контроля раны обрабатывали мазевой основой, группе сравнения – официнальной 10% метилурациловой мазью (МУМ). Опытным группам на рану наносили 0,2%, 0,5% и 5% бетулиновую мазь. Раны обрабатывали со 2 суток ежедневно. Все животные находились в индивидуальных клетках.

Эффективность препаратов оценивали по скорости сокращения раневой поверхности, срокам отхождения струпа, гистоморфологической картине раневого процесса на 7, 14 и 21 сутки и по срокам полного заживления.

Противоожоговые свойства изучали на 15 кроликах по общепринятой методике (в нашей модификации). Зафиксированным животным к выстриженному участку наружной поверхности ушной раковины прижимали на 10 сек соединённый с нагревательным элементом раскалённый до 150°С цилиндрический стержень диаметром 1 см.

Животных разделили на 3 группы (по 5 кроликов в каждой). Контрольной группе животных ожоги обрабатывали мазевой основой. Группе сравнения на ожоговую поверхность наносили официнальный препарат «Пантенол» [7]. Поверхность ожога опытной группы смазывали 0,5% бетулиновой мазью. Ожоги обрабатывали со 2 сут. ежедневно.

Эффективность препаратов оценивали по скорости сокращения ожоговой поверхности, характеру гиперемии в различные сроки процесса, гистоморфологической картине ожогового процесса на 3, 8 и 13 сутки и срокам полного заживления.

Для определения скорости сокращения раневой и ожоговой поверхности использовали планиметрический метод в модификации Т.Н. Шнякиной [8]. Площадь гиперемии определялась планиметрическим методом на внутренней (более светлой) части ушной раковины кролика. При морфологическом исследовании срезы окрашивали гематоксилином и эозином. Препараты изучали при помощи светооптического микроскопа ЛОМО МИКМЕД 5 при увеличении х100 и х200. Микрофотографирование препаратов проводили при помощи цифровой фотокамеры Nikon D70s.

Статистическую обработку данных проводили с помощью программы SPSS v.17.0 для Windows. Проверку на нормальное распределение проводили по методу Колмогорова–Смирнова.

Результаты и обсуждение. Визуальное изучение кожно-плоскостных ран в определенные сроки раневого процесса показало, что струп в опытных группах с обработкой ран бетулином в 0,2%, 0,5% и 5% концентрации отошел на 11±1, 12±1 и 11±1 сут, соответственно. В группе с обработкой ран МУМ струп отошел на 13±1 сут, а в группе контроля – 14±1сут. У животных контрольной группы экссудат в ране был гнойным, во всех остальных группах — серозным. Скорость сокращения площади раны у животных с обработкой ран бетулиновой мазью 0,2 %, 0,5 % и 5 % концентрации до 7 сут включительно составила 5,5 %, 6,8 %, 6,8 %, до 14 сут включительно – 10,5 %, 10,7 %, 11,1 %, до 21 сут включительно – 6,7 %, 9,5%, 8% в сут, соответственно. У метилурациловой мази как препарата сравнения на 7, 14 и 21 сут – 6,6%, 5,2%, 3,35% в сут, а в группе контроля – 2,6%, 11,7%, 5,5% в сутки (рис. 1).

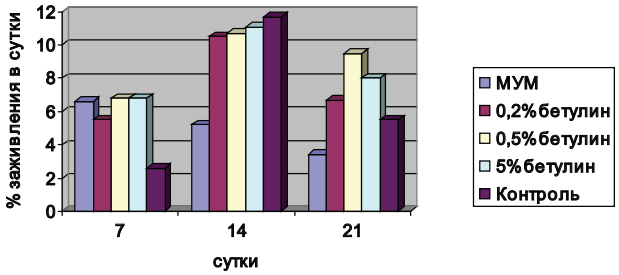


Рис. 1. Влияние бетулина (мазь 0,2%, 0,5% и 5%) на скорость сокращения ран

Согласно полученным данным, наибольшая скорость сокращения была у животных, чьи раны обрабатывали бетулиновой мазью 0,5% концентрации. Наибольший интервал скорости заживления наблюдался в контрольной группе животных. До 7 сут. площадь раны сокращалась незначительно в связи с её расползанием уже 2–3 сут под действием гнойного экссудата. До 14 сут. рана сокращалась с наибольшей скоростью, что, по–видимому, объясняется рубцовым стягиванием раны.

Гистоморфологическое исследование показало, что несмотря на позднее отхождение струпа (12 сут.), эпителизация раны, обрабатываемой бетулином в 0,5% концентрации завершалась уже на 7 сут., тогда как при использовании бетулиновой мази 0,2% и 5% концентрации эпителизация полностью завершилась только к 14 сут.кам. Для МУМ эти сроки полной эпителизации — 21 сут., а в группе контроля эпителизация у ряда животных превысила 29 сут. (таблица).

Таблица. Влияние различных концентраций бетулина на сроки полной эпителизации ран

Препарат	Сроки полной эпителизации, сут.
контроль (без обработки)	29±1 **
10% метилурациловая мазь	21±1 *
0,2% бетулин	14±1 **
0,5% бетулин	7±0,5 **
5% бетулин	14±1**

** - различия достоверны по сравнению с контролем, p<0,05*

*** - различия достоверны по сравнению с метилурациловой мазью, p<0,05*

Макроскопическое исследование ожоговых ран в определенные сроки ожогового процесса показало, что скорость сокращения площади ожога в группе с 0,5% бетулином, «Пантенолом» и мазевой основой до 3 сут. включительно составила 11,5%, 5,5% и 10,1%, до 8 сут. включительно – 0,8%, – 1,5% и – 0,36%, до 13 сут.ок включительно 1,5%, 1,1% и 0,36% в сут., соответственно. Полученные данные свидетельствуют о более быстром сокращении площади ожоговой поверхности под воздействием бетулина в 0,5% концентрации (рис. 2).

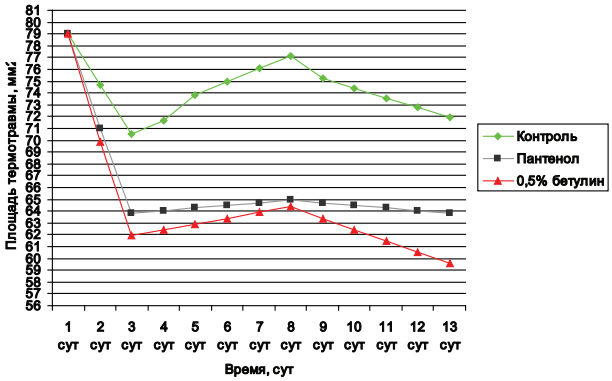
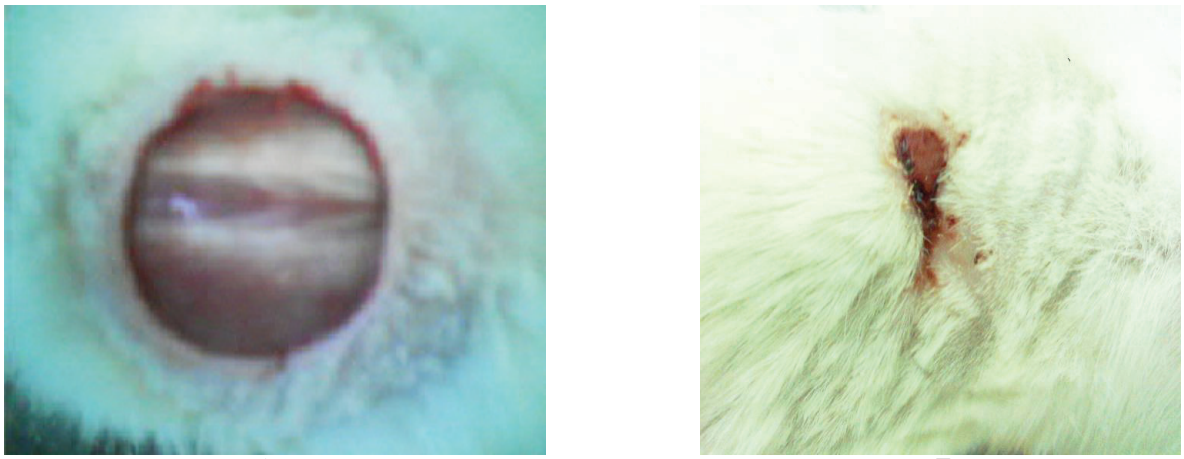


Рис. 2. Скорость сокращения площади ожоговой поверхности

Первоначальная площадь ожога составляла 79 мм². Первоначальное увеличение площади ожога (отрицательные данные) обусловлены последующими реактивными изменениями в соединительной ткани, то есть переходом поврежденных тканей из состояния некробиоза в некроз. Гистоморфологическая картина показала различия в динамике репарации у исследуемых групп животных. В группе контроля (мазевая основа) — процессы репарации проходили неравномерно. В первую очередь, площадь некроза в этой группе была максимальной. После полного отторжения некротизированных участков, соединительная ткань заметно опережала наползающий на нее эпидермис по скорости роста и дифференцировки. То есть у контрольной группы животных, заживление проходило с образованием грубого деформирующего рубца. В группе с обработкой ран «Пантенолом» нет тенденции к полному отторжению некроза, а дифференцировка соединительной ткани и эпителия проходят более синхронно, что говорит о более полноценном заживлении (рис. 3). В опытной группе с обработкой ран 0,5% бетулиновой мазью некроз обожженной ткани минимален, восстанавливается хрящевая пластинка, позволяя ране полноценно эпителизироваться. В группах контроля и сравнения часть некротизированной ткани отторгается на всю толщу уха, оставляя круглые отверстия, примерно равные диаметру ожоговой поверхности (контроль) или значительно меньше ожоговой поверхности («Пантенол»). Побочных эффектов при использовании бетулиновых мазей во всех изучаемых концентрациях не наблюдалось.



А Б

Рис. 3. Течение раневого процесса до лечения (А) и в процессе лечения (Б) 0,5% бетулиновой мазью

С давних времен известны целебные свойства березового дегтя. Получаемый путем сухой перегонки бересты, он обладает антисептическими, ранозаживляющими и местнораздражающими свойствами. Березовый деготь входит в состав мазей Вилькинсона и линимента Вишневского [6]. В состав березового дегтя входит огромное количество биологически активных веществ: фенол, крезолы, диокси-бензолы, гваякол и др. При этом изучали ранозаживляющие свойства 1% мази диникотината бетулина в сравнении с 5% МУМ на аналогичной модели [5]. Скорость сокращения раны на 10 сут.ки под действием диникотината бетулина составила 66%, под действием МУМ 55%, а в группе контроля 45%, что говорит о наличии у диникотината бетулина выраженных ранозаживляющих свойств. В нашей работе также удалось доказать эффективность исследуемого вещества (бетулина) во всех концентрациях по скорости сокращения раны. Это подтверждают данные полученные другими авторами [9,10]. Однако качественные различия в репарации удалось выявить лишь по срокам полной эпителизации ран посредством гистоморфологического исследования. Л.В. Яковлева и соавт., изучали противоожоговые свойства субстанции фенольного гидрофобного препарата прополиса (ФГПП), являющейся основным действующим веществом мази «Пролидоксид». В данной работе показано, что к 21–м сут. ФГПП превосходит по скорости сокращения ожоговой поверхности как группу контроля, так и препарат сравнения (3% прополисовая мазь). В нашем исследовании снижение достоверности полученных также результатов могло быть обусловлено выбором модели исследования. Это связано с тем, что на данной модели невозможно дозировать силу прижатия раскаленного металлического стержня к уху, что обусловливает некоторые различия в глубине ожога у каждого отдельно взятого животного.

Выводы.

1. Бетулинсодержащие мази обладают ранозаживляющими свойствами во всех исследуемых концентрациях.

2. Мазь бетулина в 0,5% концентрации обладает выраженными противоожоговыми свойствами, не уступая при этом препарату сравнения «Пантенол».
3. Наружное применение бетулина не сопровождается побочными эффектами.

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SUMMARY

SURGICALLY CAUSED INJURY AND WOUND-HEALING PROPERTIES OF BETULIN (EXPERIMENTAL STUDY)

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According to the experimental data a triterpene alcohol betulin have anti-inflammatory, wound- and burn-healing activity. Previous data reports, that betulin was used in not less than 5% concentrations. That is why studying less concentrations is of major interest.

The goal of this investigation is to study anti-inflammatory properties of betulin-containing ointments on models of full-thickness skin and burn wounds.

Betulin activity was studied on 170 white outbred rats with a back full-thickness skin wounds and 15 rabbits with ear skin burns. Efficiency of preparations was estimated according to a speed of wound (burn) surface reduction, time of a scab rejection (for wounds), character of hyperaemia reduction (for burns), histological data of wound (burn) preparations on the 7, 14 and 21 (3, 8 and 13) days and complete healing time of wound. Betulin-containing 0,2%, 0,5% and 5% ointments were studied. The highest wound-healing activity has shown 0,5% betulinic ointment. Burn-healing effects of 0,5% betulin-containing ointment were also more expressed, than in other groups. Full epithelization of wounds was seen on the 7 day (p=0,02). Speed of burn surface reduction of treated with 0,5% betulinic ointment was equal to that treated with «Pantenol», and even surpassed it according to histological data.

Keywords: betulin, wounds, burns.

РЕЗЮМЕ

ХИРУРГИЧЕСКИ ВЫЗВАННАЯ ТРАВМА И РАНОЗАЖИВЛЯЮЩИЕ СВОЙСТВА БЕТУЛИНСОДЕРЖАЩИХ МАЗЕЙ (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

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Целью исследования явилось изучение противовоспалительных свойств бетулинсодержащих мазей на моделях кожно–плоскостной и ожоговой ран.

Активность бетулина изучали на 170 белых беспородных крысах с кожно–плоскостной раной и 15 кроликах с ожоговой раной. Эффективность препаратов оценивали по скорости сокращения раневой (ожоговой) поверхности и срокам отхождения струпа (для ран), характеру гиперемии (для ожогов), а также гистоморфологической картине раневого (ожогового) процесса на 7, 14 и 21 (3, 8 и 13) сутки и по срокам полного заживления.

Скорость сокращения раневой поверхности была максимальной в группе с обработкой ран 0,5% бетулиновой мазью (изучали 0,2%, 0,5% и 5% мазевые композиции), полная эпителизация раны наступила уже на 7 сутки (p=0,02). Скорость сокращения ожоговой поверхности под действием бетулина в 0,5% концентрации не уступала по своим показателям препарату «Пантенол», а согласно гистологическим данным, даже превосходила его.

Результаты проведенного исследования показали, что наибольшую ранозаживляющую активность проявила мазь бетулина в 0,5% концентрации. Противоожоговые свойства 0,5% бетулиновой мази также оказались более выражены.

რეზიუმე

ქირურგიული ტრავმა და ბეტულინშემცველი მალამოების ჭრილობის შემახორცებელი თვისებები (ექსპერიმენტული კვლევა)

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კვლევის მიზანს წარმოადგენდა ბეტულინშემცველი მალამოების ანტიანთებითი თვისებების შესწავლა ნაფლეთი და დამწვრობითი ჭრილობების მოდელებზე.

ბეტულინის აქტივობა შესწავლილია 170 თეთრ უჯიშო ვირთაგვაზე ნაფლეთი ჭრილობით და 15 ბოცვერზე დამწვრობითი ჭრილობით. პრეპარატის ეფექტურობა შეფასდა ჭრილობის (დამწვრობითი) ზედაპირის შემცირების სიჩქარით, ფუფხის მოცილების ვადებით (ჭრილობისათვის), ჰიპერემიის ხასიათით (დამწვრობისათვის), ასევე, ჭრილობის (დამწვრობის) პროცესის ჰისტომორფოლოგიური სურათით მე-7, მე-14 და 21-ე (3, 8 და 13) დღეს და სრული შე-ხორცების ვადების მიხედვით. ჭრილობის ზედაპირის შემცირების სიჩქარე მაქსიმალური იყო ჯგუფში, სადაც ჭრილობა მუშავდებოდა ბეტულინის 0,5%-იანი მალამოთი (შესწავლილი იყო 0,2%-, 0,5%- და 5%-იანი მალამოების კომბინაციები), ჭრილობის სრული ეპითელიზაცია განვითარდა უკვე მე-7 დღეს ($p=0,02$). დამწვრობითი ზედაპირის შემცირების სიჩქარე 0,5%-იანი ბეტულინის გავლენით თავისი მახასიათებლებით არ ჩამორჩებოდა პრეპარატ "პანთენოლს", ხოლო ჰისტოლოგიური მონაცემებით აღემატებოდა კიდეც მას.

ჩატარებული კვლევის შედეგებმა აჩვენა, რომ მაქსიმალური ჭრილობის შემახორცებელი აქტივობა გამოავლინა ბეტულინმა 0,5%-იანი კონცენტრაციით. ბეტულინის 0,5%-იანი მალამოს დამწვრობის საწინააღმდეგო თვისებებიც მეტადაა გამოხატული.

STRUCTURAL CHANGES AND MORPHOMETRIC ANALYSIS OF CARDIOMYOCYTES IN RATS WITH ALLOXAN DIABETES

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In patients with type 1 diabetes as well as type 2 diabetes, cardiovascular complications are rather more common than in patients without diabetes [24,25,35,41,43]. For example, the development of cardiovascular disease in type 1 diabetes is at least 10 times higher than in the population without diabetes [9,25]. Accordingly, a number of both experimental [18] and clinical [10] studies have focused on the study of cardiovascular complications in conditions of diabetes mellitus. Diabetic cardiomyopathy is a severe complication associated with functional and structural dysfunction of the myocardium and is not related to other conventional factors such as coronary heart disease, hypertension, congenital heart defects, and heart valve defects [4,28,31].

From the viewpoint of a number of authors, [26] but not all of them [29,37] there is a strong link between hyperglycemia and cardiovascular disease, however, the nature and pathogenesis of these changes are not fully understood [44].

Currently, it is believed that the activation of peroxidation processes and the reduction of NADPH-oxidase levels play an important role in the pathogenesis of chronic complications of diabetes mellitus, including the development of cardiovascular complications [3,13,15,16,38]. These changes result in cardiomyopathy, which in turn causes the apoptosis of cardiomyocytes, along with myocardial hypertrophy and an increase in the amount of collagen deposition [13,14,27]. Hypertrophy of cardiomyocytes with subsequent infarction, apoptosis, and fibrosis is a structural change of the diabetic cardiomyopathy. manifested in changes in the size of the heart chambers, as well as a number of functional disorders in the form of systolic and diastolic dysfunction [12].

Interestingly, according to some studies, changes in type 1 diabetes develop only in the left ventricle chambers due to an increase in wall thickness, which is mainly caused by the disruption of microcirculation [18,21,44]. According to other studies, changes in type 1 diabetes also develop in the right chambers of the heart [21,23]. It should be noted that impaired function of the right chambers of the heart in patients with diabetes mellitus, in conditions of heart failure, pulmonary hypertension, and earlier infarction, significantly affects the quality of life and the prognosis of survival [21,30].

Most studies indicate the development of diabetic cardiomyopathy in the later stages of diabetes mellitus, usually in the 8th to 12th week after inducing diabetes [1]. Available studies are mainly aimed at studying the changes in the left chambers of the heart, while the ongoing changes in the right chambers of the heart are studied less.

Based on the above, the aim of our study is to study the ongoing morphological changes in the right chambers of the heart during experimental diabetes.

Materials and methods. The experiment was performed on 20 Wistar rats of both sexes, weighing 200-250 g. Of these, 10 rats were controls, and 10 ones with experimental diabetes. We were inducing experimental diabetes by intravenous administration of 150 mg 10% alloxan solution. The control and target animals were placed in standard Vivarium conditions. We diagnosed diabetes by blood glucose levels. The animals were withdrawn from the experiment by injecting 1% etaminal-sodium into the abdominal cavity (intraperitoneally). We took the material from the left and right chambers of the heart.

In the histological examination, the material was fixed in 10% formalin and Karnua fixation mixture. The 5, 10, and 30 mcg. paraffin slices were stained with hematoxylin-eosin and picrofuxin by Van Gieson method.

In the biochemical examination, the blood glucose levels were determined in both control and target animals. We determined blood glucose levels by means of standard Medi-test indicators.

Computer programs Adobe Photoshop and Image J software were used for morphometric analysis. 5 animals from each group underwent morphometric analysis, and 10 slices were studied from the right and left ventricles and atria of each animal's heart. The size of the bounded area was recorded by a computer program in microns (μm) and automatically transferred to Microsoft Excel spreadsheets.

The Student's T-test was used to test the confidence of the difference between the data indicators

Results of histological examination. Based on a study we conducted earlier [2] at the early stage of diabetes (1 month) after the administration of alloxan, rats showed a decrease in weight. At the early stage of the experiment, namely 1 month after the start of the experiment, the major structures of the myocardium underwent minor changes during the mildly ongoing pathological process. At this stage, most cardiomyocytes maintained their usual structure and did not differ from those of the control animals. Only a few cardiomyocytes showed dystrophic changes and necrosis. During a severe pathological process, at the same stage e.g. 1 month after the start of the experiment, the marked dystrophic changes in cardiomyocytes increased, especially in the left chamber of the heart. No significant changes were observed in the right chambers at the same stage of the experiment (1 month). In histological examination, 3 months after the administration of alloxan, especially in severe experimental diabetes, hypertrophic changes in cardiomyocytes were found along with dystrophic and necrotic changes in the left chambers of the heart. The structure of the myocardium in the right chambers of the heart was disordered as compared to that of the left chambers. Cardiomyocytes experienced the severe dystrophic and necrotic changes, with apoptotic cells found in them In addition, the number of hypertrophic cells was dramatically increased. Interstitial and perivascular fibrosis were found. At the same stage, there were found the changes in the microcirculatory network of the myocardial venous system - manifested venous stasis and quite intense vascular congestion. The blood vessels were dilated, and the aggregation and agglutination of red blood cells were observed in several blood vessels. Dramatic destructive changes in endothelial cells were detected (Fig.).

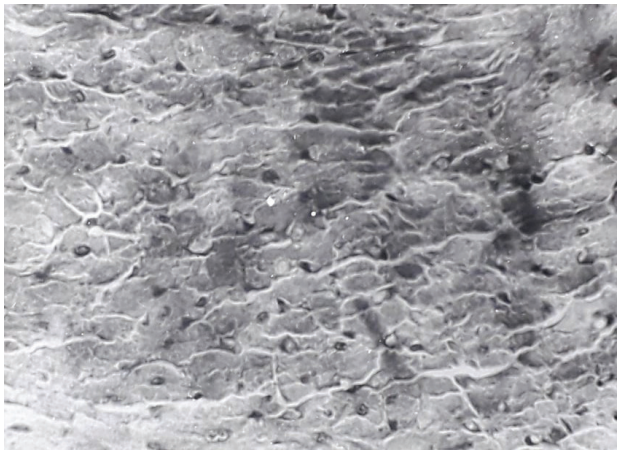

Fig. Micrographs of heart. Myocardium.Right ventricule section. Cardiomyocytes experienced the severe dystrophic and necrotic changes, hypertrophic cells. Interstitial edema. The blood vessels were dilated, and the aggregation and agglutination of red blood cells were observed in several blood vessels. Haematoxylin-Eosin

In alloxan diabetes, changes in the diameter of the cardiomyocytes on myocardial slices were detected in the entire heart. In 1 month after the start of the experiment, the average diameter of the cardiomyocytes in the right and left chambers of the heart was insignificantly increased. In 3 months after the administration of alloxan, the average diameter of cardiomyocytes increased significantly in the right atrium and made 12.992±0.35, i.e. increased by 26.8% ($P<0.05$) as compared to the controls, while in the right ventricle it was 14.935±0.25 and increased by 17.9% as compared to the controls ($P<0.05$). The mean diameter of cardiomyocytes in the left ventricle and atrium was insignificantly increased at 3 months of the experiment and made 13.60±0.3 and 13.900±0.4, respectively, increased by 2% ($P<0.05$) as compared to the control group values. The results of our study match the data of several researchers [5,11,19] (Table).

Therefore, a significant increase in the diameter of the cardiomyocytes in the right chambers of the heart was observed at a later stage and an insignificant increase in the diameter of the cardiomyocytes in the left atrium and ventricle of the animals ($P<0.05$). In the study, hypertrophy of the cardiomyocytes, which was observed in diabetic heart chambers, led to the enlargement of the right chambers, while the changes in the left chambers were insignificantly manifested. These results are consistent with the results of the Charissa E van den Brom., 2010 study, however, there are different data obtained in rats in other studies [18,20]. Ongoing studies on diabetes provide

Table. Changes in body mass, glucose levels, and cardiomyocyte diameter in control and experimental rats

Wistar rat	Control group (n-10)	Alloxan diabetes 4 weeks (n=5)	Alloxan diabetes 12 weeks (n=5)	p
Body weight (g)	250±14,5	225±15,6	210±16,7	<0.05
Glucose mmol/L	6,3±0,2	13,7±0,5	17,9±2,9	<0.001
RV CD (μm)	12.661±0.24	12.722 ±0.24	14.935±0.25	<0.05
LV CD (μm)	13.342±0.37	13.450±0.37	13.620± 0.3	<0.05
RA CD (μm)	10.238±0.27	10.270±0.27	12.992±0.35	<0.05
LA CD (μm)	13.615±0.72	13.790±0.72	13.900±0.4	<0.05

*CD - cardiomyocyte diameter; RV – the right ventricle; LV – the left ventricle; RA – the right atrium; LA – the left atrium. The difference is statistically reliable * P<0.05 compared with the control animals*

different results in terms of changes in cardiomyocyte sizes. The results of our study match with the results of several researchers [7,8,11,17,36]. However, according to other studies, the size of cardiomyocytes in animal experimental diabetes models either did not change at all [22], or there were no changes in the diameter of cardiomyocytes, and only variations in the length of cardiomyocytes were observed [6]. The results of our study directly contradict the findings of a number of researchers [34,40] where a reduction in the diameter of cardiomyocytes in both RV and LV of the diabetic heart was observed.

Conclusion. The obtained results indicate that at a later stage, in particular, 3 months after the start of the experiment, there was a disruption of microcirculation in the myocardium (endothelial lesion, vascular dilatation, stasis, erythrocyte aggregation, and agglutination), interstitial and perivascular fibrosis, dystrophic changes in cardiomyocytes, necrosis, and apoptosis. Cardiomyocyte hypertrophy was observed in several areas. Changes in the diameter of the cardiomyocytes were observed, with a significant increase in the diameter of the cardiomyocytes, especially in the right chambers of the heart, while there were observed insignificant changes in the diameter of the cardiomyocytes in the left chambers. It appears that functional and structural changes in the right chambers of the heart are directly related to systemic sensitivity to insulin [7,32,33]. It is likely that these changes are due to the above metabolic shifts [39,42].

Based on the above, it is possible to assume that the impact (influence) of diabetes mellitus on the structure and function of the right chambers may be more noteworthy than considered earlier.

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SUMMARY

STRUCTURAL CHANGES AND MORPHOMETRIC ANALYSIS OF CARDIOMYOCYTES IN RATS WITH ALLOXAN DIABETES

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The aim of this research was to study the ongoing structural changes in rat cardiomyocytes during alloxan diabetes and their morphometric analysis in dynamics, in particular 1 and 3 months after the start of the experiment.

The experiment was performed on 20 Wistar rats of both sexes, weighing 200-250 g. Of these, 10 rats were controls, and 10 ones with experimental diabetes. We were inducing experimental diabetes by intravenous administration of 150 mg 10% alloxan solution. Histological, biochemical, morphometric, and statistical methods of research were used in the experiment.

Based on the histological examinations it was stated that dystrophic changes, necrosis, and apoptosis of cardiomyocytes were found in alloxan diabetes.

Microcirculation was disrupted in the myocardium (endothelial lesion, stasis, red blood cell aggregation, and agglutination). At the later stage, all of the above changes were more pronounced in the right chambers of the heart. 3 months after the start of the experiment, along with all the above changes there was found the hypertrophy of cardiomyocytes,

The morphometric study revealed that at the later stage, a significant increase in the diameter of cardiomyocytes, especially in the right chambers of the heart observed, which was most likely caused by the specific functional and structural features of the right chambers of the heart. All this gives us reason to assume that the impact of metabolic changes caused by diabetes mellitus on the right chambers of the heart is quite significant and noteworthy.

Keywords: alloxan, diabetes mellius, cardiomyocytes, rat heart.

РЕЗЮМЕ

СТРУКТУРНЫЕ ИЗМЕНЕНИЯ И МОРФОМЕТРИЧЕСКИЙ АНАЛИЗ КАРДИОМИОЦИТОВ КРЫС ПРИ АЛЛОКСАНОВОМ ДИАБЕТЕ

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Целью исследования явилось изучение структурных изменений, происходящих в кардиомиоцитах крыс, и их морфометрический анализ при аллоксановом диабете в динамике, в частности спустя 1 и 3 месяца после начала эксперимента.

Эксперимент проведен на 20 крысах линии Вистар обоего пола массой 200-250 г. Из них 10 крыс были контрольными, а 10 - целевыми. Экспериментальный диабет вызывали посредстаовм внутривенного введения 150 мг 10% раствора аллоксана. В эксперименте использовались гистологические, биохимические, морфометрические и статистические методы исследования.

Гистологические исследования показали, что при аллоксановом диабете наблюдаются дистрофические изменения, некроз и апоптоз кардиомиоцитов; нарушение микроциркуляции в миокарде (повреждение эндотелия, стаз, агрегация эритроцитов, агглютинация). На более поздних сроках, в частности спустя 3 месяца от начала эксперимента вышеперечисленные изменения в миокарде были более выраженными, отмечалась гипертрофия кардиомиоцитов.

Морфометрическое исследование показало значительное увеличение диаметра кардиомиоцитов, особенно в правых отделах сердца, что, очевидно, вызвано специфическими функциональными и структурными особенностями правых камер сердца.

Результаты проведенного исследования позволяют заключить, что влияние на правые камеры сердца метаболических изменений, вызванных сахарным диабетом, весьма значительны и заслуживают особого внимания.

რეზიუმე

ვირთაგვების კარდიომიოციტების სტრუქტურული ცვლილებები და მორფომეტრიული ანალიზი ალოქსანური დიაბეტის დროს

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კვლევის მიზანს წარმოადგენდა ალოქსანური დიაბეტის დროს ვირთაგვების კარდიომიოციტებში მიმდინარე სტრუქტურული ცვლილებების შესწავლა და მათი მორფომეტრიული ანალიზი დინამიკაში, კერძოდ ექსპერიმენტის დაწყებიდან 1 და 3 თვის შემდეგ.

ექსპერიმენტში გამოყენებული იყო ორივე სქესის Wistar-ის ჯიშის 20 ვირთაგვა, წონით 200 – 250 გრ. აქედან 10 ვირთაგვა იყო სამიზნე, ხოლო 10 - საკონტროლო. დიაბეტს ვიწვევდით ალოქსანის 150 მგ 10% - იანი ხსნარის ერთჯერადი შეყვანით ინტრავენურად.

ექსპერიმენტში გამოყენებული იყო კვლევის ჰისტოლოგიური, ბიოქიმიური, მორფომეტრიული და სტატისტიკური მეთოდები.

ჰისტოლოგიური კვლევის საფუძველზე გამოვლინდა, რომ ალოქსანური დიაბეტის დროს აღინიშნება კარდიომიოციტების დისტროფიული ცვლილებები, ნეკროზი, აპოპტოზი. ადგილი ჰქონდა მიკროცირკულაციის მოშლას მიოკარდიუმში (ენდოთელის დაზიანება, სტაზი, ერითროციტების აგრეგაცია, აგლუტინაცია). მოგვიანებით ვადაზე ზემოჩამოთლილი ცვლილებები უფრო მეტად გამოხატული იყო გულის მარჯვენა კანებში.

მოგვიანებით ვადაზე, კერძოდ ექსპერიმენტის დაწყებიდან 3 თვის შემდეგ ზემოჩამოთვლილ ცვლილებებთან ერთად აღინიშნა კარდიომიოციტების ჰიპერტროფია. მორფომეტრიული კვლევით დადგინდა კარდიომიოციტების დიამეტრის მნიშვნელოვანი ზრდა, განსაკუთრებით გულის მარჯვენა კანებში, რაც, სავარაუდოთ, გამოწვეული იყო გულის მარჯვენა კანების სპეციფიური ფუნქციური და სტრუქტურული თავისებურებებით.

კვლევის შედეგები იძლევა ვარაუდის საფუძველს, რომ შაქრიანი დიაბეტით გამოწვეული მეტაბოლური ცვლილებების ზემოქმედება გულის მარჯვენა კანებზე საკმაოდ მნიშვნელოვანი და საყურადღებოა.

ФАРМАКОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА ЛЕВОФЛОКСАЦИНА И ЕГО КЛИНИЧЕСКОЕ ПРИМЕНЕНИЕ (ОБЗОР)

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С открытием антибиотиков такие тяжелые инфекционные процессы, как сепсис, перитонит, гангрена, казалось, стали управляемыми, однако по сей день продолжают уносить жизни миллионов людей. Причина этого явления - растущая устойчивость бактерий к антимикробным препаратам [28,32,35].

На сегодняшний день в мире разрабатывается весьма небольшое количество новых антибактериальных препаратов, причем с каждым годом их производство все меньше и меньше, причиной чего является высокая стоимость создания каждого такого препарата (до 1 млрд. долларов), и фармацевтические концерны, учитывая быстрое развитие резистентности болезнетворных микробов к антибиотикам, все с меньшей охотой берутся за такие разработки.

Развитие резистентности к антимикробным препаратам у многих бактериальных патогенов обусловливает неэффек-

тивность традиционной терапии, в результате лечение инфекций становится более сложным и дорогим. В развитии и распространении резистентности играют роль три фактора: мутации в обычных генах, приводящие к расширению спектра резистентности, передача резистентности генов от одних микроорганизмов к другим и усиление селективного давления условий среды в больницах и за их пределами, что ведет к активизации процесса развития резистентных организмов [25,48]. Некоторые новые механизмы резистентности с трудом поддаются выявлению лабораторными методами. Таким образом, резистентные микроорганизмы часто остаются нераспознанными вплоть широкого распространения в больнице.

Микробиологическая активность левофлоксацина (группа фторхинолонов) при лечении инфекций различного происхождения представляет особый научный интерес. Известно, что левофлоксацин относится к антибактериальным средствам группы фторхинолонов (ФХ), обладающих выраженной противомикробной активностью и широко применяются в медицине как антибиотик широкого спектра действия [5]. По широте спектра противомикробного действия, активности и показаниям к применению ФХ близки к антибиотикам, однако отличаются от них по химической структуре и происхождению, указанные препараты не имеют природного аналога. Левофлоксацин обладает преимущественно бактерицидным действием. Фторхинолоны оказывают бактерицидный эффект, подавляя жизненноважный фермент микробной клетки ДНК-гиразы и нарушая биосинтез ДНК.

Ведущие позиции в арсенале современных антибактериальных средств ФХ занимают благодаря своим свойствам: уникальный для антимикробных средств механизм действия ингибирование фермента бактериальной клетки - ДНК-гидразы; высокая степень антибактериальной активности; широкий спектр антимикробного действия, включая грамотрицательные и грамположительные аэробные бактерии, (некоторые препараты ФХ активны в отношении анаэробов), микобактерии, хламидии, микоплазмы [21]; невысокая частота резистентности микроорганизмов к ФХ; высокая биодоступность при приеме per os; высокая степень проникновения в ткани и клетки макроорганизма [16]; продолжительный период полувыведения и наличие постанабиотического эффекта определяет удобное дозирование - 1-2 раза в сутки; возможность сочетанного применения с другими группами антибактериальных средств (беталактамсы аминогликозиды, макролиды, гликопептиды, линкозамиды, нитроимидазолы); высокая эффективность при лечении внебольничных и госпитальных инфекций практически любой локализации [15]; возможности применения для эмпирической терапии, в том числе монотерапии, в случае тяжелых инфекций в стационаре [29]; удовлетворительная переносимость препаратов, невысокая частота побочных эффектов.

ФХ, в том числе левофлоксацин (ЛФ), являются препаратами с широкими показаниями к применению при инфекциях различной этиологии и локализации инфекционного процесса. Благодаря оптимальной фармакокинетике с высокой степенью биодоступности, устойчивости к трансформации в организме, достаточно медленным выведением из организма, в основном, путем почечной секреции, обеспечении высокой концентрации в моче в неизмененном виде, они соответствуют практически всем необходимым требованиям, которые предъявляются к препаратам для лечения именно инфекций мочевыводящих путей. В тканях мочеполовой системы концентрация левофлоксацина при терапевтических дозах соответствует или превышает концентрацию в сыворотке крови [34].

ЛФ, аналогично офлоксацину, характеризуется широким антибактериальным спектром действия, охватывающим основной спектр аэробных возбудителей бактериальных заболеваний: грамположительные и грамотрицательные условно-патогенные бактерии: *N.gonorrhoeae, Chlamydia trachomatis, U. urealyticum, M. hominis*. Значимым свойством препарата является его высокая активность в отношении внутриклеточных патогенов [6,22,23,41,46,49].

ЛФ относится к III поколению дифторхинолонов, это синтетическое химиотерапевтическое вещество, фторированный карбоксихинолин, свободный от остатков S-энантиомера рацемического сообщения - ЛС офлоксацина, является L-изомер офлоксацином. Поскольку на левофлоксацин приходится практически вся противомикробная активность в рацемической смеси изомеров, его активность *in vitro* в два раза превышает активность офлоксацина. Молекула существует в виде амфиона при значениях pH, соответствующих среде тонкого кишечника. Обладает свойством к образованию стабильных соединений с ионами многих металлов.

Из данных научной литературы известно, что биодоступность препарата составляет 99%, а особенности его фармакокинетики таковы, что 87% препарата выводится с мочой в неизмененном виде. По данным мировой и отечественной научной литературы левофлоксацин является высокоактивным антибиотиком относительно следующих микроорганизмов: стрептококков (*S. pneumoniae*), стафилококков, хламидий, микоплазм, легионелл, иерсиний, сальмонелл, *H. parainfluenzae, M. catarrhalis, K. pneumoniae, B. pertussis, , Citrobacter spp., E. coli, Enterobacter spp., Acinetobacter spp., P. spp., Neisseria spp., C. perfringens, B. urealyticus* [4,20].

In vitro резистентность к левофлоксацину, которая является результатом спонтанных мутаций, формируется редко. Несмотря на появление резистентности к нему среди S.pneumoniae, она остается на стабильно низком уровне (1%). Например, по данным исследования TRUST S. pneumoniae проявляли устойчивость к двум и более антибиотикам разных классов, при этом 99,1% из них сохраняли чувствительность к левофлоксацину (к цефуроксиму - только 18,3%, к азитромицину - 16,8%) [4].

Несмотря на то, что между левофлоксацином и другими фторхинолонами наблюдается перекрестная резистентность, некоторые устойчивые к другим ФХ микроорганизмы могут быть чувствительными к левофлоксацину. Левофлоксацин предназначен для медикаментозной терапии инфекционно-воспалительных процессов, вызванных чувствительными к нему различными штаммами микроорганизмов, в частности: грамположительные аэробы - *Enterococcus faecalis, Staphylococcus aureus* (метициллинчувствительные штаммы), *Staphylococcus epidermidis* (метициллинчувствительные штаммы), *Staphylococcus saprophyticus, Streptococcus pneumoniae* (в т.ч. мультирезистентные штаммы - MDRSP), Streptococcus pyogenes, грамотрицательные аэробы - *Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens* [19].

Следует отметить, что в опытах *in vitro* левофлоксацин имел высокую антибактериальную активность в отношении грамотрицательных микроорганизмов, включая предста-

вителей семейства *Enterobacteriaceae* и неферментирующих грамотрицательных бактерий. Так, при изучении чувствительности 2980 клинических штаммов *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter cloacae* минимальная подавляющая концентрация для 90% исследованных штаммов (МПК90) составила 0,5 мкг/мл и ниже [27].

По отношению к неферментирующим грамотрицательным бактериям ЛФ имеет менее выраженную активность. В отношении синегнойной палочки активность ЛФ выше, чем у ранних ФХ, за исключением цефалоспоринов (ЦФ). Резистентные к ЦФ штаммы синегнойной палочки, выделенные из дыхательных путей больных инфекциями нижних отделов респираторного тракта, были резистентными и к ЛФ [26].

Что касается клинических штаммов *Acinetobacter spp.*, выделенных у пациентов отделений интенсивной терапии гематологии и онкологии, определена 100% чувствительность к ЛФ. При лечении пациентов с инфекциями дыхательных путей отмечено, что ЛФ проявляет высокую активность в отношении чувствительных и резистентных к ампициллину штаммов *Haemophilus influenzae*, а также по отношению к продуцирующим и не продуцирующим беталактамазу штаммам *Moraxella catarrhalis* [43].

Значимым качеством ЛФ, принципиально отличающим его от ранних ФХ, является высокая активность в отношении «проблемных» грамположительных кокков. Так, ЛФ высоко активен в отношении *Streptococcus pneumoniae* (МПК составляет 0,25-0,2 мг/л), включая пенициллинорезистентные, и относительно других стрептококков (*S. pyogenes, S. agalactiae, S. viridans*) [47].

Высокая активность ЛФ установлена относительно *Staphylococcus aureus* и других стафилококков (диапазон МПК 0,06-64 мг/л при МПК90 0,25-16 мг/л), ЛФ несколько менее активен в отношении энтерококков, хотя в отношении некоторых штаммов величины МПК составляют 0,5-1 мг/л [19].

ФХ активны как в отношении большинства грамотрицательных бактерий, в том числе E. coli (включая энтеротоксигенные штаммы), *Shigella spp., Salmonella spp., Enterobacter spp., Klebsiella spp., Proteus spp., Serratia spp., Providencia spp., Citrobacter spp., M. morganii, Vibrio spp., Haemophilus spp., Neisseria spp., Pasteurella spp., Pseudomonas spp., Legionella spp., Brucella spp., Listeria spp.* так и грамположительных аэробных бактерий, включая *Staphylococcus spp.,* за исключением метицилинстойких штаммов [2].

ЛФ активен в отношении *Chlamydia spp., Mycoplasma spp., M. tuberculosis,* быстрорастущих атипичных микобактерий (*M. avium*), энтерококков, *Corynebacterium spp., Campylobacter spp., H.pylori, U. urealyticum.* Препарат высокоактивный в отношении *Listeria monocitogenes, Corinebacterium diphtheriae* [6,33].

ЛФ имеет меньшую активность в отношении анаэробных бактерий. Они устойчивы или умеренно чувствительны к фторхинолонам, поэтому при лечении больных со смешанной аэробной и анаэробной инфекцией, например, интраабдоминальной и гинекологической, ФХ целесообразно сочетать с метронидазолом или линкозамидами. Исследования последних лет показали хорошую эффективность применения левофлоксацина при лечении осложненной и неосложненной урогенитальной инфекции (УГИ) [1,7,10,24]. Неосложненные УГИ более чем в 95% случаев вызываются одним микроорганизмом, наиболее часто из семейства *Enterobacteriaceae*. Основным возбудителем является *E.coli* - 80-90%, гораздо реже *S.saprophyticus* (3-5%), *Klebsiella spp*, *P.mirabilis*. При осложненных УГИ частота выделения *E.coli* снижается, чаще встречаются другие возбудители - *Proteus spp, Pseudomonas spp, Klebsiella spp*, грибы (преимущественно *C.albicans*).

Все хинолоны хорошо всасываются желудочно-кишечным трактом. Пища может замедлять всасывание хинолонов, однако не оказывает существенного влияния на биодоступность, которая составляет 99%. Максимальные концентрации в крови достигаются, в среднем, спустя 1-3 часа после приема внутрь. Наиболее высокие максимальные концентрации в крови после однократного приема внутрь достигаются при применении левофлоксацина (5,2 мг/л). Он проходит плацентарный барьер и в небольших количествах проникает в грудное молоко. Выводится из организма преимущественно почками и создает высокие концентрации в моче, частично выводится через желчь.

Фармакокинетика ЛФ носит линейный характер и предсказуема при однократном и повторном введении внутрь, в/в и не зависит от возраста, пола и расы пациента [4]. Постоянная концентрация в плазме крови достигается спустя 48 ч после приеме в дозе 500-750 мг 1 раз в сутки и составляет 99%. Широко распределяется в тканях организма (объем распределения 89112 л), хорошо проникает в ткань легких (концентрация в легких в 25 раз выше концентрации в плазме). В исследовани *in vitro* и *in vivo* левофлоксацин в пределах терапевтических концентраций не оказывает индуцирующего или ингибирующего действия на ферментные системы, таким образом, не ожидается фермент-опосредованного влияния на метаболизм других лекарственных средств [42].

Под действием ЛФ отмечено повышение функции полиморфноядерных лимфоцитов у здоровых добровольцев и ВИЧ-инфицированных пациентов. Показано его иммуномодулирующее влияние на тонзиллярные лимфоциты у больных хроническим тонзиллитом. Полученные данные позволяют судить не только об антибактериальной активности, но и о синергическом противовоспалительном и противоаллергическом действии ЛФ. Удобство применения ЛФ один раз в сутки является еще одним преимуществом этого антимикробного препарата.

ФХ одобрены комиссией по контролю качества продуктов и лекарств США для лечения инфекций мочевых путей (цистит, простатит, осложненные инфекции мочевыводящих путей - ИМП и острый пиелонефрит) включают ципрофлоксацин, норфлоксацин, офлоксацин, левофлоксацин [14,42 47,48]. Запатентованный в 1987 г., имевший первое клиническое применение в Японии в 1993 г., ЛФ получил дальнейшее одобрение FDA для лечения тяжелых и опасных для жизни бактериальных инфекций.

ЛФ, в первую очередь, рассматривается как антимикробное средство, которое лучше всего подходит для лечения различных инфекций дыхательных путей, вызванных чувствительными микроорганизмами и получил одобрение для использования в лечении инфекций кожи и кожных структур. В результате различных клинических испытаний, ЛФ доказал свою эффективность при лечении различных форм ИМП с использованием различных доз и длительности лечения в разных группах пациентов. Он уникален тем, что принято его применение для схем короткого курса (5 дней) при осложненных ИМП и пиелонефрите, что делает его одним из наиболее часто применяемых антибактериальных препаратов для этого назначения.

Результаты клинических исследований (КИ) являются основанием для регистрации показаний к использованию

антибиотиков. В настоящее время в США, странах Европы и Азии зарегистрированы следующие показания к применению левофлоксацина [18]: инфекции дыхательных путей [17,36]: а) острый бактериальный синусит; б) бактериальное обострение хронического бронхита; в) внебольничная пневмония; г) нозокомиальная пневмония;
- осложненные и неосложненные инфекции кожи и мягких тканей, костей и суставов;
- инфекции мочеполовых путей [8-10]: а) неосложненные и осложненные инфекции мочевыводящих путей; б) острый пиелонефрит; в) хронический простатит;
- интраабдоминальные инфекции;
- кишечные инфекции;
- сепсис, менингит [13]:
- постингаляционная сибирская язва.

Регистрация перечисленных показаний означает, что результаты КИ подтвердили сравнительную эффективность или предпочтение ЛФ над традиционно используемыми антибиотиками при сохранении приемлемой безопасности и хорошей переносимости.

Оценивая значение ФХ в терапии УГИ, необходимо учитывать их относительно слабую активность против бактероидов. ФХ не активны в отношении возбудителя сифилиса, трихомонад, вирусных инфекций и микозов. Поэтому при смешанных УГИ необходимо комбинировать ФХ с антимикробными препаратами других классов. Положительным свойством ФХ является их хорошая совместимость с антианаэробными препаратами, антимикотиками, антипротозойными и антивирусными препаратами [39].

Препаратами выбора для лечения инфекций мочевыводящих путей во всем мире являются антибактериальные препараты группы ФХ. Исследования, которые проведены в Корее с 2015 по 2018 гг. выявили, что показатели резистентности кишечной палочки к ЛФ, изолированной от больных ИМП, которые находились на амбулаторном лечении, были высокие и достигали более 25%. Факторами риска, влияющими на эти показатели, являлись нейрогенный мочевой пузырь, применение ципрофлоксацина и левофлоксацина в прошлом, мочекаменная болезнь и старший возраст. Итак, левофлоксацин следует назначать с осторожностью у пациентов с такими факторами риска.

Дальнейшие исследования фармакокинетики ципрофлоксацина и левофлоксацина продемонстрировали преимущество ЛФ (более высокая концентрация в простатическом секрете), что позволяет препарату стать хорошей альтернативой в лечении хронического бактериального простатита.

На основе проведенных исследований и анализа антимикробной активности ФХ в урологии на базе МГМСУ им. Н.А. Семашко получены следующие выводы: ФХ сохраняют лидирующее положение в лечении инфекций мочевых путей. По клинической эффективности эти препараты сходны с аминогликозидами и цефалоспоринами нового поколения, а в некоторых случаях (при смешанных инфекциях) превосходят их. Действие препаратов носит преимущественно патогенетический характер и направлено на элиминацию из организма возбудителей воспаления [11].

Респираторные хинолоны рассматриваются целым рядом авторов [17,20,42] в качестве препаратов выбора для лечения пневмонии, вызванной бензилпенициллин-резистентными штаммами пневмококка (ПРП). Целесообразность назначения ФХ госпитализированным пациентам с внебольничной пневмонией очевидна: представители этой группы антимикробных средств подтвердили свою эффективность у данной категории больных с тяжелым течением пневмонии и высоким риском смерти. При этом ФХ остаются активными даже в отношении возбудителей, которые выработали резистентность к другим массово используемым антибиотикам, в то время как резистентность к ФХ развивается медленнее.

Хронические бактериальные инфекции дыхательных путей имеют широкое распространение у пациентов с муковисцидозом (МВ). Среди патогенов наиболее часто выделяющихся из мокроты больных МВ, являются *Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Alcaligenes xylosoxidans, Burkholderia cepacia complex, u Staphylococcus aureus*. Высокие пиковые уровни после приема аэрозоля с левофлоксацином, как ожидается, ведут к быстрому противобактерицидному действию и подавляют появление устойчивых мутантов (проведены исследования в пробирке). Таким образом, ЛФ является значимым агентом в форме аэрозоля для управления хроническими инфекциями легких у пациентов с МВ [17].

При хирургическом лечении больных перитонитом различной этиологии долгое время (последние 10 лет) применялась схема антибиотикотерапии, в которую входили цефалоспорины III поколения (цефтриаксон) и метронидазол.

С появлением на рынке Украины ЛФ при лечении больных деструктивной формой аппендицита, холециститом, перфоративной язвой стало возможным проведение монотерапии препаратом, принимая во внимание особенности инфекции при данных патологических состояниях [40].

В результате применения препарата отмечена его высокая эффективность при комплексном лечении больных с абдоминальной инфекцией. Послеоперационных осложнений не выявлено, хорошая переносимость, не вызывает негативных реакций и применяется в качестве монотерапии для большинства больных с перитонитом.

Анализ научных публикаций последних лет показал, что ЛФ используется в качестве основного антимикробного препарата для лечения ИМП. Обладая исключительным фармакокинетическим и фармакодинамическим действиями, широким спектром антимикробной активности относительно большинства уропатогенов и показателем безопасности, которые выдержали испытание временем, ЛФ, несомненно, играет значимую роль в лечении ИМП и имея статус препарата «стандарта помощи» при указанных инфекциях [14].

По данным научной литературы [8], резистентность грамотрицательных уропатогенов ставит под угрозу продолжение эмпирического использования ЛФ для любых формах ИМП, ввиду чего отмечается высокая стоимость лечения и левофлоксацин рекомендуется отнести к лечению инфекций дыхательных путей.

Широкое применение ФХ привело к росту резистентности, которая в настоящее время наблюдается среди *E. coli, Klebsiella pneumoniae* и *Proteus mirabilis*. Тревожный прирост расширенного спектра кишечной палочки с продуцированием бета-лактамазы и других грамотрицательных бактерий играет значимую роль в резистентности к ФХ. Подавляющее большинство этих штаммов имеют устойчивые детерминанты ко всем доступным фторхинолоновым препаратам [27].

Применение ФХ имеет свои ограничения: не рекомендуется применять у детей, во время беременности, родов и в период лактации ввиду угрозы осложнений у плода (новорожденного). Противопоказаниями являются гиперчувствительность (в т.ч. к другим хинолонам), возраст до 18 лет

(безопасность и эффективность применения не определены); следует иметь в виду, что ЛФ вызывает артропатию и остеохондроз у молодых растущих животных разных видов (не рекомендуется использование в педиатрии) [45].

С осторожностью следует использовать при диагностированных или предполагаемых заболеваниях ЦНС, сопровождающихся склонностью к судорогам или снижением порога судорожной готовности (эпилепсия, тяжелый церебральный атеросклероз); наличии других факторов риска развития судорог или при снижении порога судорожной готовности (одновременный прием некоторых лекарственных средств, нарушение функции почек) одновременном лечении кортикостероидами (повышенный риск развития тендинита), недостаточности глюкозо-6-фосфатдегидрогеназы (возможен гемолиз).

Согласно данным научной литературы, ФХ хорошо переносятся больными, частота нежелательных реакций при их применении колеблется в пределах от 3 до 20% [2,12,32].

Нежелательные реакции, которые могут возникать при применении ФХ:

I. Общие для всех хинолонов: желудочно-кишечный тракт - изжога, боль в эпигастральной области, нарушение аппетита, тошнота, рвота, диарея [40];

- ЦНС - ототоксичность, нарушение сна, головная боль, нарушение зрения, парестезии, тремор, судороги.

- аллергические реакции - сыпь, зуд, ангионевротический отек, фотосенсибилизация, наиболее характерна для ломефлоксацина и спарфлоксацина. Под воздействием солнечных лучей или ультрафиолетового излучения ФХ вызывают фототоксические реакции, что связано с фотодеградацией молекулы хинолина под воздействием УФ-лучей с образованием свободных радикалов кислорода, которые повреждают структуры кожи. Описаны случаи тяжелого фотодерматита. Важно, что фототоксические реакции могут развиваться в течение нескольких дней после отмены препарата. Практически не вызывают этого осложнения новые ФХ - левофлоксацин, гатифлоксацин, моксифлоксацин (<0,5%). Контролируемые клинические исследования показали, что побочные реакции при применении ЛФ возникают редко и в основном несерьезные.

Как со всеми другими антибактериальными препаратами, побочные эффекты, о которых наиболее часто сообщает FDA, приписанные использованию ЛФ, отмечаются со стороны желудочно-кишечного тракта, в частности: анорексия, тошнота, рвота, изжога, боль в эпигастральной области, диарея.

Побочные эффекты со стороны ЦГС отмечают при заболеваниях различной локализации от 1% до 11% пациентов, принимающих ФХ - умеренная и сильная головная боль, головокружение, нарушение мышления, бессонница и колебания настроения. Аллергическая реакция в виде сыпи на лечение ЛФ происходит гораздо реже в сравнении с беталактамами, его редко связывают с анафилактической реакцией (≤1,2 случая на 100 000). Возможная реакция фототоксичности, которая проявляется сильным загаром в незащищенных областях, появляется в течение часа после нахождения под действием ультрафиолетового излучения.

Сообщается о серьезной токсичности, уникальной для семьи фторхинолоновых антибактериальных агентов, которая проявилась при использовании ЛФ [5]. Это тендинопатия в виде тендинита или разрыва сухожилия, в основном, затрагивая ахиллово сухожилие, а в некоторых случаях с привлечением и других сухожилий.

Удлинение интервала QT на ЭКГ приводит к аритмии, что является также серьезным признаком токсичности, которая может возникнуть во время приема фторхинолоновых препаратов: блокируя калиевые каналы, тем самым задерживая желудочковые реполяризации, они могут вызвать потенциально опасную для жизни реакцию, особенно у определенных групп пациентов с повышенным риском развития сердечных аритмий. К удлинению интервала QT при лечении ЛФ более склонны лица, имеющие заболевания сердца, нарушения обмена электролитов (гипокалиемия, гипомагниемия) и/или которые получают другие лекарства, удлиняющие интервал QT - I или III классы антиаритмических препаратов. ЛФ и ципрофлоксацин, как доказано, меньше влияют на удлинение интервала QT в сравнении с другими ФХ препаратами [38].

В отличие от некоторых ФХ, являющихся причиной подъема уровня глюкозы в крови (гипергликемия), при лечении ЛФ отмечается незначительное повышение риска гипогликемии. Механизмом действия, как полагают [38], является увеличение секреции инсулина поджелудочной железой путем ингибирования АТФ-чувствительных калиевых каналов бета-клеток.

При лечении больных осложненными ИМП побочные эффекты отмечены у 4% пациентов при применении ЛФ. Наиболее часто встречающиеся побочные эффекты - тошнота (1,3%), диарея (1,1%), головокружение (0,4%) и бессонница (0,3%). Вышеуказанные эффекты дозозависимы и быстро исчезают после снижения дозы или отмены препарата [37].

Частота побочных реакций, связанных с приемом ЛФ, в клинических испытаниях фазы 3, проведенных в Северной Америке, составила 6,3%. Терапия была прекращена у 3,9% пациентов ввиду возникновения побочных эффектов, связанных с приемом лекарств.

Среди нежелательных явлений, независимо от того, связаны они или нет с использованием левофлоксацина, чаще регистрировались неблагоприятные реакции со стороны желудочно-кишечного тракта (ЖКТ). В целом, безопасность ЛФ оказалась сопоставимой с таковой пенициллинов (амоксициллин/клавуланат), макролидов (азитромицин, кларитромицин), цефалоспоринов (цефадроксил, цефуроксим аксетил, цефотаксим), карбапенемов (имипенем) [31,44].

Несмотря на то, что растворимость ЛФ выше других хинолонов, необходимо поддерживать адекватную гидратацию во время лечения левофлоксацином во избежание образования избыточно концентрированной мочи. Антибиотики группы ФХ следует с осторожностью назначать при почечной недостаточности.

Обобщая данные лит-ры более чем двадцатилетнего опыта использования ЛФ следует отметить, что Левофлоксацин имеет широкий спектр действия, включающий большинство грамположительных и грамотрицательных возбудителей, в том числе внутриклеточно расположенных, в отличие от других ФХ, высокоактивный в отношении грамположительных кокков, в том числе пневмококков, устойчивых к пенициллину, эритромицину. Кроме того, ЛФ более активен в отношении атипичных возбудителей, обладает удобными фармакокинетическими свойствами: высокой биодоступностью, длительным периодом полувыведения, что позволяет использовать его раз в сутки, создает высокие тканевые и внутриклеточные концентрации [5]. Препарат не метаболизируется в печени, не имеет нежелательных лекарственных взаимодействий, не требует коррекции дозы у больных пожилого возраста, хорошо переносится и является одним из самых безопасных антибактериальных препаратов. Существование двух форм препарата - для парентерального

и перорального применения - позволяет использовать его в режиме ступенчатой терапии, наряду с возможностью однократного приема значительно облегчает труд медперсонала и удобно для пациента.

Таким образрм, высокая клиническая и микробиологическая эффективность при широком спектре инфекционных заболеваний, низкий уровень приобретенной резистентности среди клинически значимых возбудителей болезни, относительная безопасность позволяет рассматривать данный антибиотик в качестве приоритетного выбора среди «новых» ФХ и важнейшей альтернативой беталактамам при невозможности или нецелесообразности их использования в терапии инфекций дыхательных и мочевыводящих путей, кожи и мягких тканей, для профилактики осложнений в хирургии, а также инфекций многих других локализаций. В тоже время следует подчеркнуть, что для предупреждения резистентности микроорганизмов к ЛФ необходим обоснованный, выбор препарата, адекватный режим его дозирования в каждом конкретном случае лечения инфекционных заболеваний, только рациональное и надлежащее использование ЛФ и других препаратов на рынке фторхинолонов снизит постоянно растущий уровень резистентности возбудителей заболеваний к ним.

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SUMMARY

CHARACTERISTICS OF LEVOFLOXACIN AND ITS CLINICAL APPLICATION (REVIEW)

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We analyzed of the effectiveness of levofloxacin in various diseases, the sensitivity of microorganisms to it and side effects.

LF does not show carcinogenic, mutagenic and teratogenic activity. It is used effectively in the treatment of infections of the respiratory and genitourinary tract, skin and soft tissues, for the prevention of complications in surgical practice, as well as infections of many other localizations. Levofloxacin has a wide spectrum of action, including most gram-positive and gram-negative pathogens, including intracellularly located, unlike other fluoroquinolones, highly active against gram-positive cocci, including pneumococci which are resistant to penicillin, erythromycin. In addition, levofloxacin is more active against atypical pathogens.

Doctors should clearly justife the appointment of LF in an adequate dose in each case, in order to avoid or reduce the occurrence of resistance of pathogens to it.

Keywords: levofloxacin, sensitivity of microorganisms, treatment of infections, side effects.

РЕЗЮМЕ

ФАРМАКОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА ЛЕВОФЛОКСАЦИНА И ЕГО КЛИНИЧЕСКОЕ ПРИМЕНЕНИЕ (ОБЗОР)

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Проведен анализ эффективности применения левофлоксацина (ЛФ) при различных заболеваниях, чувствительности к нему микроорганизмов и побочных действий.

ЛФ не проявляет канцерогенной, мутагенной и тератогенной активности. Эффективно используется в терапии инфекций дыхательных и мочеполовых путей, кожи и мягких тканей, а также многих других локализаций, для профилактики осложнений в хирургической практике. Левофлоксацин имеет широкий спектр действия, включающий большинство грамположительных и грамотрицательных возбудителей, в том числе внутриклеточно расположенных. В отличие от других фторхинолонов, ЛФ высокоактивный в отношении грамположительных кокков, в том числе пневмококков, устойчивых к пенициллину, эритромицину. ЛФ более активен в отношении атипичных возбудителей.

Необходимо четкое обоснование назначения ЛФ в адекватной дозе в каждом конкретном случае с целью избежания или уменьшения возникновения резистентности возбудителей заболеваний к нему.

რეზიუმე

ლევოფლოქსაცინის ფარამაკოლოგიური დახასიათება და მისი კლინიკური გამოყენება (მიმოხილვა)

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ხარკოვის ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

კვლევაში გაანალიზებულია ლევოფლოქსაცინის გამოყენების ეფექტურობა სხვადასხვა დაავადების დროს, მიკროორგანიზმების მგრძნობელობა მის მიმართ და გვერდითი ეფექტები.

ლევოფლოქსაცინი არ ავლენს კანცეროგენულ, მუტაგენურ და ტერატოგენურ აქტივობას. იგი ეფექტურად გამოიყენება სასუნთქი და შარდსასქესო გზების, კანის და რბილი ქსოვილების ინფექციების თერაპიაში, გართულებების პროფილაქტიკისათვის ქირურგიულ პრაქტიკაში, ასევე, მრავალი სხვა ლოკალიზაციის ინფექციის პრევენციისათვის. ლევოფლოქსაცინს აქვს მოქმედების ფართო სპექტრი, მოიცავს გრამდადებით და გრამუარყოფით, მათ შორის უჯრედშიდა, გამომწვევებს. სხვა ფთორქინოლებისაგან განსხვავებით, ლევოფლოქსაცინი მაღალაქტიურია პენიცილინისა და ერითრომიცინის მიმართ მდგრადი გრამდადებითი კოკების, მათ შორის პნევმოკოკების, მიმართ. ლევოფლოქსაცინი უფრო აქტიურია ატიპური გამომწვევების მიმართ.

ლევოფლოქსაცინის მიმართ დაავადების გამომწვევების რეზისტენტობის განვითარების თავიდან აცილების ან შემცირების მიზნით, ყოველ კონკრეტულ შემთხვევაში ლევოფლოქსაცინის ადეკვატური დოზით დანიშვნა აუცილებლად მკაფიოდ უნდა იყოს დასაბუთებული.

MEDICINES: TECHNOLOGY TRANSFER TO PRODUCTION, CESSION OF OWNERSHIP RIGHTS FOR REGISTRATION CERTIFICATES AND TRANSFER OF PRODUCTION IN CONDITIONS OF MODERN CHALLENGES TO NATIONAL AND INTERNATIONAL SECURITY

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At present day, in the context of the SARS-CoV-2 coronavirus, not just competition between countries for the sphere of influence on the market of medicines, but also the struggle for development of the vaccine to ensure the public interest in health care has gained new strength. This requires increasing effectiveness of international cooperation between countries in the field of technology transfer to production of medicines. Also, the existing global production network of medicines is changing in order to meet special type of public interests, that is international and/or national security. Thus, the complication of relations between countries, conflicts (including armed ones) and their aggravation cause measures to be taken by one particular country for securement of international and national security aimed at suspending the entry and the circulation of medicines on its market manufactured in another country.

In particular, the Ministry of Health of Ukraine (hereinafter – MOH of Ukraine) has taken measures to withdraw from circulation within Ukraine drugs manufactured in the Russian Federation, as well as in Ukrainian territories, which are not under the control of the Government of Ukraine, motivated by inability to ensure proper observation for the quality of drugs production. The MOH of Ukraine posted a letter dated 04.07.2017

№18.1-07/18369 on its official website addressed to applicants for medicinal products, alternative and/or potential manufacturers, applicants-holders of registration certificates of which there are subjects of the Russian Federation, urgently take measures to amend registration materials for medicines on purpose for withdrawal of manufacturers/applicants being subjects of the Russian Federation. The MOH of Ukraine received a request from Subsidiary Enterprise (hereinafter – SE) "Stada-Ukraine" being the representative of joint stock company "Nizhpharm" as a member of the STADA Group of Companies, dated 13.11.2017 № 313, in which the company informed about the decision of the parent company STADA to take all legal and organizational measures to transfer ownership rights to SE "Stada-Ukraine" for registration certificates on all medicines of joint stock company "Nizhpharm" registered in Ukraine, and further to transfer the production of these medicines to Ukraine and to Germany. The enterprise provided arguments indicating the seriousness of the company's intentions to implement its decision, proposed terms for the implementation of the plan to transfer production to Ukrainian enterprises, also providing a letter of the joint stock company "Technologist", Ukraine, as for readiness to enter into a long-term agreement with SE "Stada-Ukraine" concerning medicines production on orders by SE "Stada-Ukraine" [2].

At the same time, taking into consideration the proposed deadlines for the implementation of the plan to transfer production of medicines from Russian enterprises, namely, 10 calendar months for changing the applicant and 10 calendar months to transfer production, all in all up to 2 years, regarding that during this period of time the manufacture and the supply of medicines mentioned in this business proposal is to be carried out by an enterprise in the Russian Federation, the MOH of Ukraine announced about impossibility of including a number of medicines into the order "On State Registration (Re-registration) of medicines (medical immunobiological drugs) with amendments to registration materials", and thereby the release into circulation and use of these drugs on the territory of Ukraine produced by joint stock company "Nizhpharm", Russian Federation. This fact led to a dispute between the SE "STADA-UKRAINE" of "BEPHA BETAILIGUNGSGEZELSHAFT FUR PHARMAVERTE MBH" (Ukraine) and Joint Stock Company "NIZHPHARM" (Russian Federation) and the MOH of Ukraine [2]. We assume that lawsuits to National Courts of Ukraine on declaration of inaction as illegal one and the obligation to take actions by the MOH of Ukraine are not be occasional.

The above mentioned indicates the relevance of the study on technology transfer to the production of medicines, cession of ownership of registration certificates and transfer of production within the current challenges to international and national security.

The purpose of this article is to identify areas of international cooperation in the field of technology transfer to the production of medicines and new approaches to the application of legal rules governing legal relations by Ukrainian Courts in the field of circulation of medicines related to the cession of ownership of registration certificates for medicines and transferring the production of medicines from one country to another.

Main part. International technology transfer to the production of medicines is a systemic international activity aimed at creating conditions for cross-border transfer of ownership of knowledge on the organization of drug development with the active interaction of developers and their potential buyers on paid or free basis [6,7]. Developing investigations of T. Androsov, L. Chernyshov, V. Kozub on «International technology transfer as a factor of innovative development of Ukraine's economy» [1] we note that the full process of international technology transfer in the production of medicines has the following phases: research and development (technology transfer is not carried out); utilization (transfer in the form of export of medicines); technological growth (transfer of technology into incompletely mastered form to developed countries); technological maturity (mutual transfer between developed countries and gradual transition of transfer to developing countries) gradually developing countries replace high-tech exports (technologies developed on the basis of the latest scientific knowledge, which in their technological level exceeds the best domestic and foreign counterparts being competitive on the world market of knowledge-intensive products) and their import); technological decline (transfer is limited to developing countries).

International cooperation in the field of technology transfer provides for the following: 1) conclusion of bilateral and multilateral international agreements of Ukraine on scientific and technical, technological, investment cooperation; 2) attracting investments into the scientific and technical complex of Ukraine; 3) promoting the introduction of international standards in Ukraine, in particular the standards of quality management system; 4) technology transfer within the framework of scientific-technical and production cooperation and investment cooperation; 5) ensuring for the participation of domestic enterprises, research institutions, organizations and higher educational institutions in international exhibitions and fairs of high-tech products and technologies; 6) participation in the development of domestic segments of international information and communication systems on intellectual property and technology transfer [8,9].

Regulatory Bills of Ukraine partially govern the activity of technology transfer to the production of medicines, although the legislative and regulatory framework is harmonized with the relevant directives and norms of the European Union [9,10]. Thus, only in the Guideline ST-N of the MOH of Ukraine 42-4.3: 2011 "Medicines. Pharmaceutical Quality System (ICH Q10) [5] transfer technology has been identified as a life cycle stage for a drug. According to this Guideline, the product life cycle includes such a stage of technical activity for new and existing drugs as technology transfer, which covers: 1) technology transfers of new products from development to production, and 2) technology transfers of products available on the market within or between production and test sites. Also, according to this Guideline, the purpose of technology transfer activities is to transfer information about products and processes depending on the goals of technology transfer. The Guidelines provide examples of the application of elements of the pharmaceutical quality system, while there are no recommendations for the process of technology transfer. Guideline ST-N of the MOH of Ukraine 42-4.3: 2011 is included into the Part 3 of the Guideline "42-4.0: 2016 "Medicines. Good Manufacturing Practice", harmonized with the EU GMP Guidelines (EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use). In the Guideline 42-4.0: 2016 there are no requirements directly to the transfer, on the contrary to the technical transfer (cession) of test methods, which is represented in the Section 6 «Quality control» of the Part 1, and for which general approaches are specified in particular [5].

In addition to the issue of technology transfer to the production of medicines, one of the topical questions is the one concerning transfer of medicines production.

The Law of Ukraine «On Fundamentals of National Security of Ukraine» in the Article 1 defines national security, inter alia,

as the protection of vital interests of people and citizens, which ensures the timely detection, prevention and neutralization of real and potential threats to national interests, in particular in the field of health care [3]. Ensuring the quality of medicines at all stages of their life cycle is the system-forming factor in achieving protection conditions of vital interests of people and citizens in the field of health care, i. e. implementation of national security in this area. In accordance with the provisions of the Paragraph 2 «Procedure for state registration (re-registration) of medicinal products and the amount of fee for their state registration (re-registration)», state registration of medicinal products is carried out by the MOH of Ukraine on the basis of the application and the results of examination on registration materials, held by State Expert Center (hereinafter – the Center) in the manner prescribed by the MOH of Ukraine. However, there is *no presumption that a medicinal product that has passed state registration is eligible to be re-registered in the future. These issues are particularly acute in the light of international and national security.* The example for this is the Court Case considered by the District Administrative Court of Kyiv which is referred to above in the introduction to this article.

Having analyzed norms of the Law, examined and evaluated the available written evidence on the inner conviction, based on direct, comprehensive, complete and objective consideration of all the circumstances of the Case in their entirety, taking into account that the plaintiff has not proved the assumption of power, that is the MOH of Ukraine, the inaction in considering the letter and the fact of violation of the plaintiff's rights, the Court concluded in this case that the allegations set forth in the statement of claim did not find their confirmation during the trial, so they have no foundations. Resolving the issue of the validity of the claims on the obligation of the MOH of Ukraine in the manner prescribed by the Law to make a decision on re-registering and amending registration documents for medicines registered by the Joint Stock Company "NIZHPHARM", the Court denoted that by its legal nature, in accordance with current legislation, the authority to decide on re-registration of medicines and amendments to registration certificates for medicines manufactured and distributed by STADA Group companies belongs exclusively to the executive body of the MOH of Ukraine, which in case of registration (re-registration) of medicines in such a way of registration (re-registration), makes the appropriate decision, and therefore endowed with discretionary powers [2].

This conclusion of the Court of the first instance was found by the Sixth Administrative Court of Appeal as erroneous, noting that the defendant is not endowed with discretionary powers, i. e. the right to act at its own discretion in making a decision on registration of medicinal products, so the Court of Appeal pays attention on making both the decision on registration and the decision on re-registration of medicinal products clearly defined by… regulatory documents, i. e. the defendant does not have the discretion in this matter [2].

In addition, the Board of Judges emphasized that "… asking the Court to oblige the defendant to decide on the re-registration of the disputed drugs, the plaintiffs are in fact asking the court to replace the defendant as the central executive body in matters within its exclusive competence" [2]. At the same time, the Board of Judges draws attention to the fact that the norms of the Code of Administrative Procedure of Ukraine (hereinafter – CAP), really allow the Administrative Court in exceptional cases to oblige the defendant being the subject of power to decide in favor of the plaintiff. Thus, in accordance with the Paragraph 4 of the second Part of the Article 245 of the CAP, that in case of satisfaction of the claim the Court may decide to declare the inaction of the subject of power as illegal and to make the obligation to take certain actions. According to the Fourth Part of the Article 245 of the CAP in the case specified in the Paragraph 4 of the Second Part of this Article, the Court may oblige the defendant as the subject of authority to make a decision in favor of the plaintiff, if all the conditions specified by the Law and such a decision does not provide for the right of the subject of power to act at its own discretion.

As it has been already mentioned, the decision on the re-registration of medicines does not provide for the right of the subject of power to act at its discretion. At the same time, in this case the Court is not entitled to establish the existence of all conditions prescribed by the Law for the decision to re-register medicines, since such conditions have not yet been established and verified in the manner prescribed by the Law as for the public authority defendant, which is responsible for resolving this issue. According to Part 2 of the Article 77 of the Code of Administrative Procedure of Ukraine, in administrative cases on the illegality of decisions, actions or inactions of the subject of power are in field of improvement of the legality of its decision, where actions or inactions are rested onto the defendant. Having assessed the evidence in the case, according to its internal conviction, based on their direct, comprehensive, complete and objective examination, the Court concluded that the plaintiff's administrative claim is not subject to satisfaction.

Conclusions. 1. The directions of international cooperation of states in the field of technology transfer to the production of medicines are as follows: 1) conclusion of bilateral and multilateral international agreements on scientific and technical, technological, investment collaboration and cooperation; 2) attraction of investments; 3) promoting the introduction of international standards for proper manufacturing practice; 4) technology transfer within the framework of scientific, technical and production cooperation and investment collaboration; 5) organization and holding of international exhibitions of equipment and technologies; 6) development of international information and communication systems on intellectual property and technology transfer.

2. The idea of the existing in domestic legal science of a special kind of public interest, that is national security, has been improved. It is argued that it is specified not only by the support of the national manufacturer, but also by the central executive body, taking up measures to withdraw from circulation of drugs within one country, that have been manufactured in another country or on the territories not controlled by the Government, motivated by inability to ensure proper quality control of medicines.

3. Decision-making on the issue of re-registration of medicinal products does not provide for the right of the subject of power to act at its own discretion. The Ministry of Health of Ukraine is not endowed with discretionary powers, that is the right to act at its discretion in making a decision on the registration of medicines because the grounds for the decision on registration/re-registration of medicines are clearly defined by Regulatory Bills of Ukraine. By asking the Court to oblige the Ministry of Health of Ukraine to take up the decision on re-registration of the disputed drugs, the plaintiffs are actually asking the Court to replace the Ministry of Health of Ukraine as the central executive body in matters within its exclusive competence.

4. The following new approaches to the application of legal norms by the courts of Ukraine governing legal relations in the field of circulation of medicinal products related to the cession of ownership of registration certificates for medicinal products and the transfer of production from one country to another have been

revealed, they are as follows: 1) MOH of Ukraine may (the term "may" is not synonymous with the term "liable") take up measures to withdraw from circulation on the territory of Ukraine medicinal products manufactured on the territory of the Russian Federation and on territories not controlled by the Government of Ukraine temporarily, including the Autonomous Republic of Crimea, motivated by the inability to ensure proper quality control; 2) The Ministry of Health of Ukraine may address to applicants for medicinal products, alternative and/or potential manufacturers, applicants-holders of registration certificates being subjects of another country (Russian Federation), urgently take up measures to amend the registration documents for medicines in order to withdraw producers/applicants that are the entities of another country (for example, the Russian Federation; 3) if during the examination of registration materials on the basis of expert assessment of updated data on the benefit/risk ratio, no confirmation of the positive ratio of expected benefits to possible risk during use of the medicinal product, the Ministry of Health of Ukraine has the right to make a decision on refusal of state re-registration of the medicinal product. At the same time, if the relevant conclusion of the expert assessment is positive, the defendant is empowered to make a decision on re-registration of the medicinal product; 4) state policy in the field of origination, production, quality control and sale of medicines is aimed at the development of production of safe medicines, ensuring the needs of the population with medicines of appropriate quality.

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SUMMARY

MEDICINES: TECHNOLOGY TRANSFER TO PRODUCTION, CESSION OF OWNERSHIP RIGHTS FOR REGISTRATION CERTIFICATES AND TRANSFER OF PRODUCTION IN CONDITIONS OF MODERN CHALLENGES TO NATIONAL AND INTERNATIONAL SECURITY

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The issue of technology transfer to the production of medicines, cession of ownership rights to registration certificates and transfer of the production of medicines in the context of modern challenges to international and national security are investigated in the article. The attention is focused on ensuring the public interest in health care. Emphasis is placed on the human right to effective, safe, high-quality medicines, on ensuring the right to entrepreneurial activity in the field of circulation of medicines. The purpose of this article is to identify areas of international cooperation in the field of technology transfer to the production of medicines and new approaches to the application of legal rules governing legal relations by Ukrainian Courts in the field of circulation of medicines related to the cession of ownership of registration certificates for medicines and transferring the production of medicines from one country to another. The object of the study is the public relations that arise during the transfer of technology to the production of medicines and public relations in the field of circulation of medicines, associated with the cession of ownership of registration certificates for medicines and the transfer of production from one country to another. The methodological basis of the research are general and special methods of scientific knowledge (formal-logical method, comparative-legal, structural-logical).

As a result of the conducted research, the directions of international cooperation of states in the field of technology transfer to the production of medicines are defined. The idea of the existing in domestic legal science of a special kind of public interest, that is national security, has been improved. It is argued that it is specified not only by the support of the national manufacturer, but also by the central executive body, taking up measures to withdraw from circulation of drugs within one country, that have been manufactured in another country or on the territories not controlled by the Government, motivated by inability to ensure proper quality control of medicines. It is emphasized that decision-making on the issue of re-registration of medicinal products does not provide for the right of the subject of power to act at its own discretion. New approaches to the application of legal norms by the courts of Ukraine governing legal relations in the field of circulation of medicinal products related to the cession of ownership of registration certificates for medicinal

products and the transfer of production from one country to another have been revealed.

Keywords: human right to effective, safe, high-quality medicines, international security, national security, medicines, technology transfer, production transfer, intellectual property, subject of power, administrative proceedings.

РЕЗЮМЕ

ЛЕКАРСТВЕННЫЕ СРЕДСТВА: ТРАНСФЕР ТЕХНОЛОГИЙ В ПРОИЗВОДСТВО, ПЕРЕДАЧА ПРАВ СОБСТВЕННОСТИ НА РЕГИСТРАЦИОННЫЕ УДОСТОВЕРЕНИЯ И ТРАНСФЕР ПРОИЗВОДСТВА В УСЛОВИЯХ СОВРЕМЕННЫХ ВЫЗОВОВ МЕЖДУНАРОДНОЙ И НАЦИОНАЛЬНОЙ БЕЗОПАСНОСТИ

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Цель исследования - выявить направления международного сотрудничества государств в сфере трансфера технологий в производство лекарственных средств и новые подходы к применению судами Украины норм права, регулирующих правоотношения в сфере обращения лекарственных средств, связанных с передачей права собственности на регистрационные удостоверения на лекарственные средства и переносом производства лекарственных средств из одной страны в другую. Объектом исследования являются общественные отношения, возникающие при трансфере технологий в производство лекарственных средств и в сфере обращения лекарственных средств, связанные с передачей права собственности на регистрационные удостоверения на лекарственные средства и переносом производства лекарственных средств из одной страны в другую. Методологической основой проведенного исследования являются общие и специальные методы научного познания (формально-логический метод, сравнительно-правовой, структурно-логический).

Выявлены направления международного сотрудничества государств в сфере трансфера технологий в производство лекарственных средств. Проанализировано существующее в украинской юридической науке представление об особом виде публичных интересов – обеспечении национальной безопасности, что заключается не только в поддержке национального товаропроизводителя, но и в принятии центральным органом исполнительной власти мер по выводу из обращения на территории одного государства лекарственных средств, изготовленных на территории другого государства или неподконтрольных правительству территориях в связи с невозможностью обеспечения надлежащего контроля за качеством производства таких лекарственных средств. Принимая то или иное решение по вопросу перерегистрации лекарственных средств субъекты властных полномочий не наделены дискреционными полномочиями. Выявлены новые подходы к применению судами Украины норм права, регулирующих правоотношения в сфере обращения лекарственных средств, что связано с передачей права собственности на регистрационные удостоверения на лекарственные средства и переносом производства лекарственных средств из одной страны в другую.

რეზიუმე

სამკურნალწამლო საშუალებები: ტექნოლოგიების ტრანსფერი წარმოებაში, რეგისტაციულ მოწმობებზე და წარმოების ტრანსფერზე მესაკუთრეობის უფლების გადაცემა თანამედროვე საერთაშორისო და ეროვნული გამოწვევების პირობებში

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კვლევის მიზანს წარმოადგენდა სახელმწიფოთა საერთაშორისო თანამშრომლობის მიმართულებების გამოვლენა სამკურნალწამლო საშუალებების წარმოებაში ტექნოლოგიების ტრანსფერის სფეროში და უკრაინის სასამართლოების ახალი მიდგომები სამართლის ნორმების გამოყენებისადმი, რომლებიც არეგულირებს სამართლებრივ ურთიერთობებს სამკურნალწამლო საშუალებების მიმოქცევის სფეროში და მესაკუთრეობის უფლების გადაცემას, წარმოების ტრანსფერს ერთი ქვეყნიდან მეორეში.

კვლევის ობიექტს წარმოადგენდა საზოგადოებრივი ურთიერთობა, წარმოიქმნილი სამკურნალწამლო საშუალების წარმოებაში ტექნოლოგიების ტრანსფერის დროს, სამკურნალწამლო საშუალების მიმოქცევის სფეროში წამლებზე სარეგისტრაციო უფლების გადაცემასთან და წარმოების ერთი ქვეყნიდან მეორეში გადატანასთან დაკავშირებით.

ჩატარებული კვლევის მეთოდოლოგიურ საფუძველს შეადგენს სამეცნიერო შემეცნების ზოგადი და სპეციალური მეთოდები - ფორმალურ-ლოგიკური, შედარებით-სამართლებრივი და სტრუქტურულ-ლოგიკური.

განსაზღვრულია სახელმწიფოთა საერთაშორისო თანამშრომლობის მიმართულებები მედიკამენტების წარმოებაში ტექნოლოგიის გადაცემის სფეროში. გაანალიზებულია უკრაინის იურიდიულ მეცნიერებაში არსებული შეხედულება საჯარო ინტერესების განსაკუთრებულ სახეობაზე - ეროვნული უსაფრთხოების უზრუნველყოფაზე, რაც გულისხმობს არა მხოლოდ ეროვნული მწარმოებლის მხარდაჭერას, არამედ ცენტრალური აღმასრულებელი ორგანოს მიერ სხვა ქვეყნის ტერიტორიაზე წარმოებული მედიკამენტების ერთი ქვეყნის ტერიტორიაზე მიმოქცევიდან ამოღების ზომების მიღებას, სახელმწიფო ან არასამთავრობო კონტროლირებადი ტერიტორიებზე ამგვარი მედიკამენტების წარმოების ხარისხზე ადეკვატური კონტროლის შეუძლებლობის გამო. გამოვლენილია ახალი მიდგომები უკრაინის სასამართლოების მიერ მედიკამენტების მიმოქცევაში სამართლებრივი ურთიერთობების მარეგულირებელი ნორმების გამოყენებისადმი, რაც ასოცირდება მედიკამენტების რეგისტრაციის მოწმობების მფლობელობის გადაცემასა და მედიკამენტების წარმოების ერთი ქვეყნიდან მეორეში გადატანასთან.

SEVERE PAIN AND SUFFERING AS EFFECTS OF TORTURE: DETECTION IN MEDICAL AND LEGAL PRACTICE

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The correct determination of the effects of cruel treatment and punishment is of great importance, since it is one of the main factors influencing taking the decision by the law enforcer about what type of ill-treatment and punishment took place. In particular, depending on severity of the effects the victim, the European Court of Human Rights (ECHR) identifies the torture, inhuman or degrading treatment and punishment[1], and the national investigative and judicial authorities qualify the offense as the said torture, torment or other criminal offense.

Solving the issue of the effects has a medical load too. The choice of the medical rehabilitation course (which means the patient's chances to return to a normal life) depends on detection of the said effects. At present, if not to take into account the work of state (municipal) healthcare institutions focused on implementation of the protocols rather than on taking into account the patient's peculiarities and his/ her real recovery, the rehabilitation, in the full sense of the word, is provided only by highly specialized centers. The International Rehabilitation Council for Torture Victims (IRCT) is the most famous of them. Its work has a high demand, and its results are quite promising. Therefore, the IRCT network is constantly growing, and today it includes more than 150 centers in 75 countries [63]. Unfortunately, the work of this center in Ukraine [71] is not characterized by the successes achieved by the IRCT center in Georgia [89]. There are also national rehabilitation centers that extend their activities over the territory of only one country. In particular, Freedom from Torture is a British institution consisting of five centers located at different points of the United Kingdom [92]. Ukraine has no such national rehabilitation center. Every year, the United Nations Voluntary Fund for Victims of Torture allocates tens of thousands of dollars, in particular, to private clinics that provide specialized support to victims of this crime [74]. The victims themselves and their families seek to receive the assistance in the specialized institutions.

The constant increase in the number of narrow-profile centers and a high demand for medical care in them, the special significance of the effects of cruel treatment and punishment for deciding on the type of offense prohibited by Article 3 of the 1950 Convention for the Protection of Human Rights and Fundamental Freedoms [67], indicate that the torture effects are far from typical and require a special attention. And that means that their detection deserves to be the subject of a separate scientific work.

The aim of the study is to identify the features and to determine the relationship between medical and legal (investigative & judicial) practice on detection of the torture effects.

Material and methods. This paper is based on a thesis study devoted to the criminal law problems of the torture, prepared by the Department of Criminal Law No. 1, Yaroslav Mudryi National Law University, Kharkiv, Ukraine [43]. Due to participation in seminars conducted by the prosecution and security services of Ukraine, the author has understood that the results of the scientific work shall be of more applied nature. For this reason, the subject of the study was expanded, and some specialists from related legal sectors were attracted to preparation of this article. In this case, the publications of rehabilitation centers for torture victims took center stage in the list of the used literature. There were also used specialized medical journals, manuals for physicians, publications of the International Association for the Study of Pain (IASP) and the Ukrainian Association for the Study of Pain. The picture of our knowledge in the field of medicine is substantially supplemented by the answers prepared by leading experts of Bogomolets National Medical University, Kyiv, Ukraine and Danylo Halytsky Lviv National Medical University, Lviv, Ukraine. Enough attention has been paid to the latest scientific achievements in the field of rehabilitation of torture survivors. The United Nations reports on assistance to victims of tortures were also taken into consideration, as well as official explanations of the Office of the United Nations High Commissioner for Human Rights (OHCHR) on understanding the nature of tortures. The legal component of the work is supported by the provisions of international treaties, criminal codes of the post-Soviet countries. The empirical basis for the study was provided by 41 final court decisions on the following cases: 726/777/14-к [3], 647/507/14-к [7], 759/7180/14-к [34], 579/952/14-к [25], 683/298/14-к [33], 686/23492/14-к [56], 11/796/9/2014 [2], 758/11330/14-к [29], 492/2080/14-к [5], 208/10261/14-к [15], 154/1557/15 [10], 219/1584/15-к [4], 676/991/15-к [19], 445/563/15-к [17], 618/641/15-к [12], 163/225/15-к [1], 283/1495/15-к [27], 387/407/16-к [14], 487/6385/16-к [16], 370/155/16-к [18], 400/77/17 [28], 473/620/17 [9], 369/4590/17 [21], 726/1160/17 [30], 635/6445/17 [35], 127/16930/17 [8], 473/1064/17 [44], 203/1165/17 [22], 609/210/17 [26], 484/1197/18 [36], 718/993/18 [23], 640/5131/18 [20], 753/17036/18 [11], 311/144/18 [57], 718/1755/18 [60], 759/19368/18 [32], 640/22678/18 [59], 310/9324/18 [58], 665/1529/18 [37], 426/24003/18 [31], 718/2744/19 [24]. These cases were selected according to the following criteria: all court decisions made under Article 127 "Torture" of the Criminal Code of Ukraine since 2014 till 2019 inclusively, being in the public domain as of March 1, 2020, on the official website of the "United State Register of Court Solutions" http://reyestr.court.gov.ua/. The article also uses 2 court decisions on cases 638/5928/18 [13], 610/3874/15-k [6], which have no legal force as of March 1, 2020, but are of interest for the purposes of this study. These decisions were not taken into account in determining the statistical indexes, but were used in the article as examples of the application of Article 127 of the Criminal Code of Ukraine.

In the course of the study, the following methods were used: analysis (when ascertaining the content of legal norms relating to prohibition of the torture; studying scientific publications related to pain-identification problems, rehabilitation of torture victims), induction, statistical method (when working with decisions of national courts), systemic method (when determining the relationship between medical and legal (investigative & judicial) practice on detection of the torture effects).

[1]For completeness of the material presentation, we have to note that not all scientists adhere to the point of view that it is the criterion of effects severity that determines the distinction between torture and inhuman or degrading treatment and punishment. In particular, the United Nations Special Rapporteur on Torture and Other Cruel, Inhuman and Degrading Treatment or Punishment, Manfred Nowak, considers the goal of the perpetrator and helplessness of the victim as such a criterion [72,79].

Results and discussion. The starting point in determining of what are really, in principle, the effects of the torture is provided with provisions of Article 1 of the 1984 Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment. The latter states that the torture should be understood as any act by which severe pain or suffering, whether physical or mental, is intentionally inflicted on a person [68]. Therefore, in particular, severe pain and suffering are the effects of torture and are the subject of assessment by the law enforcer at the stage of qualification of the offense committed by the perpetrator. Undoubtedly, there is a certain conventionality in such a conclusion, since pain, by its nature, is inseparably associated with the violence itself and is rather its companion than the result. Perhaps that is why the OHCHR, while interpreting the torture, does not distinguish pain and suffering as independent elements of this definition [72]. At the same time, we see that OHCHR refers to the ECHR practice, according to which, the European Court evaluates the power of pain and suffering in each case [72]. The ECHR position is quite justified. For the same cruel treatment or punishment, quite different effects can occur (for example, for a child and for an adult), which means that the types of offence will be different. It is possible to take into account the difference in cases, using some kind of formal element. In this case, this element is the power of pain and suffering. In addition, only on the background or as a result of strong negative reactions of the body, can such "breakdown" of the body and personality occur, which is described by the physicians working with victims of the tortures [69]. Therefore, it is simply impossible not to single out severe pain and suffering as self-sufficient effects. When comprehensed, the above convenality turns out to be truly justified. However, this justification is possible only in the context of the tortures. Not without reason, Metin Başoğlu writes that pain and suffering are an independent subject of proving *only* in the torture court proceedings [91].

In the criminal codes of the post-Soviet countries, we find provisions on pain and suffering, which are similar to those contained in Article 1 of the 1984 Convention. In particular, these effects of the torture are indicated in Art. 113, 293 of the Criminal Code of the Azerbaijan Republic [45], Art. 119 of the Criminal Code of Armenia [46], Art. 144^1 of the Criminal Code of Georgia [47], Art. 128 of the Criminal Code of the Republic of Belarus [49], Art. 166^1 of the Criminal Code of the Republic of Moldova [51], Art. 182^1 of the Criminal Code of the Republic of Turkmenistan [53], Art. 127 of the Criminal Code of Ukraine [39]. Only suffering is mentioned in Art. 143 of the Criminal Code of the Kyrgyz Republic [48], Art. 117 of the Criminal Code of the Russian Federation [55], Art. 146 of the Criminal Code of the Republic of Kazakhstan [50], Art. 143^1 of the Criminal Code of the Republic of Tajikistan [52]. Only the legislator of the Republic of Uzbekistan omitted the formalization of pain and suffering - see Art. 235 of the Criminal Code of the Republic of Uzbekistan [54]. The aforementioned means that the investigative and judicial authorities of the post-Soviet space countries shall have the same approach to the proving of torture as that of the ECHR: in particular, the detection of severe pain and suffering shall be a mandatory part of the work in establishing of the elements of the crime in question.

Below, we will present information that is basic and allows medical workers (general practitioners and narrowly focused practitioners, forensic experts) and the law enforcer (investigators, prosecutors, judges) to interact successfully with each other in detection the torture effects. Until today, medicine has not been able to study in the full scope the biopsychosocial phenomenon of pain. The IASP defines it as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [70]. The concept of "suffering" is not used in neurological practice at all [40]. The scientists state that the following points of view regarding the pain shall be recognized as relevant: 1) an unpleasant sensory feeling that is associated with a possible or existing tissue damage; 2) an affective state of the body, which includes emotional, somatic and vegetative reactions; 3) a motivating state that modifies all organs and body system, creating an appropriate model of its reaction aimed at eliminating the causes of pain; 4) an integral function that mobilizes different functional systems to protect the body from the influence of harmful factors [61].

The classical diagnostics of pain is aimed at determining its physical and psychoemotional components with subsequent clarification of the features of their interaction [41]. To detect the physical component of pain, the neurophysiological techniques are, in particular, used, which by the mechanism of their implementation are reduced to mechanical, electrical and (or) thermal actions on the body. And the psychoemotional component is determined on the basis of the patient's answers. Among the questionnaires that help the patient to characterize their pain, known to us, it's possible to call: McGill Pain Questionnaire (MPQ), Visual Analogue Scale (VAS), Numeric Pain Scale (NPS), Categorical Pain Scale (CPS) [38], DN4 questionnaire, Leeds Assessment of Neuropathic Symptoms and Sings (LANSS), painDETECT questionnaire [62], face images pain rating scale. The principle of their use is quite simple - the patient is offered, according to pre-established criteria, to characterize by themselves the pain they experience. For example, according to MPQ, the patient determines pain by 20 points, analyzing his sensory and emotional sensations, assessing the intensity of pain and reflecting the whole variety of pain syndrome. According to VAS, he points on a 10 cm ruler the intensity of his pain sensation from "0" ("no pain") to "10" ("unbearable pain"). It is worth to note that, when assessing their pain, the IRCT patients choose the highest indicators "8-10", marking a large number of pain areas on the body [42].

The self-analysis carried out by the patient himself is at the heart of pain diagnostics. A completely objective study of pain turns out to be impossible [40]. Due to it, the question arises: is it possible that a medical worker, on the basis of only the patient's answers, can determine the intensity of the pain, and the law enforcer, after him, can automatically transfer this to the field of jurisprudence (in particular, taking the medical conclusion to determine how serious are the effects that have occurred and, accordingly, what type of cruel treatment and punishment is there)? Of course not. Otherwise, the role of the medical worker and law enforcer would be of a purely technical nature.

First of all, it is necessary to note that it is the medical worker who determines the physical component of pain and its relationship with the psychoemotional component. This allows him to critically evaluate the patient's conclusions on pain. In particular, a neurotic person can evaluate even a minor mechanical effect as the factor causing the maximum pain. And the medical worker, realizing the inadequacy of the subjective assessment of a particular patient, will never issue a medical conclusion that there a severe pain took place. In addition, the medical worker has in his arsenal indirect methods of determining the pain intensity, namely: accounting the quantity of analgesics taken by the patient; monitoring his behavior (for example, can he breathe deeply or make active movements); monitoring the stress hormones, etc. Therefore, he can always put into question the pa-

tient's answers, having the results of an objective examination. For example, the assessments of the patient who performs physical exercises without obstruction, but at the same time assesses the pain as unbearable, are unlikely to be taken as a basis when the medical worker ascertains the intensity of pain. In turn, the law enforcer identifies, in a sense, a "conventional" effects, and, therefore, can give it a purely legal assessment. For example, to identify a severe pain, the following assessment criteria are suitable: objective one (intensity, duration) and subjective one (intolerance) [43]. Therefore, the work on detection of severe pain on the part of the medical worker and the law enforcer is filled with in-depth analysis and critical comprehension of its results.

Here the following important question arises: can the said subjects independently, without interacting with each other, detection the effects of the torture? Certainly not. The subject of proving in the cases of torture is the effects identified by Article 1 of the 1984 Convention. The physician does not work for the purpose of law enforcement. The forensic expert does not always take into account the peculiarities of legal regulation. For example, during the investigation of case 638/5928/18, the expert stated that the disability certificate of the victim, a child suffering from infantile cerebral paralysis, is not relevant to the essence of the investigation [13]. We strongly disagree with this, not least because the characteristics of the victim are directly related to identification of the pain strength. The law enforcer, even if he identifies the «conventional» effects, must state a result which, by its nature, tends towards the field of medicine. Therefore, his conclusions themselves are also not self-sufficient. That is why only the joint medical and legal detection of the severe pain and suffering is the prerequisite of a correct solution to the issue of the presence or absence of the torture effects.

It should be noted that we have not met in the national judicial practice a single case, in which a joint medical and legal detection of the effects of torture was carried out. This is connected: firstly, with the deep-rooted traditions in the work of investigative and judicial authorities - to identify the gravity of bodily injuries (in cases on crimes against life and health), but not the degree of pain and suffering; secondly, with the lack of recommendations on joint medical and legal identification of the intensity of pain and suffering in the Manual on the Effective Investigation and Documentation of Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment (Istanbul Protocol) [73].

With consideration of specific nature of the Istanbul Protocol contents, as well as the fact that it is intended to serve as international guidelines for the *assessment of persons* who allege torture and ill-treatment, the lack in it of recommendations on the joint medical and legal detection of the severe pain and suffering does not deserve praise. However, the said omission itself can be explained by the fact that, in the Istanbul Protocol, the tortures are understood in the meaning of Article 1 of the 1984 Convention, the official interpretation of which does not provide for separation of severe pain and suffering as an independent element of the torture.

The absence of traditions and recommendations on identification of severe pain and suffering as a effects of torture leads to errors in the work of the investigative & judicial authorities. For example, in case 676/991/15-k, the perpetrator was prosecuted for intentional light bodily injury resulting in a short-term health disorder (Part 2 of Article 125 of the Criminal Code of Ukraine) and for torture (Part 1 of Article 127 of the Criminal Code Ukraine) in connection with the infliction of three blows with hand in the face during a five-minute domestic quarrel, one blow with a kitchen knife in the hip and one burning the stab and slash wound with a cigarette [19]. In this case, the torture was identified only in relation to the last of the said episodes. Undoubtedly, the pain from burning with a cigarette is not similar to the pain of being hit. But in connection of what, did the law enforcer recognize a situational pain from burn as a severe pain mentioned in Article 1 of the 1984 Convention? The answer is not given by law enforce, and we have certain doubts about availability in this case of the effects that are characteristic of the torture. It is obviously that, in the future, in order to prevent such mistakes, the law enforcer shall have the appropriate recommendations on detect of severe pain and suffering. Therefore, the development of such recommendations is one of the main tasks for the scientific community.

We'd like to note that the ECHR, alongside with raising European standards for the protection of human rights, has lowered the bar for severity of the effects, upon the occurrence of which the offence could be considered as a torture. At the same time, the "upper limits" remained unchanged. In particular, there are still tortures, which in their cruelty are not inferior to medieval ones. Their effects are so serious that the victims require long years of rehabilitation [77]. The victims themselves state that they remain patients for their entire life [66]. The perpetrator destroys their personality, self-respect, and sense of self-worth [78]. After what they suffered, they are afraid to go further and believe that no one can understand their suffering [83]. The physicians who work with such patients describe them as "broken persons" [69]. What it takes to survive the drowning torture, during which there are: breath holding, fighting, physical exhaustion, rising levels of carbon dioxide, inhalation and ingestion of liquid, coughing, vomiting, loss of consciousness, respiratory and heart failure with a possible climax in the form of death [76]. During tortures, even the Near Death Experience phenomenon is possible, which is associated with the "exit" of consciousness from the body (a person "rises" to the ceiling and watches what is happening around his physical body) [80]. The studies prove that the effects of the crime in question arise at all levels - physical, psychological, social, spiritual, cultural, etc. Therefore, the treatment of such patients requires an integral approach [65], sometimes, with the use of non-standard methods (for example, art therapy [65], music therapy [87], etc.).

Given the condition of the victim of torture, the scientific literature has expressed the opinion that there exists a "torture syndrome" [42, 86] and the "breakdown of the person's autonomous self-regulation program" [43]. A special psychophysiological state appears with any torture. However, it manifests itself, to a greater extent, in availability of the so-called "remote" effects of this crime (that is, those ones that arise against the background or as a result of severe pain and suffering - muscle dysfunction, post-traumatic disorder, etc.). The Istanbul Protocol contains recommendations focused exactly on identifying the "remote" effects of torture. Wherein, studies conducted by the University of Edinburgh prove that even with the developed protocols, detecting these effects is not an easy task. And the more limited the clinical and legal resources of the state are, and the lower the level of its institutional potential is, the more difficulties arise when doing this work [64].

The "remote" effects of torture can be divided into three groups: physical, psychosomatic and mental. It is no mere chance that Article 1 of the 1984 Convention describes the effects of torture as: severe pain (which is most closely associated with physical changes), physical suffering (primarily related to psychosomatic effects), and mental suffering (mainly related to mental disorders).

Since the torture itself is aimed at destroying the person as a personality, the rehabilitation center physicians place the mental deviations in the first place among the effects of torture (chronic fear, depression, situational loss of connection with reality (flashback), negative self-perception [42]). The literature also describes psychosis, avoidance behavior, persistent personality changes, irritability, hyperactivity [75] and others. Much attention is paid to depression (MDD) and Post-Traumatic Stress Disorder (PTSD) [75, 81, 86]. The latter are called in the Istanbul Protocol the main mental effects of torture (Item 236) [73]. In science, it has even been suggested that the torture is erroneously associated with pain. For example, some Spanish scientists state that the torture implies a process aimed at submission and obedience, humiliation and psychological breakdown, and, therefore, a modern psychological torture displaces a pain-type one and is a more effective tool aimed at achieving the desired result in a short time [85]. Despite all this, we would not completely discount the pain as a effects of torture. Until today, many forms of this crime are associated with physical action on the human body. In addition, historically, the torture has formed as a crime aimed at destroying the personality through pain. Evidently, it was a tribute to the history and nature of this crime that brought a severe pain to the first place among the effects in Article 1 of the 1984 Convention. And in the Istanbul Protocol, the physical evidence of torture is described earlier than the psychological evidence (sections V, VI) [73].

Diagnosing the mental health of the torture victim is a key point in the work of physician since the impact on this type of health during this crime is quite serious and has effects that go far beyond physical changes [90]. The Istanbul Protocol states that a psychological examination and assessment of the psychological state of the alleged torture victim are mandatory (paragraph 104) [73]. In addition to examination for diagnostics of mental disorders in case of craniocerebral injury, PTSD and related diagnoses, a neuropsychological assessment is also recommended (Items 292, 298) [73].

Among physical effects of torture we may call pathological pain, persistent change in hormone levels and body temperature, functional changes in the heart functioning, vasospasms, fractures, torn ligaments, hemorrhages, and skin rashes. The physicians of rehabilitation centers also note blurred and double vision, diminished hearing, buzzing in ears, dizziness, loss of balance, difficulty in nasal breathing, loss of teeth, reflex cough, nausea, vomiting, disorder of gastrointestinal tract, weight loss, convulsions, dysuria, pollakiuria, oligomenorrhea, ulcers, wounds, dysfunction of joints and muscles, paresthesia, neuralgia, neurogenic pain, etc. [42]. The Istanbul Protocol associates identification of these effects with survey, medical anamnesis and medical examination (Items 163, 168, 173) [73]. The recommendations on conducting the medical examination are clearly stated as for organs and systems (skin, eyes, ears, nose, mouth and teeth, chest and abdominal cavity, musculoskeletal system, genitourinary system, central and peripheral nervous systems, Items 176–186) [73], as well as in connection with the form of torture (beating and other types of blunt injuries, hitting the feet, suspension, torture by position, electric shock, action on the teeth, strangulation, rape and sexual violence, Items 189–232) [73]. At the same time, the Istanbul Protocol does not contain restrictions on the methods of diagnostic research, indicating among the possible ones: x-ray visualization (x-ray images, radioisotope scintigraphy, computed tomography, nuclear magnetic resonance imaging, ultrasound imaging), biopsy for electric shock injury [73]. The latter is quite important. For example, in some cases, functional disorders may be more significant than morphological ones. Accordingly, the functional visualization can provide more insight into the extent of traumatic injuries and their functional effects. In this case, a scintillation imaging will be indispensable [88]. Besides, many forms of tortures do not leave visible marks (such as, for example, musical torture [82]). The changes that inevitably will come require to be detected. And any medical achievements are suitable for this purpose.

We attribute to the psychosomatic effects the irritable bowel syndrome (colon irritabile), psychomyogenic headache, etc. At the same time, we emphasize that the torture is an extreme event in human life and causes severe stress, which echoes are often not associated with pathological changes, but always comprise psychosomatic effects. That is why the patients often complain of pain, the organic nature of which cannot be explained by the physician. The Istanbul Protocol mentions identification of this group of effects in the context of determination of psychological deviations (Item 259) [73].

The physical, psychosomatic and mental effects of torture are “taken off the table” for this crime. That is, they are not an obligatory element of torture. But in most cases they inevitably come. In this aspect, it suffices to pay attention to the national judicial practice. In particular, physical, psychosomatic and mental changes are defined by the forensic expert as bodily injuries. The results of analysis of the national judicial practice show that among 41 cases of torture, bodily injuries occurred in 37 of them. That is, causing physical, psychosomatic and (or) mental changes, determined by the forensic expert as causing bodily injures, occurs in 9 out of 10 cases of torture. Below we present diagrams showing percentage and quantitative incidence of bodily injuries inflicted during torture.

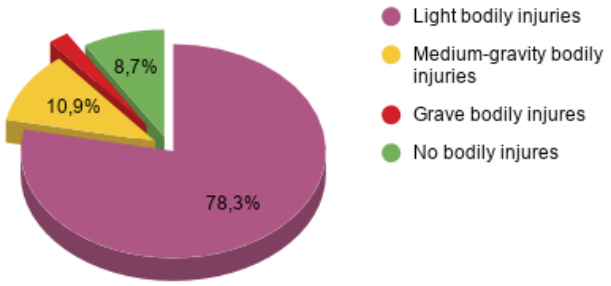

Fig. 1. Percentage of bodily injuries suffered during torture

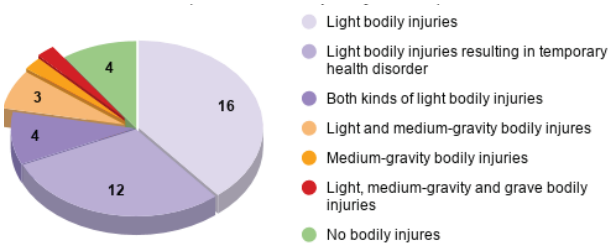

Fig. 2. Identification of infliction of bodily injuries during tortures (with reference to quantity of cases)

The detection of the physical, psychosomatic and mental effects of torture is the prerogative of the physician. For the law enforcer, the medical identification of the latter is another key to detection of severe pain and suffering. The presence of physical, psychosomatic and mental effects makes it possible to understand whether the effects that are provided for in Article 1 of the 1984 Convention have occurred. For example, during examina-

tion of case 492/2080/14-k by forensic expert, it was found that, judging by the number of physical injuries, there were at least 48 points of application of traumatic force [5]. Only this indicates that the pain should have been severe.

In the torture cases, bodily injuries and their gravity are determined by the forensic expert or on the basis of medical documentation fixing the physical, psychosomatic and (or) mental effects of torture (in particular, see case 718/1755/18 [60]), or on the basis of the examination of the victim (for example, see case 203/1165/17 [22]).

Conducting the forensic psychiatric examination in the torture cases is the exception rather than the standard procedure. With consideration of the Istanbul Protocol recommendations and the nature of the crime in question, this cannot be called satisfactory. Among 41 court decisions, only in 2 of them, we find an indication to conducting such an examination. According to case 487/6385/16-k, the perpetrator forced the minor to stand on salt for 16 hours, which led not only to bodily injures, but also to post-traumatic stress disorder determined by a comprehensive psychological and psychiatric examination [16]. And in the framework of the consideration of case 686/23492/14-k, the subject of such an examination was determination of the possibility of a minor victim to correctly perceive the circumstances of the case. In this case, his state of mind was not evaluated [56]. This raises a number of questions. In particular, according to the case file, at about 10 pm, the perpetrator kicked the victim, tied his hands and suspended him on the door. Then he stopped his mouth with a cloth and hit him with a metal stick in different parts of his body. The next day, having waked the child, the perpetrator again suspended him in the same way, stopped his mouth and hit him. In addition to the above, he hit the minor with a brick in the back of his head. Leaving a brick on his head, the perpetrator said that if the brick falls, he will hit the victim still harder. After returning in a while and noticing that the brick fell, the perpetrator continued hitting [56]. With consideration of the case circumstances, it remains a mystery why the mental state of the child who survived such a crime was not the subject of evaluation by the experts.

In investigative & judicial practice on detection of severe pain and suffering, a special attention is attracted by the tools that are not associated with the use of medical conclusions. In particular, to determine the effects of torture, the law enforcer rather often takes into account the testimony of both the victim and the witnesses. For example, in case 387/407/16-k, the court took into consideration the testimony of: a) the victim's son who indicated that he had found his mother tied to a tree, completely naked and drenched in solution of brilliant green; b) a medical assistant who explained that the victim complained of pain throughout her entire body, so he did her an injection of analgesic [14]. When examining case 610/3874/15-k, the court identified appearance of severe physical pain from the use of an electric shocker, paying attention to the protocol of search of the house of the accused, in which there was found a flashlight with electric shocker [6]. By the way, in view of the Istanbul Protocol recommendations [73] and those of the physicians of rehabilitation centers [84] on advisability of conducting the histological studies in cases of use of electric current, the approaches of the national law enforcer to this issue are inferior in their relevance. In the framework of examination of case 283/1495/15-k, the court found that the perpetrator forced the victim to be in a cold river. In assessing the effects of this offence, the law enforcer took into account the conclusion of the regional hydrometeorology center regarding temporarily low air and water temperatures [27]. Thus, indirect evidence is also taken into account by the law enforcer when detectioning the severe pain and suffering.

Summing up the results of the study, let's define its main **conclusions**:

1) the statutory effects of torture are severe pain and suffering, both physical and mental (Article 1 of the 1984 Convention, Article 127 of the Criminal Code of Ukraine), therefore, these effects are included in the subject of evidence in the cases about torture. The "torture syndrome", "breakdown of the person's autonomous self-regulation program" are scientific developments, therefore, their detection is not binding in the context of law enforcement;

2) only the joint medical and legal detection of severe pain and suffering is the key to the correct solution for the issue of presence or absence of the effects of torture. A medical assessment is not self-sufficient, since it does not work for the purpose of law enforcement (it is aimed more at identifying the patient's health problems and assisting him, rather than creating the foundation for qualifying the committed offence). The work of the expert still remains the work of the medical worker; therefore, the conclusions are not always based on the take into account of the peculiarities of legal regulation. In the legal assessment not supported by medical knowledge, the incompleteness and excessive conventionality are always seen;

3) the Istanbul Protocol contains no recommendations regarding the joint medical and legal detection of severe pain and suffering. With consideration of the constitutive nature of the effects of torture, the development of these recommendations is one of the main tasks facing the scientific community;

4) the peculiarity of medical practice on detecting the effects of torture consist of is the need to establish both statutory (severe pain and suffering) and "remote" (physical, psychosomatic and mental) effects of this crime;

5) the specificity of investigative & judicial practice in detecting severe pain and suffering (as effects of torture) lies in the need to use a wide range of tools: a) scientific and legal methods for determination of severe pain and suffering (for example, objective (intensity, duration) and subjective (intolerance) pain assessment criteria); b) medical conclusions on the intensity of pain and suffering; medical documentation on fixation the "remote" effects of torture; c) the conclusions of forensic examinations on identifying the gravity of bodily injuries, psychological and psychiatric examinations on identifying the state of the victim after committing the crime against him; d) testimonies and protocols of interrogation of the victim and witnesses, protocols of inspection of the crime scene, those of search, investigative experiment, examination of material evidence.

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SUMMARY

SEVERE PAIN AND SUFFERING AS EFFECTS OF TORTURE: DETECTION IN MEDICAL AND LEGAL PRACTICE

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The aim of the study is to identify the features and to determine the relationship between medical and legal (investigative & judicial) practice on detection of the torture effects.

It is emphasized that the paper is a continuation of the thesis study on the criminal law problems of torture, which were prepared by the Department of Criminal Law No. 1, Yaroslav Mudryi National Law University, Kharkiv, Ukraine. During the preparation of this article, the following material were used: the publications issued by the centers for rehabilitation of torture victims, specialized medical journals, manuals for physicians, publications by the IASP and the Ukrainian Association for the Study of Pain, explanations by leading specialists of Bogomolets National Medical University, Kyiv, Ukraine, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine, UN reports, OHCHR official explanations, international treaties on prohibition of torture, criminal codes of post-Soviet countries. The empirical basis of the study was provided by 41 final decisions of the court on torture cases of taken since 2014 till 2019. To achieve the aim of the study the analysis and induction methods, as well as statistical and systemic methods were applied.

According to the results of the study, it is concluded that only the joint medical and legal detection of severe pain and suffering is the key to the correct solution of the issue of presence or absence of the torture effects. It is noted that neither medical nor law enforcement assessments are self-sufficient and require addition of the mutual contexts. Attention is drawn to the fact that development of the guidelines on the joint medical and legal detection of severe pain and suffering is one of the main tasks for the scientific community.

It is proved that the peculiarity of medical practice on detecting the effects of torture consist of is the need to determine both statutory (severe pain and suffering) and "remote" (physical, psychosomatic and mental) effects of this crime. The reasonable arguments are put forward that the specificity of legal (investigative & judicial) practice in detection of severe pain and suffering (as effects of torture) is associated with the need to use a wide range of tools: scientific and legal methods used for determination of severe pain and suffering, medical reports on intensity of pain and suffering, medical documentation on fixation of "remote" effects of torture, reports on forensic, psychological and psychiatric examinations, testimonies and protocols of interrogation of the victim and witnesses, protocols of inspection of crime-committing scene, search, investigative experiment, inspection of material evidence, etc.

Keywords: severe pain, physical suffering, mental suffering, physical effects of the torture, psychosomatic effects of the torture, mental effects of the torture, torture syndrome, person's autonomous self-regulation program.

РЕЗЮМЕ

СИЛЬНАЯ БОЛЬ И СТРАДАНИЯ КАК ПОСЛЕДСТВИЯ ПЫТКИ: МЕДИКО-ПРАВОВАЯ ПРАКТИКА УСТАНОВЛЕНИЯ (ОБЗОР)

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Цель исследования - определить особенности и взаимосвязь между медицинской и юридической - следственно-судебной, практикой по установлению сильной боли и страданий как последствий пытки.

Исследование посвящено уголовно-правовой проблематике пыток. В ходе исследования использованы публикации центров реабилитации жертв пыток, профильные медицинские журналы, пособия для врачей, публикации Международной ассоциации и Украинской ассоциации по изучению боли, разъяснения ведущих специалистов Национального медицинского университета им. А.А. Богомольца (Киев, Украина), Львовского национального медицинского университета им. Данилы Галицкого (Львов, Украина), сообщения ООН и официальные разъяснения Управления Верховного комиссара ООН по правам человека, международные договора о запрете пыток, уголовные кодексы стран постсоветского пространства. Эмпирической базой исследования явились окончательные судебные решения по делам о применении пыток (n=41), вынесенные в период с 2014 по 2019 гг. Для достижения поставленной цели применены методы анализа, индукции, статистический и системный методы. По результатам исследования сделан вывод о том, что лишь медико-правовое установление сильной боли и страданий является залогом правильного решения вопроса о наличии или отсутствии последствий пытки. Отмечено, что ни медицинская, ни правоприменительная оценки не являются самодостаточными и требуют дополнения взаимными контекстами. Подчеркивается, что разработка методических рекомендаций по медико-правовому установлению сильной боли и страданий является одной из основных задач научного сообщества. Доказано, что особенностью медицинской практики по констатации последствий пытки является необходимость установления как нормативно определенных (сильная боль и страдания), так и «отдаленных» (физические, психосоматические и психические) последствий этого преступления.

Аргументировано, что специфика следственно-судебной практики по констатации сильной боли и страданий как последствий пытки связана с необходимостью использования широкого инструментария: научно-правовых методик по установлению сильной боли и страданий, медицинских заключений о силе боли и страданиях, медицинской документации по фиксации «отдаленных» последствий пытки, заключений судебно-медицинских и психолого-психиатрических экспертиз, показаний и протоколов допроса потерпевшего, свидетелей, протоколов осмотра места совершения преступления, обыска, проведения следственного эксперимента, осмотра вещественных доказательств.

რეზიუმე

ძლიერი ტკივილი და ტანჯვა, როგორც წამების შედეგები: დადგენის სამედიცინო-სამართლებრივი პრაქტიკა (მიმოხილვა)

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კვლევის მიზნას წარმოადგენდა ძლიერი ტკივილის და ტანჯვის, როგორც წამების შედეგების დადგენა სამედიცინო და იურიდიული (საგამოძიებო და სასამართლო) პრაქტიკებს შორის ურთიერთკავშირის აღმოჩენა და თავისებურებების გამოვლენა. კვლევა ეძღვნება სისხლის სამართლის პრობლემატიკას ძლიერი ტკივილის და ტანჯვის, როგორც წამების შედეგების, დადგენის დროს. კვლევაში გამოყენებულია წამების მსხვერპლთა სარეაბილიტაციო ცენტრების პუბლიკაციები, პროფილური სამედიცინო ჟურნალები, ექიმების დამხმარე სახელმძღვანელოები, ტკივილის შემსწავლელი საერთაშორისო ასოციაციისა და უკრაინული ასოციაციის პუბლიკაციები, ა.ბოგომოლცის სახ. ეროვნული სამედიცინო უნივერსიტეტის (კიევი,უკრაინა),დანილა გალიცკის სახ. ლვოვის ეროვნული სამედიცინო უნივერსიტეტის (ლვოვი, უკრაინა) წამყვანი სპეციალისტების განმარტებები, გაეროს შეტყობინებები, გაეროს ადამიანის უფლებათა უმაღლესი კომისრის სამმართველოს ოფიციალური განმარტებები, საერთაშორისო ხელშეკრულებები წამების აკრძალვის შესახებ, პოსტსაბჭოთა ქვეყნების სისხლის სამართლის კოდექსები. კვლევის ემპირიულ ბაზას წარმოადგენდა 2014-დან 2019 წწ. გამოტანილი 41 საბოლოო სასამართლო გადაწყვეტილება წამების გამოყენების საქმეებზე. დასახული მიზნის მისაღწევად გამოყენებულია ანალიზის, ინდუქციის, სტატისტიკური და სისტემური მეთოდები.

კვლევის შედეგების მიხედვით გამოტანილია დასკვნა იმის შესახებ, რომ მხოლოდ ძლიერი ტკივილისა და ტანჯვის სამედიცინო-სამართლებრივი დადგენა არის წამების შედეგების არსებობის ან არარსებობის შესახებ საკითხის სწორი გადაწყვეტის საწინდარი. აღნიშნულია, რომ არც სამედიცინო, არც სამართლებრივი შეფასება არ არის თვითკმარი და მოითხოვს ურთიერთ კონტექსტებით დამატებებს. ყურადღება გამახვილებულია, რომ ძლიერი ტკივილისა და ტანჯვის სამედიცინო-სამართლებრივი დადგენის მეთოდიკური რეკომენდაციების შემუშავება წარმოადგენს ერთ-ერთ ძირითად ამოცანას სამეცნიერო საზოგადოებისთვის.

დამტკიცებულია, რომ წამების შედეგების კონსტატაციის სამედიცინო პრაქტიკის თავისებურებას წარმოადგენს ამ დანაშაულის, როგორც ნორმატიულად განსაზღვრული (ძლიერი ტკივილი და ტანჯვა), ასევე „შორეული“ (ფიზიკური, ფსიქოსომატური და ფსიქიკური) შედეგების დადგენა. არგუმენტირებულია, რომ ძლიერი ტკივილისა და ტანჯვის, როგორც წამების შედეგების, კონსტატაციის საგამოძიებო და სასამართლო პრაქტიკის სპეციფიკა დაკავშირებულია ფართო სპექტრის ინსტრუმენტების გამოყენების საჭიროებასთან: ძლიერი ტკივილისა და ტანჯვის დადგენის სამეცნიერო-სამართლებრივი მეთოდიკა, სამედიცინო დასკვნები ტკივილისა და ტანჯვის სიძლიერის შესახებ, წამების „შორეული“ შედეგების ფიქსაციის სამედიცინო დოკუმენტაცია, სასამართლო-სამედიცინო და ფსიქოლოგიურ-ფსიქიატრიული ექსპერტიზების დასკვნები, დაზარალებულის, მოწმეების დაკითხვის ოქმები და ჩვენებები, ჩადენილი დანაშაულის ადგილის დათვალიერების, ჩხრეკის, საგამოძიებო ექსპერიმენტის ჩატარების, ნივთიერი მტკიცებულების დათვალიერების ოქმები.

DISTRIBUTION OF SEX HORMONES AND LYMPHOCYTES IN REPRODUCTIVE WOMAN WITH THYROID PAPILLARY CARCINOMA AND HASHIMOTO'S THYROIDITIS

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The incidence of papillary thyroid carcinoma is increasing around the world [11]. During last years the incidence of thyroid carcinoma has been increased to 16.3% per 100.000 women. It also represents the fifth most common cause of cancer mortality amongst women [1]. In Georgia, thyroid carcinoma moved from 20th place to 2nd place according to the data of national cancer registry. It is recorded in all age groups and unfortunately it represents the number one malignancy in puberty age girls [8]. The reason for increased incidence is unknown.

Papillary thyroid cancer is the most common subtype of thyroid carcinoma [5]. Its incidence is markedly higher in women compared to men and the female male ratio represents 4:1 [5]. The causative factor of papillary thyroid carcinoma is unknown. However, familial adenomatous polyposis [1], Gardner's disease [9] Cowden disease [7] and Carney complex I [2] spotty skin pigmentation, and endocrine overactivity (of the adrenal, the pituitary, and the testis are considered as pathogenic factors. One of the causes of the development of papillary thyroid carcinoma might be Hashimoto's thyroiditis. However, this association is not very well studied. Although, there are number of pathologies associated with papillary thyroid carcinoma, the most frequently the association with Hashimoto's thyroiditis has been seen [3]. Hashimoto's thyroiditis represents the autoimmune disease, which is mediated by organ-specific T lymphocytes. It is characterised with the presence of lymphoid infiltrate,

including germinal centre formation [6]. There are number of cell groups in Hashimoto's thyroiditis which are characterised with hypochromasia and papillary cancer like features. They express epithelial marker CK19 and mesothelial cell marker HMBE1 similar to papillary thyroid carcinoma [6]. However, the relationship between Hashimoto's thyroiditis and papillary thyroid cancer is still obscure. In addition, there is no information about the role of sex hormone receptor expression or the proliferative characteristics in Hashimoto's thyroiditis and papillary carcinoma.

Therefore, the aim of our study was to analyse the expression of steroid sex hormone receptors, including oestrogen receptor (ER) and progesterone receptors (PR), lymphocytic infiltration and thyreocyte/lymphocyte proliferation index in different types of papillary carcinoma, in Hashimoto's thyroiditis and in co-occurrence of Hashimoto's thyroiditis and papillary carcinoma.

Material and methods. Study included 115 formalin-fixed and paraffin-embedded tissue material from the teaching, research and diagnostic laboratory of Tbilisi State Medical University. Study material was divided into following groups: normal thyroid gland (15 cases), Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) (15 cases), classic papillary carcinoma (20 cases), follicular variant of papillary carcinoma (17 cases), cylindric-cell variant of papillary carcinoma (9 cases), Hashimoto's thyroiditis (25 cases) and the co-occurrence of Hashimoto's thyroiditis and papillary carcinoma (14 cases).

4μ FFPE tissue sections were deparaffinized in xylene, rehydrated by using serial dilutions of ethanol (96%, 80%, 70%) and heat mediated antigen retrieval has been performed. Ready to use antibodies against the following antigens were used: ER, PR, Ki67, CK19, CD56. Staining and visualization has been performed using Bond polymer refine detection system. The number of positive cells were counted in 20HPF and the percentage of marker positive cells were estimated. For ER and PR absence of staining considered as negative, 1-10% of positively stained nuclei was considered as weak expression and >10% positively stained nuclei was considered as strong expression. Thyreocyte and lymphocyte proliferation index was made based on the percentage of Ki67 positive thyreocytes and lymphocytes in 20HPF respectively. In addition thyreocyte/lymphocyte proliferation index was made as the ratio of Ki67 positive thyreocytes to Ki67 positive lymphocytes.

Non-germinal centre lymphocytes were counted in standard haematoxylin and eosin stained specimens as the percentage of lymphocytes covering total area of the lesion. The absence of lymphocytic infiltration considered as negative. Lymphocytic infiltration ≤10% considered as low and lymphocytic infiltration >10% considered as high.

Comparisons between groups were made using Kruskal-Wallis test. The Kruskal-Wallis test is a nonparametric (distribution free) test, and is used when the assumptions of one-way ANOVA are not met. The Kruskal-Wallis test can be used for both continuous and ordinal-level dependent variables. Correlations were assessed using Spearman's rank correlation. The Spearman's rank correlation is also used when data is non-parametrically distributed. P values <0.05 were considered as significant. All statistical tests were performed using SPSS software V19.00.

Results and discussion. 9/15 (60%) cases of normal thyroid gland were negative for ER and there was weak ER expression present in 6/15 (40%) cases of normal thyroid gland. Strong ER expression was not detected in normal thyroid gland. ER negativity was not detected in any of the NIFTP cases, weak ER expression was detected in 10/15 (70%) of the NIFTP cases and strong ER expression was detected in 5/15 (30%) of NIFTP cases. ER negativity was detected in 9/20 (45%) classic papillary carcinoma cases, weak ER expression was detected in 5/20 (25%) classic papillary carcinoma cases and strong ER expression was detected in 6/20 (30%) classic papillary carcinoma cases. In follicular variant of papillary carcinoma ER negativity was detected in 7/17 (41.2%) cases, weak ER expression was detected in 3/17 (17.6%) cases and strong ER expression was detected in 7/17 (41.2%) cases. In cylindric-cell variant of papillary carcinoma 3/9 (33.3%) cases were negative for ER expression, 1/9 (11.1%) case revealed weak ER expression and 5/9 (55.6%) cases revealed strong ER expression. In Hashimoto's thyroiditis 12/25 (48%) cases were negative for ER and 13/25 cases showed weak ER (52%) expression. In cases with the co-occurrence of Hashimoto's thyroiditis and papillary carcinoma, ER negativity was not detected when evaluated both lesions together, weak expression was detected in 5/14 (35%) cases and strong expression was detected in 9/14 (65%) cases. When evaluated separately ER negativity was detected in 6/14 (42.9%) cases of Hashimoto's thyroiditis component and 5/14 (35.7%) cases of Hashimoto's thyroiditis component revealed weak ER positivity and 3/14 (21.4%) Hashimoto's thyroiditis component revealed strong ER positivity. In papillary carcinoma component weak expression was detected in 5/14 (35%) cases and strong expression was detected in 9/14 (65%) cases.

13/15 (86.7%) cases of normal thyroid gland were negative for PR and there was weak ER expression present in 2/15 (13.3%) cases of normal thyroid gland. Strong PR expression was not detected in normal thyroid gland. PR negativity was not detected in any of the NIFTP cases, weak PR expression was detected in 9/15 (60%) of the NIFTP cases and strong PR expression was detected in 6/15 (40%) of NIFTP cases. PR negativity was detected in 5/20 (25%) classic papillary carcinoma cases, weak PR expression was detected in 6/20 (30%) classic papillary carcinoma cases and strong PR expression was detected in 9/20 (45%) classic papillary carcinoma cases. In follicular variant of papillary carcinoma PR negativity was detected in 4/17 (23.5%) cases, weak PR expression was detected in 4/17 (23.5%) cases and strong PR expression was detected in 9/17 (52.9%) cases. In cylindric-cell variant of papillary carcinoma 2/9 (22.2%) cases were negative for PR expression, 1/9 (11.1%) case revealed weak PR expression and 6/9 (66.7%) cases revealed strong ER expression. In Hashimoto's thyroiditis 20/25 (80%) cases were negative for PR and 5/25 (20%) cases showed weak PR expression. In cases with the co-occurrence of Hashimoto's thyroiditis and papillary carcinoma, PR negativity was detected in 4/14 (28.6%) cases when evaluated both lesions together, weak expression was detected in 3/14 (21.4%) cases and strong expression was detected in 7/14 (50%) cases. When evaluated separately PR negativity was detected in 7/14 (50%) cases of Hashimoto's thyroiditis component, and 3/14 (21.4%) cases of Hashimoto's thyroiditis component revealed weak PR positivity and 4/14 (28.6%) Hashimoto's thyroiditis component revealed strong PR positivity. In papillary carcinoma component weak negative expression was detected in 4/14 (28.6%) cases, weak expression was detected in 3/14(21.4%) cases and strong expression was detected in 7/14 (50%) cases.

Table 1. Distribution of ER and PR percentage values in groups. Green cells represent highest percentage of cases and red cells represent the lowest percentage of cases, yellow, orange and light green cells represent the moderate percentage of cases

	ER			PR		
	Negative	**Weak**	**Strong**	**Negative**	**Weak**	**Strong**
Normal Thyroid Gland	60.0%	40.0%	0.0%	86.7%	13.3%	0.0%
NIFTP	0.0%	70.0%	30.0%	0.0%	60.0%	40.0%
Classic Papillary Carcinoma	45.0%	25.0%	30.0%	25.0%	30.0%	45.0%
Follicular Variant of Papillary Carcinoma	41.2%	17.6%	41.2%	23.5%	23.5%	52.9%
Cylindric-cell Variant of Papillary Carcinoma	33.3%	11.1%	55.6%	22.2%	11.1%	66.7%
Hashimoto's Thyroiditis	48.0%	52.0%	0.0%	80.0%	20.0%	0.0%
Hashimoto's Thyroiditis + Papillary Carcinoma	0.0%	35.0%	65.0%	28.6%	21.4%	50.0%

Table 2. The distribution of lymphocytic infiltration in groups

	Lymphocyte count			
	<10% N/%		**≥10% N/%**	
Normal Thyroid Gland	15	100.0%	0	0.0%
NIFTP	8	53.3%	7	46.7%
Classic Papillary Carcinoma	12	60.0%	8	40.0%
Follicular Variant of Papillary Carcinoma	11	64.7%	6	35.3%
Cylindric-cell Variant of Papillary Carcinoma	7	77.8%	2	22.2%
Hashimoto's Thyroiditis	0	0.0%	25	100.0%
Hashimoto's Thyroiditis + Papillary Carcinoma	0	0.0%	14	100.0%

The study of lymphocyte distribution showed following results: in normal thyroid gland all cases were characterised with <10% lymphocytes. In NIFTP 8/15 (53.3%) of cases were characterised with <10% lymphocytes and 7/15 (46.7%) cases were characterised with ≥10% lymphocytes. In classic papillary carcinoma 12/20 (60%) cases were characterised with the presence of <10% lymphocytes and 8/20 (40%) of cases were characterised with the presence of ≥10% lymphocytes. In follicular variant of papillary carcinoma 11/17 (64.7%) of cases were characterised with <10% lymphocytic infiltrate and 6/17 (35.3%) of cases were characterised with ≥10% lymphocytic infiltrate. In cylindric-cell variant of papillary carcinoma 7/9 (77.8%) cases showed <10% lymphocytic infiltrate and 2/9 (22.2%) cases showed ≥10% lymphocytic infiltrate. When examined together none of the cases of Hashimoto's thyroiditis or combined Hashimoto's thyroiditis with papillary carcinoma showed <10% lymphocytic infiltrate. When examined as separate components, Hashimoto's thyroiditis component does not show <10% lymphocytic infiltrate in any of the cases. In papillary carcinoma component 9/14 (64.3%) cases were characterised with <10% lymphocytic infiltrate and 6/14(35.7%) of cases were characterised with ≥10% lymphocytic infiltrate.

The study of thyreocyte Ki67 proliferation index distribution in groups showed the following results: in normal thyroid gland Ki67 activity was not detected. In NIFTP average Ki67 proliferation index was 2±0.3; In classic papillary carcinoma average Ki67 proliferation index was 3±0.7; In Follicular variant of papillary carcinoma the average Ki67 proliferation index was 4±1.1; In Cylindric-cell variant of papillary carcinoma the average Ki67 proliferation index was 5±1.8; In epithelial component of Hashimoto's thyroiditis the average Ki67 proliferation index was 7±2.4 and in combined Hashimoto's thyroiditis and papillary carcinoma cases the average Ki67 proliferation index was 10±3.1 when examined both components together. When each component examined separately the average Ki67 proliferation index in Hashimoto's thyroiditis component was 8±3.2 and in papillary carcinoma component was 6±2.5.

The study of lymphocyte Ki67 proliferation index distribution in groups showed the following results: in normal thyroid gland Ki67 activity in lymphocytes was not detected. In NIFTP average lymphocyte Ki67 proliferation index was 3 ± 0.9; In classic papillary carcinoma average lymphocyte Ki67 proliferation index was 2.5±0.6; In Follicular variant of papillary carcinoma the average lymphocyte Ki67 proliferation index was 2±0.4; In Cylindric-cell variant of papillary carcinoma the average lymphocyte Ki67 proliferation index was 1.7±0.2; In epithelial component of Hashimoto's thyroiditis the average lymphocyte Ki67 proliferation index was 4.5±1.7 and in combined Hashimoto's thyroiditis and papillary carcinoma cases the average lymphocyte Ki67 proliferation index was 4±1.3 when examined both components together. When each component examined separately the average lymphocyte Ki67 proliferation index in Hashimoto's thyroiditis component was 4±2.2 and in papillary carcinoma component was 2±0.8.

The study of thyreocite/lymphocyte proliferation index (Ki67 thyr/lymph IND) in groups showed following results: in normal thyroid gland the Ki67 thyr/lymph IND was 0.00; In NIFTP the Ki67 thyr/lymph IND was 0.67±0.3; In classic papillary carcinoma the average Ki67 thyr/lymph IND was 1.2±1.1; In follicular variant of papillary carcinoma the average Ki67 thyr/lymph IND was 2±1.75; In Cylindric-cell variant of papillary carcinoma the average Ki67 thyr/lymph IND was 2.94±1.98; In Hashimoto's thyroiditis the average Ki67 thyr/lymph IND was 1.56±0.94; In combined Hashimoto's thyroiditis and papillary carcinoma the average thyr/lymph IND was 2.50±1.7 when examined together. When examined separately, the average thyr/lymph IND was 2±1.9 in Hashimoto's thyroiditis component and 3±2.1 in papillary carcinoma component.

Table 3. The distribution of Ki67 thyreocyte index, Ki67 lymphocyte index and Ki67 thyreocyte/lymphocyte index in groups

	Ki67/Thyr.	Ki67/Lymph.	Ki67 Thyr/Lymph IND
Normal Thyroid Gland	0.00%	0.00%	0.00
NIFTP	2%±0.3	3%±0.9	0.67±0.3
Classic Papillary Carcinoma	3% ± 0.7	2.5%±0.6	1.20±1.1
Follicular Variant of Papillary Carcinoma	4%±1.1	2%±0.4	2.00±1.75
Cylindric-cell Variant of Papillary Carcinoma	5%±1.8	1.7%±0.2	2.94±1.98
Hashimoto's Thyroiditis	7%±2.4	4.5%±1.7	1.56±0.94
Hashimoto's Thyroiditis + Papillary Carcinoma	10%±3.1	4%±1.3	2.50±1.7

Table 4. The distribution of CK19 and CD56 staining in groups.

	CK19		CD56	
	Negative	Positive	Negative	Positive
Normal Thyroid Gland	100.00%	0.00%	0.00%	100.00%
NIFTP	60.00%	40.00%	53.30%	46.70%
Classic Papillary Carcinoma	0.00%	100.00%	100.00%	0.00%
Follicular Variant of Papillary Carcinoma	29.50%	70.50%	100.00%	0.00%
Cylindric-cell Variant of Papillary Carcinoma	44.50%	55.50%	100.00%	0.00%
Hashimoto's Thyroiditis	76.00%	24.00%	24.00%	74.00%
Hashimoto's Thyroiditis + Papillary Carcinoma	42.90%	57.10%	57.10%	42.90%

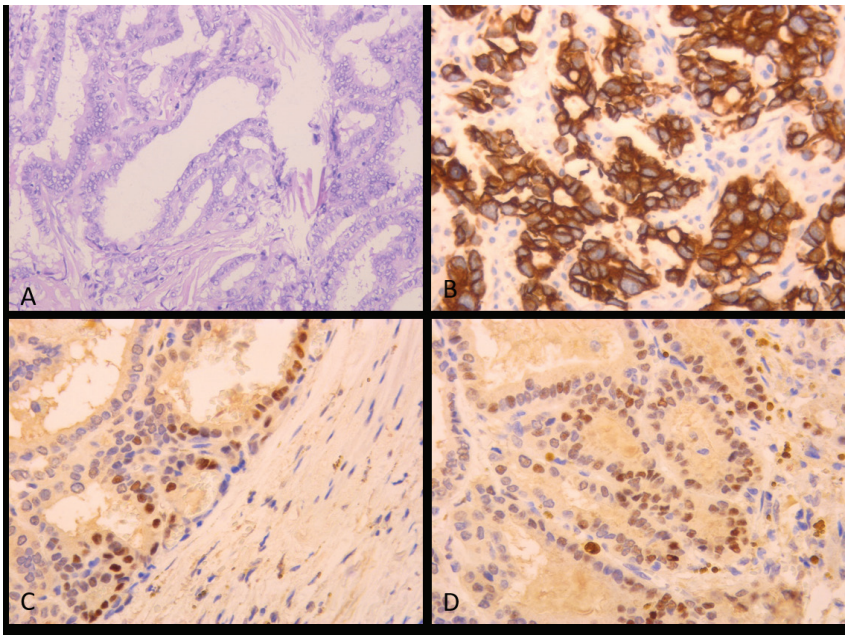


Fig. 1. A. Papillary thyroid carcinoma, H&E, x100, B. CK19 expression, IHC, x200, C. ER expression, IHC, x200 and D. PR expression, IHC, x200

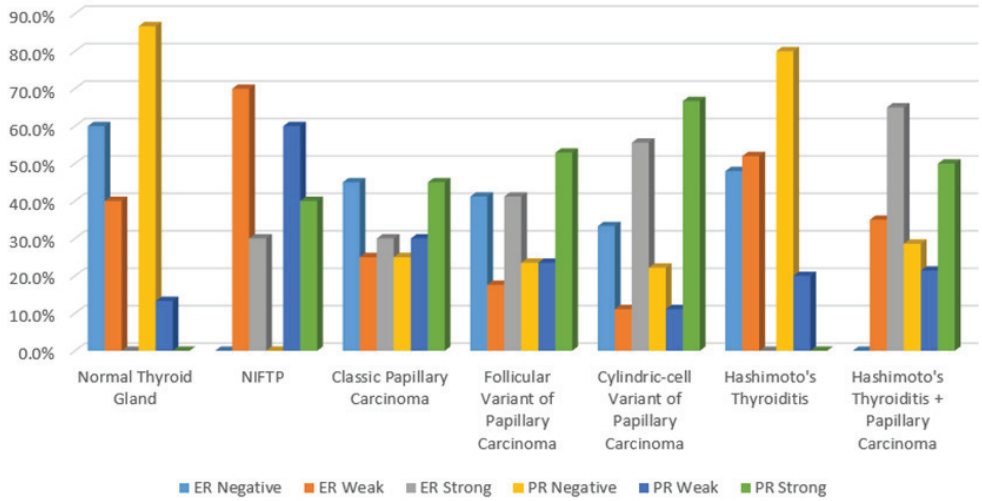
The study of the distribution of CK19 in groups showed following results: in normal thyroid gland all 15/15 (100%) cases were negative for CK19 expression. In NIFTP 9/15 (60%) cases were negative for CK19 expression and 6/15 (40%) of cases were positive for CK19 expression. In classic papillary carcinoma 0/20 (0%) were negative and 20/20 (100%) of cases were positive for CK19 expression. In follicular variant of papillary carcinoma 5/17 (29.5%) cases were negative and 12/17 (70.5%) cases were positive for CK19 expression. In cylindric-cell variant of papillary carcinoma 4/9 (44.5%) cases were negative and 5/9 (55.5%) cases were positive for CK19 expression. In Hashimoto's thyroiditis 19/25 (76%) was negative for CK19 expression and 6/25 (24%) was positive for CK19 expression. In combined Hashimoto's thyroiditis and papillary carcinoma 6/14 (42.9%) of cases were negative for CK19 expression and 8/14 (57.1%) of cases were positive for CK19 expression when evaluated together.

The study of the distribution of CD56 in groups showed the following results: in normal thyroid gland all 15/15 (100%) cases were positive for CD56. In NIFTP 8/15 (53.3%) cases were negative and 7/15 (46.7%) cases were positive for CD56. In classic papillary carcinoma 20/20 (100%) cases were negative for CD56. Similarly, in follicular variant of papillary carcinoma and cylindric-cell variant of papillary carcinoma all 17/17 (100%)

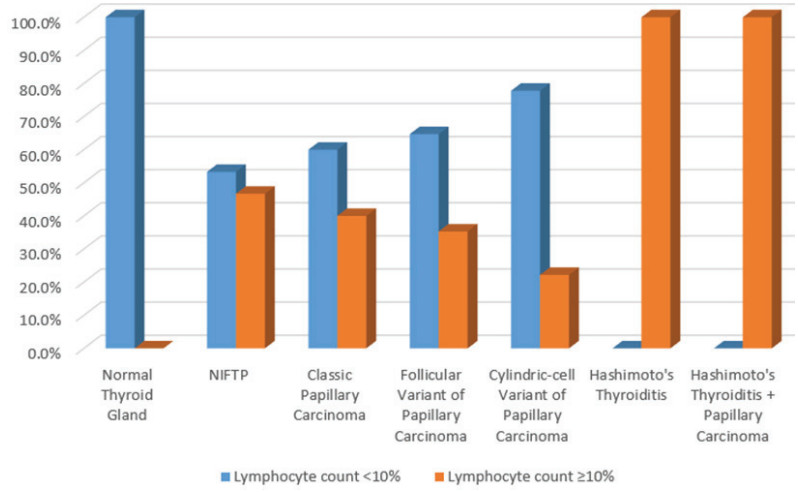
and 9/9 (100%) of cases were negative for CD56 respectively. In Hashimoto's thyroiditis 6/25 (24%) of cases were negative and 19/25 (74%) of cases were positive for CD56 staining. In combined cases of Hashimoto's thyroiditis and papillary carcinoma 8/14 (57%) cases were negative and 6/14 (43%) of cases were positive for CD56 staining.

The analysis of results showed that the lowest ER expression is seen in normal thyroid gland and the highest ER expression is seen in papillary carcinoma component of combined Hashimoto's thyroiditis and papillary carcinoma. Also, amongst three types of papillary carcinoma, including: classic, follicular and cylindric-cell variants, the expression of ER is gradually increased and reaches it's maximum in cylindric-cell variant, which is considered as the most aggressive type of thyroid papillary carcinoma amongst others. The lowest rates of PR expression are seen in normal thyroid gland and in Hashimoto's thyroiditis. Similarly, to ER the PR expression is also gradually increased amongst classic, follicular and cylindric-cell variant of papillary carcinoma and reaches it's maximum in cylindric-cell variant.

The comparative analysis of lymphocyte counts in groups showed that the highest amount of lymphocytic infiltrate was present in Hashimoto's thyroiditis and the lowest amount was present in normal thyroid gland. In NIFTP there was an average lymphocyte count present. Interestingly, lymphocyte count was markedly decreased between classic, follicular and cylincric-cell variant of papillary carcinoma, showing the lowest amount of lymphocytic infiltration in cylindric-cell variant of papillary carcinoma.



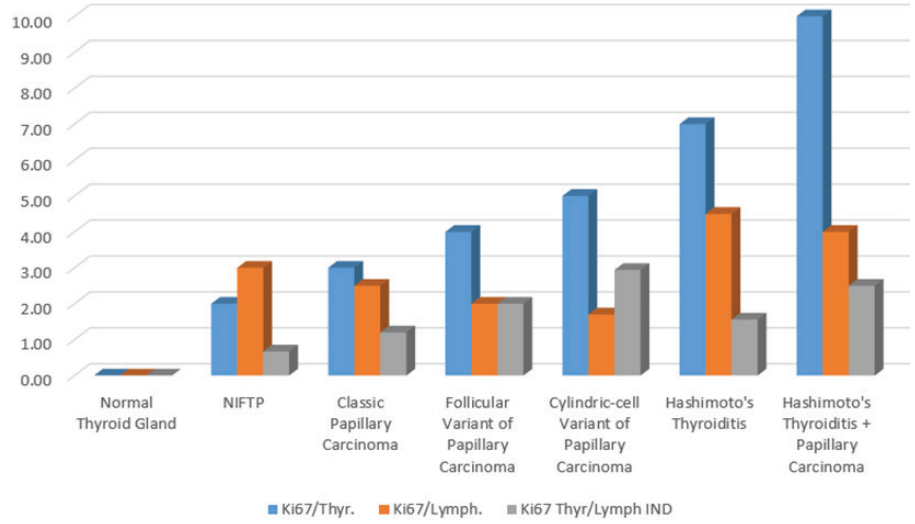
Graph 1. The distribution of ER and PR in groups



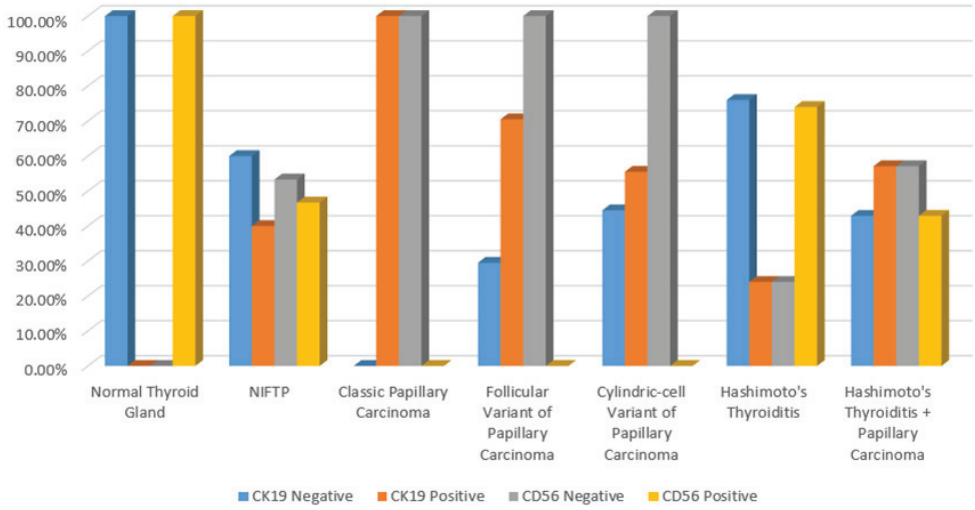
Graph 2. The distribution of lymphocyte count in groups

The comparative analysis of Ki67 thyreocyte proliferation index showed that it is gradually increased from NIFTP to papillary carcinoma and its variants. The highest Ki67 thyreocyte proliferation index was seen in Hashimoto's thyroiditis and in combined cases of Hashimoto's thyroiditis and papillary carcinoma. The comparative analysis of lymphocyte Ki67 proliferation index showed that the highest lymphocyte Ki67 proliferation index is seen in Hashimoto's thyroiditis, followed by co-occurrence of Hashimoto's thyroiditis and papillary carcinoma cases. In cases of classic papillary carcinoma, folicullar and cylindric-cell variants it is gradually decreased, with the minimal lymphocyte KI67 proliferation index in cylindric-cell variant of papillary carcinoma.

The comparative analysis of Ki67 thyreocyte/lymphocyte proliferation index (Ki67 Thyr/lymph IND), showed that it is gradually increased from NIFTP, to papillary carcinoma and it variants, showing the maximum degree in cylincric-cell variant of papillary carcinoma. In Hashimoto's thyroiditis Ki67 Thyr/lymph IND is relatively low compared to combined cases of Hashimoto's thyroiditis and papillary carcinoma.



Graph 3. The distribution of Ki67 thyreocyte, Ki67 lymphocyte and Ki67 Thyreocyte/lymphocyte index (Ki67 Thyr/lymph IND) in groups



Graph 4. The distribution of CK19 and CD56 in groups

The analysis of CK19 and CD56 showed that CK19 is significantly and negatively correlates with the expression of CD56 in all groups ($p<0.001$). Meaning that in cases with high CK19 expression CD56 shows lowest expression and in cases of low CK19 expression or negativity CD56 shows highest expression.

Previously Rajoria et al. evaluated thyroid cells for the presence of ER and also cell response to estrogen, showing the important role of estrogen in cell division, migration and invasion [10]. Kansakar et al. found that the expression of ER and PR in thyroid neoplasms was higher in comparison with normal thyroid tissue and our study results are in line with the findings of Kansakar et al., we have also found the marked increase of ER and PR in carcinoma cases compared to normal thyroid tissue [4]. To the best of our knowledge we are first who examined ER and PR status in co-occurrence of Hashimoto's thyroiditis and papillary carcinoma. Also, to the best of our knowledge we are first who examined thyreocite/lymphocyte proliferation index.

Conclusions. The expression level of ER and PR is even higher in cases where Hashimoto's thyroiditis and papillary carcinoma co-occur. Therefore, we can conclude that Hashimoto's thyroiditis may play an important role in the development of papillary thyroid carcinoma.

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SUMMARY

DISTRIBUTION OF SEX HORMONES AND LYMPHOCYTES IN REPRODUCTIVE WOMAN WITH THYROID PAPILLARY CARCINOMA AND HASHIMOTO'S THYROIDITIS

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The incidence of papillary thyroid carcinoma is characterised with increasing tendency, with unknown reasons. Frequently the co-occurrence of papillary thyroid carcinoma and Hashimoto's thyroiditis has been observed.

The aim of our study was to analyse the expression of hormone receptors, lymphocytic infiltration and thyreocyte/lymphocyte proliferation index in thyroid papillary carcinoma and in Hashimoto's thyroiditis.

Study included 115 formalin-fixed and paraffin-embedded tissue material from the teaching, research and diagnostic laboratory of Tbilisi State Medical University. Study material was divided into following groups: normal thyroid gland (n=15), Non-invasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features (NIFTP) (n=15), classic papillary carcinoma (CPC)(n=20), follicular variant of papillary carcinoma (FPC) (n=17), cylindric-cell variant of papillary carcinoma (CCPC)(n=9), Hashimoto's thyroiditis (HT) (n=25) and the co-occurrence of Hashimoto's thyroiditis and papillary carcinoma (HTPC) (n=14). Standard immunohistochemistry was used to detect ER, PR, Ki67, CK19, CD56. In addition, lymphocytic infiltration was evaluated in H&E stained specimens. Study results showed that ER and PR expression is higher in FPC, CCPC and HTPC compared to CPC ($p<0.001$), whilst lymphocytic infiltrate is lower in FPC and CCPC compared to CPC ($p<0.05$). In addition, ER and PR expression is higher in HTPC compared to HT only ($p<0.001$). The thyreocyte/lymphocyte proliferation index is increased in FPC and CCPC compared to CPC and it is also higher in HTPC compared to only HT and CPC ($p<0.05$). The expression of sex steroid hormones plays an important role in the pathogenesis of papillary thyroid carcinoma. The expression level of ER and PR is even higher in cases where Hashimoto's thyroiditis and papillary carcinoma co-occur. Therefore, we can conclude that Hashimoto's thyroiditis may play an important role in the development of papillary thyroid carcinoma.

Keywords: papillary-papillary thyroid carcinoma, Hashimotos's thyroiditis, sex hormones.

РЕЗЮМЕ

ОСОБЕННОСТИ РАСПРЕДЕЛЕНИЯ ПОЛОВЫХ ГОРМОНОВ И ЛИМФОЦИТАРНОЙ ИНФИЛЬТРАЦИИ ПРИ СОСУЩЕСТВОВАНИИ ТИРЕОИДИТА ХАСИМОТО И ПАПИЛЛЯРНОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА

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Инцидентность папиллярной карциномы щитовидной железы характеризуется тенденцией к увеличению. Часто отмечается сосуществование папиллярного рака щитовидной железы и тиреоидита Хасимото. Целью исследования явилось изучение гормональных рецепторов, лимфоцитарной инфильтрации и тиреоцит-лимфоцитарного пролиферативного индекса при папиллярной карциноме щитовидной железы и тиреоидите Хасимото.

Исследование проводилось в "Учебной, научной и диагностической лаборатории Тбилисского государственного медицинского университета" на 115 тканевых образцах, фиксированных в формалине и залитых в парафин. Материал разделён на следующие группы: нормальная ткань щитовидной железы (n=15), неинвазивная неоплазия щитовидной железы с ядрами, похожими на папиллярный рак (NIFTP, n=15), классическая папиллярная карцинома (CPC, n=20), фолликулярный вариант папиллярной карциномы (FPC, n=17), цилиндр-клеточный вариант папиллярной карциномы (CCPC, n=9), тиреоидит Хасимото (HT, n=25) и случаи сосуществования тиреоидита Хасимото и папиллярного рака щитовидной железы (HTPC, n=14). Стандартным иммуногистохимическим методом изучены следующие молекулярные маркеры: ER, PR, Ki67, CK19, CD56. В препаратах, окрашенных стандартным гематоксилином и эозином, оценена лимфоцитарная инфильтрация. Результаты исследования показали, что экспрессия ER и PR высокая в FPC, CCPC и HTPC в сравнении с CPC ($p<0,001$), а лимфоцитарная инфильтрация низкая в FPC, CCPC и HTPC в сравнении с CPC ($p<0.05$). Экспрессия ER и PR высокая при HTPC в сравнении с HT и CPC ($p<0,05$). Следует заключить, что повышенная экспрессия гормональных рецепторов играет значимую роль в патогенезе папиллярной карциномы и тиреоидита Хасимото и представляет один из главных риск факторов развития папиллярной карциномы.

რეზიუმე

სასქესო ჰორმონების და ლიმფოციტური ინფილტრაციის განაწილების თავისებურებები რეპროდუქციული ასაკის ქალებში ჰასიმოტოს თირეოიდიტით და ფარისებრი ჯირკვლის პაპილური კარცინომით

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ფარისებრი ჯირკვლის პაპილური კარცინომის ინციდენტობა ხასიათდება მზარდი ტენდენციით. ხშირ

შემთხვევაში აღინიშნება ფარისებრი ჯირკვლის პაპილური კარცინომისა და ჰასიმოტოს თირეოიდიტის თანაარსებობა.

კვლევის მიზანს წარმოაგენდა ჰორმონული რეცეპტორების, ლიმფოციტური ინფილტრაციის და თირეოციტ-ლიმფოციტური პროლიფერაციის ინდექსის შესწავლა ფარისებრი ჯირკვლის პაპილურ კარცინომასა და ჰასიმოტოს თირეოიდიტში.

კვლევა მოიცავდა 115 ფორმალინში დაფიქსირებულ და პარაფინში ჩაყალიბებულ ქსოვილოვან მასალას თსსუ სასწავლო, სამეცნიერო და დიაგნოსტიკური ლაბორატორიიდან. საკვლევი მასალა დაყოფილი იყო შემდეგ ჯგუფებად: ფარისებრი ჯირკვლის ნორმალური ქსოვილი (n=15), ფარისებრი ჯირკვლის არაინვაზიური ნეოპლაზია პაპილურის მსგავსი ბირთვებით (NIFTP - n=15), კლასიკური პაპილური კარცინომა (CPC - n=20), პაპილური კარცინომის ფოლიკულური ვარიანტი (FPC - n=17), პაპილური კარცინომის ცილინდრულ უჯრედული ვარიანტი (CCPC - n=9), ჰასიმოტოს თირეოიდიტი (HT - n=25) და შემთხვევები ჰასიმოტოს თირეოიდიტის და პაპილური კარცინომის თანაარსებობით (HTPC - n=14). სტანდარტული იმუნოჰისტოქიმიური მეთოდით გამოვლენილია ER, PR, Ki67, CK19, CD56. ჰემატოქსილინით და ეოზინით შეღებილ ანათლებში შეფასდა ლიმფოციტური ინფილტრაცია.

კვლევის შედეგებმა აჩვენა, რომ ER და PR ექსპრესია მაღალია FPC, CCPC და HTPC-ში შედარებით CPC-თან ($p<0,001$), ხოლო ლიმფოციტური ინფილტრაცია დაბალია FPC, CCPC და HTPC-ში შედარებით CPC-თან ($p<0,05$). ER და PR ექსპრესია მაღალია HTPC-ში შედარებით HT-თან და CPC-თან ($p<0,05$). კვლევის შედეგად გამოტანილია დასკვნა, რომ ჰორმონული რეცეპტორების მომატებული ექსპრესია მნიშვნელოვან როლს თამაშობს პაპილური კარცინომის პათოგენეზში და ჰაშიმოტოს თირეოიდიტი შესაძლებელია წარმოადგენდეს პაპილური კარცინომის განვითარების ერთ-ერთ მთავარ რისკ-ფაქტორს.

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