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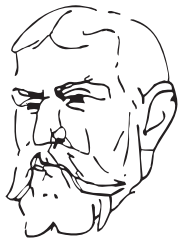

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ORIGINAL ARTICLE

PSYCHOLOGICAL FEATURES OF MODERN ELDERLY PEOPLE'S ACTIVE LIFE POSITION

DOI: 10.36740/WLek202202101

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ABSTRACT

The aim: The research is devoted to the analysis of theoretical and empirical determinants of formation of structural components of an active life position of modern elderly people.

Materials and methods: Psychodiagnostic techniques were selected as tools for data collection. Experiment participants were people aged 65-72 years old (total number – 78 people). Data processing was done by means of the computer program SPSS 21.0.

Results: The psychological features of the formation of elderly people's active life position were determined by the fact that more than 50% of respondents had an average level of cognitive development, more than 60% demonstrated a low level of emotional-volitional component and more than 50% were at medium level of motivational-behavioural component. Most respondents' high level of cognitive component development does not correlate with a high level of emotional-volitional component development. The leading role in the formation of elderly people's active life position is played by the motivational-behavioural component.

Conclusions: Based on the theoretical and empirical research of the issue of formation of elderly people's active life position, three structural components of the phenomenon under study were identified: cognitive, emotional-volitional and motivational-behavioural. The results of the experiment suggest that most respondents had medium-low levels of active life position. The main determinant of the elderly people's reduced vitality is their low level of emotional-volitional component development. The research outcomes allowed us to track the dependence of the level of active life position on the motivational-behavioral component.

KEY WORDS: active life position, elderly people, cognitive component, emotional-volitional component, motivational-behavioural component

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INTRODUCTION

The era of computerization, digitalization, technologization, flexibilization is rapidly changing the modern world. Due to various circumstances elderly people are not always able to master information and communication technology. It causes their insecurity and uncertainty, which negatively affects the perception of reality and reduces vitality, facilitates the phenomenon of rumination, stimulates a kind of protest against innovation. As a result, a number of elderly people are characterized by a rejection of personal significance, regret for unrealized life projects, denial and rejection of the fact of transition to a new age category. The process of adaptation to new conditions of functioning and life creation is being complicated. That is why one of the priorities of social policy in Ukraine is the development of effective measures, aimed at the development of elderly people's positive personal attitude to a new social role. Today, there appear new challenges, related to the situation of COVID-19, forced quarantine measures, which lead to the emergence of elderly people's emotional depression, it also slows down their own rhythm of activity. So, the issue of the formation of elderly people's active life position becomes relevant. It is necessary to identify the psychological features of the formation of this phenomenon, determine the degree of its development and research its leading structural components. Numerous modern studies show that the elderly population is characterized by significant diversity. The policy of states should be aimed at creating conditions for people to achieve a positive trajectory of aging, to destroy obstacles that limit the continuation of social participation and contribution of older people, and to use innovative methods of work (World health organization) [1].

THE AIM

The subject of research is elderly people's active life position. Scope of research: psychological features of elderly people's active life position. The aim of research is a theoretical and empirical study of the formation of structural

components of modern elderly people's active life position. ***Objectives of research***: 1) to identify and substantiate levels and indicators of the formation of elderly people's active life position; 2) to record the findings, analyze them and draw conclusions on the psychological features of the development of elderly people's active life position and the degree of its structural components formation.

MATERIALS AND METHODS

Theoretical framework of methodology. According to the classification of the World Health Organization, in our research the elderly people category includes individuals aged 60-75 years old. In order to identify the main problems and the most acceptable ways to organize a work with the elderly people, it is necessary to characterize this age group's socio-psychological features. Most authors (Bobrovska, Bowling, Stephens, Breheny, & Mansvelt) believe that chronological age, which often serves as a criterion for an old age, does not directly affect a person's physical functioning and mental abilities. It depends on a number of factors: lifestyle and standard of living; work and rest conditions; family situation; personal attitude to age changes (Krasnova & Liders) [2, 3, 4, 5]. It happens quite often that psychological "portrait" of an elderly person has negative characteristics. In the intellectual sphere there is a decrease in sensitivity, weakening of the level of short-term and strengthening of long-term memory, slowing of cognitive operations, etc. In the emotional-volitional sphere there is a decrease in determination and purposefulness and an increase in self-doubt. There appear strong uncontrolled emotional reactions, dissatisfaction with themselves and others, fear for their own health and tomorrow, etc. [6]. In elderly people's motivational-behavioural sphere there is an intensification of such traits as pettiness, stinginess, pedantry, irritability, conservatism, lack of initiative, adaptive rigidity to changing or unpredictable situations, helplessness, etc. All these changes are individual, but in case of an active life, some people may not experience them at all, or these changes may be minimal and situational. Cognitive abilities and interests often depend on a person's inner mood, desire for self-development, social well-being.

The results of theoretical analysis allowed us to identify *the components* of the elderly people's active life position, in particular:

1) cognitive component – the emergence and degree of stability of elderly people's cognitive needs, their intellectual abilities, ability to analyze and realistically evaluate their own actions and deeds;

2) emotional-volitional component – the experience of identity, self-esteem of their individual abilities, characteristics and positive self-attitude;

3) motivational-behavioural component – the external side of personal activity, elderly people's ability to be guided by their own goals, motives, attitudes, principles, beliefs, ability to resist the influence of the external environment, predict their own behavioural actions, and function as a full human being.

The degree of formation of elderly people's active life position was identified in accordance with the following ***levels and indicators***:

• *high level* – a stable cognitive interest that arises regardless of external circumstances and requirements; awareness and acceptance of elderly people's own positive and negative sides; striving for independence, activity, achieving the desired, overcoming difficulties in achieving their own goals, which leads to a high life product. These people are flexible in their adaption to changing environmental conditions.

• *medium level* – cognitive interest arises situationally, personal interests are unstable, criticality is manifested selectively, empathy – situationally; activity requires an external stimulus and depends on the positive assessment of others; while solving problematic life situations these people are guided by the motivation to avoid failure and choose trivial ways. They experience difficulties to accept the changes, taking place in the environment, it is difficult for them to adapt to these changes.

• *low level* – insignificant manifestations of cognitive interest, stereotyped thinking, inability to generate ideas, dependence on evaluative judgments of others, criticism and empathy are at a low level, lack of ability to independently plan one's own actions, activity is manifested only in the initial stages of algorithmic actions. They are unable to adapt to the changing conditions of social life.

Study sample are described. The selection of participants of the empirical research on elderly people's active life position was carried out with the participation of members of public organizations, caring for the elderly people, and volunteers. Demographic information about participants was collected by self-report and included data on age, gender, years of study, marital status. The group of respondents included only those who did not have any significant psychiatric or physical illnesses, who received more than 26 points on the assessment of cognitive function according to the MoCA test.

Experiment participants were people aged 65-72 years old (total number – 78 people), marital status – 2/3 of respondents were married, the rest – single, divorced and widowed. The participation of respondents was voluntary. They did not receive any financial donations, but got free psychological counselling from practicing psychologists. The data collection was carried out by trained volunteers, students of the Faculty of Psychology of National Pedagogical University M.P. Drahomanov, Institute of Human of Borys Grinchenko Kyiv University and Bogdan Khmelnytsky Melitopol State Pedagogical University in Ukraine.

According to the pilot research results, two groups of respondents were selected for the empirical stage. 43 respondents maintained an active life position and represented various spheres of professional employment and 35 respondents were retired and voluntarily did not join any sphere of professional activity and were not involved in the process of active social interpersonal interaction. Thus, in our research we managed to involve into the program of empirical study the respondents from different

socio-economic layers, different nature of social activity and emotional attitude to the events. Two categories of elderly people were selected in order to identify differences or similarities in the formation of structural components of their active life position. Empirical data were collected during individual conversations, group workshops on the formation of elderly people's active life position. The research was conducted during October 2019 - March 2020.

Research tools. In order to achieve the research objectives, theoretical and empirical methods, standardization, systematization and generalization of the obtained theoretical and empirical data were used. Psychodiagnostic techniques were selected as tools for data collection. The selection of psychodiagnostic techniques was carried out in accordance with the outlined components of the formation of elderly people's active life position. They allowed us to identify the degree of formation of structural components of elderly people's active life position:

1 – cognitive component – technique of personal self-conception research by S. Panteleev (http://www.miu.by/kaf_new/mpp/082.pdf, http://testoteka.narod.ru/lichn/1/41.html);

2 – emotional-volitional – a technique of diagnosis of personality's social isolation level by D. Russell and M. Ferguson (https://psylist.net/praktikum/adusil.htm); self-actualization test (SAT) by E. Shostrom (scales "Competence in time", "Self-acceptance", "Expectation of support or self reliance") (https://hrliga.com/index.php?-module=profession&op=view&id=1063) ;

3 – motivational-behavioural – a technique of a subjective control level research by J. Rotter (adapted by E. Bazhin and others) (scales "General internality", "Internality in relation to health and disease") (http://personal.in.ua/article.php?ida=186).

Data collection procedure and methods of analysis. The technique of personal self-conception research by S. Panteleev allowed us to reveal the degree of impact of one's own "Me" or external circumstances on the formation of elderly people's active life position. This indicator is a part of the cognitive component of elderly people's active life position. The technique of the diagnosis of personality's social isolation level by D. Russell and M. Ferguson was aimed at the identification of the degree of individual's subjective feeling of loneliness, peculiarities of his or her interaction with others, interpersonal skills development and expression of their own feelings. Technique SAT (self-actualization test by E. Shostrom, adapted by Yu. Alioshin and others) was used to identify the emotional-volitional component of elderly people's active life position.

The technique of subjective control level research by J. Rotter (adapted by E. Bazhin) helped us to assess the level of externality-internality as a multidimensional feature, which components are tied to different types of social situations. These indicators reflect the level of formation of the motivational-behavioural component of elderly people's active life position. Data processing was done by means of the computer program SPSS 21.0

RESULTS

Researchers studied various aspects of this issue, including psychological mechanisms of aging (Bezrukov, Dubiley, & Rushkevich), personal development of elderly people, self-esteem, self-concept and self-identification, personal changes in old age, spiritual development, features of elderly people's life path, cognitive sphere of aging, socio-psychological contacts in old age, in particular, in the family and nursing homes [7,8].

The problem of distinguishing the boundaries of aging is very complex. The boundaries of the periods of maturity and the beginning of aging are blurred and constantly changing. Some scholars generally claim that there are no clear boundaries for old age. Usually, when we talk about the elderly, we are guided by the retirement age, although this age varies greatly in different countries, for different occupational groups, for men and women. According to the World Health Organization, this category includes people aged 60 and over. In geriatrics and gerontology, it is reasonable to believe that the physiological and psychological traits of the elderly change significantly every five years.

The following scheme of age periodization is most widely used in modern science: old age: 60-74 years for men, 55-74 years for women; old age: 75-90 years for men and women; longevity: 90 years and older for men and women. Groups of elderly and senile people differ significantly. The first group is characterized by maintaining a high level of functioning of psychological components. The most significant problems for them are socio-psychological maladaptation and reduced quality of life. At the forefront of the problems for the second group (old age) are problems of a purely medical nature (deteriorating health, the need for third-party care and social support). Sometimes scientists divide people over the age of 65 into the third and fourth ages. The term "third age" itself refers to an active and relatively independent lifestyle, and "fourth age" - the final stage of human life, which involves full or partial dependence on others. This terminology has found wide acceptance in society and is used in scientific research, as it helps to avoid negative emotional coloring of the terms "elderly" and "senile". The onset of old age varies widely. At the same time, most researchers associate the beginning of old age with the sixtieth birthday. In addition, the process of the onset of old age is defined as a long period of life, which proceeds in different ways for different groups of individuals of a given age.

The issue of mastering new competencies by elderly people remains relevant in the 21st century. Research done by Boulton-Lewis, Buys & Lovie-Kitchin proves that elderly person's intelligence is characterized by compensators [9]. It is manifested in the fact that the decrease in the amount of information processing is offset by the increased use of practical functions and everyday intellectual experience (Schaie & Willis) [10]. A research, done by Moody, who studied cognitive development and learning abilities of elderly people, showed that they are

Table I. Levels of formation of components of elderly people's active life position

Levels/ Components	Components of elderly people's active life position (%)		
	Cognitive	Emotional-volitional	Motivational-behavioural
high	12,6	27,1	26,5
medium	54.2	6.2	53.4
low	33.2	66.7	20.1

Note. N= 78

able to learn in a line with the younger generation [11]. In 2002 in order to improve the elderly people's quality of life the World Health Organization proposed a model of active aging through lifelong learning. The effectiveness of this model is proved by the results of research, done by gerontologists (Bowling, Kim & Merriam, Stephens, Breheny, & Mansvelt), who empirically substantiated the relationship between the level of intellectual development and elderly people's vitality [12]. Thus, in the analyzed research works elderly people's active life position is manifested in the following: 1) skills and abilities to adequately correlate external conditions with their own aspirations, goals, motives; 2) awareness and acceptance of the existing system of life values; 3) ability to live an independent, active, socially prosperous and meaningful life; 4) flexibility of adaptation to changing environmental conditions, caused by various social or economic factors.

We have turned the test assessments of psychodiagnostic techniques (mentioned above) into a standard form according to the formula 1:

$$Z=\frac{x-y}{\sigma} \quad (1)$$

Z – standardized indicator of the subject under the research,

x – "draft" indicator,

y – assessment of the subject under the research,

σ – standard deviation.

Standardization has summarized the results of the research according to the relevant structural components of elderly people's active life position. The levels of formation of components of elderly people's active life position are presented in table 1.

As it can be seen from table 1, respondents with a high level of cognitive component development (12.6%) experience more negative emotions about their own social status, do not accept new social roles, sweat it about age and lack of computer competency, they are inclined to experience rumination, scepticism in their evaluation of the present day, they are apathetic and suffer from low self-esteem. Their most commonly used phrases are as follows: "everything was wrong…", "sorry, I didn't have time to…", "if I could go at least ten years back...". A high level of elderly people's emotional-volitional component development (27.1%) was not synchronized with a high level of cognitive component. A majority of respondents of this category is characterized by a low level of cognitive and a medium level of motivational-behavioural components. A characteristic feature of these respondents is an optimistic mood, a completely positive acceptance of themselves and their own behavioural actions; they do not resort to self-reflection and are maximally isolated from negative thoughts or relatives with negative or aggressive life attitudes. Only in two cases a high level of elderly people's motivational-behavioural component development (26.5%) was synchronized with a high cognitive level and a medium level of emotional-volitional component development. An individual conversation with respondents of this category allowed us to single out people, who are focused on success in life, energetic, active, positive and satisfied with the current life situation. Even a lack of certain competency (computer literacy) did not upset these individuals, but on the contrary stimulated them to be more active in a search to increase their cognitive activity.

Thus, the psychological features of the formation of elderly people's active life position were determined by the fact that more than 50% of respondents had an average level of cognitive development, more than 60% demonstrated a low level of emotional-volitional component and more than 50% were at medium level of motivational-behavioural component. Detailed analysis of empirical data showed the facts of incomparability of the *degree of formation of structural components of elderly people's active life position*. Thus, most respondents' high level of cognitive component development does not correlate with a high level of emotional-volitional component development. On the contrary, a vast majority of elderly people with a high level of cognitive component development had a low level of emotional-volitional and a medium level of motivational-behavioural components development.

Thus, the leading role in the formation of elderly people's active life position is played by the motivational-behavioural component, which allows a person to maintain a sufficient degree of positive communicative interaction, positive self-perception, self-support. Providing support to others, these people experience a sense of self-importance, demand and group belonging.

DISCUSSION

Responding to modern challenges and taking into account the WHO's tasks to provide conditions for maintaining elderly people's active life position in our research we have revealed the following issues: a) this problem is a complex, multi-vector and intersectoral in nature and is considered to be one of the priorities of public policy; b) despite a

large number of studies on various aspects of population aging, the issue of formation of active life position has not been given due attention; c) we believe that the policy, dealing with the elderly people, should be based on the principles of an active life position, which contributes to the implementation of a comprehensive long-term impact on various aspects of life of this category of people. It is worth paying attention to the cognitive, emotional-volitional and motivational-behavioural components of elderly people's active life position. However, in the situation of the COVID-19 pandemic, forced self-isolation, fear for one's own life, and inability to socialize, have triggered elderly people's feelings of loneliness and uselessness. In order to avoid the above mentioned feelings, it is important to develop elderly people's IT skills, as it will enable them to use gadgets for communication, distract from depressive thoughts, regain faith in their own abilities and strengthen personal well-being, social support and security in today's transformational society.

We see the prospects for further research in the study of possibilities of using technological applications, aimed at maintaining social contacts between elderly people, which will directly stimulate the preservation of their active life position.

CONCLUSIONS

Currently, life offers new challenges, which require personal activity, motivation, self-sufficiency, resilience, communication and competence. The traditional pattern of elderly people's behaviour is a search for personal significance, which is realized in their active life position. The current way of elderly people's life has been complicated by the pandemic, caused by COVID-19. Based on the theoretical and empirical research of the issue of formation of elderly people's active life position, three structural components of the phenomenon under study were identified: cognitive, emotional-volitional and motivational-behavioural. The results of the experiment suggest that most respondents had medium-low levels of active life position. This age group demonstrated minor manifestations of cognitive interest, dependence of their judgments on others, difficulty in accepting changes in the environment and in mastering modern information technology, concerns and barriers to their use. A high level of cognitive component development without its connection to the emotional-volitional and motivational-behavioural components is insufficient and does not ensure the formation of elderly people's active life position. The main determinant of the elderly people's reduced vitality is their low level of emotional-volitional component development, which reduces the level of interpersonal interaction and behavioural activity. The research outcomes allowed us to track the dependence of the level of active life position on the motivational-behavioural component. Motivation for activity contributes to the search for a personal psychological resource, activation of one's own potential, adaptation and reflection as prerequisites for self-knowledge, self-regulation and active life position.

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ORIGINAL ARTICLE

IMPACT OF PERCUTANEOUS CORONARY INTERVENTION ON PROTHROMBOGENIC POTENTIAL IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND DIABETES MELLITUS TYPE 2

DOI: 10.36740/WLek202202102

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ABSTRACT

The aim: Aim of study is to assess the influence of urgent reperfusion strategy on the levels of vWf, PAI-1 and sCD40L in patients with acute myocardial infarction (AMI) and concomitant diabetes mellitus type 2 (DM2).

Materials and methods: 255 patients with acute myocardial infarction took part in the study, they were divided into four groups depending on the presence of concomitant diabetes mellitus type 2 and performed treatment: I group – 83 diabetic patients who were underwent urgent reperfusion therapy; II group – 60 diabetic patients who received standard anticoagulant therapy; III group – 65 non-diabetic patients who were underwent urgent reperfusion therapy; IV group – 47 non-diabetic patients who received standard anticoagulant therapy. The levels of von Willebrand factor, PAI-1 and sCD40L were determined by enzyme-linked immunosorbent assay. Statistical data were processed using the Mann–Whitney U-test, the Kruskal-Wallis H-test, quantitative variables were described by the following parameters: median (Me), 25th and 75th percentiles (Q1; Q3).

Results: According to obtained data, we can conclude that patients with acute myocardial infarction and concomitant type 2 diabetes mellitus have higher levels of von Willebrand factor, PAI-1 and sCD40L compared to non-diabetic patients with AMI, which leads to the increasing of the platelets adhesion and aggregation and decreasing of fibrinolysis.

Conclusions: Urgent restoration of blood supply in occluded artery contributed to a statistically significant reduction in levels of von Willebrand factor, PAI-1 and sCD40L levels in both diabetics and non-diabetic patients, reducing the risk of thromboembolic complications and thus improving the prognosis.

KEY WORDS: acute myocardial infarction, diabetes mellitus, reperfusion therapy, prothrombogenic potential

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INTRODUCTION

Acute myocardial infarction is one of the leading medical problems currently. Its association with diabetes mellitus type 2 (DM2) is accompanied by higher risk of complications, including thromboembolic ones [1].

It is well known that the main cause of coronary artery occlusion is thrombosis at the site of a ruptured atherosclerotic plaque. The main components of the formed thrombus are blood cells and fibrin. It was found that at the beginning of thrombus formation its main cellular components presented by activated platelets, which are rapidly stabilized by fibrin fibers [2].

The formation of initial thrombi depends mainly on the adhesive and aggregating properties of platelets. Adhesion of activated platelets is initiated by von Willebrand factor (vWF), released from the damaged endothelial cells [3]. Activated platelets express CD40L that being a ligand of glycoprotein IIb/IIIa enhances platelets aggregation [4]. Recent studies showed its association with insulin resistance [5] and complicated course of acute coronary syndrome [6].

Under the normal circumstances, in response to thrombus formation, fibrinolysis is activated due to the synthesis of tPA, aimed at its dissolution. But in patients with type 2 diabetes the balance of these processes is usually disturbed and fibrinolysis inhibitors predominate over its activators [7]. PAI-1 is a major fibrinolysis inhibitor that suppresses the dissolution of fibrin filaments [8]. Increased levels of PAI-1 correlate with degree of insulin resistance [9].

Considering all mentioned above it becomes obvious that presence of diabetes mellitus type 2 (DM2) contributes to the formation of the prothrombogenic status [10] due to enhanced adhesive-aggregation properties of platelets and imbalance between coagulation and fibrinolytic substances.

Given the absolute priority of urgent reperfusion strategy in patients with AMI due to its proven positive effect on short and long-term prognosis [11], we also decided to evaluate its effect on the prothrombotic potential associated with type 2 diabetes.

THE AIM

Aim of study is to evaluate the influence of urgent reperfusion on the levels of vWf, PAI-1 and sCD40L in patients with acute myocardial infarction (AMI) and concomitant diabetes mellitus type 2 (DM2).

Table I. Levels of vWf, PAI-1, sCD40L measured on the 1st day of AMI depending on the presence of concomitant DM2 (Me [Q1; Q3])

Parameter	Patients with AMI+DM2 (n=73)	Patients with AMI (n=57)	Significance of differences
vWf, AU/ml	1,97 [1,82; 2,18]	1,54 [1,36; 1,72]	U=151,5; p<0,01
PAI-1, ng/ml	68,85 [60,95; 71,1]	53,1 [43,38; 59,6]	U=800,5; p<0,01
sCD40L, ng/ml	3,78 [3,67; 3,9]	3,35 [2,88; 3,63]	U=403; p<0,01

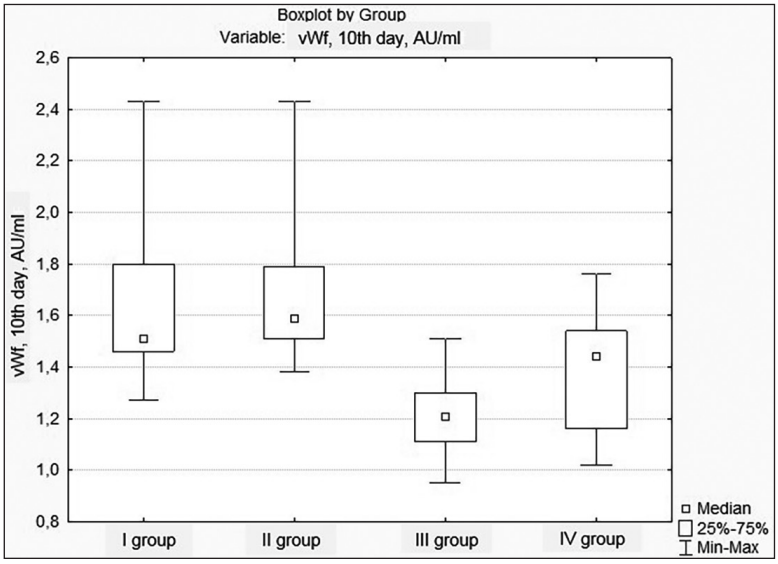

Fig 1. Box graphs of vWf values measured on the 10th day of AMI depending on the presence of concomitant DM2 and performed treatment

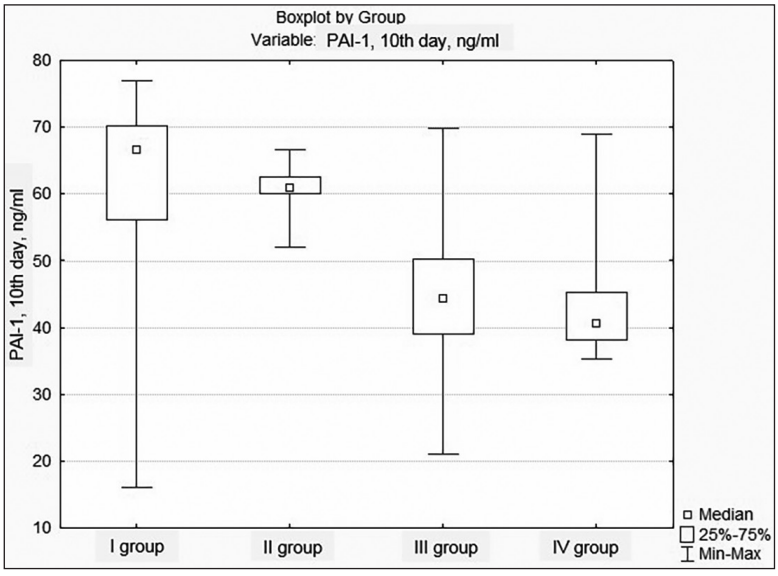

Fig 2. Box graphs of PAI-1 values measured on the 10th day of AMI depending on the presence of concomitant DM2 and performed treatment

MATERIALS AND METHODS

255 patients with acute myocardial infarction were enrolled in the study. They were divided into 4 groups depending on the presence of concomitant diabetes mellitus type 2 and performed treatment: I group – 83 diabetic patients who were underwent urgent reperfusion; II group – 60 diabetic patients who received standard anticoagulant therapy; III group – 65 non-diabetic patients who were underwent urgent reperfusion; IV group – 47 non-diabetic patients who received standard anticoagulant therapy.

This research was carried out in compliance with all relevant diagnostic and treatment standards of the requirements for the ethical component of clinical trials (GCP, 1997). Before the study, patients were informed about the essence of the study, its purpose and possible results. All participants signed up the informed agreement. This study was approved by the local ethics committee in accordance to the recommendations of the ethical committees for biomedical research, Ukrainian legislation on health protection, the 2000 Helsinki Declaration and the directives

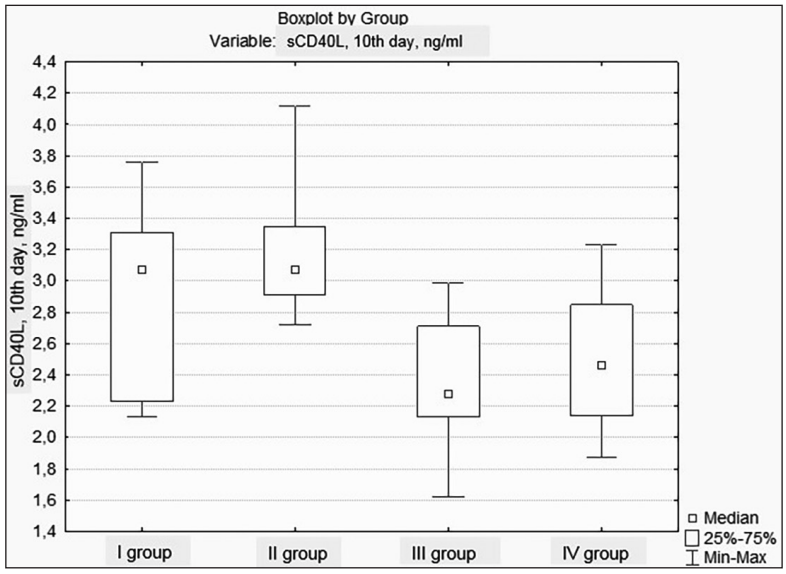

Fig 3. Box graphs of sCD40L values measured on the 10th day of AMI depending on the presence of concomitant DM2 and performed treatment

of the European Partnership 86/609 on the participation of people in biomedical research.

Acute myocardial infarction was diagnosed according to the Order of the Ministry of Health of Ukraine №455 dated 02.07.2014 «Unified clinical protocol of emergent, primary, secondary (specialized) and tertiary (highly specialized) medical aid and medical rehabilitation of the patients with acute coronary syndrome with elevated ST segment» on the basis of clinical, echocardiographic and biochemical criteria. Type 2 DM was diagnosed according to the Order of the Ministry of Health of Ukraine № 1118 dated 21.12.2012 «Standardized Clinical Protocol «Diabetes Mellitus Type 2».

Blood samples were obtained on the 1st and 10th days of AMI under the basal conditions, vWf blood serum levels were determined with commercial enzyme linked immunosorbent assay ELISA kit (Technoclone GmbH, Austria), PAI-1 blood serum levels were determined with commercial enzyme linked immunosorbent assay ELISA kit (Technoclone GmbH, Austria), sCD40-ligand blood serum levels were determined with commercial enzyme linked immunosorbent assay ELISA kit (YH Biosearch Laboratory, China) on the Automated EIA Analyzer "LabLine-90" (Austria). Statistical processing of results was performed using IBM SPSS Statistics software: quantitative variables were described by the following parameters: median (Me), 25th and 75th percentiles (Q1; Q3), the Mann–Whitney U-test was used for the assessment of the differences between two independent groups, the Kruskal-Wallis H-test was used for the assessment of the differences between four independent groups, p-statistical significance ($p<0,05$ is considered statistically significant).

RESULTS

Analyzing the levels of vWf on the first day of myocardial infarction (table I), we detected that in the group of diabetic patients the median vWf was considerably higher than in the group of non-diabetic – 1,97 AU/ml and 1,54 AU/ml respectively ($U=151,5$; $p<0,01$), that indicates significantly more intense processes of platelets adhesion under conditions of concomitant disorders of carbohydrate metabolism.

Similar statistically significant differences between the study groups were found for the level of PAI-1: the median PAI-1 in diabetic patients was 68,85 ng/ml while in non-diabetic patients – 53,1 ng/ml respectively ($U=800,5$; $p<0,01$) which can contribute to inhibition of lysis of blood clots.

A similar trend was found for sCD40L, the median of which was significantly higher in the group of patients with concomitant type 2 diabetes compared to patients without concomitant type 2 diabetes – 3,78 ng/ml and 3,35 ng/ml respectively ($U=403$; $p<0,01$), indicating a high platelet aggregation potential.

Taking into account these results, it can be established that patients with acute myocardial infarction and concomitant type 2 diabetes mellitus experience prothrombotic status due to increased adhesion and aggregation properties of platelets on the background of inhibited fibrinolysis.

Urgent reperfusion strategy helps to improve outcomes for patients due to its positive impact on short and long-term prognosis [11]. However, it is interesting to note that in patients with AMI with concomitant DM2, urgent endovascular intervention is performed significantly less often than in patients without diabetes, although, according to modern guidelines for high-risk patients, tactics require greater determination aimed at reduction of the incidence of complications, including thromboembolic complications, to which these patients are prone [12]. We decided to analyze how PCI affects the mediators of thrombosis studied by us and whether there are differences depending on the co-existing DM2.

According to obtained data, we can conclude that urgent reperfusion had a positive impact on the dynamics of the studied indicators, determined on the 10th day of

AMI: reperfusion therapy contributed to a statistically significant reduction in the levels of vWf (H=60,421; p<0,01) (fig.1), PAI-1 (H=48,434; p<0,01) (fig.2), sCD40L (H=47,614; p<0,01) (fig.3) in the groups of diabetic and non-diabetic patients.

DISCUSSION

Obtained results correlate with recent studies that showed positive impact of PCI on the vWF dynamics and significantly higher risk of development of major adverse cardiovascular events in patients with increased residual levels of vWF after performed PCI due to myocardial infarction. The authors confidently call the Willebrand factor an essential risk marker in patients with acute coronary syndrome and offer to use it for the assessment of long-term prognosis after acute coronary events [13].

The positive effect of percutaneous coronary intervention on the marker of platelet aggregation activity-sCD40L was demonstrated in several recent investigations where invasive approach to the treatment of acute coronary syndrome also contributed to a more significant reduction in sCD40L compared with conservative therapy in diabetic [12] and non-diabetic patients [14].

PCI was also accompanied by a decrease in the level of PAI-1 in the dynamics of patients with and without disorders of carbohydrate metabolism, but still in the literature there are conflicting data on its prognostic value in predicting of adverse cardiovascular events [15].

Given the results, it can be argued that urgent reperfusion strategy reduces the prothrombotic potential in patients with acute myocardial infarction, regardless of concomitant insulin resistance by reducing the adhesive-aggregation properties of platelets and inhibition of antifibrinolytic effects.

CONCLUSIONS

Patients with acute myocardial infarction and concomitant type 2 diabetes mellitus have higher levels of von Willebrand factor, PAI-1 and sCD40L compared to non-diabetic patients with AMI, which contributes to the formation of prothrombotic potential.

Reperfusion therapy has significantly reduced levels of von Willebrand factor, PAI-1 and sCD40L levels in both diabetics and non-diabetic patients with acute myocardial infarction, reducing the risk of thromboembolic complications and thus improving the prognosis.

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ORIGINAL ARTICLE

MANIFESTATIONS OF EXCESSIVE DAYTIME SLEEPINESS AND GHRELIN LEVEL IN CASE OF GASTROESOPHAGEAL REFLUX DISEASE IN PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE

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ABSTRACT

The aim of the study was to discover the interrelation between the severity of gastroesophageal reflux disease (GERD) symptoms, acid exposure time (AET), excessive daytime sleepiness (EDS) and the level of active blood plasma ghrelin in the patients with undifferentiated connective tissue disease (UCTD).

Materials and methods: The study included 120 patients with GERD. All the patients were divided in two groups: Group I - GERD was not accompanied by the signs of connective tissue disease (n=45) and Group II - GERD developed on the background of UCTD syndrome (n=75). Daily transnasal pH monitoring was performed to determine the nature of pathological refluxes. EDS was detected by The Epworth Sleepiness Scale. Active ghrelin in blood plasma samples was determined by ELISA.

Results: 80% of the patients of Group II and 35.48% of Group I suffered from EDS ($p<0.05$). The mean daily AET index was 5.48±0.4% in Group II and 6±0.2% in Group I, in the night hours mostly when patients were in the upright position. This phenomenon contributed to a deterioration of sleep quality and the appearance of EDS and was supported by a connection between AET and EDS ($r=+0.827$ for Group I and $r=+0.768$ for Group II). The mean De Meester index was higher in the patients of Group II (23.01±2.24 in Group I vs 31.08±2.4 in Group II; $p<0.05$).

Conclusions: GERD manifestations are strongly related to the level to AET and intensity of EDS. The EDS symptoms depend on circulating ghrelin level.

KEY WORDS: gastroesophageal reflux disease; undifferentiated connective tissue disease; ghrelin; excessive daytime sleepiness

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INTRODUCTION

Connective tissue diseases (CTD) are genetically determined conditions characterized by defects in fibrous structures and the ground substance of the connective tissue. CTD lead to the violation of organs and systems formation and have a progredient course. Undifferentiated connective tissue disease (UCTD) refers to unclassified systemic autoimmune pathologies having common clinical and serologic manifestations with certain connective tissue conditions (CTC) but do not respond to any of CTD classification criteria [1]. CTC are naturally heterogeneous, with clinical intersecting overlapping features, and therefore require careful differential diagnosis [2]. According to the recommendations [1, 2, 3], patients diagnosed with UCTD should be under constant, active follow-up in order to identify new signs of CTC.

The gastrointestinal tract is one of the systems that are most often involved in the pathological process on the background of UCTD. Esophageal diseases constitute about 80% of the total gastrointestinal pathology [4]. The important pathogenic component of gastroesophageal reflux disease (GERD) development is a functional abnormality of the lower esophageal sphincter (LES) [5]. In addition, dysplastic changes in the connective tissue create a premorbid background for the development of many pathological conditions and chronic diseases of whole organs. They affect the changes in the clinical picture, difficulties in early diagnosis, and more frequently promoted complications as a consequence. All of the above mentioned in patients with UCTD results in lower quality of life compared to the general population [6]. In addition, the daily discomfort, repeated visits to the doctor, the need for diagnostic interventions, and long-term but not always effective treatment are associated with high financial costs [7].

Despite the fact that heartburn is the main symptom of GERD, patients with concomitant UCTD may suffer from a number of other symptoms. According to UCTD criteria, such concomitant manifestations as Reynaud's Syndrome, arthralgia, photosensitization, unmotivated body weight loss, morning stiffness, dry mouth (xerostomia) and/or dry eye (xerophthalmia), dysphagia, recurrence of groundless fever, cutaneous lesions (rash), mouth ulcers, non-androgenic

alopecia, proximal muscular weakness may occur in such patients secondary to pathological gastroesophageal reflux [1]. All of them significantly complicate the diagnosis, the course of both the underlying and concomitant disease.

The intestinal hormone ghrelin modifies motility and the processes of GIT evacuation [8]. Furthermore, ghrelin affects the circadian rhythms of the body indirectly, via food intake [9]. The level of ghrelin in blood plasma fluctuates every day, with a peak during the day and decrease at night [10]. Its level also varies depending on the time of eating. Oin Wang et al. have experimentally demonstrated that ghrelin plays an important role in circadian rhythm disorders in case of fatty liver disease [11].

Ghrelin is one of the main hormones also responding to poor sleep and related disorders [12]. Experimental restriction of sleep duration was accompanied by an increase in ghrelin level, salt retention in the body, inflammatory markers, and promoted a decrease in insulin and leptin sensitivity [13, 14]. Since ghrelin is able to promote slow falling asleep and induce deep sleep [15], its level is likely to be able to affect sleepiness. At the same time, the knowledge related to the role of ghrelin in the case of GERD in general and in case of its combination with UCTD it is limited. Moreover, sleep and the circadian cycle play an essential role in the regulation of energy metabolism, affecting food intake, hunger, satiety, and regulates ghrelin secretion [16, 17]. Poor sleep quality may have a negative impact on metabolism since energy homeostasis is supported by the release of key hormones according to the daily circadian cycle. Experimental and clinical studies in adults have shown that both acute and chronic decrease in sleep lead to higher levels of ghrelin [13, 18]. In particular, Broussard et al. demonstrated that experimental sleep restriction in healthy young thin men led to increased ghrelin level [9]. McHill et al. found that circulating ghrelin level was affected by both circadian rhythms and the sleep-insomnia system [16]. However, they did not detect a reliable relationship between the changes in the circadian profile stability and subjective feelings of hunger.

Duration as well as the quality of sleep, affects the working efficiency during the day and the appearance of excessive daytime sleepiness. According to the scientific data about 80% of patients with GERD have particular nighttime symptoms, and every fourth person has the frequent ones that cause awakening and worsening of sleep [19]. Approximately 25% of the total population and 50% of patients with GERD inform about heartburn that disturbs sleep at night [19]. Many patients with GERD also experience short-term awakening during reflux, which contributes to sleep fragmentation and promotes low-quality sleep. Poor quality of sleep may increase sensitivity to intra-esophageal stimuli through brain-esophagus interaction [20]. Moreover, the LES relaxation allows the acid gastric contents enter the esophagus that could promote GERD symptoms. The number of spontaneous relaxations in their sleep increases in the patients with GERD, especially in rapid eye movement sleep, unlike in healthy individuals. According to the scientific data, rapid eye movement sleep is characterized by a decrease in the tonus of the skeletal muscle and sympathetic nervous system [20]. It has been scientifically confirmed that pathological GERD negatively affect sleep quality and, as a result, manifestations of excessive daytime sleepiness, however, these phenomena remain insufficiently studied in the patients with GERD associated with UCTD.

THE AIM

Based on the above we conclude that the issue of the GERD/sleep/ghrelin interrelation requires to be studied in more detail. This is why the aim of the study was to investigate the interrelation between the severity of GERD symptoms, acid exposure time (AET), excessive daytime sleepiness (EDS) and the level of active blood plasma ghrelin in the patients with undifferentiated connective tissue disease syndrome.

MATERIALS AND METHODS

The patients with GERD (in total n=120) treated at the Therapeutic Department of the University Clinic of Ivano-Frankivsk National Medical University (IFNMU) and the Therapeutic Department №2 of Ivano-Frankivsk Central City Clinical Hospital during 2016-2018 were examined upon the condition of the voluntary informed consent in accordance with the principles of bioethics and deontology. All the patients were divided in two groups: Group I - GERD was not accompanied by the signs of connective tissue disease (n=45) and Group II - GERD developed on the background of UCTD syndrome (n=75). UCTD syndrome was diagnosed according to the criteria recommended by M. Moska et al., A. Doria et al., T. I. Kadurina, L. M Abbakumova in the modification of T. Milkovskaya-Dimitrova. To assess the totality and severity of UCTD clinical manifestations, the Smolnova's scale was used. Symptoms of connective tissue dysplasia were divided into severe and mild. According to this scale, the total points up to 9 corresponded to the mild degree of CTD severity diagnosed in patients, from 10 to 16 – average degree of severity, from 17 and more – severe degree [1, 3]. GERD was diagnosed according to the criteria of the unified clinical protocol (the Order of the Ministry of Health of Ukraine from October 31, 2013 № 943). The criteria included typical for GERD complaints such as heartburn, dysphagia, regurgitation, esophagitis of different degrees according to the results of esophagogastroduodenoscopy (EGD), the data of daily pH monitoring. Los Angeles (LA) classification was used for the endoscopic assessment of the degree of esophagus lesion [18, 19]. In order to determine the nature of refluxes, daily pH was recorded in the lower third of the esophagus using transnasal pH Acidogastrograph with the registrar 1 pH-M (LLC "Start", Vinnitsa). Then patients completed a GERD – Q questionnaire for the symptoms of reflux disease. The information was also collected according to standard clinical examination. All patients were interviewed according to the Berlin questionnaire (1997) in order to evaluate the risk of obstructive sleep apnea syndrome (OSAS). [20]. Patients with a medium or high risk of OSAS were excluded from the study. The intensity of daytime sleepiness was detected using an adapted special scale for sleeping determination [22]. Briefly, the patients were asked to answer eight questions to assess their chances of falling asleep

while doing different activities. Their response was evaluated from 0 to 3 points depending on the probability of nodding. A person who scored 1-6 points had a normal sleep; 7-8 points meant moderate sleepiness; 9 points or more – a person was considered to have a significant daytime sleepiness .

Active ghrelin in blood plasma samples was determined by immuno-enzyme analysis with the use of The RayBio® Human Ghrelin Ensyme Immunoassay Kit (RayBiotech, Inc. USA). In order to preserve the ghrelin molecule stability, esterase activity was inhibited in all biological samples, following the recommendations of the test system manufacturer. Optical density reading was conducted with the use of immunoassay analyser (ImmunoChem-2100 Microplate Reader) at a wavelength of 450 nm.

The research was approved by the Bioethics Committee of Ivano-Frankivsk National Medical University and conducted according to the provisions of Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (1997) and the principles of the World Medical Association (WMA) Declaration of Helsinki – Ethical Principles For Medical Research Involving Human Subjects (1964, revised by the 59th WMA General Assembly, Seoul, October 2008).

Statistical processing was performed using STATISTICA 7.0 and the statistical package of the Microsoft Excel 2016. The Student's-t test was used to confirm statistical differences ($p \leq 0.05$) between the indices in the groups. Correlation level between two selected parameters was determined using the Spearman's coefficient.

RESULTS AND DISCUSSION

The results of the ESS scale showed that 80% of the patients of Group II and 35.48% of the patients of Group I suffered from daytime sleepiness ($p<0.05$). Majority of the patients of Group II (n= 45, 60%; Fig. 1) suffered from moderate daytime sleepiness which was recorded more than twice compared to the patients with GERD without concomitant pathology ($p<0.05$). The signs of significant daytime sleepiness were present in 20% of the patients of Group II and in 8.88% of Group I ($p<0.05$).

According to the results of endoscopic examination, esophagitis severity in the patients of Group I was noted to correspond to LA-A, whereas it corresponded to LA-B more frequently in the examined patients of Group II. Stated differently, the endoscopic picture of the patients in Group II was characterized by severe hyperemia and persistent, frequently generalized mucosal edema.

According to the analysis of daily pH monitoring of the esophagus, total acid exposure time (AET) in the esophagus with the duration above normal was diagnosed in 57 (76%) patients of Group II and in 12 (28.8%) patients of Group I; the percentage of time with pH<4 in the upright position was noted in 36 (48%) patients of Group II and only in 8 (17.7%) patients of Group I; pH<4 in prone position constituted 60 (80%) vs. 10 (22.2%); the total duration of GER episodes lasting > 5 min was noted in 63 (84%) patients vs.13(28.8%) patients.

The number of refluxes per day constituted 57±8 (mean±SD) episodes with a total duration of 67±3 minutes in the patients of Group I, respectively, AET was 4.6±0.2% of the total monitoring period (Fig. 2A).

The number of acid refluxes constituted 79±6 episodes in the patients of Group II, total duration constituted 87±8 minutes, AET amounted 5.48±0.4% of the total monitoring period (Fig. 2B). Direct correlation between AET and EDS in both study groups was found: $r=+0.827$, $p<0.05$ in the GERD group and $r=+0.7684$, $p<0.05$ in the group of GERD associated with UCTD. The determination coefficient (R^2) indicated that the variation of the first indicator was caused by the variation of the second one by 68.4% among the patients of Group I and by 59.0% among the patients of Group II (Fig.2).

The mean De Meester index constituted 23.01±2.24 in the patients with GERD and 31.08±2.4 in the patients with GERD and UCTD combination ($p<0.05$). The percentage of time with pH<4 in the upright position and prone position increased from 10.2±0.4% and 5.8%±0.1 respectively in the patients of Group I, to 12.3%±0.05 and 7.4±0.1% in the patients with combined pathology ($p<0.01$). The duration of the longest pathological gastroesophageal reflux constituted 67±8 and 37±12 minutes among the patients of Groups II and I, respectively ($p<0.05$). The comparative pictures of the daily intra-esophageal pH-metry results typical for the examined patients are presented in Fig. 3.

In the course of the study, ghrelin indices were found to be significantly higher in the patients with GERD associated with UCTD in comparison with the patients with GERD without dysplasia signs (Fig.4.).

This index constituted 2413.18868±31.857 pg/ml on average in the patients of Group II and 471.499±14.472 ($p<0.05$) in the patients of Group I. The mean values of this index were 1.37 times higher in case of GERD and 7.03 times higher in case of its development secondary to UCTD compared to the control group.

A direct correlation between the manifestations of daytime sleepiness and the severity of pathological gastroesophageal reflux (GER) was also established. In particular, the occurrence of refluxes with pH<4 and a duration over 5 minutes correlated positively with the degree of excessive daytime sleepiness manifestation ($r=0.859$; $p<0.05$). Concurrently, we observed a direct linear dependence between the occurrence of refluxes with pH<4 and a duration over 5 minutes and the level of ghrelin in blood plasma – $r=0.659$, $p<0.05$ in the patients of Group I; the occurrence of refluxes with pH<4 and a duration over 5 minutes and the concentration of ghrelin in blood plasma – $r=0.786$, $p<0.05$- in Group II.

According to the correlation and regression analyses, a strong, direct, reliable correlation ($r=+0.86$; $p<0.05$) between the severity of excessive daytime sleepiness and the level of ghrelin was noted in the patients of Group I, and the determination coefficient (R^2) indicated that the variation of the first indicator was caused by a variation of the second one by 73.9%. The indices constituted +0.80, $p<0.05$ and 64.1% in the patients of Group II, respectively. The graphical representation of the analysis results is shown in Fig. 5A) and 5B).

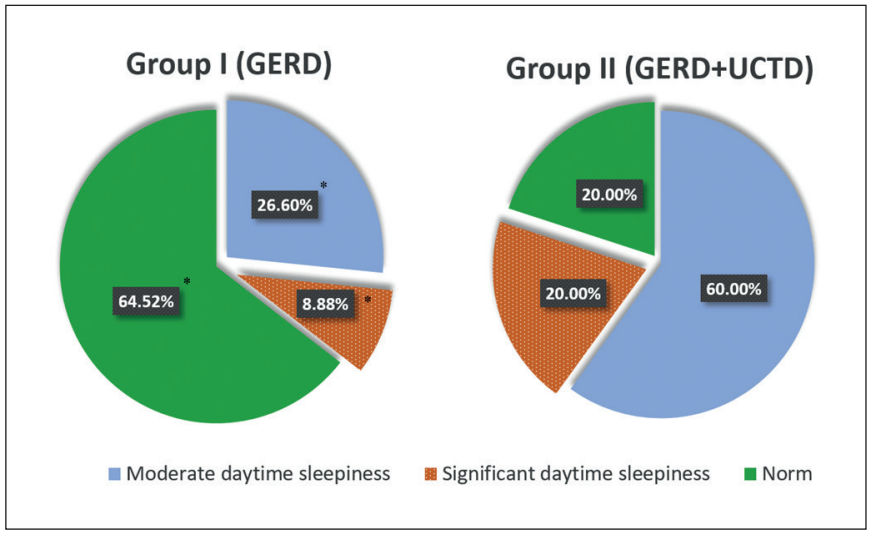

Fig. 1. The distribution of the patients according to the Epworth Sleepiness Scale. Significant differences ($p<0.05$) were found when comparing the reliable data between the research groups.

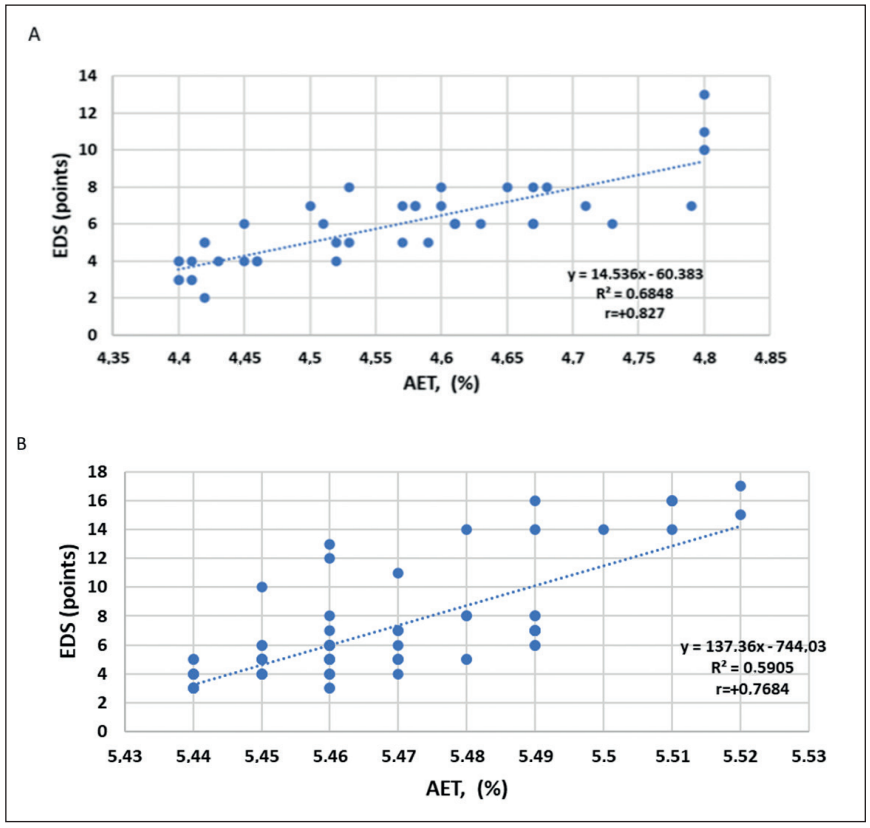

Fig. 2. Relation between EDS index on The Epworth Sleepiness Scale and AET. A) in the patients with GERD. Correlation field and regression line (with equation) describing it ($r = +0.827$; $p<0.05$); B) in the patients with GERD associated with UCTD. Correlation field and regression line (with equation) describing it ($r=+0.768$; $p<0.05$); R^2 is the determination coefficient.

DISCUSSION

According to the conducted research, the presence of UCTD complicated the condition of the patients with GERD. Severe sleep disturbances were proved to occur in the patients with GERD associated with UCTD leading to excessive daytime sleepiness. The data were compliant with provisions of National Sleep Foundation (NSF), according to which, people who experience heartburn at night are more likely to suffer from insomnia and excessive daytime sleepiness than those who do not have heartburn at night.

The patients with GERD associated with UCTD complained of superficial sleep with frequent awakening significantly more often ($p<0.05$). According to the analysis of daily pH monitoring of the esophagus, AET index constituted 5.48±0.4% in the patients with combined pathology and 6±0.2% in the patients with GERD mainly on account of the night hours when the patients were in prone position. This phenomenon contributed to the decrease in sleep quality and the occurrence of excessive daytime sleepiness, as it was evidenced by the direct strong relationship between AET and EDS in both research groups: $r=+0.827$, $p<0.05$ in the group of patients with GERD and $r=+0.7684$, $p<0.05$ in the group of patients with GERD associated with UCTD. The data were compliant with the scientific data of Yamasaki T. with co-authors. According to them, sleep deficiency increased the number of pathological GER, contributed to the increase

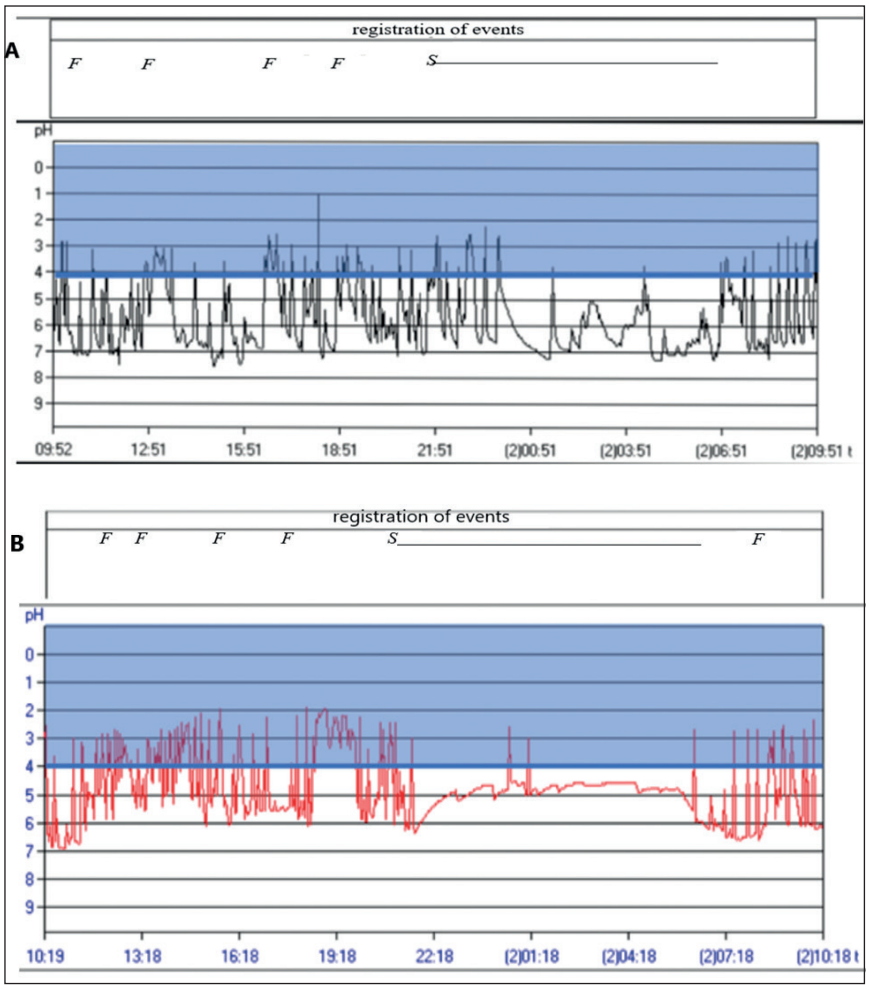

Fig. 3. Typical daily intra-esophageal pH-metry of a patient with GERD (A) and patient with GERD associated with UCTD (B). Conventional symbol: F- food; S-sleep.

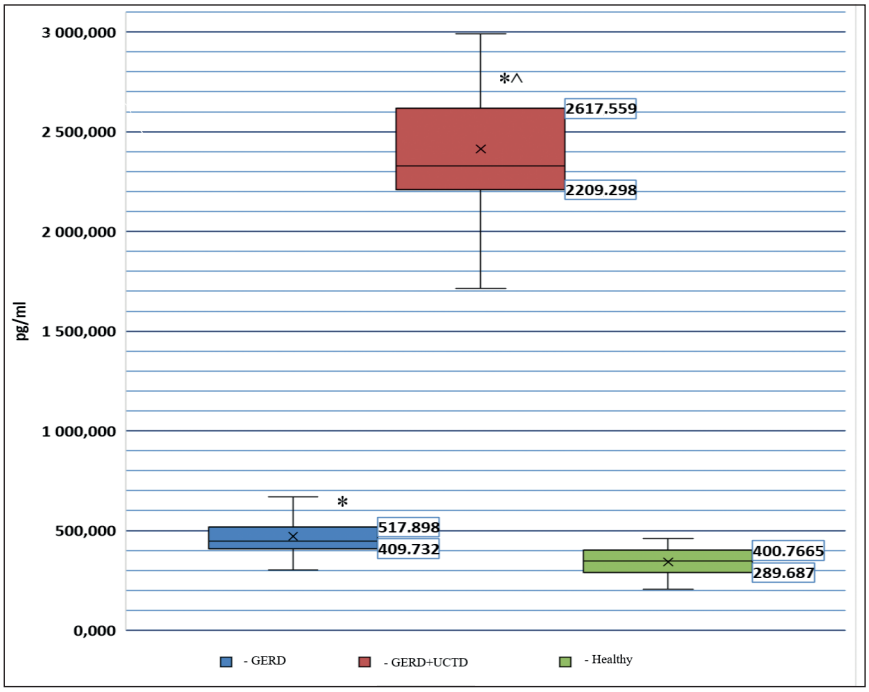

Fig.4. Ghrelin indices in the blood plasma of the patients with GERD in combination with UCTD and GERD without concomitant pathology. Mo - mode, Me - median, and interquartile range: lower - higher quartile (LQ-HQ) were used for non-normal distribution.
* – ($p<0.05$) the data are reliable in comparison with the indices of healthy individuals;
^ – ($p<0.05$) the data are reliable in comparison between the research groups.

in the duration of acid exposure from the mucosa of the lower third of the esophagus both in the healthy individuals of the control group and in patients with GERD on the basis of daily pH-metry [21]. Meanwhile, Navarro-Solera M. and co-authors found no relation between sleep duration and ghrelin level [23].

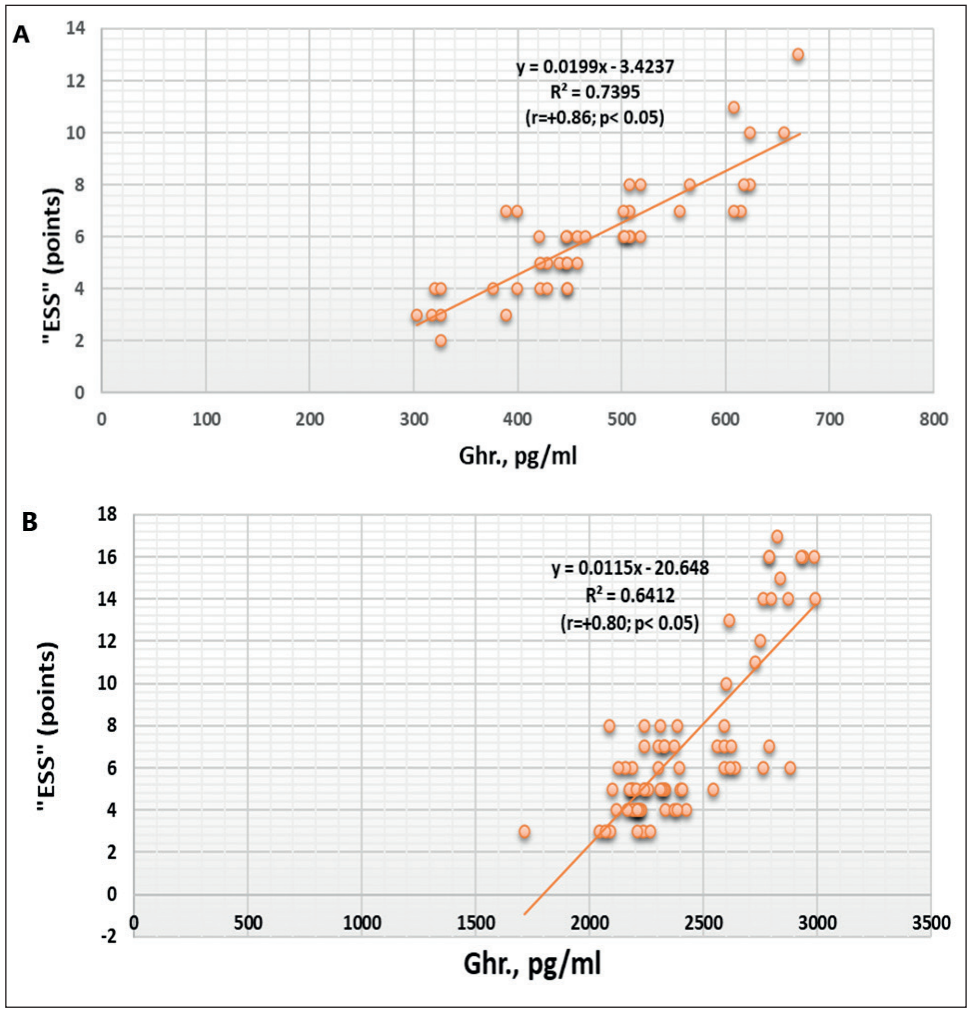

Fig. 5. Relation between EDS index on The Epworth Sleepiness Scale and ghrelin level in the patients with GERD (A) and in the patients with GERD associated with UCTD (B). Correlation field and regression line (with equation) describing it. ($r=+0.80$; $p<0.05$); R^2 is the determination coefficient.

A direct correlation between the severity of excessive daytime sleepiness and the level of ghrelin was also established: I Group – r = + 0.86; p<0.05; II Group – r = +0.80, p<0.05. The obtained results were comparable to the following scientific data. Circulating in the body, ghrelin may impact the circadian system as a potential feedback signal. Laermans J. and co-workers have found that ghrelin can regulate peripheral circadian rhythm fluctuations [24]. Since the circadian system of the body is highly-sensitive, the latter authors assume that its imbalance may be considered as the first manifestations of the disease. Motivala S. and co-author's study published in the Psychoneuroendocrinology journal experimentally found that chronic insomnia violated ghrelin circulation in the body contributing to its decrease at night and increase during the day. The same tendency was observed in the cases of the reduction of falling asleep time and decrease in total sleep time [15]. Hagen E. and co-authors found that there was significant inverse relationship between ghrelin and sleep duration (r=-0.18, p=0.04) [25]. A significant inverse association between sleep duration and ghrelin level was also confirmed in the works of Al-Disi D. [26] and Broussard J. [9].

CONCLUSIONS

Thus, the more severe were the manifestations of GERD and AET, the higher was the degree of excessive daytime sleepiness manifestation which had direct correlation with circulating ghrelin level. The possible role of ghrelin in the sleep regulation in the patients with GERD and UCTD combination was also indicated by the direct relation between the frequency of reflux with pH<4 and its duration over 5 minutes and ghrelin level in blood serum.

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ORIGINAL ARTICLE

ASSOCIATION OF CLINICAL AND EARLY ROUTINE LABORATORY FINDINGS WITH SEVERITY OF ACUTE PANCREATITIS

DOI: 10.36740/WLek202202104

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ABSTRACT

The aim: To identify the association of clinical and simple laboratory data determined during hospitalization of the patient with severity of acute pancreatitis.

Materials and methods: Clinical and laboratory parameters of 229 patients with acute pancreatitis were analyzed. All patients were divided into two groups depending on the severity of acute pancreatitis: in the group with mild AP were 130 (56.8%) patients and the group, which included moderately severe and severe degree of AP consisted of 99 (43.2%) patients.

Results: The association of the age group of 61-70 years with the severity of acute pancreatitis was revealed (p 0.05). We did not find an association between the causes of acute pancreatitis and its severity. In the group with moderate-severe acute pancreatitis, the frequency of concomitant pathology was significantly higher than in the group with mild acute pancreatitis – 92.9% (92) and 78.5% (102) cases ($p<0.05$). The association between the severity of acute pancreatitis and the following laboratory parameters: blood sugar, leukocyte levels, the level of stabs, lymphocytes, total protein, serum amylase, urinary diastase, creatinine, ALT, AST, prothrombin index, neutrophil-lymphocyte ratio was revealed ($p<0.05$).

Conclusions: The study did not reveal a significant difference between compared groups in the time of hospitalization; found no association between the causes of acute pancreatitis and its severity. Instead, the association between female sex, the presence of concomitant pathology and some routine laboratory findings with the severity of acute pancreatitis was proved.

KEY WORDS: acute pancreatitis, severity, clinical data, laboratory data

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INTRODUCTION

Acute pancreatitis (AP) is an acute inflammation of the pancreas with frequent involvement of peripancreatic tissue in the process. According to the Atlanta classification, there are three forms of its severity: mild, moderate and severe [1]. Mortality in acute pancreatitis is associated with the severity of its clinical course and ranges from 3.9% to 6% [2,3]. With moderate and severe acute pancreatitis, the mortality rate increases to 9.4%, and in case of joining the infection to the source of necrosis, the mortality rate reaches 30% [4,5].

The timeliness of the treatment of patients with acute pancreatitis significantly affects its effectiveness. An important task is the early diagnosis of its severe forms, especially at the stage of initial assessment of severity [6]. Predicting the severity and mortality of acute pancreatitis is an integral part of the treatment and diagnostic process, especially in the admission department, because it allows to quickly orient and determine the further treatment of the patient – in a surgical department or in the intensive care unit. The initial assessment of the severity of a patient with acute pancreatitis includes an assessment of both clinical and laboratory parameters. A large number of scales have been developed to assess the severity of acute pancreatitis and to predict mortality. Due to the variety of clinical and morphological forms of acute pancreatitis there is a need to develop integrated scales with a comprehensive assessment of clinical, laboratory data and data of additional methods of examination – Ranson, APACHE II, SAPS, Glasgow-Imrie, MODS, SOFA [7,8] .

The proposed clinical, laboratory markers of severity of acute pancreatitis and indicators of special methods of examination have different sensitivity and specificity, so they need further study to find the most sensitive indicators in the early period since the onset of disease [9]. Recent studies have shown a link between C-reactive protein, AST, creatinine and albumin and the severity of acute pancreatitis [10,11,12]. However, C-reactive protein reaches its diagnostic values only in 2-4 days, so it cannot be used to assess the severity of acute pancreatitis in the early stages of the process [13].

The variety of predictors of severity and mortality in acute pancreatitis has necessitated numerous studies. Laboratory relationships such as neutrophil-lymphocyte, platelet-lymphocyte ratios with the severity of acute pancreatitis, the duration of hospital stay and mortality in acute pancreatitis have also been shown [14]. In recent years, more and more publications have appeared about the predicting performance of red-cell distribution width, red-cell distribution width to total serum calcium ratio

and blood urea nitrogen for severity and mortality acute pancreatitis [15,16].

The literature we analyzed describes many prognostic clinical factors and laboratory markers that are related to the severity and mortality of acute pancreatitis. However, not all of them are early markers, developed for the specific capabilities of each clinic, some are quite expensive and impossible to use as obligatory in the emergency department at hospitalization of patients with acute pancreatitis. Therefore, today there is an active search for those early markers wich can be possible to determine in an emergency hospital, taking into account the diagnostic and financial capabilities of medical establishment.

THE AIM

The aim of the study was to identify the association of clinical and simple laboratory data determined during hospitalization of the patient with the severity of acute pancreatitis.

MATERIALS AND METHODS

Clinical and laboratory parameters of 229 patients with acute pancreatitis who were hospitalized in the city clinical emergency hospital of Vinnytsia from 2018 to 2020 were analyzed. The age of patients ranged from 18 to 88 years. The mean age was 46.6±14.7 years. Among the examined patients, there were 73 women (31.9%) and 156 men (68.1%), respectively.

The diagnosis of acute pancreatitis was made on the basis of the criteria recommended in the Atlanta 2012 classification, in the presence of any two of three criteria: characteristic abdominal pain (acute epigastric pain, often irradiating to the back), increased serum lipase / amylase levels (in 3 times and above the upper limit of normal), and appropriate findings on computed tomography, magnetic resonance imaging or transabdominal sonogram [1]. According to this classification, the severity of acute pancreatitis was distinguished between mild, moderate and severe, based on the presence of local and systemic complications, organ failure. Organ failure was determined using the criteria of a modified Marshall scoring system.

All patients with acute pancreatitis underwent a comprehensive clinical and laboratory examination, electrocardiography, chest X-ray, esophagogastroduodenoscopy, ultrasound examination of the abdominal cavity and retroperitoneal space, using Siemens Healthineers, ACUSON Juniper ultrasound scanner, for patients with severe acute pancreatitis computed tomography of the abdominal cavity was done, using Siemens Somatom go.up computer tomograph.

The following parameters were evaluated: age, sex, body mass index, etiology of acute pancreatitis, time from the onset of the disease to the moment of hospitalization, form of acute pancreatitis, concomitant pathology, complications of acute pancreatitis, hemoglobin in blood, blood sugar, leukocytes level with formula, erythrocytes, hematocrit, ESR, total protein level, total bilirubin, serum amylase, urinary diastase, AST, ALT, urea, creatinine, prothrombin index, calculated the neutrophil-leukocyte ratio. The laboratory parameters, that were evaluated, were obtained at hospitalization.

All patients were divided into two groups depending on the degrees of severity of acute pancreatitis: the group with mild AP and the group, which combined moderately severe and severe degree of AP (we called it moderate-severe AP group). In the group with mild AP there were 130 (56.8%) patients with a mean age of 44.9±14.4 years. The group with moderate-severe AP consisted of 99 (43.2%) patients with a mean age of 48.9±14.9 ($p<0.05$). The gender distribution of patients in groups was as follows: in the group of patients with mild AP there were 96 men (73.8%) and 34 (26.2%) women; in the group of patients with moderate-severe AP there were 60 men (60.6%) and 39 (39.4%) women respectively ($p<0.05$). 174 (75.9%) patients had acute edematous type of AP, 55 (24.1%) patients had acute necrotising type of AP. The average hospital-stay in the group with a mild degree was 7,1±3,2 day, in the group with moderate-severe was 15,4±8,2 day.

All patients were analyzed for the time from the onset of the disease to the time of hospitalization. As the time of the onset of the disease was considered the appearance of abdominal pain.

The causes of acute pancreatitis were determined. In 151 (65.9%) patients the cause of pancreatitis was alimentary factor, in 43 (18.8%) patients was an alcohol factor, gallstone disease became the cause of AP in 17 (7.4%) patients. In addition, the causes of acute pancreatitis in 4 (1.7%) patients was taking medication for other diseases, in 2 (0.9%) cases acute pancreatitis developed after surgery, in 1 (0.4%) patient acute pancreatitis developed after falling from a height. In 31 (13.5%) patients it was not possible to determine the cause of AP.

Clinically significant comorbidity occurred in 194 (84.7%) patients with acute pancreatitis. Often there was a combination of several pathologies in one patient.

Complications of acute pancreatitis developed in 63 (63.6%) patients from moderate-severe group of AP and were absent in the group of patients with mild degree. Often the same patients had a combination of several complications.

Surgical treatment was performed in 28 (28.3%) patients from moderate- severe group of acute pancreatitis. Among all 28 surgical interventions, minimally invasive interventions were performed in 6 (21.4%) patients, open surgical interventions were performed in 22 (78.5%) patients with acute pancreatitis.

The overall mortality among 229 patients with acute pancreatitis was 21 (9.2%). Postoperative mortality was 25% (7).

RESULTS

Men predominated in the gender structure of all patients with acute pancreatitis. The ratio of women to men was 1

Table I. Distribution of patients with acute pancreatitis by severity and age

Age of patients with AP (n=229)	Group with mild AP (n=130)	Group with moderate-severe AP (n=99)	P
Age, years	44,9±14,4	48,9±14,9	0,04
21-30 years	20 (15,4%)	10 (10,1%)	ns
31-40 years	37 (28,5%)	23 (23,2%)	ns
41-50 years	33 (25,4%)	20 (20,2%)	ns
51-60 years	23 (17,7%)	21 (21,2%)	ns
61-70 years	9 (6,9%)	18 (18,2%)	0,009
over 70 years	8 (6,2%)	7 (7,1%)	ns

ns - not significant difference

Table II. Distribution of patients by severity and type of acute pancreatitis

Type of AP n=229	Group with mild AP (n=130)	Group with moderate-severe AP (n=99)	P
Edematous (interstitial)	130 (100%)	44 (44,4%)	<0,0001
Necrotic (aseptic)	0 (0)	43 (43,4%)	<0,0001
Necrotic (infected)	0 (0)	12 (12,1%)	0,0001

Table III. Distribution of patients with acute pancreatitis by severity and time from the onset of the disease to hospitalization

Time from the onset of the disease to hospitalization, hours (n=229)	Group with mild AP (n=130)	Group with moderate-severe AP (n=99)	P
Up to 6 hours	14 (10,8%)	13 (13,1%)	0,58
6-24 hours	41 (31,5%)	28 (28,3%)	0,59
24-48 hours	42 (32,3%)	29 (29,3%)	0,62
> 48 hours	33 (25,4%)	29 (29,3%)	0,53

Table IV. Distribution of patients with acute pancreatitis by severity and causes

The reason of AP (n=229)	Group with mild AP (n=130)	Group with moderate-severe AP (n=99)	P
Alimentary	85 (65,4%)	66 (66,7%)	0,83
Alcoholic	26 (20,0%)	17 (17,2%)	0,58
Biliary	7 (5,4%)	10 (10,1%)	0,17
Caused by drugs	2 (1,5%)	2 (2,0%)	0,78
Postoperative	1 (0,8%)	1 (1,0%)	0,84
Posttraumatic	1 (0,8%)	0 (0)	0,38
Of unknown etiology	8 (6,1%)	3(3,0%)	0,16

to 2.1 ($\chi 2 = 60.2$, $p < 0.0001$). There was a predominance of women in the group with severe acute pancreatitis compared with the number of women in the group with mild pancreatitis – 34 (26.2%) and 39 (39.4%), respectively ($p<0.05$).

The mean age of patients in the group with moderate-severe AP was higher than the mean age in the group with mild AP ($p<0.05$). A significant age difference between the compared groups was observed in the age group from 61 to 70 years ($p<0.05$) (Table I).

The number of patients with edematous type of AP in the group with mild degree of severety dominated the analogical rate in the group with moderate-severe degree – 130 (100.0%) and 44 (44.4%) cases, respectively ($p<0.0001$) (Table II).

The time from the onset of the disease to the time of hospitalization is especially important when it comes to severe degrees of acute pancreatitis with rapid progression of hemodynamic disorders and organ dysfunction. We noted low early (up to 6 hours) hospitalization of patients with acute pancreatitis – 27 (11.8%) patients in both groups. More than half of patients (61.1%) in both groups were hospitalized for 6 to 48 hours. However, we did not note a significant difference when comparing the terms of hospitalization between groups with mild and moderate-severe acute pancreatitis ($p>0.05$) (Table III).

Table V. Distribution of patients with acute pancreatitis by severity and laboratory parameters

Laboratory indicator	Group with mild AP (n=130)	Group with moderate-severe AP (n=99)	P
Hemoglobin, g/L	141,0±16,6	142,7±25,5	0,55
Blood sugar, mmol/L	5,7±1,9	7,7±4,2	<0,0001
Erythrocytes, ×1012 /L	4,7±0,6	4,5±0,8	0,18
Leukocytes, ×109 /L	9,7±3,2	12,2±4,7	<0,0001
Stabs neutrophils, %	7,4±6,4	16,3±12,2	<0,0001
Segmented neutrophils, %	67,4±11,0	66,5±10,9	0,53
Lymphocytes, %	18,7±8,9	12,8±7,7	<0,0001
Monocytes, %	4,0±2,2	3,9±3,0	0,72
Neutrophil-lymphocute ratio	5,5±4,1	10,8±10,0	<0,0001
Hematocrit (Hct)	47,5±5,3	45,4±10,9	0,38
ESR, mm/hour	17,0±2,7	20,8±3,4	0,11
Total protein, g/L	66,6±7,9	70,0±10,0	0,02
Total blood bilirubin, micromol/L	27,8±7,6	29,7±7,7	0,66
Serum amylase, units/L	332,4±29,3	949,1±47,7	<0,0001
Urinary diastase,units	1601,5±93,1	5242,7±102,3	<0,0001
ALT, units/L	50,5±11,5	71,1±8,3	<0,0001
AST, units/L	108,9±48,7	139,3±104,0	0,004
Serum urea, micromol/L	7,6±4,5	8,4±4,7	0,31
Creatinine, micromol/L	117,5±29,0	126,3±33,5	0,02
Prothrombin index, %	92,3±8,1	87,2±12,1	0,002

Among the causes of acute pancreatitis, alcohol abuse and fatty / fried foods dominated – 194 (84.7%) cases. Alcohol abuse was the main cause of acute pancreatitis in 38 (88.4%) men among 43. In women, the dominant cause of acute pancreatitis was gallstone disease. Thus, among 17 patients with acute biliary pancreatitis 13 (76,5%) were women. Together, alimentary, alcohol and biliary factors caused the development of acute pancreatitis in 211 (92.1%) patients. We did not note a significant difference in the etiological factor of acute pancreatitis between the comparison groups (Table IV).

Postoperative pancreatitis, which developed in 2 (0.9%) patients, deserves special attention. In one patient it occurred after splenectomy, in another patient it developed after left hemicolectomy for a tumor of the colon. The occurrence of postoperative pancreatitis has some difficulties for early diagnosis, because its clinical symptoms are superimposed on the early postoperative period with its characteristic postoperative pain, functional intestinal paresis, the introduction of nonsteroidal anti-inflammatory drugs. All this erases the clinical picture of postoperative pancreatitis and makes it unclear for diagnosis.

The presence of concomitant pathology undoubtedly affects the course of acute pancreatitis, exacerbates disorders of the systems and organs that are compromised by the underlying disease, and often becomes the reason for prolonging hospital stay. Among the comparison groups in the group with moderate-severe acute pancreatitis, the frequency of concomitant pathology was significantly higher than in the group with mild acute pancreatitis – 92.9% (92) cases and 78.5% (102) cases, respectively ($p<0.05$). A significant predominance of the number of cases of concomitant pathology in the group of patients with moderate-severe AP compared with the group of patients with mild AP was observed in the following pathologies: diabetes mellitus – 12 (12.1%) and 5 (3.8%) ($p<0.05$); gallstone disease – 19 (19.2%) and 12 (9.2%), respectively ($p<0.05$); concomitant pathology of the stomach and duodenum – 67 (67.7%) and 58 (44.6%), respectively ($p<0.05$); obesity – 13 (13.1%) and 4 (3.1%), respectively ($p<0.05$).

The analysis of laboratory parameters determined during hospitalization of patients, revealed a significant difference in the comparison groups between the following indicators: blood sugar, leukocyte level, the level of stabs, lymphocytes, total protein, serum amylase, urinary diastase, ALT, AST, creatinine level, prothrombin index, neutrophil-lymphocyte ratio ($p<0,05$) (Table V).

In the structure of complications in patients from moderate-severe AP group transient organ failure and persistent organ failure developed in 63 (63.6%) cases, pleuritis – in 27 (27.3%) cases, fluid collections – in 16 (16.2%) cases, phlegmon of the retroperitoneal space in 11 (11.1%) cases, peritonitis – in 16 (16.2%) cases, pseudocyst of the pancreas – in 7 (7.1%), pancreatogenic diabetes mellitus – in 3 (3.0%) cases, parapancreatic abscess – in 1 (1.0%) case, other complications – in 34 (34.3%) cases.

DISCUSSION

In total, 29 early laboratory biomarkers for the severity in acute pancreatitis were reported in 181 studies [17]. In recent years at the stage of hospitalization much attention is paid to the study of hemogram as a simple and cost-effective method of outcome prediction in patients with acute pancreatitis [18]. In the current study, we have studied the association of almost 20 early routine laboratory indicators with severity of acute pancreatitis. The group of patients with moderate-severe acute pancreatitis has showed simultaneous significant increase in the level of enzymes in the blood and urine during hospitalization, which indicated the presence of active inflammation of the pancreas.

Changes in the general analysis of blood in patients with acute pancreatitis in the early phase of the disease are not strictly specific [9]. Related to this is the difficulty of differential diagnosis between aseptic and septic types of AP in early stage. In the group of patients with moderate-severe acute pancreatitis there was moderate leukocytosis – $12.2\pm4.7\times10^9$ / L, a shift of the leukocyte formula to the left –16.3 ± 12.2% of stabs and a decrease of lymphocytes to 12.8±7.7% compared with similar indicators in the group with mild acute pancreatitis ($p<0.05$).

The significant relationship between stress hyperglycemia and adverse clinical outcomes in acute pancreatitis was proved [19]. The presence of hyperglycemia 7.7±4.2 mmol/L in the group of patients with moderate-severe AP indicates an impression of the pancreatic parenchyma and is an unfavorable prognostic factor.

The prothrombin index in patients with moderately-severe AP was lower than in the mild group ($p<0.05$), which can be explained by the development of hyper- and dysmetabolism syndrome, which is more expressed in severe types of AP.

In this study, there was a significant increase in the neutrophil-lymphocyte ratio (NLR) in the group of patients with moderate-severe AP compared with the same indicator in the group with mild degree ($p<0.05$). The increase in NLR can be explained by the fact that in the presence of a powerful source of inflammation, the number of neutrophils increases. At the same time, severe impressions exhaust the immune system and reduce the number of lymphocytes [14]. Therefore, the higher the NLR, the more severe the patient's condition.

The overall mortality rate in acute pancreatitis is associated with its severity and increases with joining the infection to the source of necrosis [2-5,20]. In our study, there were no fatalities in the group of patients with mild AP. There were 21deaths in the group of patients with moderate-severe AP, including 20 in patients with severe disease and 1 in patient with moderate disease. Among all patients, who died, 7 (33.3%) were operated on. Postoperative mortality was 25%.

CONCLUSIONS

1. Men predominated in the structure of all patients with acute pancreatitis, but there was a significant predominance of women in the group with severe AP compared with mild – 34 (26.2%) and 39 (39.4%), respectively ($p<0.05$). The association of the age group of 61-70 years with the severity of acute pancreatitis was revealed ($p<0.05$).
2. Most often (61.1%) patients were hospitalized in the period from 6 to 48 hours from the onset of the disease. There was no significant difference between the terms of hospitalization in the groups of patients with mild and moderately-severe acute pancreatitis ($p>0.05$).
3. We did not find an association between the causes of acute pancreatitis and its severity. In both comparison groups, the dominant causes of AP were alimentary-alcohol and biliary factors – in 211 (92.1%) patients. There were gender differences in the structure of the causes of AP: alcohol abuse was the main cause of acute pancreatitis in men, in women the dominant cause was gallstone disease.
4. In the group of patients with moderate-severe acute pancreatitis, the frequency of concomitant pathology was significantly higher than in the group with mild acute pancreatitis – 92.9% (92) cases and 78.5% (102) cases, respectively due to diabetes, gallstone disease, pathology of the stomach and duodenum and obesity ($p<0.05$).
5. The association between the severity of acute pancreatitis and the following laboratory parameters determined during hospitalization of patients: blood sugar, leukocyte levels, the level of stabs, lymphocytes, total protein, serum amylase, urinary diastase, creatinine, ALT, AST, prothrombin index, neutrophil-lymphocyte ratio was revealed ($p<0.05$).

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ORIGINAL ARTICLE

AGE FEATURES OF DECIDUOUS TEETH CARIES PARAMETERS IN 3-6 YEARS OLD AGED CHILDREN

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ABSTRACT

The aim: Estimation of caries prevalence and intensity, determination for treatment necessity of deciduous teeth in 3-6 years old aged children from Poltava region for further effective development of programs for caries and its complications prevention.

Materials and methods: Totally 335 children from 3 to 6 years old of preschool institutions of Poltava and Poltava region aged were examined with the signed accordance of their parents. All children were examined for the prevalence (%) and intensity of caries of deciduous teeth by the Decay Extracted Filling index (DEF index). Quantitative parameters were processed by standard statistic methods. The calculation of the highest caries intensity (Significant Index of Caries) was performed according to the D. Bratthol`s method. The level of dental aid (LDA) was assessed by the DEF index according to P.A. Leus recommendations. Treatment necessity of children was also determined.

Results: The research in caries prevalence of deciduous teeth of revealed that the number of children with caries increases with their age. The most significant parameter growth is observed at the age of 4 to 5 years. Carious lesions intensity increases at the age from 4 to 5 and from 5 to 6 years most significantly.

Conclusions: The most common indicator in all studied groups was a D-parameter, which indicates low parents awareness about deciduous teeth treatment necessity. That case confirms low level of dental aid (14%) and significant treatment need which is 50.7 %. Affection of molars always exceeds the affection of other groups of teeth. We did not find a significant difference in caries distribution among children of different genders. The obtained results encourage realization of sanitary and educational propagation on the awareness of parents on dental healthcare of their children.

KEY WORDS: children, deciduous teeth, caries, prevalence, intensity

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INTRODUCTION

Despite the numerous achievements in dentistry dental caries remains one of the prior problems in children. This statement is proved by epidemiological studies held in different regions of Ukraine in different time periods, which indicate a significant prevalence of this dental disease. The above-mentioned investigations indicate a significant impact of environmental features of the region on dental morbidity. The prevalence of caries in different age groups varies from 62% to 96.5% along with the intensity of carious lesions from 3.2 to 7.2 teeth [1-6]. Significantly higher rates of dental caries are found in rural children in comparison to children living in cities [7,8].

Particular disturbance is arised by the high incidence of early dental caries in children, which has 62% spread among children under 2 years old, and 70.3% spread in 3 years old children. This issue induces epidemiological studies performance in order to determine priority areas for deciduous teeth caries prevention in preschool children [9,10]. Receiving of up-to-date data on the prevalence and intensity of major dental diseases of different age groups provides dental scientists with a possibility to objectively assess the necessity in developing and implementation of effective prevention programs and measures. Effective prevention programs and early treatment allow to improve the quality of children dental health and their general somatic health quality respectively [10,11].

THE AIM

Estimation of caries prevalence and intensity, determination for treatment necessity of deciduous teeth in 3-6 years old aged children from Poltava region for further effective development of programs for caries and its complications prevention.

MATERIALS AND METHODS

Totally 335 children from 3 to 6 years old of preschool institutions of Poltava and Poltava region aged were examined with the signed accordance of their parents.

Examinations were held in medical cabinets of preschool institutions of Poltava and its region in compliance with the rules of humane treatment of patients in accordance with the Tokyo Declaration of the World Medical Association, international recommendations of the Declaration of Human Rights of Helsinki, the Council of Europe Convention on Human Rights and Biomedicine and Scientists Code of Ethics.

All children were examined for the prevalence (%) and intensity of caries of deciduous teeth by the DEF-index, according to which "D" is for decayed, "E" is for extracted due to caries

Table I. Prevalence and intensity deciduous teeth caries in children of 3 to 6 years old (M±m)

Age (years old)	Quantity of children	Caries prevalence		Caries intensity (DEF index)
		absolute	%	
3	53	18	34,0±6,57	1,3±0,36
4	86	31	36,0±5,20	1,5±0,31
	P^{3-4}	>0,05 t=0,25		>0,05 t=0,41
5	101	64	63,4±4,82	2,0±0,32
	P^{3-5}	<0,01 t=3,61		<0,01 t=2,61
	P^{4-5}		<0,01 t=3,85	<0,01 t=2,40
6	95	66	69,5±4,75	3,1±0,44
	P^{3-6}	<0,001 t=4,38		<0,001 t=3,52
	P^{4-6}	<0,01 t=2,91		<0,01 t=2,68
	P^{5-6}	>0,05 t=0,90		>0,05 t=1,37
Total	335	182	53,4±2,72	2,3±0,21

Note. P^{3-4}. . .- difference probability of parameters in children of different age.

Table II. Caries indices of deciduous teeth in children of 3 to 6 years old with gender consideration (M±m)

Age (years old)	Total	Gender, quantity		Caries indices		
				Prevalence		Caries intensity (DEF index)
				abs.	%	
3	53	girls	26	9	34,6±9,51	0,88±0,43
		boys	27	9	33,3±9,25	1,74±0,56
		$P^{3\ b-g}$		>0,05 t=0,10		>0,05 t=1,21
4	86	girls	39	10	25,6±7,08	1,05±0,40
		boys	47	21	44,7±7,33	1,89±0,44
		$P^{4\ b-g}$		>0,05 t=1,87		>0,05 t=1,40
5	101	girls	43	27	26,7±3,9	2,62±0,50
		boys	58	37	38,9±4,4	2,53 ±0,42
		$P^{5\ b-g}$		>0,05 t=0,14		>,05 t=0,14
6	95	girls	39	27	62,8±6,8	3,67 ± 0,91
		boys	56	39	67,2±6,0	3,09 ± 0,56
		$P^{6\ b-g}$		>0,05 t=0,49		>0,05 t=0,53
3-6	335	girls	147	73	49,7 ± 14,5	2,18 ± 0,30
		boys	188	106	56,4 ± 14,1	2,43 ± 0,24
		$P^{3-6\ b-g}$		>0,05 t=0,33		>0,05 t=0,64

Note. P^{3} b-g . . .- difference probability of parameters in children of different gender in each age group.

complications, "F" is for filled deciduous teeth. Quantitative parameters were processed by standard statistic methods.

The calculation of the highest caries intensity (Significant Index of Caries) was performed according to M. Nishi and D. Bratthol`s method [12], which supposed the estimation of individual DEF index for each child, followed by the definition of 1/3 of children with the highest values of caries intensity. Afterwards the calculation of the average DEF index of the selected subgroup was performed.

The level of dental aid (LDA) was assessed by the DEF index according to P.A. Leus recommendations using the following formula:

$$LDA = 100\% - 100^{x}(D/DEF),$$

where D is the average number of untreated carious (decayed) lesions, including secondary caries, DEF is the average intensity of caries of deciduous teeth in the researched group [13].

LDA should be interpreted as the following: 0-9% - poor level; 10-49% - insufficient level; 50-74% - satisfactory level; 75-100% - good level.

Necessity of caries treatment of children is an indicator that determines the percentage of children who require dental care. This figure was calculated by the following formula:

Table III. Caries affection of different deciduous teeth groups of maxilla and mandible in children of 3 to 6 years

Age (years old)		Quantity of affected teeth, %					
		I	II	III	IV	V	Total
3	Maxilla	11,4±5,59	8,6±5,72	0	24,3±7,34	17,1±6,30	61,4±11,52
4		15,4±4,56	11,5±3,88	0,8±0,77	15,4±4,29	14,6±4,28	57,7±8,14
5		16,9±3,37	8,5±2,44	1,2±1,30	13,8±2,72	14,6±3,05	55,0±5,85
6		15,2±2,81	9,5±2,35	3,2±1,43	17,1±2,81	14,2±2,66	59,2±5,40
3-6		15,5±1,85	9,4±1,47	1,8±0,78	16,4±1,76	15,7±1,72	57,7±2,94
3	Mandible	0	0	0	22,9±6,80	15,7±6,32	38,6±8,70
4		0	0	0,8±0,77	20,0±4,95	21,5±5,33	42,3±6,96
5		0,8±1,27	0,8±1,27	0,8±1,14	23,1±3,65	19,6±3,39	45,0±5,12
6		2,2±1,35	1,3±1,01	1,6±1,22	20,3±3,21	15,5±2,71	40,8±4,50
3-6		1,2±0,61	0,8±5,43	1,0±7,07	21,4±2,07	17,9±1,88	42,3±2,65

Table IV. The value of the deciduous teeth caries intensity components in children of 3 to 6 years old

Age (years old)	Quantity of children	DEF index	The value of DEF index components					
			D		F		E	
			absolute	%	absolute	%	absolute	%
3	53	70	62	88,6±27,42	8	11,4±5,95	0	0
4	86	130	117	90,0±20,04	9	6,9±4,91	4	3,1±3,08
5	101	260	232	89,3±13,32	23	8,8±3,06	5	1,9±1,15
6	95	316	260	81,9±13,76	40	12,9±4,17	16	5,2±2,93
Total	335	776	671	86,3±8,27	80	10,4±2,21	25	3,3±1,35

Need of caries treatment = n / N x100%; "n" is the number of children who have intreated carious teeth, "N" is the number of examined children.

RESULTS

The prevalence of deciduous teeth caries in children increases from the age of 3 to 6 years old (Table I). The largest growth in the number of children with carious lesions is observed within the age 4 to 5 years old (27.4%). Comparison of other age periods revealed a slight increasement in the prevalence of deciduous teeth caries: from the age 3 to 4 years - 2% and from the age 5 to 6 years - 1%.

Caries intensity increases of 3 to 6 years old in children and most significantly within period of 5 to 6 years old. The average rate of caries intesity in 6-year-old children was higher by 1,1 teeth compared to the 5-year-olds children. The increasement was less significant in other age periods (within 3 to 4 years old - by 0.2; within 4 to 5 years old - by 0.5 teeth). The intensity of deciduous teeth caries increases by 2.4 times in the age of 3 to 6 years old children ($p < 0{,}001$).

The study of the deciduous teeth caries prevalence and intensity in 3 to 6 years old children did not reveal a significant difference between both genders (Table II). I.e the frequency of caries in girls and boys is even. However, the quantity of boys with caries is higher both in general at the age of 3-6 years old and in each age period as well as the caries intensity is slightly higher ($p > 0.05$) than in girls.

At the age of 3 caries caries was found 1.6 times more often in maxillary teeth than in mandibular ones. We did not observe any case of affected incisors or canines on mandible and canines on maxilla (Table III). In 80% of cases deciduous molars were affected by caries in 3 years old children. At the age of 4 years old 71.5% of molars were carious, while in 5 years old the percentage was 70.7% and 66.2% in 6 years old children. Generally, deciduous molars are affected in 69.9% of cases at the age of 3-6 years. This group of teeth provides such functions of the masticatory apparatus as chewing, maintaining the height of the bite. Therefore, prevention and early treatment of deciduous molars at this age are very important for maintainance the integrity of the dentition and the possibility of adequate mastication.

The research in components of DEF index is considered to be important. Great attention is drawn by the significant quantity of carious teeth in all age groups and in children of 3 to 6 years old, in paricular (Table IV). 86.3% of carious teeth stay unfilled while the percentage of treated and filled teeth makes 10.4% only. 3.3% of teeth are extrected due to caries complications.

The level of dental care among 335 children of 3 to 6 years old is 14% (LDA = 100% -100% (3.7 / 4.3)), which corresponds to an insufficient level. The treatment need of children makes 50.7% (170/335 x100%). The received results evidences that parents of children of the studied age do not pay sufficient attention to maintaining of dental health of their children.

The calculation of the highest caries intensity (Significant Index of Caries) of children with affected teeth was calculated. For 3 years old children this indicator of was 3,8 ± 0,76, while in 4-year-olds increased to 4,4 ± 0,62. In 5-year-olds the parameter grew to 6,3 ± 0,51. The highest SIC index was in 6-year-old children which made 8, 2 ± 0.75. The analysis of the obtained data revealed a statistically significant increase in the SIC index with the children age. The average highest rate of caries intensity in 3 to 6 years old children was determined at the level of 5.8 ± 0.35.

DISCUSSION

The prevalence of caries of deciduous teeth in 3-6 years old aged children from Poltava region is 53.4 ± 2.72%, the intensity is 2.3 ± 0.21 teeth, which is lower than in other regions of Ukraine, where such studies were conducted. For example, in children of Precarpathian region the prevalence of caries of deciduous teeth in preschool children is 90.95 ± 2.66%, the intensity of caries is 3.52 ± 0.43 teeth [14], and in children of Transcarpathian region the prevalence of caries among children aged 5-6 years was 98.0 ± 2.2% (98.1 ± 2.1% among boys and 97.9 ± 2.3% among girls), and DEF index was 14.9 ± 1.9 regardless of the sex of the subjects [15]. This requires a detailed study of risk factors for dental pathology in children of different regions of residence. We determined the treatment necessity of children, it is 50.7%, which is much better than in other areas [14,15]. We also found that temporary molars of children aged 3-6 years are affected in 69.9% of cases, and according to clinicians of Precarpathian region - 51.29 ± 2.47% [15], in Transcarpathian region - 89.5% [14] . This group of teeth provides certain important functions of the dentition (chewing, maintaining the height of the bite). Therefore, prevention and early treatment of deciduous molars at this age are very important to maintain the integrity of the dentition. The results indicate the need for timely detection and treatment of dental caries in children, which should draw the attention of parents and emphasize their attention to strengthening measures to preserve the dental health of children.

CONCLUSIONS

The study of deciduous teeth cariest prevalence in children revealed that the number of children with caries increases with age. The most significant growths of the index is observed at the age of 4 to 5. The intensity of carious lesions increases at the age of 4 to 5 and 5 to 6 most significantly. In all investigated age groups the most common index was a "D" index, which indicates low parents awareness about deciduous teeth treatment necessity. Also, it confirms the low level of dental aid (14%) and a significant need for treatment, which is 50.7%. The affection of molars always exceeds the affection of other groups of teeth. We did not find a significant difference in teeth affection between children of different gender. The obtained results encourage realization of sanitary and educational propagation on the awareness of parents on dental healthcare of their children.

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ORIGINAL ARTICLE

CORRELATION OF CARDIAC BIOMARKERS WITH THE LEVELS OF SELENIUM AND ANTIOXIDANT ENZYMES IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND A HISTORY OF HYPERTENSION

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ABSTRACT

The aim: To determine the interrelations between the levels of antioxidant enzymes, selenium and the markers of myocardial injury in patients with non-ST segment elevation myocardial infarction and a history of antecedent arterial hypertension.

Materials and methods: A total of 72 patients with non-ST segment elevation myocardial infarctionwere examined (42 with antecedent hypertension - group 1; 30-without hypertension – group2).

Results: Patients of group 1 were characterized by significantly higher troponin I levels ($p = 0.006$), creatine kinase MB levels ($p=0.008$) and lower levels of superoxide dismutase ($p=0.005$), catalase ($p=0.003$) and selenium ($p=0.008$) as compared with group 2. In both groups, the activity of superoxide dismutase had an inverse correlation with troponin I: ($r = -0.46$, $p = 0.005$) and ($r = -0.38$, $p = 0.004$), respectively. A significant inverse relationships were found between selenium levels and both markers of myocardial injury in group 1 ($p \leq 0.009$), whereas in group 2 a weak correlation was found between the levels of selenium and troponin I only ($p=0.006$).

Conclusions: The obtained data suggest that the levels of selenium and antioxidant enzymes in blood of all patients with non-ST elevation myocardial infarction inversely correlate with cardiac biomarkers. Patients with non-ST elevation myocardial infarction and a history of hypertension have significantly lower levels of antioxidant agents, higher levels of markers of myocardial injury, and stronger connections between them, indicating the development of more significant myocardial injury.

KEY WORDS: myocardial infarction, hypertension, cardiac biomarkers, selenium, antioxidant enzymes

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INTRODUCTION

Acute myocardial infarction is one of the leading causes of mortality and a widespread cause of disability worldwide. A major advances in the treatment of acute coronary syndromes and myocardial infarction have occurred over the past several decades. Interventional cardiologic or thrombolytic approaches had become a major breakthrough due to the ability to quickly restore blood flow to the myocardium during heart attack [1]. Thought 'reperfusion' is considered as a major therapeutic aim, the process of ischemia followed by reperfusion is often accompanied by the activation of a damaging cascade. While the pathophysiology of ischemia-reperfusion is complex and not completely understood, there is substantial proof implicating reactive oxygen species as an inceptive cause of the damage [2,3]. Free radicals formed during oxidative stress can oxidize proteins to inactive states, initiate lipid peroxidation and cause DNA strand breaks, all potentially harmful to normal cellular function [4]. Free radicals have been shown to be generated following routine clinical procedures such as thrombolysis and coronary bypass surgery, due to the inevitable episode of ischemia-reperfusion. Moreover, they have been associated with poor recovery of myocardium after ischemia, and recent studies provide an evidence of their role in the development of infarction, apoptosis, necrosis, arrhythmogenesis and endothelial dysfunction following ischemia-reperfusion [5].

Endogenous free radical scavengers such as superoxide dismutase, catalase and selenocysteine dependent enzymes are the key agents of the antioxidant system that act synergistically and protect cardiomyocytes during ischemic and reperfusion injury [6, 7]. Superoxide dismutase, which operates primarily within cells and in extracellular matrices, catalyzes the dismutation of the superoxide anion into hydrogen peroxide. It is the most effective antioxidant enzyme in humans [8]. In turn, catalase and selenocysteine dependent enzymes remove hydrogen peroxide and maintain the cellular redox balance, thus complementing and finishing the cycle of reactive species deactivation [9].

Therefore, a determination of antioxidant status and its influence on the level of myocardial injury in patients with non-ST segment elevation myocardial infarction and antecedent hypertension is a topical issue of treatment of such patients.

Table I. The levels of cardiac biomarkers and antioxidant agents in blood of examined patients.

Indicator	Group 1 (NSTEMI + hypertension)	Group 2 (NSTEMI)	p
Troponin I, ng / mL	28.3 ± 3.23	20.9 ± 2.46	0.006
CK-MB, units / L	186.3 ± 24.4	150.5 ± 19.8	0.008
SOD, units/mgHb	2.1 ± 0.02	2.7 ± 0.07	0.005
CAT, mcmol/min ×mgHb	412.3± 35.6	643.4± 32.1	0.003
Selenium, mcg/ml	0.21 ± 0.02	0.26 ± 0.01	0.001

Table II. Correlation between the levels of cardiac biomarkers and antioxidant agents in blood of examined patients.

Indicator	Group 1 (NSTEMI + hypertension)	Group 2 (NSTEMI)
SOD and troponin I	r = -0.46, p = 0.005	r = -0.38, p = 0.004
SOD and CK-MB	r = -0.34, p = 0.004	r = -0.22, p = 0.018
CAT and troponin I	r = -0.28, p = 0.006	r = -0.25, p = 0.003
CAT and CK-MB	r = -0.61, p = 0.003	r = -0.14, p = 0.022
Selenium and troponin I	r= -0.32, p = 0.009	r= -0.12, p = 0.006

THE AIM

The aim of our study was to determine the interrelations between the levels of antioxidant enzymes, selenium and the markers of myocardial injury in patients with non-ST segment elevation myocardial infarction and a history of antecedent arterial hypertension.

MATERIALS AND METHODS

42 patients with NSTEMI and antecedent hypertension were examined in the Cardiological unit of Kharkiv Regional Clinical Hospital, Kharkiv, Ukraine. The mean age of patients was 61.82 ± 7.65 years; there were 11 women and 31 men; the duration of hypertension history was 9.62 ± 3.16 years. All these patients were included in group 1. Also, 30 patients with NSTEMI without previous history of hypertension were examined and formed group 2. Groups were comparable by age and gender.

All patients were examined by general clinical, anthropometric, laboratory and instrumental investigation methods. 12-lead electrocardiogram and transthoracic echocardiography were performed in all of patients by conventional methods. Standard general and biochemical assays of blood plasma were conducted.

The levels of troponin I (TnI) and creatine kinase-MB fraction (CK-MB) were determined in blood of all patients by immunochemical analyzer AQT90 FLEX, "Radiometer". Selenium level was measured by fluorometric method (Fluorat 02-2M, Czech Republic). The activity of superoxide dismutase (SOD) and catalase (CAT) was determined by spectrophotometric method (Specord M-40, Germany). All blood samples were taken when admitting patients to the hospital.

The diagnosis of NSTEMI was established in accordance with the Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of European Society of Cardiology, 2015 [10] and International Disease Classification of 10th revision.

Medical aid was provided to the examined patients on in-patient basis according to the clinical protocols of the Ministry of Healthcare of Ukraine and local protocols.

All patients signed an informed consent to participate in the study. Ethical approval was obtained from the Bioethics Commission of the Kharkiv National Medical University of Ukraine.

Statistical analysis was performed with SPSS 19 software for Windows. Student's t-test (t) was applied for evaluating credibility between mean quantitative positions of two samples. The Pearson's correlation coefficient (r) between different indicators was analyzed. A value of $p \leq 0.05$ was considered as statistically significant.

RESULTS

During our research we have obtained the following results: patients of group 1, who had NSTEMI and a history of hypertension, demonstrated more intense myocardial injury according to the significantly higher levels of troponin I and creatine kinase-MB, while the activity of antioxidant defenses was notably lower as compared with group 2. The results of study are presented in table I. It should be noted, that the level of troponin I in patients with NSTEMI and antecedent hypertension was 26.1% higher than in patients with NSTEMI only, and the level of CK-MB was 19.3% higher, respectively.

In the same time, all studied indices of antioxidant agents were significantly lower in patients of group 1: SOD - 22.2%, CAT - 35.9%, selenium - 19.2% lower, respectively.

The study of the interrelations between the levels of biomarkers of myocardial injury and indicators of the antioxidant system in blood of examined patients allowed

us to establish the presence of correlations of varying degrees between the content of troponin I, CK-MB and the levels of SOD, CAT and selenium. The predominance of correlations' number and strength was observed in patients with NSTEMI and antecedent hypertension. The results of study are presented in table II. In both groups, the activity of superoxide dismutase had a negative correlation with troponin I: ($r = -0.46$, $p = 0.005$) and ($r = -0.38$, $p = 0.004$), respectively. The same pattern of correlation was observed between catalase and troponin I, however, the strength of connections was slightly weaker in both groups. So, the lower was the level of endogenous antioxidant enzymes, the higher was the level of myocardial injury during NSTEMI with or without hypertension.

The study of correlations between catalase and creatine kinase-MB levels demonstrated a strong negative correlation ($r = -0.61$, $p = 0.003$) between the studied indices in group 1, while a weak negative relationship ($r = -0.14$, $p = 0.022$) was revealed in group 2. The correlation between superoxide dismutase and creatine kinase-MB levels has shown moderate inverse interdependence in group 1 and weak negative relationship in group 2.

Significant negative relationships were found between selenium levels and the indices of cardiac biomarkers in group 1: both with troponin I ($r=-0.32$, $p=0.009$) and creatine kinase-MB ($r=-0.18$, $p=0.005$), whereas in group 2 a weak correlation was found between the levels of Se and troponin I only ($r=-0.12$, $p=0.006$).

DISCUSSION

As seen from our research, patients with NSTEMI and antecedent hypertension demonstrated more evident myocardial injury according to the significantly higher levels of cardiac biomarkers, while the activity of antioxidant defenses was notably lower as compared with NSTEMI patients with no hypertension history. It is well known, that cardiac troponins are more sensitive and specific markers of cardiomyocyte injury than MB isoenzyme of creatine kinase [10]. However, in this case both biomarkers have shown reliable differences between studied groups.

As seen in table I, patients with NSTEMI and antecedent hypertension experience more significant depletion of antioxidant defense resources. In pathological underlying situations, particularly atherosclerosis or hypertension, the release of reactive oxygen species exceeds endogenous antioxidant capacity, leading to cell injury. Therefore, development of acute myocardial infarction against the background of hypertension accelerates free radical injury, inhibits defensive abilities of antioxidant system and slows down the recovery of its components [11, 12].

The study of the correlations between the levels of biomarkers of myocardial injury and the activity of antioxidant defenses demonstrates the fact that the activity of antioxidant enzymes directly influences the degree of myocardial injury during NSTEMI. Stronger negative connections between the antioxidant enzymes and the markers of myocardial injury in patients with antecedent hypertension suggest that there is a certain "exhaustion" of the enzymatic component of antioxidant system going on in patients, who experience almost a 10-years history of antecedent hypertension.

Selenium is a trace element, which possesses some degree of its own antioxidant activity or can act as a component of selenoproteins [13]. The provision of membranes with selenium, along with other factors that determine the resistance of cells to oxidative stress, is of fundamental importance for cardiomyocytes [14]. Low level of selenium in blood of patients with NSTEMI, especially in those with antecedent hypertension, and its inverse relationship to troponin I reflects significant disorders of lipoperoxide homeostasis, reduction of protective capabilities of the antioxidant system, which in turn causes disruption of the structural and functional organization of cardiomyocyte membranes and indicates the important role of initiation of oxidative stress as a pathogenetic mechanism in the development of acute myocardial infarction and hypertension.

CONCLUSIONS

The obtained data demonstrate that selenium levels and the activity of antioxidant enzymes in blood of patients with NSTEMI inversely correlate with cardiac biomarkers. Patients with NSTEMI and a history of hypertension have significantly lower levels of antioxidant agents, higher levels of troponin I and creatine kinase-MB, and stronger connections between them, indicating the development of more significant myocardial injury. Further research should be performed in this realm to find effective methods of correction of antioxidant status in patients with acute myocardial infarction in order to prevent worsening of myocardial injury.

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ORIGINAL ARTICLE

IMPLEMENTATION OF THE POLISH-UKRAINIAN PROJECT "SELF-DIAGNOSIS OF BREAST CANCER IN YOUNG UKRAINIAN WOMEN" WITHIN THE FRAMEWORK OF THE RITA PROGRAM – CHANGES IN THE REGION AT THE KHARKIV STATE ACADEMY OF PHYSICAL CULTURE

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ABSTRACT

The aim: To prove the effectiveness and necessity of implementation of the Polish-Ukrainian project"Self-diagnosis of breast cancer in young Ukrainian women within the framework of the RITA program-changes in the region(on the example of the Kharkiv State Academy of PhysicalCulture)

Materials and methods: 200 people took part in the study: 100 students and 100 lecturers and employees of the Kharkov State Academy of Physical Culture, attended lectures on epidemiology and prevention, risk factors and clinical features of breast cancer; took part in practical exercises on visual methods of breast cancer screening and the formation of self-examination skills. Each participant in the project was tested at the beginning and at the end of training, the tests included 20 questions about risk factors and clinical signs of breast cancer and an algorithm for its self-examination. Each question to which the correct answer was given was scored 1 point (the maximum number of points for one test was 20 points)

Results: During the testing, it was found that the awareness of applicants and employees of the Kharkiv State Academy of Physical Culture regarding risk factors and clinical features of breast cancer, as well as the self-examination procedure, increased by 68% and 67%, respectively

Conclusions: The study confirms that the transfer of Polish experience to the project "Self-diagnosis of breast cancer in young Ukrainian women" contributes to the formation of a culture of disease prevention through self-observation and self-examination of young Ukrainian women, which can save human lives, since raising public awareness and gaining practical knowledge will certainly change the fate of many people

KEY WORDS: RITA project, breast cancer, Ukrainian youth, health of the nation

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INTRODUCTION

Breast cancer occupies a leading place in the structure of cancer incidence among the female population in most countries of the world. This determines the relevance and importance of the search and development of new methods of anticancer treatment. Due to the wide spread in the world and the first place in the structure of malignant neoplasms in women, the problem of breast cancer is one of the most urgent in modern oncology. Recently, an increase in the incidence and mortality of breast cancer has been observed throughout the world. More than 1 million new cases of breast cancer are registered in the world every year [1-5].

Analysis of the dynamics of malignant neoplasms affecting the population of Ukraine indicates an increase in the incidence of breast cancer for the period from 1993-2003. From 40,0 to 60,9 per 100 thousand population, or more than 1,5 times. According to the National Cancer Registry, in 2018, 15,017 cases of breast cancer were registered in Ukraine (14,872 women and 145 men), and 5726 people died as a result of this disease (5679 women and 47 men). The highest incidence rates of breast cancer are among Ukrainian women over 60, although from the age of 30, cases of the disease are significantly increasing. Every fourth woman is diagnosed with breast cancer already at stage III-IV, when the effectiveness of treatment is significantly reduced [6].

The detection of breast cancer during preventive examinations in the country as a whole remains low, and the neglect rate, which is the leading criterion for the quality of diagnostics, on the contrary, is high. The real way to improve the results of treatment of breast tumors is early, and

Fig. 1. Teaching models for breast examination within the framework of the Polish-Ukrainian project RITA - Changes in the region "Self-diagnosis of breast cancer in young Ukrainian women", funded by the Polish-American Freedom Foundation

in some cases - preclinical diagnosis. This problem can be solved only if complex diagnostic methods are used. [7-10].

Measures for the early detection of breast cancer are primarily primary and secondary prevention. Early detection of breast cancer is especially important and can speed up the treatment process and reduce mortality.

Awareness of the risks of developing and early detection of breast cancer is the basis for reducing mortality from this disease. Regular breast self-examination is one of the most cost-effective methods for early detection of breast cancer in women. Unfortunately, the practice of self-examination of breast health in Ukraine remains low and requires popularization.

THE AIM

Purpose of the study is to prove the effectiveness and necessity of implementing the Polish-Ukrainian project "Self-diagnosis of breast cancer in young Ukrainian women" within the RITA program - changes in the region (on the example of the Kharkov State Academy of Physical Culture).

MATERIALS AND METHODS

The study involved 200 people: 100 students and 100 lecturers and employees of the Kharkov State Academy of Physical Culture, attended lectures on epidemiology and prevention, risk factors and clinical features of breast cancer; took part in practical exercises on visual methods of breast cancer screening and the formation of self-examination skills. Each participant in the project was tested at the beginning and at the end of training, the tests included 20 questions about risk factors and clinical signs of breast cancer and an algorithm for its self-examination. Each question to which the correct answer was given was scored 1 point (the maximum number of points for one test was 20 points).

RESULTS

Taking into account the problem of the incidence of breast cancer, a group of Polish and Ukrainian scientists from six higher educational institutions developed an innovative project aimed at increasing the knowledge of Ukrainian students about self-examination and prevention of breast cancer. The project is funded by the Polish-American Freedom Foundation within the framework of the RITA program - "Changes in the Region", which is implemented by the Education for Democracy Foundation [11].

The project "Self-diagnosis of breast cancer in young Ukrainian women" is aimed at transferring Polish experience to professional prevention of breast cancer among women

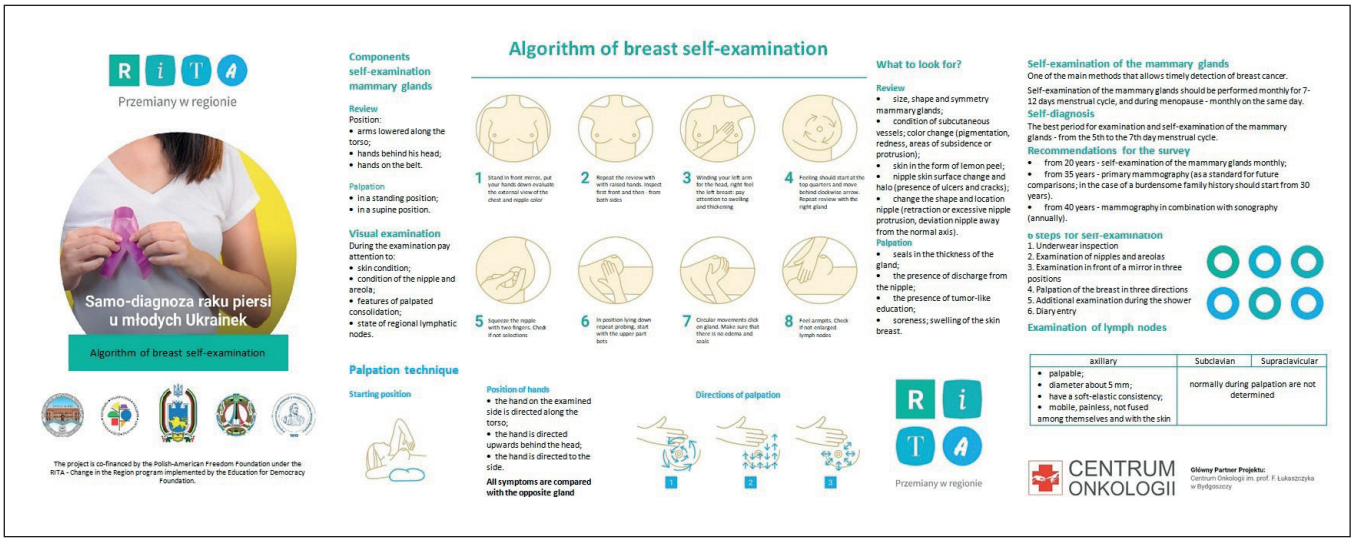

Fig. 2. Teaching materials developed within the Polish-Ukrainian project RITA - Changes in the region "Self-diagnosis of breast cancer in young Ukrainian women", funded by the Polish-American Freedom Foundation

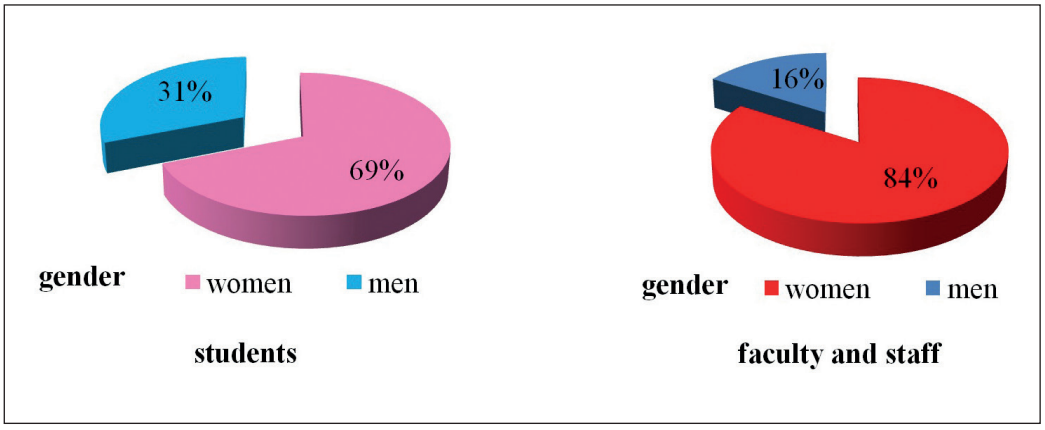

Fig. 3. Gender distribution of persons who took part in the training of breast self-examination within the framework of the Polish-Ukrainian project RITA - Changes in the region "Self-diagnosis of breast cancer in young Ukrainian women"

in Ukraine by self-examination and conducting training sessions for students and staff of five higher educational institutions from different regions of Ukraine. This project aims to demonstrate that civic engagement and scientific collaboration can be very effective and can lead to systemic change. So, introducing in Ukraine the training of self-examination of the mammary glands, it is planned to teach 965 people (students and staff), to introduce such changes in the future and change the culture of self-prophylaxis among citizens of Ukraine [12, 13].

Within the framework of the project, all partner universities, including the Kharkiv State Academy of Physical Culture, received training models (Fig. 1) and training materials (Fig. 2) necessary for conducting training sessions for students and employees.

The training was attended by 200 people: 100 students and 100 scientific and pedagogical workers and employees. Both women and men took part: among applicants for higher education, girls accounted for 69%, and boys - 31%, among teachers and staff, 84% of women took part, and men - 16% (Fig. 3).

Participation in the training of self-examination of the mammary glands took students from 16 to 45 years old, according to different courses and levels of higher education (Fig. 4). The greatest interest was shown by girls 18-21 years old (2-3 courses) and children 16-19 years old (1-2 courses).

Based on the results of monitoring the age and position of scientific and pedagogical workers and employees, it was established that employees of the Kharkov State Academy of Physical Culture from 20 to 73 years old took part in the training of self-examination of the mammary glands (Fig. 5). The most active were associate professors (26 women and 10 men), senior lecturer (19 women) and employees (17 women).

During the testing, it was found that the awareness of applicants and employees of the Kharkov State Academy of Physical Culture regarding risk factors and clinical features of breast cancer, as well as the self-examination procedure, increased by 68% and 67%, respectively (Fig. 6).

Thus, it was found that at the beginning of the implementation of the Polish-Ukrainian project "Self-diagnosis of breast cancer in young Ukrainian women" at the Kharkov State Academy of Physical Culture, the level of awareness of both students and employees regarding risk factors and clinical features of breast cancer, as well as self-examination procedure was low. In the process of attending lectures by students and employees on epidemiology, clinical features and prevention of breast cancer and practical exercises

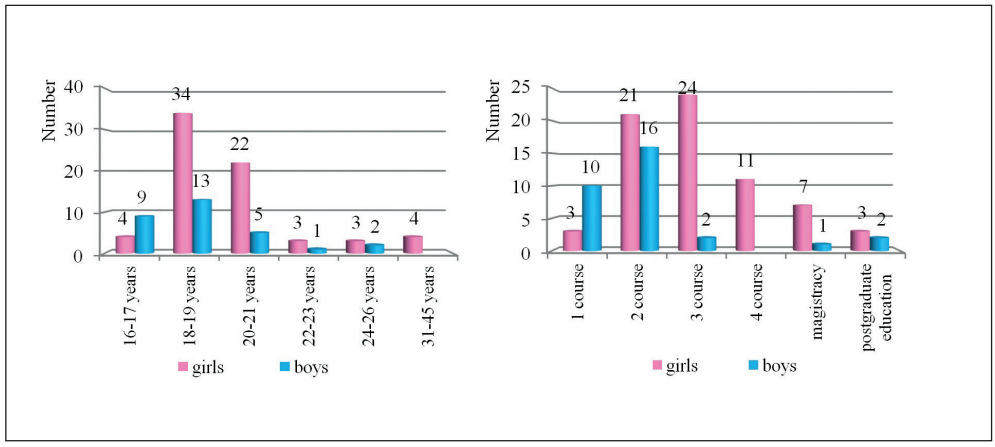

Fig. 4. Age and course of students who took part in the training of breast self-examination in the framework of the Polish-Ukrainian project RITA - Changes in the region "Self-diagnosis of breast cancer in young Ukrainian women"

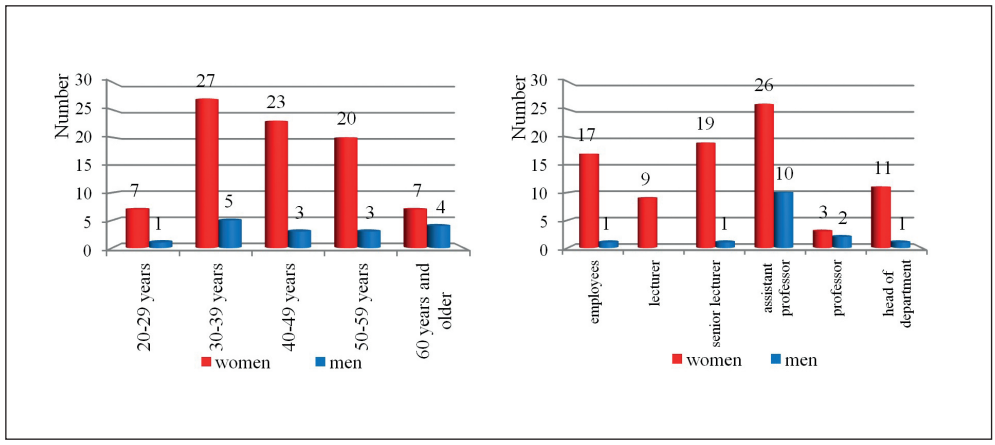

Fig. 5. Age and position of employees who took part in the training of breast self-examination in the framework of the Polish-Ukrainian project RITA - Changes in the region "Self-diagnosis of breast cancer in young Ukrainian women"

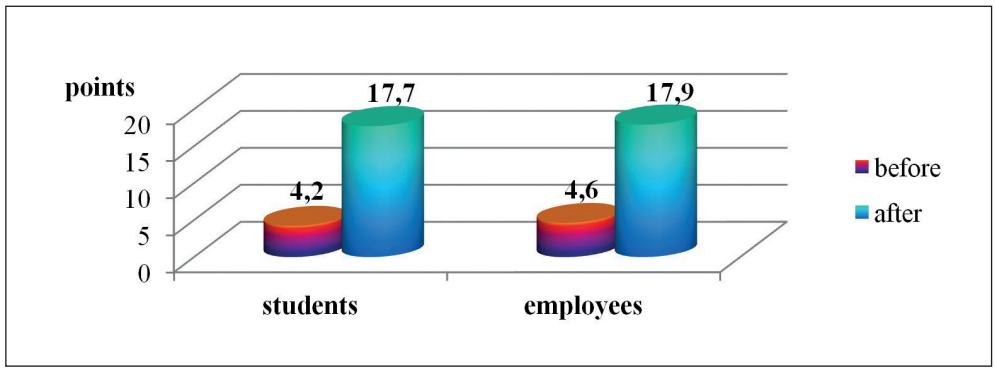

Fig. 6. The results of the assimilation of the material by students and employees of the Kharkiv State Academy of Physical Education regarding risk factors and clinical features of breast cancer in the framework of the Polish-Ukrainian project RITA - Changes in the region "Self-diagnosis of breast cancer in young Ukrainian women" (the maximum number of points for one test was 20 points)

Table I. The level of awareness of students and employees of the Kharkov State Academy of Physical Education regarding risk factors and clinical features of breast cancer (the maximum number of points for one test was 20 points)

Persons who took part in the project	At the beginning of training		At the end of training		Evaluation of reliability	
	points	%	points	%	t	p
Students	4,2±2,1	21%	17,7±1,6	89%	5,04	p<0,001
Scientific and pedagogical workers and employees	4,6±1,9	23%	17,9±1,4	90%	5,68	p<0,001

on visual methods of breast cancer screening and the formation of examination skills, the level of knowledge and skills significantly increased, as among students (t = 5,04; p <0,001) and employees (t = 5,68; p <0,001) (Table I).

Thus, it can be argued that the implementation of the Polish-Ukrainian project "Self-diagnosis of breast cancer in young Ukrainian women" at the Kharkov State Academy of Physical Culture is effective and should have its long-term continuation to popularize the method and practice of breast self-diagnosis as one of the effective means of cancer prevention breast.

DISCUSSION

Breast cancer is the most common cancer among women worldwide. There are many studies on breast self-examina-

tion [14-16]. It has been proven that early detection and treatment of the disease reduce the mortality rate [17, 18], but most breast cancer patients learn about their diagnosis at a late stage of the disease, negatively affects the survival rate [19]. Therefore, an early detection procedure is very important, and breast self-examination is one of the best methods for identifying the problem. Especially in low- and middle-income countries where health-related resources are limited and where socio-cultural influences tend to make women more hesitant about breast health issues, empowering women on their own is an important first step to examine them [20-22].

The findings of this study suggest that the implementation of the project "Self-diagnosis of breast cancer in young Ukrainian women" within the framework of the RITA - changes in the region will increase the level of awareness of the risk factors and clinical features of breast cancer, as well as the examination procedure, as the level of knowledge has increased in project participants by 67-68%.

At the third stage of the project, a visit of a Polish group of experts to partner universities of Ukraine is planned (Zhytomyr State University named after Ivan Franko, Kharkiv State Academy of Physical Culture, Communal Institution of Higher Education "Khortytsya National Educational and Rehabilitation Academy", Kherson State University, Lviv State University of Physical culture named after Ivan Bobersky) for holding consolidated and promotional events in the form of an organized "All-Ukrainian marathon of academic days of fighting breast cancer". The problem of breast cancer will be widely publicized through government bodies and the media, and about 10,000 people will become indirect recipients. Such actions can be implemented by other organizations and universities not included in the project, which ultimately consists in significantly accelerating the detection of breast cancer at an early stage, which can reduce mortality from this disease.

CONCLUSIONS

1. The study confirms that the transfer of Polish experience to the project "Self-diagnosis of breast cancer in young Ukrainian women" will contribute to the formation of a culture of disease prevention through self-observation and self-examination of young Ukrainian women, which can save human lives, since raising public awareness and gaining practical knowledge will certainly change the fate of many people.
2. This project aims to show that civic engagement and collaboration between scientists can be very effective and can lead to systemic change. In Ukraine, where the incidence of breast cancer has one of the highest rates, a number of preventive programs are proposed that largely popularize the methods and practices of breast self-diagnosis as an effective means of prevention.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

INTRABDOMINAL PRESSURE AND ITS CORRECTION IN ACUTE SURGICAL PATHOLOGY

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ABSTRACT

The aim: Improving the results of treatment of patients with acute surgical pathology of the abdominal cavity by correcting intra-abdominal hypertension (IAH).

Materials and methods: The results of examination and treatment of 187 patients with acute surgical pathology, which was accompanied by elevation of IAP. To compare the results, depending on the chosen diagnostic and treatment tactics, patients were divided into two groups: comparison and main. The comparison group (85 people (45,5%) included patients who have been treated with traditional approaches in diagnosis and treatment according to existing treatment protocols. The main group (102 people (54,5%) included patients in whose treatment we additionally used our proposed step-by-step approach in the treatment of IAH.

Results: Systemic complications occurred in 12 patients of the main group (11,8%) and in 46 patients of the comparison group (54,1%), while in the second group the frequency of systemic complications was significantly higher ($\chi 2 = 38,6$, CI 29,3-53,6, $p < 0,0001$). 20 patients (10,7%) died (2 patients of the main group (1,96%) and 18 patients of the comparison group (21,2%) ($\chi 2 = 17,85$, CI 10,4-29,18, $p < 0,0001$).

Conclusions: Use in the complex treatment of patients with acute surgical pathology of the abdominal cavity, accompanied by IAH, the proposed step-by-step approach has improved treatment outcomes by reducing the incidence of systemic complications from 54,1% to 11,8%, total mortality from 21,2% to 1,96% and postoperative mortality - from 22,4% to 2,4%.

KEY WORDS: intra-abdominal hypertension, abdominal compartment syndrome, staged treatment

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INTRODUCTION

Increased IAP remains an urgent problem, which occurs in acute surgical pathology of organs of the abdominal cavity and retroperitoneal space. Thus, according to the literature data, abdominal traumas, acute pancreatitis and other diseases of the abdominal cavity manifest the increase of IAP in 83,6% of patients leading to ACS development in 16,8% of cases [1,2]. In turn, ACS is accompanied by the development of severe dysfunction of body systems and causes mortality in 45,2% -95% of cases [3].

The pathogenesis of elevated IAP is based on increasing intra-abdominal volume due to paresis or pathological volume in the abdominal cavity, intestinal edema and mesenteric tissue in acute inflammatory processes of the abdominal cavity (acute pancreatitis, closed abdominal trauma, acute peritonitis) [4]. Surgical interventions in this category of patients increase the phenomena of dynamic intestinal obstruction in the early postoperative period, leading to the elevation of IAP [5].

Elevation of IAP can also occur with decreased abdominall cavity volume after various types of gernio- and/or abdominoplasty [6]. Separately, we should focus on laparoscopic technology, which is used in most cases to create carboxyperitoneum, which leads to increased pressure in the abdominal cavity. This limits the use of laparoscopic surgery for IAH in the setting of urgent care [7].

It should be noted that there are many methods of IAH treatment, most of which are invasive and require an anesthesiologist, and are limited for use in patients treated conservatively [8]. There is also no clearly formulated algorithm of actions to prevent ACS development that would solve the problem of complex abdominal pressure correction depending on the cause of ACS elevation (external, internal), the nature of the patient's breathing (mechanical ventilation, spontaneous breathing), etc. [9].

THE AIM

The purpose of the work is to improve the results of treatment of patients with acute surgical pathology of the abdominal cavity by correcting intra-abdominal hypertension.

MATERIALS AND METHODS

The results of examination and treatment of 187 patients with acute surgical pathology, which was accompanied by elevated IAP, who were hospitalized in the hospital of the Department of Surgery № 2 of the Bogomolets national medical university in the period from 2012 to 2020 were analyzed. The World Society of the Abdominal Compartment Syndrome (WSACS) classification was used to assess

the degree of IAH. There were 117 men (62,6%) and 70 women (37,4%). To compare the results depending on the chosen diagnostic and treatment tactics, the patients were divided into two groups: the comparison group and the main group. The comparison group (85 people (45,5%) included patients who have been treated with traditional approaches to diagnosis and treatment according to current treatment protocols. The main group (102 patients (54,5%) included patients in the treatment of which we additionally used our proposed step-by-step approach in the treatment of IAH. The study group consisted of 64 males (62,7%), 38 females (37,3%), and the comparison group consisted of 53 (62,4%) and 32 (37,4%) subjects respectively (groups representative of the statistic (p>0,05). The patients' age ranged from 21 to 85 years, mean age was 46,25±1,12 years. The patients of the two groups did not differ significantly in age and nosological forms of acute surgical pathology. The mean age of the main group and the comparison group was 46,18±1,59 and 46,33±1,57 years respectively (p>0,05). The study included patients with the following nosological forms of acute surgical pathology: strangulated abdominal wall hernia was observed in 28 (15%) patients, closed abdominal trauma with damage to internal organs - 36 (19,3%) patients, acute pancreatitis - 35 (18,7%) patients, perforated duodenal ulcer - 11 (5,9%) patients, tumor perforation - 3 (1,6%) patients, acute intestinal obstruction - 30 (16%) patients, acute calculous cholecystitis - 22 (11,8%) patients, acute appendicitis - 22 (11,8%) patients. 139 (74.3%) patients were operated. Among the patients of the main group were operated 77 patients (75.5%) and the comparison group – 62 (72,9%), patients in both groups did not differ significantly in the type of surgical interventions (p>0,05).

For the determination of IAP we used the method of monitoring the pressure in the bladder (MBP), and during the laparoscopic intervention, the pressure was measured directly using an insufflator manometer.

Treatment tactics for patients with acute surgical pathology of the abdominal cavity, accompanied by IAH, were chosen depending on the underlying disease. First of all, the main factor of IAP increase was revealed - increase in abdominal volume (increase in intestinal volume due to paresis, intestinal edema, accumulation of fluid, gas in the abdominal cavity, etc.) - 159 (85,02%) patients and decrease in volume abdominal cavity due to surgery on the anterior abdominal wall (hernioplasty, abdominoplasty), its compression in the early postoperative period with compression bandages, etc.), as well as a combination of these factors - 28 (14,97%) patients.

Prophylaxis and treatment of IAH in the main group were divided into 3 stages. For normalization of IAP in *the first stage* the following was used: 1) decompression of the upper digestive tract, 2) drug control of intestinal flatulence, 3) evacuation of pathological contents. The patients were monitored for adequate pain relief and sedation, also avoided the use of compression bandages and corsets in the early postoperative period. If the patient was on a mechanical ventilation, normalization of IAP was achieved by correcting the ventilator settings: decreasing the volume of inspiration and increasing the respiratory rate on the machine (the inspiratory pressure should be less than 30 cm Hg).

The second stage included optimization of systematic and regionary perfusion in the direction of decreased water balance (zero or negative) through the use of hypertonic and colloidal solutions, and in stable patients - through the use of diuretics. In the case of prolonged intestinal paresis, peristalsis was stimulated by using lavage and siphon enemas. Liquid formations of the abdominal cavity were eliminated by puncture drainage under ultrasound control. Part of the patients was fed both parenterally and by enteral tube feeding (ETF). During the third phase of treatment, prolonged epidural anaesthesia (PEA) and complete refusal of ETF were used. If the IAP was no lower than 20 mmHg as a result of these measures, surgical treatment (decompression laparostomy) or laparolifting systems were used.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistica 10 (Serial Number: STA999K347150-W) and MEDCALC® (open-access website, https://www.medcalc.org/calc/). Data distribution normality was checked using the Shapiro-Uilk criterion. Comparison of the data between the groups was carried out using the paired Student's t-criterion for unrelated samples. Comparison of the indicators in dynamics was carried out using Student's t-criterion for related samples. No abnormal distribution was observed in the study. To compare the frequency of the signs in the unrelated samples, we used «n-1» xi-square test ($\chi 2$) according to Campbell (2007) and Richardson's (2011) recommendations. The confidence intervals given in the article were constructed for the confidence level of 95%.

RESULTS

Main group patients with *acute pancreatitis* had markedly lower IAP than hospitalized patients even after 24 years of treatment (16,59 ± 0,74 and 15,29 ± 0,77 mmHg, p < 0,05, respectively) and continued to decrease, returning to the group average values on the last day of therapy (11,82 ± 0,71 mmHg). In patients of the comparison group, on the contrary, the IAP significantly increased in the first (16,38 ± 0,66 and 17,26 ± 0,71 mm Hg, p <0,05, respectively) and the second day (16,38 ± 0,66 and 17,25 ± 0,77 mm Hg, p <0,05, respectively), and a probable decrease in IAP was registered only on the 10th day of therapy (16,38 ± 0,66 and 13,41 ± 0,95 mm Hg, p <0,05, respectively).

However, in 7 patients (20%) the signs of IAH not only did not subside during the first week but even tended to grow slowly, IAP exceeded 21 mm Hg, which was subsequently the reason for decompression laparostomy in two patients of the comparison group and surgical treatment in six patients (17,1%).

Complications occurred in 12 patients with severe acute pancreatitis (34,3%), the incidence of side effects in the

comparison group was probably higher, (52,9 and 16,7%, respectively, $\chi 2 = 4,9$, $p = 0,03$). In the main group, the development of these complications was registered in three (16,7%) patients (one (5,6%) patient with a lethal outcome), in the comparison group in 9 (52,9%) patients, of which - 6 (35, 3%) of patients (three operated and three non-operated) with lethal outcome, that is the total mortality was reduced from 35,3% to 5,6% ($\chi 2 = 4,7$, $p = 0,03$).

When comparing the results of treatment in patients with *acute intestinal obstruction* from the first day of the postoperative period in patients of the main group there was a statistically significant decrease in IAP (from 17,2 ± 0,8 to 15,5 ± 0,9 mm Hg $p < 0,05$ by Student's t-test for related samples). In patients of the comparison group, despite intensive care, a probable increase in IAP on the first day after surgery (up to 17,7±1,1 mm Hg, $p < 0,05$) compared with hospitalization, a probable decrease in this indicator was achieved only on the 7th day of treatment (up to 14,7±1,1 mm Hg). Total complications occurred in 4 urgently operated patients (22,2%): three people in the comparison group (42,9%) and one - the main group (9,1%). Two patients of the comparison group died in the early postoperative period due to progressive cardiovascular failure. Complications also occurred in 4 patients (33,3%), in whom during the conservative measures were eliminated acute intestinal obstruction: three patients of the comparison group (75%) and one - the main group (respiratory failure - eliminated conservatively) (16,7%). One patient in the comparison group died due to the progression of renal failure. Thus, the use of a step-by-step approach in the complex treatment of IAH in patients with acute intestinal obstruction has significantly reduced the overall incidence of complications from 46,2% to 11,8% ($\chi 2=3,92$, $p<0,05$), the incidence of postoperative complications - from 55,6% to 8,3% ($\chi 2=4,79$, $p < 0,05$), and postoperative mortality - from 33,3% to a minimum ($\chi 2=4,44$, $p < 0,05$).

When comparing the results of treatment of patients with *acute peritonitis*, probably lower IAP values were registered in the main group starting from 3rd day of therapy (14,3±0,8 and 16,8±0,6 mm Hg, $p < 0,05$). The dynamics of indicators after surgery deserves special attention. In patients of the main group, elevated IAP values after surgery returned to baseline on the second day, and in patients of the comparison group - on the fourth. In addition, in the main group on the first day the IAP indicator/ values was on average higher by 5,6%, and in the comparison group - by 17,6%.

In total, complications were found in 8 patients with acute peritonitis (36,4%). The incidence of complications was exponentially higher in the comparison group: 6 out of 10 patients in the comparison group (60%) and in 2 out of 12 patients in the main group (16,7%), ($\chi 2 = 4,16$, $p<0,05$). In one patient of the comparison group with destructive cholecystitis (stage II IAH) and concomitant chronic renal failure, chronic renal failure progressed, resulting in death of the patient from multiple organ dysfunction syndrome (MODS). The second patient with perforation of the colon tumor (stage III IAH) developed acute cardiovascular insufficiency, which, despite intensive therapy, steadily progressed, leading to death. In the third patient of the comparison group with perforated duodenal ulcer (stage III IAH), the phenomena of MODS progressed, which led to his death (postoperative and overall mortality - 30%). Two patients of the main group developed acute respiratory failure, which was eliminated conservatively. That is, postoperative mortality was reduced from 30% to a minimum ($\chi 2 = 4,50$, $p < 0,05$).

When comparing the results of treatment in patients with *closed abdominal trauma* in patients of the main group after 3 days, a statistically significant decrease in IAP was obtained (from 17,5 ± 0,8 to 16,0 ± 0,6 mm Hg, $p < 0,05$). At patients of the comparison group, significant differences of indicators from basic were received on the fourth day of treatment. When comparing the results of treatment in the two groups, probably lower IAP values were registered in the main group starting from 9 days of therapy (9,6 ± 0,4 and 12,9±0,9 mm Hg, $p < 0,05$). Complications developed in 9 patients with closed abdominal trauma (25%): in 7 (out of 17) (41,2%) patients of the comparison group and in two (out of 19) (10,5%) - the main group ($\chi 2=4,2$, $p<0,05$). Two patients of the comparison group died (11,8%): due to the progression of MODS in pancreatic slaughter and thromboembolic complications after splenectomy. In the main group, complications occurred in 2 patients: acute respiratory distress syndrome in a patient with pancreatic contusion and acute liver failure in a patient with splenic injury (the patient died). That is, we managed to identify a tendency to reduce postoperative mortality from 11,8% to 5,2% ($p > 0,05$).

When comparing the results of treatment in patients with *strangulated abdominal wall hernia* in patients of the main group, IAP values were probably lower in a day after hospitalization (16,34±0,75 and 13,8±0,63 mm Hg, respectively, $p<0,05$). In patients of the comparison group, on the contrary, the IAP probably increased one day after the start of therapy (16,79 ± 0,94 and 18,26±0,77 mm Hg, respectively, $p < 0,05$), returned on the second day to baseline and became significantly lower only on the seventh day of therapy (16,79 ± 0,94 and 13,83±1,11 mm Hg, respectively, $p < 0,05$). Complications in the early postoperative period occurred in 10 patients with strangulated hernias of the abdominal wall (35,7%): 2 patients (13,3%) of the main group and 8 patients (61,5%) of the comparison group ($p<0,01$). In one patient with a strangulated postoperative ventral hernia from the comparison group, acute respiratory failure progressed, leading to death. Three patients in the comparison group developed thromboembolic complications, which led to the death of patients. That is, mortality in the comparison group was probably higher, four patients of the comparison group died and none in the main group ($\chi 2 = 5,5$, $p < 0,05$).

In *laparoscopically operated patients*, an important factor in the control of IAH was the elimination of postoperative pain by multimodal analgesia (systemic and local use of non-narcotic analgesics), which in a set of treatment mea-

Table I. The structure of systemic complications

Complications	Total	Groups of patients				Differences in the frequency of complications
		The main		The comparison group		
		n	%	n	%	
Acute respiratory failure	24(12,8)	6	5,9	18	21,2	P=0,002 χ^2=9,6
Cardiovascular insufficiency	14(7,5)	4	3,9	10	11,8	P=0,002 χ^2=9,6
Acute liver failure	2(1,1)	1	0,9	1	1,1	P=0,9 χ^2=0,02
Multiple organ failure	13(7,0)	1	0,9	12	14,1	P=0,02 χ^2=15,4
Thromboembolic complications	5(2,7)	–	–	5	5,9	P=0,0004 χ^2=12,5
Total	58(31,0)	12	11,8	46	54,1	P=0,0001 χ^2=38,6

sures contributed to a statistically significant reduction in IAP in the main group compared to the comparison group, starting from the 2nd day of the postoperative period. (11,8 ± 0,8 and 15,2 ± 1,2 mm Hg, p <0,001). Postoperative complications occurred in 11 patients (30,6%) (in one patient of the main group (4,8%) and in 10 patients (66,7%) - comparison ($\chi2$ = 14,3, P = 0,0002).

To summarise the above, the structure of systemic complications in patients who received comprehensive treatment is shown in Table I.

Thus, systemic complications occurred in 12 patients in the main group (11,8%) and in 46 patients in the comparison group (54,1%), and in the second group the frequency of systemic complications was significantly higher ($\chi2$ = 38.6, p <0, 0001). 20 patients (10,7%) died (2 patients in the main group (1,96%) and 18 patients in the comparison group (21,2%) ($\chi2$ = 17,85, p<0,0001).

DISCUSSION

The development of IAH in acute surgical pathology of the abdominal cavity is caused by both internal factors (increase in intestinal volume due to paresis, intestinal edema, accumulation of fluid, gas in the abdominal cavity, etc.) and external factors (decrease in the volume of the anterior abdominal wall by abdomino - or hernioplasty, its compression in the early postoperative period with bandages, etc.), as well as a combination of these factors. It should be noted that the measurement of IAP by prolonged monitoring of MBP enables to timely select and initiate the necessary treatment tactics aimed at combating IAH and avoid the development of ACS. It is clear that the stage of care for patients with IAH syndrome is conditional. Thus, in acute pancreatitis, the fight against intestinal paresis in the early stages of the disease includes, in addition to medical correction, decompression of the gastrointestinal tract and cleansing enemas, and PEA [10]. However, the use of a staged approach in the prevention and treatment of intra-abdominal hypertension immediately after hospitalization allows to limit the measures of the first level in 67,6% of cases, the second - in 22,5% and to avoid decompression laparostomy. It is well known that the effectiveness of ETF depends on the timing of recovery of intestinal motor function and intestinal absorption [11]. Even after normalization of these functions, an increase in the volume and concentration of the solution for ETF can cause an increase in intestinal dysphagia and, as a consequence, the progression of IAH. Therefore, in the 2nd stage, you should reduce the volume of the solution, avoid the use of concentrated solutions.

CONCLUSIONS

1. IAH is an important factor in the pathogenesis of acute surgical pathology of the abdominal cavity, which significantly affects the prognosis.
2. The development of IAH in acute surgical pathology of the abdominal cavity is caused by both internal factors (paresis, intestinal edema, accumulation of fluid, gas) and external factors (reduction of the volume of the anterior abdominal wall due to surgery or its external compression), as well as a combination these factors.
3. The use in the complex treatment of patients with acute surgical pathology of the abdominal cavity, accompanied by IAH, the proposed step-by-step approach has improved the treatment of this category of patients by reducing the incidence of systemic complications from 54,1% to 11,8%, overall mortality from 21,2% to 1,96% and postoperative mortality - from 22,4% to 2,4%.

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ORIGINAL ARTICLE

THE PECULIARITIES OF MORPOLOGICAL CHANGES OF RATS' OVARY AND BIOCHEMICAL STATE UNDER THE DAMAGE WITH DIFFERENT DOSES OF LEAD ACETATE

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ABSTRACT

The aim of the study was to study the effect of low and high doses of lead acetate on biochemical parameters and morphological status of rat ovaries in the experiment.

Materials and methods: The study was performed on 36 nonlinear female rats weighing 180-210 g, aged 4 months, divided into 3 experimental groups: I - control (C), II - rats, which were given 30 days to drink a solution of lead acetate with at the rate of 0,05 mg / kg of animal weight, group III - rats, which were given for 30 days to drink a solution of lead acetate at the rate of 60 mg/kg of animal weight. Biochemical research methods were included determination of diene conjugate concentration in animals' blood, concentration of TBA-active products, study of oxidative modification of proteins in blood plasma, determination of superoxide dismutase and catalase activities. Endogenous intoxication was assessed by the definition of medium-mass molecules, the content was expressed in units of extinction. The material for light microscopy investigation from the ovary was performed according to the generally accepted method.

Results: Lead acetate causes activation of peroxidation of lipids and proteins in the body of female rats, which is directly dependent on the dose of lead. In response to the activation of free radical oxidation there are changes in the antioxidant system, which depend on the dose of lead acetate: at a dose of 0.05 mg / kg superoxide dismutase and catalase activity increase, at a dose of 60 mg / kg superoxide dismutase and catalase activity. Small doses of lead do not cause endogenous intoxication. Lead acetate causes the development of endogenous intoxication in animals only in large doses: increases the formation of toxic compounds, cell apoptosis, decreased excretory function of the kidneys, which is associated with multiorgan disorders. As a result of the action of lead acetate, morphological changes of the ovaries were observed, which increased with increasing dose of lead acetate. There was a dose-dependent decrease in massometric parameters, the number of follicles and changes in the thickness of the surface structures of the ovary, which is more pronounced at 60 mg/kg.

Conclusions: Under the influence of small and large doses of lead acetate on biochemical changes in blood and morphological changes in the ovaries in male rats the oxidative stress is developed. Under the influence of small doses, the changes are adaptive, and under the influence of large doses - damaging.

KEY WORDS: ovary, female rats, plumbum, lead intoxication, morphological changes, biochemical changes in blood

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INTRODUCTION

According to the WHO, plumbum is one of the most global and dangerous pollutants, because this metal has a wide sphere of using in various sectors of the economy and household, as well as large volumes of production and world trade, which leads to a regular supply of lead to the environment, where it spreads over considerable distances from sources of pollution [1, 2].

Plumbum as an environmental pollutant and a classic toxicant continues to be the focus of attention not only of ecologists, toxicologists and hygienists, but also of morphologists and clinicians representing various fields of medicine and biology. This is due to the fact that in a relatively short period of time the content of this potentially toxic chemical substance in the environment has increased tens or even hundreds of times, and most importantly, acquired a global character [2, 3].

Poisoning by lead compounds is accompanied by dysfunction of the nervous, cardiovascular, digestive and other systems and organs, lesions of hematopoiesis, reproductive system [4, 5, 6], so the study of structural and functional aspects of lead intoxication is an actual task.

Of particular interest is the effect of plumbum on the reproductive system, which leads to various disorders in fetal development, as confirmed by experimental and clinical studies [2, 7, 8].

THE AIM

The purpose of the research**:** to study the effect of low and high doses of lead acetate on biochemical parameters and morphological status of rat ovaries in the experiment.

MATERIALS AND METHODS

The work was doing at the Central Research Laboratory of I. Horbachevsky Ternopil National Medical University.

All experiments were performed in the morning in a specially designated room at a temperature of 18-22°C,

Table I. Groups of experimental animals

Group	Characteristics of the experimental model group	Number of animals
I	Intact white rats (control)	12
II	Lead acetate (0.05 mg/kg)	12
III	Lead acetate (60 mg/kg)	12

relative humidity of 40-60% and illumination of 250 lux. Animals were kept and experiments on them in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals used for research and other scientific purposes [9].

The study was performed on 36 nonlinear female rats weighing 180-210 g, aged 4 months, divided into 3 experimental groups (Table I): I - control (C), II - rats, which were given 30 days to drink a solution of lead acetate with at the rate of 0,05 mg / kg of animal weight [10], group III - rats, which were given for 30 days to drink a solution of lead acetate at the rate of 60 mg / kg of animal weight [8]. Each rat was kept in a separate cage to reduce the risk of uneven consumption of the toxicant with drinking water. Rats were kept in standard vivarium conditions with free access to food and water, which was given only after the animal drank lead acetate solution.

Euthanasia of rats was performed by total bloodletting from the heart after previous thiopental-sodium anesthesia (60 mg kg^{-1} body weight intraperitoneally). After removing the animals from the experiment, blood was taken for biochemical examination and ovary was taken for histological examination. The fence was carried out at the same time of day from 11^{00} to 15^{00} hours indoors at an air temperature of 18-20 °C.

Biochemical research methods were included determination of diene conjugate (DC) concentration in animals' blood, concentration of TBA-active products, study of oxidative modification of proteins in blood plasma, determination of superoxide dismutase and catalase activities. Endogenous intoxication was assessed by the definition of medium-mass molecules, the content was expressed in units of extinction [11, 12, 13].

The material for light microscopy investigation was performed according to the generally accepted method [14]. After removing the ovary, it was weighed and cut from the middle part of the organ pieces. The material was fixed for 2-3 weeks in a 10% solution of neutral formalin with three changes of fixative, then dehydrated in alcohols of increasing concentration, and then poured into paraffin blocks. Microtome sections 5 μm thick were stained with hematoxylin-eosin. Microscopic examination of the specimens was performed using the world microscope «Nicon Eclipse Ci» (made in Japan), using lenses x 4, 10, 20 and eyepiece x 10. Photographed histological specimens with a Sigeta camera (made in Japan).

Statistical processing of digital data was performed using Excel software (Microsoft, USA) and STATISTICA 7.0 (Statsoft, USA) using parametric and non-parametric methods of data evaluation. The values of the arithmetic mean (M), its variance and the error of the mean (m) were calculated for all indicators. The reliability of the difference between the values between the independent quantitative values was determined at the normal distribution by the Mann-Whitney test.

RESULTS

The analysis of lipid peroxidation (LPO) in animals of group II, which were given low-dose levels of lead that did not exceed the general toxic effect, showed an increase in DC by 46,4% ($p<0,001$) compared with animals of the control group, and TB-active products - by 36,8% ($p<0,001$), respectively.

Animals of group III, which were given large doses of lead, causing intoxication in the body, showed an increase in DC in 6,3 times ($p<0,001$), compared with animals in the control group, and TBA-active products – 3,7 times ($p<0,001$), respectively.

When comparing the degree of toxic effects of lead on LPO processes, it was found that in group III animals compared to group II, DCs were 4,3 times higher ($p<0,001$), TBA-active products were found 2,7 times more ($p<0,001$).

Thus, lead acetate causes dose-dependent activation of lipid peroxidation processes in rats.

The analysis of oxidatively modified proteins (OMP) in animals of group II, which were given low-dose levels of lead acetate, not exceeding the general toxic effect, revealed a decrease in redox proteins, in particular the value of OMP_{370}, decreased by 2,95% compared to animals of the control group, OMP_{430}, by 3,41% ($p<0,001$), respectively.

In animals III, which were given large doses of lead, causing intoxication in the body, found an increase in OMP_{370} 1,23 times ($p<0,001$) compared with animals in the control group, OMP_{430}, 1,41 times ($p<0,001$).

When comparing the degree of toxic effects of lead, it was found that in group III animals, compared with II, OMP were higher RP_{370} 1,24 times and OMP_{430} 1,45 times, respectively ($p<0,001$).

Thus, lead acetate causes dose-dependent activation of lipid peroxidation processes in rats.

Serum of rats of group II, which were given low-dose levels of lead that did not exceed the general toxic effect, showed an increase in SOD by 54% ($p<0,001$) compared with animals of the control group, and catalase activity increased 2,5 times.

In animals III, a decrease in SOD by 43% ($p<0,001$) compared with animals in the control group, and catalase activity - by 66,3% ($p<0,001$), respectively.

When comparing the degree of toxic effects of lead on the enzyme system of antioxidant protection of female rats, it

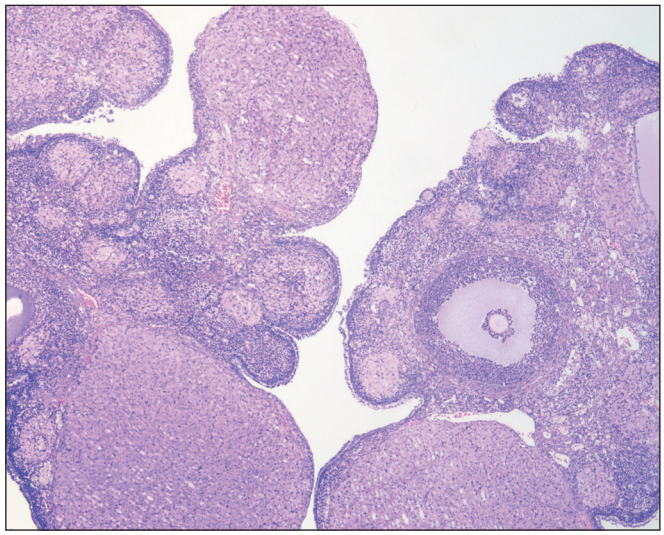

Fig. 1. Structural organization of the ovary of the control animals group. Follicles at different stages of development in the cortex. Stained with hematoxylin-eosin x 40.

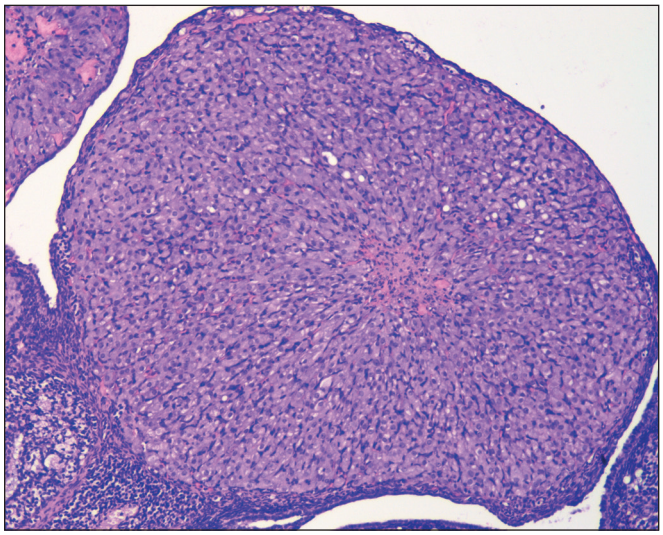

Fig. 2. The structure of the corpus luteum in the cortex of the ovary of the animal under the influence of small doses of lead acetate. Luteocytes in the corpus luteum. Stained with hematoxylin-eosin x 100.

was found that in group III animals, compared with group II, SOD was lower by 63% (p<0,001), catalase activity - by 86,6% (p<0,001).

Thus, lead acetate activates antioxidants only in small doses, and large doses cause inhibition of antioxidant activity.

Since the experiments showed an increase in oxidative processes, it was advisable to study the content of molecules of medium weight (MMW).

It was found that in the second group of animals there were no significant changes in the MMW of any of the studied fractions.

In the third group of animals, compared with the control, there was also an increase in all fractions of MMW: MMW_{238} increased by 67,1% (p<0,001), MMW_{254} – 2,2 times (p<0,001), MMW_{260} – 2,1 times (p<0.001), MMW_{280} – 2,6 times (p<0,001).

It was found that all fractions of MMW increase with increasing dose of lead acetate. Comparing groups II and III, the latter showed higher indicators of MMW_{238} by 60,8% (p<0,001), MMW_{254} – 2 times (p<0,001), MMW_{260} – 2,2 times (p<0.001), MMW_{280} – in 2,4 times (p<0,001).

Therefore, only large doses of lead acetate cause an increase of molecules of medium weight.

Light microscopy has shown that the ovaries are a parenchymal gland with endocrine function, which is realized through the production of sex hormones by theca cells, granulosa follicle cells and the corpus luteum.

Morphological studies of the ovaries in animals of the control group showed that the organ is covered mainly by a single layer of cuboidal epithelium, but there were areas of prismatic and squamous epithelium, on the apical surface of which microvilli are visualized. The results of light microscopy of the ovaries showed that under the epithelium is a tunica albuginea, which consists mainly of collagen and elastic fibers, as well as a small number of smooth myocytes.

The structural organization of the organ is clearly visualized external cortex and internal medulla (Fig. 1).

The cortex of the ovaries of group I surrounds the medulla in the form of a horseshoe. The stroma is formed by connective tissue containing collagen and a small amount of elastic fibers, as well as a large number of fibroblasts (interstitial cells). The parenchyma of the ovaries of rats of group I is represented by follicles of different stages of their maturity (primordial, primary, secondary, tertiary follicles), which were mainly go to physiological atresia, corpus luteum and blood vessels. Primordial follicles were located under the tunica albuginea in the cortex. The medulla is represented by a connective tissue stroma, which contains a large number of elastic fibers, many blood vessels, nerve fibers and nerve endings.

Histological examination of the ovaries of group II rats found that the structural organization of the ovary of experimental animals is almost no different from the control. During this period of the experiment in the cortex and medulla of the ovaries there is a dense network of collagen fibers in tunica albuginea. Light microscopy reveals single primordial follicles that contain an oocyte surrounded by a single layer of squamous epithelial cells. Primary follicles are surrounded by a single layer of cuboidal epithelium. Secondary follicles were characterized by a well-defined transparent shell, the oocyte is surrounded by a multilayered epithelium of cuboidal shape. Also a characteristic feature of secondary follicles is the appearance of a layer of granulosa cells around it, which provides a separate blood supply to the follicle.

Tertiary follicles are also well visualized, which are characterized by the formation of a cavity in the thickness of follicular cells, which is filled with follicular fluid. A mature (preovulatory) follicle has a fully formed cavity with follicular fluid in which the egg floats freely.

However, it was found that in the cortex of the ovaries of rats of group II increases the relative area occupied by

corpus luteum than in control animals. In all animals, the yellow bodies are externally covered with a connective tissue capsule, have a rounded shape. In the thickness of the corpus luteum, connective tissue layers are visualized, in which there are blood and lymphatic vessels. The corpus luteum is based on luteocytes - cells of irregular shape, with basophilic stained nuclei in the center of the cell and eosinophilic cytoplasm, which indicates active steroidogenesis. Luteocytes differ in size depending on the location in the corpus luteum - the periphery is dominated by small, star-shaped cells with a large oval nucleus (Fig. 2).

Morphological studies of ovaries in animals of group III, which were administered high doses of lead acetate, showed that compared with the control, macroscopically there is a decrease in ovarian size, hyperemia, reduction in surface epithelial thickness and tunica albuginea thickness.

Light microscopy examination of ovaries of rats of group III found that the number of follicles in the cortex at all stages of their development and maturation: almost no primary and secondary and tertiary follicles, there is a small number of primordial follicles located on the periphery of the ovarian cortex and single corpus luteum, which are chaotically localized in the parenchyma of the organ.

Thus, with increasing dose of lead acetate, morphological changes in both cortex and medulla of rat ovaries deepen, leading to changes in the thickness of ovarian surface structures and a decrease in the number of follicles, indicating impaired growth and maturation.

DISCUSSION

Harmfulness of plumbum for humans is determined by its significant toxicity and high cumulative capacity [2, 6]. It has pronounced membrane-toxic properties, changes the activity of enzymes and the course of biochemical processes, is capable of material and functional accumulation and causes long-term exposure to long-term negative bioeffects [2, 15]. Lead is a poison with a polytropic mechanism of action, which manifests itself in specific toxic effects on hematopoietic organs, lesions of the central and peripheral nervous system, gastrointestinal tract, cardiovascular and immune systems. It has a detrimental effect on the liver, kidneys, disrupts metabolic processes, including protein synthesis, has gonadal and embryotoxic effects [7, 10, 16].

Studies have shown the damaging effect of lead on the sex and urinary systems, its direct gonadotoxicity and adverse effects on reproductive function [2]. In 49% there is a decrease in the average concentration of sperm, changes in shape and motility at high doses, increases the number of chromosomal aberrations, decreases testosterone in blood plasma, there are violations of sperm structure [4].

The experiment proved the ability of lead to cross the placental barrier at 12-14 weeks of pregnancy. At high blood concentrations, lead has an abortive effect. At low levels of lead in the mother's body, it accumulates in the tissues of the fetus, causing premature birth, low fetal weight. There is evidence of neurological disorders in children born to women whose blood levels were more than 10 mg / dL [4, 7, 8].

At any influences on an organism there is a nonspecific reaction of an organism, processes of free radical oxidation of lipids and proteins are activated. In our experiments we see the growth of LPO products. Such changes were dose-dependent, with high doses of lead acetate there was a significantly greater increase in DC and TBA-active products compared to low doses. The obtained results indicate damage to the lipid layer of cell membranes. Changes in OMP are multidirectional: at a dose of 0.05 mg / kg, their content decreases, at 60 mg / kg - increases.

In our experiments in females with low doses of lead acetate, the MMW decreases, which indicates an adaptive mechanism aimed at preserving cell membrane proteins. This variant of MMW changes is the most appropriate, which prevents DNA damage, as obtained by scientists who did not find abnormalities in fetal development when using small doses of lead acetate. Obviously, at low doses, the reverse primary carbonylation of proteins occurs, and at large - irreversible. Therefore, at high doses, fetal malformations may occur.

Also an important role in reducing the products of WMD play an increase in the activity and content of antioxidants. Therefore, the next step was to analyze the activity of antioxidants. Lead is known to reduce the potency of the glutathione system because it binds to proteins, primarily due to free SH groups [17]. Since the glutathione system under the action of lead acetate has already been well studied, we investigated superoxide dismutase and catalase activity. It was found that at low doses of lead acetate enzyme activity increases. It is possible to think that there is an activation of processes of peroxidation of lipids, but at the same time there is a protection against free radical damage of proteins, and also lipids. The correctness of this conclusion is evidenced by changes in the ovaries, where there is an increase in the number of corpora lutea. These changes can occur under any stress of low and medium intensity, under the influence of any substances, the action of ionizing radiation in small doses. That is, such a reaction is nonspecific. However, they can lead to diseases of adaptation, premature aging of the body. Indeed, histological specimens show an increase in the number of connective tissue fibers, thickening of the ovarian capsule, signs of steroidogenesis. Such changes indicate that the possible development of secondary infertility (on the one hand, the number of corpora lutea increased, which contributes to multiple pregnancies, and on the other - thickening the capsule reduces the possibility of sperm penetration) with prolonged exposure to lead acetate [18, 19]. Given the fact that the sexual cycle in female rats lasts 5 days, and lead acetate was used for 30 days, in terms of human life expectancy - it is six months, which is quite short-lived. Signs of steroidogenesis can be regarded as an imbalance in the work not only of sex steroids, but also in the work of mineral and glucocorticoids, which may indicate a stress response of the body, leading to an imbalance of steroid hormones.

When exposed to large doses of lead acetate, antioxidant enzymes are reduced, which contributes to the activation

of prooxidants and damage to the body. Indeed, the ovaries in rats decreased in size, which may be due to a decrease in hormonal activity. They were hyperemic, indicating the development of inflammation. Signs of dystrophy were noted (the thickness of the germinal epithelium and tunica albuginea decreased). Such changes indicate the development of infertility. At light microscopic examination almost all follicles are absent, there are single corpus luteum which are chaotically localized in an organ parenchyma. Therefore, biochemical changes are confirmed by morphological ones. Given the signs of inflammation in which the cytokine cascade is activated, one can think of the possibility of rapid tumor development, which requires more research.

Thus, the effect of small and large doses of lead acetate on biochemical changes in blood and morphological changes in the ovaries in male rats was studied. The development of oxidative stress, which causes damage, has been established. Under the influence of small doses, the changes are adaptive, and under the influence of large doses - damaging.

CONCLUSIONS

1. Lead acetate causes activation of peroxidation of lipids and proteins in the body of female rats, which is directly dependent on the dose of lead.
2. In response to the activation of free radical oxidation there are changes in the antioxidant system, which depend on the dose of lead acetate: at a dose of 0.05 mg / kg superoxide dismutase and catalase activity increase, at a dose of 60 mg / kg superoxide dismutase and catalase activity.
3. Small doses of lead do not cause endogenous intoxication. Lead acetate causes the development of endogenous intoxication in animals only in large doses: increases the formation of toxic compounds, cell apoptosis, decreased excretory function of the kidneys, which is associated with multiorgan disorders.
4. As a result of the action of lead acetate, morphological changes of the ovaries were observed, which increased with increasing dose of lead acetate. There was a dose-dependent decrease in massometric parameters, the number of follicles and changes in the thickness of the surface structures of the ovary, which is more pronounced at 60 mg/kg.

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ORIGINAL ARTICLE

RESULTS OF PREVENTIVE METHODS OF OCCURRENCE CERVICAL ANASTOMOTIC COMPLICATIONS IN ESOPHAGOPLASTY

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ABSTRACT

The aim: The aim of the study was to improve the results of surgical treatment in patients with corrosive esophageal strictures using the designed comprehensive surgical management program in esophagoplasty to decrease cervical anastomotic complications.

Materials and methods: The results of surgical treatment of 116 patients with esophageal strictures were studied. 45 patients had post-burn corrosive strictures, 17 – postoperative corrosive strictures, 10 - peptic strictures due to reflux esophagitis and 44 patients - esophageal cancer. All patients were divided into two groups: the control group, consisting of 55 patients who underwent conventional surgical treatment of corrosive esophageal strictures during 2005-2011, and experimental group involving 61 patients operated on during 2012-2020, in whom an individual approach to the choice of surgical method was applied using diagnostic and treatment algorithm as well as the designed surgical management program.

Results: In early postoperative period the proportion of specific and non-specific complications was significantly lower in experimental group as compared to the control group: cervical anastomotic leak - 16.36 % versus 4.392 %; strictures of cervical anastomosis – 20.0% versus 6.56 % ($p<0.05$). There were six postoperative deaths - four in the control group and two in experimental group.

Conclusions: To prevent the development of cervical anastomotic complications and mortality in esophagoplasty proper therapeutic approach with consideration of all prognostic criteria and risk factors should be chosen and designed surgical management program should be applied.

KEY WORDS: anastomotic leak, stricture, treatment program

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INTRODUCTION

Although esophageal corrosive strictures most often develop after esophageal burns, surgery, reflux-esophagitis, esophageal cancer, they can also result from radiation therapy, sclerosis of esophageal varices, mycosis, infectious diseases, collagen disease etc. Those conditions associated with III-IV degrees of esophageal obstruction require reconstructive surgery on the esophagus - esophagoplasty [1-3]. The most common specific complications after subtotal esophagoplasty are complications associated with esophago-organ anastomotic leakage, especially cervical anastomosis. The incidence of cervical esophago-organ anastomotic leaks reaches 15%, and that of the strictures - 10% [4, 5].

THE AIM

The aim of the study was to improve the results of surgical treatment in patients with corrosive esophageal strictures using the designed comprehensive surgical management program in esophagoplasty to decrease cervical esophageal anastomotic complications.

MATERIALS AND METHODS

The research was conducted in compliance with the major principles of GCP guidelines (1996), Council of Europe Convention on Human Rights and Biomedicine (1997), World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects (1964-2000) and Order of Ministry of Health of Ukraine № 281 of November 1, 2000, being approved by the Committee on Bioethics of National Pirogov Memorial Medical University, Vinnytsia.

116 patients with corrosive esophageal strictures operatively treated at surgery clinic of Vinnytsia National Pirogov Memorial Medical University and the Department of esophagus and gastro-intestinal tract surgery of state institution "V.T. Zaitsev Institute of General and Emergency Surgery of National Academy of Medical Sciences" during the period of 2005-2020 were studied. The majority of patients were 21-60 years old, i.e. working-age individuals. There were 79 males (68.10 %) and 37 females (31.90 %). 45 patients had post-burn strictures, 17 - postoperative corrosive strictures, 10 – peptic strictures due to reflux-esophagitis, 44 – esophageal cancer.

All patients were divided into two groups: the control group, consisting of 55 patients who underwent conventional surgical treatment of corrosive esophageal strictures during 2005-2011, and experimental (study) group, matched by sex, age and pathologic conditions, involving 61 patients (52.59 %) operated on during 2012-2020, in whom an individual approach to the choice of surgical procedure was

Table I. Types of esophagoplasty in patients of experimental and control groups

Pathology	Type of surgery	Control group (n=55)	Experi-mental group (n=61)
Post-burn corrosive strictures	Clinically modified colon patch esophagoplasty	-	15
	Retrosternal plastics with the right half of the colon	20	3
	Clinically modified gastric tube esophagoplasty	2	5
Postoperative corrosive strictures	Reconstruction of esophagogastric anastomosis	0	2
	Gastric tube esophagoplasty	8	-
	Clinically modified gastric tube esophagoplasty	-	7
Strictures after reflux-esophagitis (peptic)	Gastric tube esophagoplasty	5	-
	Clinically modified gastric tube esophagoplasty	-	5
Esophageal cancer	Clinically modified colon patch esophagoplasty	-	7
	Retrosternal plastics with the right half of the colon		
	Gastric tube esophagoplasty	6	-
	Transhiatal esophageal resection and clinically	14	-
	modified gastric tube esophagoplasty	-	17

Table II. Nonspecific and specific postoperative complications

Complications	Control group (n=55)	Experimental group (n=61)
Nonspecific complications		
Pleurisy	18 (32.73 %)	10 (16.39 %)**
Pneumonia	14 (25.45 %)	6 (9.84 %)**
Pleural empyema	2 (3.64 %)	-*
Mediastinitis	2 (3.64 %)	-*
Pneumothorax	7 (12.73 %)	3 (4.92 %)*
Postoperative seroma	7 (12.73 %)	6 (9.84 %)*
Postoperative wound abscess	12 (21.82 %)	5 (8.20 %)**
Recurrent laryngeal nerve paralysis	2 (3.64 %)	-*
Bleeding	3 (5.45 %)	-*
Anastomotic leaks after intestinal anastomosis	1 (1.82 %)	-*
Acute intestinal obstruction	2 (3.64 %)	1 (1.64 %)*
Acute pancreatitis	1 (1.82 %)	1 (1.64 %)*
Pulmonary embolism	2 (3.64 %)	1 (1.64 %)*
Myocardial infarction	1 (1.82 %)	-*
Anaphylactic shock	1 (1.82 %)	-*
Multiple organ failure	2 (3.64 %)	-*
Sepsis	2 (3.64 %)	-*
Specific complications		
Esophago-organ anastomotic leakage	9 (16.36 %)	3 (4.92 %)**
- esophagoplasty with gastric tube	8	2
- colon patch esophagoplasty	1	1
Strictures of esophago-organ anastomosis	11 (20.0 %)	4 (6.56 %)**
- esophagoplasty with gastric tube	9	3
- colon patch esophagoplasty	2	1

Notes: * – $p>0.05$ – insignificant difference; ** – $p<0.05$ – significant difference.

applied using diagnostic and treatment algorithm, as well as the designed surgical management program.

Minimally invasive methods of treatment and stenting were required in patients of experimental group having increased risk for the development of cervical anastomotic complications. Such patients were selected according to the following prognostic criteria: anemia, decreased albumin level below 25 g/l, diabetes mellitus, complete esopha-

geal obstruction, non-use of the designed management program and suggested instrumental method of forming cervical anastomosis. Distribution of patients according to pathologic conditions and types of surgical procedures in study groups is presented in table I.

Three-stage comprehensive surgical management program was developed and introduced in clinical practice for patients of experimental group with esophageal strictures.

The first stage implied careful preoperative preparation of the patient. It involved correction of protein metabolism in verified hypoproteinemia, particularly in albumin level decrease below 25 g/l, correction of anemia, hyperglycemia and other types of metabolism. The changes in administered therapy of the patient were made by anesthesiologist to improve laboratory and biochemical parameters. In severe debilitation, parenteral nutrition ("all-in-one" systems) was instituted as well, using the systems of multicomponent mixture "Oliclinomel" and "Nutriflex Lipid Pery". To reduce ischemic changes in the graft and prevent complications (leaks and strictures of cervical anastomosis), solutions of pentoxifylline, reosorbilact and tivortin were administered. This infusion therapy was performed for five days before surgery by intravenous drip of 100 ml of tivortin twice a day, 200 ml of reosorbilact twice a day and 200 mg of pentoxifylline per 200 ml of 0.9% sodium chloride solution intravenously twice a day (useful model patent of Ukraine № 141214 of 25.03.2020). When pathogenic oropharyngeal microflora was detected, decontamination with decamethoxine solution (Decasan) was performed three times a day for 5 days to prevent postoperative complications.

The second stage involved the procedure of reconstructive surgery. Esophagoplasty with the stomach was performed in 63 patients, 35 of them - clinically modified gastric tube esophagoplasty. During surgery transhiatal extirpation of the esophagus was performed with subsequent formation of gastric tube. To achieve the sufficient length of gastric tube, the proposed technique was used consisting of transverse incision of gastric tube up to 2 cm in the pyloric area, longitudinal closure and additional mobilization of the duodenum and tissues around head of the pancreas. After formation of the graft and its placement on the neck area through the posterior mediastinum, instrumental circular cervical esophagogastric anastomosis was formed through cervical approach according to the designed technique (useful model patent of Ukraine № 132523 of 25.02.2019). If the formation of such mechanical anastomosis was considered technically impossible, hand-sewn esophagogastric anastomosis was formed, mainly end-to-end anastomosis by invagination technique.

Colon patch esophagoplasty was performed in 48 patients, predominantly by the technique developed in clinic – hepatic flexure, transverse colon, splenic flexure and part of descending colon were included in the graft with preservation of the left colic artery. The graft was placed in isoperistaltic orientation on the neck area through artificially created retrosternal tunnel. The graft length was sufficient to form proximal cervical anastomosis. During mobilization and formation of colon graft, mesenteric vessels were assessed by illumination of colon mesentery from the opposite side using additional weak light source. After placement of colon graft via retrosternal approach on the neck area, instrumental circular stapler cervical esophagocolonic anastomosis was formed according to the developed method. When technical difficulties during the formation of the anastomosis occurred, hand-sewn end-to-end anastomosis was created by invagination technique.

The third stage of comprehensive surgical treatment program was the postoperative management of patients according to the suggested method. Postoperative intravenous administration of tivortin, reosorbilact and pentoxifylline solutions was continued twice a day for seven days to prevent ischemic complications of the graft. In addition, antibacterial, antisecretory, detoxification, anti-inflammatory infusion therapy was administered. Nutritional support was provided using commercially prepared formulas (Peptamen, etc.) through intraoperative nasogastric tube. On postoperative day seven, esophagography with water-soluble contrast agent was performed to assess the status of cervical esophago-organ anastomosis and the graft.

RESULTS

Early and late postoperative complications, specific and nonspecific, occurred in patients of both groups. The major nonspecific complications in both groups were: pleurisy - in 18 (32.73%) patients of the control group and 10 (16.39%) patients of experimental group, pneumonia - in 14 (25.45%) and 6 (9.84%) patients, respectively. Besides, pleural empyema and mediastinitis were registered in 2 control subjects each (3.64%), while no such complications developed in study patients of experimental group. Other nonspecific complications included: pneumothorax - in 7 (12.73%) and 3 (4.92%) patients, postoperative seroma - in 7 (12.73%) and 6 (9.84%) patients, postoperative wound abscess - in 12 (21.82%) and 5 (8.20%) patients, acute pancreatitis - in 1 (1.82%) and 1 (1.64%) patient, acute intestinal obstruction - in 2 (3.64%) and 1 (1.64%) patients, pulmonary embolism - in 2 (3.64%) and 1 (1.64%) patients of experimental and control groups, respectively. In addition, the following complications developed in control subjects: bleeding - in 3 (5.45%), recurrent laryngeal nerve paralysis - in 2 (3.64%), anastomotic leaks after intestinal anastomosis - in 1 (1.82%), myocardial infarction - in 1 (1.82%), anaphylactic shock - in 1 (1.82%), sepsis - in 2 (3.64%), multiple organ failure - in 2 (3.64%) patients (Table II).

Leakage of cervical anastomosis in early postoperative period and strictures in late postoperative period were major specific complications. Anastomotic leaks occurred in 4.92% of patients in experimental group and 16.36% of those in the control group.

DISCUSSION

Anastomotic leakage was found to be more common in gastric tube esophagoplasty - in 8 patients of comparison

group versus 2 patients of experimental group, than in colon patch esophagoplasty - in 1 and 1 patient, respectively. Thus, the results obtained proved the frequency of cervical anastomotic leakage to be significantly higher in gastric tube esophagoplasty than in colon patch esophagoplasty ($p < 0.05$). No cases of anastomotic leaks were registered in cervical anastomosis formed by the proposed instrumental method [6-8].

Strictures developed in 20.0% of patients in the control group and 6.56% of those in experimental group. Strictures of cervical anastomosis were observed more often in gastric tube esophagoplasty - in 9 patients of the control group and 3 patients of experimental group, than in colon patch esophagoplasty - in 2 and 1 patient, respectively. Thus, the results obtained demonstrated the occurrence of strictures to be significantly higher in gastric tube esophagoplasty than in colon patch esophagoplasty ($p < 0.05$).

Complications developed after esophagoplasty in patients of experimental group were treated using minimally invasive methods, stenting in particular, which was performed in seven patients: in 3- with anastomotic leaks and in 4 – with strictures. It should be noted that in early postoperative anastomotic leaks, stenting insures complete sealing of the defect in the area of leakage, prevents the outflow of esophageal contents, provides proper conditions for fistula healing and adequate tube feeding, thus resulting in decreased duration of hospital stay and postoperative mortality. In addition to stenting, antibacterial, anti-inflammatory, infusion therapy was administered to correct metabolism disorders.

There were six deaths in the postoperative period: four in the control group and two in experimental group.

CONCLUSIONS

To prevent the development of postoperative complications and mortality, proper therapeutic approach should be chosen with consideration of all prognostic criteria and risk factors. Comprehensive three-stage management program for surgical patients with esophageal strictures was suggested. It involves conservative prevention of ischemic changes in the graft; use of improved mobilization methods in formation of gastric tube and colonic graft, the designed instrumental method of cervical esophago-organ anastomosis, modern method in treatment of cervical anastomotic complications – stenting. Introduction of such comprehensive program was associated with significantly lower incidence of leaks and strictures of esophago-organ anastomosis, reduced duration of hospital stay – from 28.2 ± 1.1 to 21.5 ± 0.5 bed-days ($p < 0.001$), decreased postoperative period - from 20.5 ± 1.1 to 16.1 ± 0.7 bed-days ($p < 0.01$), decreased postoperative mortality rate – from 7.27% to 3.28%.

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ORIGINAL ARTICLE

DIABETES MELLITUS TYPE 1 IN ADOLESCENTS: IMPACT OF VITAMIN D STATUS

DOI: 10.36740/WLek202202111

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ABSTRACT

The aim: To evaluate the effect of vitamin D deficiency or insufficiency on the compensation of the disease in adolescents with diabetes mellitus type 1.

Materials and methods: 124 patients were examined, among them: 33 from the control group, 91 adolescents with type 1 diabetes mellitus. All patients were between 10-18 years old and were residents of the Podillya region of Ukraine.

Results: According to the results of the study Vitamin D levels in adolescents with type 1 diabetes mellitus are significantly lower, comparing with healthy adolescents of the same age group. Vitamin D levels among boys with type 1 diabetes mellitus were significantly lower comparing to girls of the same group. The boys of the control group had significantly higher levels of vitamin D in the blood comparing to boys with type 1 diabetes mellitus, $p < 0.001$.

Conclusions: The majority of adolescents aged 13-18 years with type 1 diabetes mellitus have vitamin D deficiency or insufficiency regardless of the state of glycemic control of the disease.

KEY WORDS: diabetes mellitus, adolescents, vitamin D, glycated hemoglobin, carbohydrate metabolism

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INTRODUCTION

Diabetes mellitus (DM) is one of the most common non-infectious diseases with the tendency to increase.

According to the International Diabetes Federation (IDF) data more than 1.1 million of children and adolescents suffer from the DM type 1. More than 128 900 new cases of diabetes in children and adolescents are diagnosed annually in the world.

In 2019 almost 300 000 children were known to have type 1 diabetes mellitus in Europe [1]. The main problem of treatment of DM remains optimization of the glycemic control especially in childhood.

Thus, the DCCT (Diabetes Control and Complication Trial) study found that normalization of blood glucose levels and disease compensation in adolescents is more difficult than in adult patients [2]. It is also known that in pubertal age there are factors that directly or indirectly can influence the achievement of optimal glycemic control. Such factors include the rapid linear growth of the child that is influenced by the action of sex hormones during puberty , intensive hormonal changes in the body, which leads to increased daily insulin needs.

DM type 1 is a result of cell-mediated autoimmune destruction of β - cells of the pancreas. According to the newest data about the effect of vitamin D, as a part of the body's hormonal system, the authors are interested in the effect of vitamin D on homeostasis not only on calcium- phosphorus metabolism, but also on carbohydrate metabolism [3].

Vitamin D deficiency is common global problem that constantly increases with the level of urbanization. Low vitamin D status effects the skeletal system, plays a significant role in the pathogenesis of diabetes, taking part in the insulin secretion [4,5]. The active metabolites of vitamin D regulate the proliferation and differentiation of cells, synthesis of lipids, proteins, enzymes and the work of organs and systems [6,7].

Patients with type 1 and type 2 diabetes mellitus have low levels of vitamin D and low values of 25(OH)D in the blood serum are associated with increased levels of glycated hemoglobin (HbA1C) [8].

The connection between vitamin D intake and a reduced risk of type 1 DM has been demonstrated in a large cohort study in Finland. It was found that the children who received 2,000 IU of cholecalciferol daily had 88% lower risk of the development of DM type 1 compared to children, who did not receive vitamin D [9]. The dose-dependent effect was found: children, who received higher doses of cholecalciferol had a lower risk of developing DM type 1 [10].

According to the published data of cross sectional study in Poland, the lowest levels of 25(OH)D (13,1 ± 4,7 ng/ml) were observed in children aged from 15 to 20 years [11].

THE AIM

To evaluate the effect of vitamin D deficiency or insufficiency on the compensation of the disease in adolescents with diabetes mellitus type 1.

Table I. Vitamin D levels among adolescents of different age groups

Vitamin D status	Adolescents with DM type 1 (n = 91)		Control group (n = 33)	
	Early puberty (10-12 years)	Intensive puberty (13-18 years)	Early puberty (10-12 years)	Intensive puberty (13-18 years)
Deficiency (ng/ml)	13.14 ± 2.06 **,*** n=10	13.42±2.31 n=54	18.12±2.48 n=2	17.96 ± 2.13 n=8
Insufficiency (ng/ml)	20.81 ± 2.12 *,** n=5	25.45 ± 2.07 n=16	25.73± 2.23 n=5	25.68 ± 2.56 n=13
Optimal level (ng/ml)	32.54 ± 3.24 n=2	32.16 ± 4.27 n=4	32.61 ± 4.32 n=1	34.32 ± 3.89 n=4

Note: The difference is significant when compared to:
* – adolescents with type 1 diabetes in early puberty and intensive puberty (p <0,05);
** – adolescents of the main and control group aged 10-12 years (p <0.05);
*** - adolescents of the main group aged 13-18 years old and adolescents of the control group of the same age.

Table II. Average vitamin D levels among different stages of compensation of diabetes mellitus type 1 in adolescents

HbA1C	Deficiency of vitamin D, ng / ml, n = 64	Insufficiency of vitamin D, ng / ml, n = 21	The rate of vitamin D, ng / ml, n = 6
Compensation of diabetes, n = 20	15.59 ± 3.82	24.83 ± 1.92	30.22
Subcompensation of diabetes, n = 21	12.45 ± 3.88	22.16 ± 1.55 *	-
Decompensation of diabetes, n = 50	13.87 ± 3.42	25.27 ± 2.67 *	39.66 ± 14.42

Note: * – reliability in the group of vitamin D deficiency between adolescents in a state of sub – and decompensation of the disease, p = 0.02.

MATERIALS AND METHODS

The study was conducted in Vinnytsia Regional Clinical Highly Specialized Endocrinology Center. The study involved 124 children aged 10-18 years (average age 14,38±2,15), among them 61 girls, 63 boys. All participants were divided in 2 groups: 91 children with type 1 DM (group 1), average age 14,43±2,18 and 33 healthy children of the same age (group 2) whose average age was 14,21±2,07.

Clinical evaluation of the patients, medical history, laboratory and statistical methods of research were used during the study. The mathematical processing was performed on a personal computer using a standard statistical package STATISTICA 6,0.

Exclusion criteria for the group 1 was: chronic concomitant diseases, as well as the presence of skeletal system disorders, which could have impact on the calcium and phosphorus metabolism. Exclusion criteria for the group 2 contained skeletal diseases, acute and chronic diseases, as well as autoimmune diseases, which could influence the metabolism of vitamin D.

The study was approved by the Ethics Committee of National Pirogov Memorial Medical University (Vinnytsya, Ukraine). All study staff prior to specimen collection voluntarily agreed to participate in the study and signed an informed consent form. All study personnel data were anonymized prior to the analysis. Ethical considerations including privacy of personal data were considered during all steps of the research.

Clinical examination of the adolescents included evaluation of physical (weight, height, body mass index) and sexual development (Tanner stage). The children were divided into periods of puberty (Tanner stage 1-2 - early puberty, Tanner stage 3-4 - late puberty). Measurements of glycated hemoglobin (HbA1C) were provided for group 1 in order to determine the state of compensation of DM (HbA1C <7.5% was considered as good compensation of the disease, 7.5-9% sufficient compensation, HbA1C > 9% - insufficient compensation of DM). The level of HbA1C was determined using the method of high performance liquid chromatography (analyzer D -10 Bio - Rad).

The concentration of 25(OH)D hydroxycholecalciferol in the blood serum was conducted using electrochemiluminescence method (Cobas analyzer). Measurements of 25(OH)D level was done during the year. Further analysis regarding the influence of the season of sample collection (autumn-winter, spring-summer) and place of living of the participant (urban/rural) on the vitamin D status in adolescents was provided [12].

The levels of total and ionized calcium were conducted using colorimetric and photometric method with Arsenazo III (analyzer AU 480 Beckman Coulter). Blood sampling was performed between 8 and 10 am.

The diagnosis of vitamin D deficiency was established according to the Endocrine Practice Guidelines Committee and Institute of Medicine. The level of vitamin D: <20 ng/ml (50 mmol/l) was marked as deficiency of vitamin D,

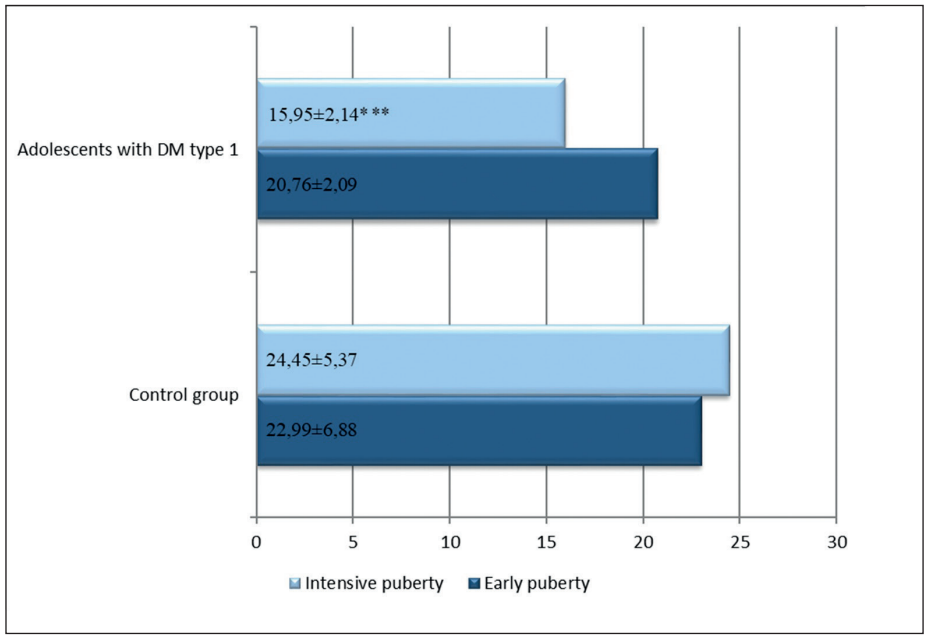

Fig. 1. Average levels of 25 (OH) D in serum (ng/ml) among age groups
Note: The difference is significant when compared to: * - adolescents with type 1 diabetes of different age groups (10-12 years and 13-18 years), p <0,05; ** - adolescents of the main and control groups aged 13-18 years, p <0,01.

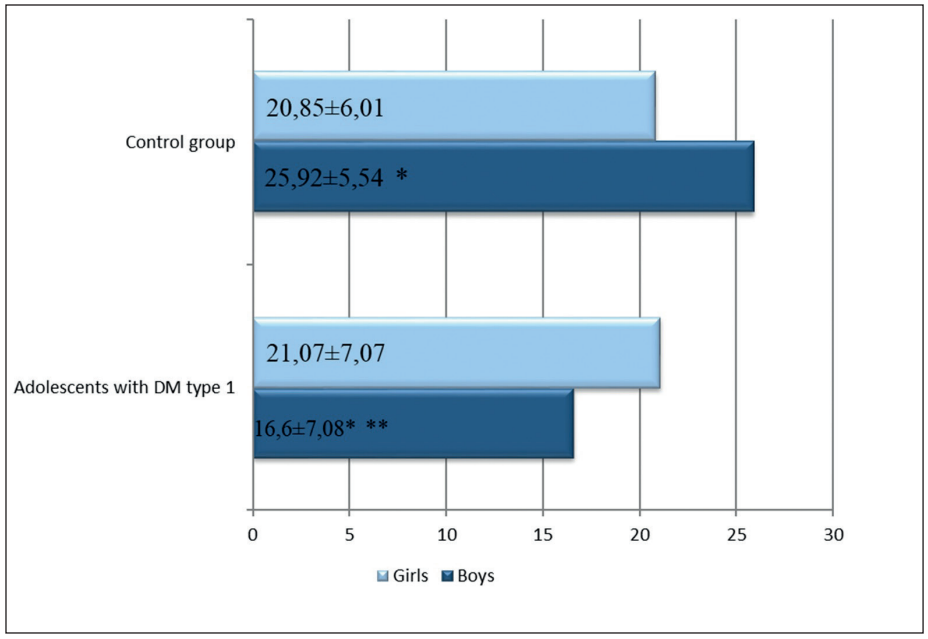

Fig. 2. Average 25 (OH) D levels (ng / ml) among girls and boys
Note: The difference is significant when compared to: * - girls with type 1 diabetes, p <0,05; ** - boys of the control group, p <0,01.

21-29 ng/ml (50.1-74.9 nmol /l) - insufficiency, above 30 ng/ml (75.0 nmol /l and more) was considered to be optimal [13, 14].

RESULTS

According to the results of the study the decreased level of 25 (OH) D in the blood serum was observed with almost the same frequency in adolescents of the main group (93.41% of the participants), as well as in the control group (84.85%).

All participants were divided according place of residence (rural /urban) and season of blood collection. Thus, we found that among adolescents with type 1 DM there was no significant difference in the average levels of vitamin D depending on the season of blood sample collection. During analysis according to the place of living of the adolescents, vitamin D deficiency was significantly more common in adolescents who live in the urban areas than in adolescents who live in the rural areas, regardless of the study group (p <0.05).

Taking into account the peculiarities of hormonal balance during puberty, after the assessment of Tanner stage, adolescents were divided into 2 groups: 10-12 years (beginning of puberty) and 13-18 years (intensive puberty with a growth spurt).

According to the vitamin D levels and for the purpose of more detailed analysis of indicators, all adolescents with type 1 DM additionally were divided: adolescents with vitamin D deficiency (n = 64), vitamin D insufficiency (n = 21), adolescents with normal levels of vitamin D in the blood (n = 6). The average levels of vitamin D in different groups are shown in table I.

The majority of adolescents with type 1 DM showed generalized vitamin D deficiency in the age of intensive puberty (54 patients, 59.34 %) which in 4.7 times dominate the participants of the same group who had early puberty (10.98 % $p < 0.05$). Among children of the control group, the majority of adolescents was characterized by vitamin D insufficiency at the age of intensive puberty (13 participants, 39.4%), $p<0,05$.

According to the results vitamin D deficiency in the group of adolescents with type 1 diabetes, as well as among adolescents of the control group at the age of 13-18 years was more common compared to adolescents of the earlier puberty (10-12 years).

In general, the data clearly reflect the absolute prevalence of low vitamin D status in adolescents: 70.33% of participants with type 1 diabetes have vitamin D deficiency, 23.08% - insufficiency. According to our study results, only 3.29% of adolescents with type 1 diabetes in early pubertal age and 4.39% of the children who were in intensive puberty had optimal vitamin D levels.

Significant difference between the average levels of vitamin D (deficiency and insufficiency) was found in adolescents of the main and control group in early pubertal age, $p<0.05$. Thus, in adolescents of the main group at the age of early puberty, with vitamin D deficiency (average level 13.14 ± 2.06 ng/ml) was significantly lower than in children of the control group (average level 18.12 ± 2.48 ng/ml), $p<0.05$. Similar results were observed in the group of vitamin D insufficiency of the main group of adolescents at the age of early puberty, $p <0.05$. Thus, the level of serum hydroxyvitamin D was significantly lower in adolescents with type 1 diabetes at the age of intensive puberty (13.42 ± 2.31 ng / ml) than in adolescents of the control group of the same age(17.96 ± 2.13 ng / ml) , $p <0.05$.

Analysis of the average vitamin D levels in blood serum depending on the period of puberty was provided (fig.1). The average level of 25 (OH) D (group 1) was found to be significantly lower among children in the intensive puberty (15,95 ± 2.14 ng/ml), and participants at the age of early puberty (20.76 ± 2.09) ng/ml, $p <0.05$. Among children of the control group, significant difference in vitamin D levels depending on age (in the group of intensive puberty the average level was 24.45 ng/ml, early puberty - 22.99 ng /ml) was not found. Thus, the lowest vitamin D status was present among the adolescents with carbohydrate metabolism disorders and had intensive puberty (13-18 years). The results are reflected in figure 1.

Taking into account the possibility of influence of the gender on vitamin D status among adolescents, the vitamin D levels among different gender groups were analyzed. The distribution by gender among adolescents of the main group was 50.55% - boys, 49.45% - girls. Among adolescents of the control group, the distribution by gender was similar. The results of average of 25 (OH) D levels are shown in figure 2.

The average levels of 25 (OH) D in the serum of adolescents of the main group had significant difference: 21.07 ± 7.07 ng/ml among girls and 16.60 ± 7.08 ng/ml among boys, $p <0.05$.

Also it was found that the boys of the control group had significantly higher levels of vitamin D (25.92 ng/ml) compared to boys with type 1 DM (16.6 ng/ml) , $p <0.001$. A similar significance of the average vitamin D level among girls of the main and control groups was not found, $p>0.05$.

Among somatically healthy adolescents (n=33) the vitamin D levels were analyzed: the average level among boys was 25,92 ng/ml. It was significantly higher compared to girls of the same group (20.85 ng/ml), p= 0,01.

Analyzing the state of calcium metabolism among the surveyed adolescents, we have found that there are no deviations of total calcium levels of adolescents. Thus, the average levels of total calcium among boys with type 1 diabetes was 2.41 ± 0.10 mmol/l, among girls it was slightly lower and was 2.38 ± 0.13 mmol/l. Among adolescents of the control group the average level of total calcium was 2.37 ± 0.09 mmol/l (boys) and 2.36 ± 0.08 (girls).

Considering the aim of detecting the effect of vitamin D status on glycemic control of the adolescents with type 1 DM, adolescents were also divided by the stage of compensation of carbohydrate metabolism (HbA1C <7.5% was considered to be compensated stage, 7.5-9% - subcompensated and HbA1C>9% - decompensation of DM). The obtained data are shown in table II.

In the group of vitamin D deficiency (n = 64) decompensation of DM was common: only 23.80% of adolescents had the level of HbA1C <7.5%; 25.39% of the examined had subcompensation of the disease (HbA1C - 7.6 -9.0%) and 50.81% of adolescents had decompensation of carbohydrate metabolism (HbA1C > 9%). In the group of insufficiency of vitamin D compensation of the disease had only 20.83% of children, while 79.17% of surveyed were sub - or decompensated.

The average level of vitamin D was significantly lower in the group of vitamin D deficiency among adolescents with HbA1C 7.5-9%, compared to adolescents whose HbA1C was> 9% (25.27 and 22.16 ng / ml, respectively) ($p = 0.02$).

DISCUSSION

The results of our study are close to the data of numerous scientific studies according the prevalence of vitamin D deficiency and insufficiency in children with type 1 DM. Thus, according to an American study concerning vitamin D status among children and adolescents with type 1 DM (n = 395) 64% of the patients had a serum 25(OH) vitamin D level below 30 ng/ml [15].

Also the attention of scientists is drawn to the levels of vitamin D in healthy adolescents. Thus, a cross-sectional study conducted in Tehran, which enrolled 444 adolescents (mean age 14.34 years), have showed that only 22.41% of participants had normal vitamin D levels (34.2% had vitamin D insufficiency, 43,3% - vitamin D deficiency). Levels of vitamin D, osteocalcin, alkaline phosphatase were significantly higher in boys compared to girls of the same age [16].The prevalence of vitamin D deficiency among healthy girls compared to boys was also confirmed in our study. Another cross-sectional study which was conducted

in Kuwait have found that 81.21% of somatically healthy adolescents had vitamin D deficiency, including 39.48% children with severe deficiency of vitamin D. Only 3.6% had a sufficient supply of vitamin D despite the fact of sufficient UV radiation of the participants [17]. In our study 84.85% of the healthy adolescents showed unsatisfactory vitamin D status.

In our study the possible impact of vitamin D deficiency on glycemic control was investigated. Literature data also indicate the dependence of vitamin D levels on the glycemic control of the disease. The results of Italian study, which compared the level of HbA1C with the level of vitamin D in adolescents with type 1 diabetes (n = 141), found that 25(OH)D levels can negatively correlate with the level of HBA1C ($p < 0.001$), as well as with the daily insulin dose ($p < 0.05$). The authors found reliable differences in the levels of vitamin D ($p<0.01$) between the teenagers with different states of metabolic control (HbA1C <7.5%, 7.5-8%,> 8%) [18].

A study conducted by Spanish researchers, which involved 64 children aged 0 to 14 years, with newly diagnosed type 1 diabetes, found a positive correlation between vitamin D levels and blood pH (r = 0.279), as well as blood bicarbonate (r = 0.338) also. In the analysis of glycemic control in this group of patients, it was found that children with vitamin D levels higher than 30 ng/ml had better glycemic control and glycated hemoglobin levels [19].

As the part of the study we would like to check glycemic changes after vitamin D supplementation of the adolescents with type 1 DM. Recently it was shown that treatment of vitamin D deficiency in patients with DM type 1 can potentially improve the glycemic control [20]. According to a German study it was found that high doses of vitamin D can reduce insulin requirements (p = 0.003 – 0.039) and improve the level of glycated hemoglobin in patients with type 1 DM ($p <.001$) [21].

As a summary, we concluded that the results of our study were similar to the data of previous scientific publications regarding the prevalence of vitamin D deficiency and it's possible impact on the glycemic control. Further studies are needed to understand the mechanisms of influence and additional cholecalciferol supplementation in adolescents with type 1 DM.

CONCLUSIONS

1. Vitamin D levels in adolescents with type 1 diabetes mellitus are significantly lower, comparing with healthy adolescents of the same age group.
2. Vitamin D levels among boys with type 1 diabetes mellitus were significantly lower comparing with girls of the same group. The boys of the control group had significantly higher levels of vitamin D in the blood comparing to boys with type 1 diabetes mellitus, $p <0.001$.
3. The majority of adolescents aged 13-18 years with type 1 diabetes mellitus have vitamin D deficiency or insufficiency regardless of the state of glycemic control of the disease. The correlations between vitamin D levels and carbohydrate metabolism in adolescents with type 1 diabetes, as well as the issue of additional supplementation with cholecalciferol should be investigated in the future studies.

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The Authors declare no conflict of interest

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ORIGINAL ARTICLE

GENDER FEATURES OF DEPRESSIVE AND ANXIOUS MANIFESTATIONS OF THE LUNG CANCER PATIENTS

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ABSTRACT

The aim: To examine the features of depressive and anxiety phenomenology in lung cancer, taking into account the gender factor.

Materials and methods: 112 patients with a primary diagnosis of stage II and III lung cancer were clinically and psychologically examined using HDRS, HARS, BDI, C. Spilberger's Reactive and Personality Anxiety Scale.

Results: It was found that the core affective psychopathological symptoms of patients with lung cancer are manifestations of depression (96.3% of men, 96.8% of women ($p > 0.05$), 96.4% together) and anxiety (77.8% , 93.5% ($p<0.05$) and 82.1%) in combination with asthenic-neurotic (67.9%, 61.3% ($p > 0.05$) and 66.1%) and affective labile (54.3%, 61.3% ($p > 0.05$) and 56.2%) manifestations; additional symptoms are apathetic (25.9%, 9.7% ($p<0.05$) and 21.4%), obsessive (19.8%, 38.7% ($p<0.05$) and 25.0%) and dysphoric (23.5%, 6.5% ($p<0.05$) and 18.7%) manifestations. The severity of depressive and anxiety of women is higher than of men; the severity of depressive-anxiety manifestations corresponds to a moderate level: depression by HDRS - 11.6±1.7 points, 15.6±6.3 points ($p<0.05$) and 12.7±4.0 points; BDI depression – 15.7±6.3 points, 23.7±13.9 points ($p<0.05$) and 17.9±9.7 points; HARS anxiety - 9.3±2.8 points, 11.5±3.7 points ($p<0.05$) and 9.9±3.2 points, and reactive anxiety - 44.4±11.1 points, 47.9±15.5 points ($p<0.05$) and 45.4±12.5 points. The identified differences can be explained by different gender models of psychological response.

Conclusions: The core affective symptoms of patients with lung cancer are manifestations of depression and anxiety in combination with asthenic-neurotic and affective-labile manifestations; additional are apathetic, obsessive and dysphoric manifestations.

KEY WORDS: lung cancer, psychopathological reactions, depression, anxiety, gender features

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INTRODUCTION

Diagnosis of cancer is a severe psycho-emotional stress for the patient [1, 2]. 51% of patients with oncological pathology experience clinically significant psycho-emotional distress, more than half of them have a high level of depression and neuroticism [3]. In addition to adverse changes in the psycho-emotional sphere, the presence of oncological pathology leads to a significant deterioration in the quality of life and psychosocial functioning of patients [4].

The basis of psychopathological symptoms associated with oncological pathology are depressive and anxiety manifestations [5]. Depression is considered a predictor of progression and mortality in cancer patients [6]. The risk of mortality is 25% higher in the presence of certain depressive symptoms in cancer patients, and 39% higher in the presence of major depressive disorder [7]. This gives grounds to consider depression and cancer as a comorbid pathology.

Lung cancer is one of the most significant oncological pathology. It is characterized by a high prevalence, high mortality and low relative survival of patients, as well as low efficiency of modern treatments [8-10]. At the same time the features of psychopathological symptomatology at lung cancer remain insufficiently studied. The separate studies have shown the presence of morphological and functional changes in the brain of the patients with lung cancer, even in the absence of metastatic lesions of the brain substance; these changes are accompanied by severe depressive symptoms and anxiety, although the nature of these relationships is complex and studied insufficiently [11].

It should be noted that the normalization of the psycho-emotional state of patients with malignant tumors is important for the overall effectiveness of treatment, helping to reduce psycho-emotional stress [12]. Recently, an interdisciplinary field has been developing dynamically, combining psychological and psychiatric sciences and oncology – the psychologic oncology, which goals to develop methods of psychological care and rehabilitation for cancer patients based on the study of somatic-psychological relationships in malignant diseases [13-15]. This highlights the need for comprehensive research in the field of oncology with the involvement of modern psychological, psychiatric and oncological science [16].

THE AIM

The aim of this study was to examine the features of depressive and anxiety phenomenology in lung cancer, taking into account the gender factor.

Table I. The structure of complaints of the psycho-emotional sphere of patients with lung cancer

Complaints	Men		Woman		Total		p
	abs.	%	abs.	%	abs.	%	
Low mood	78	96,3	30	96,8	108	96,4	0,694
Anxiety or fear	63	77,8	29	93,5	92	82,1	0.040
Mood irritable	44	54,3	19	61,3	63	56,2	0,327
Aggression	19	23,5	2	6,5	21	18,7	0.030
Fast fatigability	55	67,9	19	61,3	74	66,1	0.328
Apathy	21	25,9	3	9,7	24	21,4	0.047
Obsessive thoughts	16	19,8	12	38,7	28	25,0	0.036

Table II. Indicators of the examined patients, that were found according to psychodiagnostic methods

Indicators	Scale value, points			p
	Men M±m/Me (Q_{25}-Q_{75})	Woman M±m/Me (Q_{25}-Q_{75})	Total M±m/Me (Q_{25}-Q_{75})	
M. Hamilton's Depression Scale (HDRS)				
Total score	11,6±1,7 / 12,0 (10,0–13,0)	15,6±6,3 / 13,0 (10,0–22,0)	12,7±4,0 / 12,0 (10,0–13,0)	0,048
Adynamic depression	8,6±1,6 / 9,0 (8,0–10,0)	11,4±4,4 / 10,0 (8,0–16,0)	9,4±3,0 / 9,0 (8,0–10,0)	0,007
Agitation depression	3,9±1,7 / 4,0 (3,0–5,0)	6,7±4,1 / 6,0 (3,0–10,0)	4,6±2,9 / 4,0 (3,0–6,0)	0,004
Depression with fear	3,6±1,8 / 4,0 (3,0–5,0)	5,9±3,3 / 5,0 (3,0–9,0)	4,3±2,5 / 4,0 (3,0–5,0)	0,002
Undifferentiated depression	2,3±1,1 / 2,0 (2,0–3,0)	3,5±1,8 / 3,0 (2,0–5,0)	2,6±1,4 / 2,0 (2,0–3,0)	0,001
M. Hamilton's Anxiety Scale (HARS)				
Total score	9,3±2,8 / 9,0 (7,0–12,0)	11,5±3,7 / 11,0 (9,0–14,0)	9,9±3,2 / 10,0 (7,0–12,0)	0,007
Psychical anxiety	7,0±1,7 / 7,0 (6,0–8,0)	8,3±2,3 / 8,0 (6,0–10,0)	7,4±2,0 / 7,0 (6,0–8,0)	0,012
Somatic anxiety	2,3±2,0 / 2,0 (1,0–4,0)	3,1±2,3 / 3,0 (2,0–4,0)	2,5±2,1 / 2,0 (1,0–4,0)	0,107
A. Beck's Depression Invertory (BDI)				
Total score	15,7±6,3 / 16,0 (11,0–20,0)	23,7±13,9 / 20,0 (11,0–37,0)	17,9±9,7 / 17,0 (11,0–22,0)	0,022
Cognitive-affective subscale	9,8±3,8 / 10,0 (7,0–12,0)	15,4±9,4 / 12,0 (6,0–24,0)	11,3±6,4 / 10,0 (7,0–13,0)	0,044
Subscale of somatic depressive manifestations	5,9±3,6 / 6,0 (3,0–8,0)	8,3±5,1 / 9,0 (4,0–12,0)	6,6±4,2 / 6,5 (3,0–9,5)	0,023
C. Spilberger's Scale of Reactive and Personality Anxiety				
Reactive anxiety	44,4±11,1 / 48,0 (32,0–53,0)	47,9±15,5 / 51,0 (32,0–62,0)	45,4±12,5 / 48,5 (32,0–55,5)	0,044
Personality anxiety	37,8±9,6 / 34,0 (31,0–44,0)	37,8±7,6 / 35,0 (31,0–43,0)	37,8±9,0 / 34,0 (31,0–43,5)	0,727

MATERIALS AND METHODS

In accordance with the principles of biomedical ethics, we clinically and psychologically examined 112 patients (81 men and 31 women) with a primary diagnosis of stage II and III lung cancer, who were treated at the Vinnytsya Regional Clinical Oncology Center during 2017-2020. The examination was performed in the period from 7 to 14 days from the date of establishment and notification of the diagnosis. The mean age of patients was 62.6 ± 14.0 years, men - 62.4 ± 13.8 years, women 63.0 ± 14.9 years.

The survey program included a clinical interview organized using a semi-structured clinical interview, determining levels of depression and anxiety using M. Hamilton's Depression [17] and Anxiety Scale [18] (HDRS and HARS), A. Beck's Depression Invertory (BDI) [19], C. Spilberger's Scale of Reactive and Personality Anxiety in Y. Khanin modification [20].

Statistical analysis of differences between groups was carried out using non-parametric Mann-Whitney test and Fisher exact one-tailed test.

RESULTS

The structure of complaints of the psycho-emotional sphere of the examined patients is given in table I.

The main place among the subjective complaints of the psycho-emotional sphere of patients with lung cancer is low mood, which was found in almost all examined patients, feelings of anxiety or fear, which occurred in more than 80% of patients (statistically more significant of women

than of men , p<0.05), as well as increased fatigue (over 65%, without significant gender differences). Irritability was detected in more than half of patients (of women significantly more often, p<0,05). Obsessive symptoms (mainly in the form of obsessive thoughts about death, illness, fate of relatives, treatment directly related to the disease, more often of women, p<0.05), apathy (more than 20% of those surveyed, more often of men) and aggression (almost 20% of respondents, more often of men, p<0.05).

Data on the quantitative indicators of the severity of depression and anxiety of patients with lung cancer according to psychodiagnostics techniques are given in table II.

As can be seen from the table, the quantitative indicators of depression on the HDRS scale of patients with lung cancer on average correspond to the level of mild (closer to moderate) depression. Depression scores on the HDRS scale of the examined patients ranged from 7 points (no depression) to 29 points (severe depression). At the same time, the severity of depression of women was significantly higher than of men. This also applies to certain types of depression (dynamic, agitated, depressed with fear and undifferentiated), the indicators of which were significantly (p <0.01) higher of women.

Anxiety rates on the HARS scale of women were also significantly higher than of men; this also applies to the indicator of mental anxiety. Regarding the indicator of somatic anxiety, although its quantitative value of women was higher than of men, the differences of the indicators are not statistically significant (p> 0.05).

The rate of depression according to the BDI questionnaire in all patients corresponds to a moderate level (from 16 to 19 points). The rate of depression of women is statistically significant (p<0.05) higher than of men, and corresponds to the average level of depression (more than 20 points), and of men - moderate. Indicators of cognitive-affective sub-scale and sub-scale of somatic depressive manifestations of the BDI scale of women with lung cancer are also significantly (p<0.05) higher than of men.

Patients with lung cancer have high levels of reactive anxiety. Thus, the average score on the scale of reactive anxiety by C. Spilberger of the studied patients exceeded 45 points; of men it was slightly lower than 45 points, which corresponded to moderate, close to a high level of reactive anxiety, and of women - more than 45 points, which corresponded to a high level. Differences in reactive anxiety rates between men and women were statistically significant (p<0.05).

The indicator of personal anxiety of the studied patients corresponded to a moderate level; of men and women it was almost the same (p> 0.05).

DISCUSSION

The study revealed certain features of depressive and anxiety manifestations of patients with lung cancer, as well as certain differences in the manifestations of depression and anxiety of men and women.

The data found in our study on the significant incidence of lung cancer of patients with depressive and anxiety symptoms are consistent with the data of studies by other authors, which revealed comorbid cancers, depressive and anxiety disorders [21-23]. At the same time, our study obtained new data on the structure of subjective disorders of the psycho-emotional sphere, as well as quantified the severity of affective manifestations of patients with lung cancer. The predominance in the structure of psychopathological phenomena of signs of affective dysfunction, in particular, dysthymia and anxiety, as well as the phenomena of asthenia and affective lability. There were significant gender differences in the severity of depression and anxiety, in particular, women have higher levels of depression (including adynamic, agitated, undifferentiated depression and depression with fear) and anxiety (especially mental). This generally corresponds to the gender characteristics of the response to the disease, described by other authors [24], as well as the gender characteristics of psychological reactions in oncological pathology [25, 26]. The tendency to more pronounced depressive and anxious manifestations of women persists both in the self-assessment of the mental state of patients and the assessment of the state of the affective sphere by a specialist.

In our opinion, the identified gender differences are primarily due to the influence of gender-specific psychological models of response to severe psycho-emotional stress, detection of severe and life-threatening disease. Women are more emotional, sensitive, prone to dramatization of the situation, combined with greater openness of feelings, externalization of affective reactions, while the male gender-role pattern of behavior involves greater restraint, secrecy of emotions, prohibition of demonstration of feelings, especially those that may present weaknesses, as well as a greater tendency to rationalize compared to women [27-29]. These features are reflected in the manifestations of depression and anxiety, primarily reactive, current in nature, which reflect the affective responses to reports of severe illness with pessimistic treatment prospects. Regarding personal anxiety, which was almost the same of men and women, in the short time that has elapsed since the detection of lung cancer and before this examination, persistent personality changes and patho-characteristic traits did not have time to form, so it is natural that there are no significant differences in personal levels of anxiety between men and women.

CONCLUSIONS

The study of the peculiarities of depressive and anxiety manifestations of patients with lung cancer revealed pronounced disorders in their affective sphere. The core affective psychopathological symptoms of patients with lung cancer are manifestations of depression and anxiety in combination with asthenic-neurotic and affective-labile manifestations; additional symptoms are apathetic, obsessive and dysphoric manifestations. The level of depression and anxiety of patients with lung cancer on average corresponds to a moderate level, and in some patients it can range from mild to great severity of affective symptoms. Significant gender differences in higher levels of depression (including adynamic, agitated, undifferentiated depression, and fear depression) and anxiety (mostly

mental) have been identified in the affective responses of lung cancer patients. The identified patterns should be taken into account in the development of treatment, rehabilitation and prevention measures for patients with lung cancer.

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ORIGINAL ARTICLE

REMOTE DONOR PRECONDITIONING FOR INCREASING TRANSPLANT SURVIVAL IN THE RECIPIENT'S BODY DURING THE KIDNEY TRANSPLANTATION FROM THE LIVING-RELATED DONOR

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ABSTRACT

The aim: To estimate the protective effect of remote ischemic preconditioning (RIPC) on kidney transplants harvested from living related donors.

Materials and methods: To achieve the claimed aim, there were examined 60 donor-recipient couples, where kidney transplant donors were living-related. All donors had the same anaesthetic management. The first group (n = 30) received RIPC which included four procedures of cuff inflations each lasting 5 minutes followed by 5-minute intervals of cuff deflation to measure blood pressure up to 40 mm Hg above systolic blood pressure on the shoulder. Patients of the second group (controls) did not experience RIPC (n = 30) and control group without RIPC.

Results: RIPC resulted in a statistically significant ($P<0.05$) increase in GFR of the transplanted kidney from 66±5 mL /min to 63±4 mL /min after 3 months, from 69±3 mL /min to 61±5 mL /min after 6 months, from 63±2.5 mL /min to 57±3 mL /min after 12 months; a 3-fold reduced partial delay of graft function; a 2-fold decreased incidence of acute kidney transplant rejection times; 1.5-fold decline in the incidence of primary non-function; and 1.4-fold tCr50 acceleration ($p = 0.16$). The follow-up period lasted for a year after transplantation.

Conclusions: RIPC during organ harvesting improved graft ischemic protection and increased functioning efficiency in the recipient.

KEY WORDS: renal ischemia, kidney transplantation, ischemia-reperfusion injury, remote ischemic preconditioning

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INTRODUCTION

Currently, kidney transplantation (KT) is the only radical treatment for end-stage renal disease (ESRD). For long-term renal replacement therapy, dialysis is an alternative to KT. However, the former is less patient-friendly and more costly compared with KT that ensures higher quality of human life (in physical, emotional, social, spiritual and financial aspects) [1-6].

Over the past few decades, KT has shifted from a risky experimental approach in the management of chronic renal failure (CRF) to a safe and life-saving measure. KT provides the full rehabilitation, including return to full-time employment, school, university, sports activity, family integration, and the ability to have children [2,5].

While performing an audit of health insurance claims data in the Netherlands, Mohnen S.M. et al. analysed the average annual healthcare costs associated with renal replacement therapy (RRT) by dialysis (in-centre haemodialysis, home haemodialysis, continuous ambulatory peritoneal dialysis, automated peritoneal dialysis and multiple dialysis modalities) per year of treatment and two transplant modalities (kidney from living and deceased donor). The total average annual healthcare costs in 2014 ranged from €77,566 for continuous ambulatory peritoneal dialysis patients to €105,833 for patients on multiple dialysis modalities, whereas costs for kidney transplant recipients were €85,127 in the year of transplantation and rapidly declined in the first and second year after successful transplantation (respectively €29,612 and €15,018); transplantation with a deceased donor kidney resulted in higher costs (€99,450) in the year of transplantation compared to living donor kidney transplantation. Due to the complexity of the calculation, such studies and calculations have not been conducted in Ukraine. However, there is evidence that after successful transplantation, annual costs decline substantially to a level that is approximately 14-19% of annual dialysis costs [4,5].

Renal ischemic reperfusion injury (IRI) is the key factor that affects survival of transplant experiencing ischemia from the moment it is cut off the donor blood supply during nephrectomy until the completion of renal artery anastomosis in the recipient. Leveling such an effect can enhance transplant function and improve the quality and life expectancy of the recipient eventually. The search for methods of protection and preservation of the graft at the stage of organ harvesting from a living family donor, including

modifying anaesthesia techniques, is relevant. As of today, according to various observations, there is no unambiguous view or solution to this problem. Apart from IRI prevention strategies, such as improved organ harvesting and preservation technologies, as well as reducing the period of cold and warm ischemia, remote ischemic conditioning (RIC), which is a new and promising approach to reduce postoperative renal IRI, has attracted much attention in recent years. Given the fact that offered techniques differ in the execution time within the perioperative period and actual conditioning methods, the efficacy of this option of preventing IRI remains debatable. Based on the execution time, RIC can be classified into three types: remote ischemic preconditioning (RIPC) which is induced before the target organ experiences ischemia; remote ischemic perconditioning induced during ischemia of the target organ, but before reperfusion; remote ischemic postconditioning induced in the time of reperfusion initiation [2, 3, 7-11].

THE AIM

To study the efficacy of the original remote ischemic preconditioning to increase the probability of survival of kidney transplants from living-related donors during anaesthesia.

MATERIALS AND METHODS

To achieve the above aim, there were examined 60 living-related kidney donors who received anaesthesia during kidney transplantation. They were divided into two groups: RIPC group (n = 30) and control group without RIPC (n = 30). RIPC was performed after anaesthesia before donor nephrectomy. The original RIPC protocol included four procedures of cuff inflations each lasting 5 minutes followed by 5-minute intervals of cuff deflation to measure blood pressure (BP) up to 40 mm Hg above systolic blood pressure on the shoulder.

All patients had the same anaesthetic management. Anaesthesia was induced with intravenous fentanyl 2-3 μg/kg, esmeron 0.6 mg/kg and propofol 2 mg / kg body weight. Supportive anaesthesia was maintained with fentanyl 1-2 μg / kg / h, esmeron 0.1-0.2 mg / kg / h and sevoflurane at age doses with 0.8 to 1.2 target minimum alveolar concentration (MAC). The depth of anaesthesia was monitored with the use of bispectral index (BIS) technology (BIS VISTA monitor, Aspect Medical Systems, USA); the target range of BIS values was 40-60. Additional measurements during anaesthesia, including ECG, pulse oximetry, capnography, blood pressure, central venous pressure (CVP), body temperature, hourly urine output , and the calculation of fluid balance at all stages of surgery, were performed using Dräger Primus® workstation (Dräger Medical, Germany).

Apart from the routine parameters of renal concentrating and excretory abilities, including acid-base balance, blood and urine biochemistry, etc., RIPC efficacy analysis was based on the parameters as follows:

1. Glomerular filtration rate (GFR), which was calculated with the modification of diet in renal disease (MDRD) equation at 0, 1, 2, 3 days after transplantation, and prior to discharge from hospital if needed [12,13].
2. An incidence of acute renal allograft rejection, which was monitored within the first year of follow-up. Acute rejection was defined by decreased renal function requiring treatment, it was biopsy-confirmed.
3. Partial delay of graft function, which was determined within the first week after transplantation. The need for dialysis in the first week following transplantation was the criterion for this condition [14].
4. An incidence of primary non-function within the first 3 months after transplantation, which was defined as a permanent lack of kidney graft function.
5. Time to a 50% decrease in baseline creatinine (tCr50).

Statistical processing was performed with IBM SPSS Statistics 23 software package. The Mann-Whitney U-test was used to compare differences between groups when the data were not normal distributed. Fisher's exact test was utilized to analyse the categorical data. Values of $p \leq 0.05$ were considered significant. We presented mean values with standard deviation and the median with 25th and 75th percentiles or n (%). The effect of the type of intervention on GFR, when observed at 3, 6 and 12 months after transplantation, was determined using a linear mixed-effect model.

The criteria for inclusion in the study were as follows: end-stage renal disease, age ≥ 18 years, ABO blood group compatibility of the donor-recipient pair. The exclusion criteria included age of patients under 18 years, ABO blood group incompatibility of the donor-recipient pair.

The follow-up period lasted for a year after transplantation.

The transplantation procedure was performed by four transplant surgeons selected at random pursuant to standard protocols, and they were not different with regard to the qualification. The immunosuppression was routine and included intravenous induction of basiliximab and methylprednisolone or oral prednisolone and oral triple maintenance therapy with calcineurin inhibitors, mycophenolate mofetil and prednisolone.

RESULTS

Donors and recipients in the two study groups were comparable with regard to age, sex, body weight, anaesthesia risk assessment score on the scale of the American Society of Anaesthesiologists (ASA), GFR, and intraoperative donor's characteristics (Table I). Glomerulonephritis, diabetes mellitus, and autoimmune diseases predominated among the primary medical conditions that had contributed to kidney damage (Table II). Cardiovascular comorbidities (mainly arterial hypertension) were noted in most recipients of both study groups (Table III). There was no difference in some intraoperative parameters between the groups (Table III).

After three months following KT, graft function was better in the RIPC group: GFR was statistically significantly higher

Table I. Characteristics of donors and recipients.

Parameters	Donors	
	Group with no RIPC (n=30)	RIPC group (n=30)
Age (years)	54 ± 9	53 ± 13
Male (n (%))	15 (50)	14 (46)
BMI (body mass index) (kg/m^2)	26.1 ± 3.7	27.4 ± 3.3
ASA I/II	21/9	22/8
GFR (mL/min)	113 ± 21	116 ± 25
Smoking (n (%))	10 (33)	11(36)
MAP (mean arterial pressure) (mm Hg)	94 ± 9	95 ± 10
	Recipients	
	n=30	n=30
Age (years)	39 ± 15	42 ± 11.5
Male (n (%))	17 (56)	15 (50)
BMI (kg/m^2)	26.1 ± 3.2	25.2 ± 3.8
ASA II/III	17/13	15/15
MAP (mm Hg)	106 ± 11.1	100 ± 15.3

Table II. CRF-underlying medical conditions in the recipient (n - number of cases)

Diabetes	5	6
Autoimmune diseases	5	7
Glomerulonephritis	7	5
Multicystic dysplastic kidney	3	5
Tubulointerstitial nephritis	2	3
Others	8	4
Cardiovascular comorbidities (n[1] (%))	25 (83)	28 (93)

[1] - number of cases

(p = 0.028) than in the control cohort (66.0 ± 4.6 ml / min versus 63.4 ± 3.8 ml / min, respectively). This pattern persisted at 6 months after KT: GFR in the RIPC group was statistically significantly higher (p = 0.0001) than the corresponding value in controls (68.7 ± 3.3 ml / min versus 61.1 ± 5.3 ml / min, respectively). Improved GFR tended to remain at 12 months after KT (63.4 ± 2.5 ml / min versus 57.4 ± 3.3 ml / min, respectively) (Table IV). Furthermore, there was seen a tendency to a reduced incidence of partial delay of graft function from 10% (3 patients) to 3% (1 patient) (p = 0.612) in the RIPC group. Similar trends were recorded for the incidence of acute renal allograft rejection - a decrease from 20% (6 patients) to 10% (3 patients) (p = 0.236), the incidence of primary graft non-function – a decline from 15% (5 patients) to 10% (3 patients). The offered RIPC technique also contributed to a decrease in tCr50 on average from 120 to 96 hours (p = 0.16). (Table V). Statistical insignificance of the data may be related to the small number of patients in each group at the time of the study.

GFR

GROUP WITHOUT RIPC

3 months (63.4 + 3.8) and 6 months (61.1 + 5.3), adjusted mean difference, 2.3 (95% CI, - 0.6-5.2), p = 0.18.

3 months (63.4 + 3.8) and 12 months (57.4 + 3.3), adjusted mean difference, 5.9 (95% CI, 3-8.8), p = 0.0001.

6 months (61.1 + 5.3) and 12 months (57.4 + 3.3), adjusted mean difference, 3.7 (95% CI, 0.8-6.6), p = 0.009.

RIPC GROUP

3 months (66.0 + 4.6) and 6 months (68.7 + 3.3), adjusted mean difference, 2.6 (95% CI, 0.3-5), p = 0.026.

3 months (66.0 + 4.6) and 12 months (63.4 + 2.5), adjusted mean difference, 2.7 (95% CI, 0.3-5.1), p = 0.021.

6 months (68.7 + 3.3) and 12 months (63.4 + 2.5), adjusted mean difference, 5.3 (95% CI, 3-7.7), p = 0.0001.

DISCUSSION

While studying a model of acute myocardial infarction in dogs more than 30 years ago, Murry C.E. et al. (1986) [12,15] 5demonstrated that the previous compression of the circumflex artery with subsequent reperfusion contributed to the higher resistance of the myocardium to prolonged ischemia and reduced the further size of the experimental infarct site by 75%. Later on, this event was termed "ischemic preconditioning". Furthermore, in vivo studies showed that this condition was universal, occurring

Table III. Some intraoperative indicators of the quality of anaesthesia of the donor and recipient.

Parameter	Donor	
	Group without RIPC (n=30)	RIPC group (n=30)
Perioperative fluid volume (mL/ kg)	57.8 ± 12.3	60.0 ± 11.1
BIS	48±7	45 ± 6
MAP (mm Hg) the moment of kidney harvesting	89 ± 9	87± 17
Blood test at the time of kidney harvesting		
pH	7.41 ± 0.03	7.39 ± 0.04
Lactate (mmol /L)	1.5 ± 0.4	1.7 ± 0.7
	Recipient	
	Group without RIPC (n=30)	RIPC group (n=30)
Graft ischemia time (min)[1]	205 ± 29	217 ± 32
Perioperative fluid volume (mL/kg)	55.9 ± 13.0	58.2 ± 17.8
BIS	42 ± 7	46 ± 7
MAP (mm Hg) at the time of kidney connection to the blood flow	92 ± 12	85 ± 8
Blood test at the time of kidney connection to the blood flow		
pH	7.35 ± 0.04	7.32 ± 0.05
Lactate (mmol /L)	1.4 ± 0.4	1.7 +0.6

Note: [1] - Graft ischemia time (min) is the period from the moment of kidney harvesting from the donor's body to the moment of inclusion of the kidney in the recipient's body.

Table IV. Evaluation of the recipient's graft function.

Parameter	Group without RIPC (n=30)		RIPC group (n=30)			
Follow-up periods	N	M+SD	N	M+SD	Difference of means (95% CI)	p
GFR						
3 months after KT	25	63.4+3.8	27	66.0+4.6	2.7 (0.3-5.0)	0.028
6 months after KT	25	61.1+5.3	27	68.7+3.3	7.6 (5.1-10)	0.0001
12 months after KT	25	57.4+3.3	27	63.4+2.5	5.9 (4.3-7.6)	0.0001

• The effect of the type of intervention on GFR, when observed at 3, 6 and 12 months after transplantation, was determined using a linear mixed-effect model.

in all biological beings [16,17,19-21]. What is more, it is characteristic not only of the myocardium, but also other organs to increase the tolerance to ischemia when exposed to ischemic preconditioning. [22-24]. While preparing kidneys for IRI in animal models, Wever K. E. et al. found that a similar effect could be achieved by remote ischemia-reperfusion to the site of vascular surgery - remote preconditioning [25-28].

The advances in surgery, anaesthesiology and intensive care promote the empowerment of KT introduction, which is currently considered as a treatment of choice for end-stage renal disease, compared with dialysis. Ischemic preconditioning is a promising method of additional protection and preservation of the graft at the stage of organ harvesting from a living related donor. However, the efficacy of this method is ambiguous for a number of reasons, including different protocols of the method, limited sample size and severity of renal transplant patients (age, comorbidities, drugs used), etc. [1, 9,11, 18, 20].

This study showed that remote preconditioning, which included four procedures of cuff inflation while measuring blood pressure on the shoulder up to 40 mm Hg above systolic blood pressure followed by 5-minute intervals of cuff deflation to achieve sublethal ischemia, resulted in a statistically significant (P <0.05) increase in GFR of the transplanted kidney: from 63.4 ± 3.8 mL / min to 66.0 ± 4.6 mL /min after 3 months, from 61.1 ± 5.3 mL /min to 68.7 ± 3.3 mL /min after 6 months, from 57.4 ± 3.3 mL / min to 63 ± 3 mL /min after 12 months; a 3-fold reduction in partial delay of graft function; a 2-fold decrease in the incidence of acute kidney transplant rejection times); 1.5-fold decline in the incidence of primary non-function; and 1.25-fold tCr50 acceleration (p = 0.094). The mechanisms of possible beneficial effects of conditioning are still being investigated. Two temporal phases of protection are assumed: early (occurs within a few minutes and lasts up to 4 hours) and late (occurs after 24 hours and lasts up to 72 hours). The key mechanisms of the early phase are related to the mediators that are released during hypoxia. They initiate a cascade of

Table V. Assessment of recipient's graft function.

Parameter	Group with no RIPC	RIPC group
Partial delay of graft function (n (%))	3 (10%)	1 (3.3%), [1] (p = 0.612)
Incidence of acute renal allograft rejection (n (%))	6 (20%)	3 (10%), [1] (p = 0.236)
Incidence of primary non-function (n (%))	5 (16%)	3 (10%), [1] (p = 0.353)
	Me (25%; 75%)	
tCr50	120 (72; 132), n = 30	96 (56; 120), n = 30 U = 338, [2] (p = 0.094)

Note: [1] - Fisher's exact test was used to analyse the categorical data. Values of p ≤0.05 were considered significant.
[2] -The Mann-Whitney U-test was employed to perform the analysis of numerical data (tCr50). Values of p ≤0.05 were considered significant.

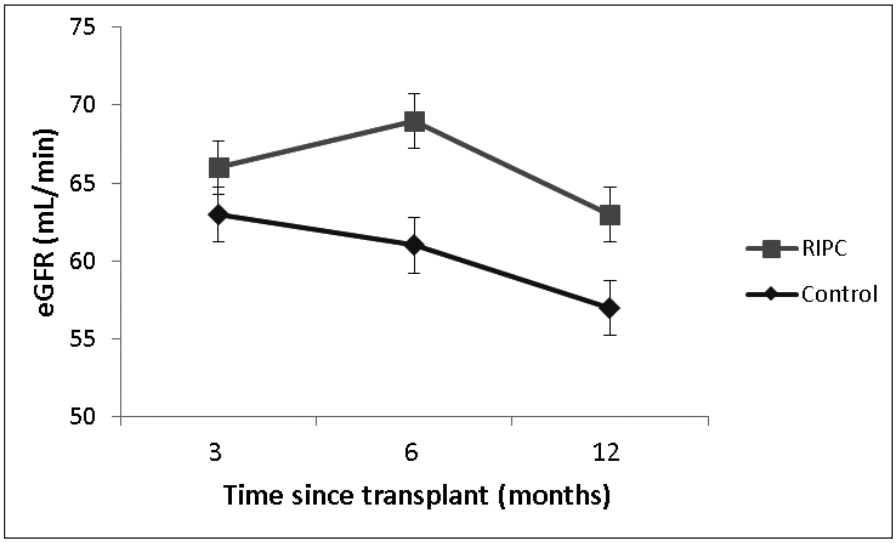

Fig. 1. Influence of remote ischemic preconditioning (RIPC) on glomerular filtration rate (GFR) at 3, 6 and 12 months of follow-up. The diagram, which is based on a linear mixed- effect model, demonstrates the marginal mean GFR values in each group with regard to the time of determination. The error bars show the +/- 1 standard error of the marginal means.

protection, involving the activation of G-protein-coupled receptors, promoting the induction of protein kinases (phosphatidylinositol-4,5-bisphosphate-3-kinase), extracellular signal-regulated kinase, mitogen-activated protein kinase, protein kinase C, etc. In turn, they activate potassium-dependent ATP channels in mitochondrial membranes, which results in blocking the permeability of membrane pores, hindering the flow of ions through those channel, including calcium ions, thus preventing the rupture of mitochondria and cell death (apoptosis). The late phase is associated with the regulation of the synthesis of anti-apoptotic and anti-inflammatory genes by humoral (accumulation of adenosine, opioids, endocannabinoids, bradykinin, CGRP and stromal cell-derived factor-1α, etc.), neuronal (stimulation of efferent nerves that protect the organ) and systemic (generation of systemic anti-inflammatory / anti-apoptotic genomic responses through regulation of anti-inflammatory gene synthesis and inhibition of leukocyte activation) pathways. Among them, it is the latter that is to a greater extent associated with remote preconditioning [16, 17, 29-34].

CONCLUSIONS

Kidney transplantation (KT) is currently the treatment of choice for end-stage renal disease, compared with a lifetime on dialysis. Therefore, the search for techniques that can empower the protection of donated kidneys from ischemic injuries is of utmost importance. The use of the original RIPC method including the induction of four procedures of sublethal ischemia, which was achieved with cuff inflation followed by 5-minute intervals of cuff deflation while measuring blood pressure on the shoulder up to 40 mm Hg above systolic blood pressure, made it possible to improve the anti-ischemic protection of the graft and increase the efficacy of its functioning, namely a statistically significant increase in GFR was found at 3, 6 and 12 months after transplantation; there was also seen a clinical decrease in the incidence of partial delay in graft function, acute allograft rejection, and primary non-function. RIPC is a safe, patient-friendly and low-cost technique that facilitates the accelerated and improved kidney transplant function, and can thus extend the life of a transplanted kidney. Even though the evidence for the effect of RIPC on our endpoints was weak, possibly due to the small number of patients and the dependence of the clinical effect of RIPC on the recipient's general condition and concomitant pathology, etc., there is strong evidence of clinically significant improvement in renal function after transplantation.

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ORIGINAL ARTICLE

RESULTS OF THE ANALYSIS OF ONCOLOGICAL COMPLICATIONS OF ANTI-TUMOR TREATMENT IN PATIENTS WITH THYROID CANCER ON THE BASIS OF MATHEMATICAL ANALYSIS OF THE CATAMNESTIC DATA

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ABSTRACT

The aim: Identification of new, non-trivial knowledge on the prediction of thyroid recurrence on the basis of follow-up data from medical histories.

Materials and methods: The development of long-term oncological effects was studied on the catamnestic data of 157 patients diagnosed with thyroid cancer who were treated according to a standard scheme, including radical surgery, radioiodine therapy and hormone therapy.

Results: It is shown that the specificity of thyroglobulin as a cancer marker for thyroid cancer is not an unambiguous question and the probability of obtaining false-positive results on its basis is quite significant.

It is shown that violation of the recommended terms for special treatment (surgical and radioiodine therapy) can be used as a factor in the prognosis of relapse, and patients who received special treatment with violation of the terms for various reasons require careful attention and more careful examination. The dose of thyroxine that should be used to achieve suppression can be used as a marker of thyroid relapse: an excess of thyroxine levels of 2.8 μg / kg is an indicator of the risk of relapse in the future.

Statistically there was no significant effect on the prevention of long-term oncological complications by prolonging the duration of suppressive hormone therapy as a component of thyroid cancer treatment, but there are grounds to believe that prolonged suppression leads to increased cardiovascular and female genital complications.

Conclusions: the use of modern information technologies in relation to the arrays of catamnestic data of medical histories allowed to obtain additional knowledge to prevent the development of distant oncological complications resulting from thyroid cancer.

KEY WORDS: Differentiated thyroid cancer, long-term effects, Data Mining technology

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INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common tumor of the endocrine system, and on average comprises 1.0 - 2.2% of all malignant neoplasms [1].

It is known that the prognosis of complete cure of differentiated thyroid cancer is quite favorable and reaches over 90% of 5, 10 and even 20 years of survival [2–4]. However, the number of recurrences and distant metastasis, which according to various authors [5,6] occur from 10 to 30%, encourage scientists to continue working towards optimizing the treatment of this disease.

State organization «Grigoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine» is one of the leading institutions of Ukraine for the treatment of the thyroid gland pathologies and has a large archive of paper medical histories starting from 1992 indexed in the official database. The availability of such a powerful source of information provides grounds for a more detailed analysis in order to obtain new knowledge about the course and consequences of thyroid cancer treatment. A possible way to conduct such an analysis is by using Data Mining, the purpose of which is to identify previously unknown non-trivial data that can be practically useful, available for new learnings and necessary for decision-making in various fields of human activity.

THE AIM

The aim of the present study was to identify new, non-trivial data about the prediction of thyroid recurrence based on catamnestic medical history of patients with thyroid cancer.

MATERIALS AND METHODS

The study included 157 medical histories of patients with thyroid cancer who underwent combined special treatment in the clinic from 1993 to 2020 and on the basis of which an appropriate electronic database (DB) which contained the

full amount of information from paper media was created.

The criterion for selecting medical histories for the database was either the appearance of any malignant disease one or more years after treatment, or the appearance of long-term therapeutic complications. The number of logical records about patients in the formed database was 463 units – one record for one consequence of each patient.

The database, in particular, contained information on the level of thyroglobulin (after surgery, before and after radioiodine therapy (RTI) and every next 6 months in the post-treatment monitoring phase), the dose of thyroxine (monitored every 3 months), the levels of thyroid-stimulating hormone (TSH) (every 2-3 months during treatment and post-treatment monitoring), the duration of suppressive hormone therapy (HST), the duration of non-compensated hypothyroidism (NHT), as well as information on age, weight, somatic complications, surgical complications, RT complications, etc. The state of suppression in patients was confirmed on the basis of TSH levels (0.1-0.5 mIU / l in the first three years after surgery and 0.1-1 mIU / l after).

For the high-risk group, the target baseline TSH level was below 0.1 mIU / L during the course of thyroxine suppressive therapy. For intermediate risk patients, the initial target TSH level was 0.1–0.5 mIU / L. For low-risk patients who received RTI after thyroidectomy and had a TG level lower than the limit of detection, the target TSH level was 0.5–2.0 mIU / L. For low-risk patients who received RTI after thyroidectomy and had low TG levels, the target TSH level was 0.1–0.5 mIU / L with monitoring for possible recurrence.

Among the patients there were 27 men (17.2%) and 130 women (82.8%). According to the histological structure, 126 (80.3%) people had papillary cancer and 25 people (16%) had follicular cancer. Papillary follicular cancer was diagnosed in 6 patients (3.7%). The most typical tumor volume ranged from 0,5 mm^3 to 8,2 mm^3. The age of patients in the general group ranged from 13 to 76 years with a median of 48 years and an interquartile range (IR) of 40 ÷ 56 years.

54 patients had oncological complications (OC), including: recurrences – 42 people (77,8 %), of which – local recurrences (in the area of the typical location of the thyroid gland) – 15 people (27,8 %), lymph nodes and / or lungs metastatic lesions (distant metastases in time (DMT) – 27 people (50 %), second cancers – 12 people (22,2 %). According to the stages of the cancer process, patients were distributed as follows: 1st stage – 13 (15,9 %) people, 2nd stage – 22 (40,7 %) people, 3rd stage – 14 (25,9 %) people, 4th stage – 5 (9,2 %) people. For the moment when OC appeared the age of the patients varied from 23 years to 76 years with IR = 42 – 63 years and a median of 51 year. The time when OC appeared was 62 months (median), varying from 10 months to 158 months (13 years), IR = 42 – 89 months.

In 12 patients (7.4%) no category of long-term effects of treatment was recorded, in 91 (58%) persons – only therapeutic complications.

The median total activity of ^{131}I was 4440 MBq, IR = 3050 – 7400 MBq.

The WizWhy package was used to conduct research and make hypotheses, which were then tested with the methods of non-parametric statistics. Statistical processing was performed using the software package Statistica Basic Academic 13 for Windows, (License Number: 139-956-866). The statistical significance of the results was assessed using Pearson's chi-squared test, Mann-Whitney test, Kruskal-Wallis test and median test.

The data are further presented as M (LQ; UQ), where M is the median of LQ is the lower quartile, UQ is the upper quartile.

RESULTS AND DISCUSSION

Thyroglobulin level (TG) was the first indicator that attracted attention based on the results of Data Mining on the array of catamnestic data on medical histories of patients with thyroid cancer. Against the background of suppressive therapy, this figure was different in patients with and without oncological complications in the future. The dependence was statistically significant (Mann-Whitney test, $p < 0,05$) (Fig.1).

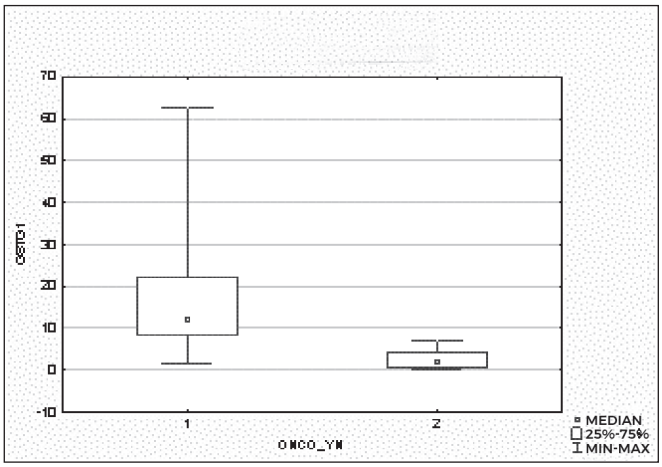
As can be seen from the figure, TG level was 11.7 (8.2; 22.1) ng / ml and ranged from 1.7 ng / ml to 62.5 ng / ml in patients with OC. In patients without OC, TG level was 2.1 (0.51; 4.4) ng / ml and ranged from 0.004 ng / ml to 11.9 ng / ml.

It is known that after removal of the thyroid gland, thyroglobulin is used as a tumor marker. Under favorable conditions, its level should be insignificant (at least <1 ng / ml and ideally go to 0 ng / ml). Our results regarding patients with OC correspond to well-known facts, but in some patients without oncological consequences in the future its level was quite significant and even reached the level of 11.9 ng / ml (Table I).

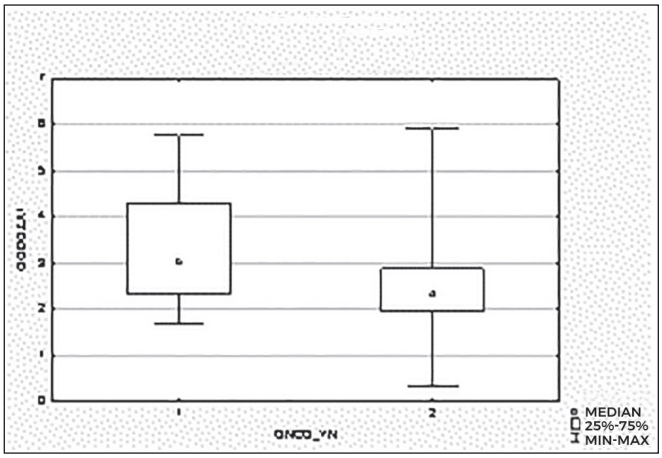
All the patients whose information is given in the table underwent regular examination after treatment and no signs of malignancy were detected.

The second indicator that attracted attention in terms of prognostic properties was the time of ablation: in patients with DMT it was 2.2 times higher than in patients without OC and was 19.5 (IR = 7.5 – 40, 5) months against 9 (IR = 5 – 22) ($p = 0.03$, Mann-Whitney test) (Fig. 2).

Thus, there are grounds to believe that if the time of ablation of thyroid tissue during the RNT exceeds the limit of 20 months it is an unfavorable factor for the appearance of distant metastases. Delay of the ablation, in our opinion, may be associated first with non-radical surgical treatment, as evidenced by the presence of residual thyroid tissue (more than 1 cm^3), the presence of micrometastases in lymph nodes and lungs that were not detected in the preoperative stage, partial radioresistance of local and distant metastases. In addition, it should be taken into account that an increase in the duration of treatment may be observed in patients with postoperative complications due to the need to correct these complications and reduce the therapeutic activity of radioiodine to prevent laryngeal edema and acute respiratory failure.



1 – group of patients with OC; 2 – group of patients without OC.
Fig. 1. Comparative graphs of TG levels on the background of suppressive therapy in patients with and without OC.



1 – group of patients with OC; 2 – group of patients without OC.
Fig. 3. Dose of thyroxine per 1 kg of body weight in patients with NHT during hormone therapy.

Table I. TG level in patients with thyroid cancer in the long term after radionuclide treatment.

Patient	TG level (ng/ml)	Number of months (after RNT)
H-n	11,9	40
F-a	4,4	20
R-o	2,45	12
O-a	2,1	13
K-a	2,1	12

The third interesting result of using Data Mining technology in relation to the problem of OC was the dose of L-thyroxine in NHT during hormone therapy (Fig. 3).

It was found that in patients with OC the dose of L-thyroxine in NHT was 3.02 (2.3; 4.3) with a total duration of NHT being 13 (9.0; 24.0) months; in patients without OC, the dose of L-thyroxine in NHT was 2.34 (1.9; 2.9) with a total duration of NHT being 9 (4.0; 16.0) months, (Mann-Whitney test, p = 0.0192).

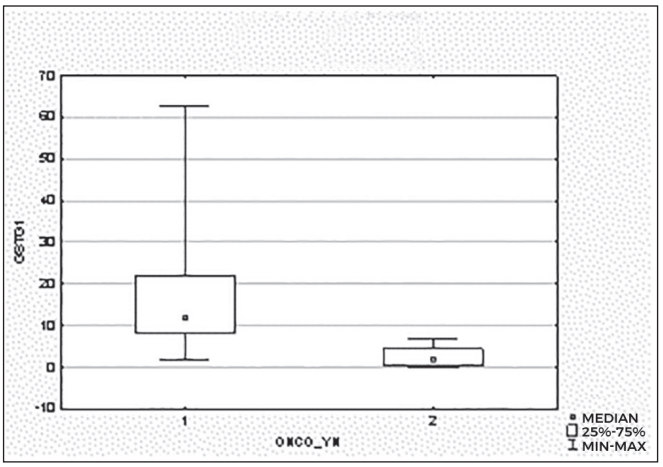
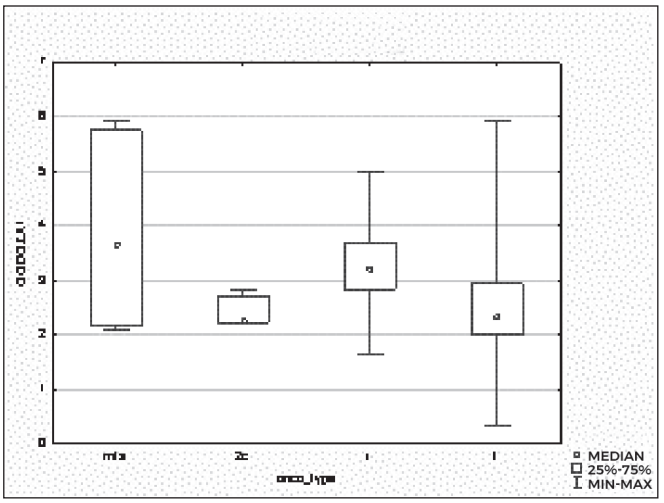


Fig. 2. Comparative graphs of long-term results of treatment (1 – appearance of OC (metastases); 2 – absence of OC).

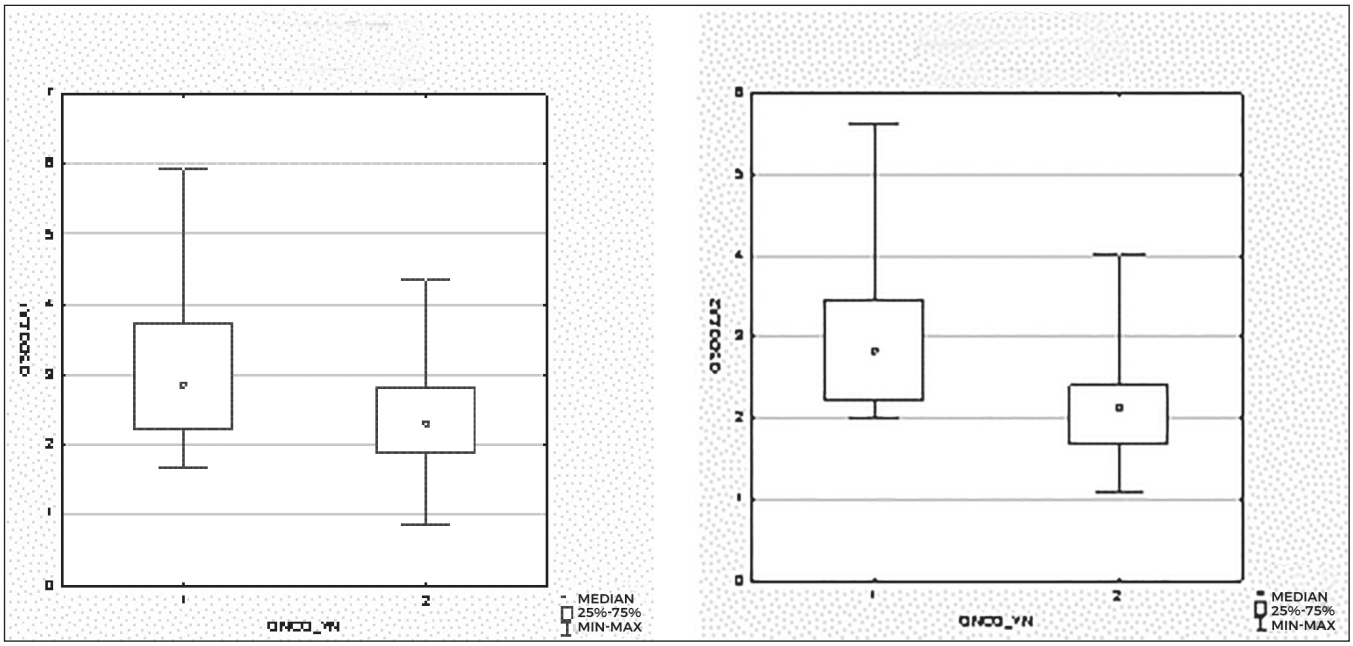


t – group of patients with therapeutic complications (without OC); mts – metastatic lesions of the lymph nodes and / or lungs; 2c – second cancer; r – local recurrences (in the area of the typical location of the thyroid gland).
Fig. 4. Dose of thyroxine per 1 kg of body weight in patients with NHT during hormone therapy

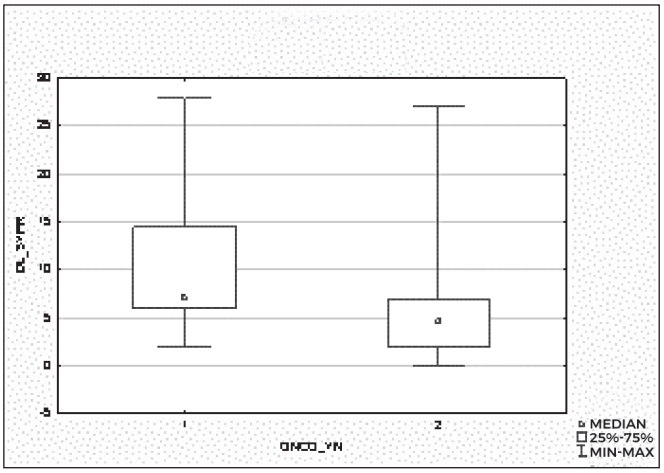
The rate of the L-thyroxine dose in NHT was different not only in groups with and without OC, but also showed markers in the division of effects into groups: without OC, metastases, recurrences, second cancers (median test, p = 0,0034).

From the box graphs of Figure 4, it can be seen that, on the one hand, patients with metastases and recurrences, and, on the other hand, patients with other cancers and patients without OC had similar dose characteristics.

These facts allow us to draw conclusions about the presence of marker signs of the L-thyroxine dose on the background of NHT as well: at a dose of 3.66 (2.2; 5.8) μg / kg there is a risk of distant metastases, and at 3.2 (2.9, 3.7) μg / kg – of local recurrences. Therefore, the presence of NHT at a hormone dose exceeding 2.8 μg / kg should also be an alarming sign of future oncological diseases.



1 – group of patients with OC; 2 – group of patients without OC.
Fig. 5. The dose of thyroxine or levothyroxine sodium per 1 kg of body weight of patients with a suppressive condition at two intervals of observation after treatment.



1 – group of patients with OC; 2 – group of patients without OC.
Fig. 6. Comparative graphs of the total duration of suppressive therapy in patients with OC and without OC.

The fourth non-trivial result of this study was the association of L-thyroxine dose in HRT: a prognostically unfavorable factor for the occurrence of distant OC is the need to increase the dose of thyroid hormone to achieve a suppressive state in patients after special treatment.

The database used in the study contained information of up to three intervals of HRT during hormone therapy. During the analysis, all 3 intervals gave almost identical results: the need to increase the dose of thyroid hormone to a level exceeding 2.8 μg / kg should cause concern about the recurrence of the oncological disease in the future (Fig. 5).

Indeed, as can be seen from the above box graphs, the median values of the suppressive dose of L-thyroxine in patients without oncological complications in the future in the first and second observation intervals are 2.3 μg / kg and 2.1 μg / kg (in the third interval – 2.1 μg / kg), while the corresponding values in patients with oncological complications are 2.9 μg / kg, 2.8 μg / kg and 3.3 μg / kg. At the 1st and 2nd intervals of observation, the dependencies were statistically significant (Mann-Whitney test, $p = 0.01$ and 0.03, respectively).

The fifth dependence, shown in Figure 6, looks quite paradoxical regarding the characteristics of HRT in terms of appearance of OC: the total duration of therapy in patients with OC is longer than the duration of HRT in patients without OC (7 (6; 14) vs. 4, 5 (2; 7)), $p = 0.03$, Mann-Whitney test.

In the analyzed sample, no dependence between the duration of HRT and the stage of the process and the age of patients as intervention factors was detected. For further analysis of the detected dependence, HRT duration interval was divided into subbands in accordance with the descriptive statistics of this indicator for patients with and without OC: 1-6 months, 7-14 months, 15 months-22 months, and more than 22 months. The results of data analysis of 42 patients who received a course of HRT (total duration from 1 month to 28 months) after surgery and radionuclide treatment in terms of the presence of OC - duration of treatment and duration of treatment - the presence of OC are shown in Tables II and III.

The results provided in the tables show that it cannot be stated unequivocally that the prolongation of the suppressive state in patients after surgery and radionuclide treatment is a guarantee of the absence of OC in the future. Note that on the background of prolonged duration of HRT patients in the study group showed a tendency to increase the number of distant cardiovascular and gynecological complications, but these dependencies were hypothetical and were not statistically confirmed in the working sample.

Table II. Total HRT duration in patients with thyroid cancer after surgery and radionuclide treatment in terms of the presence of OC – duration of treatment

Group of patients	Duration of suppressive therapy				Total abs.
	1-6 months abs., (%)	7-14 months abs., (%)	15-21 months abs., (%)	more than 22 months abs., (%)	
With OC	4 (33,33)	5 (41,67)	2 (16,67)	1 (8,33)	12
Without OC	22 (73,33)	4 (13,33)	2 (6,67)	2 (6,67)	30
Total	26	9	4	3	42

Table III. Total duration of HRT in patients with thyroid cancer after surgery and radionuclide treatment in terms of duration of treatment – the presence of OC

Duration of suppressive therapy	Presence of OC		
	With OC abs., (%)	Without OC abs., (%)	total abs.
1 -6 months	4 (15,38)	22 (84,62)	26
7-14 months	5 (55,56)	4 (44,44)	9
15 -21 months	2 (50,00)	2 (50,00)	4
more than 22 months	1 (33,33)	2 (66,67)	3
Total	12	30	42

Thus, according to our observations, the specificity of TG as a tumor marker is not an unambiguous issue and the probability of obtaining false-positive results on its basis is quite significant.

The data that the lack of compensation for hypothyroidism is an unfavorable factor in the prognosis of thyroid recurrence are fully confirmed and coincide with the data of other researchers. In addition, it has been shown that violation of the recommended terms for special treatment (surgery and radioiodine therapy) can also be used as a prognostic factor for relapse (patients undergoing special treatment with delays for various reasons need careful attention and more careful examination).

Another interesting fact was that the dose of thyroxine that must be used to achieve suppression can be used as a marker of recurrence of thyroid cancer. It has been shown that the higher the dose, the worse the prognosis regarding the likelihood of future oncological consequences. Taking into consideration the fact that among patients in the observation group the duration of OC ranged from 10 months to 158 months (13 years), a useful practical aspect of post-treatment monitoring is the need for regular monitoring, at least for 13 years with a particularly meticulous attitude to patients receiving or having prescribed a suppressive dose of thyroxine during treatment excessing 2.8 μg / kg.

In addition, we did not find a statistically significant effect on the prevention of remote OC by prolonging the duration of suppressive hormone therapy as a component of thyroid cancer treatment, but there are grounds to believe that prolonged suppression leads to increased cardiovascular and female genital complications..

CONCLUSIONS

Thus, using the new knowledge about the factors predicting the development of cancer complications of the thyroid gland it is possible to:

– increase the accuracy of the prognosis for all stages of thyroid cancer;
– increase the 5 and 10-year survival of patients;
– reduce the average time to detect recurrence of the disease;
– provide less aggressive treatment of recurrence due to its timely detection;
– improve the quality of life of patients by reducing their disability.

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ORIGINAL ARTICLE

THE EFFECT OF DIET ENRICHED WITH PYROPHOSPHATE (E450) ON MORPHOLOGICAL CHANGES OF TOOTH GERMS OF MOUSE EMBRYOS

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ABSTRACT

The aim: To reveal the effect of pyrophosphates on the tooth germ structure in the mandible of embryos (17th day of pregnancy) gestated by females, kept on a pyrophosphate-rich diet since 30 days before fertilization to gestation.

Materials and methods: The effect of food supplements was studied in «Overload phosphates model». Experiments were carried out on white nonlinear outbred mice with mass 25-28g (n= 40). The females from the control group were fed with standard rodent food, whereas the experimental females were fed with pyrophosphate-enriched food. The material for the morphological study were the mandible of 17-day-old mouse embryos (E-17), which were examined under a microscope with subsequent photofixation.

Results: The examination of the mandible of 17-day-old mouse embryos, gestated by females on a pyrophosphate-rich diet, showed morphological changes in tooth germs at the dental follicle development stage.

Conclusions: The experimentation revealed that the pyrophosphate excessive intake during dental follicle development leads to early dentinogenesis and oppression of ectodermal structures of tooth germs.

KEY WORDS: pyrophosphate diet, odontoblasts, enamel, dentin, mouse embryo mandible, food supplement E-450 (pyrophosphate)

Wiad Lek. 2022;75(2):410-415

INTRODUCTION

Diet is an important determinant of offspring health, starting from the conception [1]. Nutritional needs increase during pregnancy to maintain maternal metabolism and tissue accretion while supporting foetal growth and development [2]. Poor dietary intakes or deficiencies in key macronutrients and micronutrients can therefore have a substantial impact on pregnancy outcomes and neonatal health. Increasing evidence suggests that the effects of foetal nutrition may persist well into adulthood, with possible intergenerational effects [2].

One of the current health concerns, particularly relevant to pregnant women, is the addition of preservatives and dyes to alimentary products [3,4].

Among the stabilizing agents our attention was drawn to a food supplement encoded E-450 (salts and esters of pyrophosphoric acid - pyrophosphates).

There are 8 types of pyrophosphates [5,6]:

(i) Disodium diphosphate;
(ii) Trisodium diphosphate;
(iii) Tetrasodium diphosphate;
(iv) Dipotassium diphosphate;
(v) Tetrapotassium diphosphate;
(vi) Dicalcium diphosphate;
(vii) Calcium dihydrogen diphosphate;
(viii) Dimagnesium diphosphate.

E-450 is widely used in food industry as a preservative, stabilizer and raising agent in the production of meat products, semi-finished products (sausages, wursts, dumplings, carbonade, deli meats, dried meat), minced meat, canned food; cheeses, processed cheeses and some dairy products (sour cream, condensed milk); canned seafood, jams, lemonades, sweets, baking soda [5,6]:

The World Health Organization (WHO) classifies the inorganic pyrophosphate as a nontoxic physiological metabolite with a maximum tolerable daily intake value (MTDI) of 70mg/kg [7].

The Food and Drug Administration (FDA) of the United States classifies the inorganic pyrophosphate as Generally Recognized Safe (GRAS), while in Europe it is designated as food supplement E-450 [8].

Dietary inorganic pyrophosphate is readily absorbed in humans [9] and its level of oral absorption, observed with human volunteers, is comparable to absorption from water [10].

Excess of phosphates impairs the absorption of calcium in the body, causing calcium-phosphorus imbalance [11, 12], which can be crucial at the tooth bud mineralization stage.

The impact of maternal nutrition on the fetal odontogenesis has been well studied, but there are no studies dealing with teeth germination disorders, caused by excessive pyrophosphate (food supplement E-450) intake.

We failed to find any published data regarding the morphological changes of tooth germs caused by excessive pyrophosphate intake by a mouse female during pregnancy, therefore we initiated a study in pursuit of the following:

examining of the impact of excessive E-450 intake on the structure of the tooth germs in the mandible of mouse embryos (17th day of pregnancy) gestated by females, kept on a pyrophosphate rich diet since 30 days before fertilization to gestation.

THE AIM

The aim of this study was to reveal the effect of pyrophosphates on the tooth germ structure in the mandible of embryos (17th day of pregnancy) gestated by females, kept on a pyrophosphate-rich diet since 30 days before fertilization to gestation.

MATERIALS AND METHODS

The *in vivo* study of the E-450 (pyrophosphate) effect was carried out on «phosphate overload model». We did not apply any modification to a basic model [12].

The experiments were performed in compliance with the «Rules and Regulations for Carrying Out Animal Research Work».

Experiments were carried out on white nonlinear outbred mice (total 40 animals, weighing 25-28g), housed in stainless steel cages under controlled conditions (50–60% relative humidity, artificial 12-h light-dark cycle). The mice were kept at 23±1°C with a 12-h light–dark cycle, light at 7 a.m., and were allowed ad libitum access to tap water and food.

The room was located in the vivarium of the Bogomoletz Institute of Physiology NAS of Ukraine.

All mice were separated into 2 groups: control group and experimental group.

Experimental hyperphosphatemia (2%) was simulated by adding to the diet food supplement E-450 (sodium pyrophosphate, chemical formula $Na_4P_2O_7$) for 60 days.

Mice of the experimental group received a diet of vivarium with the addition of 2g. sodium pyrophosphate (made in Israel) per 100 gr. stern.

Mice in the control group received a diet of vivarium (24% protein, 11% fat, 48% carbohydrates, 5.5% fiber, 6% vitamin 5.5% ash).

Females in proestrus or estrus phase were kept with the males in proportion 4:1 30 days later.

The presence of spermatozoa in the vaginal smear was considered as an indicator of fertilization and first day of pregnancy.

Pregnant females were kept in cages and fed with standard food (control group) or pyrophosphate rich food (experimental group).

Pregnant mice (n=6 per group) were sacrificed by the carbon dioxide expose on the 17th day of pregnancy (E–17).

The object of the morphological investigation were the mandibles of 17-day-old mouse embryos (E-17), when odontogenesis underwent the stage of the bell (period from 16.5 to 18.5 days of pregnancy) [13].

Experiments were performed in accordance with the European Community Standards.

The mandibles were fixed by 2% glutaraldehyde in cacodylate buffer followed by decalcification, postfixation in 1 % osmium oxide and embedding in epoxy resin. Semithin sections were stained with methylene blue and fuchsine that allowed identification of mesenchymal and epithelial tissues. Obtained morphological sections had 1,0-1,5 μm in thickness. The images were obtained using *Nikon Eclipse E200 (Fryer Co., Huntley, IL,* USA*)* microscope in combination with *Nikon DS-F11* camera.

To describe micrographs with magnification x10, x20, x40 we used a schematic representation of successive stages of differentiation of ameloblast cells (Fig. 1).

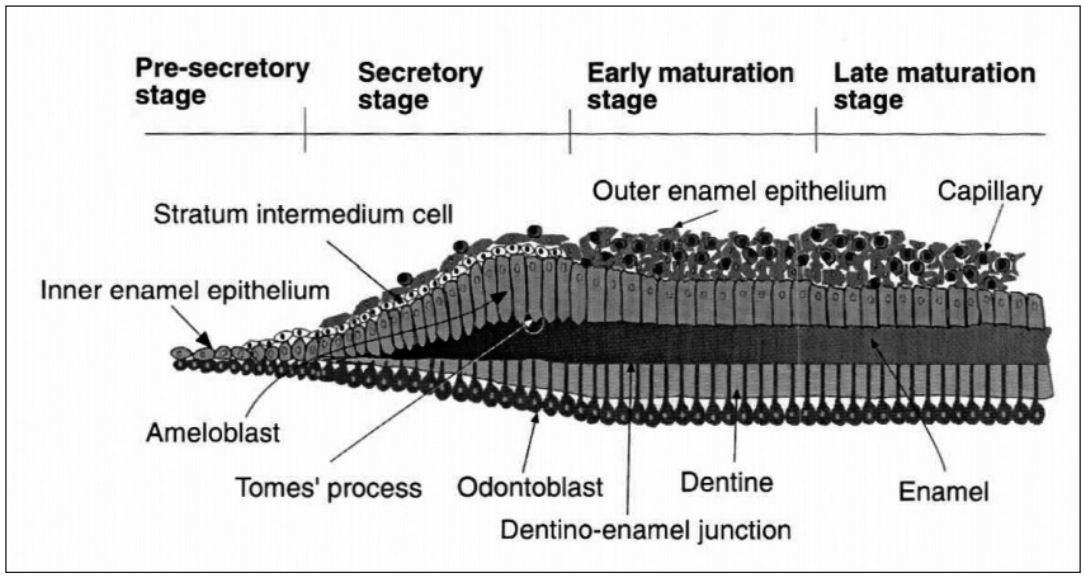

Fig. 1. Schematic representation of the sequence of stages of ameloblast cells differentiation [14]

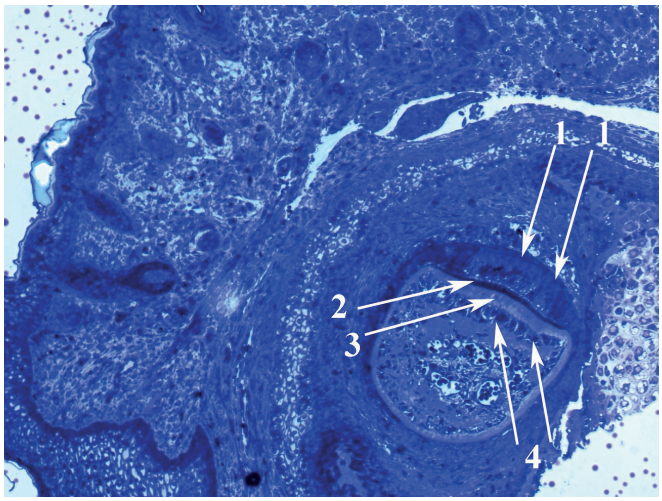

Fig. 2. Morphological study of the tooth germs of a 17-day-old embryo of control mice, x10, staining with methylene blue: 1 - ameloblasts, 2 - enamel, 3 - dentin, 4 - odontoblasts.

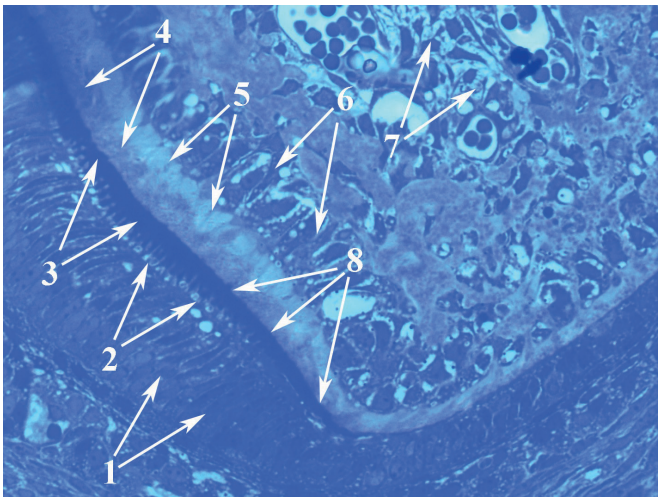

Fig. 3. Morphological study of the tooth germs of a 17-day-old embryo of control mice, x40, staining with methylene blue: 1 - ameloblasts, 2 - Thomes' processes, 3 - enamel, 4 - dentin, 5 - predentin, 6 - odontoblasts, 7 - pulp, 8 - enamel-dentin connection.

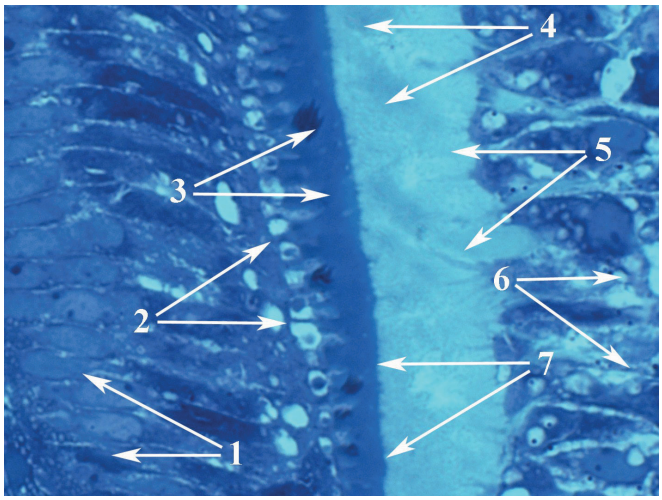

Fig. 4. Morphological study of the tooth germs of a 17-day-old embryo of control mice, x100, staining with methylene blue: 1 - ameloblasts, 2 - Thomes' processes, 3 - enamel, 4 - dentin, 5 – predentin, 6 - odontoblasts, 7 - enamel-dentin connection.

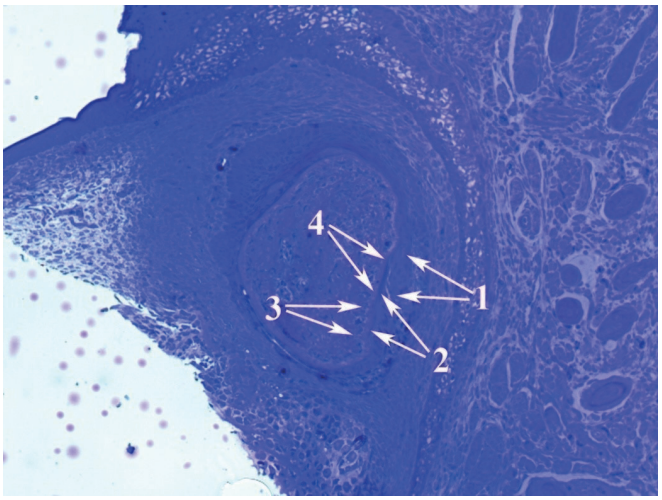

Fig. 5. Micrograph of the dental germ structure of a 17-day-old embryo of experimental mice (pyrophosphate (E450) rich diet). Magnification: x10; staining: methylene blue. 1 - ameloblasts, 2, 4 - enamel, 3 – odontoblasts.

STATISTICAL ANALYSIS

Statistical analysis of obtained data was performed using *Excel* 2000 and *Origin* 7.0. Probability distribution of mean ($P<0.05$) was calculated using Student's t-test.

RESULTS

Our morphological research of dental germs from embryos gestated by mice kept on a pyrophosphate-enriched diet before and during pregnancy showed tooth morphogenesis disturbances.

The obtained micrographs of the control group showed the following.

At an increase of x10 in the control group, ameloblasts formed a uniform layer with clear polarization, on the apical part of cylindrical cells there were narrowed areas - Tomes' processes, key structures responsible for the secretion of the enamel matrix, the presence of which indicates high differentiation of ameloblasts and corresponds to secretory stage development of these cells. The functional activity of the ameloblast layer was reflected by the presence of a pronounced dark-dark band between the dentin and ameloblasts, which morphologically corresponds to tooth enamel (Fig. 2).

With increasing x40 in the control group (Fig.3), observed was the formation of a uniform layer of odontoblasts, which took a cylindrical shape, were located in parallel and formed processes in the predentin layer. Dentin and predentin had the form of two tightly connected but evenly spaced bands, differing in color by about one tone - predentin lighter, dentin darker. When the predentin layer reaches a thickness of 40-80 μm, it is pushed to the periphery by the newly formed layers of predentin, in which the fibers have a different direction - they are located parallel to

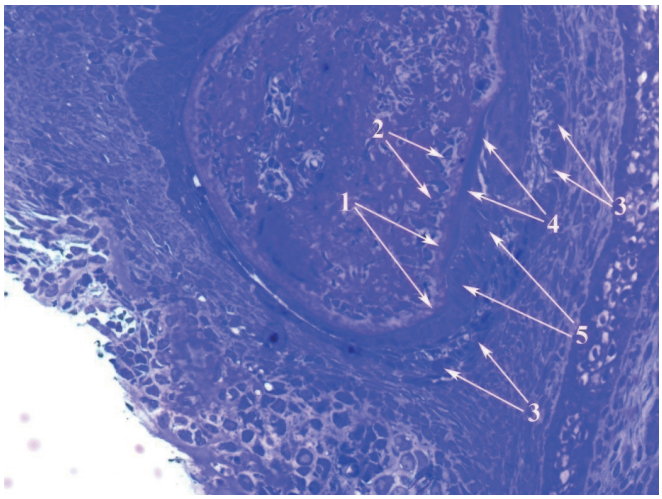

Fig. 6. Micrograph of the dental germ structure of a 17-day-old embryo of experimental mice (pyrophosphate (E450) rich diet). Magnification: x20; staining: methylene blue. 1 – dentin, 2 – odontoblasts, 3- outer enamel epithelium, 4 – enamel, 5 – ameloblasts.

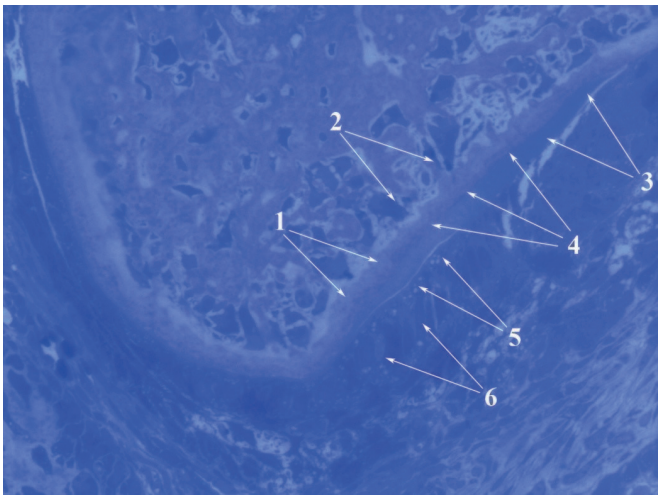

Fig. 7. Micrograph of the dental germ structure of a 17-day-old embryo of experimental mice (pyrophosphate (E450) rich diet). Magnification: x40; staining: methylene blue. 1 – dentin, 2 – odontoblasts, 3 – enamel, 4 – enamel-dentin connection, 5 – Tomes' process, 6 – ameloblasts.

the surface of the papilla. Subsequently, these inner layers of dentin, rich in tangential fibers, form pulp dentin in the formed tooth, and the radial fibers lying in the outer layers of dentin, which was formed first, - mantle dentin.

With increasing x100 in the control group (Fig. 4), the uniform distribution of dentin and predentin bands on lighter and darker was observed. There is a higher differentiation of cells of both odontoblasts and ameloblasts. Ameloblasts have a cylindrical shape with pronounced thinning in the apical part, the clear location and uniform distribution of cell layers allow us to conclude about the high differentiation and sequence of function of all cells.

The following differences are observed in the obtained micrographs of the experimental group.

With an increase in x10 in the experimental group (Fig. 5), the enamel was expressed in form of uneven barely noticeable line in a limited area. It was probably resulted from significant structural alterations in ameloblast layer, to be more precise – in formation of unevenly ordered layer composed from unpolarized cells with feebly pronounced cylindrical shape.

With increasing x20 in the experimental group (Fig. 6) the outer enamel epithelium was expressed in form of uneven layers of chaotically distributed cells distinguishable by their polarization and intensity of staining.

With increasing x40 in the experimental group (Fig. 7) the line of hard tissues formation contained nonuniform bands in teeth from experimental group, a phenomenon that was observed in none of the control samples. The thinnings on the apical part of ameloblasts were observable only on the very limited area, determined thinning - *Tomes' process* (Fig 7).

The hypertrophic nucleuses of ameloblasts occupied almost the entire cytoplasmic space, that indicates decreased cell differentiation and only the beginning of cell transition from *pre-secretory* into *secretory* phase of differentiation (Fig. 7).

Unevenly located ameloblasts differed from each other by phase of their maturation (most of them were on the *early maturation stage).* The unpolarized chaotically distributed cell aggregations were observed, in front of which the enamel was not disclosed (Fig 5, 6).

Some slight disorientation and disorganization of odontoblasts, as like as absolute their absence in some areas of the organ, was observed at x40. Dentin has the appearance of a light irregular strip without distinctive division between the predentin and dentin. Since predentin and dentin could not be distinguished in the preparation, it is clear that the specimens from the experimental group underwent some alterations caused by uneven and even sometimes chaotic arrangement of dentine collagen fibers and disbalance of process of dentine layer satiation with organic and inorganic components. The thin layer of dentin is one more indicator of its reduction; the disorganization of the odontoblasts layer was also observed (Fig. 7).

DISCUSSION

The experiment focused on the features of morphogenesis of tooth germs of 17-day-old mouse embryos. In mice of the experimental group the study revealed changes in the morphological structure of teeth, caused by the sodium pyrophosphate (food additive E450) rich diet, including significant structural changes in the layer of ameloblasts, uneven layers of chaotically arranged cells of the outer enamel, nonuniform bands in the line of hard tissues formation. Tomes' processes were determined in a very limited area of apical parts of ameloblasts, hypertrophied nuclei of ameloblasts covered almost the entire cytoplasmic space, unevenly spaced ameloblasts were mainly at the stage of early maturation, disorientation and disorganization of individual odontoblasts. In the experimental group there were changes caused by uneven and sometimes chaotic

arrangement of dentin collagen fibers, imbalance in the saturation of the dentin layer with organic and inorganic components.

Thus, in all samples of the tooth germs of the experimental group there were significant differences as opposed to the control ones. This is due to the fact that the most pronounced effect of food additive E450 (pyrophosphate) occurs during the follicular development of teeth, which leads to early dentinogenesis and inhibition of ectodermal structures of tooth germs.

The researchers [15] conducted the study of the effect of excessive amounts of pyrophosphates in the diet of pregnant mouse females on the expression of BMP2 mRNA and osteocalcin. It was found that a diet, enriched with sodium pyrophosphate, does not alter BMP2 gene expression [15]. Given that BMP2 is a key factor of odontoblasts differentiation [16], we can hypothesize that excessive pyrophosphate in maternal diet would not influence the odontogenesis in the embryo. However, sodium pyrophosphate rich diet is likely to increase the expression of osteocalcin [15]. On the one hand, raised osteocalcin expression seems to be a positive sign, since osteocalcin ensures the mineralization of the tooth bud tissues, and that means intensification of apatite formation in animals with gained expression of osteocalcin. But on the other hand, the hyperexpression of osteocalcin could cause the premature tooth mineralization that can disrupt the processes of teeth formation and odontogenesis all in all.

Studies of pathohistological changes in the tooth germs of the mandible of 17-day-old mouse embryos allowed to compare genetic changes [16] with pathomorphological and to establish the functional significance of changes in the expression of the studied genes.

Under clinical conditions, this creates a favorable basis for the development of systemic hypoplasia of the enamel, and in the long run - focal demineralization of hard tissues and carious process [17].

CONCLUSIONS

Experiments on the mandible of 17-day-old mouse embryos, influenced by food supplement E-450 (pyrophosphate), showed the availability of morphological changes in teeth buds. In all samples of the experimental group there were significant structural differences in the formation of tooth germs as opposed to the samples of the control group. The study has revealed that food supplement E-450 (pyrophosphate) can cause early dentinogenesis and oppression of ectoderm derived structures of teeth at the stage of their follicular development. In clinical conditions, it may induce the development of system enamel hypoplasia, focal demineralization of hard tissues and hereafter may cause caries.

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ORIGINAL ARTICLE

RETROSPECTIVE CHART ANALYSIS OF PATIENTS DIGNOSED WITH ACANTHOLYTIC PEMPHIGUS FOR THE PERIOD 2008-2018

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ABSTRACT

The aim: Determine the clinical and anamnestic criteria that cause the acantholytic pemphigus (AP) morbidity in the course of the treatment.

Materials and methods: Analysis of medical histories of patients who underwent the therapy on the basis of the clinic for 10 years. In the analysis of 174 medical case histories were determined the factors provoking the onset and exacerbation of the disease. The disease severity was assessed using the IKEDA index.

Results: During the analysis, patients were divided into two groups. The I group - patients who required combination therapy - systemic glucocorticosteroids (SGCs) and immunosuppressant (azathioprine (AZA)). For patients of group II used SGCs - according to the indications. The presence of intoxication and signs of pyoderma were more common in patients of group I. The number of exacerbations per year for an unknown reason in group I was almost 3 times higher. The ineffectiveness of high starting doses of SGCs was 20.2% of cases compared with those in group II.

Conclusions: According to clinical and anamnestic data, during the retrospective analysis of case histories, the criteria determining the severity of acantholytic pemphigus during treatment were determined: the age of patients, the diagnosis period, the prevalence of lesions and severity of dermatosis according to the IKEDA index, the selection of adequate treatment tactics, taking into the complications caused as a result of the systemic glucocorticosteroids therapy.

KEY WORDS: acantholytic pemphigus, retrospective analysis, systemic glucocorticosteroid therapy, immunosuppressive therapy

Wiad Lek. 2022;75(2):416-421

INTRODUCTION

Acantholytic pemphigus (AP) belongs to a group of particularly severe skin and/or mucosal diseases that lead to disability or death [1]. This is an autoimmune disease whose morphological feature is acantholysis induced by autoantibodies to desmosomal proteins of keratinocytes [2].

Before the advent of steroids, the mortality rate reached almost 100%. From 1950 to the present day, mortality has decreased 10 fold due to the use of SGCs [3].

In terms of prevalence, the global average incidence of AP is low and is regionally dependent. Thus, in European countries it is as follows: Finland – 0.08, France – 0.17, Bulgaria – 0.47 and Greece – 0.93 cases per 100 thousand population. AP is most common in Jews and people of Mediterranean and Middle East origin. In Israel, the incidence of pemphigus reaches 1.62, in Tehran – 1.6, in Iran – 1.0 cases per 100 thousand population, which is much higher than in Europe. [4].

It is important to note that the grave condition of patients with this pathology occurs due to the impaired skin barrier function and mucous membranes, secondary infection, loss of biologically active trace substances, fluid, protein, carbohydrate and lipid metabolism, which promotes the vicious loop of pathogenesis. The development of intoxication, septicemia, etc. in the absence of pathogenetic therapy affects the somatic condition. The combination of the above factors is the foundation of disability and mortality among patients of the given nosology [5]. High doses of SGCs, the duration of their use has side effects caused by the endocrine system [6, 7], cardiovascular system [8, 9], gastrointestinal tract [10], musculoskeletal system [11, 12], skin, eye diseases [13], psycho-neurological disorders [14], changes in the water-electrolytic composition of blood [9]. All the above-mentioned aggravates the progression of dermatosis.

Current methods of treating AP, to date, do not always have a positive effect on the disease progression. Determining the clinical and anamnestic criteria, which cause the pemphigus morbidity in the course of the treatment, will contribute to the prescription of adequate therapy in the early stages of observation, which will be of great medical and social importance.

THE AIM

Analyze the factors that contributed to the onset of acantholytic pemphigus (AP) and trigger factors for exacerbation of dermatosis, the number of relapses per year, age and gender dependence for the correction of therapeutic tactics, taking into account the severity of the dermatological process and comorbid conditions.

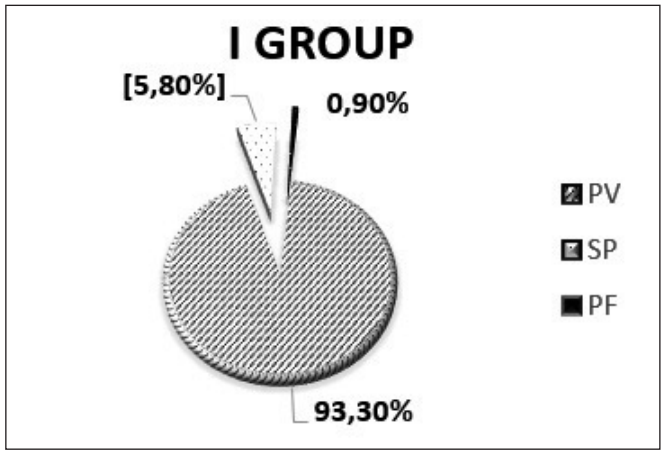

Fig. 1. Clinical forms of group I

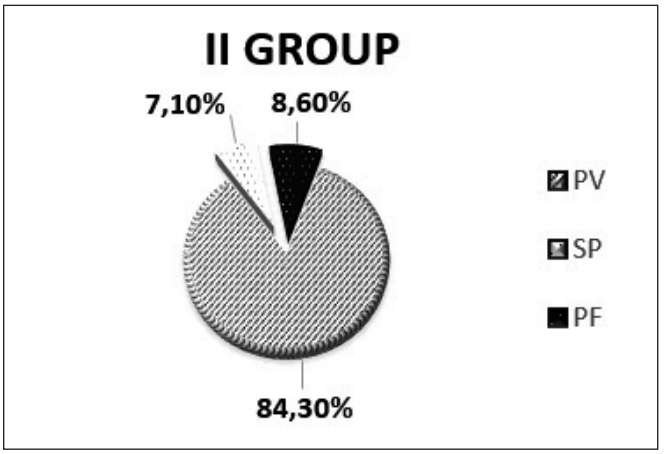

Fig. 2. Clinical forms of group II

MATERIALS AND METHODS

A retrospective analysis of the archival material of medical histories of patients diagnosed with AP who were treated in the dermatological department of the SE "IDV OF NAMS of UKRAINE" in Kharkiv for 10 years (period 2008 - 2018) was conducted.

In the analysis of 174 medical case histories, they determined the factors provoking the onset and exacerbation of the disease; the disease duration at the time of hospitalization in the clinic and the timing of diagnosing the AP since the onset of primary rash; recorded the primary location of the rash, analyzed the previously established diagnoses; the therapy assigned based on these diagnoses; the specialists consulted by patients in the first instance; assessed the general condition of patients at the time of hospitalization; took into account the starting dose of SGCs depending on the dermatosis severity; determined the number of exacerbations per year, the cause of their occurrence and the dose of SGCs that triggered exacerbations.

The disease severity was assessed using the IKEDA index [15]. The following parameters were studied: the area of skin lesions, the presence or absence of rashes on the mucous membranes, the severity of Nikolskyi's symptom and the number of new vesicles caused per day. Each of the parameters was evaluated on a four-point scale from 0 to 3 points. The maximum value of the IKEDA index constitutes 12 points. The following forms of the disease were estimated by the sum of points: 12-8 points – severe form, 5-7 points – moderate form and <5 points - mild form [15, 16]. During the cytological examination, the acantholytic cells (AC) in smears taken from the vesicle bottom/erosion, namely their presence, number and morphological characteristics, taking into account the severity of dermatosis, were evaluated.

Thus, the initial dose of SGCs was specifically prescribed taking into account the severity, the weight, and the concomitant somatic pathology. In terms of prednisolone, the daily dose ranged from 160 to 45 mg. Patients with a severe course of disease received 160-100 mg/d, patents with a moderate course of disease received 100-60 mg/d, and those with a mild course were given 60-45 mg/d. Preference was given to the combined method of administering medication, namely intramuscularly and orally each having different effect.

The results of bacteriological examination of the skin area affected by vesicles and/or erosions (for cause) were evaluated.

RESULTS

In a retrospective analysis, 174 case histories of patients diagnosed with AP were divided into 2 groups according to treatment tactics. The first group had 104 case histories, where patients had received SGCs and AZA. The second group had 70 case histories in the treatment of which they used the SGCs therapy.

In the I group, patients according to anamnestic data in 93.3% of cases (97 out of 104) were diagnosed with PV, SP – in 5.8% of cases (6 out of 104) and PF in 0.9% of cases (1 out of 104) (Fig. 1A). The mean age of patients was 50.8 ± 1.3 (25 to 80 years). The ratio of women/men was 2/1. The average duration of the disease was 5.8 ± 0.4 years. The term of establishing the diagnosis was 6.7 ± 0.2 months (Fig. 2). Primary rash in almost 79% of cases (82 cases out of 104) was observed on the mucous membranes and the vermilion border, so patients received therapy from dentists for stomatitis of various origins and otorhinolaryngologists. For the treatment of seborrheic and allergic dermatitis, toxicoderma, family doctors prescribed systemic prolonged steroid drugs.

The cause of the disease onset was noted to be stress - 28.8% (in 30 cases out of 104), SARS – 24.0% (25 cases out of 104), dental treatment - 10.6% (11 cases out of 104). In 3.9% cases (4 of 104), the onset of dermatosis was associated with other factors (sun insolation, vaccination, chemotherapy for lymphocytic leukemia). It was not possible to establish the cause of the rash in 32.7% of patients (34 of 104) (Fig. 3).

At the time of hospitalization, patients of I group, by severity were distributed as follows: in 30.8% (32 out of 104) cases, severity was recorded (12-8 points according to the IKEDA index), in 52.9% cases (55 of 104) – moderate

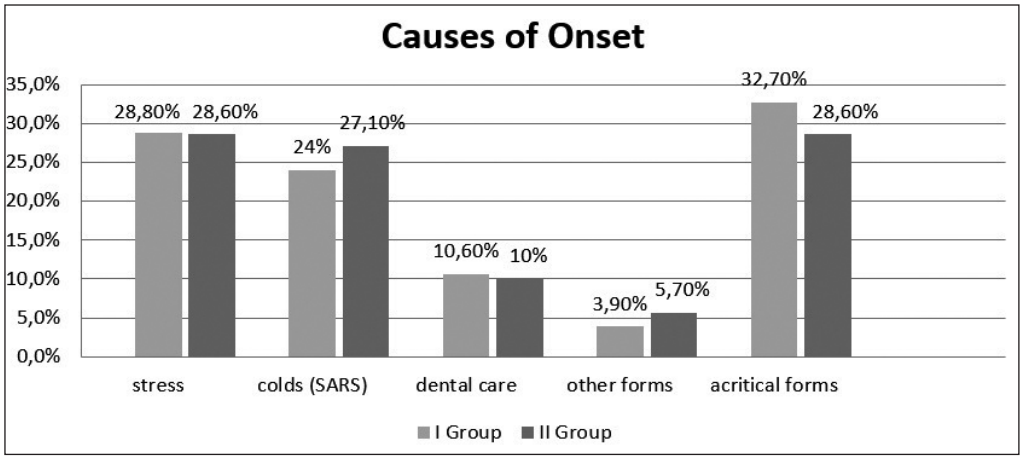

Fig. 3. Causes of dermatosis onset in groups I and II

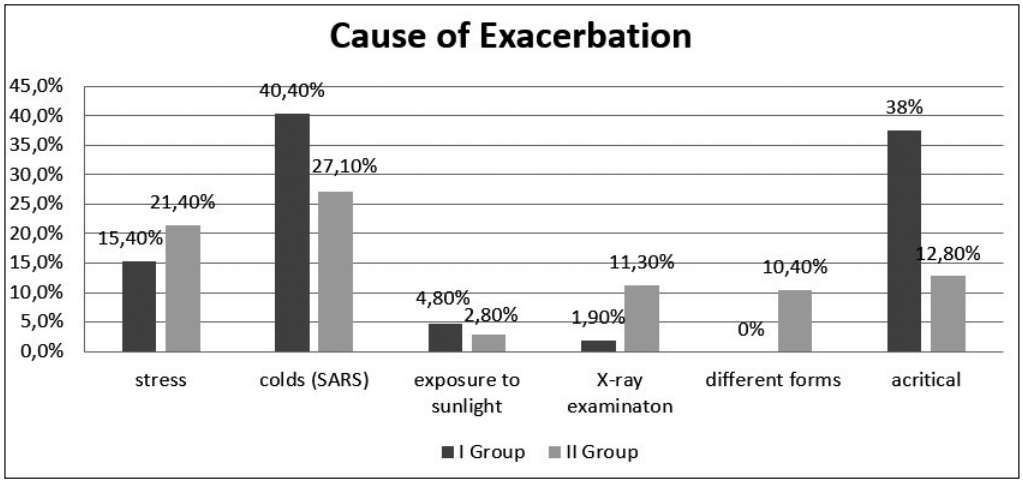

Fig. 4. Causes of dermatosis exacerbation in groups I and II

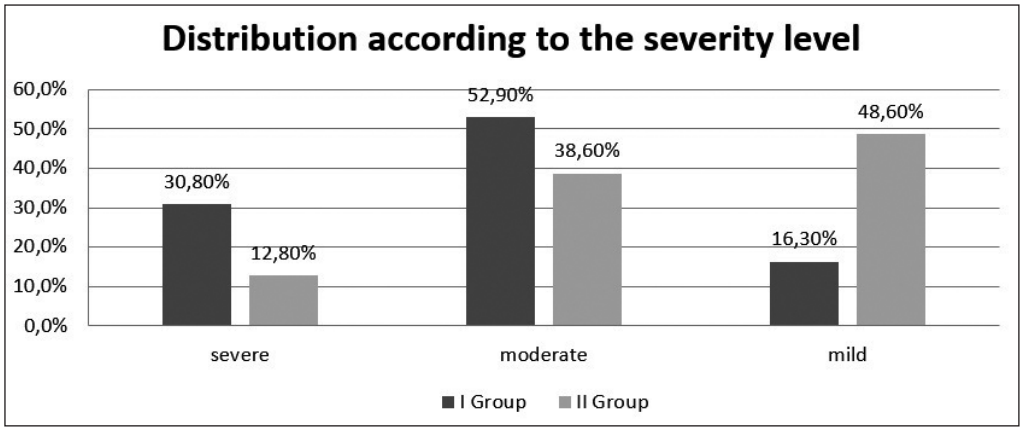

Fig. 5. Distribution of dermatosis by severity among patients of groups I and II

disease course (5-7 points) and mild disease course (<5 points) in 16.3% of cases (17 out of 104) (Fig. 4).

At cytological examination from the bottom of erosive surfaces in 62.5% of cases (65 out of 104) ACs were present. According to the analysis of cytological examination for identifying ACs, by severity it had the following form: in patients with a severe course of disease, ACs were revealed in almost 28.0% of cases (29 out of 104) that were located in layers. In 31.7% cases (33 out of 104) along with moderate severity of and in 2.9% (3 of 104) of mild cases.

Signs of pyoderma were observed in 59.6% (62 of 104) of cases: 16.3% (17 cases out of 104) – severe, 34.6% (36 cases out of 104) – moderate, 8.7% (9 cases out of 104) – mild.

The intoxication syndrome was diagnosed in 54.8% of cases (57 case histories out of 104): 15.4% (16 out of 104 cases) - patients with severity, 32.7% (34 out of 104 cases) – moderate severity and 6.7 % (7 out of 104 cases) – mild severity. Clinical manifestations of the intoxication syndrome were diagnosed in the form of chills and fever, muscle and joint pain, general weakness, subfebrile and febrile fever, the presence of hypotension and tachycardia, tachypnea, sleep disturbances. It was laboratory-confirmed by neutrophilic leukocytosis and increased ESR.

The starting dose of SGCs was 160-60 mg/d of SGCs depending on the distribution of the skin process, the patient's weight, and the available accompanying somatic pathology

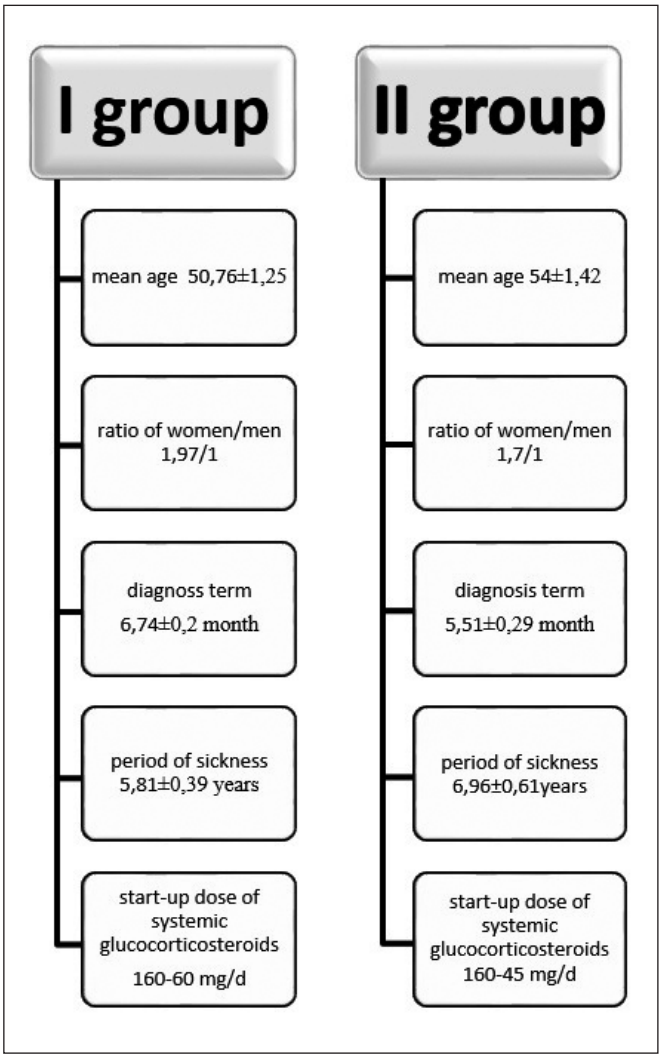

Fig. 6. Comparison of performance of both groups

(Fig. 2). Lack of therapeutic effect of high doses of SGCs in the first 7-10 days was observed in 20.2% (21 cases out of 104). The cytologic picture retained the previous characteristics. When trying to reduce SGCs by 15-20% of the maximum starting dose, exacerbation occurred in 21.2% (22 of 104 cases). When observing cytological drugs in the dynamics, there was an increase in the number of AC while maintaining morphological characteristics (due to the influence of glucocorticoid drugs). In 58.6% of cases (61 cases out of 104), in the 2nd week of treatment there was noted stabilization of the skin process. When reducing the dose of SGCs to 37.5 - 35 mg/d over a period of 2 - 3 months from the date of patient's discharge there was noted an exacerbation of dermatosis in these patients. Dermatosis was common; severity was found. The patient required hospitalization. In each case, patients in this group in addition to SGCs therapy were prescribed AZA at a dose of 100-50 mg/d.

According to the analysis of factors contributing to the exacerbation of the disease, psycho-emotional overload was indicated in 15.4% (16 case histories out of 104), colds – 40.4% (42 case histories out of 104), solar insolation – 4.8% (5 case histories out of 104), X-ray examination – 1.9% (2 case histories out of 104). The exacerbating factor could not be established in 37.5% (39 cases out of 104) (Fig. 5).

Indications for prescription of AZA were the following: lack of therapeutic effect of SGCs therapy; the appearance of new lesions when trying to gradually reduce the dose of SGCs; exacerbation of dermatosis during the first year.

The II group included 70 case histories of patients with AP in the treatment of which they used SGCs drugs. PV was established in 59 cases out of 70 (84.3%), PF – 6 cases out of 70 (8.6%) and PS – 5 case histories out of 70 (7.1%) (Fig. 1B). In most cases, the primary rash was localized on the mucous membranes – 70.0% (49 cases out of 70). Patients, as with group I, received therapy for stomatitis. According to anamnestic data, patients aged 26 to 79 (mean age 54 ± 1.4) in the ratio of women/men 1.7/1. The diagnosis period lasted 5.5 ± 0.3 months. Over time, the average duration of dermatosis was equal to 7.0 ± 0.6 years in the above-mentioned group of patients (Fig. 2).

The cause of the primary rash was psycho-emotional overload in 20 cases out of 70 (28.6%), colds (SARS) in 19 case histories out of 70 (27.1%). The presence of rash after dental treatment was noted in 7 of 70 cases (10.0%). Excessive sun exposure and burns were reported in 4 cases out of 70 (5.7%). It was not possible to determine the cause of the rash in 20 out of 70 cases (28.6%) (Fig. 3).

According to the status localis assessment, severe dermatosis (12-8 points) was noted in 12.8% (9 cases out of 70), medium (7-5 points) – in 38.6% (27 out of 70) and mild (<5 points) – in 48.6% (34 out of 70 cases) (Fig. 4).

Cytological examination of the material obtained from the bottom of the rash foci revealed AC in 18 cases out of 70, which constituted almost 25.7%. In the case histories of patients with a severe disease course – 5.7% (4 cases out of 70), medium – 17.1% (12 cases out of 70) and mild – 2.9% (2 cases out of 70), AC had different quantitative and morphological signs depending on the severity of dermatosis.

Signs of pyoderma were observed in 17 out of 70 cases (24.3%): in 5 cases out of 70 with a severe course – 7.1%; 8 out of 70 cases (11.4%) – moderate and 4 case histories out of 70 (5.7%) – mild.

With intoxication syndrome were observed in 11 cases out of 70 (15.7%): 4 case histories out of 70 (5.7%) – severe and in 7 cases out of 70 (10.0%) – moderate. Patients with mild dermatosis had no signs of intoxication.

According to the distribution of the skin process, the weight, and the concomitant somatic pathology, the starting dose of SGCs ranged from 120 to 45 mg/d (Fig. 2). Assessing the course of the disease, it was found that new vesicles did not form on the 5-7th day of treatment. In the second week of treatment there were signs of erosion inlay (dense multilayered crusts were formed whose edges were raised on the periphery and epithelialization was observed), negation of Nikolsky's symptom was observed and a program of gradual reduction of SGCs to 25-20 mg/d was started for 9-12 months under the supervision of a district dermatologist.

Exacerbations occurred in 1-2 years after discharge from hospital. The reasons included: SARS – in 19 cases out of 70 (27.1%); stress was observed in 15 case histories out of 70

(21.4%); refusal of basic maintenance therapy in 10 cases out of 70 (14.2%); radiological irradiation was noted in 8 cases out of 70 (11.3%); unsystematic use of NSAIDs 4 cases out of 70 (5.6%). The use of penicillin antibiotics provoked an exacerbation in 3 cases out of 70 (4.8%) and solar exposure was indicated in 2 case histories out of 70 (2.8%). The cause of dermatosis exacerbation could not be determined in 9 cases out of 70 cases (12, 8%) (Fig. 5).

To date, 80.7% of patients have a disability based on the following diagnosis: AP corticosteroid dependent form. It is known that 8.8% of patients died within the first 7 years after the onset of primary dermatosis manifestations due to complications caused by the SGCs therapy.

DISCUSSIONS

According to clinical and anamnestic data, during the retrospective analysis of case histories, the criteria determining the severity of AP during treatment were determined: the age of patients, the diagnosis period, the prevalence of lesions and severity of dermatosis according to the IKEDA index [15], the selection of adequate treatment tactics, taking into the complications caused as a result of the SGCs therapy [10].

Thus, it was found that patients of group I were younger than persons of group II by 3.2 ± 0.2 years, and despite this, in terms of the severity of clinical manifestations and the course of AP, they prevailed in patients of group I (30.8% in group I versus 12.8% in group II).

The period of diagnosis establishment in patients of group II was shorter, varying up to 6 months, which makes it possible to state the typicality of the clinical picture and course in this group of patients. The prescription of SGCs to patients had taken place earlier and did not lead to steroid resistance. Thus, in group II, the number of patients with a severe disease course was lower by 20.0% than in patients of group I.

The presence of intoxication and signs of pyoderma were more common in patients of group I receiving therapy with prescription of SGCs and AZA. The number of exacerbations per year for an unknown reason in group I was almost 3 times higher. The ineffectiveness of high starting doses of SGCs was 20.2% of cases compared with those in group II.

The analysis of case histories showed the impossibility of achieving the level of maintenance dose of SGCs without prescription of additional immunosuppressive therapy in 79.8% of cases for group I.

The above factors complicate the course of dermatosis due to the prevalence of dermatosis, the presence of bacterial complications [5, 6], loss of biologically active trace substances, fluid, protein, carbohydrate and lipid metabolism [8, 9], the development of resistant forms to SGCs [11, 17]. As a consequence to high doses of immunosuppressive therapy which leads to disability and mortality in some cases were showed in previous studies [3, 17].

CONCLUSIONS

Analysis of case histories of patients with AP who received medical care in the dermatological department of the SE "IDV OF NAMS of UKRAINE" in Kharkiv for the period 2008-2018 showed the impossibility of achieving the level of maintenance dose of SGCs without the appointment of additional immunosuppressive therapy in 41.4% of cases of patients of group I in the first three months of therapy and in 58.6% of cases of patients of group I in the second half a year. While patients of group II reached a maintenance dose of basic therapy of 25-20 mg / d during the first 3 months and did not have exacerbation of dermatosis during the first year if the recommendations are followed.

Clinical signs of steroid resistance in patients were established: the appearance of new elements at a high dose of SGCs - AZA was prescribed in the second week after hospitalization; the appearance of new blisters with a gradual decrease in the dose of SGCs by 15-20% of the initial - AZA was prescribed for 3-4 weeks of treatment; exacerbation from 2 times a year during the first year.

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ORIGINAL ARTICLE

STUDY OF IMMUNO-PATHOGENETIC FEATURES OF PSORIASIS AND ACNE'S COURSE

DOI: 10.36740/WLek202202117

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ABSTRACT

The aim: The objective of our work was to improve the diagnostics of common chronic dermatoses (acne, psoriasis, AP) taking into account some indicators of the immune system and features of the disease course to specify their role in pathogenesis of these disease.

Materials and methods: A total of 114 patients with acne and 128 patients with psoriasis were observed.

Results: Regardless of the disease duration period, we have detected in blood serum of psoriasis patients probable changes in concentrations of stress-response mediators (decreased parameters of cellular immunity (CD3+, CD3+CD4+, CD3+CD8+ of T-lymphocytes, CD22+ fraction of B-lymphocytes and compensatory increased CD16+ of T-cells, cytokines – IL-1β, IL-8, IL- 17, IL-22, immunoglobulins IgM, IgG, and CIC), which indicate tension of their stress-induced mechanisms even despite occasional clinical stabilization of skin and articular process. Consequently, most of the patients with acne had varying degrees of changes in rates of systemic immunity. The most significant changes in rates of systemic immunity with the depletion of T-cell immunity were found in patients with papular-pustular and pustular acne, and still more significant – in patients with acne conglobate.

Conclusions: In patients with acne and psoriasis, changes in systemic immunity indexes that indicate the formation of secondary immunodeficiency state T-cell link, amid an adequate humoral immunity have been found. Relationship between the causes of changes of systemic immunity has been established.

KEY WORDS: acne, psoriasis, clinical course, immunity, diagnostic

Wiad Lek. 2022;75(2):422-426

INTRODUCTION

The most common in dermatological practice are psoriasis and acne (acne occurs in at least 90% of adolescens, and psoriasis affects about 2% of the population) the pathogenesis of which today is considered from the standpoint of immunopathological diseases[1,2].

Acne is chronic recurrent dermatosis, one of the essential skin inflammation in the structure of dermatological pathology, especially in young people of working age, often caused by persistent cicatricial changes in the skin, and affecting negatively the psychoemotional state of patients, their quality of life and working capacity [1,3]. It has been established by today that the pathogenesis acne is complex and multifactorial, and the changes of immune reactivity of the organism play an important role in its clinical course development [4] The high level of acne incidence, the tendency to a chronic course of formation of resistance to treatment, frequent cases of development of deep forms determine the important medical and social significance of the problem. [3,5] However, the information about the immune system in these patients is often ambiguous and contradictory – it is often recorded as manifestation of increased immune activity and the formation of secondary immunodeficiency state, which may contribute to chronic dermatoses and their resistance to standard therapy tools [4,6,7]. In this regard, the urgent task of modern dermatology is to establish the nature of changes of systemic immunity in patients with acne with different clinical course in order to clarify the pathogenetic factors and develop differentiated methods of treatment.

At the present stage, psoriasis is considered to be a systemic disease that affects not only skin but also joints of patients and is accompanied by possible development of typical comorbid states (cardiovascular pathology, chronic inflammatory intestinal canal diseases, and metabolic syndrome). Psoriasis affects about 2% of population. In 30-40% of occurrences arthropathic psoriasis (AP) is diagnosed and leads to 11-19% of disability cases development [1,8].

The chronic-relapsing course of psoriasis and steady progression of the disease associated with disability cases result in a significant deterioration in the quality of life of patients, which determines its medical and social significance [1,9]. Taking into account the importance of components of stress-induced immune-endocrine system at the psoriasis development it is important to clarify the role of main indicators of the immune system and cortisol stress hormone in the disease pathogenesis [10-12]. Substantial immunological changes (of humoral and cell sections of immunity), hormone and biochemical disorders, disorder of calcium-phosphorus balance naturally influence bone metabolism and cause systemic disorders in structural and functional state of bone and cartilage system in patients with AP [1,13-15]. No less actual is the relation of detected clinical-instrumental disorders, changes of some indices of hormone, immune and cytokine state.

THE AIM

The objective of our work was to improve the diagnostics of common chronic dermatoses (acne, psoriasis, AP) taking into account some indicators of the immune-endocrine system and features of the disease course to specify their role in pathogenesis of these disease.

MATERIALS AND METHODS

114 patients with acne aged from 18 to 35, among which 66 women (57,89 %) and 48 men (42,11 %) and 128 patients with psoriasis aged from 18 to 55, among which 46 women (35,94 %) and 82 men (64,06 %) were observed and examined systematically. They had been selected for the study according to the following criteria: clinical signs of acne, age 18+, absence of chronic somatic diseases or their exacerbations at the moment of the study.

A comprehensive survey of patients has been performed in a randomized manner concurrently with BD pre-stratification upon obtaining written consent in accordance with the principles of Helsinki Declaration of Human Rights, Convention of Council of Europe on Human Rights and Biomedicine, and relevant laws of Ukraine.

To assess the state of systemic immunity in patients with acne we determined: the number of total lymphocytes and their subpopulations in terms of CD3 +, CD3 + CD4 +, CD3 + CD8 +, CD19 + by indirect immunofluorescence with monoclonal antibodies to differentiated antigens of the cell surface, as well as the content of serum immunoglobulins (Ig) of classes M, G, A.

We have examined AP patients with varying severity of process development, generalization and the severity of skin and osseous-articular apparatus damage, the presence of associated pathology. The diagnosis of AP was verified under the diagnostic criteria of the Institute of Rheumatology of RAMS. All patients with suspected or proved AP had their damaged joints examined radiologically (ultrasonography if necessary). Additional level of T- and B-lymphocytes subpopulations in patients with AP was determined under the guidelines on the application of erythrocyte diagnostic preparations to detect human T- and B-lymphocytes subpopulations "Anti-CD 3", "Anti-CD 4", "Anti-CD 8", "Anti-CD 16", "Anti-CD 22" produced by RDPF Granum LLC (Kharkiv). The concentration of general immuniblibulines of M (IgM) and G (IgG) classes in blood serum was determined by immune-enzyme analysis using "IgM (IgG) general - IFA – BEST" set produced by CJSC "Vector-Best –BEST", Novosibirsk. The content of IL-1β, IL-8, IL-17, IL-22 in blood serum was studied in accordance with the techniques and guidelines using appropriate test systems (CJSC "Vector-Best –BEST", Novosibirsk) which are based on the sandwich-method of solid phase immune-enzyme analysis.

Statistical analysis of the results of research was carried out by methods of statistical analysis using the computer program Statistica 7.0, the probable average difference was considered at $p<0,05$.

RESULTS

According to the clinical criteria, 22 patients (19.3%) were diagnosed with comedonal form of acne, 34 patients (29.83%) had papules, 8 people (7.02%) –papular-pustular acne, 25 of the observed (21.93%) had pustules, 9 patients (7.03%) suffered from acne conglobata, and 14 patients (10.94%) were diagnosed with post-acne. The control group consisted of 34 practically healthy people (donors) of the same age.

In determining the indices of systemic immunity in patients with acne, there were established their probable changes which indicate the development of secondary immune deficiency in these patients, byT-cell population mainly, as well as a disturbance of absolute number of total lymphocytes, T-helper ones (with CD3 +CD4 +) and T suppressor (with CD3 + CD8 +) lymphocytes, while the most significant changes in these parameters were established in patients with moderate and severe acne with chronic and deep forms [6,9].

While determining the indicators of the systemic immunity in 114 patients with acne, we established their probable ($p<0.001$) changes, as compared with the indicators for patients in the control group: decrease in relative and absolute number of total lymphocytes pool – by 20.4 % (28.9±0.69 %, in the control group – 36.1±0.92 %) and by 21.2 % (1.92±0.053 G/l (this index marks giga-/ liter) in the control group – 2.41±0.10 G/l), T-lymphocytes (CD3+) – by 19.2 % (47.1±1.31 %, in the control group – 58.3±1.07 %) and 33.7 % (0.955±0.033 G/l in the control group – 1.42±0.078 G/l), T-helpers (CD3+CD4+) lymphocyte subpopulations – accordingly by 11.7 % (33.2±0.32 %, in the control group – 37.3±0.88 %) and by 22.9 % (0.613±0.022 G/l in the control group – 0.792±0.052 G/l), and the relative number of T-suppressors (CD3+CD8+) lymphocytes – by 13.9 % (18,5±0,15 %, in the control group – 21.5±0.93 %) against the backdrop of increasing relative and absolute number of B lymphocytes (CD19+) – by 14.3 % (25.6±0.30 %, in the control group – 22.4±0.81 %) and 35,2 % (0,488±0,014 G/l in the control group – 0,360±0,020 G/l) and IgM levels – by 25.7 % (1.81±0.047 G/l in the control group – 1.44±0.06 G/l) and IgG – by 40.4 % (12.9±0.25 G/l in the control group – 9.52±0.36 G/l) (Fig.1).

The analysis of systemic immune system indexes in patients with acne, taking into account its different the clinical form and depth of skin lesions presented in the table, has showed that in patients with comedonal form of acne there is a decrease in the relative amount of the total pool of lymphocytes by 10.9 %, $p<0.05$, with papular form of acne – by 13.9 %, $p<0.01$, a decrease in the relative and absolute amount of T-lymphocytes (with comedonal form – by 8.5 % and by 21.5 %, $p<0.01$, with papular form – by 7.5%, $p<0.001$ and by 20.1 %, $p<0.01$, with post-acne – by 12.2 %, $p<0.001$ and by 18.7 %, $p<0.05$), the relative amount of T-helpers (CD3+CD4+) with comedonal form of acne – by 9.9 %, $p<0.001$, with papular form – by 6.24% and with post-acne – by 8,1%, $p<0.05$ and absolute amount of B lymphocytes (with comedonal form – by 29.4 %, with

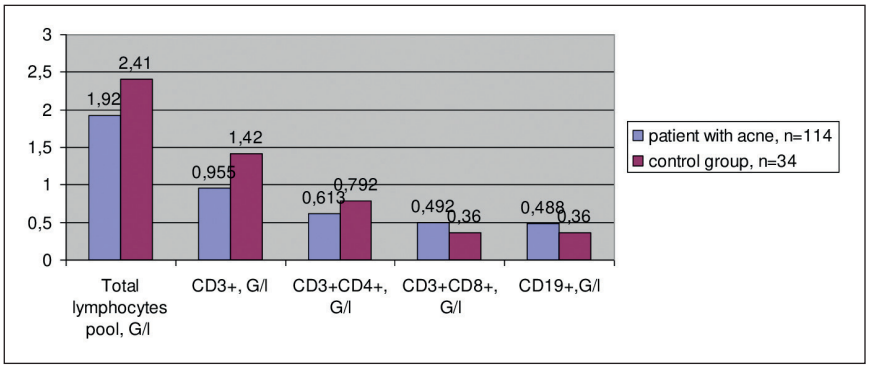

Fig. 1. Indicators of the systemic immunity in patients with acne

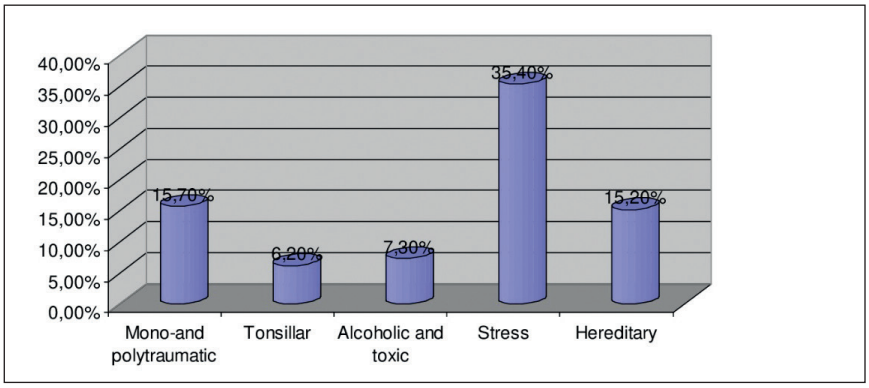

Fig. 2. Trigger factor in the development of psoriasis in examined patients

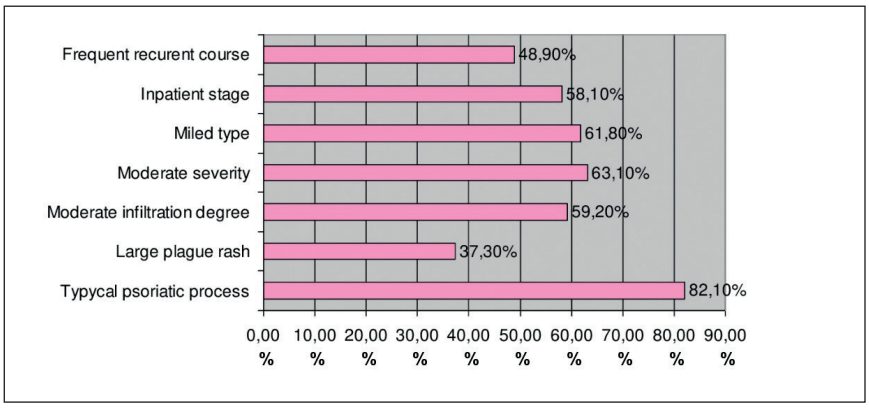

Fig. 3. Trigger factor in the development of psoriasis in examined patients

papular form – by 35.7 %, and with post-acne – by 47.4 %, p<0.001.

At the same time, probable decrease (p<0.001) in the absolute and relative amount of the total pool of lymphocytes was identified in patients with papular-pustular acne, as compared with the control group: by 33.9 % and by 47.9 %, with pustular acne – by 35.4 % and by 46.8 %, with acne conglobata – by 45.3 % and by 33.9 % correspondingly. These patents were also defined with probable decrease in the relative and absolute amount of T-lymphocytes (CD3+), as compared with the control group: in patients with papular-pustular acne – by 24.2 % and by 62.3 %, in patients with pustular acne – by 15.8 % and by 34.7 %, and in patients with acne conglobata – by 28.9 % and by 54.5 %, p<0.001) accordingly. Alongside, a decrease in the relative and absolute amount of T-helping (CD3+CD4+) lymphocytes has been identified, as compared with the control group: in patients with papular-pustular acne – by 27.5 % and by 56.3 %, p<0.001, in patients with pustular acne – by 17.5 %, p<0.001 and by 21.9 %, p<0.01; in patients with acne conglobata – by 33.5 % and by 49.8 %, p<0.001).

The analysis of indicators of systemic humoral immunity in patients with different clinical forms of acne revealed a significant increase in the relative and absolute amount of B-lymphocytes (CD19+), as compared with the control group: in patients with papular-pustular acne (correspondingly, by 15.6 %, p<0,05 and by 33.8 %, p<0,001), in patients with pustular (by 23.4 % and by 51.4 %, p<0,001), and in patients with acne conglobate (by 38.4 % та 35.1 %, p<0,001). Moreover, in patients with certain clinical forms of acne, a probable increase in levels IgM and IgG has been observed, as compared with the relative indexes of control (correspondingly, in patients with papular-pustular acne – by 45.6 % and by 63.2 %, with papular form of acne – by 53.9 % and by 67.5 %, with acne conglobate – by 98.4 % and by 90.7 % p<0.001).

In 84 (65.63%) out of 128 examined AP patients joints were damaged in 5-15 years after the onset of skin psori-

atic process. In 59 (46.09%) cases the dependence of the onset of joint damage with the subsequent manifestations of psoriatic skin rash was detected. According to medical history data, the examined patients typically associated the onset of psoriatic skin and joints damage with hereditary (15.62%), stress (35.16%), alcoholic and toxic (7.03%), tonsillar (6.25%), mono- and polytraumatic (16.41%) factors (Fig.2).

In 89 (69.5%) AP patients the prevalence of generalized skin psoriatic process with typical (82.1%), large plaque rash (37.3%), moderate infiltration degree (59.2%), moderate severity (63.1%), mixed type (61.8%), inpatient stage (58.1%) and frequent recurrent course (48.9%) was observed (Fig.3).

It has been established that in 83 (64.84%) AP patients joints damage occurred in 5-15 years after the onset of skin psoriatic process. In 89 (69.5%) of examined patients the prevalence of generalized skin psoriatic process with typical 106 (82.81%), moderate infiltration degree 78 (60.93%), frequent recurrent course 56(43.75%), nails psoriatic damage and polyarthritis complicated with the damage of small joints of hands or feet was observed 107 (83.59%).

Upon conducting functional tests (in order to determine sacroilitis – Kushelevsky 1-2, Patrick, Mennel and spondylitis – Shober, Thomayer), sacroilitis has been revealed and further instrumentally confirmed in 4 (3.13%) cases and spondylitis of thoracic and lumbar sections in 8 (6.25%) cases. Using the RAIS index, in 113 (88.28%) of patients it has been verified moderate-severe and severe dermatosis course. A significant impact of AP on the quality of life of patients per the DLQI index has been recorded in 71 (55.47%), and very significant in 56 (43.75%). A pronounced correlation between the increase in joints functional deficiency, the AP course duration and the deterioration in the quality of life of patients has been established. A high degree of polyarthritis detection rate complicated with the damage of small joints of hands or feet associated with a functional insufficiency of average degree of activity 73 (57.03%) though the preservation of professional ability has been diagnosed in 56 (43.75%) of patients.

In this context we have determined pathognomonic signs of AP, which include simultaneous psoriatic damage of skin 128 (100%) and nails 89 (69,53%); asymmetric 102 (79,69%) mono- or oligoarthritis 91 (71.09%) mainly of peripheral joints and especially associated with the hand DIPJ damage 114 (89.06%); osteolysis 112 (87.5%); negative reaction for rheumatoid factor 124 (96,88%).

We have pathogenetically grounded the primary localization of pathological joint process in AP patients in the areas of increased traumatization of tendon-ligamentous apparatus and its relationship with nails psoriatic damage. Therefore, ultrasound diagnostics and MRI examination of joints for the purpose of determination of periarticular and articular damages is justified since in 14 (10.94%) of examined patients enthesopathy and osteitis in the absence of abnormal articular X-ray changes have been detected by ultrasound diagnostics and MRI. In our opinion, osteitis in psoriatic patients signals an early premonitory symptom of the AP development.

During radiological examination of patients with AP it was detected 65 (50.78 %) cases of AP and 52 (40.62 %) cases of deforming AP, at that, in 91 (71.01 %) of cases AP was the dominant disease on clinical picture in the form of poly- or periarthritis of distal interphalangeal joints, at that, in 14 (10.94 %) of cases it was associated with axial affection of spine. At early stages of AP development using radiological examination the following facts were accurately defined more frequently than the others: non-uniform narrowing of joint gap, osteoporosis in bone epimetaphys area, erosions of distal flanges of feet and hands. In the case of progressing – partial or total destruction of closing plates with prevailing osteo-destructive (osteolysis, ankylosis) and osteo-proliferated (hyperostosis, periostitis) pathological processes over osteoporosis.

In 79 (61.72%) AP patients the presence of inflammatory biochemical serum and cholecystobiliary syndromes has been testified, which indicates metabolic character of the disease course. The analysis of laboratory examinations indicates the decreased number of thrombocytes, expressed hypoalbuminemia, hypergammaglobulinemia. In 1/3 of patients with AP anaemia was identified as well as increasing of BSR within the limits of 15-20 mm/h, from 21 to 40 mm/h – in 26 (20.31 %) of patients, more than 40 mm/h – 14 (10.93%). The increased glucose level was identified in 31 (24.22 %) of patients, cholesterol and LDL – in 90 (70.31 %), creatinine – in 58 (45.32 %). Alkaline phosphatase (AP) and its bone izoenzyme activity were within the limits of normal values except the patients who have been suffering from the disease for more than 20 years. This means that AP activity exceeds the norm more than 2.3-2.5 times and bone izoenzyme AP decreased in 2.6-2.7 times. Creatinine content in blood serum was lower than the norm in 60 (46.88%) of patients notwithstanding the duration of the disease.

DISCUSSION

The current problem of modern dermatology are psoriasis and acne, the pathogenesis of which today is considered from the standpoint of immunopathological diseases [1,2].

According to literature [4,11] in patients with acne and psoriasis changes in systemic and humoral immunity indexes have been found. It has been established by today that the pathogenesis acne, psoriasis and arthropathic psoriasis is complex and multifactorial, and the changes of immune reactivity of the organism play an important role in its clinical course development. But the information about the immune system in these patients is often ambiguous and contradictory.

Most of the patients with acne had varying degrees of changes in rates of systemic immunity – the likely reduction in relative and absolute number of total lymphocytes, T-lymphocytes and their subpopulations against the growing number of B lymphocytes and the level of IgM and IgG, which generally indicates the formation in these patients secondary immunodeficiency state of T-link intensified by activation of humoral immunity in response to the development of skin

inflammation. The most significant changes in rates of systemic immunity with the depletion of T-cell immunity were found in patients with papular-pustular and pustular acne, and still more significant – in patients with acne conglobate, which justifies differentiated treatment by immunomotropic drugs for these patients.

It has been determined that the occurrence of pathological immune process in all variants of AP course was triggered by a possible blood serum decrease ($p<0.01$) of immunocompetent cells of phenotype CD3+ by 49.43 %, CD 22+(B-lymphocytes) by 46.62 %, moderate decrease of CD3+CD4+ by 12.91%, CD3+CD8+ by 19.6 % and increased content of CD16+ by 18.42 %; increased levels of cytokines IL-1β by 5-11 times, IL-8 by 60 times, IL-17 by tenfold, IL-22 by 5 times, IgG by 5 times and immunoglobulins IgM by threefold, which testify the fact of tension of stress-induced mechanisms in patients even at the stage of clinical stabilization of skin and joint process. A statistically significant increase of the above cytokine concentration in blood serum (by more than 2-3 times) and in synovial fluid (by more than 2-5 times against the respective values in blood serum ($p <0.05$)) during the first months starting from the PD joint syndrome onset can serve as an additional diagnostic criterion for early AP diagnostics.

It has been set that the character of correlation between changed indicators of immune-endocrine system in AP patients indicated the autoimmune nature of the disease chronicity and development. It has been justified that decreased levels of cytokines IL-1β, IL-8, IL-17, IL-22, IgM, IgG are the key mediators of the immune system since they cause inflammation and osteolysis on the one hand and regulate the processes of articular contractions formation on the other hand.

CONCLUSIONS

In patients with acne and psoriasis, changes in systemic immunity indexes that indicate the formation of secondary immunodeficiency state T-cell link, amid an adequate humoral immunity have been found. Relationship between the causes of changes of systemic immunity has been established. The improvement of patients with acne and psoriasis diagnostics taking into account some indicators of the immune-endocrine system and specifics of the disease course, will contribute to improving therapy and mended quality of life of patients.

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The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

ASSOCIATION BETWEEN PLACENTAL MORPHOMETRIC PARAMETERS AND BIRTH WEIGHT IN DICHORIONIC DIAMNIOTIC TWINS

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ABSTRACT

The aim: To assess morphometric parameters of placentas and to evaluate the correlation between the placental disk shape, the site of the umbilical cord insertion and the birth weight of dichorionic twins.

Materials and methods: The geometry of placentas, distances between umbilical cord insertion sites and the centroids of the disks were measured in 135 pairs of dichorionic diamniotic twins. The impact of the above-mentioned parameters on the birth weight and placental mass was analyzed.

Results: In terms of weight and geometric parameters of placentas, no proven discrepancy between different types of twins and inside pairs was found. A strong correlation was established between the placental weight and birth weight ($r = 0.71$, $p < 0.05$). Both the placental weight and birth weight showed the strong correlation with S*Circ ($r = 0.62$, $p < 0.05$). The displacement of the umbilical cord insertion site from the centroid of the placenta was negatively correlated with its mass ($r = -0.428$, $p < 0.0001$) and birth weight ($r = -0.6115$, $p < 0.0001$). The displacement along the maximum axis proved to play a significant role.

Conclusions: In dichorionic diamniotic twins, the area of the placentas plays the determining role in the functional activity of the organ, which increases when its shape approaches the circle. The area of the placenta multiplied by its circularity had the strongest correlation with birth weight and placental mass. The farther from the centre the umbilical cord is inserted, the lower the functional capacity of the placenta is.

KEY WORDS: birth weight, placental mass, dichorionic diamniotic twins, umbilical cord insertion

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INTRODUCTION

Multiple pregnancies are associated with an essentially higher risk of perinatal complications compared to singleton pregnancies: stillbirth, neonatal death and morbidity, preterm delivery, foetal growth restriction and congenital disorders [1–3]. The number of twin pregnancies has increased significantly over the past decades and, taking into account the increasing introduction of assisted reproductive technologies into clinical practice, of course, will continue to grow [4,5]. In terms of obstetric prognosis, dichorionic twins look better than monochorionic, but foetal birth discordance and growth restriction are not uncommon in them too [6,7].

Dichorionic diamniotic (DCDA) twins are unique in that both foetuses develop in the same environment and have the same or similar genetic material. The identification of differences between the fetuses suggests they occur due to the different characteristics of their placentas [1,8]. The gross assessment of placentas has attracted the attention of researchers for many decades. Most of the scientists focus on the evaluation of mass and linear size of the placenta, and the search for a correlation between them and birth weight [9,10]. Following certain standards of evaluation [11], the weight of the placenta and the linear dimensions are determined quite accurately. This cannot be said about determining the area and shape of the placental disk. The latter is usually approximated to the shape of an ellipse and an equation for calculating the area of this geometric figure is used. The symmetry of the placenta is mostly assessed in the same way as the symmetry of an ellipse by dividing the larger axis by the smaller one [1,2]. In our opinion, such calculations give a very approximate result.

It is customary to classify the umbilical cord insertion sites (UCIS) in the placenta as central (more than 90%), eccentric (> 2cm from the placental edge), marginal (7%, < 2 cm from the edge), and velamentous or membranous (1% in singletons) [12Medline, CINAHL, Scopus, Web of Science, ClinicalTrials.gov, and Cochrane Databases were searched in December 2016 (from inception to December 2016]. The last two are considered to be abnormal [13]. The umbilical cord rarely inserts in the very centre of the placental disk. The question remains open to what extent the displacement of the insertion site from the geometric centre of the placenta affects the development of the child.

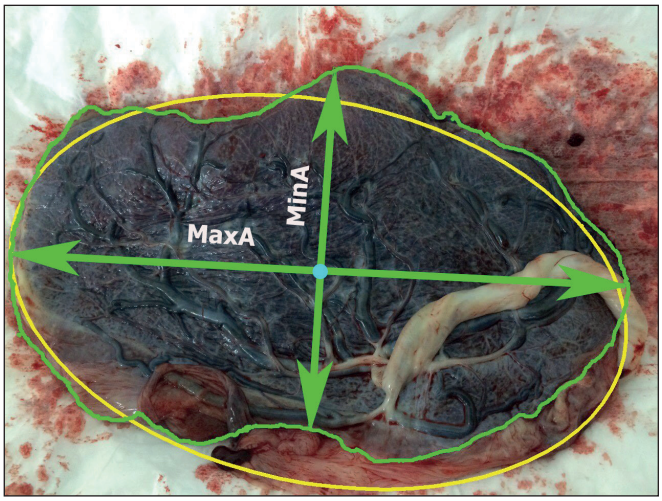

Fig. 1. The outside boundary of the placenta is outlined (green) and the program determined the centroid ( ); yellow line – approximation of the shape of the placenta to the ellipse

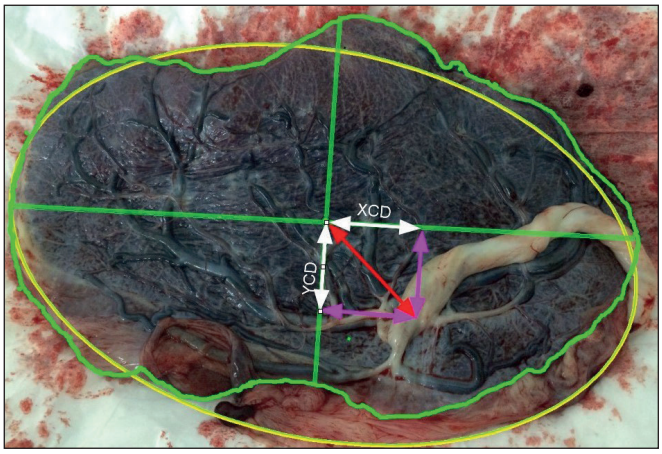

Fig. 3. Measurement of the cord insertion site displacement along the diameters of the placental disk

Fig. 5. Partial fusion of two placentas, inter-placental anastomoses were not verified.

THE AIM

The objective of this study was to assess morphometric parameters of placentas and to evaluate the correlation between the placental disk shape, the site of the umbilical cord insertion and the birth weight of dichorionic twins.

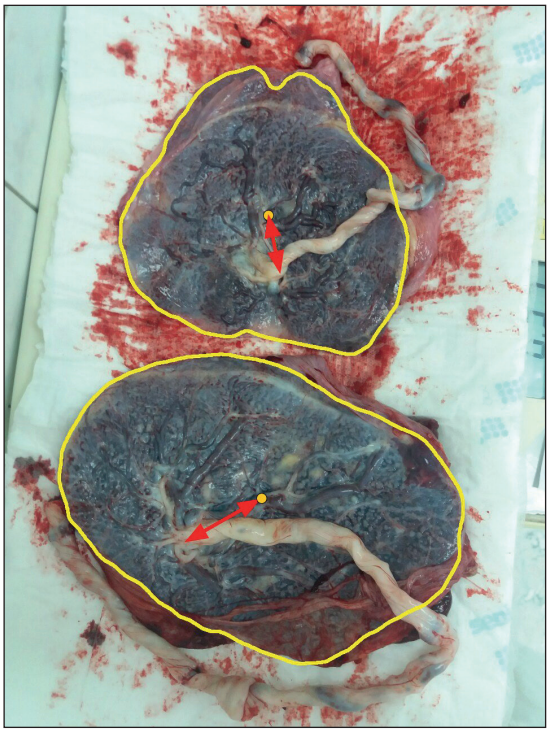

Fig. 2. Absolute cord displacement measurement (red arrows)

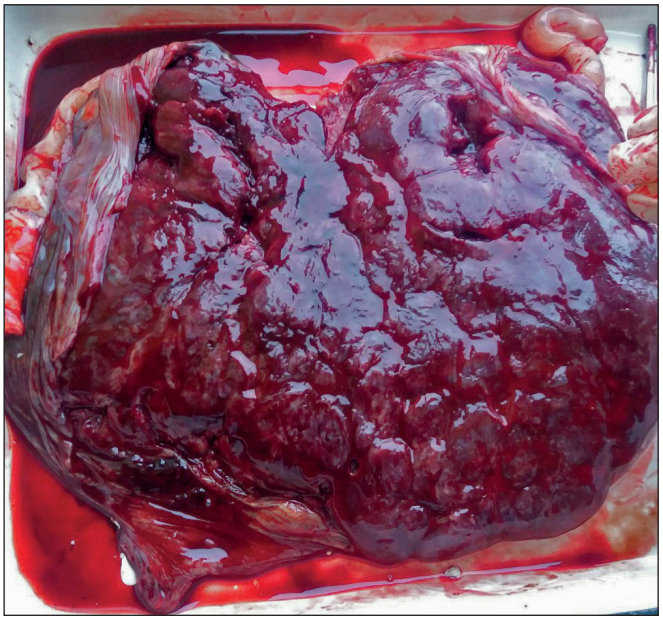

Fig. 4. The fused dichorionic diamniotic opposite-sex twins' placentas that look like one placental mass

MATERIALS AND METHODS

The placentas of 135 pairs of DCDA twins were examined prospectively. Sixty-eight of them were opposite-sex, 32 same-sex females and 35 same-sex males. The gestational age in these groups ranged from 28.5 to 39.5 weeks. Gross examination was performed following a consensus-determined protocol developed by the Amsterdam Placental Workshop Group [11]. First of all, the digital pictures of both sides of the horizontally located placental disk were taken by the commercially available digital camera

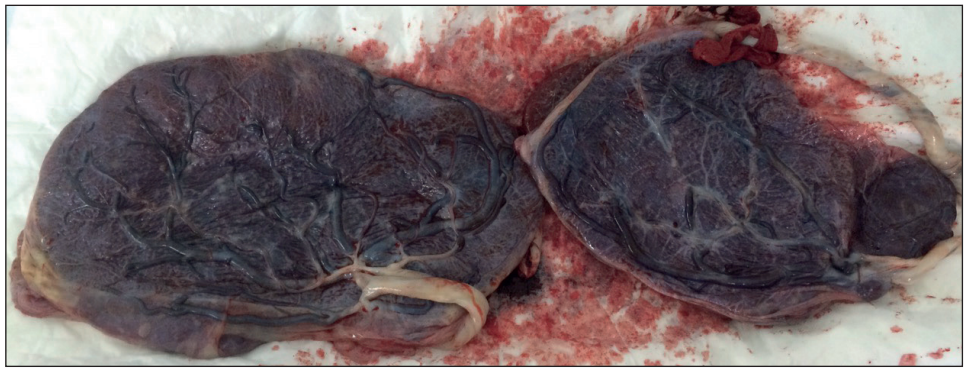

Fig. 6. Marginal cord insertion at the edges of both placentas.

Fig. 7. Velamentous umbilical cord insertion.

Panasonic DMX LC 15, with the camera located strictly vertically above the object and parallel to it. A ruler or centimetre tape was placed in the area of the upper surface of the placental disk for further calibration of the camera. Further image transformations and measurements were performed using the program ImageJ/Fiji 1.46r, inspired by NIH Image 9 (the latest version can always be obtained from http://imagej.nih.gov/ij/docs/guide). After performing line measurements and weighing the placentas, their geometry was assessed. Since the shape of the placentas can differ significantly from the ellipse, their outside boundaries were outlined using the above-mentioned software (Fig. 1). Then their maximum (MaxA) and minimum (MinA) diameters (command Feret's diameter), the ratio of the maximum to the minimum diameter (AR), the area of the placental disk (S), and its perimeter (Perim) were calculated. The program itself determined the coordinates of the centroid – the centre point of a geometric figure. It was manually marked by the dot.

Two shape descriptors were determined. Circularity was calculated as: . The roundness of the placental disk was estimated as: . The closer these indicators are to 1.0, the more round the placenta is. The sense of calculating both indicators is that the circularity largely depends on how smooth the edge of the placenta is, and roundness more accurately characterizes the overall shape of the disk, the ratio of large and small diameters. In the presence of additional lobes of the placenta, its area was determined as the sum of the areas of the main disk and the additional lobules.

The umbilical cord insertion in the disk was assessed visually, and then the distance between this site and the centroid of the disk was measured (Fig. 2). We termed it an absolute cord displacement (ACD).

Then the displacement of the UCIS relative to the maximum (XCD) and minimum (YCD) axes was measured and expressed as a percentage of half the length of the corresponding axis (Fig. 3).

The fused placentas before measurements were carefully separated along the line of the fusion. Birth weight was compared to the geometry of the placental disk and the UCIS. Mothers' weight, height, body mass index (BMI), bad habits and comorbidities were also registered.

Statistical data processing was performed using Statistica 8.0 (Statsoft Inc., USA) and Microsoft Office Excel 2010 statistics. The samples with normal distribution were presented as mean and standard deviation ($M \pm \sigma$). The samples that do not fit normal distribution were characterised as median (Me), first (Q1) and third (Q3) quartiles and results presented as Me (Q1; Q3). The differences between two normally distributed samples were evaluated by the Student's t-test for independent samples and considered as significant at $p < 0.05$. The difference between two non-normally distributed samples was assessed with the nonparametric Kolmogorov-Smirnov test. The statistical relationship between the continuous variables was evaluated calculating the Pearson's correlation coefficient (r) and estimation of its reliability (p).

All the postpartum women involved in the study gave their informed consent before the investigation.

Table I. Geometric parameters of the placental disks depending on the type of twins

Indicator	Type of the twins					
	f + m M ± σ		f + f M ± σ		m + m M ± σ	
Number of the twins	68		32		35	
Twins' order	I	II	I	II	I	II
Birth weight (g)	2588.4 ± 471.87	2615.4 ± 478.02	2566.7 ± 510.55	2427.7 ± 620.20	2624.7 ± 392.43	2595.1 ± 492.52
Placental mass (g)	477.2 ± 109.60	482.0 ± 116.66	486.3 ± 109.29	485.8 ± 143.81	483.0 ± 99.59	485.6 ± 113.27
MaxA (cm)	18.6 ± 3.29	19.0 ± 1.73	19.5 ± 2.86	19.4 ± 3.19	19.3 ± 2.14	19.6 ± 2.32
MinA (cm)	13.2 ± 2.45	13.7 ± 2.30	14.3 ± 2.36	14.2 ± 2.34	13.8 ± 2.66	14.5 ± 2.74
AR	1.8 ± 0.53	1.4 ± 0.27	1.4 ± 0.20	1.4 ± 0.19	1.4 ± 0.23	1.4 ± 0.35
S (cm^2)	196.0 ± 57.86	206.3 ± 43.46	221.3 ± 57.42	220.2 ± 67.69	212.4 ± 57.51	223.8 ± 53.53
Perim (cm)	55.9 ± 9.21	56.5 ± 5.19	60.3 ± 6.18	58.5 ± 6.22	58.9 ± 5.89	58.8 ± 5.07
Circ	0.787 ± 0.1308	0.804 ± 0.0843	0.751 ± 0.0952	0.790 ± 0.0932	0.758 ± 0.1193	0.802 ± 0.0832
Round	0.734 ± 0.1353	0.725 ± 0.1239	0.740 ± 0.1058	0.737 ± 0.0999	0.713 ± 0.1097	0.748 ± 0.1506
S*Round	144.7 ± 53.15	152.6 ± 48.95	164.6 ± 51.95	162.4 ± 52.46	155.0 ± 57.87	170.9 ± 63.11
S*Circ	155.5 ± 55.03	167.8 ± 46.14	170.0 ± 58.12	1788 ± 73.24	165.3 ± 62.19	182.8 ± 59.90

Table II. The relationship between indicators that characterize the shape of the placenta, and its weight, and the birth weight of the neonates

Indicators	Weight of the placenta		Birth weight	
	r	p	r	p
MaxA	0.47	< 0.05	0.41	< 0.05
MinA	0.47	< 0.05	0.38	< 0.05
S	0.57	< 0.05	0.49	< 0.05
AR	-0.02	> 0.05	0.02	> 0.05
Perim	0.42	< 0.05	0.26	< 0.05
Circ	0.39	< 0.05	0.51	< 0.05
Round	0.13	< 0.05	0.12	< 0.05
S*Round	0.50	< 0.05	0.47	< 0.05
S*Circ	0.62	< 0.05	0.64	< 0.05

RESULTS

Maternal age ranged from 19 to 46 years. The mean age was 30.1 ± 5.52 years. Primiparity in women who delivered opposite-sex foetuses took place in 14 (20.6%) cases, in a group of same-sex female twins – in 9 (28.1%) and a group of same-sex male neonates – 12 (35.0%).

There was no statistically significant difference in anthropometric indicators (height, body weight, BMI), the presence of comorbidities (diabetes, hypertension, preeclampsia and eclampsia) and bad habits (smoking, drug use) between mothers of different groups of twins during pregnancy. The percentage of vaginal delivery in the studied groups also did not differ. The median bodyweight of primiparous women was 78.0 (Q_1 – 72.0; Q_3 – 94.0) kg. It had no statistical difference from that of multiparous women – 78.0 (Q_1 – 72.5; Q_3 – 86.5) kg, Kolmogorov-Smirnov Test $p > 0.10$. The same situation was with BMI (29.7 ± 5.17 kg/m^2 and 29.3 ± 4.25 kg/m^2 respectively, $p = 0.6592$). Mean gestational age was 36.4 ± 1.74 weeks.

The mean birth weight of the neonates was 2579.1 ± 490.17 g. The comparison with international standards for assessing neonatal growth [14] revealed 25 (9.3%) newborns that were small for gestational age.

Among the entire sample, the average morphometric parameters of the placentas were as follows: surface area – 210.2 ± 55.66 cm^2, MaxA – 19.1 ± 2.63 cm, MinA – 13.8 ± 2.48 cm, AR – 1.5 ± 0.39. The placental weight of I and II babies in same-sex female couples, same-sex male couples and opposite-sex couples did not differ significantly ($p = 0.9891$; $p = 0.9196$ and $p = 0.8066$ respectively). Geometric parameters of placental disks demonstrate no essential difference between different types of twins (Table.I).

Inside pairs, no difference between the studied indicators of the first and second foetuses, except for a significantly larger AR in the placentas of the first foetuses of the opposite-sex twins compared with placentas of the second foetuses ($p < 0.0001$) was found. The placental areas of the I opposite-sex twins were smaller than the placental area of the II foetuses of the same-sex male couples ($p = 0.0200$). The perimeters of the I opposite-sex twins' placentas were less than the perimeters of the placentas of the I same-sex female couples ($p = 0.0170$) as well as the II opposite-sex twins' placental perimeters were smaller than perimeters of the I same-sex female couples ($p = 0.0022$). The circularity of the placentas in I female same-sex was lower than that of II from same-sex male twins ($p = 0.0210$).

The indicator S*Round of the placentas of I foetuses of opposite-sex twins was also significantly lower than the similar index of II foetuses of male same-sex twins ($p = 0.0249$). The circularity of the placentas in I female same-sex placentas was lower than that of II new-borns from same-sex male twins ($p = 0.0210$).

A strong correlation was observed between the placental weight and the newborn birth weight ($r = 0.71$, $p < 0.05$). Both the weight of the placentas and the birth weight of newborn infants correlated with almost all investigated indicators of the disk shape, excluding the AR. The strongest, however, was the association with the S*Circ (Table II). A moderate correlation was found between S of the placental disks and another, proposed by us, index – S*Round.

Eccentric placentas have lesser surface area insofar as Circ showed a significant positive correlation with the area ($r = 0.4671$, $p < 0.0001$).

In the group we examined, the number of fused placentas (Fig. 4) corresponded to the results of other studies and was 59 (43.7%) cases: among 68 opposite-sex couples – 29 (42.6%), among male-male pairs – 17 (48.6%), same-sex female pairs – 13 (40.6%).

During the blunt separation, which in the majority of cases was easily done, no vascular interplacental anastomoses were found (Fig. 5).

The average mass of two separate placentas (547.5 ± 86.74) exceeded the average mass of fused placentas (398.4 ± 87.34, $p < 0.0001$). This indicates that chorionic disks implanting close to each other lead to their early fusion and serious limitation of the development.

Sometimes the UCIS almost coincided with the centroid of the placental disk. However, this was not common. In most cases, the umbilical cord was fixed eccentrically. In the group with abnormal placental cord insertion (PCI), there were included all cases of velamentous and marginal (< 2 cm from the edge) insertion. Totally 32 pairs (23.7% of 135 examined DCDA couples) were included. In 24 pairs one placenta had abnormal PCI, in the other 8 couples, both placentas had abnormal PCI (Fig. 6). Out of the whole abnormal PCI group, there were 16 (23.5%) opposite-sex couples, 8 females (25.0%) same-sex couples and 8 (22.9%) same-sex male couples. This means that difference in frequency of abnormal PCI was not statistically significant ($p > 0.1$), but exceeds the frequency of abnormal PCI in singleton pregnancies [12Medline, CINAHL, Scopus, Web of Science, ClinicalTrials.gov, and Cochrane Databases were searched in December 2016 (from inception to December 2016].

Velamentous cord insertion was detected in 9 (6.7%) placentas. One of the cords inserted into the membranes 5-7 cm from the disk (Fig. 7). In this situation, vessels were not protected by Wharton's jelly.

There was no correlation between the age of women and the degree of eccentricity of umbilical cord insertion, which is displayed by ACD ($p = -0.0342$, $p > 0.05$), as well as no relationship, was found between UCIS and the number of deliveries in anamnesis, weight gain during pregnancy, smoking and gender of the children.

Sometimes the site of cord insertion almost coincided with the centroid of the placental disk. The displacement of the UCIS from the centroid of the placenta was negatively correlated with its mass ($r = -0.428$, $p < 0.0001$). A strong reverse correlation was found between the foetal BW and ACD ($r = -0.6115$, $p < 0.0001$). It turned out that the PM and foetuses' BW depend not only on the absolute displacement of the UCIS but also on the direction of this displacement. The study of the UCIS displacement from the centroid along the maximum and minimum axes of the placental disk, expressed as a percentage of the length of the corresponding semiaxis, showed a stronger correlation between BW and the distance along the maximum axis ($r = -0.7131$, $p < 0.0001$) than along the minimum one ($r = -0.2981$, $p < 0.0001$). A similar situation takes place between the displacement of the insertion site of the umbilical cord from the centroid and the mass of the placenta, but with a slightly weaker correlation (PM vs. XCD correlation: $r = -0.5027$, $p < 0.0001$; PM vs. YCD correlation: $r = -0.2942$, $p < 0.0001$). The figures demonstrate that the distance from the place of umbilical cord insertion in the placental disk along the maximum diameter of the latter was of greater importance. There is a weak negative correlation between ACD and placental disk circularity ($r = -0.315950$, $p < 0.0001$) and a moderate connection between XCD and circularity of the placenta ($r = -0.408214$, $p < 0.0001$).

DISCUSSION

When conducting this study, more accurate objective data were obtained on the relationship between the geometric shape of the placental disk and the site of the umbilical cord insertion in it with the foetuses' BW of the different types of the DCDA twins, as well as the weight of the placenta itself. The high degree of association between the mass of the placenta and the weight of the foetus at birth with the parameter we proposed – the area of the placenta multiplied by the indicator of its circularity – demonstrates that the larger the contact area of the placental disk with the uterine wall, the better the supply of nutrients and oxygen diffusion to the foetus. It can be assumed that the conditions of haemocirculation are better in the placentas, which have a round shape.

In the investigated group, 43.7% placentas were fused. This data corresponds to different publications that approximately in half DCDA twins the placentas fuse [8,14,15] The fusion of two placentas may cause their asymmetrical

growth. We consider this as one of the factors contributing to the insertion of the umbilical cord not in the central part of the placental disk. The asymmetric fusion causes the placenta to occupy different areas, which may result in a discordant growth of the foetuses.

The greater weight of new-borns with placentas having central UCIS indicates that the displacement of the fixation point to the periphery leads to deterioration in the functional capacity of the placenta. Placentas with a non-central cord insertion, even though having round shape, demonstrate less metabolically effective vasculature. Our data show that the displacement along the greater axis of the placenta has a more pronounced effect on the PM and the BW than the displacement along the smallest axis. In our opinion, this occurs due to a significantly greater elongation of the placental vessels to reach the distant pole of the disk.

CONCLUSIONS

The correlation of the birth weight (r = 0.49,) as well as the placental mass (r = 0.57) with the placental area, indicates the determining role of the size of the contact zone with the uterine wall on the functional activity of the organ.

A moderate correlation between the birth weight and placental circularity (r = 0.51) indicates that its functional activity increases when the shape approaches the circle.

For a more accurate assessment of the functional suitability of the placenta, it is necessary to simultaneously assess its area and circularity, which means to calculate S*Circ (r = 0.64).

Placentas with a non-central umbilical cord insertion demonstrate less metabolically effective vasculature. The distance by which the insertion site of the umbilical cord is displaced along the maximum diameter of the placental disk is of greater importance.

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ORIGINAL ARTICLE

CO-OCCURRING NECK-PAIN WITH MYOFASCIAL DYSFUNCTION IN PATIENTS WITH EPISODIC MIGRAINE

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ABSTRACT

The aim: To determine the influence of co-occurring neck pain with cervical myofascial dysfunction on the development of psychoemotional disorders and the number of analgesics taken in patients with episodic migraine.

Materials and methods: The study included 92 patients, 24 male and 68 female, mean age 42.5±15.5 years. Three groups were identify based on type headache: 1) both episodic migraine and cervicogenic headache with neck pain; 2) episodic migraine only; 3) neck pain only. Visual analogue scale (VAS) for pain syndrome, Migraine Disability Assessment (MIDAS) score, Headache Impact Test (HIT-6), Neck Disability Index, State-Trait Anxiety Inventory (STAI), Beck's Depression Inventory (BDI) and numbers days with analgesics intake were assessment.

Results: In patients, who suffered on episodic migraine combine with cervicogenic headache and neck pain number days with headache was more (p=0.000052), intensity attack was higher (p=0.003750) and number days with analgesics intake was greater (p=0.000003), compare with group with migraine only. The depression and anxiety state was more significant in patients with migraine and co-occurring neck pain comparable with migraine alone, but we found no significance differences between groups with migraine with neck pain and neck pain only. We observed significant correlation between STAI and Neck Disability Index (r=-0.5155), Neck Disability Index and HIT-6 (r=-0.4819). No correlation found between VAS for migraine, MIDAS and STAI and BDI.

Conclusions: Our study demonstrate, that co-occurring neck pain in patients with episodic migraine increasing of numbers days with headache, negatively impacts on mood disorders, daily activity and associated with greater acute analgesics use.

KEY WORDS: episodic migraine, neck pain, psychoemotional disorders, analgesic intake

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INTRODUCTION

Migraine affects an estimated 12% of the population. Approximately 2.5% of persons with episodic migraine progress to chronic migraine, which affects 1% to 2% of the global population. Migraine progression is associated with higher headache-related disability/impact, medical and psychiatric comorbidities, health care resource use, direct and indirect costs, lower socioeconomic status, and health-related quality of life [1]. Latest Global disease estimate and public health failure revealed that migraine was the second most disabling condition worldwide [2]. Part of the burden of migraine comes from its greater-than-chance association with a number of other disorders. Migraine is comorbid with epilepsy, depression, anxiety disorders, bipolar disease, and other pain disorders. Headache pain intensity was associated with higher risk for comorbidities and co-occurring conditions [3]. Diseases are said to be co-occurring if the same person has more than one disease. Approximately 15% of persons with migraine met criteria for acute medication overuse [4]. Overuse of analgesics is common problem in patients with primary headache especially in persons who suffered of other pain syndrome such neck or low back pain and self-medicate [5]. Understanding comorbidity has implications for revealing disease pathophysiology and clinical care.

THE AIM

The aim of this study to research the influence of co-occurring neck pain with cervical myofascial dysfunction on the development of psychoemotional disorders and the number of analgesics taken in patients with episodic migraine.

MATERIALS AND METHODS

We evaluated consecutive 92 patients, male 24, female 68, age ranged from 18 to 58 (mean 42,5±15,5 years). All patients divided for three groups. Group I included 31 patients (male/female 4/27) with episodic migraine (with typical aura 7 and without aura 24 patients) and co-existing neck pain. Group II included 30 patients (male/female 9/21) with episodic migraine (with typical aura 6 and without aura 24) without neck-pain. III group included 31 patients (male/female 11/20) with cervicogenic headache (CH) and neck pain. Episodic migraine were diagnosed according to the International Classification of Headache

– 3rd edition [6]. Duration of the disease ranged from 3 months to 32 years, a frequency of 4 to 7 attacks per month (average frequency of 5.4). Neck pain was assessed by reporting neck pain for more than 3 months and intensity 3 on the numerical scale of pain. Exclusion criteria was other primary headache or secondary headaches, arterial hypertension, ischemic heart disease, anamnesis of stroke, diabetes mellitus, other pain syndromes, pregnancy. Radiography of the cervical spine with functional load was performed for all patients; as a result, severe degenerative-dystrophic changes in the spine, disc herniation and root compression phenomena were excluded. All of the patients presented with the muscle tonic disorders due to of various grade scoliosis of the cervical and thoracic spine (29 patients), functional blockade of the joints of the cervical spine (31 patients) accompanied by tension of pericranial muscles and reflex muscle-tonic syndromes of the cervical region (cervicalgia, cervicobrachial syndrome). A visual analogue scale (VAS) was used to evaluate the dynamics of the quantitative characteristics of the pain syndrome, according to which patients were assessing the intensity of the pain syndrome of a migraine attack in the range from 1 to 100 mm [7; 8]. The MIDAS (Migraine Disability Assessment) scale was used to assess the effect of migraine on daily activity and performance for 3 months [9]. A quantitative assessment of the impact of the severity of subjective and objective symptoms of headache was carried out using the "Headache impact test" - "HIT-6" TM [10], which is a questionnaire that allows to determine the degree of influence of headache on the patient's daily activities. The number of points indicates the severity of the negative impact of a headache on a patient's life. The questionnaire consists of six questions with five possible answers for each one of them corresponding to a certain number of points. Neck Disability Index [11]. Mood and depression disorder evaluated according the Beck Depression Inventory (BDI), two subscales are distinguished in this technique: points 1-13 present the cognitive-affective subscale (CA) and points 14-21 present the subscale for somatic manifestations of depression (SP) [12]. To assess the level of personal anxiety the Spilberger-Hanin's anxiety scale was used [13]. All patients completed a headache and neck pain diary for to calculate presence or absence headache, headache frequency and duration, the number of days with analgesics intake.

The work performed in accordance with the principles of the World Health Association Helsinki Declaration "Ethical Principles of Medical Research with Human Involvement as Object of Study". Before inclusion in the study, patients and their relatives were inform with the study protocol and signed voluntary informed consent.

The statistical analyses were carried out with the SPSS statistical package (10.0 Version). Results are expressed as mean and error standard of the mean (M ± m) for the studied parameters. Statistical analysis was conducted with a confidence level of 95%. A p-value less than 0.05 was considered statistically significant. To analyze the normal distribution of the variables, the Kolmogorov-Smirnov test was used. The difference in the mean values of indicators in the groups was confirmed by parametric analysis of variance ($p < 0.05$). For pairwise comparison of groups, the Scheffe test was used. Association between characteristics was ascertained using Pearson's correlation.

RESULTS

The results of the study showed that the number of days with headache for 3 months in patients from group I with a co-occurring of migraine and cervicogenic headache and neck pain was significantly greater than in the group with migraine only, but did not differ significantly from group III with neck pain without migraine (figure 1). The intensity of pain during a migraine attack on the VAS scale was higher and the disability according to the MIDAS questionnaire was more significant in patients I groups versus group II (table I). Degree of influence of headache on the patient's daily activity according HIT-6 was more substantial in group with co-occurring of migraine and cervicogenic headache and neck pain comparable with group with migraine alone or neck pain alone.

When evaluating psychoemotional disorders, it was noted that the level of the state and trait anxiety was the lowest in patients group II with episodic migraine only in comparison with groups of patients who had neck pain. The level of depression in the examined patients was generally insignificant, but the lowest was in patients group II with migraine alone. Number days with analgesic intake per month was greater in I group of patients (figure 2).

Our data showing that patients with migraine alone almost use simple analgesics such acetaminophen (paracetamol) or ibuprofen, or triptan for treatment acute attack. Patients with co-occuring migraine and neck-pain often intake combine analgesics (acetominophen+metamizole sodium+coffeine) or non-steroidal anti-inflammatory drugs (NSAID), and 6 (19.35%) of them had sigh of medication overuse - >10 day for month. Patients with neck pain only often used NSAID. The majority of patients with episodic migraine and neck pain used acute medications for headache more than one class of medication. The rates of monotherapies were highest in NSAIDs, although the majority used at least one additional class of medication.

In I patients group there was a correlation between the number of days with headache and trait anxiety (r=0.4159) and number days with combined analgesics (r=0.4279), also in this group NDI correlated with HIT-6 (r=-0.4819). In III group significance correlation found between number of days with headache and BDS (r=0.4761), NDI with State anxiety (r=-0.5155), Trait anxiety (r=0.51690) and number days with combined analgesics (r=0.4445). In II patients group with migraine only significance correlation found only between days with headache for 3 months c days with simple analgesics (r=0.5053).

Thus, our study showed that the co-occurring of episodic migraine with cervicogenic headache and neck pain is associated with an increase in anxiety manifestations, an increase in the number days with headache for 3 months

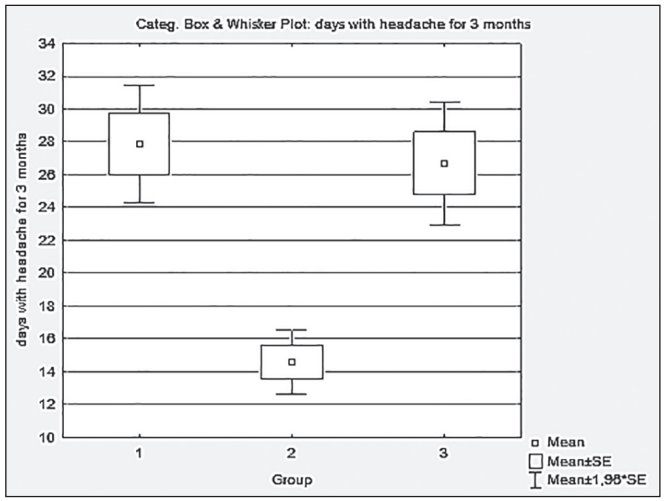

Fig. 1. Differences between groups to number day with headache for 3 months ($p<0.05$).

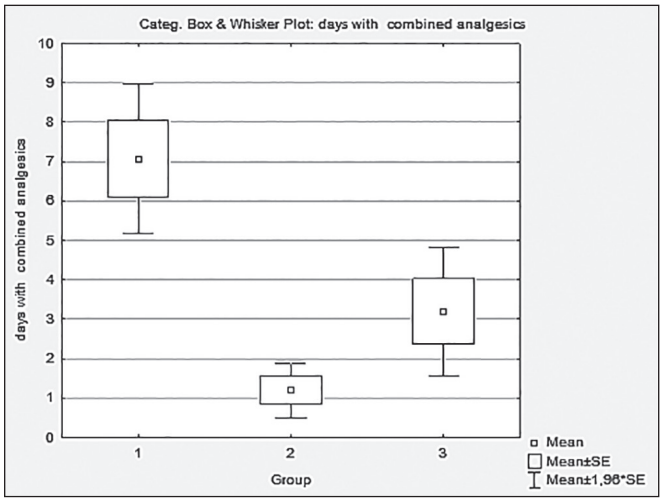

Fig. 2. Differences between groups to number day with combine analgesic intake ($p<0.05$).

Table I. General characteristics for different headache group patients

Characteristics	Group I n=31	Group II n=30	Group III n=31	P value
Number days with headache for 3 months	27,87±1,84	14,60±1,01	26,71±1,91	p=0,000052
VAS of migraine	8,77±0,17	7,96±0,20	0	p=0,003750
VAS of CH	4,87±0,24	0	6,83±0,25	p=0,000001
MIDAS	42,8±3,11	30,03±1,39	0	p=0,000482
HIT-6	62,09±0,70	56,63±0,75	58,06±1,47	p=0,000001
State anxiety	48,19±1,01	42,40±0,95	47,52±1,09	p=0,000001
Trait anxiety	51,80±0,81	47,03±0,92	50,25±0,81	p=0,000002
Beck Depression Scale	8,80±0,86	5,40±0,47	8,93±0,84	p=0,000001
Neck Disability Index	11,25±0,84	2,90±0,16	15,12±0,77	p=0,000001
Number days with simple analgesics per month	1,90±0,75	3,63±0,53	3,87±0,75	p=0,094177
Number days with combined analgesics/ triptans per month	7,06±0,96	1,20±0,35	3,19±0,83	p=0,000003

and an increase in the number of days with the use of combined analgesics.

DISCUSSION

In our study we examined relationship between migraine and cervicogenic headache and neck pain. Migraine is a highly prevalent headache disorder of people worldwide. Neck pain also one of the most common complaints in medicine, affecting 14–71% of adults. Different features of neck pain such as pericranial muscle tenderness, myofascial referred pain from neck muscles, and the dysfunction of the joints of the upper cervical spine have been associated with headache. Many migraine sufferers report neck discomfort and stiffness before and/or during an attack [14]. Comorbid and co-occuring diseases are risk factors for the progression of episodic migraine to chronic migraine. Pericranial tension and pain are one of the reasons for the decline in the quality of life of patients with migraine in the period between attacks [15]. "Multimorbidity" is associated with acute medication overuse and chronification of migraine [16].

Co-occuring migraine and neck pain is most likely associated with dysfunction of antinociceptive systems and trigeminal-cervical system, which leads to activation of motor neurons and the formation of muscular-tonic syndrome and myofascial dysfunction in the head and neck. In some studies described that noxious stimuli from the cervical structures and muscles may play role in the pathogenesis of migraine headache by enhanced of central sensitization. Prolonged nociceptive stimuli from the neck structures could be important for producing continuous afferent bombardment of the trigeminal nerve nucleus caudalis, and, hence, activation of the trigeminovascular system. Clinical findings suggest a relationship between migraine headache on the one hand and neck pain, or

neck-muscle stiffness or tenderness, on the other hand. In addition, there is convergence of trigeminovascular and cervical-muscle nociceptive afferents in the area of the upper cervical cord, referred to as trigeminocervical nucleus. [17]. Analgesic overuse may induce alterations in nociceptive neural networks, and it has been reported that patients without a previous history of headache taking analgesics on a regular basis for other conditions do not develop chronic headache [18]. Subgroups of migraine identified by comorbidity classes at cross-section predicted progression from episodic migraine (with ≥1 comorbidity at baseline) to chronic migraine. The relationship of comorbidity group to chronic migraine onset remained after adjusting for indicators of migraine severity, such as MIDAS [19]. Results of studies confirm that chronic neck and low-back pain are highly prevalent in the general population, but they indicate that the association between analgesic overuse and chronic headache is stronger than the association between analgesic overuse and chronic neck or chronic low-back pain. This study also showed that the association between analgesic overuse and headache is stronger for migraine than nonmigrainous headache. Higher intake of analgesics among headache sufferers simply reflects a more severe pain in this group than in those with neck pain [20].

Migraine is highly comorbid with both mood and anxiety disorders. The presence of a comorbid mood disorder predicts greater decreases in disability over the course of behavioral and pharmacological migraine treatment. Presence of neck pain in patients with migraine is associated with poorer treatment response [21; 22]. The high number of individuals with analgesic overuse has important clinical implications, and physicians should be aware of the potential risk of analgesic overuse among those with chronic pain, especially among those with migraine. Information about the hazards of frequent intake of symptomatic medication is important, and prophylactic treatment should possibly be considers at an early stage to prevent an "overuse" pattern and subsequent risk for medication overuse headache. Our study confirm the association between episodic migraine, neck pain and psychoemotional disorders.

CONCLUSIONS

1. Patients with co-occurring migraine and neck-pain with myofascial dysfunction had greater number days with headache for 3 month, more intensive pain during attack and greater disability according MIDAS.
2. Co-occurring neck-pain in patients with episodic migraine associated with mood and anxiety disorders.
3. In patients with combined episodic migraine and neck-pain observed increase number days with analgesic intake especially combine analgesic that may be risk for chronification headache. Neck pain is a better predictor of adverse treatment outcome of headache. Evaluating and correction myofascial dysfunction in migraineurs patients is an important step towards optimizing interventions for migraine care to better manage their condition, improve their ability.

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ORIGINAL ARTICLE

COMPARATIVE ANALYSIS OF FRACTAL DIMENSIONS OF HUMAN CEREBELLUM: IMPACT OF IMAGE PREPROCESSING AND FRACTAL ANALYSIS METHODS

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ABSTRACT

The aim: To compare the values of the fractal dimensions of human cerebellum obtained using different algorithms of image preprocessing and different methods of fractal analysis.
Materials and methods: The study involved 120 people without structural changes in the brain (age 18-86 years, 55 men and 65 women). T1- and T2-weighted MR brain images were studied. Fractal analysis was performed using box counting and pixel dilatation methods. Fractal dimensions of cerebellar tissue as a whole, cerebellar cortex and its individual layers, cerebellar white matter were measured and compared to each other and to fractal dimension of cerebellar white matter determined in cadaveric cerebella.
Results: It was no significant difference between fractal dimension values of cerebellar tissue as a whole measured on T1 and T2 weighted magnetic resonance images of cerebellum, and fractal dimension values measured on the same images using different methods of fractal analysis – pixel dilatation and box counting. T2 weighted images are preferable for fractal analysis of different components of cerebellar tissue. Segmentation according to pixel luminance is the preferable image preprocessing method for fractal analysis of cerebellar cortex as a whole, individual cortical layers and cerebellar tissue as a whole; skeletonizing of cerebellar magnetic resonance images is the preferable method of the image preprocessing for fractal analysis of cerebellar white matter.
Conclusions: The algorithm of image preprocessing, magnetic resonance imaging sequence and method of fractal analysis should be chosen according to aim of quantitative study of cerebellar magnetic resonance images and features of the studied structure of cerebellum.

KEY WORDS: cerebellum, fractal analysis, fractal dimension, magnetic resonance imaging, neuroimaging

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INTRODUCTION

In recent years, fractal analysis is increasingly used in morphological investigations of fractal biological structures. Fractal analysis provides quantitative and objective determination of the spatial complexity degree of different structures of human organism [1-3].

Spatial configuration of different structures of human cerebellum has fractal properties. Cerebellar white matter has a sophisticated tree-like branching pattern. It may be considered as fractal structure as well as cerebellar cortex, which forms a three-dimensional convoluted foliated structure, duplicating external contour of white matter [4]. Fractal analysis is one of the main morphometric techniques that may provide a quantitative morphological assessment of cerebellum [5-9].

For fractal analysis it is necessary to clearly define the boundaries of the studied structure. In view of this, the true fractal dimension of some cerebellar structures can be determined only via study of the anatomical sections of cerebellum, because neuroimaging methods may not have sufficient resolution to clearly define the boundaries of cerebellum and the boundaries between different components of cerebellar tissue. In our previous study, we determined the fractal dimension of white matter on the midsagittal sections of cadaveric cerebella [10]. In further studies we determined the fractal dimensions of cerebellum and its individual components (white matter and cortex) on the magnetic resonance (MR) images [11-13]; but we faced the problem of adapting these results to clinical practice to quantify MR brain images.

Different image preprocessing algorithms and various fractal analysis methods were used in different studies. The box counting method was applied in the studies of Akar E. at al. [5-7] and in the study of Wu Y.T. et al. [8]; the pixel dilatation modification was applied in the study of Liu J.Z. at al. [9]. In our previous studies we applied both methods: box counting [10, 11] and pixel dilatation [12, 13].

Therefore, to determine the best algorithm for fractal analysis of cerebellar MR images, we decided to compare the true FD values measured in cadaveric cerebella [10] and FD values measured in T1- and T2-weighted MR brain images, with different image preprocessing algorithms and using different fractal analysis methods [11-13]. The present study is a continuation and summarizing of our previous research on fractal analysis of human cerebellum [10-13].

THE AIM

The aim of the study was to compare the values of human cerebellum fractal dimensions obtained using different

algorithms of image preprocessing and different methods of fractal analysis.

MATERIALS AND METHODS

The study involved 120 people without structural changes in the brain (age 18-86 years, 55 men and 65 women). All participants provided written informed consent.

The conclusion of the Commission on Ethics and Bioethics of Kharkiv National Medical University confirms that the study was conducted in compliance with human rights, in accordance with current legislation in Ukraine, meets international ethical requirements and does not violate ethical standards in science and standards of biomedical research (minutes of the meeting of the Commission on Ethics and Bioethics of KhNMU №10 from 07.11.2018).

T1- and T2-weighted MR brain images were studied. MRI was performed on a 1.5 T MRI machine. The image parameters included the following. T1-weighted images: TE (echo time) was 14 ms, TR (repetition time) was 500 ms; section thickness was 5 mm; T2-weighted images: TE was 122 ms, TR was 4520 ms; section thickness was 5 mm. Sagittal MRI projection was chosen for the study (Fig. 1).

Initial preprocessing included segmentation of images. A 2 × 2-inch (128 × 128-pixels) fragments containing the midsagittal sections of the cerebella were copied from the digital magnetic resonance (MR) images (Fig. 1, A, D). The fragments of MR images were segmented using the Adobe Photoshop CS5 software. The structures surrounding the cerebella were initially removed from the images (Fig. 1, B, E), and the pixels in these areas were colored black (T1-weighted images, luminance value of 0 – Fig. 1, B) or white (T-2 weighted images, luminance value of 255 – Fig. 1, E). Segmentation was performed according to the pixels' luminance value using the "threshold" tool. The images were segmented into two components: the studied structure (colored white in T1-weighted images or colored black in T2-weighted images) and background (colored black in T1-weighted images or colored white in T2-weighted images). An empirical luminance threshold value of 100 was used for segmentation of T1- and T2-weighted MR images; it revealed the cerebellar tissue as a whole without segmentation into individual components (Fig. 1, C, F).

Fractal analysis was performed using two different methods: pixel dilatation method in the author's modification [14] and box counting method with the Image J software [15]; two-dimensional fractal dimensions (2D FD) were determined [11-13].

Initially, fractal analysis of cerebellar tissue as a whole was carried out using pixel dilatation method. Two fractal dimensions were measured: FD of T1-weighted images (FD(1)) and FD of T2-weighted images (FD(2)). T2-weighted images were more heterogeneous than T1-weighted images, thus, the T2-weighted images were chosen for the study of individual components of cerebellar tissue.

For the further investigations, we selected T2-weighted MR brain images of 30 young adults (18-30 years age range, 15 men and 15 women) among the MR images of 120 persons enrolled in the study. FD values were measured on the same MR images using two different methods of fractal analysis: pixel dilatation method (FD(3)) and box counting method (FD(4)).

Afterwards, the studied MR images were additionally segmented into individual components of cerebellar tissue (Fig. 2, A-E). For that purpose, the "threshold" tool was used. Fractal analysis of individual components of cerebellar tissue was carried out using the pixel dilatation method. We determined FD of cerebellar cortex as a whole (FD(5)), FD of granular layer of cerebellar cortex (FD(6)), FD of molecular layer of cerebellar cortex (FD(7)) and FD of cerebellar white matter (FD(8)).

After the initial segmentation, the image skeletonizing procedure was performed (Fig. 2, F). We used the "skeletonize" tool of Image J software. This tool revealed the main branches of the cerebellar white matter. FD of skeletonized images (FD(9)) was determined using a box counting method.

The obtained FD values were compared with each other and were compared to the FD values of cerebellar white matter obtained in our previous study of cadaveric cerebella [10] (FD(10), FD(11)). The study [10] was carried out on cadaveric specimens: 100 cerebella of people of both sexes who died from causes not related to brain diseases (62 male and 38 female; age range of 20-95 years). Cerebella were obtained during forensic autopsies. The macrophotographs of the midsagittal sections of cerebellar vermis were studied, the box counting method was utilized for fractal analysis; the counting was manual due to impossibility of the automatic image segmentation which is necessary for the automatic box counting with Image J software. The true values of FD of cerebellar white matter were determined (FD(10)). We additionally selected 14 cadaveric cerebella (20-30 years age range) for the present study and calculated FD value of the cerebellar white matter of those objects (FD(11)) to compare with FD values measured on 30 MR images of young persons (18-30 years age range).

A statistical data processing was performed using Excel 2010 software. The following values were calculated: the sample mean (M) and the standard error of the mean (m), the median value (Me, percentile 50) with interquartile ranges (the values of percentiles 25 and 75), the minimum (min) and the maximum (max) values. The significance of statistical differences between the FD values was assessed using the Kruskal-Wallis H test with Bonferroni adjustment for multiple comparisons. The significance level for all results was accepted as $p<0.05$.

RESULTS

We analyzed FD values of different structures of cerebellum, obtained using different image preprocessing algorithms and different methods of fractal analysis. The obtained values of the analyzed fractal dimensions of human cerebellum are listed in Table I and the distribution of the FD values is shown in Fig. 3. The statistical significance

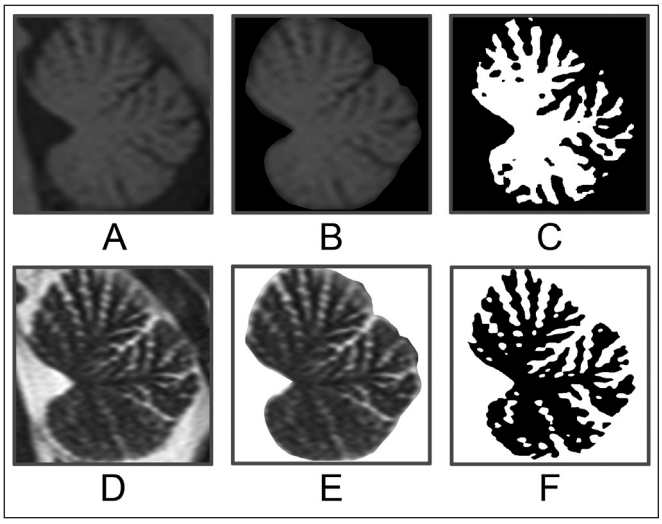

Fig. 1. Pre-processing of cerebellar MR images: segmentation of T1-weighted images (A, B, C) and T2-weighted images (D, E, F).

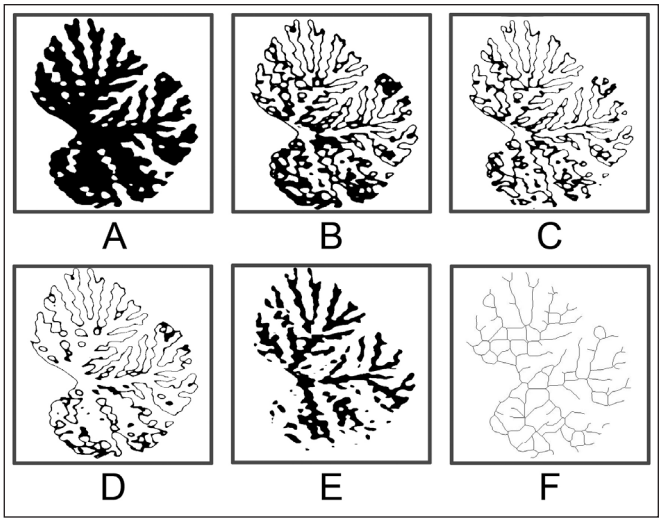

Fig. 2. Pre-processing of T2-weighted MR images of cerebellum. A-E – image segmentation using "threshold" tool: A – cerebellar tissue as a whole (threshold 100), B – cortex as a whole (difference between thresholds 100 and 80), C – granular layer of cerebellar cortex (difference between thresholds 90 and 80), D – molecular layer of cerebellar cortex (difference between thresholds 100 and 90), E – white matter (threshold 80). F – image skeletonizing using "skeletonize" tool: skeleton of white matter.

of the difference between FD values was assessed and null hypothesis was rejected; the difference between the mean ranks of compared FD values was statistically significant. Thus, the multiple paired comparisons between different FD values were provided.

It was no significant difference between FD values of cerebellar tissue as a whole, including FD(1) value measured on T1 weighted images using pixel dilatation method, FD(2) and FD(3) values measured on T2 weighted images using pixel dilatation method and FD(4) value measured on T2 weighted images using box counting method.

FD(1) and FD(2) values were measured on the MR images of the same persons, using the same image preprocessing and the same fractal analysis method (pixel dilatation), but *different MRI sequences* were utilized to obtain the studied MR images. The FD values determined on T1 and T2 weighted images were not significantly different and had close comparable parameters of statistical distribution. Therefore, T1 and T2-weighted MR images may be used for fractal analysis.

FD(3) and FD(4) values were measured on the T2-weighted MR images of the same persons and with the same image preprocessing, but *different fractal analysis methods* were applied. The FD values determined utilizing different methods of fractal analysis (FD(3) – pixel dilatation, FD(4) – box counting) coincided and were not significantly different. This indicates that both methods of fractal analysis may be used to determine FD values of cerebellar tissue as a whole.

All FD values of cerebellar tissue as a whole (FD(1-4)) were significantly different from the FD values of individual components of cerebellar tissue: FD(5-8), FD(9) (FD of skeletonized images) and FD of cerebellar white matter measured on cadaveric material (FD(10-11). There was significant difference between FD(5) value (cortex) and all other FD values, but there was no significant difference between values of FD(6) (molecular layer of cortex), FD(7) (granular layer of cortex) and FD(8) (white matter) compared to each other.

The FD values corresponding to cerebellar white matter were measured on the same T2-weighted MR images of the same persons, but with *different image preprocessing*: FD(8) – segmentation with a threshold of 80 and FD(9) – image skeletonizing. The FD(8) and FD(9) values were not significantly different.

The FD values were determined on the *different materials* (MR images and cadaveric material). FD values of cerebellar white matter measured on the MR images (FD(8) and FD(9)), were compared to FD values of white matter measured on the midsagittal sections of cadaveric cerebella. There was no significant difference between FD(8) and FD (10). But there was a significant difference between FD(9) and FD(10) ($p<0.05$). This may be caused by difference in the age range: 18-30 years for FD(9) and 20-95 years for FD(10). In our previous study, it was established that FD of cerebellar white matter had a significant strong negative correlation relationship with age ($r=-0.917$, $p<0.001$). According to this fact, we selected 14 cadaveric specimens (among 100) in the compatible age range (20-30 years) and calculated FD(11). There was no significant difference between FD(9) and FD(11). FD(9) and FD(11) values coincided and had close comparable parameters of statistical distribution and variance of the values. FD(8) values have a much larger variance compared to FD(9) and FD(11) values; this parameter may not be as accurate as the FD of skeletonized images (FD(9)). Thus, FD(9) (measured on skeletonized MR images) may be considered as a best parameter that corresponds to the true fractal dimension of the cerebellar white matter (FD(11)) which can be only measured by direct study of the anatomical sections of cadaveric cerebella. Skeletonizing of the cerebellar MR images is the preferred image pre-processing technique for fractal analysis of the cerebellar white matter.

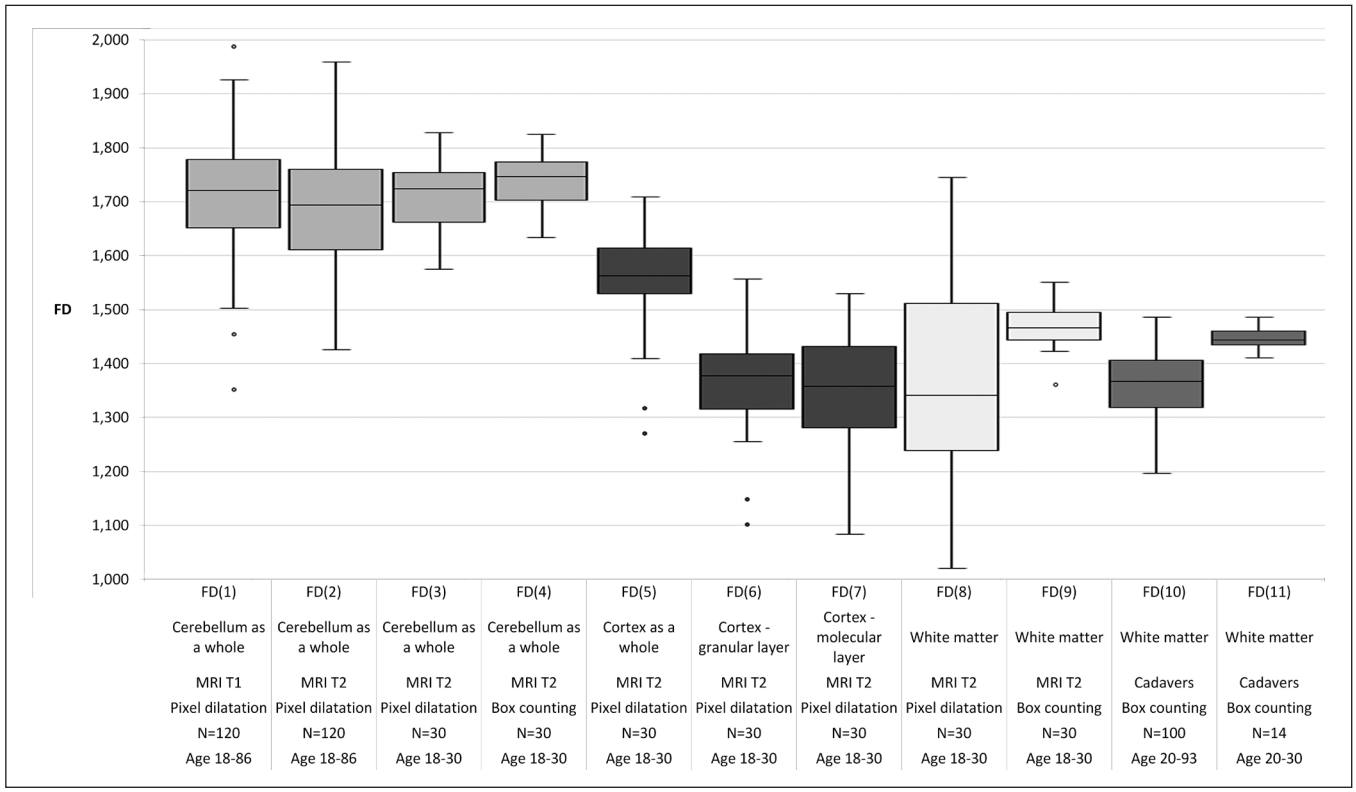

Fig. 3. The distribution of the fractal dimension values of human cerebellum.

Table I. The fractal dimension values of human cerebellum

FD	Cerebellar structure	Image type	Image preprocessing method	Pixels' luminance threshold	Fractal analysis method	Number of objects (N)	Age range, years	FD, M±m
FD(1)	Cerebellar tissue as a whole	MRI T1	segmentation	100	pixel dilatation	120	18-86	1.714±0.009
FD(2)		MRI T2						1.691±0.01
FD(3)						30	18-30	1.707±0.013
FD(4)					box counting			1.738±0.009
FD(5)	Cerebellar cortex as a whole	MRI T2	segmentation	100-80	pixel dilatation	30	18-30	1.564±0.018
FD(6)	Cerebellar cortex – granular layer			90-80				1.377±0.02
FD(7)	Cerebellar cortex – molecular layer			100-90				1.353±0.02
FD(8)	Cerebellar white matter	MRI T2	segmentation	80	pixel dilatation	30	18-30	1.318±0.05
FD(9)			skeletonizing		box counting 14			1.469±0.007
FD(10)		Macro-photo-graphs of cadaveric cerebella	visual assessment			100	20-95	1.372±0.006
FD(11)						20-30		1.447±0.005

DISCUSSION

Fractal analysis of MR brain images is an important area of modern neuroscience, since it allows diagnostics of various diseases of the nervous system. There are some studies which involved fractal analysis of human cerebellum [5-9]. The T1-weighted MR brain images were analyzed in all research works found in accessible literature. Different modifications of fractal analysis were applied: box counting [5-8] or pixel dilatation modification [9] and different fractal dimensions were determined: 2D (two-dimensional fractal dimension; the values vary from 1 to 2) [5, 6] or 3D (three-dimensional fractal dimension; the values vary from 2 to 3) [7-9]. Different components of cerebellar tissue were assessed (white matter and cortex), but FD of individual layers of cerebellar cortex were not measured in these studies.

In the studies of Akar E. at al. the 2D and 3D box counting methods were applied [5-7]. MR brain images were segmented into white matter, gray matter of cerebellum and cerebrospinal fluid. The mean value of 2D FD of cerebellar white matter was 1.49±0.06 and the mean value of the 2D FD of cerebellar gray matter was 1.56±0.05 [5, 6]. The mean value of 3D FD of cerebellar white matter was 2.26±0.05 and the mean value of the 3D FD of cerebellar gray matter was 2.49±0.04 [7].

In the study of Wu Y.T. et al. the 3D box counting method was utilized [8]. Automated 3D segmentation techniques were used; the cerebellar MR images were also segmented into white matter, gray matter and cerebrospinal fluid. The mean value of 3D FD of cerebellar white matter was 2.2746±0.0446 and the mean value of the 3D FD of cerebellar gray matter was 2.5267±0.0228 [8].

In the study of Liu J.Z. at al. the 3D pixel dilatation method was applied [9]. The image skeletonizing was used as a preprocessing method. The mean value of the 3D fractal dimension of the cerebellar white matter skeleton was 2.57±0.01 [9].

Thus, the present study and the studies of other researchers demonstrate that the values of the fractal dimension of cerebellum and individual components of cerebellar tissue may be quite different depending on utilized modification of the fractal analysis (box counting or pixel dilatation, two or three dimensional fractal analysis), type of studied material (MRI or cadaveric specimens), MR sequence (T1 or T2), and the algorithms of image preprocessing (segmentation, skeletonizing, etc.).

CONCLUSIONS

1. The values of fractal dimension of cerebellar tissue as a whole determined on the T1- and T2-weighted MR brain images were not significantly different; both MRI sequences may be used to obtain the MR scans for the fractal analysis.
2. There was no significant difference between FD values measured on the same images but using different fractal analysis methods – pixel dilatation and box counting; both methods give comparable results.
3. Segmentation of the T2-weighted MR brain images using "threshold" tool according to pixel luminance is the preferable image preprocessing method for fractal analysis of cerebellar cortex as a whole, individual cortical layers and cerebellar tissue as a whole.
4. Skeletonizing of the MR images is the preferable image preprocessing method for fractal analysis of cerebellar white matter.
5. The algorithm of image preprocessing, MRI sequence and method of fractal analysis should be chosen according to the aim of study and features of the studied structure.

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ORIGINAL ARTICLE

DISORDERS OF ADAPTATION OF COMBATANTS AND THEIR MEDICAL AND PSYCHOLOGICAL REHABILITATION AT THE SANATORIUM STAGE OF TREATMENT

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ABSTRACT

The aim of the study was on the basis of the study of clinical manifestations and mechanisms of the formation of disorders of psychological adaptation among the combatants, to develop the principles and program of their medical and psychological rehabilitation.

Materials and methods: The study was attended by 153 people at the sanatorium and resort stage of treatment, of which 98 people were combatants and 55 people were civilians. The study used a set of methods aimed at the study of emotional disorders (HDRS, BDI, Spielberger Scale, "Asthenic state scale"), individual psychological features (Multilevel personal questionnaire "Adaptability," Test questionnaire G. Shmishek, K. Leonhard), features of psychosocial functioning (Mississippian scale of PTSD-military version) and quality of life (WHOQOL-BREF).

Results: At the stage of sanatorium treatment of combatants is important readaptation to peaceful living conditions. A clinical and psychological analysis of combatants showed that the presence of experienced state of subjective distress and emotional disorder leads to a decrease in the productivity of adaptation to a stressful event. The stress factor disrupted the integrity of the micro-social network of combatants and their system of social support and social values, with the prevailing sense of inability to overcome problems and build plans. A detailed analysis of the nature of depressive and anxiety manifestations was carried out, which allowed to determine the predictors of the violation of adaptation in combatants.

Thus, on the basis of the study of clinical manifestations and mechanisms of the formation of disorders of psychological adaptation among the participants of hostilities, the principles of their medical and psychological rehabilitation at the sanatorium and resort stage of treatment are developed.

Conclusions: The peculiarities of stress response in combatants as a component of personal potential play a role in the formation of predictors of psychological adaptation disorders among combatants. Psychological intervention at the tertiary stage of rehabilitation (sanatorium-resort) should be targeted, taking into account individual-psychological characteristics (preventors) and psychosocial factors (predictors)

KEY WORDS: stress reactions, disruption of psychological adaptation, post-traumatic stress disorder, stress, depression, anxiety, quality of life

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INTRODUCTION

Today, the population of Ukraine is massively under the influence of potentially traumatic events [1-6]. According to the UN data from April 14, 2014 to March 31, 2020, the total number of casualties from hostilities in the East of Ukraine was about 41-44 thousand people, of whom 13-13.2 thousand people were killed and 29-31 thousand people were wounded (UN, 14.04.2020) [7].

Psychological and psychopathological consequences of armed conflicts are manifested by a wide range of maladaptive reactions and painful conditions, the formation of which is determined by numerous factors [8-10]. At present, it is determined that post-war psychopathological changes in the form of disruption of psychological adaptation take place in the vast majority of combatants [11, 12].

The problem of preserving the health and efficiency of combatants participating in military conflicts is the main task of medical and psychological rehabilitation. However, the social and psychological aspects of the content and peculiarities of the implementation of complex programs of medical and psychological rehabilitation, focused on certain categories of wounded, on the specifics of manifestations of somatic and mental disorders among the combatants, are not developed enough today [13-19].

Today, rehabilitation and medical and psychological events for combatants are concentrated in the early stages, where numerous works are devoted to early response to mental disorders. Our attention was focused on the organization of medical and psychological rehabilitation of combatants at the sanatorium and resort stage, which is most close to a peaceful life.

THE AIM

The purpose of the study was to develop the principles and program of medical and psychological rehabilitation of combatants, based on the study of clinical manifestations and mechanisms of forming in them post-stress psychological disadaptation at the sanatorium-resort stage of treatment.

MATERIALS AND METHODS

The sample of the study was made up of 153 male persons, of whom 98 persons who were participants of hostilities in the area of the Joint Forces Operation in the East of Ukraine made up the main group, and the other 55 civilians who received spa treatment and had complaints about somatic and psycho-emotional state - a comparison group.

The following set of methods were used in the study: Hamilton's Scale of Anxiety and Depression (Hamilton, HDRS, HARS, 1967), A.T. Beck's Scale (BDI, 1961), C.D. Spielberger's Scale , Method "Asthenic state scale", Multilevel personal questionnaire "Adaptability", Mississippi PTSD scale (military variant), Test questionnaire G. Shmishek, K. Leongarda, WHOQOL-BREF . The results were processed using statistical methods using the computer program "SPSS for Windows"; The mathematical and statistical method was represented by a dispersive (used t-criterion of Studente, λ- criterion Kolmogorov-Smirnov, φ - Fischer) analysis.

The survey of combatants was carried out under the conditions of informed consent and with the implementation of international standards of bioethics. Diagnosis and basic treatment were conducted according to the criteria of diagnosis and treatment of psychiatric and behavioral disorders and clinical protocols for providing psychiatric care to the adult population of Ukraine.

The first stage of the study was aimed at screening complaints and forming groups according to the criteria for inclusion at the stage of sanatorium treatment in the SE "Clinical sanatorium" Resort Berezovsky mineral waters". The main group included 98 combatants, which are divided into two subgroups according to the indicators of stress response: with signs of disruption of adaptation - 74 people; with signs of PTSD - 24 people.

At the second stage, clinical manifestations and mechanisms of formation of disorders of psychological adaptation were studied.

The final stage of the study was the justification and development of the principles and program of medical and psychological rehabilitation among the participants of combat operations at the stage of sanatorium treatment.

RESULTS

Analysis of the nature of complaints among combatants at the stage of sanatorium treatment showed their diversity. On average, 89% had complaints in the form of: affective spectrum (depression, anxiety, fear, feeling confused, reduced mood background and irritability, flashes of aggression) ideomotor-asthenic spectrum (excitement, rapid fatigue after mental activity and weakness after minimal physical effort, obsessive thoughts and memories, exhaustion of attention and memory) headaches, sleep disorders and frightening dreams and complaints of changes in the functioning of body systems. Whereas in the comparison group, somatic case complaints that had a chronic nature of the course of the disease were more prevalent.

Using the Mississippi scale, the PTSD military variant determined the degree of expressiveness of post-traumatic stress reactions in the main group of combatants at the stage of sanatorium treatment. For subgroups with signs of adaptation disorders, the symptoms of "avoidance" are more characteristic in 92% and in 85% of symptoms of physiological excitability, where lockdown in yourself, your feelings and thoughts lead to the formation of a sense of physiological tension and changes in perception and reactions. In subgroups with signs of PTSD, all symptoms are distinct, where the feeling of guilt in 87% and the symptoms of "invasion" in 100% are a common manifestation and moral regulator of socially acceptable behavior.

According to the objective assessment of the emotional state of the Hamilton scale, depressive symptoms prevailed in individuals of the main group: in 10% there were depressive disorders of moderate severity, in 71% - mild level. According to subjective assessment on the Beck scale, expressiveness varies between mild levels - in 43% and average manifestations of depression in 38%. Comparing the results with the results of a group of civilians, it was found that they had significantly lower depression indicators both by objective and subjective assessment: according to the Hamilton questionnaire, 62% had no depressive symptoms, and only 31% had mild depressive manifestations. According to the Beck scale, 58% - no manifestations of depressive symptoms and 36% - have mild subdepressant complaints associated with a somatic state.

The results obtained on the distribution of the level of depression in the subgroups of combatants indicate the severity of emotional experience and inhibition of the adaptation process. In the adaptation disorders subgroup by objective evaluation, 81% have a mild degree of depression, and according to subjective self-esteem, only 51% note the presence of mild levels of depression. In the subgroup with signs of PTSD, depressive symptoms prevailed by an average degree, both by an objective assessment of 37% and by subjective ones - by 50%. The mild level of depression was 62% on the Hamilton scale and 17% on the Beck scale, which generally reflects a more threatening state of the emotional sphere in the subgroup with signs of PTSD.

In 77% of participants of hostilities with signs of adaptation disorders, depressive symptoms are based on complaints of psycho-emotional tension, namely a feeling of tension, a decrease in performance, an unreasonable feeling of anxiety in the absence of a threat to the mental state of their health. Whereas for 82% of combatants with signs of PTSD, manifestations of depression are accompanied not only by physiological discomfort and changes in physical condition (inhibition, tension, lack of sleep, decreased

libido, general symptoms and somatic anxiety), but also by psychoemotional overload with guilt with suicidal thoughts.

An analysis of anxiety by objective evaluation in the main group showed that 36% of combatants had an average level of anxiety symptoms and 50.00% - an easy level, which was significantly more prevalent than in the comparison group, where 54% had mild anxiety manifestations. According to the Spielberger survey, 77% of the main group had high jet alarm rates and 63% - personal anxiety. In the group of comparison by objective assessment, alarming symptoms were obtained in 56%, and 45% - absent at all. Along with this, according to the questionnaire Spielberger, only 25% of civilians noted the average level of anxious jet-type symptomatic and 49% - personal anxiety.

The next stage of the study was to determine the level of quality of psychosocial functioning. The overall score of the quality of life of the respondents of the main group varied from 39 to 52 points. The average arithmetic estimate of quality of life was 43.6 points. In turn, the comparison group received high indicators of quality of life in 82%, where the average score was 79.3 points. Especially increased indicators of micro- and macro- social support. In the group of combatants with signs of adaptation disorders, the indicator of social well-being was especially reduced, which reflected the level of satisfaction with the environment, its position and capabilities. For combatants with signs of PTSD, the indicators of self-perception and microsocial support were reduced, due to increased criticism.

For combatants, the most inherent accentuations were demonstrative, alarming-stimulating type and stuck type. Whereas individuals of the comparison group are characterized by an exalted-emotive type of accentuation. In the subgroup of combatants with signs of adaptation disorders, the characteristic features of demonstrative, exciting, hyperthymic and cyclothymic types were characterized. Extreme expressiveness of these types of accentuations - expresses violations of affective-volitional processes that affect the control of behavior and characterize a certain behavioral style of realization of life position and personal needs. For combatants of PTSD, the types of accentuations of extreme degree of stuck, pedantic and exalted types that form the basis for the development of aggressive-fixative psychopathological symptoms aimed at themselves were inherent. Whereas in the comparison group the scale had an average range of expressiveness without extreme expressiveness, but the most characteristic scales are "sensitivity" (12±0,58 points) and "exalted" (11,8±0,47 points).

The study of personal adaptive potential of combatants showed a low level of regulation of behavior and communication orientation, as evidenced by low indicators on the "Adaptability" scale and "neuro-psychological instability." In the group of comparison, the whisky indicators on the scale of "behavioral regulation" and "adaptability" are obtained. In the subgroup with adaptation disorders signs, indicators of moral normality and behavioral regulation are significantly reduced, while in the subgroup with signs of PTSD, the indicator of communicative potential is reduced.

Analysis and generalization of the results made it possible to conclude that subgroups of combatants are characterized by different types of maladaptation disorders. For subgroup 1 there are psychotic reactions due to low indicators of neuro-mental instability, high conflictogenicity in interpersonal relationships and tendency to affective arousal; for subgroup 2 are asthenic reactions that indicate the type of maladaptive manifestations in the form of deterioration of somatic functioning, with a prevalence of deterioration in sleep, appetite, a sense of tension, a decrease in performance with hypochondriac fixation.

Next, we identified both predictors and preventors (protective personal resources) of post-stress psychological disadaptation in combatants at the sanatorium-resort stage of treatment.

For persons with signs of adaptation disorders in the system of formation of violation of adaptation, there are "distorted" thoughts about the displacement of the value of their role at the microsocial level, the loss of a certain significant position. Predictors of disruption of psychological adaptation among combatants with signs of adaptation disorders are:

– low indicators of moral normality that structure thoughts and help in interpreting and analyzing negative events of stressful level. Irrational perception of its role in the system of social functioning at micro and macro levels, which leads to a shift in the centralization of attention to aspects that will help restore the past system of life. On the one hand, this is a protective model of "avoiding" the problem, not the desire to face in thoughts with painful conclusions about his "I," which allowed to preserve the remnants of control of the situation and emotional comfort. And, on the other hand, it blocks the possibility of rethinking and transforming the experience gained, and in emotional regulation does not make it possible to verbalize their feelings and their origins.
– emotional instability, which is due to the personal radical of "exciting" and "cyclotic-hyperthymic" types of accentuation, which leads to excessive affective excitation and subsequent exhaustion. Characterologically, the instability of emotional experience is determined, which does not allow to be fixed on a certain emotion and understand its formation, the causes of experience.
– psychotic type of reaction of maladaptation disorder, as a tendency to respond to high neuro-mental tension on the challenges of stressful situations, low tolerance to adverse factors and because of decreased motivation and productive activity.

The preventors of disruption of psychological adaptation are:

– sufficient level of communicative potential, which lies in the structure of personal adaptation potential. as the need for a social environment and the possibilities of implementation, that is, the possibility of receiving from the social environment a sense of support, reinforcing self-esteem, motivation for activity, the certainty of the goals of future projects.
– personal radical by "demonstrative" type of accentuation acts as a strong side, thereby achieving the result of significance at all social levels.

Fig. 1. Algorithm of medical and psychological rehabilitation of combatants at the stage of sanatorium treatment.

For a subgroup of combatants with signs of PTSD, "distorted automatic thoughts" there is a hyperbolized sense of guilt and shame. Predictors of disruption of psychological adaptation among combatants with signs of PTSD are:

low communicative potential, which, with a significant impact of stressogenic factors, isolates from close social interaction and prevents family members from affecting the emotional state. Support from the family is leveled and perceived as a trigger for irritation;

fixation of attention on the sharpness of emotional experiences, support in the tone of negative manifestations, as a form of punishment. It also acts as a way to maintain control of their values in the system of life and an attempt to reorient for the future. But the level of guilt is so high that it has no limit of punishment. Therefore, this method of emotional response very quickly leads to exhaustion at all levels, and mental and somatic;

asthenic reaction of maladaptive disorder, which immediately invades the system of satisfaction of basic needs and disrupts physiological functioning, shifting attention to somatic complaints.

The preventors of disruption of psychological adaptation among the participants of combat operations with signs of PTSD are established:

– moral normalcy, which ensures understanding of their position and adequately perceive the defined social role. In this case, the unfavorable role of the combatants is distinguished from their own internalized norms of accepted behavior. But it allows you to determine new norms;
– due to emotional fixation, the process of reevaluating past events, information received, understanding of their position takes place. That is, there is a constant search for a new understanding of the stressful situation that can satisfy the needs of the individual;
– an "exalted" type of accentuation, which acts as a certain social barrier, is directed to the desire for social usefulness, which corresponds to the vital position of combatants with signs of PTSD.

Based on the study of clinical manifestations and mechanisms for the formation of disorders of psychological adaptation, the principles of medical and psychological rehabilitation of combatants at the stage of sanatorium treatment, which included:

1. principle of maximum synergistic cooperation: doctor/psychologist - patient - therapeutic complex;
2. multi-level nature of sanogenic measures;
3. combined nature of biological and psychological-oriented influences;
4. the sequence and stage of the events;
5. an integrated approach to solving clinical problems, that is, a combined consistent effect on all etiopathogenetic links of functional disorders;
6. the principle of optimality of the use of medical-psychological, psychotherapeutic, natural, preformed, drug and non-drug factors;
7. the principle of structuring the construction of sessions (structured psychological interview).

Due to certain targets of psychocorrectional intervention, a program of medical and psychological rehabilitation of combatants was developed at the stage of sanatorium treatment, taking into account the presence of signs of RA and PTSD. This program includes three main stages: initial, rehabilitation and support. The structuring of the sessions of the medical and psychological rehabilitation program was in compliance with a certain algorithm of certain sessions, depending on the subgroup of the study with signs of PA or PTSD.

For persons with signs of RA, rehabilitation is aimed at stabilizing the psycho-emotional state through self-regulation skills, psycho-educational sessions aimed at understanding the peculiarities of conflict resolution, soppersons of reflection with family members, understanding and assessing their condition with subsequent constructive response to symptoms.

For persons with signs of PTSD, rehabilitation was aimed at the resource-supporting aspect with the transformation of self-reliance and awareness of internal manifestations with the subsequent need for continued psycho-correctional intervention. Skills of self-regulation and grounding techniques were also acquired, in situations of high psycho-emotional stress.

The structuring of the sessions of the medical and psychological rehabilitation program was in compliance with a certain algorithm of certain sessions, depending on the subgroup of the study with signs of PA or PTSD (Fig. 1).

The effectiveness of these measures has been proven by improving the performance of reactive anxiety and quality of life, and reducing the feeling of asthenization. Participants of hostilities with signs of RA saw a decrease in the level of jet alarm in 50.0% (presence from 74.32% to 24.32%), no feeling of asthenization in 45.95% (a decrease from 58.11% to 12.16%) and an increase in the overall quality of life from 11.58 points to 17.85 points; in subgroup 2 with signs of PTSD decrease in reactive anxiety level in 50.0% (presence from 87.5% to 37.5%), there is no feeling of asthenization in 33.83% (decrease from 79.16% to 45.33%) and an increase in the overall quality of life from 10.37 points to 18.26 points.

DISCUSSION

We all face this problem when people who have participated in hostilities return to peaceful life, and it turns out that they need psychological help. In this case, it is confirmed that the cessation of participation in hostilities is not yet the cessation of the impact on the psyche of the same hostilities. All these consequences have participants in combat, in similar circumstances, and in other countries of the world. In the study on the results, we should note that the consequences have a prolonged effect. The results of the work of Svetlana Vyazmitinova proved that there are different options for violation of adaptation that require comprehensive assistance. It is very important that the system of sanatoriums is used, because this mechanism exists in our country and it is traditionally used to improve the state of health, because the influence of natural factors has always been very significant for the human body. In this case, it is important to provide comprehensive assistance.

It is still noteworthy that, very often, as we see, the participants in the fighting do not recognize the need for psychological and psychiatric assistance. On this occasion, they avoid, to seek specialized assistance in psychiatric institutions. The use of the sanatorium allows you to naturally connect the mechanism of providing medical and psychological assistance to the complex of restorative institutions, without causing dissatisfaction with the fighters. The article thoroughly examines the components of personal, the basis of the occurrence of these psychological disorders. A phased model of assistance was worked out. This is very important, because it is a work for the future - the formation of new mechanisms, new adaptation skills that will help return the participants of the fighting to society, an effective peaceful life, because it suffers the most.

The period when our country got into a state of hostilities, we studied the experience of other countries that have faced this before. Undoubtedly, these are American studies, Israeli and Croatian. Our tactics regarding medical and psychological rehabilitation in relation to combatants were based on the studies of our colleagues. Now we have a rich personal experience. But the vast majority of works that would study the psychological state of combatants or active military, participating in hostilities, they relate to or the period of direct participation, or the period that arises after the end of participation in hostilities, that is, it is a military hospital, or just a return to peaceful life, if he is not somatically injured, and if he does not have clinically defined expressed disorders of the psychological sphere, then he comes home. But we understand that most disorders of psychological adaptation have a pre-natological level of impression. That is, such persons do not fall under the supervision of psychiatrists. And it is specialists in medical psychology that should work first. Another important point is that we have programs of medical and psychological rehabilitation, psychological correction of disorders of psychological adaptation of soldiers in the early stages of receiving specialized medical care. This work is the first to analyze the condition of the soldier at the stage of sanatorium treatment. New and important was found that most of the fighters, who already received specialized medical care, still got into sanatorium treatment with signs of disorders of psychological adaptation of different levels. The second value of Svetlana's work is that 2 clinical and psychological variants of disorders of psychological adaptation were determined, namely: with signs of adaptation disorders and with signs of PTSD, in this case it is not about clinically defined, but about pre-natological (syndromological) manifestations. This differentiation helped the author to determine the psychopathogenesis of these disorders, namely, to determine the predictors and preventors of each type of disorder and they turned out to be specific, differentiated for each of the options. This was the key to the development of a personalized program of medical and psychological rehabilitation. Now our medicine lives

in the trend of personification of medical care. Of course, each person is a separate world. While the nosological diagnosis may be the same, the approach to each patient should be as individual as possible. This work helps to personalize the approach to medical and psychological work with such patients.

CONCLUSIONS

The work analyzes the phenomenon of post-stress psychological disadaptation of combatants at the late - spa - stage of rehabilitation, and justifies the need to provide them with medical and psychological assistance at this stage, because the vast majority of modern research is devoted to the development of programs of medical and psychological rehabilitation, psychological correction of disorders of psychological adaptation of UBD in the previous, earlier stages of specialized medical care. Two clinical variants of the occurrence and course of pre-nosological manifestations of post-stress psychological disadaptation at the sanatorium stage of medical care - according to the type of disorder of adaptation with the predominance of the rod pathopsychological response such as "avoidance," and by the type of post-traumatic stress disorder with pathopsychological radicals "invasion" and "feelings of passage were identified

A program of medical and psychological rehabilitation of combatants at the stage of sanatorium treatment, taking into account the options of their stress response, which provides them with personalized medical care aimed at improving their rehabilitation potential, level of social functioning and quality of life, has been developed.

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ORIGINAL ARTICLE

DYNAMICS OF CHANGES OF C-REACTIVE PROTEIN LEVEL IN BLOOD SERUM IN THE DEVELOPMENT AND COURSE OF EXPERIMENTAL PERIODONTITIS AND THEIR CORRECTION BY FLAVONOL

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ABSTRACT

The aim: To study the value of C-reactive protein in the experimental animals blood serum with bacterial-immune periodontitis and its correction with quercetin.

Materials and methods: Modeling of periodontitis was performed by the following method: after thiopental anesthesia (at a dose of 40 mg / kg intramuscularly) rats were fixed. A subcostal injection of 0.01 ml of egg protein with cultures of Streptococcus hemolytic and Staphylococcus aureus at a dose of 4 CFU was performed in the area of periodontal tissues of the lower incisor as an initiating inflammatory factor. To enhance the immune process, a complete Freund's adjuvant was introduced into the animal's hind limb at the same time.

Results: Analysis of the results of the study of the content of C-reactive protein in the blood serum of animals with experimental bacteria and immune periodontitis, receiving injections of quercetin, showed a significant decrease by 1.31 times, compared with animals with this simulated pathology on the 14th day of the experiment without the use of flavonol. When comparing this indicator on the 14th day of development of experimental periodontitis with correction, it was found that it remained slightly higher than the indicators of the intact group of rats.

Conclusions: The level of C-reactive protein in the blood serum of experimental animals is an important indicator of the immune-inflammatory response, which increases its activation of the inflammatory system. The administration of flavonoid quercetin for 7 days helps to reduce the level of C-reactive protein in the blood serum of animals with experimental bacterial and immune periodontitis.

KEY WORDS: Protein level, Blood serum, Experimental periodontitis, Flavonol

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INTRODUCTION

Currently, there is an active search for new biomarkers of inflammation in patients with generalized periodontitis, with high prognostic value and assessment of factors, including carbohydrate metabolism disorders that affect the activation of various inflammatory mechanisms. Among the biomarkers known today, C-reactive protein (CRP) is probably one of the most promising indicators of inflammation and its definition occupies a special place among many clinical and laboratory tests. This is due to its ability to reflect the activity of the inflammatory process caused by bacterial infections and immunological diseases [1]. C-reactive protein is a short form of pentraxin that belongs to plasma proteins bound to calcium-dependent ligands, a superfamily of soluble pattern recognition molecules, and is mainly found as a pentameric compound [2]. The role of the protein is to facilitate the removal of microorganisms and necrotic tissues by activating cellular cytotoxic cascades. As a standard for assessing the level of systemic inflammation in patients, a highly sensitive C-reactive protein is used, which is not inferior in prognostic significance to other markers of inflammatory processes in the body. Microbe-inflammatory and destructive processes occurring in the body are characterized by changes in the concentration of plasma proteins [3].

In recent decades, the world medical community has paid special attention to the treatment and prevention of periodontal disease [4]. Eliminating the development and consequences of inflammatory processes in the periodontal complex means solving one of the global problems of oral health – tooth loss and, as a consequence, reduced masticatory efficiency and quality of life [5]. Therefore, an interesting and promising area is the study of organoprotective capabilities of quercetin, which has antioxidant, antitoxic, antiischemic, anti-inflammatory and membrane-stabilizing properties [6], which will determine new aspects of its use in patients of this category. The bioflavonoid quercetin belongs to the family of polyphenolic phytocompounds with pronounced antioxidant and anti-inflammatory properties. It is a powerful free absorber, antioxidant and anti-inflammatory agent [7]. The therapeutic effect of the drug, which belongs to the class of polyphenolic biofla-

Table I. Indices of C-reactive protein in the serum of experimental animals in different periods of development and course of experimental periodontitis and the use of quercetin (M ± m)

Conditions and indicator of the experiment	Control group (intact animals)	White rats with experimental periodontitis			
		No correction			With correction
Experiment duration (days)	-	7	14	30	14
Number of animals	10	8	8	8	8
C-reactive protein, mg / l	0,45 ± 0,01	0,75 ± 0,02 p_1<0,01	0,67 ± 0,01 p_1<0,01; p_2<0,01	0,64 ± 0,02 p_1<0,01; p_2<0,01; p_3<0,05	0,51 ± 0,02 p_1<0,05; p_3<0,01

Marking: p_1 - the significance of the differences with intact animals; p_2 - the significance of the differences with animals with experimental periodontitis on 7th day of the study; p_3 - the significance of the differences with animals with experimental periodontitis on 14th day of the study without correction by quercetin.

vonoids, is due to its anti-inflammatory and antioxidant activity. Quercetin reduces inflammation by inhibiting the production of cytokines such as interleukin-6, interleukin-8 and tumor necrosis factor, as well as by inhibiting the activation of nuclear factor κB (NF-κβ) [8]. In addition, a study in an animal model of inflammatory pain origin showed that quercetin reduces pain, oxidative stress and cytokine production [9].

THE AIM

To study the value of C-reactive protein in the experimental animals blood serum with bacterial-immune periodontitis and its correction with quercetin.

MATERIALS AND METHODS

Experiments and research were conducted on the basis of the Central Research Laboratory (certificate of technical competence № 001/18 from 26.09.2018 to 28.12.2023) and the Interdepartmental training and research laboratory (certificate of technical competence № 132/17 from 29.12.2017 to 28.12.2022) of I. Horbachevsky Ternopil National Medical University on 42 nonlinear white mature male rats aged 7-8 months. Animals selected for the study were in the vivarium on a standard diet in accordance with sanitary and hygienic standards and GLP requirements. Operations were carried out in compliance with the general rules and provisions of the European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes (Strasbourg, 1986), the General Ethical Principles of Animal Experiments (Kyiv, 2001).

Modeling of periodontitis was performed by the following method: after thiopental anesthesia (at a dose of 40 mg / kg intramuscularly) rats were fixed. A subcostal injection of 0.01 ml of egg protein with cultures of Streptococcus hemolytic and Staphylococcus aureus at a dose of 4 CFU was performed in the area of periodontal tissues of the lower incisor as an initiating inflammatory factor. To enhance the immune process, a complete Freund's adjuvant was introduced into the animal's hind limb at the same time. These groups of animals were studied on the 7th and 14th days (groups II and III). Group IV animals were re-injected with adjuvant pathogen on the 14th day of the development of the inflammatory process in the periodontal complex and were examined on the 30th day. Due to this, an increase in the reproduction efficiency of bacterial and immune periodontitis was achieved. As established by our previous studies, microbial contamination coincided with that in humans [10].

The level of C-reactive protein in the serum was determined by enzyme-linked immunosorbent assay according to the instructions (High Sensitivity CRP (hs-CRP) Test System «Monobind Inc.», USA). The study was performed as follows: after selecting the required number of wells, added 25 mcl of standards, controls and test samples and 100 mcl of Enzyme Reagent CRP in each well. Carefully stir them for 20-30 seconds. Incubate for 15 minutes at room temperature. The contents of the wells were removed by aspiration. 350 mcl of wash buffer and 100 mcl of substrate working solution were added to each well, incubated for 15 min at room temperature. Stopped the development of color by adding to each well 50 mcl of stop solution and stirred for 15-20 seconds. The absorbance values of the wells at a wavelength of 450 nm were measured (measurements were performed at a reference wavelength of 620-630 nm). During the analysis, Streptavidine sorbed in the cells and biotinylated antibodies to the C-reactive protein interacted on the surface of the microwells. When mixing biotinylated antibodies and serum containing CRP antigen, between CRP antigen and antibodies there was a reaction to form an antibody-antigen complex. Sequentially, the biotin bound to the antibody interacted with Streptavidine deposited in the wells, resulting in immobilization of the complex. The results were displayed in mg / l [11].

Statistical processing of digital data was performed using the software «STATISTICA» 10.0 («Statsoft», USA) using variational-statistical methods of evaluation of the obtained data. The values of the arithmetic mean (M), its variance and error of the mean (m), the sample size (n) were calculated for all indicators. The reliability of the difference between the values of the independent quan-

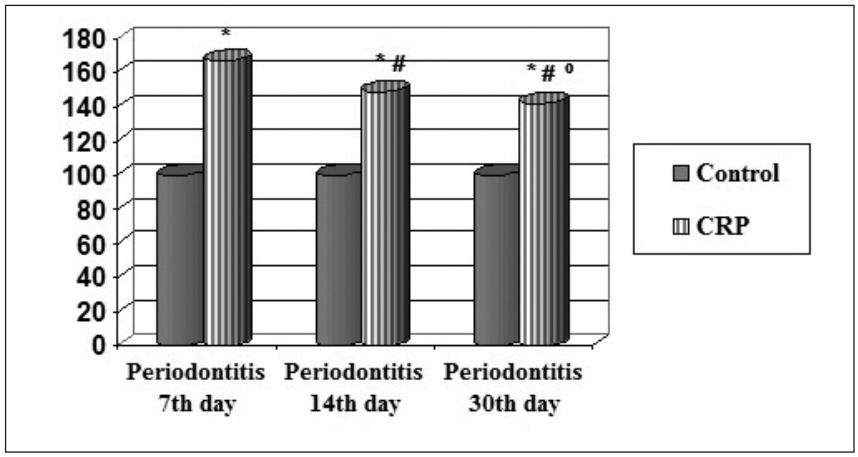

Fig. 1. Dynamics of C-reactive protein content in white rats blood serum with experimental periodontitis (% of control)

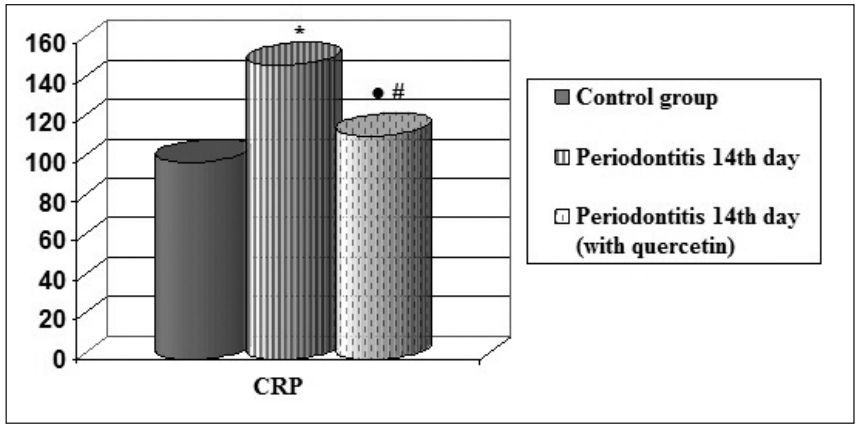

Fig. 2. The effect of quercetin on the content of C-reactive protein in white rats blood serum with experimental periodontitis (% of control)

titative values was determined at the normal distribution by the Mann-Whitney U-test. The difference in the results of the study was considered probable when the reliability coefficient was less than 0.05 [12].

RESULTS

Regarding the change in the content of C-reactive protein in the serum of experimental animals with periodontitis, it should be noted that its content on the 7th day of the experiment significantly exceeded (by 1.67 times; $p<0.01$) indicators that were in animals of the control group (Table I, Fig. 1).

In the rats of the experimental group, which were observed on the 14th day of the study, compared with the group of animals that were studied on the 7th day, there was a statistically significant increase the level of C-reactive protein in blood serum (by 1.12 times; $p<0.01$) (Fig. 1).

Also in this period there was a probable increase in the values of this indicator of inflammation (by 1.49 times; $p<0.01$) relative to the corresponding control. Analysis of the results obtained on the 30th day of the study showed a similar nature of changes, ie a probable increase in C-reactive protein, relative to the data of the control group (by 1.42 times; $p<0.01$).

The determination of the level of C-reactive protein in the serum on the 30th day of the experiment showed that its content in the blood was significantly lower than the data on the 7th and 14th day of observation – by 1.17 times ($p<0.01$) and by 1.05 times ($p<0.05$), respectively.

Analysis of the results of the study of the content of C-reactive protein in the blood serum of animals with experimental bacteria and immune periodontitis, receiving injections of quercetin, showed a significant decrease by 1.31 times ($p<0.01$), compared with animals with this simulated pathology on the 14th day of the experiment without the use of flavonol (Table).

However, when comparing this indicator on the 14th day of development of experimental periodontitis with correction, it was found that it remained slightly higher (by 1.13 times; $p<0.05$) than the indicators of the intact group of rats (Fig. 2).

DISCUSSION

One of the indicators of tissue damage in inflammatory processes is C-reactive protein, which belongs to the so-called acute phase proteins. C-reactive protein is involved in the interaction of T- and B-lymphocytes, activates complement in the classical way. C-reactive protein stimulates protective reactions, activates immunity [13]. CRP is produced in the liver and in much smaller numbers by peripheral blood lymphocytes, during acute episodes of inflammation or infection. Determination of serum C-reactive protein level is used in the clinic as a non-specific marker for inflammation, infection and tissue damage

associated with the acute phase [14]. It should be noted that CRP is a biomarker of elevated levels of IL-1, IL-6 and TNF-α. In addition to its role in humoral innate immune responses, C-protein recognizes and binds several intrinsic ligands, such as the complement system, leading to a significant increase in infarct size, cell receptors, apoptotic cells, growth factors, and extracellular matrix components, and therefore contributes to the progression of cardiovascular disease [15]. Inflammation releases interleukin-6 and other cytokines that cause CRP and fibrinogen synthesis in the liver. In the process of inflammation, C-reactive protein stimulates the synthesis of pro-inflammatory factors: the release IL-1β, IL-6, TNF-α by monocytes, the expression of human endothelial cells of adhesion molecules and protein chemotaxis of monocytes-1 [16]. It also activates cholesterol synthesis, reduces the expression and activity of nitrogen monoxide (NO) in the vascular endothelium. Thus, CRP is not only a marker of the inflammatory process, but also its inducer. C-reactive protein plays a key role at all stages of this inflammatory process: it stimulates immune responses, including phagocytosis, participates in the interaction of T- and B-lymphocytes and can actively influence the activation of the complement system by inducing apoptosis, vascular cell activation, involvement leukocytes, lipid accumulation, platelet aggregation [17]. On the surface of many bacteria, the C-reactive protein forms compounds with phosphatidylcholine molecules that are strong opsonins, ie antibodies and complement factors that enhance macrophage phagocytosis and stimulate the digestion of microorganisms. C-reactive protein is a very sensitive element of blood, one of the first to respond to tissue damage [18, 19]. The presence or increase in the level of CRP in the serum is a sign of inflammation, damage, penetration of foreign microorganisms, parasites and fungi. Thus, increasing the concentration of CRP is a biochemical marker of the development of both the inflammatory process in the body in general and periodontitis in particular.

CONCLUSIONS

1. The level of C-reactive protein in the blood serum of experimental animals is an important indicator of the immune-inflammatory response, which increases its activation of the inflammatory system. The development and course of simulated inflammation of bacterial-immune genesis is accompanied by an increase in serum concentrations of CRP throughout the period of formation of the inflammatory focus in the periodontal complex, which is associated with the response of innate humoral immune responses to antigen stimulation.
2. The administration of flavonoid quercetin for 7 days helps to reduce the level of C-reactive protein in the blood serum of animals with experimental bacterial and immune periodontitis, which may be a sign of stabilization and attenuation of the inflammatory process and one of the indicators of its effective influence on this pathogenetic link of inflammatory process in the periodontal complex.

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ORIGINAL ARTICLE

PATHOMORPHOLOGICAL FEATURES OF GASTROESOPHAGEAL REFLUX DISEASE REALIZATION IN YOUNG PEOPLE WITH AUTOIMMUNE THYROIDITIS

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ABSTRACT

The aim: To evaluate the pathomorphological features of the esophageal mucous membrane in young people with GERD and autoimmune thyroiditis.

Materials and methods: 120 patients with GERD and AIT and 45 people with isolated GERD matched for age, gender and social status were examined. Esophagogastroduodenoscopy, histological study and comparative morphometry of the esophageal mucosa were performed.

Results: The frequency of erosive GERD in the examined groups of patients did not statistically differ. At the same time, integral analysis of the structure of erosive forms of GERD revealed statistically significant redistribution of grades of esophagitis towards its enhancement in patients with comorbid pathology. The histological study showed that in patients with GERD and AIT all the morphometric parameters studied had a significantly more severe course and exceeded similar indicators of the group with isolated GERD: epithelium total thickness, epithelium basal layer thickness, connective tissue papillae height, intercellular space. The analysis of morphological changes frequency showed that epithelium basal layer hyperplasia, dystrophic changes and epithelial edema, elongation of papillae and dilation of intercellular space were significantly more frequent in the group with comorbid pathology.

Conclusions: GERD and euthyroid AIT comorbidity in the student population is accompanied by a statistically significant redistribution of esophagitis grades towards its aggravation. The presence of concomitant euthyroid AIT in patients with non-erosive GERD leads to statistically more pronounced disorganization of esophageal mucosal epithelium.

KEY WORDS: gastroesophageal reflux disease, autoimmune thyroiditis, oesophageal biopsy, pathomorphological study, young population

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INTRODUCTION

The traditional interpretation of gastroesophageal reflux disease (GERD) etiopathogenesis as a chronic disease caused by disorders of gastroesophageal motor-evacuation function with regular reflux of gastric and/or duodenal contents into the esophagus has undergone significant changes [1-3].Not rejecting the importance of chemo-mechanistic aspects («chemical burn» theory) in the development of GERD, modern studies supplement the pathogenesis of the disease with new data on the role of the chronic inflammatory process in the course of nosology; there is an assessment of universal mediators and the search for esophageal-specific mediators of inflammation and sources of their production.

According to the classical «chemical burn» theory, acid-induced death of superficial cells of the esophageal epithelium was thought to provoke an acute granulocytic inflammatory response, which begins in the epithelium and then progresses to the mucosal lamina, with the formation of a defect in the submucosal layer. It has also been suggested that loss of superficial cells of the esophageal mucosa stimulates hyperplasia of progenitor cells in the basal layer of the squamous epithelium, which is a characteristic histological sign of GERD [4-6].

In 2009, the pathogenetic concept of the «chemical burn» was challenged in an animal model of GERD caused by esophagoduodenostomy[7]. Reflux esophagitis in rats did not start from superficial cell death and epithelial infiltration by granulocytes, but rather from T-lymphocytes that first infiltrated the esophageal submucosa and then infiltrated the lamina propria and epithelium. Superficial erosions did not appear until several weeks after esophagoduodenostomy, and basal cell hyperplasia occurred long before the loss of mucosal superficial cells. A culture study of human esophageal epithelial cells found that acids and bile salts caused the release of pro-inflammatory and proliferative cytokines, such as interleukin-8. Based on such data, an alternative hypothesis of GERD pathogenesis was proposed, in which refluxate did not directly destroy esophageal epithelial cells, but rather stimulated them to secrete cytokines [8-10]. The latter caused proliferative changes in the epithelium and mobilized T-lymphocytes and other inflammatory cells, which eventually damaged the mucosa [11-13].

An important factor in pathomorphological realization of GERD may be its combination with other diseases, including autoimmune thyroiditis (AIT), which creates unfavorable immune and humoral background that may contribute to the worsening of GERD course [14,15].

Table I. The incidence structure of different esophagitis grades in the examined patients

Esophagitis grades	GERD and AIT (n=34)	GERD (n=11)	Significance of differences 1
A	6 (17.7%)	7 (63.6%)	df=3 χ^2=8.772 p=0.033
B	18 (52.9%)	3 (27.3%)	
C	8 (23.5%)	1 (9.1%)	
D	2 (5.9%)	0 (0%)	

Note: p<0.05 – the difference is statistically significant between groups

Table II. Mucous membrane morphometric parameters of the distal part of the esophagus in the studied patients, M±m

Groups		GERD (n=35)	GERD+AIT (n=50)	Significance of differences 1
Epithelium total thickness, μm		286.1±8.2	319.3±9.1	p<0.01
Epithelium basal layer thickness	μm	49.7±2.1	79.6±3.2	p<0.01
	%	17.3±0.3	25.1±2.9	p<0.01
Connective tissue papillae height	μm	172.7±4.6	224.8±7.3	p<0.01
	%	60.4±3.3	72.3±3.1	p<0.01
Intercellular space, μm		1.12±0.09	1.55±0.11	p<0.01

Note: p<0.05 – the difference is statistically significant between groups

THE AIM

The objective of the study was to evaluate the pathomorphological features of the esophageal mucous membrane in young people with GERD and autoimmune thyroiditis.

MATERIALS AND METHODS

The study was conducted at the Department of General Practice - Family Medicine and Internal Diseases, the Department of Pathological Anatomy, the Department of Internal Medicine no. 1 of Kharkiv National Medical University, Ukraine, between 2017 and 2019. The study was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University. All the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

Criteria for inclusion: students 18 - 25 years old; verified diagnosis of GERD; for the main group - verified diagnosis of AIT.

Criteria for exclusion: hypothyroidism, hyperthyroidism, other endocrine and GIT pathology; diseases of the cardiovascular system, kidneys, lungs; cancer; mental illness; pregnancy and lactation; minority; patient's refusal to participate in the study.

165 patients were examined, including 120 patients with comorbidity of GERD and AIT (main group) and 45 people with isolated GERD (comparison group). The mean age in the groups was 21.9 ± 2.7 and 21.2 ± 2.4 years, respectively (p>0.05). The contingent was represented by students from various universities of Kharkiv (Ukraine); 93 patients (77.5%) of the main group and 34 examined persons (75.56%) of the comparison group were women, 27 (22.5%) and 11 (24.44%) respectively were men. Standard values were obtained while examining 20 almost healthy patients of the same age, gender and social status.

Autoimmune thyroiditis was confirmed by the presence of antibodies to thyroperoxidase and thyroglobulin and thyroid gland ultrasound. The functional state of the thyroid gland was assessed in the previous stages of the study on the content of thyroid-stimulating hormone, free triiodothyronine and thyroxine, all patients were diagnosed with euthyroid status.

The diagnosis of GERD was confirmed by typical complaints, history, clinical and instrumental data. Visual assessment of the esophageal mucous membrane was performed by endoscopic examination of the esophagus (videoendoscopic system "Fuginon", Japan) with biopsy and subsequent histological examination of the material.

Material for the histological study was taken from the mucous membrane of the distal esophagus 3 cm above the conventional circular line connecting the stomach and esophagus. Pieces of the mucosa of the distal esophagus were fixed in formalin, passed through alcohols in increasing concentration, embedded in paraffin and prepared 5 μm thick sections that were stained with hematoxylin-eosin and picro-fuchsin according to Van Gieson method. Microscopic examinations were performed on an Olympus BX-41 microscope. Morphometric parameters were obtained using the Olympus DP-Soft (Version 3: 1). The total thickness of the epithelium, basal layer thickness, the height of connective tissue papillae and intercellular space were determined in 10 random fields of view in high (x40 lens, x10 eyepiece).

Statistical processing was performed using Statistica software. The results were analyzed using methods of descriptive statistics: calculation of arithmetic mean, 95% confidence interval, and standard error in the sample. Differences obtained by paired comparisons were considered statistically significant at $p < 0.05$.

Table III. The frequency of morphological changes of the esophageal mucosa in the studied patients

Sign	GERD (n=35)		GERD and AIT (n=50)		Significance of differences (χ2)1
	Abs.	%	Abs.	%	
Epithelium basal layer hyperplasia	22	62.9	44	88.0	df=1 χ2=7.499 p=0.006
Epithelial edema	21	60.0	41	82.0	df=1 χ2=5.049 p=0.025
Connective tissue papillae elongation	20	57.1	41	82.0	df=1 χ2=6.278 p=0.012
Submucosal fibrosis	19	54.3	36	72.0	df=1 χ2=2.829 p=0.093
Intercellular space dilation	19	54.3	39	78.0	df=1 χ2=5.342 p=0.021
Dystrophic changes	23	65.7	45	90.0	df=1 χ2=7.589 p=0.006
Leukocyte infiltration	22	62.9	39	78.0	df=1 χ2=2.33 p=0.127

Note: $p<0.05$ – the difference is statistically significant between groups

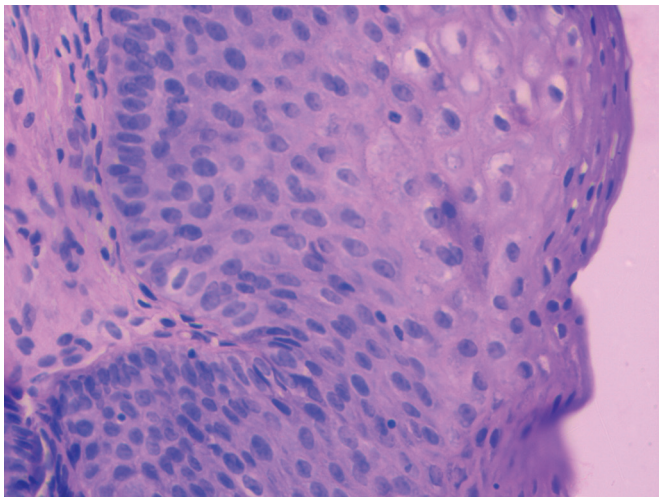

Fig. 1. Esophageal epithelium thickening due to the basal zone hyperplasia in a patient with comorbid pathology (staining with hematoxylin and eosin, x 400)

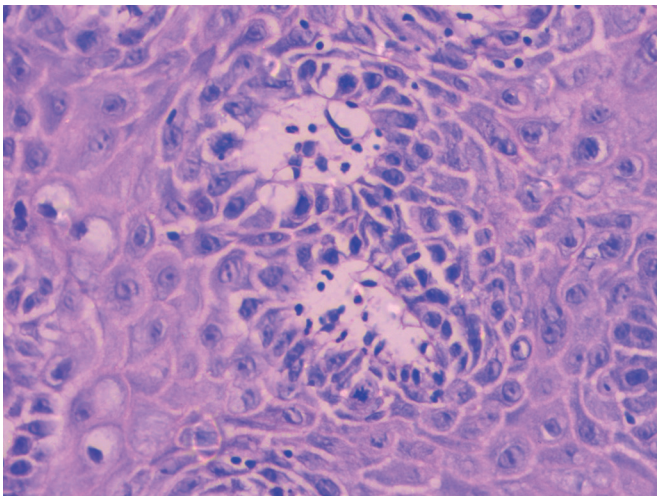

Fig. 2. Leukocyte infiltration of the esophageal mucosa with the presence of rare eosinophils in a patient with comorbid pathology (staining with hematoxylin and eosin, x 400)

RESULTS

The endoscopic examination of patients with comorbid GERD and AIT revealed erosive lesions of the esophagus in 34 (28.3%) and nonerosive – in 86 (71.7%) cases. In the comparison group, erosive GERD was found in 11 (24.4%) and nonerosive – in 34 (75.6%) patients. The grade of esophagitis was determined according to the Los Angeles classification (Tab. I).

The frequency of erosive GERD in the examined groups of patients did not statistically differ (df=1, χ^2=0.250, p=0.618). At the same time, integral analysis of the structure of erosive forms of GERD revealed statistically significant redistribution of grades of esophagitis towards its enhancement in patients with comorbid pathology (df=3, χ^2=8.772, p=0.033).

Taking into account the fact that erosive esophageal lesions were observed in a small number of patients, who also had different grades of esophagitis, which made statistical processing impossible. Thus, samples of patients

with a non-erosive form were chosen for histological study: 35 cases of isolated GERD and 50 – of GERD and AIT comorbidity.

The following histological peculiarities of esophageal mucosal epithelium were noticeable during the examination of biopsy material in both groups of patients. First of all, significant changes in multilayer squamous epithelium were noted: quite often stratification of its layers was disturbed, basal zone hyperplasia and elongation of stromal papillae were noted.

As a rule, the thickness of the basal layer is formed by a few cells and is less than 15% of the total thickness of the epithelium, and the length of the papillae does not exceed 50%[16-18]. In the studied groups, the thickness of the basal epithelium zone was greater both in absolute value and in relation to the total thickness of the epithelium. (Tab. II)

It should be noted that in GERD and AIT group, the epithelium thickening was mainly due to the basal layer, which was 25.1%, whereas in GERD isolated group this index was close to the physiological norm at the level of 17.3% (Fig.1).

During the histological examination, it was noticed an increase in the size of the nuclei, their hyperchromicity, the presence of physiological mitoses, which also indicated the activation of regenerative processes. Characterizing histological changes in epithelial cells in patients with isolated GERD, we should note significant dystrophic and focal necrotic changes on the background of pronounced edema of the spinous and basal layers.

At the same time, in patients with GERD and AIT comorbidity, epithelial cells were polymorphic with cytoplasm vacuolization, some of them were sharply increased in size with signs of parenchymatous protein (hydropic) degeneration and nuclear dislocation to the cell periphery. The above changes in the epithelium were observed in combination with significant intercellular edema with loss of normal orientation of superficial epithelial cells, in some places with the presence of intercellular bridges.

Morphologically, a significant increase in the length of papillae was detected both in isolated GERD and in combined pathology. However, an intergroup comparison revealed that in patients with GERD and AIT the thickness of the basal epithelial layer and the length of connective tissue papillae was significantly greater (Tab.II).

It should be noted that the increased thickness of the basal layer may reflect the increased proliferative activity (intensification of regenerative processes) of its cells. The length of connective tissue papillae reached 75% of the epithelial layer, and its increase is most likely explained by secretion of inflammatory mediators, stimulating proliferation of fibroblasts, endothelium and smooth muscle cells. The submucosal layer showed morphological signs of fibrosis with sclerotic changes in the lamina propria with thickening of collagen fibers, which also can cause changes in the shape and length of villi.

The leukocytic infiltration in submucosa was less pronounced in the group with isolated GERD, where lymphocytes and macrophages predominated in the infiltrate. In the group of combined pathology, infiltration was more intensive and polymorphic, the presence of neutrophilic leukocytes, especially in foci of dystrophic and necrotic changes was determined, accumulation of eosinophils was observed in some preparations (Fig. 2).

Thus, the main morphological signs of reflux esophagitis in both groups were: basal layer hyperplasia; elongation of connective tissue papillae; intercellular edema with the intercellular space dilation; dystrophic changes with cytoplasm vacuolization, and in some places focal necrotic changes of epithelial cells; the presence of marked inflammatory infiltration in submucosa layer. In spite of the fact that above mentioned signs were noticed both in patients with a combination of GERD and AIT and with isolated GERD, the intergroup comparison revealed some significant differences in these values (Tab. III).

Thus, epithelium basal layer hyperplasia, dystrophic changes and epithelial edema, elongation of papillae and dilation of intercellular space were significantly more frequent in the group with comorbid pathology. Besides, patients with GERD and AIT had a higher frequency of inflammatory leukocytic infiltration (78%) combined with signs of submucosal fibrosis (72%) in comparison with the group of isolated GERD – 62.9% та 54.3% respectively, however, these differences were not significant.

DISCUSSION

Research data of recent years indicate significant progress in the study of pathogenetic links, pathways and mechanisms of GERD progression, naturally accompanied by optimization of diagnostic approaches and therapeutic strategy. Therefore, in recent years, the increasing attention of scientists is attracted by the comorbid course of GERD with other diseases. This problem is of particular importance when combining with autoimmune pathology, which is usually associated with the development of systemic inflammation that can act as an additional factor of GERD progression. The development of GERD in young people is of great importance, since the formation of chronic pathology at an early age, especially in the presence of such " insidious" companion as AIT, may be accompanied by rapid progression of nosology and early development of complications.

However, at the current stage of medical science development, there are practically no studies of pathomorphological features of the esophagus in young patients with GERD and AIT comorbidity.

The presented study identified the significant dilation of the intercellular space in patients of both groups, which is considered by the overwhelming majority of scientists to be a classic marker of GERD. At the same time, some authors believe that dilation of the intercellular space in the esophageal epithelium is not a pathognomonic sign of GERD and can be observed in patients with psychological stress [19], which is relevant to the student population and may have been an additional trigger in this category of patients. In addition, according to Lori A Orlando et al., dilation of the intercellular space may be a sign of epithelial barrier disorder due to increased intercellular permeability [20].

The study of Jeremy R Parfiftt et al. compared the histological picture of esophageal mucosa in GERD and in eosinophilic esophagitis and showed the commonality of certain changes for both nosologies – elongation of villi, hyperplasia of the mucosal basal layer and intercellular edema [21]. Meanwhile, the key differential diagnostic criteria for eosinophilic esophagitis are the presence of 15 or more eosinophils in the field of view, eosinophilic micro abscesses, superficial eosinophilic infiltrates and eosinophil degranulation. Eosinophilic esophagitis is known to be an immune-mediated inflammatory disease of the esophagus, so the presence of eosinophil accumulation in selected preparations of patients with comorbid pathology may have been a consequence of the influence of an additional autoimmune inflammatory component brought on by AIT.

It should be noted that eosinophils are physiologically present in the GI tract, but their presence in the esophagus is pathological. Eosinophilic infiltration leads to thickening of the esophageal mucosa, basal layer hyperplasia, and villous deformity [22]. In addition, eosinophils are able to secrete cytotoxic granules, directly act on neurons and damage axons of the esophageal sphincter muscle fibers. The latter leads to decreased tone and progression of GERD [23,24]. The presence of chronic inflammation in the mucosa and submucosa layer of the esophagus also leads to the activation of fibroblasts and causes the formation of fibrosis and esophageal stenosis [25].

CONCLUSIONS

GERD and euthyroid AIT comorbidity in the student population is not associated with the prevalence of an erosive form of GERD, but it is accompanied by a statistically significant redistribution of esophagitis grades towards its aggravation.

The presence of concomitant euthyroid AIT in patients with non-erosive GERD leads to statistically more pronounced disorganization of esophageal mucosal epithelium due to basal layer hyperplasia, edema of spinous and basal layers, dilation of intercellular space, elongation and deformity of connective tissue papillae.

Signs of submucosal fibrosis, marked dystrophic and in some places, necrotic changes in epithelial cells and inflammatory infiltration in the submucosal layer should also be considered as characteristic features of GERD in the examined patients, meanwhile, the presence of concomitant euthyroid AIT non significantly, but increases the expressiveness of these deviations.

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Conflict of interest:
The Authors declare no conflict of interest.

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ORIGINAL ARTICLE

PECULIARITIES OF DISTRIBUTION OF ANTIBIOTIC RESISTANT STRAINS OF *E. COLI - E. FAECALIS* ASSOCIATION IN THE UROGENITAL TRACT OF PREGNANT WOMEN

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ABSTRACT

The aim: To investigate the prevalence of antibiotic-resistant strains from the association of *E. coli - E. faecalis* in the urogenital tract of pregnant women.

Materials and methods: Used bacteriological method of sectoral culture of urine on nutrient media and identification of strains to the species. The susceptibility of strains to antibiotics was determined by disk-diffusion method, the interpretation of results - according to current EUCAST recommendations. Statistical processing was performed in MS Excel (Analysis of variance (ANOVA)).

Results: The number of resistant to cefuroxime, cephalexin, nitrofurantoin, norfloxacin and trimethoprim uropathogenic strains of Escherichia coli does not change depending on the monostrain and associated strain of *E. coli* from the urine of pregnant women in Dnipro. It was found that the differences in the number of fosfomycin-resistant uropathogenic strains of *E. coli* depending on the type of culture - the number of fosfomycintolerant urostrains *E. coli* is 2 times higher among the associated strains, compared with monostains of the studied microorganism. The number of uropathogenic strains of *E. faecalis* resistant to ampicillin, trimethoprim, nitrofurantoin and norfloxacin does not change depending on the type of culture isolated from the urine of pregnant women in Dnipro.

Conclusions: The symbiotic type of existence of two representatives of the normal intestinal flora on the uroepithelium of pregnant women may be associated with the development of *Escherichia coli* antibiotic resistance only to fosfomycin compared with monoinfection caused by each of these microorganisms.

KEY WORDS: antibiotic resistance, pregnancy, urogenital tract, urine, fosfomycin-resistans

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INTRODUCTION

Uncontrolled use of ABD in everyday life, the lack of a well-established prescription release in pharmacies, leads to the creation of a reservoir of resistance determinants among pathogenic and, above all, opportunistic bacteria [1-3]. Bacterial resistance to antibiotics is considered one of the main modern problems of clinical microbiology and general therapeutic activity of clinicians. The development of bioengineering and modern biotechnological progress contribute to the discovery and development of new antibacterial drugs (ABD) in the pharmaceutical market in Ukraine and the world, but not all antibiotics are widely used clinically [4, 5]. The problem with antibiotic resistance is primarily that bacteria have a high capacity for phenotypic and genetic variability. They are able to adapt even to those ABD that are considered universal and starting in the treatment of bacterial infections [6, 7]. Bacteriologists and epidemiologists are increasingly registering strains of Escherichia coli and Enterococcus faecalis that become resistant to antibiotics. These microorganisms are opportunistic pathogens for humans and are in close symbiosis with our body, playing a role in the digestive system and the creation of colonization resistance of the gastrointestinal mucosa [2, 8, 9]. Usually these microorganisms are considered to be representatives of the normal intestinal flora, however, some strains of these bacteria are already polyresistant. This has no effect on the breakdown function of nutrients, but when immunoreactivity is impaired, they can alter loci of residence, causing infections such as urinary tract infections (UTI) in pregnant women. Given that Escherichia coli and Enterococcus faecalis are components of the biofilm of the intestinal mucosa, have intercellular contact in symbiosis, are partly represented by multidrug-resistant strains, there is an increased risk of complex superinfections. The study of biofilms and the association of bacteria contributes to the development of certain provisions on their antibiotic sensitivity and contributes to a scientifically sound revision of UTI treatment protocols in pregnant women, taking into account the dose of ABD, the behavior of bacteria in biofilms under different drug concentrations and the establishment of antibiotic resistance [10].

THE AIM

The objectives of the study of the spread of antibiotic-resistant strains from the association of *E. coli - E. faecalis* in the urogenital tract of pregnant women are to study antibiotic resistance to ABD isolates and to establish differences between antibiotic resistance of *E. coli* and *E. faecalis* isolates under conditions of monostrains and association strains.

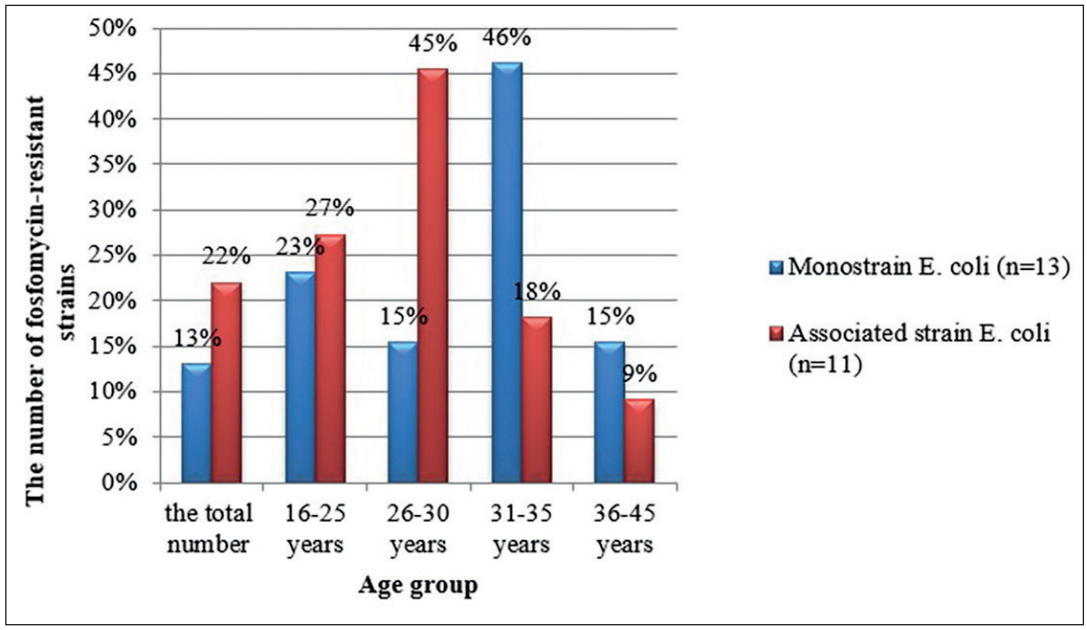

Fig. 1. Frequency of detection of fosfomycin-resistant strains of *E. coli* in women of different ages

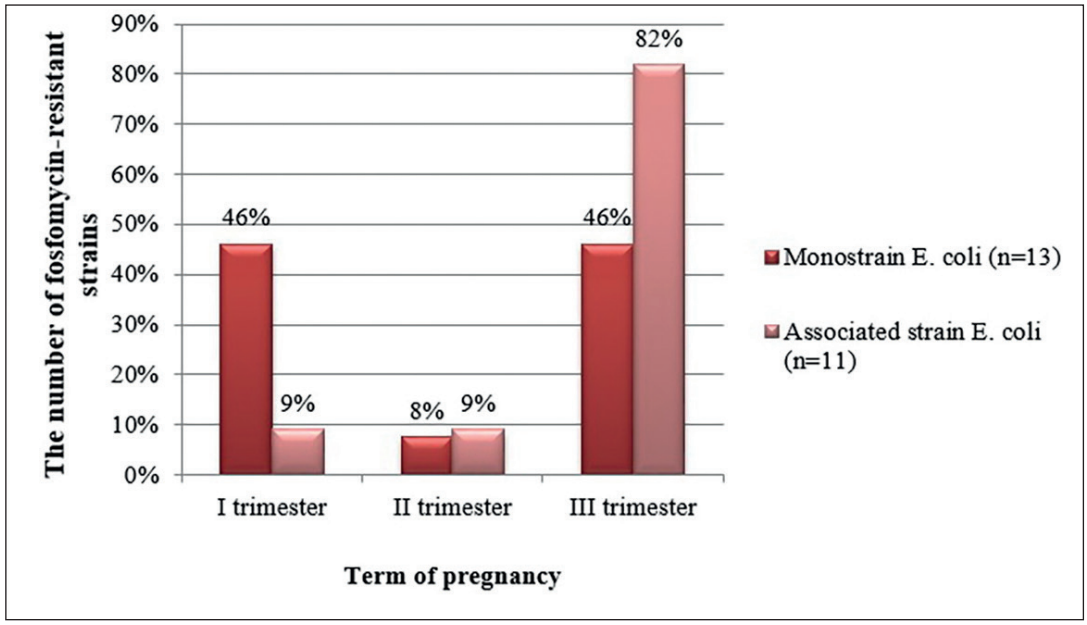

Fig. 2. Frequency of detection of fosfomycin-resistant *E. coli* strains in women of different groups depending on the gestational age

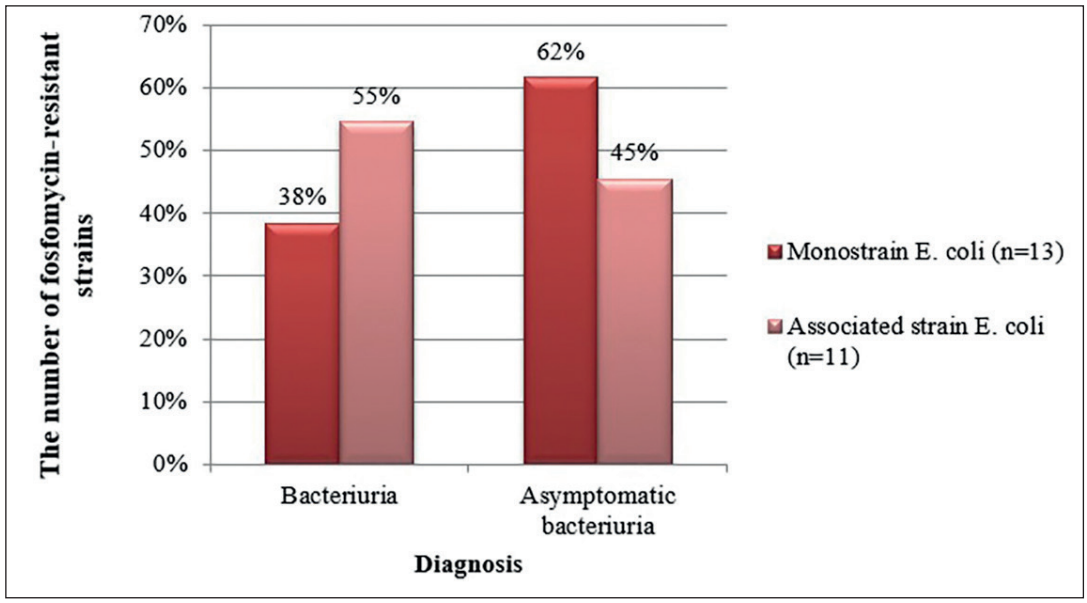

Fig. 3. Frequency of detection of fosfomycin-resistant strains of *E. coli* depending on the diagnosis

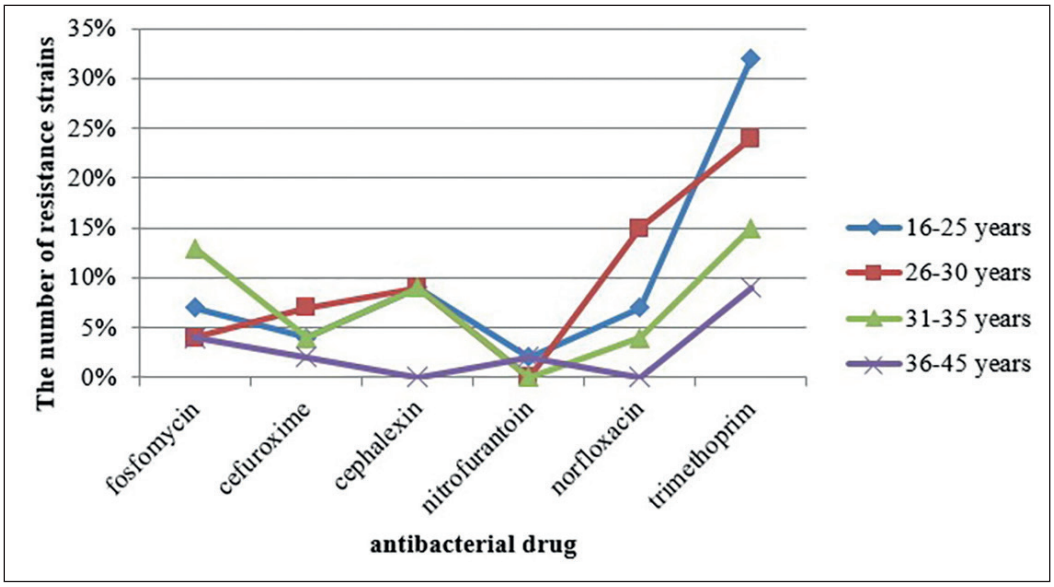

Fig. 4. Frequency of detection of antibiotic-resistant *E. coli* monostrains (n = 45) in different age groups of pregnant women

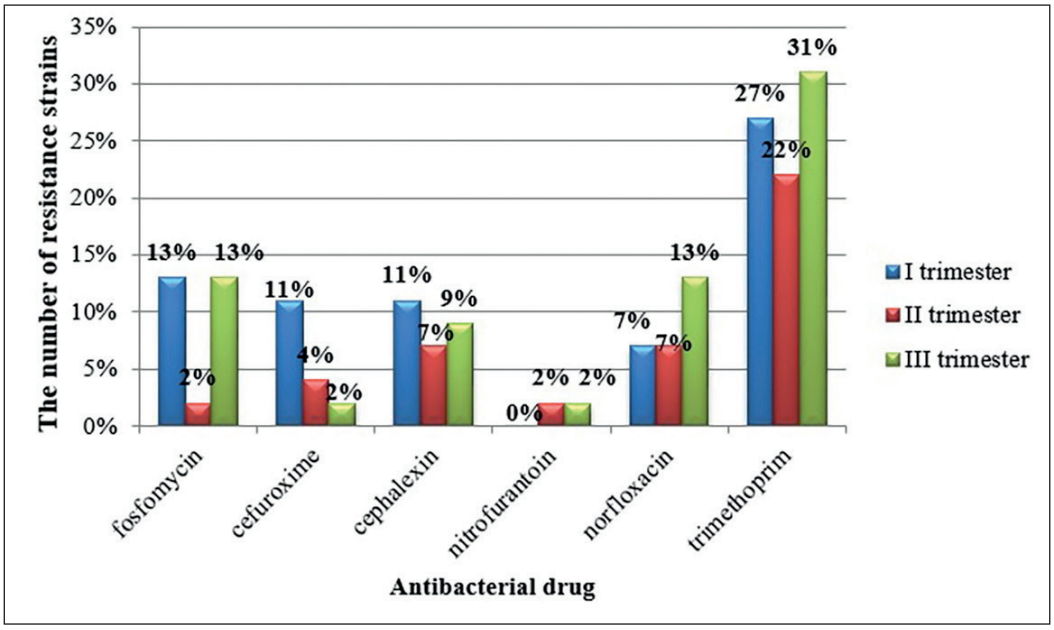

Fig. 5. Frequency of detection of antibiotic-resistant strains of *E. coli* (n = 45) depending on the gestational age

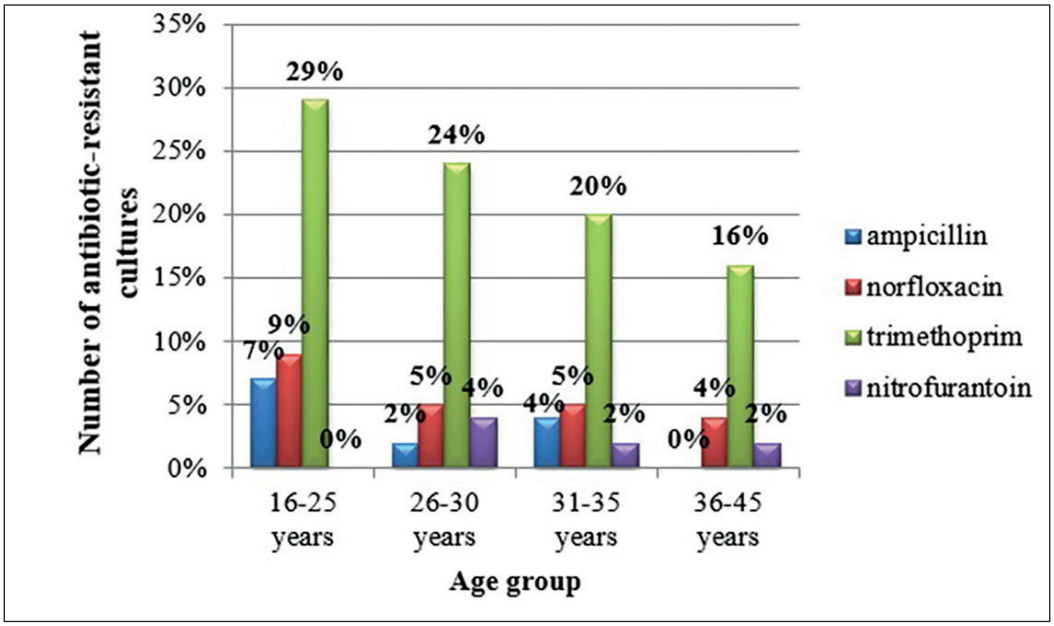

Fig. 6. Frequency of detection of antibiotic-resistant strains of *E. faecalis* (n=55) in different age groups of examined pregnant women

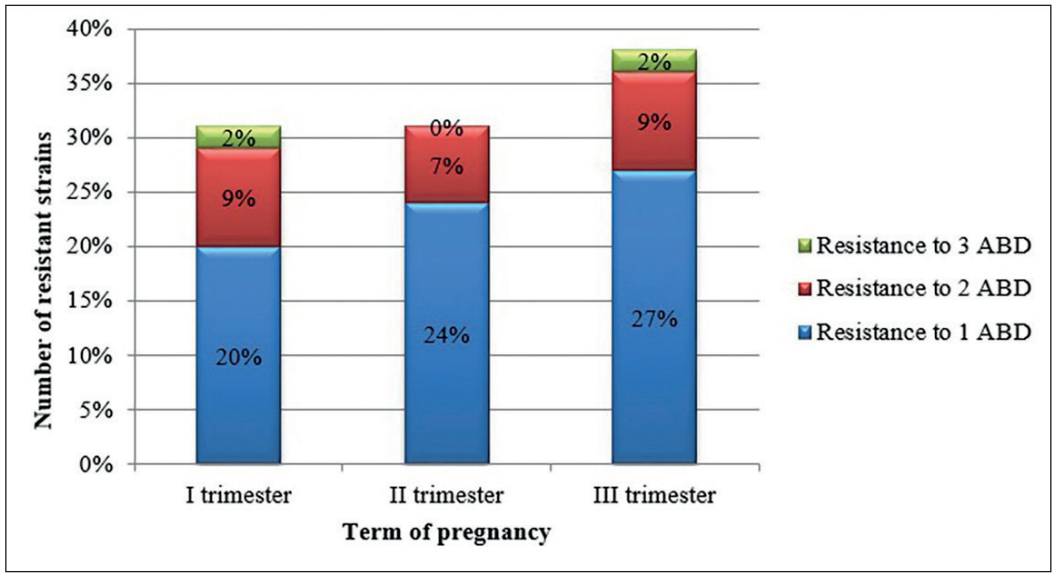

Fig. 7. Frequency of detection of mono- and polyresistant strains of *E. faecalis* (n=55) in women of the examined groups at different stages of pregnancy

MATERIALS AND METHODS

250 urine samples (v = 100 ml) were taken from 250 women for the study. Selection was performed in sterile disposable urine containers. Delivery of biomaterial to the laboratory was not more than 2 hours. Primary culture of urine for sterility was performed by the method of sector cultures on agar Columbia with 5% sheep blood (Grasko, Poland) and 0.25% glucose broth. Petri dishes and tubes with plates on lamellar and liquid nutrient media were incubated at 37 ° C for 18-24 hours. The next day we studied the morphological, tinctorial properties of selected strains, put biochemical tests to identify E. coli and E. faecalis. Incubation of tubes with nutrient media was performed at 37 ° C for 18-24 hours. On the third day, the results of biochemical tests were taken into account, the susceptibility of selected strains of microorganisms was determined by the disk-diffusion method in accordance with the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The results of antibiotikograms of selected strains of E. coli (n = 100), E. faecalis (n = 100) and association E. coli-E. faecalis (n = 50) from the urine of pregnant women were selected for the study. Statistical data processing was performed using ANOVA analysis of variance to find the dependence in the obtained data by studying the significance of differences in averages and correlations.

RESULTS

According to the results of analysis of variance ANOVA growth retardation zones for each antibacterial drug monostrain *E. coli* and its strain from the association *E. coli - E. faecalis* found a significant difference in the two samples of growth retardation zones to fosfomycin - the criterion of significance (P-value) is <0.05, which indicates the presence of statistically significant differences. The criterion of reliability of individual samples of growth retardation zones to cefuroxime, cephalexin, nitrofurantoin, norfloxacin and trimethoprim of two strains of *Escherichia coli* is P> 0.1, which indicates the absence of differences in them.

According to the results of analysis of variance ANOVA growth retardation zones for each antibacterial drug mono strain *E. faecalis* and its strain from the association *E. coli-E. faecalis*, no differences were found in the respective samples - criterion P> 0.1 (for ampicillin, trimethoprim, nitrofurantoin and norfloxacin).

It was found that the number of fosfomycin-resistant mono strains of *E. coli* isolated from the urine of pregnant women is 13 cultures (13% of 100 strains studied), and associated strains of *E. coli* - 11 cultures (22% of the 50 studied strains), which in 1,7 times more.

The number of fosfomycin-resistant strains of *E. coli* depending on the type of culture and age group of pregnant women is presented in Fig. 1.

According to the results of correlation analysis, there is no dependence (coefficient is 0) between the number of fosfomycin-resistant *E. coli* monostains and age, but there is an inverse relationship (coefficient -0.6) between the number of fosfomycin-resistant associated strains of *E. coli* and age that indicates a decrease in the number of such strains depending on the increase in the age category of pregnant women. It was found that among pregnant women aged 16-25 years, the number of fosfomycin-resistant monosteps of *Escherichia coli* isolated from urine is 3 strains (23% of 13 resistant strains), associated *E. coli* - 3 strains (27% of 11 resistant strains). Among pregnant women aged 26-30 years, the number of fosfomycin-resistant monostrains of *Escherichia coli* isolated from urine is 2 strains (15% of 13 resistant strains), associated *E. coli* - 5 strains (45% of 11 resistant strains).

Among pregnant women aged 31-35 years, the number of fosfomycin-resistant monostrains of *E. coli* isolated from urine is 6 strains (46% of 13 resistant strains), associated with *E. coli* - 2 strains (18% of 11 resistant strains).

Among pregnant women aged 36-45 years, the number of phosphomycin-resistant monostrains of *Escherichia coli*

isolated from urine is 2 strains (15% of 13 resistant strains), associated *E. coli* - 1 strain (9% of 11 resistant strains).

Thus, the largest number of fosfomycin-resistant monostrains of *Escherichia coli* (45%) is observed among pregnant women aged 26-30 years, and associated strains of *E. coli* (46%) - among pregnant women aged 31-35 years.

The number of fosfomycin-resistant strains of *E. coli* excreted in the urine, depending on the type of culture and trimester of pregnancy is presented in Fig. 2.

Correlation analysis showed no relationship (coefficient 0) between the number of fosfomycin-resistant *E. coli* monostrains and gestational age, but there is a straightforward relationship (coefficient 0.8) between the number of fosfomycin-resistant *E. coli* strains of pregnancy and trimester pregnancy that is indicating an increase in the number of such strains depending on the increase in gestational age.

It was found that the number of fosfomycin-resistant uropathogenic *Escherichia coli* strains in the first and third trimesters of pregnancy is 6 strains (46% of 13 resistant strains), in the second trimester - 1 strain (8%).

The number of fosfomycin-resistant associated strains of *E. coli* in the first and second trimesters of pregnancy is 1 strain (9% of 11 cultures), in the third trimester - 9 strains (82%).

The number of fosfomycin-resistant strains of *E. coli* isolated from the urine of pregnant women, depending on the type of culture and diagnosis is presented in Fig. 3.

The number of fosfomycin-resistant monostrains of *E. coli* isolated from the urine of pregnant women with bacteriuria is 5 strains (38% of 13 cultures), associated strains - 6 cultures (55% of 11 strains).

The number of fosfomycin-resistant monostrains of *E. coli* isolated from the urine of pregnant women with asymptomatic bacteriuria is 8 strains (62% of 13 cultures), associated strains - 5 cultures (45% of 11 strains).

The distribution of antibiotic-resistant monostrains of *E. coli* depending on the antibacterial drug and age group is presented in Fig. 4

It was found that among fosfomycin-resistant monostrains of *E. coli* (n = 13) isolated from the urine of pregnant women, there is no correlation (coefficient - 0.06) between increasing age and the number of resistant isolates to this ABD, of which the largest number - 6 strains (13% of the 45 isolates) were isolated among pregnant women aged 31-35 years.

Among resistant *Escherichia coli* to cefuroxime (n = 8), there is a negative correlation (coefficient of -0.6) between the number of such strains and age, namely the number of resistant strains decreases depending on the growth of age among pregnant women.

The correlation between the age of pregnant women and the number of resistant urostrains of *E. coli* to cephalexin (n = 12) is -0.7. It was found that among women aged 16-35 years the number of such isolates is distributed evenly (4 strains) between each age group, except for pregnant women aged 36-45 years, among which no resistant to Escherichia coli strain was isolated.

The number of *Escherichia coli* resistant to nitrofurantoin is 2 strains isolated from pregnant women of I and IV age groups.

There is a negative correlation between the number of norfloxacin-resistant urostrains of *E. coli* (n = 12) and the age of pregnant women, that is the number of resistant strains decreases with age. The largest number of such strains (7 cultures (15% of 45 isolates) was isolated from the urine of pregnant women aged 26-30 years).

Correlation analysis of the data showed that there is a strong negative relationship between the number of trimethoprim-resistant *Escherichia coli* and the age group of pregnant women. The correlation coefficient is -0.9. The number of such strains for women aged 16-25 years is 14 strains (32% of 45 cultures), aged 26-30 years - 11 cultures (24%), aged 31-35 years - 7 strains (15%) and aged 36- 45 years - 4 strains (9%).

The distribution of antibiotic-resistant monostrains of *E. coli* depending on the antibacterial drug and the trimester of pregnancy is presented in Fig. 5.

According to the results of correlation analysis, it was found that the number of fosfomycin-resistant monostains of *E. coli* (coefficient is 0) does not change with increasing gestational age, but from 45 strains 6 isolates (13%) were excreted in the urine of pregnant women in the first and third trimesters.

There was a negative correlation (coefficient of -1) of the number of *Escherichia coli*-resistant strains to cefuroxime and cephalexin depending on the increase in gestational age, namely, the larger the trimester of pregnancy, the less resistant strains to these cephalosporins are released. The number of *E. coli* urostrains resistant to cefuroxime in the first trimester is 5 cultures (11% of 45 resistant isolates), in the second trimester - 2 cultures (4%), in the third trimester - 1 culture (2%).

The correlation between the number of norfloxacin-resistant *Escherichia coli* strains and trimesters of pregnancy was identified as straightforward (coefficient is 1) - the larger the trimester, the greater the number of resistant *E. coli* monostrains (I trimester - 3 strains (7% of the total), III trimester - 6 strains (13%)).

There is a straight line correlation (coefficient is 1) in the number of trimethoprim-resistant *E. coli* monostrains depending on the growth of the gestational age, that is the larger trimester of pregnancy, the more allocated resistant strains to this ABD. The number of resistant to trimethoprim *E. coli* in the first trimester is 12 cultures (27% of 45 resistant isolates), the second trimester - 10 cultures (22%), the third trimester - 14 cultures (31%).

The distribution of antibiotic-resistant urostrains of *E. faecalis* (n = 55) depending on the age group of pregnant women and ABD is presented in Fig. 6

According to the results of correlation analysis, an inverse relationship (correlation coefficient is -0.8) was found between the number of ampicillin-resistant *E. faecalis* monostrains and the age of pregnant women, which indicates a decrease in the number of ampicillin-resistant strains depending on age. The number of ampicillin-resistant

E. faecalis isolated from the urine of pregnant women aged 16-25 years is 4 strains (7% of 55 resistant strains), from 26-30 years - 1 strain (2%), from 31-35 years - 2 isolates (4%).

The relationship between the number of norfloxacin-resistant *E. faecalis* urostrains and the age of pregnant women is a reverse linear trend (correlation coefficient is -0.8), indicating a decrease in the number of norfloxacin-resistant enterococcal strains depending on age. The number of norfloxacin-resistant cultures of fecal enterococci isolated from the urine of pregnant women aged 16-25 years is 5 strains (9% of 55 isolates), from 26-30 years - 3 strains (5%), from 31-35 years - 3 strains 5%), from 36-45 years - 2 cultures (4%).

There is a rapid trend and an inverse correlation (coefficient of -0.9) between the number of trimethoprim-resistant *E. faecalis* monostrains and the age of pregnant women, indicating a clear tendency to decrease trimethoprim-resistant enterococcal urostrains depending on the increase in the age of pregnant women. The number of trimethoprim-resistant urocultures of *E. faecalis* isolated from the urine of women aged 16-25 years is 16 strains (29% of 55 resistant isolates), from 26-30 years - 13 strains (24%), from 31-35 years - 11 cultures. 20%), from 36-45 years - 9 strains (16%).

There was no correlation (coefficient is -0.3) between the number of resistant strains to nitrofurantoin and the age of pregnant women. The number of resistant to nitrofurantoin strains of *E. faecalis* isolated from the urine of pregnant women aged 26-30 years - 2 strains (4%), from 31-35 years - 1 strain (2%), from 36-45 years - 1 isolate (2 %).

The frequency of isolation of antibiotic-resistant monostrains of *E. faecalis* depending on the trimester of pregnancy and the number of ABP to which antibiotic tolerance has been registered is presented in Fig. 7.

According to the results of correlation analysis of the dependence of the number of *E. faecalis* urostrains resistant to 1 ABD (n = 39) and the gestational age, a strong straightforward relationship was established (correlation coefficient is 1), which indicates a rapid increase in the number of such strains. Among pregnant women, the number of resistant to 1 ABD enterococci in the first trimester of pregnancy is 11 cultures (20% of 55 isolates), in the second trimester - 13 strains (24%), in the third trimester - 15 strains (27%).

The number of resistant to 2 ABP monostrains of *E. faecalis* (n = 14) among pregnant women in the first trimester of pregnancy is 5 cultures (9% of 55 isolates), in the second trimester - 4 strains (7%), in the third trimester - 5 strains (9%).

The number of multidrug-resistant urostrains of *E. faecalis* isolated from pregnant women in the first trimester is 1 culture (2%), in the third trimester - 1 strain (2%).

DISCUSSION

Ramos et al. established that of the 50 strains of *Escherichia coli* isolated from the urine of pregnant women from Sweden, 2 strains (4%) are resistant to cephalexin, 2 strains (4%) - to norfloxacin, 25% - to trimethoprim. The authors found that from the urine of pregnant women from Uganda, the number of E. coli strains resistant to cephalexin is 12 strains (21%), to norfloxacin - 13 strains (23%), to trimethoprim - 49 strains (88%). From the urine of pregnant women in Vietnam, researchers isolated 4 strains (9%) of Escherichia coli resistant to cephalexin, 15 strains (36%) to norfloxacin, 29 strains (70%) to trimethoprim [11]. Comparing the obtained data of own research it is established:

- the number of cephalexin-resistant strains of *E. coli* (12 strains) corresponds to the data obtained from women from Vietnam, lower than the number of such strains isolated from women from Uganda, and higher than the number of strains isolated from the urine of women from Sweden;
- the number of *E. coli* strains resistant to norfloxacin (12 strains) is higher than the number of such strains excreted in the urine of pregnant women from Sweden, and lower than the number of norfloxacin-resistant strains of *Escherichia coli* excreted in the urine of women from Uganda and Vietnam;
- the number of trimethoprim-resistant strains of *E. coli* (36 strains) correlates with the obtained data of the authors - resistance of uropathogenic *Escherichia coli* to this antibacterial drug has high values.

Ballesteros-Monrreal et al. found that among pregnant women in Sonora (Mexico) isolated 50 strains of uropathogenic *E. coli*, of which 4% are resistant to fosfomycin, 82% - to cefuroxime, 40% - to nitrofurantoin, 56% - to norfloxacin, 64% - to trimethoprim [12]. In comparison with own data, it is established:

- the number of fosfomycin-resistant *Escherichia coli* (n = 13) isolated from the urine of pregnant women in Dnipro is 9% higher than among such a contingent of the state of Sonora (Mexico);
- the number of cefuroxime-resistant growths of *E. coli* is 10 times lower among pregnant women in Dnipro;
- the number of nitrofurantoin-resistant urostrains of *Escherichia coli* is 38% lower than the data obtained among pregnant women in the state of Sonora;
- the number of norfloxacin-resistant urostrains *Escherichia coli* is 44% lower than the results obtained in the state of Sonora;
- the number of trimethoprim-resistant urostrains *E. coli* is 2 times higher, but there is a high resistance to this ABD.

CONCLUSIONS

Thus, the results of the study of antibiotic resistance strains of the association of *E. coli - E. faecalis* partially confirmed the hypotheses:

1. The number of resistant to cefuroxime, cephalexin, nitrofurantoin, norfloxacin and trimethoprim uropathogenic strains of *E. coli* does not change depending on the monostep and associated strain of *Escherichia coli* from the urine of pregnant women in Dnipro.
2. It was found that the differences in the number of fosfomycin-resistant uropathogenic strains of *E. coli* depending on the type of culture - the number of fos-

fomycintolerant strains of *Escherichia coli* is 2 times higher among the associated strains, compared with monostrains of the studied microorganism.

3. The amount of uropathogenic strains of *E. faecalis* resistant to ampicillin, trimethoprim, nitrofurantoin and norfloxacin does not change depending on the type of culture isolated from the urine of pregnant women in Dnipro.

Thus, the symbiotic type of existence of two members of the normal intestinal flora on the uroepithelium of pregnant women may be associated with the development of *Escherichia coli* antibiotic resistance only to fosfomycin compared with monoinfection caused by each of these microorganisms.

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ORIGINAL ARTICLE

CLINICAL AND NEUROPHYSIOLOGICAL PARALLELS OF THE BRACHIAL PLEXOPATHY IN THE STRUCTURE OF NEUROGENIC THORACIC OUTLET SYNDROME

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ABSTRACT

The aim: Was assessment of the neurophysiological data and features of clinical picture in patients with neurogenic thoracic outlet syndrome (TOS).

Materials and methods: 103 patients with upper extremity pain and/or paresthesia or hypotrophy, or a combination of these symptoms were examined. The examination algorithm included: cervical spine radiography, cervical spine and brachial plexuses magnetic resonance imaging (MRI), upper extremity soft tissues and vessels ultrasonic examination, stimulation electroneuromiography with F-waves registration.

Results: Neurogenic TOS was diagnosed in 29 patients. A significant relationship between the following complaints and neurophysiological parameters was observed: pain, numbness during physical activity and decreased medial anrebrachial cutaneous nerve response amplitude by ≥25% compared to the contralateral side; hypothenar hypotrophy and decrease of ulnar nerve motor/sensory response amplitude; the 4-5th fingers hypoesthesia and decrease of ulnar nerve sensory response amplitude.

Conclusions: Medial antebrachial cutaneous nerve amplitudes asymmetry indices of ≥25% or lack of response may be considered to be a marker of true neurogenic TOS.

KEY WORDS: brachial plexopathy, upper extremity pain, thoracic outlet syndrome, neurophysiological diagnostics

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INTRODUCTION

Thoracic outlet syndrome (TOS) involves compression of the subclavian artery, vein, brachial plexus in one of the following sites: spatium interscalenum, spatium costoclaviculare or the space behind the pectoralis minor muscle tendon to the processus coracoideus fixation site [1-3]. It should be noted that the neurovascular bundle lesion at the scalene triangle level is characterized arterial and neurogenic symptoms, because the subclavian vein joins these structures after leaving the interscalene triangle. The term TOS was introduced by R. M. Peet in 1956 and despite the long history of this nosology, its clear diagnostic criteria are not established till nowadays. This situation has arisen probably due to the presence of non-specific complaints, which may be misinterpreted as traumatic, orthopedic or vertebrogenic pathology.

According to compression of vessels and/or nerve fibers TOS is classified into vascular and neurogenic. The prevalence of neurogenic TOS is about 95% among all TOS forms. Neurogenic TOS is therefore divided into true neurogenic and disputed [3-5].

The true neurogenic TOS etiological factors are classified into congenital and acquired. Congenital anomalies are further divided into bone and fibromuscular anomalies [1-6]. A combination of congenital and acquired anomalies is often observed.

The true neurogenic TOS usually manifests with pain, hypoesthesia, paresthesias of localization, typical for the brachial plexus level involvement, gradually progressive atrophies, and is accompanied by pathological changes in instrumental examination methods findings, and medical history of cervical and thoracic injuries [4, 7-9]. Clinical picture of disputed TOS is similar to the true neurogenic one, but there are no pathognomonic changes found in additional examination methods results.

THE AIM

The aim of study was to analyze the clinical and neurophysiological features of brachial plexopathy in the neurogenic TOS structure in order to formulate the diagnostic algorithm.

MATERIALS AND METHODS

The study was performed on the basis of the neurology and neurosurgery department of Ivano-Frankivsk National Medical University during 2017 and the Research and Practical Center of neurophysiological studies during 2018-2020. Totally there were 103 patients examined with upper extremity pain and/or paresthesia or hypotrophy, or a combination of these symptoms. The patients' mean age of was 37.39±5.17 years, 61 (63%) of them were females.

The algorithm of the planned examination included: cervical spine radiography, cervical spine and brachial plexuses magnetic resonance imaging (MRI) (Siemens 1.5

T), upper extremity soft tissues and vessels ultrasonic examination, stimulation electroneuromiography (ENMG) with F-waves registration (Neurosoft, Neuro EMG-micro, 2004). Doppler ultrasonography was performed in the position with the upper extremity lowered along the torso and during the Adson's, Eden's, Wright's and EAST provocation tests.

Exclusion criteria:

- cervical spine discoradicular conflict, myelopathy, syringomyelia (verified by MRI);
- tunnel neuropathy, polyneuropathies (diagnosed by ENMG);
- traumatic/orthopedic pathology (verified after orthopedist consultation with the radiological examination (X-ray / MRI and ultrasonic study of the musculoskeletal system);
- upper extremities blood vessels thrombosis (according to ultrasonic examination data);
- neoplastic and postradiation lesion of the chest and upper extremity girdle.

After the examination and data comparison with the inclusion/exclusion criteria 29 patients remained under our supervision. Statistical processing of the study results was performed with the use of computer with a software environment for statistical calculations " R " (R Core Team RR . A language and environment for statistical computing. R Foundation for statistical computing [Internet]. 2018. Available from: URL: https:// www.r-project.org/).

RESULTS

Complaints on pain occurred in 21 (72.4%) cases; pain was localized in the rhomboid muscles, anterior chest surface, neck area, brachioscapular area, forearm, hand.

The abovementioned complaints mostly corresponded to the dominant arm, which was observed in 17 (80.9%) patients. In addition, the pain which occurred during physical activity, persisted also after the termination of activity.

26 (89.6%) patients complained on numbness, which in 4 (15.4%) cases was permanent, in 4 (15.4%) cases it was positional, in 5 (19.2%) patients numbness occurred during physical activity, 6 (23.1%) patients experienced it during nighttime, and 7 (26.9%) patients noted a combination of complaints on numbness in certain position and during nighttime.

The feeling upper extremity weakness was noted by 17 (58.6%) patients; 7 (41.1%) of them complained on the 4^{th}-5^{th} fingers, 4 (23.5%) patients felt it in the entire hand, in 6 (35.3%) cases it involved all muscles of the upper extremity. In order to objectify the complaints, the muscle strength of the upper extremity was assessed; the strength decrease was detected in 4 (23.5%) cases, namely in m. abductor pollicis brevis and m. interosseus dorsalis I.

Complaints on hand fine motor skills impairment were observed in 13 (44.8%) cases, and were objectively detected in 3 (10.3%) patients. The feeling of hand discomfort bothered 5 (17.2%) patients.

In neurological status hypothenar hypotrophy was observed in 2 (6.8%) cases; in 1 (3.4%) patient thenar, hypothenar and interosseous muscles hypotrophy were observed. Triceps hyporeflexia on the symptomatic side was observed in 1 (3.4%) patient.

Skin hypoesthesia in the 4^{th}-5^{th} fingers along was determined in 4 (13.8%) patients; in 3 (10.3%) cases it included the 4^{th}-5^{th} fingers and the ulnar aspect of forearm.

Supraclavicular region palpation was painful in 5 (17.2%) patients, and in 2 (6.9%) cases it was accompanied by numbness in comparison with the asymptomatic extremity. Intrescalene trigon palpation elicited pain in 4 (13.7%) cases, palpation of the pectoralis minor muscle projection site was painful in 1 (3.4%) patient.

Raynaud's syndrome was observed in 6 (20.6%) cases; it was characterized by presence of symptoms only on the symptomatic side, which differs from the primary Raynaud's syndrome. The majority of authors tend to think that Raynaud's syndrome is a manifestation of the vascular TOS variant [7]. Due to exclusion of the vascular TOS from out study it may be considered to be its secondary variant caused by irritation of the brachial plexus sympathetic fibers. R. T. Alekperov (2014) mentioned the possibility of the primary Raynaud›s syndrome misdiagnosis in case of TOS [10], which leads to inadequate treatment tactics.

Bone abnormalities were radiologically diagnosed. In 3 (10.4%) patients an additional cervical rib was detected; in 2 (6.9%) cases the C7 transverse processus elongation up to 20 mm and 23 mm (N=13-17 mm) was found out; in 1 (3.4%) patient the costoclavicular space narrowing due to the formation excessive osteocallus formation after clavicular injury was detected. Gruber (1869) suggested classification of cervical ribs into 4 groups, where the 3^{rd} and 4^{th} groups includes the cervical rib presence with the fixed fibrous cords, which are radiologically negative.

MRI revealed fibrous cord in the interscalene triangle in 1 (3.4%) person. V. K. Singh (2014) after evaluation of the MRI preoperative findings and postoperative results indicates that the sensitivity of this method is 41%, specificity is 33%.

In order to assess the neurophysiological examination data, the study included 20 apparently healthy individuals.

The neurophysiological investigation results are presented in table I; the parameters of the motor responses, the F - wave latency, the sensory responses amplitude and latency were studied.

The most informative parameters during the neurophysiological data comparison of patients with the upper extremity pain and AHI were the MACN indicators. All patients who were included into the study had unilateral complaints, so we decided to compare the obtained results with the same data of asymptomatic limb (Table II).

During evaluation of the medial antebrachial cutaneous nerve response amplitude in 5 patients the amplitude difference between two sides was ≥25%; in 3 of them the response could not be registered.

Data of significant relation between the complaints and ENMG parameters are presented in Table III.

Table I. ENMG parameters of patients with the neurogenic TOS and apparently healthy individuals

	UN		MN		MACN	
ENMG parameters	AHI	TOS	AHI	TOS	AHI	TOS
Motor response amplitude, μV	9.83 ± 2.71	6.48 ± 1.57	10.69 ± 2.64	8.32 ± 2.86	-	-
Sensory response amplitude, μV	7.36 ± 3.04	6.09 ± 3.62	10.53 ± 2.09	8.63 ± 2.47	18.7 ± 4.91	6.52 ± 3.84
Sensory response latency, ms	2.29 ± 0.3 3	2.11 ± 0.67	1.82 ± 0.78	2.05 ± 0.26	2.13 ± 0.28	2 .68 ± 0.48
F-wave latency, ms	28.91 ± 1.32	29.61 ± 4.78	27.01 ± 2.78	28.13 ± 1.64	-	-

Note: UN - ulnar nerve; MN - median nerve; MACN - medial antebrachial cutaneous nerve; AHI - apparently healthy individuals; TOS - patients with TOS.

Table II. ENMG parameters of medial antebrachial cutaneous nerve of symptomatic and asymptomatic upper extremity

N patient	Sensory response amplitude (μV)		Sensory response latency, ms	
	Symptomatic arm	Asymptomatic arm	Symptomatic arm	Asymptomatic arm
1	14	30	3.1	2.8
2	0	18	-	2.2
3	0	21	-	1.8
4	11	24	2.2	2.1
5	5	19	2.9	1.6
6	0	14	-	1.9
7	8	31	3.0	2.9
8	17	35	2.4	2.4

Table III. Significance of relation between the complaints and ENMG parameters

		Q	X^2	P
1.	**Pain intensification/occurrence after physical activity** the difference of the MACN response amplitudes D/S ≥ 25 %	0.54	2.8	<0.05
2.	**Hypoesthesia of the 4-5 fingers** the amplitude of the UN sensory response	0.54	2.8	<0.05
3.	**Numbness intensification/occurrence after physical activity** the difference of the MACN response amplitudes D/S ≥ 25 %	-0.71	3.0	<0.05
4.	**Hypothenar hypotrophy** the amplitude of the UN motor response	-0.71	3.0	<0.05
5.	**Hypothenar hypotrophy** the amplitude of the UN sensory response	-0.53	1.1	<0.05
6.	**Paresthesia of the ulnar aspect of forearm and hand** the difference of the MACN response amplitudes D/S ≥ 25 %	-0.51	3.8	<0.05

Note: UN - ulnar nerve; MACN - medial antebrachial cutaneous nerve.

After assessment of patients' complaints, disease history, neurological status and of instrumental examination methods results, the true neurogenic TOS was diagnosed in 13 (44.8%) patients, the disputed neurogenic TOS was diagnosed in 16 (55.2%) patients. There were no changes detected in ENMG in patients with disputed neurogenic TOS. In our opinion, the lack of neurophysiological changes in patients with disputed neurogenic TOS may be associated with technical difficulties in the brachial plexus stimulation in the supraclavicular area, which leads to difficulties in diagnosing local demyelination / conduction block, especially in case of excessive body weight and / or Kovtunovych's pseudotumor. In some patients with controversial neurogenic TOS complaints occurred only at a certain limb position or at certain movements and regressed after position changing, so apparently they were accompanied by a short-term nerve fiber compression and therefore absence of neurophysiological abnormalities.

Neurophysiological changes in patients with true neurogenic TOS were observed in 8 (61.5%) cases. A significant difference of the medial antebrachial cutaneous nerve sensory response between the symptomatic and asymptomatic extremities was observed in 87.8% cases; decrease by ≥25% compared to the asymptomatic limb or lack of response were considered to be pathological.

DISCUSSION

Serror (2002) was the first to suggest that the difference of the medial antebrachial cutaneous nerve amplitude re-

sponse of more than 50% should be considered abnormal [12]. B. E Tsao et al. (2014) provided data of a retrospective review of the neurophysiological parameters in patients with surgically verified true neurogenic TOS, where the difference of the sensory response amplitude was assessed, and amplitude of less than 50% compared to the contralateral limb was regarded as abnormal [11].

The role of neurophysiological studies in the diagnosis of neurogenic TOS is quite controversial. R. Rousseff et al. (2005) describe 20 surgically verified cases of neurovascular compression in the thoracic aperture, but differences from the normal neurophysiological parameters were determined in only 2 patients. B. Machanic (2008) described his own observation where 41 patients with neurogenic TOS were undergoing the ENMG examination and in 40 of them deviations from the normal parameters were observed; the latency, the medial antebrachial cutaneous nerve amplitude asymmetry of more than 50%, stimulation of C8 spinal root were assessed. Later all these patients underwent surgical treatment of the compression at the interscalene trigon level; diagnosis was confirmed intraoperatively in all patients. After surgery regression of all symptoms, increase of amplitude and decrease of latency of the medial antebrachial cutaneous nerve were observed in all of the patients.

The sensitivity of determination of the medial antebrachial cutaneous nerve amplitudes asymmetries in patients with true neurogenic TOS of ≥25% or lack of response, which we obtained in our study, is 33.33%; its specificity is 83.33%, test accuracy is 64.86%, the prognostic value of a positive test result (PVP) is 66.66%, and the prognostic value of a negative test result (PVN) is 64%.

CONCLUSIONS

According to the literature data and the results of our study, the most sensitive neurophysiological parameters in the diagnosis of the true neurogenic TOS are the medial antebrachial cutaneous nerve amplitude with the following results evaluation in comparison with the asymptomatic limb. During assessment of the medial antebrachial cutaneous nerve amplitudes asymmetry the difference of ≥25% or lack of response should be taken into account. According to the results of our study, the sensitivity of determination of the medial antebrachial cutaneous nerve amplitudes asymmetries in patients with the true neurogenic TOS of ≥25% or lack of response, which we obtained in our study, is 33.33%; its specificity is 83.33%, test accuracy is 64.86%, which demonstrates the feasibility of the study in patients with possible neurogenic TOS.

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ORIGINAL ARTICLE

NEW POSSIBILITIES FOR MODIFYING THE COURSE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: THE EFFECT OF TIOTROPIUM BROMIDE ON CERTAIN PATHOGENETIC LINKS OF NEOCOLLAGENOGENESIS AND LOCAL IMMUNE DEFENCE OF THE BRONCHIAL TREE

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ABSTRACT

The aim: To evaluate the dynamics of the interferon and collagen-IV systems in bronchoalveolar lavage in the treatment of chronic obstructive pulmonary disease using the tiotropium bromide medication.

Materials and methods: The study involved 60 COPD patients with bronchial obstruction of the II degree before and on days 30 and 60 of therapy using conventional treatment regimens and inhalations of tiotropium bromide a the dose of 18 mcg once a day. The collagen-IV levels in bronchoalveolar fluid were determined by means of enzyme-linked immunoassay using "StatFax 303 Plus" analyzer and "Biotrin Collagen IV EIA" reagents. The level of IFN-γ was identified with the help of enzyme-linked immunoassay using "StatFax 303 Plus" analyzer and "ProKon" reagents (LLC "Protein Contour", Russia) in bronchoalveolar fluid obtained during fiber-optic bronchoscopy.

Results: When examining Group I patients on the 30th day we found out that the content of collagen-IV in the bronchoalveolar fluid had decreased by only 10.29% ($p < 0.05$). Detection of collagen-IV indices in Group II patients on the 30th day of tiotropium bromide use showed the 29.43% ($p < 0.05$) decrease in its content as compared to the initial indices. In Group III patients, the concentration of collagen-IV had a maximum tendency to normalize and made up (24.72 ± 1.15) ng/ml, and decreased by 2.44 times ($p < 0.05$) as compared to the initial indices. Our examination of 12 patients from the comparison group I on the 60th day of treatment revealed even a slight increase in the content of collagen-IV in the bronchoalveolar fluid, as compared with the data obtained on the 30th day. The identified IFN-γ deficiency is indicative for the COPD of the II degree of bronchial obstruction, and its indices were 2.29 times lower than those observed in people from the control group. On day 30, we found out that the content of IFN-γ in Group I patients increased by only 10.29% ($p > 0.05$). Detection of IFN-γ in Group II patients showed 42.27% ($p < 0,05$) increase in its content as compared to the initial indices. The most favorable dynamics of IFN-γ levels in bronchoalveolar contents was observed in Group III patients, and at the time of observation it made up (1.16 ± 0.08) pg/ml, having 2 times ($p < 0.05$) increased as compared to the initial indices. However, in contrast to those taking tiotropium bromide, we examined 12 patients from Group I on the 60th day of treatment and found no significant positive dynamics of IFN-γ content in bronchoalveolar fluid as compared to the indices obtained on day 30.

Conclusions: The obtained findings indicate the effect of tiotropium bromide on the reduction of interferon-γ and reduce of collagen-IV levels, which depend on the duration of its use.

KEY WORDS: chronic obstructive pulmonary disease, tiotropium bromide, collagen-IV, IFN-γ

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most serious diseases in terms of disability and economic costs, the second most common infectious disease in the world, ranks fourth in the structure of mortality and is characterized by the persisted tendency for its constantly increasing prevalence rates due to the spread of bad habits on the one hand and extending life expectancy on the other [1, 2]. In the "European Lung White Book" Ukraine is presented as one of the countries with the highest mortality rate due to respiratory pathologies among men [3]. During the period of 2015–2016, the incidence of chronic bronchitis in Ukraine has increased by 0.51%, which puts this pathology in the category of strategic issues of domestic medicine [4]. Despite the fact that the development of treatment methods for COPD is well financed, it still continues to be one of the leading causes of death in the world.

The course of COPD becomes especially aggressive in the II degree of bronchial obstruction with the onset of morphological changes of the airways (sclerosis, fibrosis, bronchospasm, edema, hypercrinia, dyscrinia), resulting in bronchial remodeling and subsequent galloping progres-

sion of its systemic manifestations. Respiratory remodeling is a pathological process observed in chronic inflammatory and obstructive respiratory diseases [5].

COPD is characterized by asymptomatic or paucisymptomatic onset of the disease with subsequent progressive increase in the severity of the condition, as well as steadily progressive reduction of the pulmonary function (PF), which is the most specific and prognostic sign of the disease. Unfortunately, this pathology is often diagnosed at later stages, when the most advanced treatment programs are not able to slow down the steady progression of the disease.

The UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) findings show that selective M3 cholinolytic tiotropium has demonstrated a long-term improvement of the lung function in the four-year treatment of COPD patients [6]. While studying the group of patients who were administered tiotropium it became possible to observe the decrease of the mortality risk by 16 % ($p = 0.016$), positive effect of such treatment on survival rate ($p = 0.034$), prevention of disease exacerbation ($p < 0.001$) and significant decrease in the COPD destabilization risk, requiring further hospitalization (risk ratio 0.86; $p < 0.002$) as compared with the control group [6]. Additionally, large-scale clinical studies suggest that the use of long-acting muscarinic antagonist tiotropium in the treatment of COPD patients delays airway deterioration in dynamics up to 4 years, which should probably contribute to the involution of morphological changes in the bronchi. [6-9].

In our opinion, the effectiveness of treatment of any pathology depends on the deep knowledge of all stages of its pathogenesis. Therefore, the study of complex and multisystem processes that occur in the body in COPD, against the background of the therapeutic standards with the inclusion of tiotropium bromide medication with its characteristic effects, is quite relevant and will contribute to modern science and understanding of the need for a long-term basic treatment by both patients and healthcare professionals.

THE AIM

The goal of this study is to evaluate the dynamics of the interferon and collagen-IV systems in bronchoalveolar lavage in the treatment of chronic obstructive pulmonary disease using the tiotropium bromide medication.

MATERIALS AND METHODS

The study involved the examination of 60 patients with COPD II degree of bronchial obstruction. The diagnosis was verified and formulated in accordance with the order №555 of the Ministry of Health of Ukraine from June 27, 2013 "On approval and introduction of medical and technological documents for standardization of care in chronic obstructive pulmonary disease" [1, 10]. The investigation was performed before the start of treatment and on days 30 and 60 of therapy which involved the use of conventional treatment regimens and the administration of tiotropium bromide by inhalation of 18 mcg, once a day.

In order to study the effectiveness of the suggested treatment programs for COPD II degree of bronchial obstruction, all patients were divided into groups depending on the prescribed treatment.

Group I – 20 patients who did not receive the selective M3 long-acting cholinolytic in their comprehensive therapy [1];

Group II – 40 patients who were prescribed a 30-day course of tiotropium bromide on the background of comprehensive treatment of the exacerbation phase.

Group III – 21 patients who were prescribed a 60-day course of tiotropium bromide on the background of comprehensive treatment of the exacerbation phase.

The control group consisted of 15 apparently healthy individuals (AHI) without any signs of diseases of the respiratory tract and other pathologies of the internal organs.

The material of study was bronchoalveolar lavage, obtained considering the localization of inflammatory lesions of the lungs during fiber-optic bronchoscopy by Clements (1967) method in modification of Ramires (1980). The collagen-IV levels in bronchoalveolar fluid were determined by means of enzyme-linked immunoassay using "StatFax 303 Plus" analyzer and "Biotrin Collagen IV EIA" reagents. The level of IFN-γ was identified with the help of enzyme-linked immunoassay using "StatFax 303 Plus" analyzer and "ProKon" reagents (LLC "Protein Contour", Russia) in bronchoalveolar fluid obtained during fiber-optic bronchoscopy.

RESULTS

The analysis of findings, obtained by fiber-optic bronchoscopy that was performed to 60 patients with COPD II degree of bronchial obstruction before the start of treatment, showed that mostly identified signs were: severe catarrhal inflammation – in 48.8% of patients and purulent inflammation – in 28.8% of the examined individuals. Occasionally, moderate catarrhal inflammation was observed in 12.8% of patients, and 6.4% of the examined individuals had atrophy of the bronchial mucosa; the structure of bronchial mucosa was close to normal – in 3.2% of patients. Repeated fiber-optic bronchoscopy, which was performed to 20 patients from Group I on the 30th day of treatment, showed mainly ($p<0.05$) moderate catarrhal inflammation in 60.0% of patients, while the marked form of catarrhal inflammation was observed in 40.0% of cases.

Particularly, we would like to emphasize the obtained findings of fiber-optic bronchoscopy performed to 20 patients from Group II on the 30th day of treatment. We revealed a significant decrease ($p<0.05$) in the proportion of severe catarrhal inflammation by 31.3% in patients from Group II, which was 1.9 times lower than among patients receiving basic treatment regimens. However, the proportion of moderate catarrhal inflammation has increased to 68.8% ($p <0.05$) among Group II patients. At the same

Table I. Indices of collagen-IV (ng/ml) in bronchoalveolar fluid of patients with chronic obstructive pulmonary disease II degree of bronchial obstruction during treatment with tiotropium bromide

Study group	Indices of collagen-IV in bronchoalveolar fluid			p
	before treatment	on day 30 of treatment	on day 60 of treatment	
I, n=20	60.21±1.08	55.21±1.12	57.08±1.27	< 0.05
II, n=40	62.86±1.25	44.36±1.19		< 0.05
III, n=21	59.07±1.33		24.72±1.15	< 0.05
AHI, n=15	9.87±0.52			

Table II. Idices of IFN-γ (pg/ml) in bronchoalveolar fluid of patients with chronic obstructive pulmonary disease II degree of bronchial obstruction during treatment with tiotropium bromide

Study group	Indices of IFN-γ in bronchoalveolar fluid			p
	before treatment	on day 30 of treatment	on day 60 of treatment	
I, n=20	0.59±0.06	0.68±0.12	0.71±0.07	> 0.05
II, n=40	0.56±0.05	0.97±0.07		< 0.05
III, n=21	0.58±0.03		1.16±0.08	< 0.05
AHI, n=15	1.28±0.11			

time, fiber-optic bronchoscopy of Group III patients on day 60 from the start of treatment, showed that the proportion of moderate catarrhal inflammation increased to 82.6% (p<0.05), and the proportion of marked catarrhal inflammation made up only – 17.4% (p<0.05). Thus, the obtained findings indicate higher effectiveness of comprehensive treatment of patients with COPD II degree of bronchial obstruction, who were administered tiotropium bromide medication as compared to the patients whose treatment regimens did not include this medication. The use of tiotropium bromide medication in the treatment of patients with COPD II degree of bronchial obstruction has also resulted in faster regression of clinical symptoms of the pathology, positive changes in the data of spirography and laboratory dynamics.

The studies have revealed that the collagen-IV level in bronchoalveolar lavage of healthy individuals was: (9.87 ± 0.52) ng/ml, and IFN-γ (1.28 ± 0.11) pg/ml. On admission of patients with COPD II degree of bronchial obstruction, there was a significant increase in levels of collagen-IV in bronchoalveolar fluid – up to (60.71 ± 1.18) ng/ml (p <0.05) on the background of IFN-γ depression to (0.56 ± 0.07) pg/ml (p<0.05).

The examination of Group I patients on the 30th day of treatment, we found out that the content of collagen-IV in bronchoalveolar fluid decreased by only 10.29% (p<0.05). Detection of collagen-IV levels in Group II patients with COPD II degree of bronchial obstruction on the 30th day of tiotropium bromide use showed the decrease in its content by 29.43% (p <0.05). A real qualitative breakthrough in the dynamics of collagen-IV levels in bronchoalveolar lavage was observed in Group III patients, who received tiotropium bromide for 60 days. At the end of observation, the concentration of collagen-IV in bronchoalveolar fluid had maximum tendency to normalize and made up (24.72 ± 1.15) ng/ml, that was 2.44 times (p<0.05) lower than the indices observed in group with baseline therapy regimens. The examination of 12 patients from the comparison group I on day 60 revealed even a slight increase in collagen-IV levels in bronchoalveolar fluid, as compared to the data obtained on day 30 (Table I).

Deficiency of IFN-γ in bronchoalveolar fluid of patients with COPD II degree of bronchial obstruction is indicative and its indices were 2.29 times lower as compared to those observed in the control group (Table II). On day 30, we found out that the content of IFN-γ in bronchoalveolar fluid of Group I patients increased only by 10.29% (p>0.05). Detection of IFN-γ indices in Group II patients with COPD II degree of bronchial obstruction on the 30th day of tiotropium bromide use showed an increase in its content by 42.27% (p<0.05), as compared to the indices observed with the use of baseline therapy regimens. As in case of collagen-IV levels, the dynamics of IFN-γ levels in bronchoalveolar fluid was the most favorable in Group III patients who received tiotropium bromide for 60 days. At the end of observation, the concentration of IFN-γ in bronchoalveolar fluid had the maximum tendency to normalize and was (1.16±0.08) pg/ml, and was 2 times (p<0.05) lower as compared to the indices observed with the use of baseline therapy. However, in contrast to those taking tiotropium bromide, we examined 12 patients from Group I on day 60 and found out no significant positive dynamics of IFN-γ in bronchoalveolar fluid, as compared to the data obtained on day 30 (Table II).

Tendency for regenaration of local IFN-γ levels in patients with COPD II degree of bronchial obstruction treated with tiotropium bromide is worth special attention, since it substantiates the whole cascade of sanogenetic mechanisms for resolving pathological changes in the inflammatory process of the bronchial tree. Currently, interferons are isolated into a special class of cytokines, which were previously considered exclusively as antiviral factors, but afterwards their antitumor and immunomodulatory activities were discovered. [11]. The antibacterial property of interferons is associated with their increased phagocytic activity, increased production of immunoglobulins and increased cytotoxicity of natural killer cells [11]. The interferon system has neither specialized cells

nor specialized organs, however, the biggest producers of interferon are immunocompetent cells. When cells are stimulated by an inducer (infectious agent), the genes encoding interferon proteins are activated and the production-translation of these proteins occurs. [11]. Thus, cells start producing interferon, which, on the one hand, inhibits the proliferation of infectious agents, and on the other – enhances the expression of molecules of the major histocompatibility complex class I on the surface of altered cells and causes activation of NK cells, which initiate cytolysis of damaged cells and produce IFN -γ, which directs the development of the immune response by T-helper-1 type [11]. Macrophages, activated by the contact with antigen and IFN-γ, produce IL-12, which stimulates the differentiation of immature CD4 lymphocytes into type 1 T-helpers, which after antigen presentation are activated and produce a number of cytokines (IL-2, TNF-α, IFN -γ) [11]. The effect of these transmitters is the activation of cytotoxic CD8 lymphocytes, which provide cytolysis of the corresponding target cells, culminating in the elimination of pathogens and sanation of the inflammatory process in the bronchi [11].

DISCUSSION

The study has also showed the reduction in collagen-IV content in bronchoalveolar fluid in patients with COPD II degree of bronchial obstruction which were treated with tiotropium bromide. In order to understand the significance of this effect, it is necessary to focus on the role and localization of collagen in the human body. It is a well-known fact that a special layer is visualized between the epithelial membrane and the underlying connective tissue, it is located directly at the base of the epithelial cells and is called the basement membrane. [11]. Typical basement membrane (40 - 120 nm thick) consists of two layers of different origin [12-14]. The first layer of the basement membrane is the basal plate – a separate homogeneous electron-dense layer with a thickness of 50-100 nm, which is located just above the "felt-like" network of reticular fibers, which actually form the second layer [13]. It has been established that the basal plate always follows the contours of the basal surface of epithelium and the distance between them makes up 40 nm [14]. Basal plates may be connected not only with epithelium but also with nerve and muscle fibers [13].

The basement membrane performs two main functions: an elastic framework and a barrier for filtration and diffusion of substances (low molecular weight compounds, intercellular fluid) [13]. It is characterized by a unique form of collagen – type IV. These structures are synthesized by fibroblasts (Latin "fibra-" meaning the fiber, and Greek "blastos-" meaning the embryo). In addition, fibroblast-related cells such as osteoclasts and chondroblasts are also capable of synthesizing collagen. [14].

Currently, ten types of collagen are identified, and they are different in composition of α-chains and a number of functions. The most studied are: Type I – connective tissue proper (loose and dense) and bone tissue, Type II – hyaline cartilage, Type III – skin of the fetus, arteries, Type IV – basement membrane, Types V - VI collagen is involved in ossification, chondroprotection. Types IX - X may play a role in the maturation of connective tissue proper [12-14].

The three α-chains are identical in all types of collagen, except for Type I [14]. However, the collagen of the basement membrane (type IV) contains much more carbohydrate side chains, as well as more hydroxylysine and hydroxyproline [13]. The presence of hydroxylysine ensures the stability of collagen fibers of the basement membrane, due to the cross-linking of collagen molecules. The hydroxylysine molecule promotes the attachment of short carbohydrate residues – galactose and glucose.

Collagen IV is synthesized in the form of a precursor – procollagen. Synthesis of α-chains of procollagen occurs by means of polyribosomes of the granular endoplasmic reticulum [14]. The synthesized chains are 13 nm longer. A certain number of included proline and lysine residues are hydroxylated within 3 min in the synthesized chain, while the synthesis of the whole chain lasts from 5 to 6 min. The residual tail regions of α-chains are cleaved by means of peptidase enzyme on the cell surface of the fibroblast, so the procollagen molecule is converted into a tropocollagen molecule, which is further transformed into collagen fibrils. [12-14]. However, type IV collagen does not lose residual peptides after the secretion by fibroblasts. These peptides promote the formation of long fibrils by means of lateral condensation "side by side" [14]. First, the two chains are joined by C-terminal divisions to form dimers that associate with the N-terminals with three other molecules and thus spreading wider. [14]. The result of this association is a mobile multilayer structure stabilized by disulfide and other covalent bonds. [14]. The composition of the basement membrane, in addition to collagen Type IV, also includes heparan sulfate proteoglycan (perlecan) and glycoproteins (laminin and entactin) [14].

Thus, we think that the increase in collagen-IV content in bronchoalveolar fluid in COPD is the evidence of increased fibroblast activity (against the background of microcirculation disorders, activation of lipid peroxidation and hypoxia), and thus manifests the thickening of basement membranes, as well as the violation of both metabolic processes in their own biological systems and the dissociation of a number of dosage forms, especially inhalations. The decrease in collagen-IV content under the influence of treatment with tiotropium bromide is a prominent evidence of physiological course of repair processes, inhibition of neocollagenogenesis in the bronchi and the implementation of a cascade of effects of remodeling inhibition.

CONCLUSIONS

1. Verification of COPD II degree of bronchial obstruction, as compared with apparently healthy individuals, is accompanied by depression of IFN-γ levels (2.29 times, $p < 0.05$) with an increase in collagen-IV level

(6.15 times, $p<0.05$) in bronchoalveolar lavage.
2. The use of tiotropium bromide as the background therapy of COPD II degree of bronchial obstruction provides a significant reduction in collagen-IV levels in the bronchoalveolar lavage, which depends on the duration of tiotropium use and is the manifestation of antisclerotic activity of this medium.
3. The use of tiotropium bromide as the background therapy of COPD II degree of bronchial obstruction along with the stabilization of clinical and laboratory indices is accompanied by the restoration of IFN-γ levels in the bronchoalveolar lavage, which increases with the prolongation of tiotropium administration, eliminates antigen load and contributes to the physiological sanitation of the inflammatory process in the bronchi.

The prospect for the follow-up studies: is to visualize morphological changes at both cellular and subcellular levels, which would allow us to evaluate the obtained data on the effects of background treatment of COPD.

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ORIGINAL ARTICLE

TYPE 2 DIABETES MELLITUS PREVALENCE IN PATIENTS WITH CARDIOVASCULAR DIEASES

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ABSTRACT

The aim: To estimate type 2 diabetes mellitus (T2DM) prevalence in patients who came for a consultation to the private practice cardiologist.

Materials and methods: 97 patients with cardiovascular diseases (CVD), visited a cardiologist in private medical center, were included (mean age 49,5 (42,8; 58,3) years, 43 (44.3 %) males) and T2DM prevalence was estimated.

Results: 84 (86.6 %) patients had arterial hypertension, 19 patients (19.6 %) had coronary artery disease. Mean body mass index was 29,4 (25,2; 33,4) kg/m2. Waist circumference above recommended was observed in 78.4 %. 30 patients (30.9 %) were overweight, 44.3 % had abdominal obesity. Almost all patients had atherogenic dyslipidemia. Total T2DM prevalence was 19.6 %, including cases of first-diagnosed diabetes (17.5 %).

Conclusions: T2DM and prediabetes prevalence in our sample of patients with CVD was higer than described for the general population. Patients with cardiovascular diseases require careful assessment of diabetes risk factors for its timely detection and for possibly improving the outcomes.

KEY WORDS: type 2 diabetes mellitus, cardiovascular diseases, dyslipidemia, arterial hypertension

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is well known risk factors for the development of cardiovascular diseases (CVD) and cardiovascular mortality; in turn, cardiovascular disease is one of the leading causes of death in diabetes. Meta-analysis of 102 prospective studies showed that diabetes mellitus in general confers a two-fold excess risk of vascular outcomes (coronary heart disease, ischaemic stroke, and vascular deaths), independent of other risk factors, especially in those with long-standing diabetes [1]. Patients with diabetes develop atherosclerosis 7-10 years earlier compared wis non-diabetic patients, and can be revealed at the stages of impaired glucose tolerance [2]. Type 2 diabetes mellitus can debuts directly as vascular complications - myocardial infarction, cerebral stroke. Even prediabetes is already not only an intermediate stage in the T2DM development, but also an independent risk factor for cardiovascular diseases. The elevated risk of coronary artery disease (CAD) starts at glucose levels below the cut-off point for DM (HR=1.11 already for patients with 5.6-6.1 mmol/L), and increases with increasing glucose levels [1]. So it is strongly recommended to identify patients with a high risk of T2DM as early as possible and actively perform the correction of hyperglycemia, dyslipidemia, arterial hypertension and other risk factors for cardiovascular diseases [3].

The presentation of type 2 diabetes is usually less noticeable compared to type 1 and its start may be completely symptomless. As a result, there is often a long pre-diagnostic period and as many as one-third to one-half of people with type 2 diabetes in the population may be undiagnosed [4]. The causes of T2DM are not completely understood but there is a strong correlation with obesity, increasing age, with ethnicity and family history. Type 2 diabetes is "getting younger" today as a result of an increasing prevalence of obesity. According to the data of International Diabetes Federation (IDF), 40.7% cases of diabetes in Europe are undiagnosed. [4].

THE AIM

To estimate T2DM prevalence in patients who came for a consultation to the private practice cardiologist.

MATERIALS AND METHODS

The results of the examination of patients, who went to a private medical center to a cardiologist were analyzed. 97 consecutive patients were included (mean age 49,5 (42,8; 58,3) years, 43 (44.3 %) males). 37 (38.1%) patients were observed by a family doctor and applied for consultation and correction of therapy, 60 (61.9 %) applied independently, as a private practice does not require prior referral. Arterial hypertension (AH), CAD and disorders of glucose metabolism were assessed according to the current recommendations [1,5,6,7]. All patients signed an informed agreement to use their data, patients who din`t

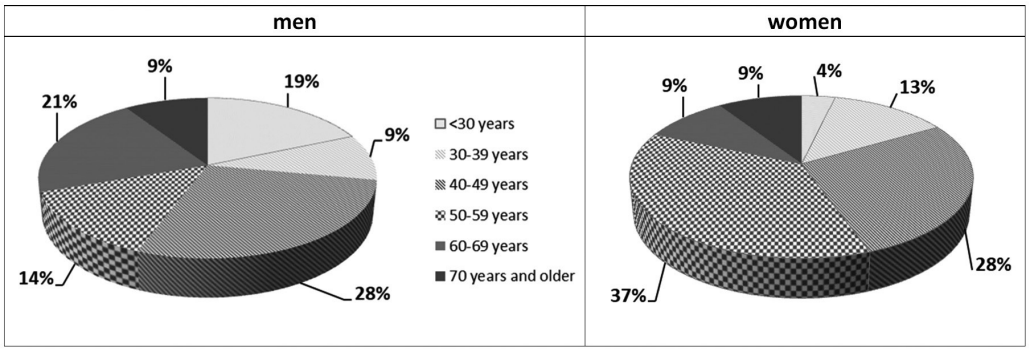

Fig.1. Distribution of the examined patients by age groups.

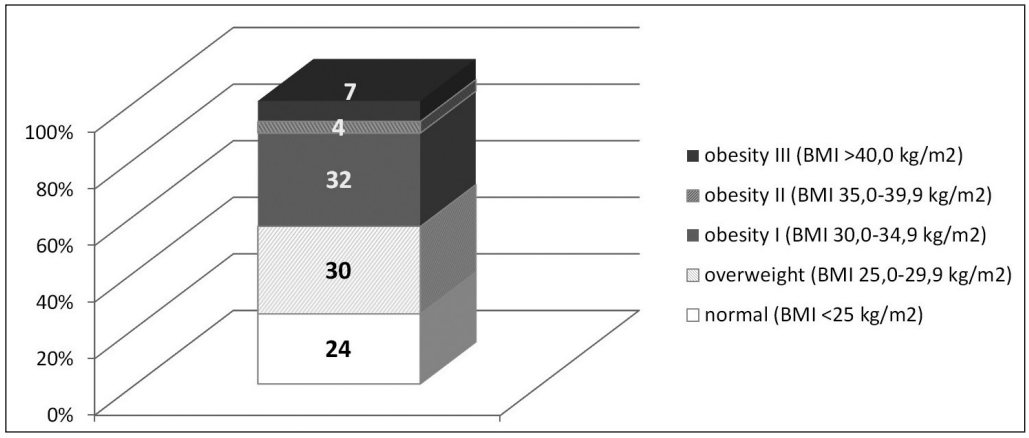

Fig.2. Distribution of the examined patients by BMI groups.

agree was excluded. The statistical analysis was performed using Excel v.10.0 (Microsoft) and STATISTICA v.13.3 (Softserve) programs. The numerical values are reported as median (lower and upper quartiles) and as a proportion of the sample size.

RESULTS

These were mainly young and middle-aged patients (fig.1), which was most likely due to the higher income level of these age categories and, accordingly, the possibility of receiving paid medical services. Mean age was 49,5 (42,8; 58,3) years. Women were slightly older than men (mean age 50.5 (48.0; 57.5) vs 46.5 (40.7; 60.5)), although this was not reliable (p=0.062). This may reflect the later manifestation of cardiac pathology in women.

Most of the patients presented with AH (only 5 patients had normal blood pressure (BP), these were young people, the reason for the visit were heart rhythm disturbance - sinus tachycardia and extrasystole). 8 patients (8.2 %) had high normal BP, 84 (86.6 %) had AH (57.2 % of them had grade 1 hypertension, 20.2 and 22.6 % - 2nd and 3d grades respectively). 19 patients (19.6 %) had CAD (5 patients with hystory of myocardial infarction, 2 patients after percutaneous coronary interventions). 2 patients presented with myocarditis. 22 (22.7 %) patients had heart failure (77.3 and 22.7 % with NYHA FC II and III respectively). 2 patients presented with T2DM. 8.2 % were smokers (all 8 patiens were males). It was revealed family history of cardiac disease in 32 (32.9 %) patients and diabetes family history in 19 (19.6 %) patients.

Thus, most patients in our sample were "non-severe" cardiological patients, many of them were "on the start" of cardiovascular disease, having relatively short duration of AH.

At the same time, mean body mass index (BMI) in our sample was 29,4 (25,2; 33,4) kg/m2, so only 24 patients (24.7 %) had normal BMI. Even in the group with normal BMI 3 patients had waist circumference higher than 94 sm for men and 80 sm for women. 30 patients (30.9 %) were overweight (all with waist circumference above the recommended) and all the other (44.3 %) had abdominal obesity (fig.2). Thus, waist circumference above recommended (as one of the components of metabolic syndrome) was observed in 78.4 % of patients. 17 patients had fasting blood glucose (FBG) results at first visit, 8 of them had increased levels (3 patients with FBG > 7.0 mmol/l, 5 patients had FBG from 5.6 to 6.9 mmol/l).

Patients were refered for further examination, including, among other prescription, lipid profile and haemoglobin A1c (HbA1c) and two-hour oral glucose tolerance test for certain patients. Only 40 patients (41.2 %) came for a follow-up visit with the test results. Almost all patients had atherogenic dyslipidemia (total cholesterol level was 6,25 (5,60; 6,42) mmol/l, high-density lipoprotein cholesterol was 1,27 (1,03; 1,60) mmol/l, low-density lipoprotein cholesterol was 3,98 (3,43; 4,32) mmol/l, triglycerides level was (1,71 (1,40; 2,05) mmol/l (only one 19-years old patient

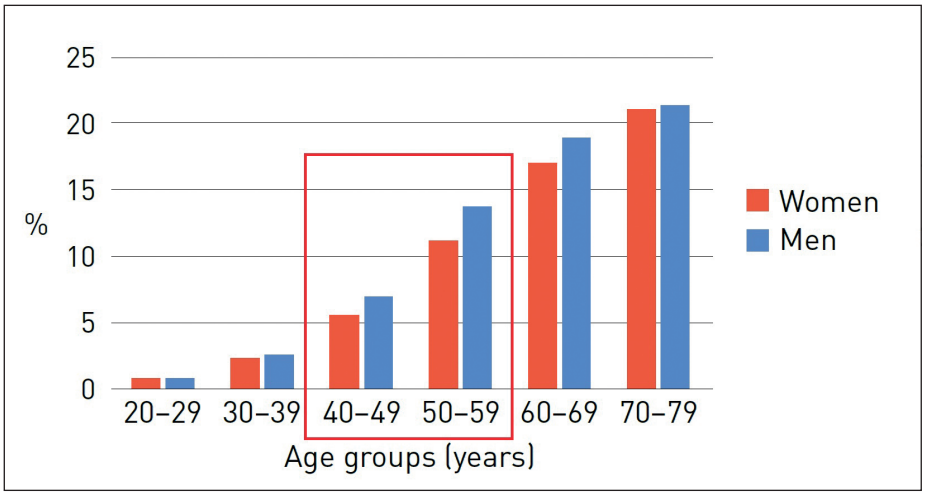

Fig.3. Prevalence (%) estimates of diabetes by age and sex, IDF Europe Region, 2019 (adopted from IDF Diabetes Atlas, 9th edition [4])

had normal lipid prifile (that was prescribed considering his family history)).

Haemoglobin A1c level over 6.5 % was revealed in 17 (17.5 %) and that were a cases of first-diagnosed diabetes. Taking into accounr patients that presented with T2DM on first visit, total T2DM prevalence in our middle-aged sample was 19.6 %. 5 patients (5.2 %) had HbA1c level from 5.9 to 6.4 %, meeting the criteria for prediabetes according to ADA 2019 recomendation. Among patients who did not came for a follow-up visit, 4 patients had FBG from 5.6 to 6.9 mmol/l and 1 patients had FBG > 7.0 mmol/l.

DISCUSSION

Our study was relatively small and thus not entirely representative, but should accent on the need for early diagnosis of diabetes, especially in patients with cardiovascular diseases (CVD), because T2DM and CVD are common comorbidities, mutually aggravating the course of each other. Total T2DM prevalence in our study (19.5 %) was higer than that given in the "Dibetes Atlas 2019" [4] for this age category (fig.3), but, on the one hand, according to the IDF, Europe prevalence of undiagnosed diabetes (20–79 years) was 40.7 % in 2019, and, on the other hand, the prevalence was estimated in patients with CVD, and our patients had high prevalence of abdominal obesity. The results could have been even higher if all patients were completely examined (only a part of patients came for a follow-up visit with the test results). In any case, these results indicate that, if the recommendations are followed (testing for prediabetes and/or type 2 diabetes in asymptomatic people should be considered in adults of any age who are overweight or obese (BMI>25 kg/m2 or >23 kg/m2 in Asian) and who have one or more additional risk factors for diabetes; for all people, testing should begin at age 45 years [7]), it improves the early diagnosis of diabetes and gives patients a chance to improve their outcomes. It is also very important to reveal cases of prediabetes becouse this patients have an increased risk of diabetes and already heightened risk of CVD, and their detection "opens the door to interventions that can lead to the prevention of type 2 diabetes" [4]. In our study patients meeting the criteria for prediabetes were identified (5.2 % of patients with HbA1c level from 5.9 to 6.4 %; and 4 patients had FBG from 5.6 to 6.9 mmol/l on the first visit who did not came for a follow-up visit).

CONCLUSIONS

1. T2DM and prediabetes prevalence in our sample of patients with CVD was higer than described for the general population.
2. Patients with cardiovascular diseases require careful assessment of diabetes risk factors for its timely detection and for possibly improving the outcomes.

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ORIGINAL ARTICLE

EVALUATION OF BACTERIAL CONTAMINATION IN THE INANIMATE ENVIRONMENT SURFACES IN ACUTE CARE HOSPITALS IN KYIV, UKRAINE

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ABSTRACT

The aim: To evaluate the quality of cleaning and disinfection of surfaces scheduled for daily cleaning and degree of bacterial contamination of hospital rooms and the patients' inanimate environment in Kyiv acute care hospitals, Ukraine.

Materials and methods: We performed a multicenter prospectively study of the quality of cleaning and disinfection of surfaces scheduled for daily cleaning in 9 acute care hospitals by use of an ultraviolet fluorescence targeting method and microbial methods.

Results: A total 9,104 environmental samples from were collected and tested. The cleaning and disinfection of surfaces were not being performed properly in most cases. Complete removal of the mark was 49.1%, partial removal was 37,5%, and mark was still visible, i.e. this area had not been processed was 13,4% when the ultraviolet fluorescence targeting method procedures were used, respectively. The predominant bacterial agents in hospital environment surfaces were: *Escherichia coli, Enterobacter* spp., *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Proteus* spp., *Citrobacter* spp., *Acinetobacter spp*., and *Enterococcus* spp. The overall proportion of extended spectrum beta-lactamase (ESBL) production among Enterobacteriaceae was 31.5% and of methicillin-resistance in *Staphylococcus aureus* (MRSA) 14.9%. Vancomycin resistance was observed in 5.2% of isolated enterococci (VRE). Resistance to third-generation cephalosporins was observed in 12.7% *E.coli* isolates and was in 11.2% *K. pneumoniae* isolates. Carbapenem resistance was identified in 24.7% of *P.aeruginosa* isolates and 59.3% of *Acinetibacter* spp. isolates.

Conclusions: In a hospital rooms, patient environmental surfaces can be a vehicle for the transmission of multidrug-resistant (MDR) bacterial agents that cause healthcare-associated infections.

KEY WORDS: healthcare-associated infections; surface contamination, cleaning, disinfection, ultraviolet fluorescence targeting method, antimicrobial resistance

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INTRODUCTION

Healthcare-associated infections (HAIs) are among the most common adverse events in patient care [1]. The emergence and spread of HAIs has become a major public health threat in worldwide. HAIs have been reported to exact a tremendous toll on patients, families and systems of care, resulting in increased morbidity and mortality and increased healthcare costs.

According to literature, HAIs contribute to patient morbidity and mortality with an estimated 1.7 million infections and 99,000 deaths costing USD $28-34 billion annually in the United States alone [2]. HAIs annually account for 37,000 attributable deaths in Europe. Annual financial losses due to HAIs are also significant, as they are estimated at approximately €7 billion in Europe, including direct costs only and reflecting 16 million extra days of hospital stay [3]. The overall prevalence of HAIs in Ukraine was 11.3%. The most frequently reported HAI types were surgical site infections (60%), respiratory tract infections (pneumonia and lower respiratory tract, 18.4%), bloodstream infections (10.2%), and urinary tract infections (9.5%). Death during hospitalization was reported in 9.7% of HAI cases [4]. Despite major advances in infection control interventions, HAIs remain a major public health problem and patient safety threat worldwide.[5].

For several decades, environmental surfaces in hospitals were considered to play little or no role in the transmission of HAIs. However, a growing body of evidence suggests that contaminated environmental surfaces can contribute to the transmission of HAIs pathogens [6]. According to the literature, in addition to hand hygiene and reprocessing of medical products, cleaning and disinfection of surfaces is also an important issue in the prevention of germ transmission and by implication infections [7,8]. Accordingly, cleaning and disinfecting environmental surfaces in patient care areas are now recognized as important elements of infection control

programs [9,10]. As a result, there is increasing interest in new technologies that can reliably decontaminate environmental surfaces in healthcare facilities. In recent years, a variety of interventions have been shown to be effective in improving cleaning and disinfection of surfaces.

Currently, in Ukrainian hospitals and other health care settings use more 500 antiseptics and disinfectants for a variety of topical and hard-surface applications. In particular, they are an essential part of infection control practices and aid in the prevention of HAIs. However, there is little understanding as to if current environmental surface disinfection practices reduce pathogen load, and subsequently HAIs in hospitals. In Ukraine, there are no studies examining how the risk of an transmission of HAI pathogens is associated with bacterial contamination of hospital rooms and the patients' inanimate environment.

THE AIM

To evaluate the quality of cleaning and disinfection of surfaces scheduled for daily cleaning and degree of bacterial contamination of hospital rooms and the patients' inanimate environment in Kyiv acute care hospitals, Ukraine.

MATERIALS AND METHODS

STUDY DESIGN

We performed from January 10st, 2021 to August 31st, 2021 a multicenter prospectively study of the quality of cleaning and disinfection of surfaces scheduled for daily cleaning in 9 acute care hospitals of Kyiv city (Ukraine) by use of an ultraviolet fluorescence targeting method (UVM) and microbial (cultural) methods. All hospitals transferred information on the quality of structure. Process quality

Table I. Monitoring the quality of the cleaning and disinfection of surfaces scheduled for daily cleaning by use of an ultraviolet fluorescence targeting method (UVM) in acute care hospitals in Kyiv, Ukraine (2021)

Hospital	Number of samples	Removal of marking from surfaces with a fluorescent liquid					
		complete removal		partial removal		mark was visible	
		n	%	n	%	n	%
A	1184	645	54.5	368	31.1	171	14.4
B	1120	618	55.2	385	34.4	117	10.4
C	1040	529	50.9	362	34.8	149	14.3
D	960	504	52.5	344	35.8	112	11.7
E	1040	481	46.3	422	40.6	137	13.2
F	1056	484	45.8	434	41.1	138	13.1
G	880	428	48.6	345	39.2	107	12.2
H	912	404	44.3	381	41.8	127	13.9
I	912	377	41.3	375	41.1	160	17.5
Total	9104	4470	49.1	3416	37.5	1218	13.4

Table II. Trend the quality of cleaning and disinfection of surfaces using ultraviolet fluorescence (UVM) targeting in acute care hospitals in Kiev, Ukraine (2021)

Hospital	Number of samples	Removal of marking from surfaces with a fluorescent liquid											
		Mondays			Wednesdays			Saturdays			Sundays		
		complete removal %	partial removal %	mark was visible %	complete removal %	partial removal %	mark was visible %	complete removal %	partial removal %	mark was visible %	complete removal %	partial removal %	mark was visible %
A	1184	67.9	27.0	5.1	64.9	30.1	5.1	55.4	34.5	10.1	29.7	32.8	37.5
B	1120	67.1	28.9	3.9	65.4	31.8	2.9	53.2	42.9	3.9	35.0	33.9	31.1
C	1040	59.6	27.7	12.7	55.8	36.9	7.3	45.0	48.1	6.9	43.1	26.5	30.4
D	960	62.1	29.2	8.8	62.9	35.4	1.7	54.6	40.8	4.6	30.4	37.9	31.7
E	1040	52.7	36.9	10.4	54.2	41.5	4.2	50.8	42.3	6.9	27.3	41.5	31.2
F	1056	47.7	40.9	11.4	48.5	48.5	3.0	45.1	48.9	6.1	42.0	26.1	31.8
G	880	46.4	44.1	9.5	60.5	37.7	1.8	55.5	40.9	3.6	32.3	34.1	33.6
H	912	45.2	45.2	9.6	51.3	46.1	2.6	50.9	44.3	4.8	29.8	31.6	38.6
I	912	42.1	43.0	14.9	47.8	49.1	3.1	43.0	51.8	5.3	32.5	20.6	46.9
Total	9104	55.2	35.4	9.4	57.1	39.3	3.6	50.4	43.6	5.9	33.7	31.8	34.6

Table III. Monitoring the effect of the cleaning and disinfection of surfaces on different department/wards by ultraviolet fluorescence (UVM) targeting in acute care hospitals in Kiev, Ukraine (2021)

Department/wards	Number of samples	Removal of marking from surfaces with a fluorescent liquid					
		complete removal		partial removal		mark was visible	
		n	%	n	%	n	%
General surgery	680	388	57.1	238	35.0	54	7.9
Digestive tract surgery	320	148	46.3	96	30.0	76	23.8
Cardiovascular surgery	360	210	58.3	138	38.3	12	3.3
Ear/nose/throat surgery	480	240	50.0	170	35.4	70	14.6
Orthopedic surgery	560	298	53.2	176	31.4	86	15.4
Neurosurgery	680	360	52.9	266	39.1	54	7.9
Urology	660	345	52.3	221	33.5	94	14.2
Burns care	460	300	65.2	104	22.6	56	12.2
Haematology	410	233	56.8	157	38.3	20	4.9
Pneumology	470	240	51.1	180	38.3	50	10.6
Obstetrics/maternity	680	360	52.9	264	38.8	56	8.2
Gynaecology	680	320	47.1	292	42.9	68	10.0
Paediatrics general	680	280	41.2	304	44.7	86	12.6
Medical ICU	420	140	33.3	189	45.0	91	21.7
Surgical ICU	420	157	37.4	159	37.9	104	37.9
Paediatric ICU	420	170	40.5	182	43.3	68	43.3
Neonatal ICU	364	141	38.7	125	34.3	98	34.3
Mixed and other ICU	360	140	38.9	145	40.3	75	40.3
Total	9104	4470	49.1	3416	37.5	1218	13.4

was obtained through direct observation during cleaning and disinfection of rooms and their plumbing units. All participating hospitals were required to have a clinical microbiology laboratory with the capacity to process cultures and at least one intensive care unit (ICU).The study was conducted in hospital wards, operating theatres and intensive care units.

DATA COLLECTION

In our study, as part of a questionnaire-based survey, data was obtained regarding the staff training and quality control, the interface of the responsibilities of house cleaning and nursing personnel, the work instructions (standard operating procedures (SOP)), the cleaning performance on weekends and holidays.

We took samples on Mondays, Wednesdays, Saturdays, and Sundays for one month and took samples from near- and extended patient areas. Infection control practitioners of the respective hospitals had marked definite points in fluorescent ink, according to the CDC recommendation [11]. On the day of the control visit, reprocessing of at least 5 four-bed rooms and bathrooms was monitored in every hospital. In during the control visit infection control practitioners, if and how these points had been removed by cleaning was determined using an ultraviolet flashlight. Cleaning performance was measured by complete removal of UVM, i.e. marking surfaces with a fluorescent liquid and testing if this mark has been sufficiently removed by cleaning and removed of bacterial contamination of hospital rooms and the patients' inanimate environmental surfaces. Complete removal of the mark was scored as two points, partial removal was given one point, and zero points were awarded if the mark was still visible, i.e. this area had not been processed.

MICROBIAL METHODS

Microbiological samples were taken from the surfaces of near- and extended patient areas. In each hospital, two infection control practitioners carried out the sampling. To sample a large surface, we used RODAC plate, 55 mm in diameter. A RODAC plate, 55 mm in diameter, was pressed on the surface to be tested, and then incubated at 36°C for 48 h. Microbial isolates were identified using standard microbiological techniques. Antibiotic susceptibility testing was performed by using the disk diffusion method according to the recommendations of the European Committee on Antimicrobial Susceptibility

Table IV. Monitoring the effect of the cleaning and disinfection of surfaces on different items in hospital room by ultraviolet fluorescence (UVM) targeting in acute care hospitals in Kiev, Ukraine (2021)

Environmental items in hospital room	Number of samples	Removal of marking from surfaces with a fluorescent liquid					
		complete removal		partial removal		mark was visible	
		n	%	n	%	n	%
Bed rails	560	270	48.2	261	46.6	29	5.2
Tray table	610	378	62.0	208	34.1	24	3.9
Bedside table handle	470	216	46.0	237	50.4	17	3.6
Bedside table	610	297	48.7	301	49.3	12	2.0
Chair	510	430	84.3	76	14.9	4	0.8
Room sink	430	192	44.7	224	52.1	14	3.3
Room light switch	640	173	27.0	421	65.8	46	7.2
Room inner door knob	640	176	27.5	441	68.9	23	3.6
Door handle	620	170	27.4	413	66.6	37	6.0
IV pump control	180	139	77.2	37	20.6	4	2.2
Multi-module monitor controls	460	137	29.8	167	36.3	156	33.9
Multi-module monitor touch screen	460	132	28.7	107	23.3	221	48.0
Multi-module monitor cables	614	121	19.7	207	33.7	286	46.6
Ventilator control panel	160	71	44.4	75	46.9	14	8.8
Infusion pump	140	68	48.6	65	46.4	7	5.0
Switches of intravenous pumps	140	51	36.4	71	50.7	18	12.9
Bathroom door	180	178	98.9	2	1.1	0	0
Shower	180	173	96.1	7	3.9	0	0
Basin fitting	180	169	93.9	11	6.1	0	0
Shower fitting	180	172	95.6	8	4.4	0	0
Bathroom sink	180	171	95.0	9	5.0	0	0
Bathroom light switch	180	171	95.0	9	5.0	0	0
Bathroom inner door knob	180	168	93.3	0	0	12	6
Bathroom handrails by toilet	200	91	45.5	11	5.5	98	49,0
Toilet seat	200	89	44.5	27	13.5	84	42,0
Toilet flush handle	200	67	33.5	21	10.5	112	56,0
Total	9104	4470	49.1	3416	37.5	1218	13,4

Testing (EUCAST). In our study, strains in the intermediate range were classified as resistant for data analysis.

ETHICS

The Shupyk National Healtcare University of Ukraine Ethics Committee approved this study.

STATISTICAL ANALYSIS

Descriptive statistical analysis was performed to provide median, minimum-maximum values range, and mean standard deviation. Parametric or nonparametric tests were applied on the basis of data distribution. The Wilcoxon, Mann-Whitney, and Fisher's Exact tests were run to analyze data statistically. For the statistical analysis, we used a significance level of $p < 0.05$.

RESULTS

EVALUATION BY ULTRAVIOLET FLUORESCENCE TARGETING METHOD

A total 9,104 environmental samples from were collected and tested for the evaluations of the quality of cleaning and disinfection of surfaces scheduled for daily cleaning in 9 acute care hospitals by use of an ultraviolet fluorescence targeting method (UVM). Cleaning and disinfection of surfaces were not being performed properly in most cases. Complete removal of the mark was 49.1% (4470/9104) [95% CI 48.4%, 49.9%, $p < 0.0001$], partial removal was 37,5% (3416/9104)[95% CI 36.7%, 38.3%, $p < 0.0001$], and mark was still visible, i.e. this area had not been processed was 13,4% (1218/9104)[95% CI 12.4%, 14.4%, $p < 0.0001$] when the UVM procedures were used, respectively.

Table V. Distribution of microorganisms isolated from the patients' inanimate environment surfaces in acute care hospitals in Kyiv, Ukraine (2021)

Microorganisms	All isolates (n=11723)	Percentages, %
Gram-positive cocci	1672	14.3
Staphylococcus aureus	248	2.1
Coagulase-negative staphylococci	529	4.5
Enterococcus spp.	717	6.1
Streptococcus spp.	178	1.5
Gram-negative bacilli	10051	85.7
Escherichia coli	3374	28.8
Citrobacter spp.	822	7.0
Enterobacter spp.	1401	12.0
Klebsiella pneumoniae	991	8.5
Proteus spp.	892	7.6
Serratia spp.	341	2.9
Acinetobacter spp.	788	6.7
Pseudomonas aeruginosa	1374	11.7
Stenotrophomonas maltophilia	68	0.6
Total	11723	100.0

Cleaning performance varied significantly between the 9 acute care hospitals. Results of monitoring the quality of the cleaning and disinfection of surfaces scheduled for daily cleaning by use of an ultraviolet fluorescence targeting method (UVM) in acute care hospitals are presented in Table I.

There were significant differences in the quality of cleaning and disinfecting environmental surfaces in hospitals on Mondays, Wednesdays, Saturdays, and Sundays. The best results of cleaning the patients' inanimate environment surfaces were achieved in Mondays and Wednesdays, the worst results in Saturdays, and Sundays (Table II). The best results of were achieved in Burns care, Cardiovascular surgery, General surgery, and Haematology departments, the worst results in intensive care units. Results of monitoring the effect of the cleaning and disinfection of surfaces on different department/wards by ultraviolet fluorescence (UVM) targeting in acute care hospitals are presented in Table III.

Evaluation the priority sites most frequently contaminated and touched by patients and/or healthcare workers found significant differences in the effectiveness of cleaning and disinfecting surfaces on various items in the hospital wards. The results of monitoring the effect of the cleaning and disinfection of surfaces on different items in hospital room by ultraviolet fluorescence (UVM) targeting in acute care hospitals are presented in Table IV.

EVALUATION BY MICROBIOLOGICAL METHOD

A total of 11723 strains isolated from 9104 the patients' inanimate environment surfaces. Gram-positive organisms accounted for 14.3% (1672/11723) [95% CI 14.4%, 15.2%, p <0.0001] of all strains and gram-negative organisms accounted 85.7% (10051/11723) [95% CI 85.4%, 86.1%, p <0.0001], respectively. Enterobacteriaceae were the most frequently isolated group of organisms from the patients' inanimate environment surfaces (67.6%, 95% CI 67.1%, 68.1%, p <0.0001). The predominant bacterial agents were: *E. coli* (28.8%), *Enterobacter* spp. (12%), *P. aeruginosa* (11.7%), *K.pneumoniae* (8.5%), *Proteus* spp. (7.6%), *Citrobacter* spp. (7%), *Acinetobacter* spp. (6.7%), and *Enterococcus* spp. (6.1%), followed by Coagulase-negative staphylococci (4.5%), *Serratia* spp. (2.9%), *S. aureus* (2.1%), *Streptococcus* spp. (1.5%), and *Stenotrophomonas maltophilia* (0.6%) (Table V). Evaluation the priority sites most frequently contaminated and touched by patients and/or healthcare workers found significant differences degree of bacterial agents contamination of environmental items in hospital rooms and the patients' inanimate environment (Table VI).

Because most commensally bacteria have natural gene transfer mechanisms and can be resistant to multiple antimicrobials, it is important to characterize the strains that have been isolated from environmental surfaces. Antimicrobial susceptibility tests were performed on a total of 1672 isolates of Gram-positive cocci and 10051 gram-negative organisms. The antimicrobials used in antimicrobial susceptibility testing included those commonly used as therapeutic agents in Ukraine. Varying degrees of resistance to most antimicrobials tested were found. Staphylococcal isolates showed susceptibility to most antimicrobials tested, although there were some differences depending on the environmental surfaces. No strains resistant to linezolid, teicoplanin, vancomycin, tigecycline, and fusidic acid were found. Methicillin-resistance was observed in 14.9% of *S. aureus*.

Table VI. Distribution of microorganisms isolated from the priority sites most frequently contaminated and touched by patients and/or healthcare workers in acute care hospitals in Kiev, Ukraine (2021)

Environmental items in hospital room	Microorganisms
Bed rails	*E.coli, Enterococcus spp., Citrobacter spp., Enterobacter spp., Proteus spp.*
Tray table	*S.aureus, Enterococcus spp., CNS, Enterobacter spp., Serratia spp., E.coli,*
Bedside table handle	*S.aureus, Enterococcus spp., CNS, Enterobacter spp., Serratia spp., E.coli,*
Bedside table	*S.aureus, Enterococcus spp., CNS, Enterobacter spp., Serratia spp., E.coli,*
Chair	*Enterobacter spp., Citrobacter spp., Proteus spp., CNS, E.coli,*
Room sink	*Enterobacter spp., E.coli, Citrobacter spp., P.aeruginosa, Enterococcus spp.,*
Room light switch	*S.aureus, Enterococcus spp., Streptococcus spp. E.coli, Citrobacter spp., Enterobacter spp., Serratia spp. P.aeruginosa, S. maltophilia*
Room inner door knob	*Enterococcus spp., E.coli, Citrobacter spp., Enterobacter spp., Serratia spp. P.aeruginosa, Proteus spp., S.aureus, CNS, Streptococcus spp.*
Door handle	*Enterococcus spp., E.coli, Citrobacter spp., Enterobacter spp., Serratia spp. P.aeruginosa, Proteus spp., S. maltophilia, S.aureus, Streptococcus spp.*
IV pump control	*Enterococcus spp., E.coli, Citrobacter spp., Enterobacter spp., Serratia spp. P.aeruginosa, Acinetobacter spp., K. pneumoniae, CNS, Streptococcus spp.*
Multi-module monitor controls	*Enterococcus spp., E.coli, Enterobacter spp., Serratia spp. P.aeruginosa, Acinetobacter spp., K. pneumoniae, CNS,*
Multi-module monitor touch screen	*E.coli, Enterobacter spp., Serratia spp. P.aeruginosa, Acinetobacter spp., K. pneumoniae, CNS. S. maltophilia, Streptococcus spp.*
Multi-module monitor cables	*E.coli, Enterobacter spp., Serratia spp. P.aeruginosa, Acinetobacter spp., K. pneumoniae, S. maltophilia, Proteus spp.,*
Ventilator control panel	*E.coli, Enterobacter spp., K. pneumoniae, Acinetobacter spp.*
Infusion pump	*E.coli, Enterobacter spp.*
Bathroom door	*E.coli, Citrobacter spp., Enterobacter spp., Serratia spp. P.aeruginosa*
Shower	*E.coli, Serratia spp. P.aeruginosa*
Basin fitting	*E.coli, Serratia spp.*
Shower fitting	*E.coli, Enterococcus spp., Citrobacter spp.,*
Bathroom sink	*E.coli, Enterobacter spp., Serratia spp. P.aeruginosa, Proteus spp., S. maltophilia*
Bathroom light switch	*E.coli, Enterobacter spp., Serratia spp. P.aeruginosa, Proteus spp., S. maltophilia,*
Bathroom inner door knob	*E.coli, Enterobacter spp., Serratia spp. P.aeruginosa*
Toilet seat	*E.coli, Enterobacter spp., Serratia spp. P.aeruginosa, Proteus spp.,*
Toilet flush handle	*E.coli, Enterobacter spp., Serratia spp. P.aeruginosa, Proteus spp.*

Regarding the genus *Enterococcus*, *E. faecalis* isolates and *E. faecium* were not sensitive to those antibiotics to which they are intrinsically resistant (cefuroxime, clindamycin, and trimethoprim-sulfamethoxazole) and 85.3% of them were resistant to erythromycin. Approximately, 20% of the *E. faecalis* isolates displayed resistance to high levels of aminoglycosides (gentamycin, tobramycin) and around 9.1% was resistant to quinolones (ciprofloxacin and levofloxacin). Vancomycin resistance was observwd in 5.2% of isolated enterococci (VRE). The overall proportion of extended spectrum beta-lactamases (ESBL) production among Enterobacteriaceae was 31.5%. The prevalence of ESBL production among *E. coli* isolates was significantly higher than in *K. pneumoniae* (36.1%, vs 16.3%, $p < 0.001$). Resistance to third-generation cephalosporins was observed in 12.7% *E.coli* isolates. No strains of *E.coli* resistant to ertapenem were found. Resistance to third-generation cephalosporins was observed in 11.2% K. pneumoniae isolates. Carbapenem resistance was identified in 24.7% of *P.aeruginosa* isolates and 59.3% of *Acinetibacter* spp. isolates.

DISCUSSION

This is the first study in Ukraine were to evaluate the quality of cleaning and disinfection of surfaces scheduled for daily cleaning and degree of bacterial contamination of hospital rooms and the patients' inanimate environment by use of an ultraviolet fluorescence targeting method (UVM) and microbial methods. In this study the cleaning and disinfection of surfaces were not being performed properly in most cases. Complete removal of the mark was 49.1%, partial removal was 37,5%, and mark was still visible, i.e. this area had not been processed was 13,4% when the UVM procedures were

used, respectively. Cleaning performance varied significantly between the 9 acute care hospitals. Contamination of hospital rooms and the patients' inanimate environment surfaces by the bacterial pathogens investigated was found to be frequent and widespread occurrence. The predominant bacterial agents were: *E. coli, Enterobacter* spp., *P. aeruginosa*, *K.pneumoniae*, *Proteus* spp., *Citrobacter* spp., *Acinetobacter* spp., and *Enterococcus* spp., followed by Coagulase-negative staphylococci (CNS), *Serratia* spp., *S. aureus, Streptococcus* spp., and *Stenotrophomonas maltophilia.*

The increasing emergence and spread of multi-resistant bacteria in hospitals is of great concern and continues to challenge infection control and hospital epidemiology practice worldwide [12]. However, only limited data concerning the colonization of a patient with multi-resistant Gram-positive and Gram-negative strains and the subsequent spread of these strains into the hospital environment are currently available. In our study a significant part of the bacterial agents isolated from the environment surfaces were resistant to many antibiotics. The overall proportion of extended spectrum beta-lactamase (ESBL) production among Enterobacteriaceae was 31.5% and of methicillin-resistance in *S. aureus* (MRSA) 14.9%. Vancomycin resistance was observed in 5.2% of isolated enterococci (VRE). Resistance to third-generation cephalosporins was observed in 12.7% *E.coli* isolates and was in 11.2% *K. pneumoniae* isolates. Carbapenem resistance was identified in 24.7% of *P.aeruginosa* isolates and 59.3% of *Acinetibacter* spp. isolates.

According to the literature, micro-organisms in the patients' inanimate environment surfaces scheduled for daily cleaning contribute to HAI [2, 12-16]. Although there is no direct proof, there is mounting evidence that the environment of patients colonized with Gram-positive and Gram-negative bacteria serves as a potential reservoir for cross-transmission and hence, possible nosocomial infections. Patients hospitalized in rooms previously occupied by people infected with HAIs are at increased odds of HAI acquisition compared to patients whose prior room occupant was negative for HAIs.

The environmental transmission pathways of pathogens and HAIs are varied. Measures to reduce the environment as a transmission pathway for HAIs are also varied. Improved cleaning procedures, training environmental service personnel, hand hygiene, and bundled disinfection interventions reduce the concentrations of pathogens on environmental surfaces and reduce HAIs in healthcare facilities. The literature has focused on multimodal strategies in infection prevention and control. Understanding the efficacy of the individual components of multi-modal strategies may help guide bundle development and may aid in decision-making in low-resource settings. However, there has not been a rigorous systematic review of the efficacy of disinfection interventions in situ.

CONCLUSIONS

Our studies have shown that in hospital rooms, most patient environmental surfaces are contaminated with multidrug-resistant bacterial agents and can be a vehicle for the transmission of healthcare-associated infections pathogens. Cleaning and disinfection processes must be improved so that there is a reduction in environmental contamination of frequent-contact surfaces in hospitals. Transmission of infectious agents from contaminated surfaces to a patient may occur via direct contact, indirectly via the hands or gloves of healthcare personnel. Failure to properly disinfect carries risk for person-to-person transmission and transmission of environmental pathogens. To reduce transmission risk of infectious agents from contaminated surfaces to the patient, more attention should be paid to the evidence-based recommendations on the preferred methods for Handwashing, cleaning and disinfecting the healthcare environment. It is important for healthcare personnel to recognize the role of patient healthcare environment as a transmission risk of multidrug-resistant infectious agents and adhere to prevention strategies for healthcare-associated infections based on current international guidelines and the literature. Further studies are needed to confirm our data and elucidate the relative importance of the patient-care items can serve as a source or reservoir for multidrug resistant bacteria in hospitals, including causation between contamination of a pathogen with a fomite and actual HAIs, elucidation of direct and indirect transmission mechanisms via a patient-care items using advanced molecular typing, and improvement of adherence to cleaning and disinfection practice.

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ORIGINAL ARTICLE

ANTIBODIES TO MICROBIAL ANTIGENS AND CYTOKINES IN THE CELLS OF THE PALATINE TONSILS AND SERUM OF CHILDREN WITH PALATINE TONSILS HYPERTROPHY AND CHRONIC TONSILLITIS

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ABSTRACT

The aim: The aim of the study is to compare the class G antibody content in serum and tissue lysate from tonsils of children with hypertrophy and chronic tonsillitis to: streptolysin–O of Str. haemolyticus, protein–A of S. aureus, proteoglycans of Klebsiela spp., as well as to compare the content of interleukins 1β, 10, TNF-α, γ-IFN and lactoferrin in serum and tissue lysate from tonsils of children with hypertrophy and chronic tonsillitis.

Materials and methods: We studied tonsils of 33 children aged 4-18 years with hypertrophy of palatine tonsils (HPT) and with chronic tonsillitis (CT). The content of interleukins 1β, 10, TNF-α, γ-IFN and lactoferrin in tonsil lysate and serum was determined by immunofluorescence assay. Antistreptolysin O was studied by neutralization test of micromethod; class G antibodies to protein A of S. aureus and proteoglycans of Klebsiela spp. were studied by treponema pallidum hemagglutination assay. All the results were statistically processed using U-test (Mann–Whitney–Wilcoxon test) and Fisher's z-transformation.

Results: The serum and tissue lysate from tonsils of patients with HPT showed significantly high level of antibodies to streptolysin O in comparison with similar studies of substrates from patients with CT. Anti-inflammatory cytokine IL-10 was detected only in the serum of patients with CT. The TNF-α concentration in the lysates of tonsils in the group of patients with HPT was 2 times higher than in the group of patients with CT. The γ-IFN concentration was significantly lower both in the serum and in the lysates of tonsils of patients with CT. The content of lactoferrin in the lysates of patients with CT was 3 times higher ($P<0.05$) than in the lysates of patients with HPT.

Conclusions: The results indicate a significant difference in the state of antibodies to microbial antigens and cytokines production in case of HPT and CT. In tonsils with HPT, there predominate reactions of antibody production to bacterial antigens and antiviral reactions like a high-level cytokines TNF-α and γ-IFN in tissue lysate of palatine tonsils.

KEY WORDS: Hypertrophy of palatine tonsils, chronic tonsillitis, immunity factors, interleukins, lactoferrin, antibodies

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INTRODUCTION

A very common abnormality in the clinical status of palatine tonsils is the state of their hypertrophy at an early age. Due to the clinical need, such tonsils are often the object for clinical intervention which involves partial resection of tonsillar tissue, that is tonsillotomy (partial tonsillectomy). The state of the palatine tonsil after such an intervention can hardly be defined as functionally preserved. In addition, taking into account present data on the role of this organ in the immune system, the development of the following local immune deficiency of mucous membranes can be assumed, an indicator of which is sIgA [1, 2]. The main pathological abnormalities in the state of tonsils are most often manifested as their hypertrophy or chronic inflammation.

Pathological characteristics and immunology research in recent decades have not identified significant differences between these conditions. And the development of new directions in immunology offered real possibilities for a more objective assessment of the tonsillar tissue state, the influence on the systemic and local immune response of various peptides formed in the palatine tonsils in case of hypertrophy and chronic inflammation [3, 4, 5, 6].

THE AIM

The aim of the study is to compare the antibody content in serum and tissue lysate from tonsils of children with hypertrophy and chronic tonsillitis to: streptolysin–O of Str. haemolyticus, protein–A of S. aureus, proteoglycans of Klebsiela spp, as well as to compare the content of interleukins 1β, 10, TNF-α, γ-IFN and lactoferrin in serum and tissue lysate from tonsils of children with hypertrophy and chronic tonsillitis.

MATERIALS AND METHODS

The content of cytokines and protective proteins in lysates of tonsil cells and serum of children with grade 2-3 hypertrophy according to Brodsky's classification and in those with with chronic tonsillitis was studied. The study involved 15 patients with CT and 18 patients with HPT aged 4-18 years.

Table I. The content of class G antibodies to microbial antigens in the lysates of the cells of tonsils and serum of children with CT and HPT.

Group of patients	Lg2 antibody titers (average) to microbial antigens					
	streptolysin O of Str. haemolyticus		protein A of S. aureus		proteoglycan of Klebsiela spp.	
	Lysate	Serum	Lysate	Serum	Lysate	Serum
CT (n=15)	1.3	4.5	0	4.0	0	2.1
HPT (n=18)	3.5*	8.5*	0	3.25	1.2*	3.6

Note: *P<0.05

Table II. The content of cytokines in the lysates of the cells of tonsils and serum of children with CT and HPT.

Group of patients	Concentration of cytokines, pg/ml							
	IL-1β		IL-10		TNF-α		γ-IFN	
	Lysate	Serum	Lysate	Serum	Lysate	Serum	Lysate	Serum
CT (n=15)	46.0	0.2	0	2.1	130.4	34.2	11.2	8.2
HPT (n=18)	41.6	0.2	0	0	236.0*	29.3	36.5*	19.6*

Note: *P<0.05

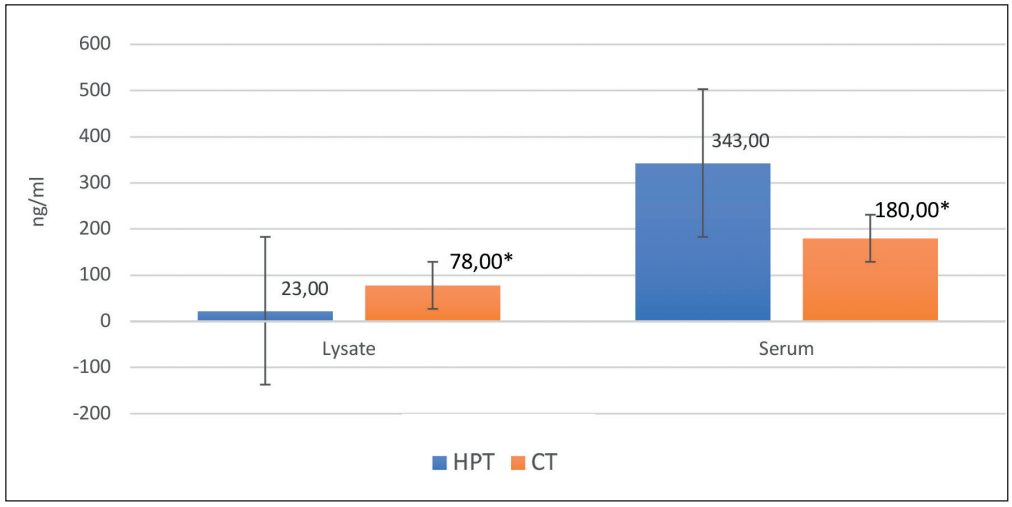

Fig. 1. The content of lactoferrin in the lysates and serum of patients with HPT (n=18) and CT (n=15). *(P<0.05).

After surgical removal, tonsillar extracts were immersed in 199 medium containing gentamicin (100 μg/ml), kept at 40°C, mechanically homogenized and filtered through a nylon sieve; the cell concentration was calculated, adjusted to a standard content of 1 ml and processed in lysis buffer, followed by incubation in isotonic saline solution and centrifugation.

Supernatants were frozen and stored for 1 month at a temperature of minus (-) 20°C, after which the concentration of cytokines and other peptides and proteins was determined. Serum was obtained from venous blood the day before surgery.

The content of IL-1, IL-10, tumour necrosis factor (TNF-α), interferon gamma (γ-IFN) and lactoferrin in tonsil lysate and serum was determined by immunoenzyme method and assay kits manufactured by "Proteinovy Kontur", "Cytokin" and "Vector-Best" (RF). A Stat-Fax-2100 reader (USA) was used as an analyzer. Antistreptolysin O was studied by neutralization test of micromethod; antibodies to protein A of S. aureus and proteoglycans of Klebsiela spp. were studied by treponema pallidum hemagglutination assay using LATEST reagent kits (RF). All the results were statistically processed using U-test (Mann–Whitney–Wilcoxon test) and Fisher's z-transformation.

RESULTS

The data on the content of class G antibodies to microbial antigens in the lysates of the cells of tonsils and serum of children with CT and HPT are presented in Table I.

As can be seen from Table I, a high level of antibodies is determined in relation to streptolysin O in the serum and lysates of the cells of tonsils in patients with HPT in comparison with similar studies of substrates from patients with CT. The antibodies to protein A of Staphylococcus aureus and proteoglycan of Klebsiela spp. were almost not detected in the lysates of tonsillar cells, and in the serum, they were at a lower level than to streptolysin O, and did not differ statistically in both comparison groups.

The data on the content of cytokines in the lysates of the cells of tonsils and serum of children with CT and HPT are presented in Table II.

As can be seen from Table II, the concentration of IL-1β in the serum of patients of both groups was minimal (<0.2 pg/ml), and in the lysates of the comparison groups it did not differ statistically. The anti-inflammatory cytokine IL-10 was detected only in the serum of patients with CT. The TNF-α concentration

in the lysates of the cells of tonsils in the group of patients with HPT was 2 times higher than in the group of patients with CT; in the serum there was no significant difference between the groups. The γ-IFN concentration was significantly lower both in the serum and lysates of the cells of tonsils of patients with CT.

When studying the concentration of lactoferrin in the lysates and serum of patients with CT and HPT, the following results were obtained (Figure 1).

As can be seen from Figure 1, the content of this iron-containing prodefensin in the lysates of the cells of patients with CT was 3 times higher (P<0.05) than in the lysates of patients with HPT, whereas in the serum the opposite significant dependence was determined.

DISCUSSION

The findings indicate a pronounced immunological activity of the tissue of the palatine tonsils both in case of hypertrophy and chronic inflammation. At the same time, a more intense production of antibodies in the tonsils with hypertrophy indicates a greater immunologic capacity of hypertrophied lymphoid tissue. This can also be evidenced by a pronounced inflammatory reaction in the palatine tonsils of patients with HPT, which is confirmed by the level of IL-1β no less than in the tonsils of patients with CT.

The analysis of the data on the TNF-α content, which was within the normal range in the serum of patients of both groups and significantly higher in the lysates of tonsillar cells of patients with HPT than those with CT, indicates an inflammatory reaction in the hypertrophied palatine tonsils, but mainly to viral antigens. This is also evidenced by a reliably high level of γ-IFN both in the lysates and serum of patients with HPT compared to similar substrates of patients with CT.

The findings indicate that the processes of antibody production to microbial antigens, especially hemolytic streptococcus, have a more intense course in the tonsils in case of HPT than in case of CT. The TNF-α content in hypertrophied tonsils is at a higher level than in CT, which, together with an increased content of γ-IFN, indicates antibody response of the immunity to infectious agents.

In addition, to gain the understanding of the role of individual parts of the immune system and allergy in the immunopathogenesis of both HPT and CT, it is necessary to conduct further studies on the range of abnormalities in the content and functional activity of molecular factors that are important in the implementation of protective reactions in the tonsils in both pathological conditions.

CONCLUSIONS

1. The level of class G antibodies to Str. haemolyticus in the lysates of patients with HPT was 2.7 times higher (P<0.05) than in those with CT, and in the serum of patients with HPT it was 1.9 times higher (P<0.05) than in those with CT.
2. The level of class G antibodies to Klebsiela spp. in the serum of patients with HPT was 1.7 times higher (P<0.05) than in those with CT.
3. The TNF-α concentration in the lysates of patients with HPT was 1.8 times higher (P<0.05) than in those with CT.
4. The γ-IFN concentration was reliably higher (P<0.05) in patients with HPT than in those with CT (3.2 times higher in the lysates, and 2.4 times higher in the serum).

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ORIGINAL ARTICLE

COMPARATIVE ANALYSIS OF CLINICAL AND LABORATORY CHARACTERISTICS OF MEASLES IN VACCINATED AND UNVACCINATED CHILDREN IN THE POLTAVA REGION (UKRAINE)

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ABSTRACT

The aim: To study the clinical and laboratory characteristics of measles, as well as to compare the course of this disease in vaccinated and unvaccinated children in the Poltava region (Ukraine).

Materials and methods: 104 inpatients with measles were examined: vaccinated (n=27) and unvaccinated (n=77). The patient examination program included: assessment of complaints and anamnestic data obtained by questioning (during admission to hospital treatment, during treatment and after discharge) and detailed analysis of medical records (Form № 003/y), physical examination, general clinical study of peripheral blood.

Statistical processing of the study results was carried out by methods of variation statistics using the program «SPSS 17.0».

Results: The clinical and laboratory picture of measles in the examined patients is typical for this disease. Measles vaccinated children are significantly less likely to have fever (p=0.001) and Koplik's spots (χ^2=3.80, p=0.051), the duration of fever (p=0.001), cough (p=0.000), and the length of hospital stay (p=0.000), as well as 3.0 times less often leukopenia is detected (p=0.043) and 2.0 times less often – acceleration of ESR (p=0.023).

Conclusions: The obtained data raise the question of expanding the explanatory work on the importance of a full course of preventive vaccination among children, as well as increasing the volume of public procurement of necessary drugs to increase public access to free vaccination.

KEY WORDS: measles, vaccination, children

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INTRODUCTION

A global strategic plan for measles and rubella control took place in the world from 2012 to 2020. Its aim was to eliminate measles by 2020 [1]. According to WHO estimated data for the period from 2000 to 2015 measles vaccination reduced the global mortality from this disease by 79 %: from 544000 cases of fatal outcomes in 2000 to 134000 – in 2015. However, the incidence of measles does not lose its relevance and, despite the possibility of effective prevention of this disease through vaccination, more than 20 million people become infected annually [2].

Outbreaks of measles periodically occur in many countries of the world, the main risk factor of which is insufficient immunological protection of the population due to factors such as increased internal and external migration, low vaccination coverage in violation of its schedules and timing, as well as unreasonable medical exemption from measles vaccination [3-7]. Mandatory vaccinal prevention, including measles, using the combined vaccine against measles, mumps and rubella, is regulated in our country by the MoH orders № 551 of 11.08.2014 «On improving the implementation of prophylactic vaccinations in Ukraine» and № 947 of 18.05.2018 «On making amendments to the calendar of prophylactic vaccinations in Ukraine». However, today Ukraine is on the list of 9 countries in the European region endemic for measles and over the past 15 years 80 % of cases of this disease have been reported among Ukrainians [8-9]. In recent years, an increase in the incidence of measles in Ukraine was observed in 2001, 2006 and 2012. [4, 10-11]. The next epidemic outbreak of this disease was recorded in the period 2017-2019, in particular in the Poltava region, which is explained by the relatively low coverage of measles vaccination in the years preceding the rise in the incidence rate [12].

Thus, the study of the clinical and laboratory characteristics of measles, as well as the comparative characteristics of the course of this disease in vaccinated and unvaccinated children, is an urgent scientific and practical task.

THE AIM

The aim of the research is to study the clinical and laboratory characteristics of measles, as well as to compare the course of this disease in vaccinated and unvaccinated children in the Poltava region (Ukraine).

MATERIALS AND METHODS

To achieve this goal 104 patients with measles were examined: girls – 54 (51.9 %), boys – 50 (48.1 %) aged 6 months to 16

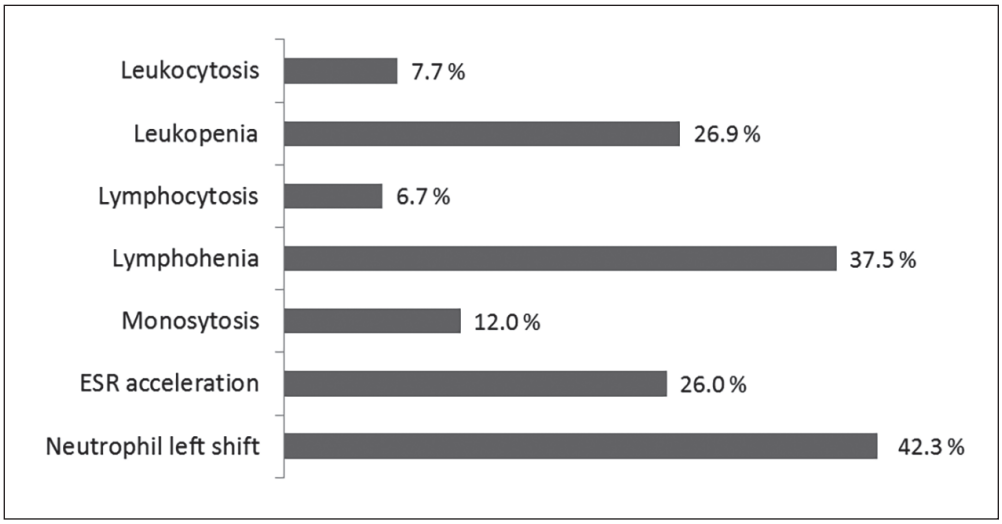

Fig. 1. An individual analysis of hemogram indicators of children with measles

Table I. Comparative characteristics of the clinical picture of measles in vaccinated and unvaccinated children

Symptoms	Groups of patients with measles		p
	I, n=27, abs. (%)	II, n=77, abs. (%)	
Maculopapular stage rash	24 (88.9)	73 (94.8)	0.372
Conjunctivitis	19 (70.4)	56 (72.7)	0.814
Koplik's spots	11 (40.7)	48 (62.3)	0.051
Dry cough	23 (85.2)	73 (94.8)	0.200
Fever	22 (81.5)	77 (100.0)	0.001

Note. The significance level was obtained using Fisher's exact test and χ^2 criterion, depending on the assumptions of the analysis.

years, average – 5.7±0.4. All patients were hospitalized in the children's infectious ward of the municipal enterprise «1st city clinical hospital of Poltava city Council» in 2017-2019. Patients' parents gave written consent to the processing of personal data.

The patient examination program included: assessment of complaints and anamnestic data obtained by questioning (during admission to hospital treatment, during treatment and after discharge) and detailed analysis of medical records (Form № 003/y), physical examination, general clinical study of peripheral blood.

Statistical processing of the findings was carried out using the program «SPSS 17.0».

To determine the central trend, the mean value and standard error of the mean value were used – in the sample n>100 or the median (*Me)* with the upper and lower quartiles *(Q1-Q3)* – in the sample n<100. The significance of differences in quantitative results was determined using the Mann-Whitney U-test, qualitative – by analyzing contingency tables using the exact Fisher test and χ^2 criterion depending on the assumptions of the analysis.

For all types of analysis, the differences were considered significant at p <0.05, at p in the range from 0.05 to ≤0.1 a tendency towards significance was marked.

RESULTS

The study found that the overall clinical picture of measles in the examined children was typical for this disease. Thus, a maculopapular stage rash occurred in 97 patients (97.3 %), conjunctivitis in 75 (72.1 %), Koplik's spots in 59 (57.6 %), dry cough in 96 (92.6 %), the average duration of which was 5.6±0.3 days and fever in 99 (95.2 %), the average duration is – 3.1±0.2 days.

General blood counts were as follows:

- erythrocytes from 3.0 to 5.0*1012/ l, on average – 3.9±0.3;
- hemoglobin from 80.0 to 160.0 g/ l, on average – 120.8±1.2;
- leukocytes from 1.9 to 12.6*109/ l, on average 5.5±0.2;
- ESR from 3.0 to 34.0 mm/h, on average 14.3±0.8;
- band neutrophils from 1.0 to 35.0 %, on average 6.9±0.5;
- segmented neutrophils from 15.0 to 78.0 %, on average 51.6±1.3;
- monocytes from от 1.0 to 14.0 %, on average 5.5±0.3;
- lymphocytes from 6.0 to 71.0 %, on average 34.1±1.4.

The data of an individual analysis of hemogram indicators of the examined patients are presented in Fig. 1.

As shown in fig. 1, leukocytosis occurred only in 7.7 % of patients, while leukopenia was 3.5 times more likely (26.9 %), lymphocytosis was 6.7 %, lymphopenia was 5.6 times more likely (37.5 %), monocytosis was 12.0%, and ESR acceleration was 26.0 %, leukocyte shift to the left – 42.3 %. Thus, the most characteristic changes in the hemogram are leukocyte shift to the left, lymphopenia and an acceleration of ESR.

The examined patients were divided into groups in order to compare the clinical and laboratory characteristics of measles in vaccinated and unvaccinated patients:

- I – vaccinated patients, n=27, girls – 10 (27.0 %), boys – 17 (63.0 %) aged 6 months to 16 years, *Me*=5,0 (2.0-11.0);
- II – unvaccinated patients, n=77, girls – 44 (57.1 %), boys – 33 (42.9 %) aged 6 months to 16 years, *Me*=4.0 (2.0-8.0).

Taking into account the low number of patients who received the full course of measles immunization (at 12

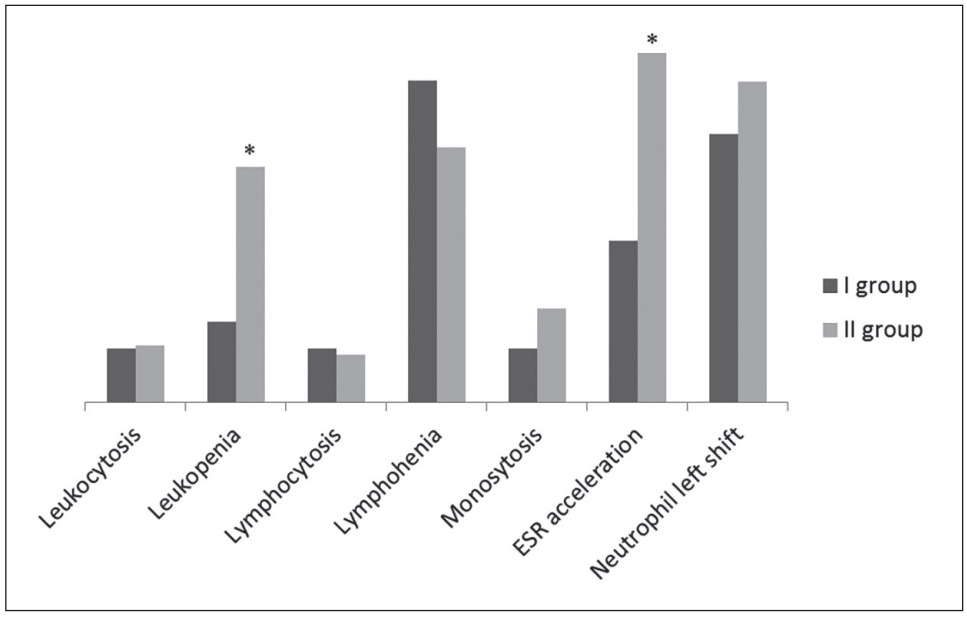

Fig. 2. Individual analysis of hemogram values for measles in vaccinated and unvaccinated children.
Note. – $p<0,05$ (significance level obtained using Fisher's exact test and χ^2 criterion depending on the assumptions of the analysis).

Table II. Comparative characteristics of hemogram indicators for measles in vaccinated and unvaccinated children

Indicators	Groups of patients with measles		p
	I, n=27, Me (Q1-Q3)	II, n=77, Me (Q1-Q3)	
Red blood cells	4.0 (3.9-4.1)	3.8 (3.6-4.2)	0.199
Hemoglobin	124.0 (118.0-130.0)	120.0 (110.0-128.0)	0.790
Leukocytes	5.2 (4.4-7.0)	5.0 (3.7-7.0)	0.272
ESR	8.0 (5.0-15.0)	16.0 (8.0-22.0)	0.005
Band neutrophils	5.0 (3.0-8.0)	6.0 (3.0-10.0)	0.769
Segmented neutrophils	53.0 (42.0-62.0)	51.0 (45.0-61.0)	0.967
Monocytes	2.0 (2.0-3.0)	6.0 (4.0-8.0)	0.000
Lymphocytes	34.0 (24.0-45.0)	35.0 (24.0-43.0)	0.798

Note. The significance level was obtained using the Mann-Whitney test.

months and 6 years) – n=3, that made statistical generalization impossible, these patients were assigned to group I.

Comparative characteristics of the clinical picture of measles in patients of groups I and II are presented in table I.

As can be seen in the table I, fever was significantly less frequently observed in patients of group I – in 22 (81.5 %) versus 77 (100.0 %) in group II (p=0.001), and also, with a tendency towards significance, Koplik's spots – 11 (40.7 %) and 48 (62.3 %) respectively (χ^2=3.80, p=0.051). By the frequency of other symptoms, there was no difference between the compared groups.

It should be noted that the fever in patients of group I lasted less than in II – from 0 to 6 days, *Me*=1.0 (1.0-4.0), while in II – from 1 to 7, *Me*=3.0 (1.0-5.0), p=0.001, the duration of cough in groups I and II was from 0 to 7 days, *Me*=3.0 (3.0-5.0) and from 0 to 14 days *Me*=6.0 (5.0-8.0) respectively, p=0.000.

Comparative characteristics of patients hemogram parameters of groups I and II are presented in table II.

As can be seen from the data in table II, in the hemogram of the examined patients, a significant difference between the I and II comparison groups was observed exclusively by the indicator of monocytes: 2.0 (2.0-3.0) % versus 6.0 (4.0-8.0) %, p=0.000, which, however, did not exceed the upper limit of normal. Other indicators were not statistically different and did not go beyond the reference values.

Then an individual comparative analysis of the hemogram data of the examined patients was carried out. The analysis revealed that significant differences in the comparison groups were observed in the frequency of registration of leukopenia and acceleration of ESR. So, in group I leukopenia was detected in 3 (11.1 %) patients, which was almost 3.0 less than in group II – in 25 (32.5 %), p=0.043, and acceleration of ESR – 2.0 times less often, 6 (22.2 %) and 37 (48.1 %) respectively, p=0.023. There was no difference in the frequency of registration of other indicators: leukocytosis – 2 (7.4 %) and 6 (7.8 %), p=1.0, left shift of the leukocyte formula – 10 (37.0 %) and 34 (44.2 %), p=0.652, monocytosis – 2 (7.4 %) and 10 (13.0 %), p=0.727, lymphocytosis – 2 (7.4 %) and 5

(6.5 %), p=1.0, lymphopenia – 12 (44.4 %) and 27 (35.1 %), p=0.386, respectively (Fig. 2).

When comparing the duration of inpatient treatment, it was also found that in patients of group I it was from 3 to 7 days, *Me*=5.0 (3.0-5.0), while patients of group II needed longer treatment and observation in a hospital – from 3 to 10 days, *Me*=7.0 (5.0-7.0), p=0,000.

DISCUSSION

As a result of our study we indicate a more severe clinical course of measles in unvaccinated children and more serious changes in laboratory parameters, which consistent with data from the scientific literature [13-15]. An increase in the length of stay in hospital was also established, which creates a significant burden on the health care system of Ukraine.

It is well known that to prevent measles outbreaks, the number of immunized people should be at least 95% [1-2]. According to official data, that the increase in the incidence of measles in the Poltava region and in Ukraine as a whole was preceded by years with a rather low coverage of the population with vaccination against this disease [4,8,12]. So, a relatively high percentage of vaccinated children in the Poltava region was observed only in 2012 and had a constant downward trend in subsequent years. During the period from 2013 to 2018, the absolute number of cases of measles registered in this region among children under 17 years old increased 13.6 times, and among adults – 24 times [12]. This disappointing situation is a consequence of the insufficient level of immunization among children, and also indicates the need for additional vaccination among adults.

However, with the joint actions of all healthcare professionals and the public, as well as appropriate financial support, in Ukraine and, in particular, in the Poltava region, there are conditions for high-quality preventive and anti-epidemic measures against measles, which meet an important strategic task related to the global elimination of this disease.

The obtained data raise the question of expanding the explanatory work on the importance of a full course of preventive vaccination among children, as well as increasing the volume of public procurement of necessary drugs to increase public access to free vaccination.

CONCLUSIONS

1. The clinical picture of measles and laboratory data in the examined patients are typical for this disease (maculopapular staged rash – 97.3 %, conjunctivitis – 72.1 %, Koplik's spots – 57.6%, dry cough – 92.6 %, fever – 95.2 %, leukocytosis – 7.7 %, leukopenia – 26.9 %, lymphocytosis – 6.7 %, lymphopenia – 37.5 %, monocytosis – 12.0 %, acceleration of ESR – 26.0%, leukocyte shift to the left – 42.3 %).
2. Measles vaccinated children are significantly less likely to have fever (p=0.001) and Koplik's spots (χ^2=3.80, p=0.051), the duration of fever (p=0.001), cough (p=0.000), and the length of hospital stay (p=0.000), as well as 3.0 times less often leukopenia is detected (p=0.043) and 2.0 times less often – acceleration of ESR (p=0.023).
3. The obtained data raise the question of expanding the explanatory work on the importance of a full course of preventive vaccination among children, as well as increasing the volume of public procurement of necessary drugs to increase public access to free vaccination.

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ORIGINAL ARTICLE

EFFICACY OF RECREATIONAL PHYSICAL ACTIVITY FOR PERIMENOPAUSAL WOMEN WITH HYPERTENSION ONSET

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ABSTRACT

The aim: To examine the effect of the developed wellness program on hemodynamic indices and psychological state of perimenopausal women.

Materials and methods: The study involved 27 women aged 39 to 47 years. Inclusion criteria: recorded perimenopause, climacteric syndrome, history of episodic increase in blood pressure up to 140/85 or 150/90 mmHg. Exclusion criteria: primary hypertension, diabetes mellitus, chronic contagious, systemic, oncology diseases, and mental illnesses. Research procedure comprised tracing of the heart rate, blood pressure registration, and pulse pressure calculation. Robinson index, the coefficient of endurance according to A. Kvas formula were calculated. The assessment of psychological state was made using the Spielberger-Khanin Inventory.

Results: Multidisciplinary professionals gave classes upon wellness program at "Women's Health" school. The program included educational conversations, healthy walking, massage, psycho-corrective exercises. The dynamics of the studied parameters was analyzed after 12 weeks. Based on the anthropometric measures findings the tested women showed improvement of 6,76% weight loss; and their body mass index decreased by 6,77%. Initial numbers of Robinson index and the coefficient of endurance were above normal values. After working under the program statistically significant dynamics was observed ($p < 0,05$), although there were still signs of cardiovascular disorders. There were statistically significant positive changes Spielberger-Khanin Inventory on State Anxiety (-9,09%) and Personal Anxiety Scales (-6,96%) ($p < 0,05$).

Conclusions: Early detection of risk factors and physical activity will help to bring a vast improvement to prognosis and quality of life of perimenopausal women with hypertension onset.

KEY WORDS: recreational physical activity, psychological state, Robinson index, coefficient of endurance

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INTRODUCTION

The first signs of perimenopause in women, that is irregular period, develop after 40, however the latest scientific data show earlier onset of this period. Perimenopause in each woman involves specific physiological changes of different organs and systems associated with ovarian failure and loss of function [1-3]. Failure to produce estrogen provokes endothelial dysfunction and increased body mass index which accounts for development of hypertension. Arterial hypertension (AHT) is rated as one of the determinants of cardiovascular death. As reported by WHO cardiovascular diseases (CVD) are the leading cause of mortality in European and American countries. In the previous decades more serious epidemiological situation was more prominent among men resulting in underestimation of the significance of precursory symptoms of AHT in women. Over the last years there has been heightened interest in women's health during menopause when persistent elevation in blood pressure starts [4-7].

Prominent autonomic balance, sympathetic nervous system activation, clinical manifestations of autonomic dysfunction progress during perimenopause [8,9]. The effect of risk factors on nosogenesis and prognosis of CVD takes attention of many scientists. Psycho-emotional stress, environmental pollutants, bad health habits, physical inactivity are associated with development of various vasculomotor, neuropsychic, endocrinous and metabolic as well as cardiovascular disorders significantly worsening not only the quality of life but also prognosis for the future [7,10,11].

From the psychosocial aspect women often associate this transition period in their life with senility. Many women may experience heavy mental workload, lack of control over their life, anxiety, confusion and emotional void. Some women seek to confront these age-related difficulties by using alcohol or drugs which aggravates the problem even more [4,10,12].

More pronounced meteosensitivity is present in women during menopause. Typically causes of such state resulting in failure of immune system, are as follows: ill-balanced and unhealthy diet; lack of fresh air; chronic fatigue and frequent stress situations; bad health habits; unfavorable ecological setting; lack of physical activity [8,9].

The development of wellness programs comprising kinesitherapy, mindset training, massage, and partnership expansion programs play the essential role in improving the quality of life of such patients. Thus, North American Menopause Society (NAMS) experts suggest that women

having mild presentation of vasculomotor symptoms initially change their lifestyle and use drug-free aids as treatment [9]. The study by Kronenberg F., Fugh-Berman A. proved the effect of breathing techniques on sympathetic nervous system and hot flash frequency reduction by 35% and more compared to muscular relaxation [cit. 13]. Nelson H.D., Haney E., Humphrey L. et al. (2005) in their study used methods of traditional Chinese medicine such as yoga, acupuncture, herbal therapy to treat hot flash, however, the efficacy of this program was not proved [11,12].

Despite the proven effects of kinesitherapy and psychocorrection methods on the state of the body system of perimenopausal women, the studies of the efficacy of the comprehensive approach to preventing AHT by drug-free modalities were not conducted. In scientific literature there are works related to the development of wellness programs for the age category of population, aimed at improving quality of life [14-17]. Considering that worldwide working age population die from CVD, and now it is not only a healthcare problem but also an economic one, AHT prevention in perimenopausal women is subject to importance of wellness programs development [18,19].

THE AIM

To examine the effect of the developed wellness program on hemodynamic indices and psychological state of perimenopausal women.

MATERIALS AND METHODS

"Women's Health" school was created at the premises of Kharkiv State Academy of Physical Culture. The study involved 27 women aged 39 to 47 years. Inclusion criteria: recorded perimenopause, climacteric syndrome, history of episodic increase in blood pressure up to 140/85 or 150/90 mmHg. Exclusion criteria: primary hypertension, diabetes mellitus, chronic contagious, systemic, oncology diseases, and mental illnesses. The research related to human use has been complied with all the relevant national regulations and institutional policies, principles of the Helsinki Declaration, adopted by the General Assembly of the World Medical Association (1964-2000), the Council of Europe Convention on Human Rights and Biomedicine (1997).

Detailed analysis of life record data showed that body weight gain, decrease in physical activity, eating disorders, lability of nervous system, response to weather condition changes in the form of headaches and elevation in blood pressure were present in all women over the last 3 to 5 years. Research procedure comprised tracing of the heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) registration, and pulse pressure (PP) calculation. Robinson index and the coefficient of endurance were calculated. The assessment of psychological state was made using the Spielberger-Khanin Inventory.

Robinson index (RI) is used to assess the level of metabolic and energy processes in the body. It is representative of the level of hemodynamic load on the cardiovascular system (CVS). RI shall be calculated using the following formula: $RI = HR_r \times SBP/100$, where HR_r – is resting heart rate, bpm; SBP – systolic blood pressure, mmHg. Average value of the RI is 81 to 90 c.u., more than 111 c.u. – is impaired regulation of CVS.

Coefficient of endurance (CoE) is a descriptor of CVS condition level while performing physical activity. It is determined from A. Kvas formula: $CoE = (HR_r \times SBP \times 10) / PP$, where HR_r – is resting heart rate, bpm; SBP – systolic blood pressure, mmHg; PP – pulse pressure, mmHg. Normative value is equal to 16 c.u., an increase in CoE indicates CVS deconditioning.

Spielberger-Khanin inventory enables differentially assessing anxiety according to two subscales both as trait and state associated with the current situation. State anxiety scale (S-anxiety) is a descriptor of individually experienced emotions at that moment. Trait anxiety scale (T-anxiety) is a constitutional trait accounting for proneness to perceive threat over a wide range of situations. The results of survey were recorded in points, and their interpretation were as follows: less than 30 points – mild anxiety, 31-45 point – moderate anxiety, 46 and more points – severe anxiety.

Statistical processing was carried out using STATISTICA 13.0 (StatSoft) statistics package.

RESULTS

The operation of "Women's Health" school was aimed at teaching recreational physical activity to women for the purpose of improving their quality of life [20,21]. A multidisciplinary team was created to work upon the program. The team included a physical therapist, teacher, rehabilitation coach, psychologist, massage therapist.

While making the program by physical therapist, the principles of physical therapy and pedagogical cooperation, specifically affordability, integrity and multidisciplinarity, were followed [22]. The program provided conversations on health promotion, healthy walking, peer massage of neck and collar area, psychocorrective exercises.

Educational part of the program included conversations with women to form their strong beliefs about the need for lifestyle changes, eating behavior correction and fulfilling recreational physical activity requirements; information on menopause, structure and functions of body systems, pathogenesis and medical and social consequences of CVD, meteosensitivity prevention.

At the beginning of the program 3 to 5 women wearing light clothing supervised by the rehabilitation coach walked every other day in the park area during 45 minutes, first at a slow pace 60 to 70 steps per minute at a distance of 500 to 700 m. Starting from day 10, the route of 800 to 1500 m was set, walking pace was gradually increased up to 80 - 90 steps per minute and lasted for 45 to 60 minutes. It was recommended to control breathing. Inhale when making the 2 steps, exhale during the next 3-4 steps. Sessions should be regular, since cumulative positive effect subsides after their cancellation [7,10].

The massage therapist ran classes with women on practical mastery of peer massage session [23]. Peer massage technique includes the following maneuvers:

Table I. Dynamics of anthropometric measures of perimenopausal women

parameter	women (n=27)		p
	initial data	data after the program	
	X ± m	X ± m	
height, cm	165,00±2,37	165,00±2,37	>0,05
weight, kg	74,00±2,18	69,00±1,43	>0,05
BMI, kg/m2	27,18±0,94	25,34±0,67	>0,05

Table II. Positive changes of hemodynamic indices of perimenopausal women with AHT onset

parameter	women (n=27)		p
	initial data	data after the program	
HR, bpm	87,08±1,31	78,55±1,56	<0,05*
SBP, mm Hg	138,13±1,59	127,78±1,39	<0,05*
DBP, mm Hg	87,22±0,74	74,73±0,63	<0,05*
PP, mm Hg	50,91±0,85	53,05±0,76	<0,05*

Note: * statistically significant differences in the dynamics of values

Table III. Dynamics of systolic heart function values of the perimenopausal women with AHT onset

parameter	women (n=27)		p
	initial data	data after the program	
Robinson index, c.u.	120,28	100,37	<0,05*
Coefficient of endurance, c.u.	17,1	14,8	<0,05*

Note:* statistically significant differences in the dynamics of values

1. Palmar surface of both hands laid on the neck and shoulder girdle; and a light spiral rubbing of the neck and shoulder girdles was performed with light force. After that palms moved to scapular and interscapular region. This rubbing was performed for 30 to 40 sec.

2. Two palms laid on shoulder girdle muscles, then one of them smoothly stretch while the other goes opposite way. The distance between palms shall be 5 to 6 cm. Quantity – 2 to 3 times each side.

3. Shoulder girdles were kneaded starting from neck and to the shoulder joints using heel of the hand; 2 to 3 passed each side; interscapular region from inferior angle of scapula up to neck-shoulder point, 2 to 3 passes; from medial border of scapula towards shoulder joints, 2 to 3 passes each side.

4. At the end 4 to 5 active moves on maximum retraction and protraction of scapula were performed. The whole session took 4 to 5 minutes [23].

The psychocorrective unit involved running 9 sessions lasting 90 minutes and doing exercises without assistance. Common activity; work in subgroups (3 to 4 women); and individual work were used. Psychocorrective unit sessions started with motivational fun games aimed at forming the atmosphere of trust within the group [24,25]. Art therapy and body-oriented therapy methods were used during psychocorrective sessions. Art therapy and body-oriented therapy methods incited women to speak through their unconscious emotions.

Respiration management was used to decrease anxiety level of the women. All respiration exercises were divided into sets: 8 repetitions per one set. Stimulating respiration exercises were performed seated or in the upright position; relaxation ones were done in a supine position. The number of repetitions increased gradually, and the quality of respiratory load also changed. To promote their mental state, the women were offered to do respiration exercises stimulating sympathetic division of nervous system: focus on inhalation (loudly, deeply), exhalation (quietly). To relax their current state women were taught diaphragmic respiration. Also, hypnosis and neurolinguistic techniques were used during psychocorrective sessions to form attitudes to preserve and strengthen mental health.

After 12 weeks the physical therapist analyzed the dynamics of the studied parameters. The following changes took places within the group of persons at "Women's Health" school. Thus, according to the results of anthropo-

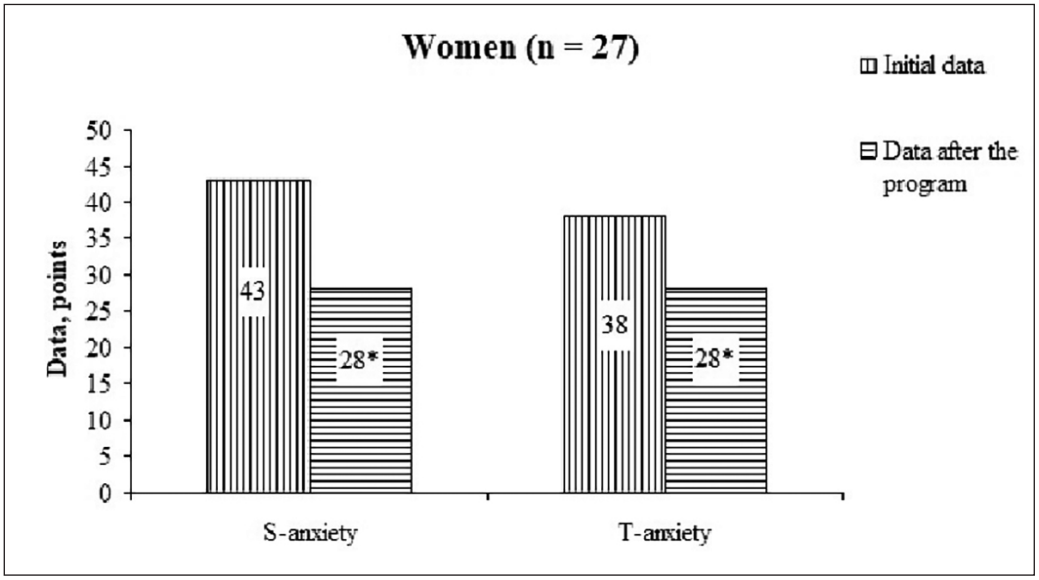

Fig. 1. Dynamics of medians of indicators of the psychological state of perimenopausal women
Note:* statistically significant differences in the dynamics of values

metric measures the tested women showed improvement of 6,76% weight loss; and their body mass index decreased by 6,77% (table I).

Although no statistically significant dynamics was observed (p>0,05), after wellness program perimenopausal women had a pronounced tendency to decrease body weight and BMI.

After working upon the program an improvement in all hemodynamic indices was observed. Thus, HR values significantly decreased by 9,80%, SBP by 7,49%, DBP by 14,32% (<0,05). PP value statistically significantly increased by 4,20% (<0,05) (table II).

Based on the findings of hemodynamic indices for quantitative assessment of systolic heart function, the Robinson index was calculated and coefficient of endurance (CoE) according to Kvas formula was estimated. At initial examination mean value of the Robinson index in the group of women was 120 c.u., which is 1,28 times higher than the normal value and is declarative of impaired regulation of cardiovascular system. CoE according to the Kvas formula during the initial calculation showed weakening of cardiovascular system: while the normal value is 16 c.u., among the tested women this parameter got the value equal to 17,1 c.u. (table III).

Analysis of the dynamics showed positive changes: Robinson index and CoE decreased by 16,55 and 13,45% respectively. After working upon the program statistically significant dynamics was observed (p <0,05), although there were still signs of cardiovascular disorders.

Considering the fact that psychological disorders are among compromising factors of AHT progress and adversely affect cardiovascular performance, the Spielberger-Khanin inventory on trait (T-anxiety) and state (S-anxiety) anxiety scales was conducted among perimenopausal women. When assessing psychological state of the tested persons, statistically significant increase in state and trait anxiety level according to Spielberger-Khanin inventory was determined compared to normal values (p <0,05). After completing the wellness program, there was a statistically significant dynamics of Spielberger-Khanin Inventory on State Anxiety Scale (-9,09%) and (-6,97%) on Trait Anxiety Scale (p <0,05) (fig.1).

Thus, there were positive changes in hemodynamic indices and psychological state of perimenopausal women with AHT onset affected by the developed wellness program.

DISCUSSION

Perimenopausal women experience persistent increase in arterial blood pressure. The issues of the quality of life of perimenopausal women are poorly covered in the literature, inadequate attention is given to the development of wellness programs, occasionally wellness programs for the elderly can be found. Development of recreational physical activity program should be aimed at meeting the needs and components to improve the quality of life of the women during this period. Health and wellness program should include physical activity, correction of eating behavior, psychocorrective exercises, behavioral components such as meteosensitivity conditioning which is shown in our study [6,8-10,19].

Perimenopausal women's data obtained during the study showed the disposition towards increase in weight and BMI emphasizing the importance of this risk factor for AHT progression. An increase in impaired regulation of CVS was indicated, which is subject to the predominance of increased BP values. An increase in anxiety level according to Spielberger-Khanin Inventory was indicated. All of the above data point to a decrease in the quality of life of perimenopausal women.

To prevent AHT it is necessary to do moderate aerobic physical activity. Prospective study shows that CVD risk is 30% higher for physically non-active middle-aged people. The study confirmed that regular moderate physical activity promotes the development of adjustment reactions, immunity to environmental exposure, increased metabolism in tissues, coping with hypoxia, heart function economy [13-17].

Nelson H.D. et el., Agmon, M. et el. [11], studied the effect of healthy walking and fitness on clinical condition of the women having symptoms associated with menopause. The analysis of the positive changes in hemodynamic indices and parameters of psychological state of the women from "Health school" confirmed the results of the similar study.

Thus, currently there is no framework defining the development of wellness programs which could detect preterm hemodynamic and psychological changes in this category of women. Early detection of risk factors and targeted influence on physical activity and psychological state will help to significantly improve the prognosis and quality of life of perimenopausal women.

CONCLUSIONS

Based on the study, the changes in hemodynamic indices and psychological state were detected in the perimenopausal women with AHT onset, which confirms the risk of CVD progression. The dynamics of the above parameters was statistically significantly positive: the general state of health improved, psychological state recovered, and the tolerance to physical and psychological stress has increased.

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ORIGINAL ARTICLE

AFFECTIVE-COGNITIVE INDICATOR OF EMOTIONAL INTELLIGENCE FORMEDNESS IN HIGH SCHOOLERS WITH INTELLECTUAL DISABILITIES

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ABSTRACT

The aim is to determine the peculiarities of the affective-cognitive indicator of emotional intelligence in high schoolers with intellectual disabilities.

Materials and methods: The study, which was conducted during 2019-2020, involved 76 high schoolers in the age of 14-17 who studied in the 7-9th grades in Kyiv schools (Ukraine) (45 high schoolers with intellectual disabilities and 31 high schoolers with normative development). The diagnosis of the high schoolers' ability to perceive, understand and identify emotions; to assimilate emotions in thoughts, to stimulate thought processes with the help of emotions was carried out. The Mayer-Salovey-Caruzo Emotional Intelligence Test, adapted for children with intellectual disabilities, was used.

Results: Insufficient formedness of the affective-cognitive indicator of emotional intelligence in high schoolers with intellectual disabilities has been determined: a decrease in the level of perception of emotions by expression; superficial perception of expressive features, vagueness of ideas about them; insufficient differentiation of the constituent elements of the emotional model; difficulties of orientation in a set of emotional signs of different modalities; lack of understanding of social emotions and the content of a moral act.

Conclusions: It has been proven that the low state of formedness of the affective-cognitive indicator of emotional intelligence results in significant difficulties that arise during interaction with each other, and this affects primarily the further socialization and integration into society.

KEY WORDS: emotional intelligence, emotionality, affective-cognitive indicator, intellectual disabilities

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INTRODUCTION

New tasks of modern education reform in relation to the teaching and upbringing of high schoolers with special educational needs require the formation of the foundations of life competence of individuals with intellectual disabilities [1-6]. One of the key determinants of the success of social adaptation of persons in this category is the formedness level of their affective-cognitive indicator of emotional intelligence. The study of the affective-cognitive indicator is a new segment in the research of emotional intelligence of an individual with special educational needs. The importance of solving the problem of emotional development is stipulated by the growing number of children with intellectual disabilities, who are officially diagnosed with low levels of cognitive processes, behavioural disorders, maladaptation in the educational and social environment [7-14].

Determining the directions of formation of affective-cognitive indicator of emotional intelligence in high schoolers with intellectual disabilities makes it possible to outline the prerequisites for their becoming as individuals, their successful inclusion in social life and ability to adapt to changing social environment.

In view of this, first of all it is necessary to characterize the concept of emotional intelligence, which is considered by scientists as ability, set of abilities, group of mental abilities, capability, regulator, indicator, factor, integral category, cognitive capability, psychological phenomenon, resource, cognitive-personal composition, etc. [15-18].

Therefore, it should be noted that the main attention in the research of emotional intelligence was paid to the study of its psychological structure and relationships with other intrapersonal manifestations. Less studied are the issues of formation of the affective-cognitive indicator of emotional intelligence, namely: perception, recognition and understanding of one's own emotions, emotions of other people at different age stages of mental development of a personality. In addition, the available research does not provide a clear understanding of psychological conditions, peculiarities, factors, mechanisms of formation of affective-cognitive indicator of emotional intelligence in high schoolers with intellectual disabilities.

THE AIM

The aim of this study is to determine the peculiarities of the affective-cognitive indicator of emotional intelligence in high schoolers with intellectual disabilities.

MATERIALS AND METHODS

The vision of emotional intelligence as a set of abilities that form an affective-cognitive construct requires a certain specificity of the organization of the ascertaining study. Thus, in order to identify the formedness of affective-cognitive indicator of emotional intelligence of high schoolers with intellectual disabilities, we conducted the experimental research, which involved 76 high schoolers in the age of 14-17 who studied in the 7-9th grades in Kyiv schools (45 children with intellectual disabilities and 31 high schoolers with normative development). The study in comparative terms makes it possible to more thoroughly identify the specific peculiarities of the affective-cognitive indicator of emotional intelligence in high schoolers with intellectual disabilities. At the same time, the performance of diagnostic tasks by children with normative development serves as an indicator of the age norm.

The study of the formedness of affective-cognitive indicator of emotional intelligence in high schoolers with intellectual disabilities was carried out in several stages according to certain criteria, which allowed determining the levels of formedness of affective-cognitive indicator of emotional intelligence of high schoolers with intellectual disabilities. The first stage involves the diagnosis of the ability to perceive, understand and identify emotions. This stage involved the usage of MSCEIT v. 2.0 (The Mayer-Salovey-Caruzo Emotional Intelligence Test), adapted for children with intellectual disabilities; the second stage includes the diagnosis of the ability to assimilate emotions in thoughts, to stimulate thought processes with the help of emotions using the method of N. Hall [19].

We used the rank correlation coefficient according to the two-sided Student's t-test (for independent, unrelated samples) to compare the results of the study. The results were considered reliable at $p < 0.05$.

The study was performed in accordance with the requirements of the Code of Ethics of Scientists of Ukraine, approved by the Resolution of the General Meeting of the National Academy of Sciences of Ukraine (Protocol No. 2 of April 15, 2009). According to its provisions, the members of the scientific community are guided by the rules of ethical conduct and professional communication; respect the principles, values, norms, rules, and conditions of academic honesty in their activities. The preliminary consent to participate in the research was obtained from all respondents.

RESULTS

The peculiarities of the affective-cognitive indicator were studied in the course of the research i. e. the perception of expressive signs of emotions, types of perception of expression. To this end, the ability to adequately recognize and verbalize the emotional state presented in the schematic image was studied.

The quantitative and qualitative analysis of the results of the study revealed that high schoolers with intellectual disabilities (ID) have mostly medium and low levels of expression perception, the number of established expressive traits is much lower (62.5%) than in high schoolers with normative development (ND) (80 %). The results of the study of the level of perception of expressive signs of emotions are presented in Table I.

The Student's t-test was used to assess the significance of differences between the levels of perception of expression found during the comparative analysis of the studied groups of high schoolers. Numerical values of the Student's t-test between the groups of children (ID and ND) are statistically significant: between the 7th grades high schoolers with ND and ID ($t = 3.63$ at $p \leq 0.05$); between the 9th grade high schoolers with ND and ID ($t = 3.23$ at $p \leq 0.05$), as well as in the groups of high schoolers: between the 7th grade high schoolers with ND and the 9th grade high schoolers with ND ($t = 3, 09$ at $p \leq 0.05$); between the 7th grade high schoolers and the 9th grade high schoolers with ID ($t = 2.05$ at $p \leq 0.05$).

Thus, the perception of expressive signs of emotions in high schoolers with intellectual disabilities is at a lower level of development, compared with the age norm. The high schoolers with ID are completely unable to perceive, recognize and understand their own emotions and the emotions of other people, they explain one emotion through another (difficulties at the stage of categorization are primarily related to the underdevelopment of mental activity, memory and imagination); lack of self-awareness and awareness of another person (indicating a low level of value of another person for adolescents with ID).

In contrast to the high schoolers with intellectual disabilities, the children with normative development correctly interpreted the meaning of the emotional pictogram focusing on their emotional experience; they could explain the presence of those signs of expression that indicated the emotion. There was a statistically significant difference in groups between the 7th grade high schoolers: between the pre-schoolers with ND and the high schoolers with ID ($t = 4.19$ at $p \leq 0.05$). The same was seen in the groups between the 9th grade high schoolers: between the children with ND and ID ($t = 2.79$ at $p \leq 0.05$); there was also a significant difference in the groups between the 7th grade high schoolers with ND and the 9th grade high schoolers with ND ($t = 1.57$ at $p \leq 0.05$).

Analysing the level of understanding of the expressive signs of high schoolers' emotions, significant differences were revealed in this indicator between the children with ND and high schoolers with ID. Three levels were identified based on the analysis of the content of understanding of emotions by high schoolers with ID: high, medium and low (Table II).

There was a statistically significant difference in the groups between the 7th grade high schoolers with ND and the 9th grade high schoolers with ND ($t = 1.32$, $p \leq 0.05$).

Table I. Comparison of the levels of expression perception in the high schoolers with ND and ID, %

Grade	The level of expressive traits perception					
	High schoolers with normative development			High schoolers with intellectual disabilities		
	High level	Medium level	Low Level	High level	Medium level	Low level
7th grade	27	51.5	21.2 %	10	46.7	43.3
9th grade	47	41.2	11.8	11.1	61.1	27.3

Table II. Comparison of the levels of understanding of expressive signs of emotions in the high schoolers with ID and ND, %

Grade	The level of understanding of expressive signs of emotions					
	High schoolers with normative development			High schoolers with intellectual disabilities		
	High level	Medium level	Low Level	High level	Medium level	Low level
7th grade	37.3	55.4	7.3	10.7	46.4	42.9
9th grade	39.5	58.8	1.8	13.6	54.6	31.8

Table III. Comparison of the levels of emotional identification in the high schoolers with ID and ND, %

Grade	The level of emotional identification					
	High schoolers with normative development			High schoolers with intellectual disabilities		
	High level	Medium level	Low Level	High level	Medium level	Low level
7th grade	37.3	61.5	1.2	17.8	39.3	42.9
9th grade	39.5	59.8	0.7	13.6	59.1	27.3

The peculiarities of emotional identification, the peculiarities of correlation of emotion expressive signs were studied in the course of performing experimental tasks. The analysis of experimental data showed that the establishment of the emotion identification was common to all categories of children. At the same time, the high schoolers with ND independently organized activities, and the high schoolers with ID did not begin to perform tasks due to the narrowing of the scope of their perception. The results of the study of the levels of identification of emotions in the high schoolers with ID and ND are presented in Table III.

In our opinion, the causes of difficulties in identifying emotions can be justified by the peculiarities of the mechanisms of identification of emotions in high schoolers with intellectual disabilities, they do not have adequate terms to describe the emotions of another person, children are able to identify an emotion based on only one source of information i. e. the situation in which the character found himself or his facial expression. On the other hand, the identification of emotions is influenced by the shortcomings of intellectual functions, as well as the conditions in which the high schoolers with ID live and are brought up.

The method of mathematical statistics revealed a significant difference in the groups between the 7th grade high schoolers: between the high schoolers with ND and ID ($t = 1.63$ at $p \leq 0.05$). A significant difference was revealed in the groups of the 9th grade high schoolers, in particular between the high schoolers with ND and ID ($t = 2.67$ at $p \leq 0.05$). There was a significant difference between the groups of the 7th grade high schoolers with ND and the 9th grade high schoolers with ND ($t = 2.44$ at $p \leq 0.05$), between the 7th grade and the 9th grade high schoolers with ID ($t = 2.44$ at $p \leq 0.05$).

DISCUSSION

The theoretical basis of our theoretical and experimental research was the position that increased emotional competence improves psychological and physiological well-being, which is a necessary condition for socialization and integration into society [6, 20-27]. In support of the position of scientists, our study showed that high schoolers with intellectual disabilities are characterised by insufficiently developed emotional competence, in contrast to high schoolers with normative development.

Our study is also a supplement to the conclusions made by Chetveryk-Burchak [28] that the mechanisms of emotional intelligence, which are based on a positive or negative attitude towards the object, the focus on the object or away from it and the modality of emotion affect the life-sustaining activities of the individual.

At the same time, our results complement the scientific research by Megías, Gutiérrez-Cobo, Fernández-Berrocal, Cabello, & Gómez-Leal [12] in terms of the fact that emotional intelligence is associated with perceptual, cognitive processes, as well as their physiological characteristics. It should be noted that the high schoolers with intellectual disabilities have mostly low and medium levels of perception, understanding of expressive signs and arbitrary expression of emotions of different modalities, which affects the formation of their personality and successful inclusion in social life and ability to adapt to changing social environment.

CONCLUSIONS

The analysis of the psychological literature showed gaps in the study of emotional intelligence in high schoolers with

intellectual disabilities. This became the basis of our experimental study. Thus, it was found that the high schoolers with intellectual disabilities are characterised by insufficiently formed affective-cognitive indicator of emotional intelligence; the low state of this indicator formedness results in significant difficulties that arise during interaction with each other.

The results of our study give the right to ascertain the existing problems in the personal development and emotional intelligence of high schoolers with intellectual disabilities. They feel unprotected, have emotional anxiety and are therefore highly dependent on their surroundings. The presence of deep originality of emotional and volitional development largely determines the low level of affective-cognitive indicator formedness, being one of the reasons for low social activity and low level of social adaptation of children in this category. This situation encourages the delineation of areas of correctional work on the formation of affective-cognitive indicator of emotional intelligence of adolescents.

We consider it promising to study the levels of emotional intelligence formedness in high schoolers with intellectual disabilities of middle and senior school age in secondary schools in comparison with their healthy peers.

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ORIGINAL ARTICLE

SURGICAL TREATMENT IMMEDIATE RESULTS OF LOWER LIMBS CHRONIC CRITICAL ISCHEMIA IN SIMMULTANEOUS DIRECT AND INDIRECT REVASCULARIZATION

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ABSTRACT

The aim: To assess the immediate results of autovenous femoral-tibial shunting in combination with rotary osteotrepanation of the tibia by studying changes in the transcutaneous ptO2 tension in the tibia and foot tissues depending on the revascularization of the tibial arteries.

Materials and methods: We analyzed the treatment of 69 patients with obliterating atherosclerosis of the vessels of the lower extremities. According to the degree of ischemia of the lower extremities, the patients were distributed as follows: III A degree of ischemia - 20 (29%), III B - 28 (40.6%), IV - 21 (30.4%) patients.

All patients had atherosclerotic lesions of the popliteal-tibial segment of the great arteries with preserved central blood flow in the aorto-iliac segment**.**

Results: Occlusion of the anterior tibial artery was recorded significantly more often than the peroneal artery (72% and 42%, respectively, $p = 0.05$), but with the same frequency compared to the posterior tibial artery (68%, $p = 0.61$).

The lesion of two or three arteries of the lower leg was recorded more often than occlusion of one ($n = 51$; 73.9% and $n = 18$; 26.1%). Occlusive-stenotic lesion of the popliteal artery was observed in 54 (78.2%) patients.

The highest incidence of lesions of the tibial arteries was observed in the basin of the anterior tibial artery in 28 (40.6%) patients. Combined lesions of the anterior tibial artery and posterior tibial artery were diagnosed in 19 (27.5%) patients. Limited lesions of the posterior tibial artery were found in 15 (21.7%) patients. The combination of lesions of the posterior tibial artery and peroneal artery was diagnosed in 7 (10.2%) patients.

Conclusions: 1. The patency of the femoral-tibial autovenous shunt during the year was 71%. High limb amputation was performed in 29% of patients.

2. According to CT data, the localization of trophic changes on the foot during critical ischemia of the lower extremities corresponds to the affected segment of the arterial angiosome, which supplies the corresponding area with blood.

3. After femoral-tibial autovenous bypass grafting, the highest levels of transcutaneous oxygen tension were observed in the basin of the posterior tibial artery and peroneal artery, and the lowest indicators of transcutaneous oxygen tension were observed in the basin of the anterior tibial artery.

4. During femoral-tibial autovenous shunting operations in combination with rotary osteotrepanation, the transcutaneous oxygen tension indices increased threefold in the angiosomal basin of the posterior tibial artery and peroneal artery, and twofold in the angiosomes of the dorsum of the foot and sole.

KEY WORDS: chronic ischemia of the lower extremities, distal autovenous femoral-tibial shunting, transcutaneous oxygen tension, angiosomal theory

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INTRODUCTION

Treatment of occlusive diseases of the arteries of the lower extremities is one of the urgent and difficult tasks of surgery. Reconstructive surgery is associated with a high risk, and in 25-40% of patients it is impossible to perform the intervention due to the prevalence of the occlusive process [1-4]. In the absence of an adequate distal vascular supply, the development of purulent-necrotic processes in the affected limb and the presence of contraindications to reconstructive surgery, conservative therapy or amputation remain the only treatment techniques [1-4]. For these patients in complex treatment, it is possible to perform indirect methods of revascularization - rotary osteotrepanation of the tibia (ROT) - as an alternative to the amputation of the lower limb [2-5].

Theoretically, for the onset of a full-fledged effect after ROT surgery, months are required, during which collateral circulation will gradually develop. Rotary osteotrapation of the tibia increases possibilities of limb salvage or performance of more favorable resection operations on the foot in patients with IV grade limb ischemia [2,3,6].

However, some authors note the effect of revascularization osteotrepanations almost immediately after surgery, which is manifest s both clinically and by an increase of the transdermal pO2 [2-5]. Rotary osteotrepanation of the tibia can be performed alone or in combination with reconstructive interventions or sympathectomy. The positive effect after combined treatment is more significant and longtermed in patients with distal forms of obliterating atherosclerosis [4, 5, 7].

Considering the above, we used a combination of direct and indirect techniques of treatment in patients with distal forms of atherosclerosis to improve the state of the limb microvasculature in order to decrease the number of postoperative thrombosis and amputations. The combination of direct and indirect revascularization technics provides an improvement in the state of the inflow and outflow pathways, a decrease in the thrombosis incidence in the postoperative period and an increase of the limb salvage rate [7,8,9].

THE AIM

To assess the immediate results of autovenous femoral-tibial shunting in combination with rotary osteotrepanation of the tibia by studying changes in the transcutaneous ptO2 tension in the tibia and foot tissues depending on the revascularization of the tibial arteries.

MATERIALS AND METHODS

We analyzed the treatment of 69 patients with obliterating atherosclerosis of the lower extremities vessels. The patients were hospitalized at the Department of Vascular Surgery of the Transcarpathian Regional Clinical Hospital n.a. Andrey Novak from 2015 to 2020yy. According to the degree of ischemia of the lower extremities, the patients were distributed follows groups: III A degree - 20 (29%), III B - 28 (40.6%), IV degree - 21 (30.4%) patients.

In the demographic structure men dominated - 64 (92.7%) patients. The average age of women (66.1 $\pm$ 5.4) was almost five years higher than the average age of men (60.9 + 8.6).

All patients had atherosclerotic lesions of the popliteal-tibial segment of the magistral arteries with preserved central blood flow in the aorto-iliac segment.

Trophic changes in the skin of the foot were observed in 30.4% of patients. Limited by a few toes necrotic changes prevailed - 42.9%, most often I and IV toes were affected. Concerning concomitant diseases, the following pathologies were diagnosed: ischemic heart disease - 45 (65.2%) cases, arterial hypertension - 51 (74%), chronic cerebrovascular insufficiencies II - III degree - 23 (33.3%) cases, diabetes mellitus 25 (36.2%), erosive and ulcerative-erosive lesions of the gastrointestinal tract - 37 (53.6%), chronic obstructive pulmonary diseases - 19 (27.5%).

The diagnostic program included ultrasound examination (US) - Doppler sonography, multispiral computed tomography with contrast enhancement, determination of the regional perfusion index based on the measurement of transcutaneous oxygen tension (TcPO2) in the basin of the anterior tibial artery, posterior tibial artery, peroneal artery and arteries of the foot in the postoperative period after three months.

For the statistical analysis of the mean values of the TcPO2 index in patients before and after operative interventions, a t-test paired two-sample for means was used. For the TcPO2 index changes we used the percentage ratio of the regional tissue perfusion index before and after surgery in relation to the norm. Microsoft Excel 2019 was used to analyze the data.

Depending on the type of surgical treatment, the patients were divided into two groups:

I group - 34 patients who underwent distal autovenous femoral-tibial bypass grafting in combination with rotary osteotrapation of the tibia.

II group - 35 patients who underwent distal autovenous femoral-tibial bypass grafting.

RESULTS

Contrast-enhanced multispiral computed tomography and ultrasound examination analysis allowed us to identify the following types of distal arterial lesions:

- occlusive-stenotic lesions of the popliteal artery , patent arteries of the lower extremity;
- occlusive stenotic lesion of the popliteal artery, occlusion of 1-2 arteries of the lower extremity;
- diffuse lesion of the popliteal-tibial segment with patency and / or with the absence of patency of the one tibial artery;

Occlusion of anterior tibial artery was recorded significantly more often than peroneal artery (72% and 42%, respectively, p = 0.05), but with the same frequency as compared with posterior tibial artery (68%, p = 0.61). The involvement of the foot arteries in the process was found in 21 (30.4%) patients.

The occlusion of two or three arteries of the lower leg was recorded more often than occlusion of one (n = 51; 73.9% and n = 18; 26.1%). Occlusive-stenotic lesion of the popliteal artery was observed in 54 (78.2%) patients.

The highest incidence of lower leg artery lesions was observed in the anterior tibial artery basin in 28 (40.6%) patients. Combined lesions of anterior tibial artery and posterior tibial artery were diagnosed in 19 (27.5%) patients. Limited posterior tibial artery lesions were found in 15 (21.7%) patients. The combination of posterior tibial artery and peroneal artery lesions was diagnosed in 7 (10.2%) patients.

Necrobiotic changes in the foot were most often observed on the dorsum of the foot distal parts and toes - 11 (52.4%) patients. Nine (42.9%) patients had necrosis on the plantar surface of the foot in the projection of the 2-5 metatarsal bones. In one patient (4.8%) trophic changes took place in the heel area.

The indices of the ankle pressure index ranged from 0.24 to 0.4 and directly proportionally depended on the level and extent of atherosclerotic alteration, ranged from 0.42 $\pm$0.15, in III B degree - 0.38$\pm$ 0, 12 and in IV degree - 0.24 $\pm$0.12.

A total of 69 operations were performed using direct revascularization (table. I).

As can be seen from the table, posterior tibial artery (34.8%), anterior tibial artery (26.1%), peroneal artery (21.7%) and tibioperoneal trunk (17.4%) were used most often for tibial bypass grafting.

Table I. Distribution of patients according to the localization and technique of the distal anastomosis

Artery	Distal anastomosis	
	«end to end»	« end to side »
Anterior tibial artery	17	1
Posterior tibial artery	20	4
Peroneal artery	15	-
Tibioperoneal trunk	8	4
Total	60	9
	69	

In this case, the advantage in the formation of the distal anastomosis was given to the "end-to-side" technique (87%).

The immediate results of direct revascularization and ROT were assessed within three months on the basis of changes in clinical symptoms, which were identified during examination before surgery, as well as the presence or absence of postoperative complications. The permeability of the reconstruction zone with direct methods of revascularization in the first three months was 69.6%. Reoperations were performed in 21 (30.4%) patients due to shunt thrombosis. In 20 patients from this group amputations were at the lower third level of the thigh, and only in one cause there was technical possibility to restore the blood flow.

Thrombosis after anterior tibial artery shunting occurred in 14 (18.8%) patients, and after posterior tibial artery shunting - in 8 (11.6%) patients.

We did not observe thrombosis of the autovenous shunt in cause of using tibioperoneal trunk and peroneal artery as a tibia shunt artery.

Despite of a rather high percentage of unsatisfactory results of the direct methods of revascularization, the oxygen tension in the angiosomes of the leg and foot increased (table. II).

According to the above data, a statistically significant difference was revealed in the regional perfusion index after surgery between the first and second groups in the angiosomal region of the posterior tibial artery and the peroneal artery ($p < 0.05$). When comparing other indicators, no statistically significant difference was found. Statistically significant differences were found in the groups ($p < 0.05$)

Table II. Index of regional perfusion of the leg and foot angiosomes after autovenous femoral-tibial shunting

Angiosoma	Surgery techniques			
	Distal autovenous femoral-tibial shunting		Distal autovenous femoral-tibial shunting + ROT	
	Before surgery	After surgery	Before surgery	After surgery
Anterior tibial artery	0,51±0,04	0,72±0,18	0,5±0,05	0,73±0,21
Posterior tibial artery	0,63±0,03	1,8±0,07	0,62±0,01	1,9±0,06
Peroneal artery	0,41±0,03	1,1±0,19	0,41±0,03	1,2±0,15
Dorsum foot	0,39±0,04	0,62±0.23	0,4±0,02	0,58±0.18
Plantar foot	0,4±0,04	0,83±0.23	0,41±0,03	0,85±0.26
t-test	p<0,05(p= 0,037)		p<0,05(p= 0,046)	

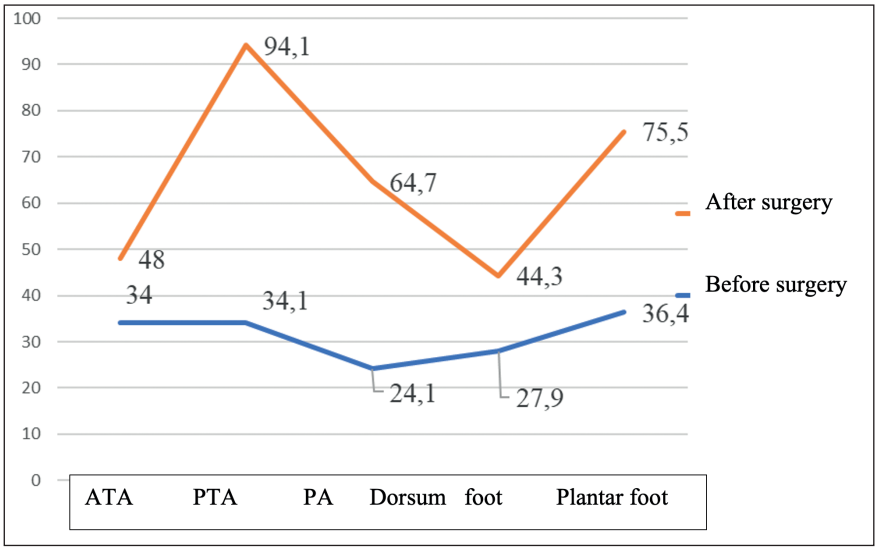

Fig. 1. Percentage ratio of tissue perfusion index relative to normal before and after surgery for distal autovenous femoral-tibial bypass grafting.

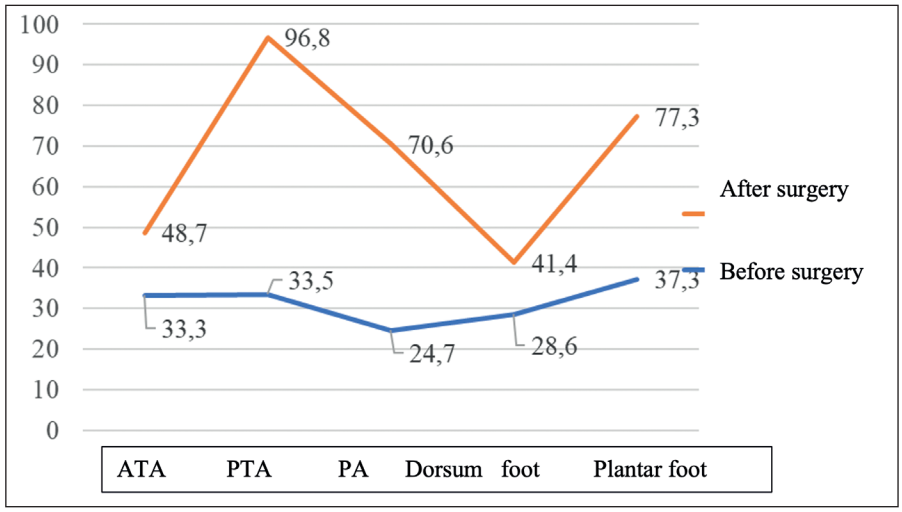

Fig. 2. Percentage ratio of tissue perfusion index relative to normal before and after surgery in cause of distal autovenous femoral-tibial bypass grafting in combination with ROT.

while comparing the indicators before and after surgery using the Student's t-test

At the same time, a stable increase in oxygen tension was observed in the angiosomes of the posterior tibial artery and / or peroneal artery in the case of the femoral-posterior tibial artery and bypass grafting of the femoral-tibioperoneal trunk; consistently low transcutaneous oxygen tension values were observed on the dorsum of the foot. In tibial arteries, the lowest regional perfusion index was observed in the anterior tibial artery basin below revascularization, despite of its usage as a receiving artery. (Fig. 1).

With the use of distal autovenous femoral-tibial bypass grafting, the indices of the regional tissue perfusion index in the angiosomes of the posterior tibial artery and peroneal artery increased almost threefold, and in the angiosomal basin of the dorsum of the foot and sole they doubled. The similar situation, even with better indicators was observed in patients who underwent distal autovenous femoral-tibial bypass grafting in combination with ROT. The indices in the angiosomes of the posterior tibial artery, peroneal artery increased threefold, the indices of regional perfusion in the angiosomes of the dorsum of the foot and sole doubled. (Fig. 2.).

DISCUSSION

In recent years, due to the development of new technologies, the frequency of the lower extremities revascularization has increased significantly [9-14]. In cases where revascularization is not possible, the amputation percentage is 50% and increases over the next five years [7,10]. In the group of patients with successfully performed revascularization it ranges from 21.2 to 60% [1,2,3,7].

The main problem today is to find a way to stimulate the blood supply of the ischemic zone. One of the possible options is the restoration of blood flow in the maximum number of leg arteries; a number of other authors estimate that it is sufficient to restore blood flow only in anterior tibial artery and / or posterior tibial artery for a positive result; according to some data, only restoration of the vessel, which supplies blood to the affected area, can lead to a positive result of revascularization [1,3].

At the same time, when comparing the CT data, and the peculiarities of the trophic changes localization in the aspect of the angiosomal theory, most often trophic changes were found in the dorsal angiosome zone of the foot (52.4%), which comes from the anterior tibial artery. In 9 (42.9%) patients, trophic changes were found in the zone of the lateral plantar angiosome, which comes from the posterior tibial artery. In 4.8% of patients, necrosis was detected in the area of the medial-calcaneal angiosome, which comes from the posterior tibial artery at the border of the angiosome area from peroneal artery intermediate branch.

Angiosomal theory, despite a large amount of research, still raises many questions. This is primarily due to the lower extremities ischemia degree , as a treatment the treatment of foot ulcers in grade IV ischemia is a complex problem, that requires an integrated approach. A very important problem is the patients selection to the study groups for comparing the direct and indirect revascularization results. As a rule, indirect revascularization is performed only in cases of technical impossibility of direct revascularization, and this factor must be taken into account when evaluating the study results. Taking into account the fact that the "angiosomal artery" is most affected by the atherosclerotic process and the combined lesions of the foot arteries make up 30.4% of cases, only the skill of surgical revascularization can lead to the ischemia liquadation of the affected segment of the limb. After performing direct bypass surgery the peripheral blood flow and the volume of the microvasculature of the lower leg increase. In this case, performing indirect revascularization in addition will be more effective than usage this technique isolately for chronic critical ischemia treatment.

CONCLUSIONS

1. The patency of the femoral-tibial autovenous shunt during the year was 71%. High limb amputation was performed in 29% of patients.
2. According to CT data, the localization of trophic changes on the foot during critical ischemia of the lower extremities corresponds to the affected segment of the arterial angiosome, which supplies the corresponding area with blood.

3. After femoral-tibial autovenous bypass grafting, the highest levels of transcutaneous oxygen tension were observed in the basin of the posterior tibial artery and peroneal artery, and the lowest indicators of transcutaneous oxygen tension were observed in the basin of the anterior tibial artery.
4. During femoral-tibial autovenous shunting operations in combination with rotary osteotrepanation, the transcutaneous oxygen tension indices increased threefold in the angiosomal basin of the posterior tibial artery and peroneal artery, and twofold in the angiosomes of the dorsum of the foot and sole.

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ORIGINAL ARTICLE

PATHOGENETIC ASPECTS OF METABOLIC SYNDROME IN EXPERIMENTAL ANIMALS

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ABSTRACT

The aim: Was to study the state of the nitric oxide system, LPO and antioxidant system in the body of experimental animals in simulated metabolic syndrome. The aim of the study was to study the state of the nitric oxide system, lipid peroxidation and antioxidant system in the body of experimental animals in simulated MS.

Materials and methods: The study was performed on 20 white male Wistar rats. Male control rats (n = 10) were fed a normal control diet. Male rats of the main group (n = 10) were fed a diet high in fat (over 60 % energy from fats) for 16 weeks, thus modeling the development of MS. The indicators of the prooxidant and antioxidant system, as well as the nitric oxide system were determined by photospectrographic method.

Results: In animals with simulated MS, intensification of lipoperoxidation (statistically significantly higher level of TBA-active products 1.84 times), depletion of antioxidant protection (statistically significantly lower level of superoxide dismutase 2 times), activation of nitric oxide system (statistically significantly higher NO-synthase level 2.15 times) were found compared with intact animals.

Conclusions: In animals with simulated MS, activation of lipid peroxidation processes, depletion of antioxidant protection and increased levels of nitrooxidative stress were found.

KEY WORDS: metabolic syndrome, peroxidation, free radicals, antioxidant protection, nitrooxidative stress

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INTRODUCTION

The prevalence of metabolic syndrome (MS), which includes a cluster of cardiovascular risk factors associated with obesity and insulin resistance, has recently increased dramatically and has become epidemic in many developed countries. This pathology is characterized by metabolic disorders such as hypertriglycerinemia, decreased levels of high-density lipoprotein, increased levels of low-density lipoprotein, insulin resistance, abnormal glucose tolerance and hypertension, which in combination with genetic predisposition to risk of type 2 diabetes, atherosclerosis and kidney, liver and heart disease [1].

MS is one of the most studied pathologies in the world due to the fact that such metabolic disorders are associated with common diseases of modern man - atherosclerosis, hypertension, type 2 diabetes, obesity. According to modern ideas, MS is characterized by a set of disorders of systemic regulation of lipid, carbohydrate, protein and other types of metabolism under the influence of external and internal factors. Separation of MS is of significant clinical importance, because on the one hand this condition is reversible, and on the other hand, it is necessary to address the tactics of such a patient due to the fact that among people with MS risk of coronary heart disease or stroke 3 times higher, with a significant increase in mortality from cardiovascular disease [2]. The effectiveness of the use of different criteria for the detection of MS is unequal, which requires the necessary discussion and comparative analysis of existing diagnostic criteria and requires further in-depth study of biochemical parameters in MS.

One of the aspects associated with the development of MS and concomitant pathology is the excess of reactive oxygen species, which initiate peroxidation processes and cause damage to various cellular components. The accumulation of products of lipid and carbohydrate metabolism triggers detoxification reactions, including free radical processes [3]. Free radical processes are aimed at maintaining homeostasis, but at high intensity they can lead to the development of oxidative stress. Oxidative stress is one of the triggers that help to activate the body's cellular adaptation. The ratio of the activity of antioxidant systems and the amount of peroxidation products may vary depending on the state of the organism, the effects of various environmental factors. A normal stress response

may be accompanied by a short-term increase in reactive oxygen species. This is due to the reaction of adaptation of the organism in extreme conditions, in which reactive oxygen species play the role of secondary messengers, participating in the transmission of signal transduction, in the expression of a number of genes. The result is a timely mobilization of antioxidant protection, which reduces the level of reactive compounds, thereby preventing the manifestations of their toxic effects [4]. The toxic effect of reactive oxygen species is manifested in conditions of oxidative stress, which is accompanied by a sharp intensification of free radical processes and a decrease in the activity of antioxidant protection. Intensification of free radical processes and the development of oxidative stress is one of the pathogenetic links of many diseases, including cardiovascular, inflammatory, and aging. There are many works devoted to the study of free radical oxidation in various pathological conditions. However, data on the development of oxidative stress in MS is clearly insufficient, and this applies primarily to studies of the activity of antioxidant enzymes [5].

Another, no less important aspect of research in the pathogenesis of MS is the study of the role of mediators of intercellular interaction, which include nitric oxide and its metabolites. Nitric oxide is a universal regulator of various biochemical processes. Previously, the role of nitric oxide was associated only with inflammation, but it is involved in many physiological and pathophysiological reactions of the body, including pure apoptosis reactions. Nitric oxide and its metabolites are essential in the development of complications of MS. It is known that MS is accompanied by endothelial dysfunction, which is characterized by increased production of nitric oxide. Therefore, the increased attention of researchers is focused on this problem. Insufficient or excessive production of nitric oxide characterizes the presence of endothelial dysfunction, which is associated with a violation of the antioxidant system under the action of free radical oxidation [6]. This phenomenon is a major risk factor for the occurrence and complication of various diseases, including MS.

It is known that nitric oxide can cause both protective and damaging effects. It plays a significant role in the processes that regulate the production of free radicals. Its molecule itself as one of the reactive forms of oxygen is involved in the initiation of oxidative stress, which has independent antioxidant properties. However, the pathogenetic mechanisms that explain the role of nitrooxidative stress, lipid peroxidation (LPO) processes, the state of the antioxidant system in the development of MS and its complications have not been fully studied [8]. There are no clear criteria that would allow to have an idea of the course of this pathology, to allow to predict the course of the disease and to prevent undesirable consequences. Equally important is the search for effective, low-cost and prognostically successful methods of treating MS.

Thus, the role of nitric oxide activity, LPO processes, antioxidant enzymes in the pathogenesis of systemic disorders in MS remains unclear.

THE AIM

The aim of the study was to study the state of the nitric oxide system, LPO and antioxidant system in the body of experimental animals in simulated MS.

MATERIALS AND METHODS

The study was performed on 20 white male Wistar rats weighing 200–250 g (age 9–10 weeks), which were kept in standard vivarium conditions (air temperature: (22 ± 2) ° C, humidity - 30-60 %, light / dark cycle: 12/12 hours). Male control rats (n = 10) were fed a normal control diet. Male rats of the main group (n = 10) were fed a diet high in fat (over 60 % energy from fat) for 16 weeks [9], thus modeling the development of MS.

At the end of the experiment, the animals were decontaminated by decapitation under thiopental anesthesia. The experiment complied with the requirements of the European Convention for the protection of vertebrate animals used for research and other scientific purposes (Strasbourg, 1986) and the European Union Directive 2010/10/63 EU on animal experiments. The Commission on Bioethics of Ternopil National Medical University named after I. Gorbachevsky (Prototol No. 12 of November 4, 2020) did not find any violations of moral and ethical norms during this study.

Determination of the content of TBA-active products (TBA-AP) was performed using the photospectrographic method. The principle of the method is the ability of secondary products of lipid peroxidation, namely malonic dialdehyde, when interacting with thiobarbituric acid (TBA) at high temperatures in an acidic environment to form a colored complex, the intensity of which is directly proportional to the content of TBA-active products (TBA-AP). Studies have been performed in and serum [10]. The content of TBK-AP was expressed in μmol / l serum.

The level of *ceruloplasmin* (CP) was also determined by photospectrographic method [11]. Principle of the method: oxidation of p-phenylenediamine in the presence of ceruloplasmin leads to the formation of colored products. The amount of ceruloplasmin is proportional to the intensity of the color. The study was subjected to blood serum without traces of hemolysis. The result was expressed in mg / l.

The principle of the method [12] for determining the activity of *catalase* (CT) is based on the ability of hydrogen peroxide to form a stable colored complex with ammonium molybdate. The study was subjected to blood serum. Catalase activity was determined by photospectrometric method and expressed in mcat / l.

The principle of the method for determining the content of *reduced glutathione* (GSH) is that the interaction of 5,5'-dithiobis2-nitrobenzoic acid (Elman's reagent) with free SN groups of reduced glutathione forms a thionitrophenyl anion, the amount of which is directly proportional to the group content of S [13]. The concentration of reduced glutathione in serum was expressed in mmol / l.

The *total antioxidant activity* of blood serum (TAA) was determined by photospectrographic method. The principle

Table I. Indicators of prooxidant-antioxidant system in the serum of experimental rats (M±m)

Indicator	Groups of animals	
	Intact rats (n=10)	Rats with MS (n=10)
	Blood plasma	
CP, mg / l	302,1±14,9	634,5±25,2*
CT, mcat / l	0,88±0,04	2,03±0,78*
ГSH, mmol / l	3,90±0,29	2,03±0,18*
TAA, %	59,43±4,09	32,65±2,36*
TBA-AP, μmol / l	8,50±0,49	15,76±1,09*
	Liver	
SOD, units / g	0,77±0,04	0,36±0,03*

Note: * - statistically significant significance of the difference between indicators compared with the control group.

of the method is the ability of TAA to inhibit the formation of peroxidation products in the homogenate of the rat brain [14]. TAA was expressed in%.

Superoxide dismutase (SOD) activity was also determined by photospectrographic method [15]. Liver tissue homogenate was taken for the study. The activity of the enzyme was determined by its ability to inhibit the recovery of nitrotetrazolium blue. The percentage of inhibition was expressed in units / g.

The total content of *nitrates and nitrites* was determined by the Griss method after reduction of nitrates to nitrites with cadmium [16]. Calculations were performed according to the calibration schedule, using sodium nitrite as a standard. The content of nitrates and nitrites was expressed in mmol / l of blood serum.

The total activity of *NO-synthase* (NOS) in blood serum was determined colorimetrically by the amount of nitrates and nitrites formed in the incubation medium [17]. The amount of nitrates and nitrites formed was determined as described below.

Statistical processing of the obtained research results was processed using the software Excel («Microsoft», USA) and Statisticav.10.1. (Statsoft, USA), by the method of variation statistics using the Mann-Whitney U-test and the Student's test. Changes at $p < 0.05$ were considered statistically significant.

RESULTS

We have established a tendency to intensify lipoperoxidation processes and reduce the protective resources of antioxidant protection. Statistically significantly higher indicators of the content of TBA-AP in the serum of animals with simulated MS were established. As the results of our studies showed, the level of TBA-AP increased statistically significantly 1.84 times in animals with simulated MS (Table 1). There were also statistically significantly lower activity rates of SOD, TAA, and the level of SH-groups in the studied animals with simulated MS compared with intact animals. However, the content of CP and CT activity in our experiment increased. Thus, we found an increase in the content of CP in the blood plasma of animals with simulated MS in 2.1 times compared with the control group of animals. CT activity increased statistically significantly in the study group of animals by 2.3 times compared with the control. At the same time, in our experiment, the activity of SOD (2 times), TAA (1.8 times) and the content of GSH (1.9 times) decreased statistically significantly. This is apparently due to the depletion of the pool of antioxidant enzymes and the negative course of MS in experimental animals. The obtained data show that experimental MS contributes to oxidative and nitrooxidative stress, depletion of the antioxidant defense system.

When evaluating nitric oxide parameters, we recorded the development of endothelial dysfunction in rats with

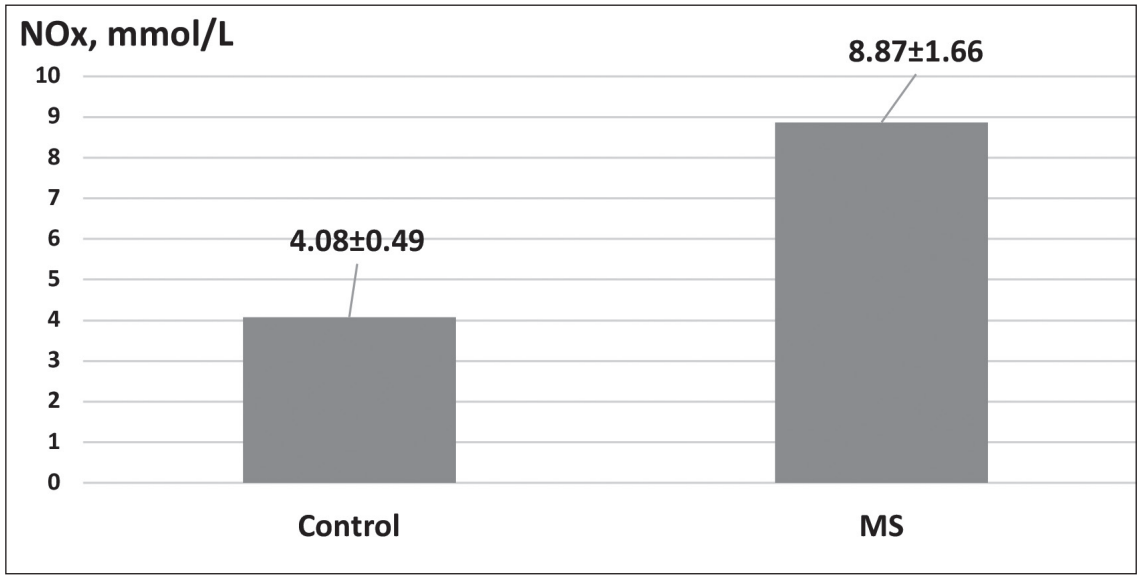

Fig. 1. Concentration of nitrates and nitrites (NOx) in the serum of experimental rats

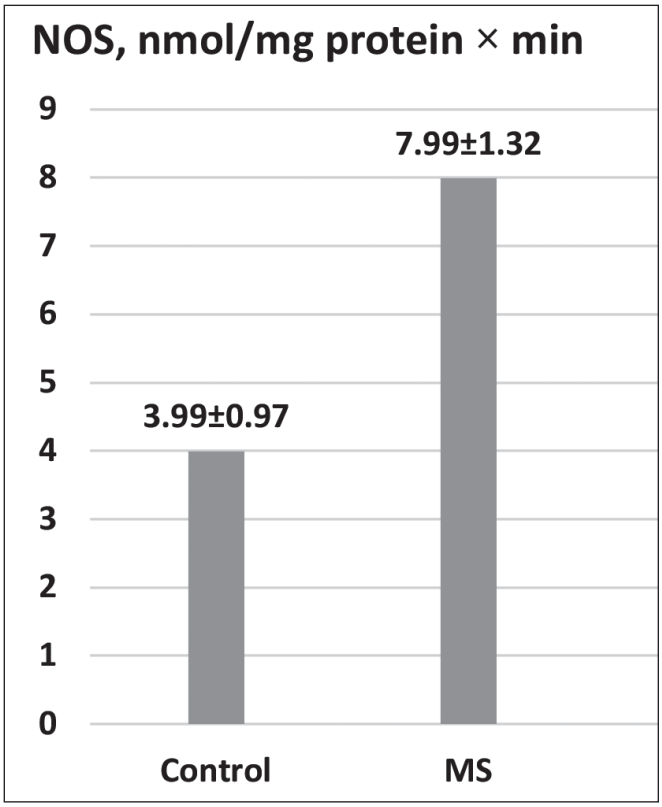

Fig. 2. Indicators of NO-synthase activity in the liver of experimental rats

simulated MS. There was a statistically significant increase in the concentration of nitrates and nitrites (NOx) in the serum of rats with experimental MS in 2 times compared with the control (Fig. 1).

We also found an increase in NO-synthase activity in the liver homogenate of animals by 2.15 times (Fig. 2). It is obvious that the increase in total NO-synthase activity registered by us is a consequence of activation of the inducible form of this enzyme, and the obtained fact of increase of nitrates and nitrites in blood serum of animals with the simulated metabolic syndrome is a consequence of excessive formation of nitric oxide and NOS. quickly converted to NOx.

Thus, the dynamics of the indicators established by us testifies to the development of nitrooxidative stress and imbalance in the prooxidant-antioxidant system in rats with simulated MS.

DISCUSSION

The obtained data show that experimental MS contributes to oxidative and nitrooxidative stress, depletion of the antioxidant defense system. We obtained data increasing the concentration of nitrates and nitrites (NOx) in the serum of rats by 2 times and increasing the activity of NO synthase in the liver homogenate of animals by 2.15 times with experimental MS compared with the control. It is obvious that the registered increase in the total activity of NO synthase is a consequence of activation of the inducible form of this enzyme, and our increase in nitrates and nitrites in the serum of animals with simulated MS is a consequence of excessive formation of nitric oxide and-NOS, which is unstable molecule and rapidly converted to NOx. At the same time, the products of partial oxygen reduction - superoxide-anion-radical - accumulate in the inflammatory focus [11-19]. In MS, high levels of NO in the body lead to interaction with the superoxide anion radical and the release of peroxynitrite anion, which in turn damages the vascular endothelium, which promotes the oxidation of lipids in cell membranes. In the presence of peroxynitrite or its breakdown products, thiol radicals of glutathione are formed, as a result of which the latter of the antioxidant is converted into a prooxidant, thereby initiating the processes of lipid peroxidation. In animals with experimental MS there is an increase in TBA-AP in 1.84 times.

Our data are consistent with the results of a number of studies, which found that in MS conditions there is increased activity of lipoperoxidation, and the oxidative stress that develops acts as an important pathogenetic mechanism of dysregulatory changes in metabolism. Changes in the prooxidant-antioxidant system under experimental MS can also contribute to the progression of metabolic disorders that are accompanied by the accumulation of lipids in cells [20]. Accordingly, free radical oxidation of lipids leads to increased levels of free fatty acids, triglycerides, cholesterol. It is known that the products formed in the intermediate stages of the peroxide cascade, in particular ketodienes and conjugated trienes, have a higher thermodynamic stability, as a result of which they are the initiators of numerous damaging effects at the level of biomembranes [21].

We can predict that the excessive accumulation of toxic products of lipoperoxidation obtained by us may further exacerbate existing damage, preceded by the appearance of more significant shifts in metabolism in MS. Overall antioxidant status is a limiting factor in the increased intensity of LPO. Activation of LPO processes leads to an imbalance in the antioxidant defense system, which deepens the development of complications in MS.

The most common in the literature data is the assessment of the intensity of free radical processes on the concentration of products of intermediate and final peroxidase catalysis: malonic dialdehyde, diene conjugates, ketodienes and trienes. The antioxidant system is studied by the activity of enzymes - SOD, CT, and indicators of non-enzymatic system of antioxidant protection - the content of GHS (SH-groups) [22].

According to the results of our own research, we have obtained data that are consistent with data from domestic and foreign studies. In particular, there is a tendency to intensify LPO processes and to reduce the protective resources of antioxidant protection. There were statistically significantly higher indicators of the content of TBA-AP, as well as statistically significantly lower indicators of activity of SOD, TAA, and the level of SH-groups in the studied animals with simulated MS compared to intact animals. However, the content of CP and CT activity in our experiment increased. Thus, we found an increase in the content of CP in the plasma of animals with

simulated MS in 2.1 times compared with the control group of animals, which may be due to the fact that the specific SOD activity of ceruloplasmin in rats is associated with an additional site for copper ion binding in this enzymes [23-24]. Since CP is to some extent able to inhibit the respiratory explosion of neutrophils due to SOD activity, it can be assumed that this mechanism of protection against oxidative stress associated with inflammation in animals with MS is more pronounced.

Also in our study, we found an increase in catalase activity in animals with MS in 2, 3 times compared with the control group of animals. The increase in the activity of the studied enzyme is associated with the inclusion of compensatory mechanisms of the antioxidant defense system. However, in our experiment, the activity of SOD (2 times), TAA (1.8 times) and the content of GHS (1.9 times) was statistically significantly reduced, which is obviously associated with the depletion of the pool of antioxidant enzymes and negative course of MS in experimental animals.

Under the conditions of our experiment, the level of free radical oxidation and inhibition of antioxidant complexes increased, which leads to the accumulation of free radicals in the serum of animals with simulated MS. In general, the presence of inflammation, hypoxia and oxidative stress enhances the synthesis of cytokines that express inducible NO-synthase, and the latter generates high levels of NO production. Changes in the processes of LPO, the state of antioxadants, the intensity of nitric oxide formation cause the development of MS [25-26]. Therefore, the question of studying the intensity of the course of pathological free radical oxidation, which causes a violation of the integrity of the vascular endothelium in MS, remains relevant. Studies confirm the fact that the activity of free radical reactions contributes to severe vascular endothelial cell dysfunction. In turn, it plays a leading role in the violation of vascular tone and the development of atherosclerotic lesions of the arteries. In this regard, the endothelium, its functions and correction of their disorders require new searches for their correction and prevention of complications of MS [27-28]. Thus, the results indicate the important role of nitrooxidative stress, activation of lipoperoxidation processes, disturbances in the system of pro- and antioxidant protection in the formation and progression of MS and the need to seek its surgical correction.

CONCLUSIONS

In animals with simulated metabolic syndrome, activation of lipid peroxidation processes (at a statistically significantly higher level of TBA-AP), depletion of antioxidant protection (at a statistically significantly lower level of SOD) and an increase in nitrooxidative stress (at a statistically significantly higher level of nitric oxide) were found. These disorders are due to the deepening of metabolic imbalance in the development of metabolic syndrome.

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ORIGINAL ARTICLE

COGNITIVE AND STRUCTURAL CHARACTERISTICS OF LATIN TERMS FOR INFECTIOUS AND INVASIVE DISEASES WITH A ZOOMORPHIC COMPONENT

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ABSTRACT

The aim was to analyze the morphological, structural and lexico-semantic presentation of the Latin terms denoting the infectious and parasitic diseases, part of which is a zoonymic component.

Materials and methods: The presentation sample was made by the method of continuous sampling based on textbooks, manuals, including the three-volume edition "Infectious and parasitic diseases", and a number of modern dictionaries. Structural, semantic and descriptive methods were used to address the aim of the research.

Results: Monolexemic composites with a zoomorphic component are formed in a suffixal way. In multi-word phrases, syntactic constructions of mixed type, are usually used and they are characterized by the combination of words of Greek and Latin origin, but these formations are few. The eponymous and toponymic formations to denote specific nosological forms in helminthology are not typical. The data on the first contribution of a researcher to the description of the disease in the name of the term is not displayed, preference is still given to the name of the pathogen, rather than the name of the researcher. The prefix-suffix-based method of formation of terms denoting infectious and parasitic diseases with a zoonymic component is observed sporadically.

Conclusions: The comparison of the above-analyzed terms with the corresponding terminological units of the English medical terminology indicates the predominant use of Latin terminological units. In contrast to many clinical terms with a zoomorphic component, where certain associative moments are taken into account.

KEY WORDS: medical terminology, Latin terms, infectious and invasive diseases, a zoomorphic component, cognitive and structural approach

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INTRODUCTION

Acquaintance with scientific publications of the last ten years testifies to the interest of researchers in terms of various sublanguages of medicine, in which a zoomorphic component is traced, although the number of studies in this direction is insignificant. Perhaps the greatest attention is paid to the coverage of zoomorphic components based on the material of Latin anatomical terms (Y. Brazhuk, 2014; O. Kharik, 2017); features of metaphorical connotative meanings of medical terms with an animal component in modern Chinese researches (K. Cui, 2014). O. Kryzhko's publications (2010, 2015) are devoted to the cognitive features of zoonymic terms of the Ukrainian language in semasiological and onomasiological aspects; 97 lexical and semantic units with zoonymic and ornithonymic components based on the material of Russian and English medical vocabulary were analyzed by A. Ryabova and O. Kozlova (2012); some remarks on the functioning of terms with an animal component in the "Infectology" terminology are set out in the research by V. Synytsia (2019). However, we have not found any studies that would comprehensively focus on the structural and semantic aspects of the nomination of Latin terms with the use of zoonyms as monolexic and terminological phrases of the microfield "infectious and invasive diseases". The choice of this area of research is also explained by the extreme prevalence of diseases caused by pathogenic protozoa, helminths or arthropods among adults and children. The number of terms with an animal component is quite numerous and requires a detailed study, which will ensure an in-depth understanding of the functioning of nominative units from the outlined microfield of medicine from the standpoint of cognitive and structural approach.

THE AIM

The aim of the research is to analyze the morphological, structural and lexico-semantic presentation of the Latin terms denoting the infectious and parasitic diseases, part of which is a zoonymic component.

MATERIALS AND METHODS

The presentation sample was made by the method of continuous sampling based on textbooks, manuals, including

the three-volume edition "Infectious and parasitic diseases", and a number of modern dictionaries [1-8]. Structural, semantic and descriptive methods were used to address the aim of the research.

RESULTS AND DISCUSSION

The largest number of terms with a zoomorphic component is found in medical helminthology, a section of medical parasitology that studies worms and the diseases they cause. The term "helminthologia" itself refers to one-word two-morpheme composites: the first position is occupied by the term element "helminth-", which comes from the noun of Greek origin ἕλμινς, ινθος – "worm" (Latin version *helmins, helminthis*, base *helminth-*) and the final term element "-logia". The lexeme *helmins, inthis f* has come down to this day due to to the surviving works of Hippocrates, and in modern dictionaries it is interpreted as "a group of parasitic worms, which includes representatives of the classes of trematodes, cestodes, nematodes; pathogens of helminthic diseases of humans and animals" [8, p. 392]. The concept of "helminthiasis / helminthiasis: a disease caused by helminths; worm infestation" is codified by the Latin terms *helminthosis* (base *helminth-* + suffix *-osis*), *helminthiasis* (base *helminth-* + suffix *-iasis*) and *helminthismus* (base *helminth-* + suffix *-ismus*). Doctors in most countries of the world attribute helminthiasis to both parasitic and infectious diseases. Focusing on the ways of transmission, the famous Soviet helminthologist, Academician K.I. Skriabin (1878-1972) and Professor R.S. Schultz (1896-1973) identified two epidemiological groups of helminthiasis and introduced the concepts "biohelminthosis" and "geohelminthosis" into medical discourse in 1937. The terms "biohelminthosis" and "geohelminthosis" refer to one-word three-component formations: *biohelminthosis* ← bi- (from the Greek noun βίος – *life*) + *helminth-* (from the Greek noun ἕλμινς - *worm*) + Greek suffix *-osis – invaders,* whose pathogens develop and are transmitted to humans through the tissues of their body [2, p. 254]; *geohelminthosis* ← ge- (from the Greek noun γῆ - *earth*) + *helminth-* (from the Greek noun ἕλμινς - *worm*) + Greek suffix *–osis – invasions*, whose causative agents develop directly (without the participation of an intermediate host) and are transmitted to humans through the elements of the environment, contaminated with invasive eggs or larvae [2, p. 254]. In 1952, Professor E.S. Shulman identified an additional group – contact helminthiasis. To denote this concept, medical dictionaries offer a two-word term "helminthosis contactilis", which is etymologically of Greek-Latin origin: single-word composite of Greek origin *helminthosis* + Latin adjective *contactilis, e,* formed by the suffix "-al" from the past participle, passive *contactus, a, um* of the verb *contingo*, *tigi*, *tactum*, *ere* – "to touch". The article by M. Teleky elaborates on the terminological units with an adjective component in the medical terminology system in more detail [9], where, in particular, the suffix "-al" is mentioned, among others, as one that belongs to a small group of deverbal adjectives, which are found in medical terminological phrases. However, analyzing the terminological phrases of infectious and invasive diseases with a zoomorphic component, we can question the above statement, because we found six phrases with adjectives, which used the suffix "-al": *myiasis intestinalis, myiasis nasalis, helminthosis naturalis et focalis, schistomiasis intestinalis, schistomiasis urogenitalis*, whereas only 4 terminological formations with the suffix "-os" were revealed: *myiasis mucosa, myiasis dermatosa, myiasis iomaginosa, myiasis oestruosa*; and with the suffix "-ic" – only two examples: *myiasis traumatica, ascaridosis hepatopancreatica*.

According to the unified nomenclature of invasive diseases, the dominant structural model is schematically represented as follows: the Greek suffix "-osis / -iasis" is added to the generic name of the parasite. For example, the term "worm disease caused by Ancylostoma duodenale or Necator americanus" is verbally denoted by the term *ankylostomosis* or its variant *ankylostomiasis* [7, p. 118]. Given the nomenclature of parasitic diseases, this nomination is structurally a two-component formation: the first position is occupied by the generic name of the pathogen *Ankylostoma* (or rather, the truncated form of *ankylostom-*), which is joined by the suffix "-osis" (or as a variant "-iasis"). However, one must not forget that the generic name of the pathogen *Ankylostoma* is etymologically derived from the Greek word ἀγκύλος – *curve* + Greek noun στόμα - *mouth* and is also a two-component formation. That is, if we "decompose" the term *ankylostomosis* / *ankylostomiasis* without taking into account the name of the pathogen, we can distinguish three morpheme components: σκλαγκύλος + στόμα + "-osis / -iasis".

The study found that the dictionaries by Arnaudov [6, p. 23] and Rudzitis [7, p.118] record spelling forms *Ankylostoma*, *ankylostomosis / ankylostomiasis*, whereas the encyclopedic dictionaries by Dornald [5, p. 100] and Petrukh [8, p. 143] – *Ancylostoma*, *ancylostomosis / ancylostomiasis*. Moreover, in the dictionary by Dornald [5] on p. XX, which lists the "The list of analytical words", two initial terminological elements are given without any explanation: "ancyl-" and "ankyl-". In our opinion, the variant "ancyl-" contradicts the rules of Latinization of the Greek words, because to transmit the sound [k], available in the Greek word ἀγκύλος, one must use the letter of Greek origin [k], because according to the phonetics of Latin, the letter [c] in the position before [y] is pronounced [ts]. It should also be remembered that the combination of the Greek letters γκ corresponds in Latin to the combination "nk", not "nc" [6, p. XVIII], which again indicates that the spelling of the above terms is not entirely correct. However, a review of recent scientific papers published on the Internet shows that the variant *Ancylostoma*, *ancylostomosis / ancylostomiasis* can be found more often in medical discourse. It is thought that one reason may be the influence of English, another – the reluctance of the medical community to take into account the etymology of a terminological unit due to lack of knowledge of the phonetic system of the language from which the term was borrowed, in this case – the ancient Greek.

In ICD-10, code B-76.0, the invasion, caused by Ankylostoma species is referred to as "ankylostomiasis/ankylostomosis", whereas the common name for code B-76 is "ankylostomidosis (hookworm disease)". Thus, the term "hookworm disease" refers to a disease that combines two invasions: ankylostomosis / ankylostomiasis, caused by Ankylostoma duodenale, and necatorosis, caused by Ankylostoma americanum, also known as Necator americanus. The term "ankylostomidosis" is formed according to a well-known model: the Greek suffix "-osis" is added to the name of the family of nematodes of the class Rhabditida Ankylostomatidae: *ankylostomidosis*.

In general, in ICD-10, subheading B65 - B99 "Helminthiasis" of heading A_{00} – B_{99} Class I. "Some infectious and parasitic diseases" record 19 nosologies, where a zoomorphic component is distinguished. Quantitative analysis of the selected terminological units is as follows: two two-component formations with the suffix "-osis", five – with the suffix "-iasis" and several word-forming variant forms, which have a common root, equivalent lexical and grammatical meaning, but the discrepancy is in the use of close by semantic load, but different in the verbal expression of suffixes: *helminthosis et helminthiasis, taeniosis et taeniasis, trichinosis et trichiniasis, bilhaziosis et bilhaziasis*; there are nine three-component one-word nominations; among them, eight are formed with the suffix "-osis" and one variant form: *ankylostomosis et ankylostomiasis*. The four-component terms are represented by three composites: word-forming variant forms *diphyllobothriosis et diphyllobothriasis* and lexemes *trichostrongyloidosis* and *angiostrongylidosis*.

Regarding the morphological nature of term components, the following conclusion can be made:

1) noun morpheme of Greek origin + suffix "-osis" or "-iasis" – these are the most numerous examples. Let us illustrate this statement with several examples: *ascaridosis* ← basis of "ascarid-" from the Greek noun ἀσκαρις – "worm", + suffix "-osis". It is known that the term "ascarid" (*Ascaris, idis f*) was introduced by Hippocrates, and the modern name Ascaris lumbricoides – a roundworm of the nematode class – was given to the helminth by Carl Linnaeus in 1758.

2) two noun morphemes of Greek origin + suffix "-osis" or "-iasis": *echinococcosis* ← base *echin-* from the Greek noun ἐχῖνος - *hedgehog* + Greek noun κόκκος – *grain* + suffix "-osis"; *cysticercosis* ← base *cyst-* from the Greek noun κύστις – *bubble* + Greek noun κέρκος – *tail* + suffix "-osis"; *trichocephalosis* ← basis *trich-* from the Greek noun θρίξ – *hair* + Greek noun κεφαλή – *head* + suffix "-osis", etc.

3) prefix of the Greek origin + adjective morpheme + suffix "-osis" / "-iasis" – three examples: *metastrangylosis* ← Greek prefix *meta* + base *strongyl-* from the Greek adjective στρογγύλος - *round* + suffix "-osis"; *metagonimosis / metagonimiasis*: ← Greek prefix μετα + base *gonim-* from the Greek adjective γόνιμος - *fruitful* + suffix "-osis" / "-iasis" and *paragonimosis / paragonimiasis*: ← Greek prefix παρα + base *gonim-* from the Greek adjective γόνιμος - *fruitful* + suffix "-iasis".

Medical terminology in general is characterized by the use of a huge number of terms, where one of the components refers to the name of a certain person, to whom we owe the functioning of a particular eponymous term. This phenomenon is inherent in the terminology of all subsystems of medicine, as evidenced, for example, by the publications on eponymous terms based on the material of English and Latin terminology [9; 12 - 17]. However, we did not find any mention of eponymous formations in the names of helminthiases, therefore, we also paid attention to this aspect. The analysis of verbal notations of the concept in the above-mentioned thematic field revealed the existence of several terms, which can be attributed to eponymous ones. In particular, it is a one-word composite *brugiosis* - helminthiasis from the group of filariasis caused by Brugia malayi. Thus, the term is based on the name of the Dutch parasitologist S.L. Brug (1879-1946), who isolated a helminth called Filaria malayi in 1927. However, in 1958 (according to other sources, in 1960), D. Buckley proposed to classify the pathogen in the genus Brugia - a genus of filamentous worms of the superfamily Filarioidea, which parasitize in humans and mammals, a new species named Brugia malayi in honor of the discoverer S.L. Brug, to which the medical community of the time responded favorably.

Another monolexemic composite is represented by the term *bilharziasis / bilharziosis*, which corresponds to the name of the German doctor Th.M. Bilharzar (1825-1862), who in 1851 described the genus of trematodes Bilharzia, parasitizing in blood vessels, and after whom this genus was named.

Another name for helminthiasis *wuchereriasis / wuchereriosis* has its origins in the name of the German physician Otto Wucherer (1820-1873), to whom we owe the existence of the name Wuchereria of the genus Nematode of the superfamily Filarioidea.

Eponymous terminological phrases include *schistosomiasis / schistosomatosis Mansoni* - infection with trematodes of the species Schistosoma mansoni, which live mainly in the superior and inferior mesenteric veins. As you one observe, the general term schistosomiasis (from the Greek adjective σχιστός - *split* Greek noun σῶμα - *body* + Greek suffix "-osis") is used to verbalize the concept, which means "helminthiasis caused by trematodes of the genus Schistosoma" and the name of the English doctor Sir Patrick Manson (1844-1922), who in 1898 proposed to distinguish between two forms of schistomosis: the intestinal (*schistosomiasis intestinalis*) and the urogenital ones (*schistosomiasis urogenitalis*). Later, in 1907, the Italian and English physician Louis Westerna Sambon (1867-1931) suggested that intestinal schistomatosis should be named after the person who first noticed helminth eggs in a patient's feces in South America, namely schistosimiasis Mansoni [10]. Modern encyclopedic medical dictionaries record two synonymous names for the transmission of tropical helminthiasis, which occurs with allergic manifestations and signs of damage to the mucous membrane of the colon by migrating eggs of the helminth Schistoma mansoni: *schistosomiasis Mansoniis* and *intestinal beniponia*. These terminological units are absolute synonyms, and their parallel functioning

in medical discourse is explained by the historical stages of the study of helminthiasis caused by the genus of trematodes of the family Schistosomatidae. Quite correct in this regard is the remark of M. Kuzmin that one scientific concept can have many different features, it can be perceived differently and have several names that reflect the different properties of the object of nomination [11, p. 78].

In addition to the eponymous formation recorded in the dictionary article "schistomatosis", we should pay attention to the two-lexemic composite with a toponymic component. It is a terminological phrase *schistosomiasis japonica* - helminthiasis of the group of trematodes, which is caused by the species Schistosoma japonicum and is characterized mainly by lesions of the gastrointestinal tract, where the term schistosomiasis occupies a constant position, and the variable part is expressed by the adjective. Since the parasite was first discovered in 1904 by the Japanese parasitologist Fujiro Katsurada (1867-1947) in a patient from Kofu, Yamanashi Prefecture (Japan), the genus Schistosoma was joined to the species japonicum, which fixed the name of the area where the helminth eggs were first isolated.

The term "loaosis" refers to "hybrid" terminological units, as the first position is not occupied by the classical (Greek or Latin) component, but by "the local word in Angola, West Africa" [5, p. 1328], *loa* – "the eye worm" [3, p. 310]. In 1778, the French surgeon F. Guyot described the parasite and gave it the name Loa loa, and the disease became known as *loaosis*.

The vast majority of the studied names of helminthiasis are characterized by terminological compatibility, which seems to us a well-motivated phenomenon: a specific pathogen that causes a specific disease, and the suffix "-osis" / "-iasis". For example, the larvae of nematodes Toxocara canis or Toxocara mystax cause severe parasitic toxocarosis; the Chinese sucker Clonorchis sinensis is the causative agent of chronic helminthiasis, known as clonorchosis; despite the two species of *Fasciola hepatica et Fasciola gigantica*, helminthiasis is codified by one term – "fasciolosis".

However, parasitism of four types of schistosomes in the human body has led to the emergence of terminological phrases, which differ depending on the predominant helminthic damage of the organ. Thus, *schistosomiasis urogenitalis* informs about the predominant lesion of the urogenital organs (*urogenitalis, e*); *schistosomiasis intestinalis* indicates intestinal invasion (*intestinalis, e*); *schistosomiasis intercalatum* is caused by Schistosoma intercalatum and is an endemic intestinal disease prevalent in West Central Africa; *schistosomiasis japonica* is characterized by damage to the digestive system and its spread in the regions of southern Japan, southern China, and the Philippine archipelago.

CONCLUSIONS

The conducted study allows us to draw the following conclusions:

1) monolexemic composites with a zoomorphic component are formed in a suffixal way: the Greek suffix "-osis" / "-iasis" is added to the name of the genus of the pathogen, which occupies the initial position; the vast majority of terms are of Greek origin;

2) in multi-word phrases, syntactic constructions of mixed type, are usually used and they are characterized by the combination of words of Greek and Latin origin, but these formations are few;

3) eponymous and toponymic formations to denote specific nosological forms in helminthology are not typical. The data on the first contribution of a researcher to the description of the disease in the name of the term is not displayed, preference is still given to the name of the pathogen, rather than the name of the researcher. For example, chronic helminthiasis with a predominant lesion of the small intestine was first described by the French physician L. Norman in 1876 under the name "Cochin-China diarrhea", because signs of the disease were found in soldiers returning from Cochin-China, one of the districts of the Mekong River Delta in southeastern Indochina. However, none of the dictionaries we relied on in the study recorded terms related to the doctor's name or geographical area. Three years later, in 1879, the eminent Italian parasitologist Giovanni Battista Grassi (1854-1925) provided in-depth information on the parasite's life cycle and proposed a name for a new genus of Stoangyloides parasites, resulting in the disease now known as *strongyloidosis / strongyloidiasis*;

4) prefix-suffix-based method of formation of terms denoting infectious and parasitic diseases with a zoonymic component is observed sporadically;

5) comparison of the above-analyzed terms with the corresponding terminological units of the English medical terminology indicates the predominant use of Latin terminological units, cf.: *schistosomiasis* (Latin and English); *strongyloidosis* (Latin and English) etc., which once again confirms the influence of Latin on the formation of the English medical terminology;

6) in contrast to many clinical terms with a zoomorphic component, where certain associative moments are taken into account, cf.: *auris felina* - cat's ear (because of similarity in shape), terms with an animal component in infectology emphasize the name of the pathogen: *onchocercosis* – from the name of the pathogen - round helminth Onchocerca volvulus (etymologically the generic name is derived from the Greek noun *onkos* – "tumor" and the Greek noun *kerkos* – "tail").

PROSPECTS FOR FURTHER RESEARCH

In our opinion, it is quite logical to carry out a comparative analysis of the terms of infectious and invasive diseases with a zoomorphic component based on the example of modern European languages, focusing on the current International Classification of Diseases, revision 10, to draw relevant conclusions about derivational characteristics of terms denoting a group of intestinal diseases caused by different types of pathogens. Our previous investigation, in particular, of the verbal codification of the concept of "a disease caused by Ascaris lumbricoides" confirmed the conclusion about the influence of Latin on the formation of national terms of infectious and invasive diseases with a zoomorphic component (Table I):

Table I. The verbal codification of the concept of "a disease caused by Ascaris lumbricoides"

Language	Term
Latin	ascaridosis, ascaridiasis, ascarisiasis
English	ascaridiasis, ascariasis
German	Askariasis, Ascaridiasis
French	ascaridiase, ascaridiose
Italian	ascaridiasi
Polish	ascaridoza
Ukrainian	аскаридоз
Russian	аскаридоз

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ORIGINAL ARTICLE

ECOLOGICAL EDUCATION AND ITS RELATIONSHIP WITH STUDENTS' HEALTH

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ABSTRACT

The aim is to assess the state of ecological education in student youth and determine its relationship to the level of students' health.

Materials and methods: The research was conducted on the basis ofthe Polissya National University (Zhytomyr, Ukraine) and the Sumy State Pedagogical University named after A.S. Makarenko (Sumy, Ukraine) in 2018-2020. The ascertaining experiment, which was conducted to assess the state of ecological education of students according to the questionnaire developed by us involved 503 students. The formative experiment aimed at studying the relationship between the level of ecological education and the level of students' health involved 59 students.

Results: The ascertaining stage of the experiment showed that the vast majority of students of different specialties revealed a low level of mastery of the components of ecological education. The formative stage of the experiment showed that the EG students significantly improved the level of all components of ecological education, as well as the level of their health ($p < 0.001$). No significant changes were revealed in the CG ($p > 0.05$).

Conclusions: The research showed that purposeful work on the formation of ecological education in the process of fitness and health recreation activities has a positive effect on all its components (knowledge, character building, worldview, culture) and the level of students' health. In general, it will help to improve the efficiency of the educational process of students, improve indicators of their life-sustaining and future professional activities..

KEY WORDS: ecological education, environmental factors, physical education, health, students

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INTRODUCTION

Today, students face a difficult task that consists in making radical changes in their consciousness and behaviour, forming and voluntarily accepting the restrictions and prohibitions dictated by the laws of nature. Fundamental changes are also needed in the education system, its values and ways of life, taking into account the environmental, economic, political, social and spiritual needs of today. Therefore, one of the ways to improve the efficiency of the educational process in physical education, the quality of sporting and mass participation as well as fitness and health recreation events including maintaining the health of student youth is to involve the issues of environmental education in the curriculum of physical education in higher educational institutions (HEI) of Ukraine, which should provide students with a system of knowledge about the positive and negative impact of environmental factors on human life and activities; to provide recommendations for exercise and sports in a polluted environment, including various temperature factors, polluted air, water, food, etc.

Excessive technological load on the environment; too slow implementation of waste-free processes; the lack of a unified environmental policy has led to the fact that much of Ukraine is in a zone of environmental disaster. This, in turn, has worsened human health, reduced life expectancy and fertility, increased the risk of poisoning from the polluted environment and the probability of consuming unsafe food i. e.the problems caused by technology-related changes in the transformation of the biosphere. These problems are called environmental, the responsibility of solving which is now laid upon the state [1, 2, 3].

Individual elements of the environment that interact with the human body are called environmental factors. Any environmental factor can be perceived by the human body positively or negatively, depending on the dose of exposure. Each person has his own optimal dose of a factor [4, 5]. The life-sustaining activities of the human body is in a continuous dynamic relationship with environmental factors. This interaction should not disrupt the adaptive mechanisms of the human body. Unconditional and conditioned reflexes are created in the human body

under the influence of various stimuli of his internal and external environment, which determine the maintenance of dynamic balance based on the exchange of substances and energy between the body and the environment [6, 7].

Environmental factors must have a positive effect on health and ensure the normal course of all human life processes. Environmental factors are divided into three groups according to their nature: 1) abiotic ones stipulated by the influence of inanimate nature (temperature, solar radiation, light, water, wind, precipitation, relief, etc.); 2) biotic ones i. e. the influences of wildlife and all relationships with it; 3) anthropogenic ones i. e. the influences caused by human activities [8. 9].

Environmental factors have a very complex physico-chemical composition, including temperature, pressure, humidity, air movement, electric and magnetic field, radiant energy, chemicals released into the air by plants, and so on. Environmental factors affect all receptors and the body as a whole due to such a complex structure. The vastness and generalization of their action is explained by the involvement of various levels of structural and functional organization in the reaction i. e. from molecular and cellular to organ and organism related ones, from peripheral nerve centres to the psycho-emotional sphere of a human being [10, 11].

The above gives grounds to ascertain that the effectiveness of educational and professional activities and in general the life of students should be based on the perception and analysis of information about the characteristics of the environment in which these activities takes place.

THE AIM

The aim is to assess the state of ecological education in student youth and determine its relationship to the level of students' health.

MATERIALS AND METHODS

Research participants. The research was conducted on the basis ofthe Polissya National University (PNU, Zhytomyr, Ukraine) and the Sumy State Pedagogical University named after A.S. Makarenko (SSPU, Sumy, Ukraine) in 2018-2020. The ascertaining experiment, which was conducted in 2018, involved 503 third and fourth year students of these higher educational institutions from different faculties: law, public administration and national security; economics and management; engineering and energy; forestry and ecology; accounting and auditing; veterinary medicine as well as agronomic and technological one and other faculties in various specialties. Assessment of the state of ecological education of students was carried out according to the questionnaire developed by us (Appendix I), which contained questions in four blocks: ecological knowledge (6 questions), ecological character building (3 questions), ecological worldview (3 questions), and ecological culture (4 questions).

A questionnaire created by the authors of this article was used for the survey in accordance with the requirements of the Codes of Ethics of PNU and SSPU. The questionnaire contains 16 questions and is aimed at studying of the state of ecological education of student youth. The questionnaire was assessed by the experts in this field (8 professors and 11 associate professors) and was approved by the Academic Council of PNU (Protocol No. 12 dated 18.08.2018) and SSPU (Protocol No. 12 dated 29.08.2018). Consent to voluntary participation in the survey was obtained from all the students involved in the study.

The completeness of the disclosure of the issue, integrity, logical sequence and knowledge were taken into account when performing written tasks. The results were assessed on the unified 100-point scale according to the current system of comprehensive assessment of students' knowledge in universities, in order to stimulate planned and systematic educational work. 90-100 points – the student shows personal creative abilities, is able to acquire knowledge independently, finds and processes the necessary information without the help of the teacher, is able to use the acquired knowledge and skills to make decisions in unusual situations, convincingly argues answers, independently reveals his own talents and inclinations. 82-89 – the student has excellent skills in the studied amount of material, applies it in practice, freely solves exercises and problems in standard situations, and independently corrects mistakes the number of which is insignificant. 75-81 – the student is able to compare, summarize, systematize information under the guidance of the teacher; as a whole is able to apply it independently in practice; to control his own activities; to correct mistakes that include significant ones, to choose arguments to confirm opinions. 64-74 – the student reproduces a significant part of the theoretical material, shows knowledge and understanding of the basic provisions; can analyse the educational material with the help of the teacher, correct mistakes that include a substantial number of significant ones. 60-63 – the student masters the educational material at a level higher than the elementary one, a significant part of it is reproduced at the reproductive level. 35-59 – the student masters the material at the level of individual fragments that make up a small part of the study material. 1-34 – the student masters the material at the level of elementary recognition and reproduction of individual facts, elements and objects.

The experimental (n = 28) and the control (n = 31) groups were created from the first year students of the PNU of the Faculty of Technology in order to conduct a formative pedagogical experiment. The formative experiment was conducted during 2019–2020, which introduced the issue of ecological education formation in students in the process of their physical education as well as fitness and health recreation events. The purpose of the formative pedagogical experiment was to find out the relationship between the students' ecological education and their level of health. The level of the students' physical health was assessed according to the method of H. L. Apanasenko [12].

One of the ways to improve the efficiency of the educational process of physical education, the quality of sporting and mass participation as well as fitness and health recre-

Table I. Indicators for assessing the state of ecological education of students (n = 503, points)

Specialties	Structural components of ecological education				Overall rating
	Ecological knowledge	Ecological character building	Ecological worldview	Ecological culture	
Veterinary hygiene, sanitation and expert investigation	66.4	66.1	70.3	71.6	68.6
Technology and processing of livestock products	63.6	61.2	68.4	59.6	63.2
Ecology	64.8	65.3	67.9	43.2	60.3
Veterinary medicine	51.3	59.8	56.4	67.5	58.8
Law	45.8	67.2	47.4	56.7	54.3
International economic relations	53.2	57.9	55.6	49.7	54.1
Horticulture and viticulture	47.1	56.2	53.5	53.4	52.6
Plant protection and quarantine	57.1	51.7	53.9	46.2	52.2
Forestry	45.8	52.4	53.7	56.5	52.1
Geodesy and land management	53.4	49.7	51.7	47.8	50.7
Agronomy	46.5	42.4	52.5	36.8	44.6
Public administration	42.6	45.8	44.3	41.2	43.5
Agricultural engineering	44.5	41.3	51.8	35.8	43.4
Industry engineering	39.5	40.6	43.7	38.5	40.6
Management	37.7	43.4	44.6	33.9	39.9
Economy	38.4	40.1	40.8	35.5	38.7
Information systems and technologies	38.3	40.2	41.6	31.7	38.0

ation events and maintaining the health of student youth included the introduction of the issues of ecological education in the curriculum of physical education of students, which provided students with knowledge of positive and negative impact of environmental factors on the state of human life-sustaining activities; provided recommendations for exercise and sports in a polluted environment, including various temperature factors, polluted air, water, food, etc. Three main issues were addressed: 1) to form the purpose of ecological education in physical education; 2) to determine the content and hierarchy of tasks of ecological education and character building in the field of physical culture and sports; 3) to substantiate the principles of implementation of ecological education and character building within the system of physical education of students.

Research methods: analysis and generalization of the scientific and methodological literature (29 sources on the topic of the article from the scientometric databases PubMed, Scopus, Web of Science Core Collection and others were analyzed), questionnaire survey, pedagogical observation, testing, pedagogical experiment, methods of mathematical statistics. The authenticity of the difference between the indicators of students of studied groups was determined by Student's t-test.

Ethics. The research was performed in accordance with the requirements of the Regulations on the system of academic honesty in educational and scientific activities of PNU (Protocol of the Academic Council No. 2 dated 18.02.2018) and SSPU (Protocol of the Academic Council No. 12 dated 18.06.2020).

RESULTS

It is established that the issues of ecological education and character building of students in European countries are of great importance. The most typical tasks that unite the views of most educationists in European countries on ecological education are: the formation of knowledge about the relationships patterns of natural phenomena, the unity of animate and inanimate nature, the interaction of a human being, society and nature; education of motives, needs and skills of ecologically expedient behaviour and activity, healthy way of life, desire to vigorous activity concerning protection of environment; development of intellectual and emotional spheres of students' psyche on the basis of causal analysis of ecological situations and emotional pain in relation to nature.

The multi-level system of environmental monitoring that exists in Ukraine makes it difficult to obtain and use the information needed by students to maintain health and safe life-sustaining activities. Therefore, most environmental monitoring issues are solved by departmental organizations that deal with their special tasks, which makes it very difficult for students to get a single picture of the state of pollution of the environment in which physical education sessions as well as various fitness and health recreation

Table II. Comparative analysis of the level of ecological education in the first and the fourth year students of the Faculty of Ecology of the PNU (n = 92, points)

Structural components of ecological education	First year students (n=49)	Fourth year students (n=43)	Difference
Ecological knowledge	65.9	78.5	12.6
Ecological character building	67.1	78.9	11.8
Ecological worldview	68.4	79.6	11.2
Ecological culture	47.6	74.8	27.2
General level	62.3	78.1	15.8

Table III. Dynamics of the components of ecological education and the level of health of the EG and the CG students during formative pedagogical experiment (n = 59, X ± m, points)

Investigated indicators	EG (n = 28)		Significance of the difference		CG(n = 31)		Significance of the difference	
	Before exper.	After exper.	t	p	Before exper.	After exper.	t	p
Ecological knowledge	38.6±1.17	77.4±3.74	9.87	<0.001	39.2±1.24	44.1±2.76	1.62	>0.05
Ecological character building	42.3±1.67	74.9±2.64	10.44	<0.001	41.5±1.75	47.2±2.34	1.95	>0.05
Ecological worldview	43.7±1.87	76.9±2.94	9.53	<0.001	42.2±1.67	48.3±2.73	1.91	>0.05
Ecological culture	36.4±1.14	53.8±1.83	8.07	<0.001	38.1±1.19	43.1±2.33	1.91	>0.05
Physical health level	3.14±0.72	9.77±0.67	6.74	<0.001	3.29±0.68	5.05±0.64	1.88	>0.05

events, sports and entertainment activities are conducted. There isno organization and state program of environmental monitoring in Ukraine at the present moment, which would carry out comprehensive, systematic control over all types of environmental pollution and provide up-to-date information on vital activity security. There are also many issues regarding the unification of departmental regulations on the use of environmental resources. At the same time, many specialties the students study at totally do not raise environmental issues, the study of the impact of environmental factors on human health, and so on. Our monitoring of the quality of ecological education of the third and the fourth year students of the PNU and the SSPU of different specialties showed different levels of students' mastery of the components of ecological education, which is directly related to maintaining students' health, environmental behaviour, the use of natural factors in order to improve efficiency, healthy nutrition, etc. (Table I).

The content of ecological education is based on a system of scientific knowledge that reflects the natural and scientific, social and economic, legal, moral and ethical, technical and ideological aspects of the existence of the natural environment and conditions of life-sustaining activities. In our research, ecological education of students was assessed on four indicators: ecological knowledge, ecological character building, ecological worldview and ecological culture.

Ecological knowledge as a component of environmental education is a holistic structure and consists of cognitive and active elements of learning. Cognitive elements include ecological knowledge and the formation of the inner culture of the individual, which will contribute to the harmonization of human relations with nature. All this helps the student to realize his place in nature and to clarify his responsibility towards it. The student has the opportunity to establish a harmonious relationship with nature on this basis. The main directions of ecological education are: education in the spirit of general ideas of environmental protection and human health, acquisition of special professional knowledge about the general laws of existence of natural and anthropogenic ecosystems.

Ecological character building forms an active environmental viewpoint of the student, which is achieved through a set of environmental and ecological education, promotion of environmental behaviour. The main function of ecological character building consisted in the acquisition and accumulation by students of experience of interaction with the environment at the cognitive, sensory and emotional as well as normative levels. It is the combination of knowledge, emotional experiences and practical skills in environmental activities that allows students to make the right decisions during their stay in the natural environment.

We defined the *ecological consciousness* of the student as an organic combination of ecological knowledge, thoughts, ideas, beliefs, feelings, and aspirations. Ecological consciousness was realized in purposeful and meaningful nature protection human activities, active defence of moral values and ecological principles. Thus, ecological knowledge is the basis for the formation of ecological consciousness of the student.

The main means of forming the *ecological culture* of students was a purposeful system of ecological education, which formed the attitude towards nature, determining the allowable degree of its transformation, mastering specific

socio-natural patterns and norms of behaviour in which further human existence is possible. To develop a strategy for the formation of ecological culture, we have created and implemented new approaches and methods of ecological education (ecologization of physical education); singled out the basic qualities of the ecologically educated personality and a technique of his step-by-step formation; correlated the content of education with the real needs and interests of students; applied ecological knowledge in physical culture and health-improving activities of students.

All this helps the student to realize his place in nature and to clarify his responsibility towards it. The student has the opportunity to establish a harmonious relationship with the environment on this basis. The obtained data confirmed the opinion that the inclusion of ecological education in physical education curriculum will significantly improve the ecological education of the individual.

It was found that students majoring in veterinary hygiene, sanitation and expert investigation showed the highest level of ecological education (68.6 points), technology and processing of livestock products (63.2 points), ecology (60.3 points), veterinary medicine (58.8 points), law (54.3 points), international economic relations (54.1 points). This indicates that these specialties are directly related to ecology, hygiene, sanitation, expertise, international attitude to ecological problems of mankind, practical attitude to environmental problems and certain practical skills as future professionals. At the same time, a large number of specialists trained at Ukrainian universities do not study the problems of the impact of the environment on human health and life-sustaining activities at all.

In addition, we conducted the comparative analysis of the level of ecological education in the first (at the end of the academic year) and the fourth year students at the Faculty of Ecology, where ecological education is the basis of their future professional activities. The analysis showed a very significant difference between the comparison contingents (Table II). The fourth year students significantly improved their indicators in all comparative components of ecological education. The research showed that the study of environmental special disciplines helps to improve the knowledge needed both to improve thestudents' own health and in general to improve their life-sustaining activities as well as future careers.

Therefore, we believe that the inclusion of ecological education in the work programs on physical education will significantly improve the level of ecological education of students of other faculties, where special environmental disciplines are not studied, which will generally improve their life-sustaining activities and health. The conducted pedagogical formative experiment with the second year students of the Faculty of Technology of the PNU showed that the purposeful formation of ecological education has a positive effect not only on the level of ecological knowledge, but also on improving the state of health and reducing the number of students assigned to a special medical group (Table III).

The research confirmed that purposeful work on ecological education in the process of fitness and health recreation activities has a positive effect on all indicators of students' life. Thus, the EG students significantly improved the level of all components of ecological education, as well as the level of their health ($p < 0.001$). At the same time, no significant changes were revealed in the CG ($p > 0.05$). Moreover, at the end of the experiment, the EG students showed a significantly better level in all studied indicators ($p < 0.001$), compared with the CG, which indicates the effectiveness of the introduction of ecological education to physical education of students of higher educational institutions. In addition, the number of students of the special medical group decreased from 8 to 7 persons in the EG during the pedagogical experiment, on the contrary, its number increased from 7 to 9 persons in the CG.

DISCUSSION

The organization of the educational process of student youth living in a polluted environment requires special attention to the formation of ecological education. The reason for this is: 1) lack of ecological knowledge of teachers of physical education departments; 2) inadequate material and technical base for conducting recreational and health-improving as well as preventive physical exercises; 3) inadequate medical examination, control over the health of young people and the environment; 4) reduced number of hours devoted to physical education as well as sporting and mass participation, fitness and health recreation events; 5) unsystematic control over physical development, mental and physical performance; 6) lack of scientific recommendations for physical activities in a polluted environment; 7) non-compliance with the requirements for the peculiarities of nutrition in a polluted environment; 8) lack of knowledge, skills and abilities of students on behaviour in the natural environment during sporting and mass participation as well as fitness and health recreation events, leisure and relaxation, etc. [1, 3, 13-17].

The main tasks of ecological education of students in the process of their physical education should be: preservation of a viable natural environment; radical restructuring of ecological education and character building of the individual on scientific principles; formation of a new ecological thinking and worldview in the relationship between man, society and nature; development of ecological education taking into account national heritage, formation of ecological thinking not only in narrow national, but also in planetary aspect; promotion of ecological education, which serves to improve the individual, his inner world, develops human dignity, humanism; human self-consciousness as a part of nature, connected with numerous inseparable ties, which allows to build adequate relationships with the environment [2, 3, 8, 18-21].

It is established that theoretical knowledge on ecology became the basis for activating the consciousness of students and determined the level of their needs for environmental safety. Assimilation of theoretical knowledge stimulated students to analyse facts, their generalization and conclusions, intensified their ability to retrospectively search for information, its systematization, analysis and synthesis, accumulation of individual environmental information experience. In addi-

tion, mastering the theoretical material attracts students to learn about the values of ecological education and character building, develops and forms the cultural potential of the student's personality, expands his worldview.

Ecological character building, which is provided during physical education sessions, is designed to form an active environmental viewpoint of the student, which is achieved through a set of environmental and ecological education, promotion of ecological behaviour. The main function of ecological character building is to acquire and accumulate students' experience of interaction with the environment at the cognitive, sensory-emotional and normative levels. It is the combination of knowledge, emotional experiences and practical skills in environmental activities that allows students to make the right decisions during their stay in the natural environment. The results of our research do not completely solve the problem, they only expand the results of research by other scientists [22-29].

CONCLUSIONS

1. The analysis of the quality of ecological education of the third and the fourth year students of the PNU and the SSPU of different specialties showed the insufficient level of students' mastery of the components of ecological education. Sufficient and satisfactory level of ecological education was shown only by the students whose future professional activities within the educational process is associated with the issues of ecological education (veterinary hygiene, sanitation and expert investigation, technology and processing of livestock products, ecology, veterinary medicine, international economic relations). At the same time, a large number of students of the higher educational institutions of Ukrainian do not study the problems of the environment impact on human health and life-sustaining activities at all.
2. It is established that the purposeful formation of ecological education in students during their physical education has a positive effect not only on the level of ecological knowledge, but also on improving the state of their health and reducing the number of students assigned to a special medical group. At the end of the pedagogical experiment, the level of all components of ecological education, as well as the level of health of the EG students significantly improved ($p < 0.001$). At the same time, no significant changes were revealed in the CG ($p > 0.05$). Moreover, at the end of the experiment, the EG students showed a significantly better level in all studied indicators, compared with the CG ($p < 0.001$).
3. Ecological education today is recognized as a priority in the character building of student youth, the formation of such patterns of behaviour in the natural environment that reproduce ecological development. The creation of a new paradigm of ecological education requires the reflection and disclosure of its content, forms and methods in all academic subjects. Therefore, one of the ways to improve the effectiveness of the educational process in physical education, the quality of sporting and mass participation as well as fitness and health recreation events and maintaining the health of student youth is the inclusion of ecological education issues in physical education curricula of the higher educational institutions of Ukraine, which should provide students with knowledge of the positive and negative impact of environmental factors on the life-sustaining activities of students; provide recommendations for exercise and sports in a polluted environment.

Prospects for further research are aimed at improving the curriculum in physical education, taking into account the ecological policy of Ukraine and the world community.

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A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

Appendix I

Questionnaire
for assessing the state of ecological education in student youth

Dear student!

In order to study and assess the state of ecological education of student youth, we ask you to sincerely answer the questions without missing any of them. Answer the questions clearly, concisely and specifically. Our assessment of your answers will allow us to prepare guidelines to protect your health from the negative effects of environmental factors. It is your level of knowledge on ecological issues that will help us build a methodology for ecological education in the process of physical education. Your answers will be used in a generalized form for scientific purposes only. Please answer all questions as accurately as possible. We hope for your responsibility, we are sincerely grateful to you in advance.

1. General data
Please provide some information about yourself (underline as applicable):
- Last name, first name _____
- gender: male, female
- the year of your training: ▪ 1st ▪ 2nd ▪ 3rd ▪ 4th
- which educational division do you belong to: special medical, basic, sports
- age of completed years: 17 years old, 8-20, 21 and more
- Your place of residence: village, town, city

2. Assessment of ecological knowledge
1. Define ecological education.
2. Explain the content of ecological education.
3. List the tasks of ecological education.
4. What is the importance of ecological education for humans?
5. Disclose the main directions of ecological education.
6. Disclose the importance of ecological education in the field of physical culture and sports.

3. Assessment of ecological character building
1. Define ecological character building.
2. What should ecological character building shape?
3. What are the functions of ecological character building in the system of physical education of students?

4. Assessment of ecological worldview
1. Define ecological consciousness?
2. What is the basis for ecological consciousness formation?
3. List the signs of ecological consciousness.

5. Assessment of ecological culture
1. Define ecological culture.
2. Means of ecological culture formation.
3. Conditions for ecological culture formation.
4. Name the most important indicators of ecological culture formedness.

Thank you for participating in the survey!

ORIGINAL ARTICLE

THE EFFECT OF NOS3 AND AGTR1 GENOTYPES ON THE COURSE OF THE ARTERIAL HYPERTENSION FOR THE OVERWEIGHT OR OBESE PATIENTS

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ABSTRACT

The aim: Objective of the research is to determine the effect of NOS3 and AGTR1 genotypes of patients with arterial hypertension and high body mass index in the course of the disease.

Materials and methods: 58 patients (22 men and 36 women) with AH and high BMI were examined. The average age of the examined patients was 53.6±8.7 years. The analysis of rs1799983 polymorphisms of the NOS3 gene (localization 7q36.1; 7:150999023) and AGTR1 (type 1 receptor for angiotensin 2 1166 A>C) was performed using TaqMan assay (Thermo Fisher Scientific, USA) by real-time PCR (Applied Biosystems, USA) using TaqMan probe amplification products. Genomic DNA samples were isolated from stabilized blood using a Genomic DNA Mini Kit reagent (Invitrogen, USA). The Statistica 10 program (StatSoft Inc.) was used for statistical processing of the obtained data, USA). The independent samples were compared using the Mann-Whitney (U) criterion. In all cases of statistical evaluation, the reliability of differences was taken into account at a value of $p<0.05$.

Results and conclusions: Polymorphism of the NOS3 and AGTR1 genes is associated with early development and complicated course of cardiovascular pathology. The combination of NOS3 and AGTR1 gene polymorphism in patients with the high body mass index increases the risk of complications in hypertension. Using a mathematical model to predict the probability (95%) of genetic mutations in two genes (NOS3 and AGTR1) increases the effectiveness of diagnosis for patients with the high risk of developing cardiovascular complications.

KEY WORDS: arterial hypertensions, NOS3 and AGTR1 genotypes, body mass index

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INTRODUCTION

The cardiovascular diseases, as arterial hypertension(AH), determine the mortality and disability of the adult population. The number of the patients with AH increases with age, which is associated with a violation of the response to vasodilating factors, this problem leads to the development of vascular diseases, accompanied by pathological vascular remodeling, impaired tissue perfusion. An early predictor of atherosclerosis and complications of cardiovascular pathology is endothelial disfunction. Vascular endothelium supports hemostasis, and endothelial dysfunction affects vascular tone, immune inflammation, and platelet activation [1, 2]. During the aging process of the endothelium, both structural and functional changes occur, in particular, angiogenesis, vascular wall tone are disrupted, and mitochondrial dysfunction occurs. In addition, endothelial disorders are affected by oxidative stress, hyperuricemia, activation of the renin-angiotensin system, and vascular inflammation [3-6].

The disorders of NO synthesis by endotheliocytes may be genetically determined The replacement of guanine with thymine at 894 positions in exon 7 of the NOS3 gene leads to a change of the enzyme activity due to a change in the amino acid sequence (glutamine is replaced with arginine at 298 positions) [7-10]. The existing T allele in patients with AH and a high body mass index (BMI) is associated with an early (on average 4.5 years) development of the disease, which was found among 39,7% of patients.

The gene AGTR1 polymorphism is associated with high vascular stiffness [11] and endothelial disfunction [12] and cardiovascular complications in pathology, which also affects the development and severity of hypertension [13-15].

Therefore, better understanding of the pathophysiology of cardiovascular diseases can be useful for optimizing prevention and treatment, and patients with AH will be provided optimal blood pressure (BP) control. Routine examinations of patients with AH can identify damage of the target-organs and determine the risks of complications, analyze the effectiveness of antihypertensive therapy, but the examinations do not show additional information on the personal treatment of such patients. A data variety about the contribution of the NOS3 and AGTR1 genes polymorphisms to the development of the disease and its complications, and the course of concomitant pathology,

in particular the 2nd type of the diabetes, obesity, hypercholesterolemia, chronic renal failure, are aimed to find a pharmacogenetic basis for the treatment choice strategy for patients with AH [16-24].

THE AIM

Objective of the research is to determine the effect of NOS3 and AGTR1 genotypes of patients with arterial hypertension and high body mass index in the course of the disease.

MATERIALS AND METHODS

58 patients (22 men and 36 women) with AH and high BMI were examined. The average age of the examined patients was 53.6±8.7 years. The analysis of rs1799983 polymorphisms of the NOS3 gene (localization 7q36.1; 7:150999023) and AGTR1 (type 1 receptor for angiotensin 2 1166 A>C) was performed using TaqMan assay (Thermo Fisher Scientific, USA) by real-time PCR (Applied Biosystems, USA) using TaqMan probe amplification products. Genomic DNA samples were isolated from stabilized blood using a Genomic DNA Mini Kit reagent (Invitrogen, USA). The Statistica 10 program (StatSoft Inc.) was used for statistical processing of the obtained data, USA). The independent samples were compared using the Mann-Whitney (U) criterion. In all cases of statistical evaluation, the reliability of differences was taken into account at a value of $p<0.05$.

RESULTS AND DISCUSSION

The Endothelial nitric oxide synthase (NOS3) is a dimeric enzyme, the activity and expression of which are regulated at the transcriptional, post – transcriptional, and prost-translational levels. The gene encoding NOS3 includes polymorphic sites (single-nucleotide polymorphisms, tandem repeats, microsatellites, and inserts). Nitric oxide synthesis may be affected by some polymorphisms due to NOS3 activity or expression. NOS3 haplotypes can increase the risk of developing diseases [25] based on endothelial dysfunction, in particular ischemic heart disease (CHD), myocardial infarction, ischemic brain stroke, hypertension, and chronic kidney disease [26-31] (table. I).

The data of the research of gene polymorphism and the link between them with risks for patients with a Cardiological profile alter in different populations. Even on the territory of the same continent and the same country, depending on the region, the population may have different genotypes of the same gene, so it is not possible to extrapolate statistics on the polymorphism of a particular gene to the entire population of the country.

Mutations in the Nos3 gene can become predictors of the 2nd type diabetes mellitus (DM) [32, 33], although the dominant AG genotype of the NOS3 rs1800779 and T2D polymorphisms is protective [34], while the GT polymorphism of the NOS3 gene is associated with the development of arterial hypertension in Brazilian women [35]. The presented meta-analysis data in the European population according to Mendelian randomization indicate an association of exon polymorphism in NOS3 (rs1799983, p.Glu298Asp) and in intron COL4A1 (rs9521634) and near DYRK1A (rs720470) with ischemic brain stroke due to changes in blood pressure levels [36]. In patients in the Antalya population, the NOS3 GT and TC polymorphism (rs2070744) is associated with hypertension [37].

Also, a prospective study shows the role of nos3 gene polymorphism in the formation of cerebral artery aneurysms, their rupture or the development of vasospasm, and the existing polymorphism can be considered a risk factor for the development of vascular complications along with smoking, hypertension, and diabetes [38]. The RS2070744 NOS3 polymorphism may be considered a factor of genetic predisposition in Sudan to hypertension [39].

A high risk of CHD was shown in Caucasians, South Asian populations, and Middle Eastern people with the existing TT and GT nos3 polymorphism. TT polymorphism significantly increases the risk (odds ratio >2) of developing ASF in 10 countries (Ukraine, Brazil, Great Britain, Egypt, India, Iran, Chile, South Korea, Morocco, Japan, etc.) [40]. A strong correlation exists in the TG Enos and AG polymorphism in Morocco [41]. Conflicting data on NOS3 polymorphism and the risk of myocardial infarction. A meta-analysis revealed an association of TC polymorphism in the NOS3 gene with the risk of myocardial infarction in Asian and European populations [42]. In patients with CHD from Pakistan, the Glu298Asp variant of the NOS3 gene showed no association with hypertension and dyslipidemia, but had a strong correlation with systolic blood pressure [43]. NOS3 polymorphism in Iranian patients is associated with the development of multiple sclerosis [44], GT, TC, and 4a/4b polymorphisms were not associated with the risk of CHD in residents of northern Iran [45]. Patients with CHD are more likely to have the rs1799983 t and rs2070744 G alleles than the GG genotype, and diastolic blood pressure increases with increasing BMI [46].

Among the examined patients, the wild allele of the NOS3 gene was found inside 35 (60.3%) individuals, the GT genotype - inside 20 (34.5%) patients, and the TT genotype – inside 3 (5.2%) subjects. It is known that the TT genotype increases the risk of hypertension by 2.3 times: the no level is lower in patients with hypertension and diabetes with GT and TT polymorphism [47, 48].

The early development of CHD with a gt gene polymorphism was found [49-51], although among the Tunisian population, the GT polymorphism is not associated with the development of CHD [52].

The pathogenesis contribution arguable data of cardiovascular diseases are presented in numerous literature reviews of the polymorphism of the AGTR1 gene. Thus, GT (rs275652) and AG (rs275653) polymorphisms are associated with severe atherosclerotic vascular damage among patients in the Mexican population [53, 54] (table. II).

Also, polymorphism of the AGTR1 gene causes sodium reabsorption in the distal tubules and the development of vascular stiffness, regardless of the level of blood pressure [55, 56]. The activation of renin-angiotensin of the aldoste-

Table I. Association of NOS3 gene polymorphisms with the development of pathological conditions

Genotype	Result	Reference
NOS3 gene polymorphism	Cerebral artery aneurysms, rupture or development of vasospasm; disseminated sclerosis	Subhas K. Konar etc., 2019; Mohammad Mehdi Heidari etc., 2017;
TT polymorphism of the NOS3 gene	AH	Jelita Siregar etc.., 2020;
GT polymorphism of the NOS3 gene	AH; the early development of IXC	Abel Barbosa Lira Neto etc. 2019; Sanaa Nassereddine etc., 2018; Boqian Zhu etc., 2017; Khalil Mahmoodi etc. 2016; Sherif Arafa etc., 2018;
Alleles rs1799983 T and rs2070744 G of the NOS3 gene	Increased diastolic blood pressure among patients with high BMI	G L Zhao and etc, 2016;
NOS3 haplotypes G894T/T-786C	Reduced NO level among patients with hypertension and diabetes; CHD; myocardial infarction; ischemic cerebral stroke; hypertension; chronic kidney disease	Robin Johns etc, 2018; Omneya Moguib etc, 2017; Jelita Siregar etc, 2020; Cecilia Vecoli, 2014; Alejandro Marín Medina etc, 2018; E A Trifonova etc, 2019; N Yu etc, 2019; Beáta Soltész etc; Gustavo H Oliveira-Paula etc, 2016; Xiang-Zhen Kong etc, 2017; Dalia El-Lebedy etc, 2018; Süleyman Ömer Anlıaçık etc, 2019; Sahar Gamil etc, 2017; Rainer Malik etc, 2018;
AG polymorphism NOS3 rs1800779 and T2D	High systolic blood pressure	Saleem Ullah Shahid etc, 2017;

Table II. Association of agtr1 gene polymorphisms with the development of pathological conditions

Genotype	Result	Reference
AGTR1 gene polymorphism	Increased vascular stiffness; Hypoxia resistance	Marcin Cwynar etc, 2016; Tatiana I Baranova etc, 2017;
Agtr1 GT (rs275652) and agtr1 AG (rs275653) polymorphisms	Systemic atherosclerosis	Tatiana S Rodríguez-Reyna etc, 2016; Zhongping Shi та ін., 2021;
genotype CC AGTR1	High renin levels; Complications of concomitant diseases	Tatyana Mulerova etc, 2020; Ana Célia Sousa etc, 2018; Keping Chen etc, 2021; Samantha Kohli etc, 2016; Sandrita Simonyte etc, 2017; Benjamin Goldstein etc, 2016; Sudhir Jain etc, 2018; Elena V Zholdybayeva etc, 2016; Roseline Wai Kuan Yap etc, 2017; Hsien-Feng Chang etc, 2018;
AC polymorphism of the AGTR1 gene	Liver damage; Insulin resistance; Endothelial dysfunction; Adipokine activation; Diabetic nephropathy; Hypertriglyceridemia; Increased low-density lipoproteins	Giovanni Musso etc,2019; Dana de Gracia Hahn etc, 2019; Yan Zhuang etc, 2018; H-L Xu etc, 2020; Xun Li etc, 2016;
Alel C in rs5186 of the AGTR1 gene	High mortality and cardiovascular complications among patients with end-stage kidney disease	Sharon M Moe etc, 2019.

rone system (RAAS) is connected with AH. The results of a meta-analysis of the genetic association between RAAS genes and chronic kidney disease indicated a reduced risk of kidney damage in the presence of the AGT rs699-T allele and the AGTR1 rs5186-a allele [57], which also depends on the population [58]. The genetic polymorphism of AGTR1 in many researches is not associated with the development of hypertension [59, 60], although the CC genotype of this gene is associated with high level of renin, which contributes to the development of hypertension, at least in some populations [61-65] and negatively affects the course of concomitant diseases [66-69].

The collected data result for the dominant type of AA homozygote of the AGTR1 gene was detected inside 39 (67.2%) patients, and the heterozygous AC polymorphism was detected inside 19 (37.8%) of the examined patients.

A number of researches have shown no association between AGTR1 gene polymorphism and insulin resistance [70], although another study found the effect of AGTR1 AC polymorphism on liver damage, the development of insulin resistance and endothelial dysfunction, the effect on the activation of adipokines, chemokines and pro-inflammatory cells in response to fat consumption [71, 72], which is important while choosing drugs. The AGTR1 gene mutation is associated with the development of diabetic nephropathy among the Asian population [73]. The research result linked the existing polymorphism to high levels of triglycerides and low-density lipoproteins [74, 75]. The C allele in rs5186 of the AGTR1 gene is associated with high mortality and cardiovascular complications in patients with end-stage kidney disease, both in the European and African populations [76]. Also, according to other authors, polymorphism of the AGTR1 gene can cause resistance to hypoxia [77].

It is known about the link of myocardial remodeling with AH, which is determined among patients with hypertension to determine the stage and control the course of the disease, namely, the relative thickness of the left ventricle (VTS LV), left ventricular myocardial mass (MMLSH), and the left ventricular myocardial mass index (MMLSH) [78, 79]. Hypercholesterolemia is also a risk factor for hypertension and requires pharmacological correction in overweight patients, even at normal blood pressure values [80-82]. Hyperuricemia increases the risk of developing complications of hypertension, and it is advisable to determine the level of uric acid (uric acid) in all patients with increased blood pressure [83-85]. Both hypertension and obesity are associated with increased immune inflammation, which promotes remodeling of the vascular wall and increases its stiffness [86-88]. Obese patients have a high risk of developing insulin resistance and diabetes of the 2nd type [89-91].

According to the results of the analysis of indicators obtained during the examination of patients with AH, the heart rate (HR) has a likely relationship with the prediction of the existing polymorphism of the NOS3 and AGTR1 genes.

As a result of performing logistic regression to model the differentiation of existing polymorphism by NOS3 or AGTR1 genes separately, no statistically significant results were found. However, with the simultaneous polymorphism of these genes, we obtained strong correlations with the given risk factors for the course of hypertension. we created a mathematical equation according to which the probability of genetic mutations for two genes (NOS3 and AGTR1) can be predicted with a probability of 95%:

$$Y = 38{,}8 \times \text{BLP HD} + 21{,}8 \times \text{BLP HD} + 0{,}75 \times \text{BLP LD} + 5{,}6 \times \text{AI} - 0{,}009 \times \text{ILVMM} - 0{,}069 \times \text{LVMM} + 0{,}86 \times \text{N} + 0{,}009 \times \text{urinary capacity} + 0{,}21 \times \text{HD AH} - 1{,}84 \times \text{TC} + 2{,}8 \times \text{FBG} + 0{,}006 \times \text{HR} - 122{,}1$$

Where:

Y is the theoretical probability of mutations;
BLP HD - high-density beta-lipoproteins;
BLP LD - low-density beta-lipoproteins;
AI - atherogenicity index;
N – neutrophil count;
HD AH - hypertension-duration of arterial hypertension;
TC - total cholesterol;
FBG - fasting blood glucose;
HR - heart rate;
LVMM - left ventricular myocardial mass;
ILVMM - left ventricular myocardial mass index;

The inclusion in the formula of the indicator – the duration of the disease, can become a criterion for an early prognosis of the AH development in this category of patients.

The definition of gene polymorphism is associated not only with the risk of developing the disease, in particular, certain gene mutations can be protective in nature. Information about the gene polymorphism helps in choosing pharmacogenetic treatment for patients with the high risk of developing cardiovascular complications.

Since these indicators can be determined while examining a patient at the primary level and do not require high economic costs, this formula will help identify individuals with the likely presence of polymorphism for two genes (NOS3 and AGTR1) and, if need, send them for additional genetic examination to correct the treatment.

CONCLUSIONS

1. Polymorphism of the NOS3 and AGTR1 genes is associated with early development and complicated course of cardiovascular pathology.
2. The combination of NOS3 and AGTR1 gene polymorphism in patients with the high body mass index increases the risk of complications in hypertension.
3. Using a mathematical model to predict the probability (95%) of genetic mutations in two genes (NOS3 and AGTR1) increases the effectiveness of diagnosis for patients with the high risk of developing cardiovascular complications.

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REVIEW ARTICLE

ON THE NEED TO IMPROVE THE SYSTEM OF PREVENTION OF ALCOHOL AND DRUG ADDICTION AMONG SERVICEMEN OF THE DEFENSE FORCES

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ABSTRACT

The aim: Analysis of the legal framework for the development of scientifically sound measures for the prevention and detection of drug addiction and substance abuse in the Armed Forces of Ukraine as an important element of the system of medical support for combat readiness of troops.

Materials and methods: The normative documents on carrying out obligatory preventive narcological examinations in the Armed Forces of Ukraine and other power ministries and departments are considered.

Conclusions: Today in Ukraine it is necessary to improve the legal framework and strengthen control over the work of military commissariats to study conscripts, collect the necessary information about alcohol and drug addiction of citizens who are called up to the Armed Forces of Ukraine.

KEY WORDS: alcohol dependence, drug addiction, preventive medicine, military medicine

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INTRODUCTION

Today, in some parts of Donetsk and Luhansk regions, as well as in the Autonomous Republic of Crimea and the city of Sevastopol, the state authorities of Ukraine do not exercise their powers, which significantly affect the drug situation not only in these regions but in the country as a whole. Events in the area of the Anti-Terrorist Operation (from April 14, 2014 to April 30, 2018) in the Donetsk and Luhansk regions necessitated the announcement of mobilization to increase the number of the Armed Forces of Ukraine (hereinafter – the Armed Forces). In the first six waves of mobilization of the Armed Forces alone, 210,000 servicemen were recruited, and some of them signed a contract and today continue their military service in the Joint Forces operation (from April 30, 2018 to the present), mostly in the newly formed military parts.

The modern army is a part of society, and all processes, both positive and negative, are reflected in military service. The prevalence of alcoholism and drug addiction among the civilian population determines the presence of these phenomena among the military.

Alcohol and drug addiction as dangerous phenomena penetrate the military environment, especially with young people who have become addicted in school and adolescence. The consequence of alcohol and drug addiction is deviant behaviour, which in combat significantly increases the risk of non-combat losses.

In total, since the beginning of the Anti-Terrorist Operation, the number of servicemen whose deaths were not directly related to the fighting has exceeded 1,300. Some non-combat casualties are related to alcohol and drug abuse among military personnel. For example, in the first half of 2017, drug-related crimes accounted for 5.6% (78) of the total. In the anti-terrorist operation zone, during the same period, they accounted for 15% (42) of the total number of crimes.

The above became the basis for the generalization of the modern regulatory framework on the organization of prevention, in particular the detection of alcoholism and drug addiction among servicemen of the Defense Forces.

THE AIM

Analysis of the legal framework for the development of scientifically sound measures for the prevention and detection of drug addiction and substance abuse in the Armed Forces of Ukraine as an important element of the system of medical support for combat readiness of troops.

MATERIALS AND METHODS

An analysis of publications related to problematic issues in the field of detection and prevention of alcohol and drug addiction among servicemen. The normative documents regulating the procedure for conducting obligatory preventive narcological examinations and examinations in the Armed Forces of Ukraine and other power ministries and departments are considered.

REVIEW AND DISCUSSION

Monitoring of the drug and alcohol situation in Ukraine is carried out in accordance with the Resolution of the Cabinet of Ministers of Ukraine of July 10, 2019 № 689 "Issues of monitoring the drug and alcohol situation in Ukraine" [1] and the Order of the Cabinet of Ministers of Ukraine of 06.02.2019 № 56-r "On approval of the action plan for 2019-2020 for the implementation of the State Drug Policy Strategy for the period up to 2020"[2].

Public information on the results of the annual monitoring is available on the website of the state institution "Center for Mental Health and Monitoring of Drugs and Alcohol of the Ministry of Health of Ukraine". According to the latest state monitoring of drugs and alcohol of the Ministry of Health of Ukraine, at the beginning of 2019 in Ukraine were registered more than 9 thousand people who were diagnosed for the first time in their lives with mental disorders related to drug use, among their share of persons aged 15 to 35 was 75.1%. The main users of drugs are men (85.2%); the share of women - 14.8%; residents of cities - 83.7%, rural areas - 16.3%. The highest prevalence of drug addiction (per 100 thousand population) was recorded in Zaporizhzhia (364.61), Kropyvnytskyi (262.2), Odessa (235.47), Mykolaiv (213.93), Dnipropetrovsk (210.3), Kherson (181.7), Chernihiv (165.93) regions and the city of Kyiv (293.87). Among the most consumed drugs, opioids account for 65.5%; cannabinoids - 9.7%; cocaine - 0.02%; hallucinogens - 0.08%; simultaneous use of several drugs and other psychoactive substances - 24.2% [3].

Thus, according to official data, at the beginning of 2019, more than 100,000 drug addicts were registered across the country. However, according to experts of the international project "European survey of students on alcohol and other drug use - ESPAD", given the hidden nature of this phenomenon, drug latency, researchers believe that the idea of the number of drug addicts in Ukraine is 450-500 thousand people is more than 1% of the total population. According to opinion polls conducted within the framework of this project, 35% of freshmen in colleges and 25% of university students have experience of drug use. Experts believe that the number of Ukrainians who cannot live without drugs is increasing by almost 8% every year [4].

In 2017, the Verkhovna Rada of Ukraine adopted the Law "On Amendments to Certain Legislative Acts of Ukraine Concerning Strengthening the Responsibility of Servicemen and Certain Other Persons" [5]. The law stipulates that the consumption of alcoholic, low-alcohol beverages or the use of narcotic drugs, psychotropic substances or their analogues by servicemen, conscripts and reservists during gatherings on the territory of military units, military facilities, or the appearance of such persons on the territory of a military unit while intoxicated state, in a state of narcotic or other intoxication, or their performance of military duties in a state of intoxication, in a state of narcotic or other intoxication, as well as the refusal of such persons to undergo an examination for alcohol, drug or other intoxication entail the imposition of a fine of seventy to one hundred and forty-five non-taxable minimum incomes or arrest with detention on guard duty for up to five days. It is provided that the participation of chiefs (commanders) and other leaders in such actions entails the imposition of a fine of one hundred forty-five to two hundred and fifteen tax-free minimum incomes or arrest with detention on guard duty for a period of five to seven days. Such acts committed during a special period or by a person who during the year was subject to an administrative penalty for the same violations, entail the imposition of a fine of two hundred and fifteen to two hundred and eighty-five non-taxable minimum incomes or arrest with detention on guard duty for a period of seven to ten days.

Analysis of crimes related to drugs and psychotropic substances among servicemen shows that in the structure of seized drugs and psychotropic substances were most often found: products of cannabis processing in the form of crushed parts of this plant (hashish, anasha, marijuana) or related to bouquet; hemp resins (black or brown tablets); products of opium poppy processing in the form of raw opium; heroin; synthetic drugs (methadone, amphetamine, opium alkaloids); pharmaceuticals; precursors (acetic anhydride, ephedrine, lysergic acid, etc.) [6, 7].

In Ukraine, in order to timely identify patients with alcoholism and drug addiction, and establish medical contraindications to certain activities, a preventive drug test has been introduced.

The procedure for drug examination is determined by:

- Resolution of the Cabinet of Ministers of Ukraine № 1238 of 06.11.1997 "On mandatory preventive narcological examination and the procedure for its conduct" (hereinafter - Resolution № 1238) [8];
- Order of the Ministry of Health of Ukraine № 339 of 28.11.1997 "On improving the system of preventive anti-alcohol and anti-drug measures and mandatory preventive drug examinations" (hereinafter - Order № 339) [9];
- Order of the Ministry of Internal Affairs of Ukraine №1296 of 04.11.2003 "On medical care in health care facilities of the Ministry of Internal Affairs of Ukraine" [10];
- Order of the Ministry of Internal Affairs of Ukraine №1340of 11.12.2014 on amendments to the order of the Ministry of Internal Affairs of Ukraine of 04 November 2003 № 1296 [11];
- Order of the Security Service of Ukraine №310 of 17.07.2012 "On the procedure for drug and psychiatric examinations in the Security Service of Ukraine" [12].

Regulatory documents provide for the passage of primary, periodic and extraordinary drug examinations. The initial examination is carried out by persons who are employed in a certain position. Periodic review is conducted at regular intervals (different ones for different professions) throughout the period of work in his position. The issue of extraordinary examination is decided individually.

A narcologist who has a certificate in the specialty "Narcology" has the right to conduct a narcological examination. Specialists who have undergone special training according to the program approved by the Ministry of Health of Ukraine, testing and received a Certificate in the form № 146/0 are allowed to work. Training on modern drug testing should take place every three years. Unauthorized narcologist cannot perform preventive examinations.

In case of detection of signs of narcological disease or in case of disagreement with the results of preventive narcological

examination, a citizen has the right to undergo additional narcological examination, psychological testing and medical laboratory examination in an inpatient department of a narcological hospital within ten days.

The procedure for preventive narcological examination was prescribed in the order of the Ministry of Health of Ukraine "On approval of clinical protocols for medical care for "Addiction" from 21.09.2009 № 681. According to this order, the final conclusion on the suitability or unsuitability of the person to perform certain work is carried out by the medical-consultative commission consisting of 3 narcologists; the examination procedure lasts up to 10 days [13]. However, this order expired, according to the order of the Ministry of Health of Ukraine dated 28.02.2020 № 590 [14].

After the preventive narcological examination and additional examination in the hospital, the citizen is issued a certificate of the results of the narcological examination (form № 140-0 (registration). Certificate a single document (according to the Order of the Ministry of Health of Ukraine № 339 of 28.11.1997), certifying the presence or absence of contraindications to the performance of functional duties and activities for which the passage of primary and periodic preventive drug testing is mandatory [9].

According to paragraph 17 of the "List of professions and activities for which primary and periodic preventive drug testing is mandatory" approved by the Cabinet of Ministers of Ukraine № 1238 of 06.11.1997 [8], in order to timely identify patients with alcoholism, drug addiction, drug addicts, Persons entering the Ministry of Defense of Ukraine, including those called up for military service, are subject to preventive narcological examination. The Ministry of Health of Ukraine has identified narcological establishments as the venue for the preventive narcological examination. The list of state health care facilities where a narcological examination can be performed is approved by the Ministry of Health of Ukraine. The list of public health facilities where a drug test can be performed is approved by local government administrations [10].

A significant part of Ukrainian citizens undergo this procedure in a narcological institution at their place of permanent residence, except for employees of: the Ministry of Internal Affairs; Security Services of Ukraine; Foreign Intelligence Service of Ukraine; State Border Guard Service of Ukraine. Persons working in the above structures undergo drug examinations in departmental medical institutions.

Thus, narcological examinations in the Security Service of Ukraine are conducted by narcologists of medical and preventive institutions of the Security Service of Ukraine, narcological examinations during medical examinations are conducted by narcologists who are members of the military medical commission.

Mandatory periodic and extraordinary narcological examinations of privates and officers of the Ministry of Internal Affairs of Ukraine, employees of bodies and subdivisions of internal affairs, regardless of subordination, are conducted by psychiatrists of medical centers of the Ministry of Internal Affairs of Ukraine.

It should be noted that the organization of mandatory preventive narcological examination of citizens and persons entering the Ministry of Defense of Ukraine and serving in the military in departmental treatment and prevention facilities is not regulated.

In addition, if it is necessary to conduct extraordinary examinations of privates and officers, law enforcement officers, servicemen, employees of the National Guard of Ukraine and in case of impossibility of conducting such examinations in departmental medical institutions, these persons are sent for extraordinary examinations to state and municipal security health institutions, where an extraordinary examination of a person is carried out on a paid basis at the expense of the customer (department). If a person has passed a narcological examination in a medical institution that is not included in the approved list, the certificate of the results of such examination is not valid.

According to the Resolution of the Cabinet of Ministers of Ukraine № 1238 of 06.11.1997 [8] preventive narcological examination is carried out according to the mandatory program, which includes drug narcological examination, psychological testing and medical laboratory examination in the manner prescribed by the Ministry of Health of Ukraine.

According to the Order of the Ministry of Health of Ukraine № 507 of December 28, 2002 "On approval of standards for medical care and quality indicators of medical care" [15], laboratory (toxicological) analysis should consist of 2 stages: preliminary diagnosis (toxicological screening) and final diagnosis (chemical-analytical methods: thin-layer, gas-liquid, high-performance liquid chromatography with mass spectrometry).

Performing two stages of toxicological research increases the reliability of the final conclusion on the presence of a narcotic or psychotropic substance and meets international standards. Today, the procedure for the use of rapid tests for alcohol and drugs during drug examinations remains unregulated. Positive results of such tests, in accordance with the requirements of the Ministry of Health of Ukraine, are not considered grounds for termination of a person's performance of official duties.

The Armed Forces of Ukraine do not have military medical institutions that have the right to conduct preventive drug examinations in full, namely, there are no laboratories that have the right to conduct medical laboratory examinations in the manner prescribed by the Ministry of Health of Ukraine. Therefore, to ensure compliance with current legislation on the procedure of drug testing, the medical service of the Armed Forces of Ukraine in case of need for special drug tests of servicemen during military service, organizes drug tests on a self-supporting basis in state and municipal health care facilities. The list of facilities where you can undergo a drug test is approved by order of the Ministry of Health of Ukraine, and at the regional level - by local state administrations.

CONCLUSIONS

Based on the study of the legal framework of Ukraine in the field of prevention of alcohol and drug addiction, in particular the procedure for organizing and conducting preventive drug examinations, it is established that certain issues of organization of prevention and detection of alcohol and drug addiction among servicemen of the Defense Forces are finally unresolved.

Based on the data obtained, we consider it necessary: development and approval of an interdepartmental order on the procedure for conducting narcological and psychiatric examinations in the Armed Forces of Ukraine; development and approval of an interdepartmental order on coordination of actions of specialists of the Ministry of Health of Ukraine and the Ministry of Defense of Ukraine in providing psychiatric and medical-psychological assistance to participants of the Anti-terrorist operation/Joint Forces Operation; strengthening control over the work of military commissariats on the study of conscription contingents, gathering the necessary information on alcohol and drug addiction of citizens who are called up to the Defense Forces.

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REVIEW ARTICLE

THE USE OF ULTRASOUND GUIDED HIGH INTENSITY FOCUSED ULTRASOUND (HIFU) IN THE TREATMENT OF UTERINE FIBROIDS: AN OVERVIEW

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ABSTRACT

Uterine fibroids are the most common benign gynecological neoplasms, with a higher prevalence in women aged between 30 and 50 years old. Fibroids may be asymptomatic, but in some cases, they can affect seriously the quality of life of the patients. In some cases, we can recommend expectant management for asymptomatic patients. Management depends on the size and location of fibroids, the age of the patient, symptoms, desire for future childbearing and the experience of the gynecologist. Medical therapy includes hormonal contraceptives, tranexamic acid, and nonsteroidal anti-inflammatory drugs (reduce heavy menstrual bleeding). Gonadotropin-releasing hormone agonists or selective progesterone receptor modulators are used mostly preoperatively. Surgical treatment includes hysterectomy, myomectomy – invasive and minimally invasive. Non-surgical management include uterine artery embolization, and focused ultrasound surgery.This review aims to present the role of High-Intensity Focused Ultrasound in the treatment of uterine fibroids.

KEY WORDS: uterine fibroids, Focused Ultrasound Surgery, High-Intensity Focused Ultrasound, Ultrasound guided High-Intensity Focused Ultrasound

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INTRODUCTION

Uterine fibroids (UF) are the most common benign tumour pathology in women. The incidence of UF is associated with age, with a higher incidence in women between 30 and 50 years [1]. UF affects between 70-80% of all women, as they could be symptomatic or in the most cases – asymptomatic. When symptomatic, patients with UF present with a range of symptoms such as abnormal uterine bleeding, anemia, feeling of pelvic pressure and / or pelvic pain, infertility dyspareunia, constipation, pollakiuria, frequent nocturnal urination, symptoms of overactive urinary bladder [2]. In some patients, the UF may present with ureteral compression with resulting hydronephrosis and pyelonephritis [3].

The pathophysiology of UF has not been discovered. Existing theories indicate the combined effect of estrogen, progesterone and insulin-like growth factors may interact together to create conditions in the uterus for fibroid formation [4]. There is a hypothesis that the growth of UF depends on the difference between content of oestrogen receptors in endometrium and myometrium. If the concentracion is lower in the myometrium than the endometrium, this oestrogen may contribute to tumour enlargement by increasing the production of extracellular matrix. There is a data that progesterone also affects UF, especially in young women, because increases the mitotic activity of myomas. Tumour enlargement may be provoked by down-regulating apoptosis in the fibroids [5].

Modern treatment approaches include the usage of medical management, surgical management – which could be invasive and minimally invasive and non-surgical methods. Surgical methods include hysterectomy (vaginal, abdominal, laparoscopic or robotic), myomectomy (hysteroscopic, laparoscopic, robotic or by laparotomy), while non-surgical management is presented by procedures like uterine artery embolization and focused ultrasound surgery [5].

The choice of treatment depends mostly on patient preference with special regard to childbearing, choice of preserving uterus, chance of success of achieving treatment milestones, improving symptoms and overall health status of the patient [6]. The medical management of uterine fibroids include anti-fibrinolytic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), combined hormonal contraceptives, progesterone-only treatments, selective progesterone receptor modulators (SPRMs), anti-progestins, aromatase inhibitors, and gonadotropin releasing hormone (GnRH) agonists or antagonists [6]. Although other pharmacologic classes are being studied, current data does not show evidence of symptom or clinical improvement [6]. The fibroids characteristics, such as number, size and location, sympthoms, patients age and fertility desire, determine the type of treatment , especially

when considering minimally-invasive versus open surgery and myomectomy versus hysterectomy [7, 8]. Non invasive methods like Focused ultrasoud surgery (FUS), are divided in two main groups MRI (Magnetic Resonance Imaging) guided and Ultrasound guided High Intensity Focused Ultrasound (USgHIFU) [9].

THE AIM

This review aims to present the role of High-Intensity Focused Ultrasound in the treatment of uterine fibroids, the importance of searching for new non-invasive ways for treatment, to reveal the mechanisms and the safety protocols, and also to compare it with the surgical treatment of uterine fibroids.

REVIEW AND DISCUSSION

HISTORICAL PERSPECTIVES AND FUTURE LANDSCAPES OF FOCUSED ULTRASOUND

The use of focussed ultrasound begins with the discovery of ultrasound as a therapeutic modality in 1930, when the thermal effects of ultrasound on tissue were discovered [10]. In particular, ultrasound was used in physiotherapy, where the newly discovered thermal effects of ultrasound were used to treat tendonitis, synovitis and bursitis [10]. The use of focused ultrasound was pioneered by the experimentation of the Fry brothers, who, in the 1950s, experimented with the use of focussed ultrasound waves for the treatment of Parkinson's disease [11].

The subsequent years of experimentation led to the development of newer devices and newer areas of possible application of High-Intensity Focused Ultrasound (HIFU). Currently, HIFU is used in gynaecology for the treatment of UF and also in the treatment of benign, non-neoplastic diseases of the vulva [12, 13]. The use of HIFU in prostate hyperplasia is its most widespread use [14].

The future of HIFU is indeed bright as more areas of its application are being discovered. Current research into the expansion of the use of HIFU in the management of oncological disease shows that it is a safe and effective non-invasive method of targeting tumours [15]. Studies have shown positive results when investigating tumour shrinkage, patient safety, post-procedure complications. HIFU, both MRI and Ultrasound guided, have a variety of future applications, especially in patients that meet the suitable criteria [15].

WORKING PRINCIPLE

High Intensity Focused Ultrasound utilizes ultrasound waves to raise the temperature of tissue above 65 degrees Celsius. The High Intensity ultrasound wave is directed towards a very specific anatomical site at particular depth. This allows the sparing of surrounding tissues and is a precise method for targeting tissues [16]. HIFU is similar to diagnostic ultrasound in principle, the only difference is that HIFU, as its name implies, functions by generating ultrasound waves at intensities that are several magnitudes higher than imaging/diagnostic ultrasound [17]. The therapeutic range of HIFU is between 100 W/cm^2 and 10,000 W/cm^2 [18]. The main objective is to utilize the thermal and mechanical effects of high intensity ultrasound waves to achieve tissue ablation through coagulative necrosis. Cell destruction through coagulative necrosis is achieved when the temperature of tissue is raised to 60 degrees celsius for 1 second. As a safety measure, the exposure does not last longer than 1 second [17].

The ultrasound wave is focussed to achieve the desired effects on tissue. HIFU transducers are designed to focus the beam through spherical, concave or sometimes flat surfaces of transducers. In some cases, acoustic lens are used for adjusting the ultrasound beam so that it is focused at a specific focal point (Fig 1). Aside from the thermal effects of HIFU, the mechanical effects of ultrasound are utilized to achieve acoustic cavitation, which aid in tissue destruction [18].

There are two major imaging modalities used in HIFU, MRI and ultrasound. Both modalities are utilized for targeting tissue, intraoperative beam localization and therapeutic monitoring post procedure [18]. MRI allows for high contrast imaging with precise spatial assessment but is limited because it does not allow real-time monitoring like ultrasound. The advantage of the MRI over ultrasound in HIFU is that it is the only modality to allow real time thermometric assessment, however, research into new technology is underway to expand the capabilities of ultrasound in this regard [18].

Contrast agents play an important role in HIFU, and the use of contrast agents in ultrasound is termed Contrast Enhanced Ultrasound (CEUS). Their application is important for the diagnosis of tumours, as a guiding tool in HIFU therapy and for assessing ablation during and after the procedure. Contrast agents form microbubbles in blood vessels which create acoustic changes in tissues, allowing for an increase in effectiveness of tumour ablation. A number of contrast agents are used, such as SonoVue (sulfur hexafluoride) and Sonazoid (Perfluorobutane), among others. A number of studies have demonstrated their safety and effectiveness [19-21]. We demonstrates a case of a patient with uterine fibroids treated USgHIFU (Fig 2A-C).

The HIFU JC system is an ultrasound guided device that allows real-time imaging during tumour ablation procedures. It consists of two transducer heads - one is diagnostic and operates at 3.5 MHz, and the other is the therapeutic, which operates at 1.6 MHz. This system lets precise targeting of tissue while monitoring patient movement and possible displacement of target point [23]. Coagulative necrosis presents as areas of hyperechoic spots (Fig. 2C). The patient is positioned on the HIFU table under which a special container filled with degassed water is placed. Degassed water is an efficient conductor of ultrasound waves and also fulfills the purpose of cooling the skin and subcutaneous tissue, preventing skin burns [22, 23].

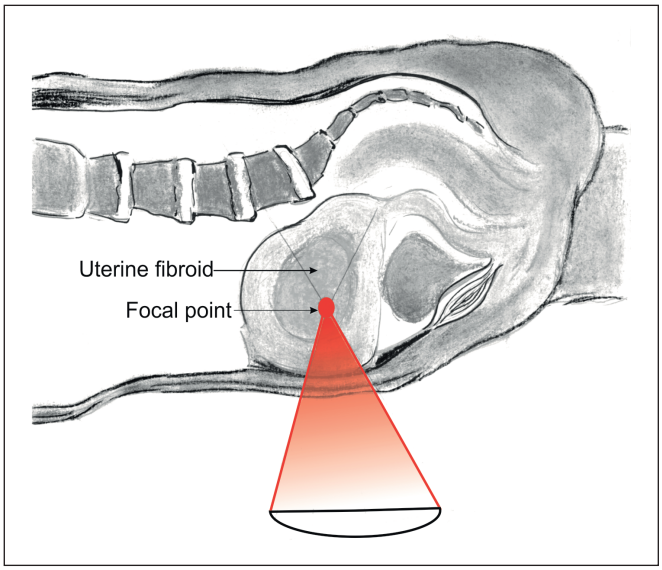

Fig. 1. Principle of HIFU ablation.

PATIENT SELECTION CRITERIA

Patient selection criteria is essential to the success of HIFU in the treatment of UF. The patient selection criteria was based on a prospective study establishing a clinical protocol for the use of HIFU in the treatment of UF, conducted by our institution (Table. I) [24]. Contrast enhanced MRI of the pelvis was used as the primary imaging modality [24].

Excluding criteria for HIFU ablation are these which may indicate a manignancy - low hemoglobin levels (less than 70 g/L), LDH exceeding 500 U/l, rapidly growing fibroid and heteroinsive zones with liquid-equivalent MRI zones.

Preoperative preparation of a patient before HIFU ablation of a myoma:

1. Taking a medical history
2. Examination by an internist
3. Gynecological examination
4. MRI examination
5. Three-day special diet before FUS
6. Preparation of the gastrointestinal tract - taking a cleanser the day before the procedure
7. Ablation is performed 3-5 days after menstruation

PROCEDURE

MAIN PROCEDURE

Preoperatively, the patient is catheterized for controlling the amount of urine in the bladder and for providing intracorporeal cooling. If required, serum at a certain temperature is introduced in the catheter and this allows for intraoperative temperature control. The patient is then sedated enough to achieve muscle relaxation but also to ensure effective communication with the operative team. The patient can communicate any discomfort or pain and the operative team can respond accordingly [24].

The patient is placed in the prone position on the operating table and the abdomen is immersed in a vat of degassed water, the temperature of which can be regulated by the operating team. A water balloon is placed between the transducer and the abdomen. The water balloon serves two functions, the first is to clear the intestinal loops around the tumour and to fixate the tumour in the acoustic pathway, the second function is to act as an acoustic lens to better focus the ultrasound beam.

Intraoperative imaging is then initiated to visualize the pelvis. After locating the tumour, the coordinates of the tumour are entered into the Model JC system for ablation planning. Sectional planes of the myoma are prepared digitally for ablation. Thermal ablation begins at low energy, usually at 50W and the patient response is noted. The energy of the HIFU beam is increased gradually till a maximum energy of 400 W. Diagnostic imaging allows for real-time visualization of the response of the tumour to ablative therapy.The presence of an hyperechogenic area indicates that coagulative necrosis has been achieved (Fig. 2C) [24].

Protocols for patient safety

Safety protocols are central to HIFU, and broadly revolve around temperature control. Factors that affect the safety

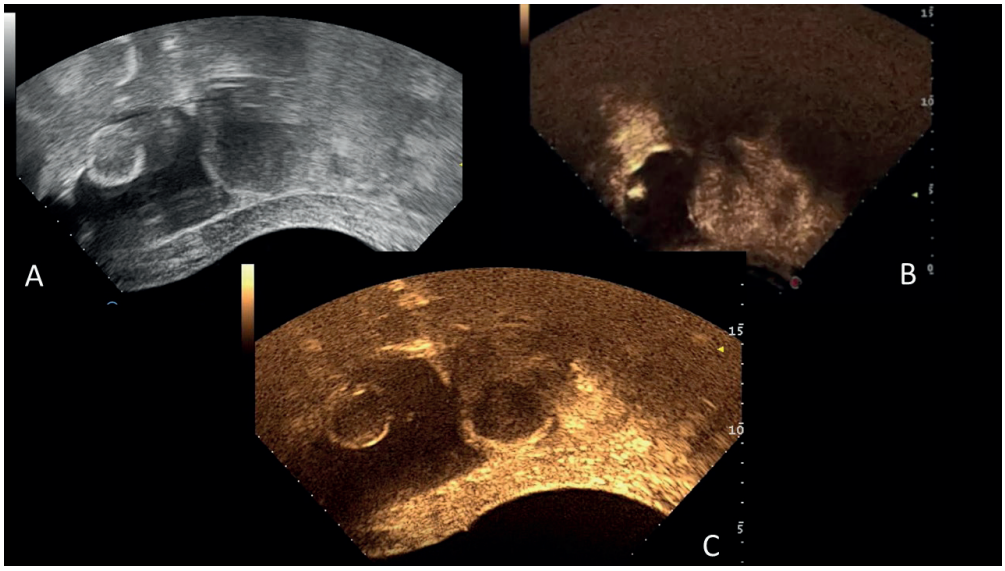

Fig. 2. An own case of a patient with uterine fibroids treated by ultrasound guided HIFU: A) a normal ultrasound image of the uterus fibroid and on the left, the urine-filled bladder and urethral catheter balloon are observed; B) 1.5 ml of Sonovue ultrasound contrast agent is injected and typical image of CEUS is observed - a well-supplied myoma is filled with "glowing" microbubbles that are present in the general circulation; C) an ablated fibroid with coagulative necrosis, as the microbubbles from the second dose of 1.5 ml Sonovue fill and enter only the uterine wall and other organs - the fibroid remains a "black" hole, which proves that the procedure was successful in achieving tumour ablation

Table I. Indicatoints and contraindications for HIFU.

Indications	Contraindications
Clinical diagnosed fibroid	Pregnancy
Dysmenorrhea, secondary anemia, sterility, abnormal menstrual cycle	Endometriosis
The diameter of the node should be greater than 2 cm when it is on the anterior uterine wall and larger than 4 cm when it is located in the area of the posterior uterine wall	Cervical fibroids
Consent to HIFU	Submocosal/Subserosal fibroid with pedicle
Consent for uterus preservation and refusal of hysterectomy	Diameter of posterior wall fibroid less than 3.5 cm
Low and moderate grade vascularization of fibroid nodules (T2 hypo to medium intense)	Large postoperative abdominal scar or foreign body implants in the acoustic path
Less than 4 fibroid nodules	Radiation dose over 45 Gy in the pelvis
BMI lower than 30	Hypovascular fibroid nodule
Distance between skin and the farthest depth of fibroid on the posterior wall is less than 9 cm.	Subcutaneous fat thickness greater than 10 cm
	Malignancy such as uterine sarcoma, endometrial cancer etc

limitations are the vascularization of the tumour, patient characteristics such as age, comorbidities and general status. The energy of the HIFU beam does not exceed 400 W and usually ranges between 200 to 400 W. An interval of 3 seconds is maintained between each successive ultrasound shot and it is not recommended to use a maximum power of 400 W. For every 300 seconds of ablation time, the procedure is paused for 5 to 7 minutes. This allows for minimizing the risk of thermal and cavitation injuries to tissues. Maintaining a distance between the mucous membrane and ultrasound rays, and between the sacrum and the ultrasound rays is central to patient safety. The procedure is stopped if tumour ablation is achieved or if the patient expresses discomfort or pain.

SonoVue dosage in HIFU is 25 mg dissolved in 5 ml of saline, with 1.5 ml being administered before, during and after HIFU ablation. After each dose, 10 ml of saline is administered intravenously [25, 26]. When using Sonazoid, it is necessary to make one application for 30 minutes before the onset of ablation and it provides the presence of contrast for about 60 minutes in the bloodstream. Reconstitution is performed according to the manufacturer's instructions [25]. After the procedure, the patient must remain in the prone position for 10 minutes to allow the cooling of abdominal skin.

POST PROCEDURE STATUS

OUTCOMES

The clinical outcomes of patients who underwent HIFU are comparable to other therapeutic interventions. HIFU is a safe measure and can be argued to be a suitable alternative to other therapeutic methods [24, 27]. Although meta-analyses comparing Uterine Artery Embolization (UAE) and HIFU have been conducted, they are limited by the low number of studies included and also do not address the outcomes as they relates to pregnancies, both successful or otherwise [28]. Patients who have undergone HIFU report lower post operative pain, fever, and return to their daily lives sooner than those who undergo invasive surgical procedures like hysterectomies [24]. The comparison between UsgHIFU and laparoscopic myomectomy shows a comparability in improvement of QoL inwomen and fewer significant clinical complications and adverse events and with faster recovery [29].

HIFU as a treatment for uterine fibroids is dependent on strict adherence to the Patient Selection criteria and deviations, such as variations in tumour size, increase reintervention rates [30]. Recovery time in patients who have underwent HIFU is lower and the number of pregnancies is also higher than those who underwent UAE or other surgical interventions [31]. The most significant advantage of HIFU was the lower incidence of postoperative pain and discomfort, these adverse outcomes did not present with permanent sequelae or death [28]. Significant improvements in the Quality of Life after 36 months indicated that patients who underwent HIFU reported comparable or higher Quality of Life [31].

The introduction of FUS as an opportunity for leading choice in patients with fibroid disease requires research and greater experience among European patients, as well as the comparison of the method with other surgical approaches. This was conducted in Oxford - IDEAL non-randomized prospective study. It involves 2411 patients with symptomatic fibroids, and they have the right to choose the treatment approach. All patients are premenopausal, the uterus is enlarged at least as much as 10 gestational weeks, with no more than 3 myomas, and the maximum allowable size of a single fibroid is 10 cm. 1353 women chose HIFU, 586 requested myomectomy and 472 underwent hysterectomy. The study proves that both quality of life and symptoms have improved significantly faster in the HIFU group. Significant side effects occurred in 0.2% of the HIFU group and in 12.6% of patients who underwent surgery. The mean time to hospitalization was 4/8/10 days for the three groups, respectively. At 6-month follow-up, the pregnancies

occurred were 7/1/0, respectively, and at 12-month follow-up 21/3/0. After 12 months, there was a need for re-intervention at 14/0/0, respectively, which is 1% for the HIFU group and 0 for those who underwent surgical treatment. The conclusion proves similar effectiveness in improving the quality of life and the response to symptoms, as in the HIFU group there is a significant short hospital stay, as well as early return to work and a small percentage of side effects [32].

COMPLICATIONS

The most common adverse effects in HIFU are postoperative pain, discomfort and mild skin burns. However, none of these adverse effects have presented with long term sequelae or death [28]. The need for reintervention is another possible complication, however, reintervention rates are consistently low in HIFU patients [27], and this can be avoided as long as patient selection criteria is adhered to [31]. Over a period of 4 years (between 2011-2015), 10,310 patients were followed up in China to investigate complications. Retrospectively, 4136 side effects were identified in 2367 patients (23%). They most often complained of pain in the lower abdomen 21.9% (2253/10310), followed by the presence of minimal vaginal discharge 11% (1136 patients), 6.9% reported sacro-coccygeal pain. The complaints subsided without treatment for about a week. Thirteen patients (0.1%) reported tingling or pain in diseased limbs that lasted between 2 weeks and 2 months. Among the more serious complications were skin burns in 21 women (0.2%) and colon damage in 2 of the patients (0.02%). The burns were of 2nd and 3rd degree and were found mainly in women with scars on the lower abdomen. It was found that patients who had perforation of the intestine did not follow the protocol for cleansing the stomach - the intestinal tract before the intervention, as well as the use of high energy in ablation [27].

CONCLUSION

The use of UsgHIFU as a therapeutic intervention for uterine fibroids is an area of promising results. Its primary advantage is that it can be performed non-invasively and without the need for general anesthesia. Clinical outcomes for HIFU in general are promising in the treatment of uterine fibroids, and should be recommended for patients who fit the selection criteria. The Patient Selection Criteria is essential to positive outcomes of UsgHIFU and care should be taken to ensure that patients meet this criteria for optimal outcomes. Further research comparing the various modalities of therapeutic interventions should be conducted to suggest standardized protocols of care.

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CASE STUDY

PRINCIPLES OF DIAGNOSIS AND TREATMENT OF ASKIN'S TUMOR IN CHILDREN: CASE REPORT

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ABSTRACT

The aim of the study was to show principles of diagnosis and treatment of Askin's tumor in children. Diagnostic procedures include physical examination, chest X-ray, CT scan and PET CT, morphological, histological and immunohistochemical examinations, cytogenetic study. Primitive neuroectodermal tumors belong to the group of low differentiated, overly aggressive neoplasms, originating from cells of the parasympathetic autonomic nervous system. Patient F., 9 years old, first consulted by pediatric oncologist in 2014 with complaints of volume formation in the chest on the right side which progressively increases. Diagnosis: PNEP (primitive neuroectodermal tumor) of the soft tissues of the chest on the right side in the 4th intercostal space along the midclavicular line T2aN0M0, stage 2a, standard risk group. We've shown results of diagnostical process, treatment and it's result in our patient. Patients who have received combination therapy, including chemotherapy, surgical removal of the tumor and radiation therapy, have better prognostic results. However, relapses often occur that require more aggressive treatment with high-dose chemotherapy, monoclonal antibodies, and bone marrow transplantation.

KEY WORDS: Askin's tumor, children

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INTRODUCTION

Primitive neuroectodermal tumors (PNET) belong to the group of low differentiated, overly aggressive neoplasms, originating from cells of the parasympathetic autonomic nervous system. The incidence is about 4-17% of all soft tissue tumors in childhood. By origin, they are divided into peripheral PNET (pPNET), identical to Ewing's sarcoma, and central PNET (cPNET), which requires differential diagnosis with medulloblastoma, epindymoma, pinealoma, rhabdomyosarcoma, and neuroblastoma with primary brain damage [1]. In 1979, Askin first described 20 cases of PNET growing from the soft tissues of the thoracic area in children and adolescents, since then they have been called «Askin's tumor». These tumors in histological, immunohistochemical, cytogenetic and phenotypic similarity belong to the Ewing's sarcoma family, but are extremely rare [2,3].

Diagnostic procedures include physical examination, chest X-ray, CT scan and PET CT, morphological, histological and immunohistochemical examinations, cytogenetic study. This tumor on palpation is slightly denser than the soft tissues of the chest wall, often there is destruction of the ribs, pleural effusion, which is visualized by chest radiography. However, it is necessary to perform CT scan of the thoracic and abdominal cavities and MRI of the chest wall to determine the size of the tumor, possible invasion of the lungs and the presence of distant metastases [3]. 26-28% of children have initially distant metastases and in about 30% of patients metastasis to the bone marrow is confirmed [4-6]. PET CT plays an equally important role in the detection of metabolically active tumors at the stage of primary diagnosis and to assess the response to treatment [4]. Morphologically, Askin's tumor is gray-white with necrotic, cystic and hemorrhagic areas in section. Histological examination reveals monomorphic small blue round cells, which probably originate from the neural crest [5]. Cytogenetic study in this case has an important diagnostic value. Thus, in 85% of cases there is a mutual translocation of t(11:22) (q24: q12) with the gene EWS-FLI-1. Checking presence of proto-oncogenes such as n-myc, c-myb, c-ets-1 and tumor markers (NSE, LDH) can be additional diagnostic criteria [7]. There are no PNET-specific markers, but CD99 is detected in most patients on immunohistochemical examination of tumor cell surfaces [8].

This tumor has rapid aggressive growth, frequent metastasis and progress during treatment. The prognosis is very poor. 2-year survival from diagnosis is less than 40%. Therefore, it is necessary to study new treatment strategies (chemotherapy, immunotherapy) in combination with autologous hematopoietic stem cell transplantation (auto THC) in order to improve the quality of life and survival of patients [9]. In their studies, Lascar S. and co-authors have shown that the best results are achieved with a combination of systemic (non-adjuvant and adjuvant) chemotherapy, surgical treatment and radiation therapy [10]. The first line of chemotherapy includes drugs such as vincristine, doxorubicin, cyclophosphamide, etoposide and ifosfamide [11, 12]. Frequent relapses and progression of the disease after first-line therapy required further research and the search for new treatment options that include cyclophos-

Table I. The result of immunohistochemical investigation

Markers	Present/absent
Monoclonal Mouse Anti-Human CD99. MIC 2 Gene Product Ewing`s Sarcoma Marker Clone 12B7 (Dako IS57)	"+"
Rabbit Monoclonal Antibody to Fli-1 (DBS RMPD025)	"+"
Monoclonal Mouse Anti0Human Cytokeratin Clone AE1/AE3 (Dako M3515)	"+"
Monoclonal Mouse Antibody to Human Leukocyte Common Antigen CD45	"-"
Monoclonal Mouse Anti- Human Neuron Specifie Enolase Clone	"-"
Monoclonal Mouse Anti-Human CD56	"-"
Polyclonal Rabbit Anti-S100 (Dako Z0311)	"-"
Monoclonal Mouse Anti-Myogenin Clone F5D (Dako IS067)	"-"
Monoclonal Mouse Antbody to MyoD1 Clone 5.2F (DBS PDM120)	"-"
Monoclonal Mouse Anti-Human Desmin Clone D33 (Dako M0760)	"-"
Monoclonal Mouse Anti-Human CD34 Class II Clone QBEnd 10 (Dako IS32)	"-"
Conclusion: according to the results of morphological and immunohistochemical studies, the phenotype characteristic of primitive neuroectodermal tumor (PNET).	

Table II. The European pediatric Soft Tissue Sarcoma Studt Group (EpSSG) RMS 2005 study higt-risk localized rhabdomyosarcoma

	IVA	IVA	IVA	IVA		IVA	IVA	IVA	IVA	IVA				
1* random	1w	4w	7w	10w	SURGERY	Radiotherapy					2* random			Stop therapy
	IVA Do	IVA Do	IVA Do	IVA Do		IVA	IVA	Maintenance therapy 6x28-day cycles of VNR plus oral CYC IVA	IVA	IVA				

phamide and topotecan, irinotecan and temozolomide in combination with high doses of ifosfamide. Nowadays, there are investigations for using of monoclonal antibodies, such as bevacizumab (Avastin) and sunitinib [13]. The long-term prognosis for Askin's tumor depends on the initial size, the presence of metastases, the level of LDH and combination therapy, namely surgery, chemotherapy and radiation therapy [14].

CASE REPORT

Patient F., 9 years old, first consulted by pediatric oncologist in 2014 with complaints of volume formation in the chest on the right side which progressively increases. He was hospitalized for additional examination and diagnosis. Results of the tests were performed:

- ultrasound of soft tissues (14.01.2014): tumor in the 2-4 ribs region, size 86 × 26 × 55 mm, with its own blood flow.
- CT scan of the chest and abdominal cavity with IV contrasting (15.01.2014): soft tissue tumor formation 81 × 58 × 25 mm (tumor volume is 62 cm^3) in the thickness of the chest wall; distant metastases to the chest, abdomen and retroperitoneal space were not detected (fig. 1).

Trepan - tumor biopsy, trepan bone marrow biopsy from 3 points and liquid bone marrow (20.01.2014). Tumor histology showed PNEP. Bone marrow without signs of damage. The result of immunohistochemical investigation present in table I.

Diagnosis: PNEP (primitive neuroectodermal tumor) of the soft tissues of the chest on the right side in the 4th intercostal space along the midclavicular line $T_{2a}N_0M_0$, stage 2a, standard risk group.

The child began treatment according to the CWS 2006 protocol on February 10, 2014.

The central venous port system was set up on March 4, 2014. After the 2nd block of chemotherapy, the tumor was not clinically determined. Control CT scan of the chest with IV contrast was performed on April 17, 2014: Residual tumor is not determined. Continuation of treatment according to the protocol on the line «complete response».

Treatment included 9 blocks of chemotherapy and radiation therapy of 40 Gr per pre-therapeutic volume of

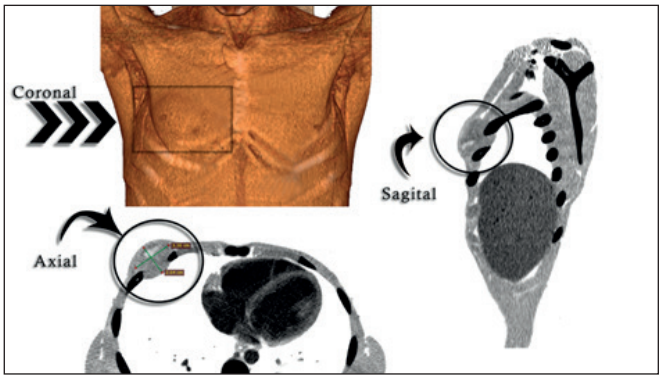

Fig. 1. CT scan of the chest and abdominal cavity shows soft tissue tumor

Fig. 2. Post operating seroma of the right sectoral area with perifocal fibrous post operating changes on CT

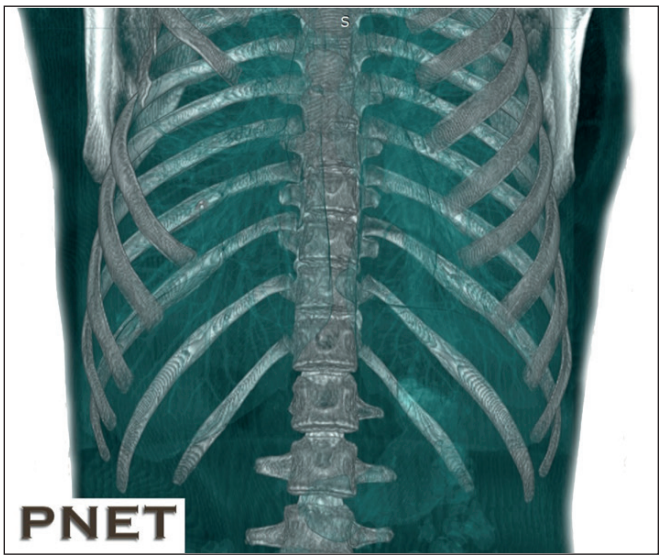

Fig. 3. Control contrast chest CT scan shows remission

the tumor (anterior surface of the chest on the right side). After this treatment child was include into the observation group (3rd clinical groups). Regularly passed routine examinations, including contrast CT scan of the chest and abdominal cavity, contrast MRI of soft tissues of the chest every 3 months. According to the results of examinations, no pathological changes were detected.

On December 6, 2016 (2 years of remission) child came for an examination with complaints of pain and the presence of a voluminous formation of the chest on the right side along the midclavicular line, and increase body temperature to 37.1C. Patient was hospitalized for further examination with diagnosis: the first recurrence of PNET?

Surveys were conducted:

Scintigraphy with radiopharmaceutical drug (9.12.2016): accumulation of the drug in the area of the head and upper third of the left femur - 280%.

Contrast CT scan of the chest (12.12.2016): additional volume formation of the anterior chest wall on the right side at the level of the anterior segments of 4 - 5 ribs on the right along the mid-clavicular line.

Surgical intervention was performed (15.12.2016): open biopsy of the tumor, trepan – biopsy of the bone marrow from the iliac crests and collected liquid bone marrow.

Extract from the investigation protocol: access over the three-dimensional formation along the midclavicular line in 4 intercostal spaces up to 3 cm, soft tissues are dissected in layers, revealed: two formations, one of which is covered with a hard fibrous capsule, the other next to the capsule - excisional biopsy of both formations.

The results of histological examination:

Tumor: growth of primitive neuroectodermal tumor (both samples)

Histological examination of the bone marrow: signs of depletion of all hematopoietic sprouts and fibrosis

Cytological examination of bone marrow: cellularity is slightly reduced, normoblastic type of hematopoiesis. When counting at low magnification about - 3 megakaryocytes.

Diagnosis: PNEP (primitive neuroectodermal tumor) of the soft tissues of the chest on the right side in the 4th intercostal space along the midclavicular line $T_{2a}N_0M_0$, stage - 2a, standard risk group. The first relapse.

The 2nd line of chemotherapy was started (table II). 2 blocks of therapy with etoposide, carboplatin, cyclophosphamide were performed as a mobilization course for the purpose of collection of autologous peripheral blood stem cells. A collection of material for autologous bone marrow transplantation was performed, but was unsuccessful due to severe aplasia.

The medical commission decided to carry out radical surgery, given the ineffectiveness of chemotherapy. Radical removal of the tumor with resection of IV and V ribs was performed on March 7, 2017. Plasticity of defect by a propylene grid, drainage of a pleural cavity and soft tissues were made. Post operating period gone without complications.

Histology: the growth of PNEP. After the operation child received 2 more chemotherapy blocks. After this treatment child had a remission and was include into the observation group.

20.09.2018 child came for routine examination with a suspicion of relapse. Surgical intervention was made (26.09.18): removal of a tumor on the right side of the chest.

There were 6 samples of the tumor resection edge:

№1 – the centers of growth of a malignant undifferentiated tumor among fibromuscular tissue;

№2 – fibrous - adipose tissue without signs of malignant growth;

№3 – fibrous - adipose tissue with hemorrhages, slight inflammation;
№4 – muscle tissue without signs of malignant growth;
№5 – muscle tissue without signs of malignant growth;
№6 – fibrous - adipose tissue without signs of malignant growth.
Trepan - biopsy of the bone marrow: the bone marrow is represented by red and yellow in a ratio of 1: 1. Red normocellular represented by all three sprouts with a predominance of granulocyte.

Morphological examination of the bone marrow (26.09.18): the cellularity of the bone marrow is reduced. Normoblastic type of hematopoiesis. 7 megakaryocytes were found at low magnification in a smear.

Contrast CT scan of the chest and abdominal cavity (05.10.18): picture of the condition after resection of the 4th - 5th ribs and soft tissues on the right side of the chest wall, accumulation of fluid in the soft tissues of the anterior chest wall on the right - surgical changes. Pneumofibrosis on the right D4 and D5. Single stable nodules D6,8. MRI of the chest with intravenous contrast (08.10.18): condition after combined treatment of PNET of the right sector. Post operating seroma of the right sectoral area with perifocal fibrous post operating changes (Fig. 2)

After surgery child received 3 courses of chimotherapy (Irinotican - Temodal).

PET/CT scan (19.02.2019): no signs of pathological radioactive pharmaceutical drug accumulation were detected. Fixation of radioactive pharmaceutical drug in a scar in soft tissues of a chest wall is more characteristic to after therapeutic changes as there are no convincing data for additional tumor with local accumulation of radioactive pharmaceutical drug. There is no convincing evidence for the presence of radioactive pharmaceutical drug active malignant process. Control of contrast CT scan of the chest (06.09.2019)(fig. 3). Remission continues.

PNET belongs to a group of highly aggressive malignant neoplasms, the histological substrate of which are small undifferentiated neuroectodermal cells [13]. Askin's tumor belongs to the group of peripheral PNET with primary lesions of the chest. It is often localized in the paravertebral areas [15]. Small cell sarcomas are a heterogeneous group of malignant neoplasms that remain diagnostically complex due to similar morphological and immunohistochemical characteristics. They are more often diagnosed in adolescents and young adults and have a prognostic course [16].

For this tumor, there are typical morphological features such as the presence of small cells with Homer-Wright rosettes. In immunohistochemical study positive CD 99. The presence of translocation t (11; 22) (q24, q12) and proto-oncogenes c-myb, n-myc, c-ets-1, which are important diagnostic criteria [7]. A significant increase in the level of LDH, relative to reference values, is considered a poor prognostic factor [19]. Usually this neoplasm recurs locally, but separate metastases can be detected [17]. This tumor is very rare and too aggressive, so the searching for new treatments that will improve the long-term prognosis is going all the time. Combined treatment involving surgical removal of the tumor with extensive resection of the edges in combination with chemotherapy (ifosfamide, vincristine, etoposide, D-actinomycin, doxorubicin) and radiation therapy has been shown to give better prognostic results and reduce the frequency of 3 recurrences [18].

CONCLUSIONS

Patients who have received combination therapy, including chemotherapy, surgical removal of the tumor and radiation therapy, have better prognostic results. However, relapses often occur that require more aggressive treatment with high-dose chemotherapy, monoclonal antibodies, and bone marrow transplantation.

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