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CONTENTS

ORIGINAL ARTICLES

Olha Prykhodko, Olga Avilova, Serhii Dmytruk, Alina Ponyrko, Olena Gordienko, Eleonora Prykhodko HISTOULTRASTRUCTURAL FEATURES OF THYMOCYTES DUE TO THE IMPACT OF THE EXPERIMENTAL	1700
GENERAL DEHYDRATION OF A MILD DEGREE	1/09
Yuliya Mozgova, Maryna Mishyna, Vasyl Syplyviy, Oleksandr levtushenko, Dmytro levtushenko, Iryna Marchenko, Yuriy Mishyn MICROBIOLOGICAL ANALYSIS OF ABDOMINAL CAVITY EXUDATE, BLOOD AND AFFECTED TISSUES SAMPLES	
FROM PATIENTS WITH INTRA-ABDOMINAL ABSCESSES IN COMPLICATED INFECTION OF ABDOMINAL CAVITY	1717
Anastasiia Ye. Alatorskykh, Pavlo V. Fedorych, Serhii B. Koval, Iaras V. Kuts TREATMENT OF COMBINED ACNE AND GENITOURINARY INFECTIONS CAUSED BY <i>CHLAMYDIA</i> AND <i>MYCOPLASMAS</i>	1725
Yulian Bursuk, Andrii Babko, Serhii Savosko, Ruslan Serhiienko, Olifirenko Oleksii, Viktor Lykhodii, Anna Kondaurova	
CHANGES IN ARTICULAR CARTILAGE OF THE HIP JOINT INDUCED BY ACETABULAR LABRUM DAMAGE	1730
Svitlana Myronchenko, Tetyana Zvyagintseva, Nina Gridina, Nataliia Kytsiuk, Yehor Zhelnin	
THE ROLE OF NITRIC OXIDE AND PEROXYNITRITE IN THE ERYTHEMAL PERIOD OF ULTRAVIOLET-INDUCED SKIN DAMAGE	1737
Hanna Lytvynenko, Olga Lytvynova, Vadym Lytvynov, Mycola Lytynenko, Sergey Latoguz CHANGES IN THE SERIIM LEVEL OF LEPTIN AND TRANSFORMING GROWTH FACTOR-B1 IN PATIENTS WITH ARTERIAL	
HYPERTENSION ON A BACKGROUND OF ABDOMINAL OBESITY	1742
Ihor Deneha, Olha Ripetska, Oleg Mokryk, Volodymyr Hrynovets, Svitlana Ushtan, Yuliia Tykhovska-Izhytska RELATIONSHIP RETWEEN THE DYSTROPHIC MANIFESTATIONS IN THE PERIODONTIJIM AND INTESTINAL DYSRACTERIOSIS	1748
	1740
Kateryna Pikul, Valentina Ilchenko, Liudmyla Syzova, Oksana Muravlova, Iryna Dvornyk	
INFECTIOUS MONONUCLEOSIS DURING THE WAR AND COVID INFECTION PANDEMIC IN UKRAINE	1754
Oleksandra Yu. Kushnir, Iryna M. Yaremii, Kyrylo A. Pantsiuk, Volodymyr V. Vivsyannuk,	
Diana M. Tymkul, Kateryna V. Vlasova, Olena V. Vlasova	
CARBOHYDRATES METABOLISM IN THE BLOOD OF RATS WITH IMPAIRED GLUCOSE TOLERANCE UNDER	1761
	1701
Yuriy Sobolevskiy, Oleksandr A. Burianov, Volodymyr Kvasha, Yevheeniy Skobenko, Taras Omelchenko, Vasyl Parii	
BIOMECHANICAL STUDY OF MINIMALLY INVASIVE TECHNIQUES IN SURGICAL TREATMENT OF THE TIBIA PROXIMAL FPIMETAPHYSIS FRACTURES	1768
	.,
Grygoriy P. Griban, Natalia A. Lyakhova, Dmytro G. Oleniev, Oksana P. Kanishcheva, Liana V. Duhina, Tetiana S. Ostrianko,	
USTAP 5. SKORUY DYNAMICS OF TOBACCO SMOKING PREVALENCE AMONG STUDENTS AND DIRECTIONS OF ITS PREVENTION	1776
	.,,,,

Vasyl I. Rusyn, Fedir M. Pavuk, Vasyl Ya. Fedusyak INFLUENCE OF THE AMOUNT OF COMPRESSION ON VENOUS AND ARTERIAL BLOOD FLOW VELOCITY AND SKIN MICROCIRCULATION OF THE LOWER EXTREMITY	1783
Vasyli B. Makarov, Ninel V. Dedukh, Olga A. Nikolchenko FEATURES OF BONE REMODELING AROUND SURFACE-MODIFIED TITANIUM AND TANTALUM IMPLANTS	1790
Olena V. Kravchenko, Olena A. Tiulienieva, Svitlana M. Yasnikovska, Alisa V. Goshovska FEATURES OF THE FUNCTIONAL MORPHOLOGY OF THE FULL-TERM PLACENTA IN WOMEN WITH THREATENED ABORTION WITH BLEEDING IN THE FIRST TRIMESTER OF GESTATION	1797
Vasyl Suvorov, Viktor Filipchuk, Michailo Melnyk THE BIOMECHANICAL ANALYSIS OF PELVIC OSTEOTOMIES APPLIED FOR DDH TREATMENT IN PEDIATRIC PATIENTS	1804
Tetiana Vasheka, Oksana Vlasova-Chmeryk, Borys Palamar, Olena Dolgova, Oleksandr Pravda, Sergii Tukaiev, Svitlana Palamar COPING STRATEGIES AND PSYCHOLOGICAL ADJUSTMENT TO THE COVID-19 PANDEMIC AMONG THE UKRAINIAN STUDENTS'YOUTH	1813
REVIEW ARTICLES Viktoriia V. Nadon , Marija V. Mendzhul, Alina V. Hus APPLICATION OF SURROGACY TECHNOLOGY BY FOREIGNERS IN UKRAINE (LEGAL CONFLICT)	1819
Liudmyla A. Vygivska, Natalia V. Derevianchenko, Lesia A. Rudenko, Oleh R. Chebotenko PREECLAMPSIA AND ITS EFFECT ON THE STATE OF CARDIOVASCULAR SYSTEM IN WOMEN	1826
Oleh E. Kanikovskyi, Ihor V. Pavlyk, Yuliia A. Punko, Oleksandr L. Machovskyi, Iryna V. Oliinyk TREATMENT OF PATIENTS WITH CHRONIC PANCREATITIS COMPLICATED BY PANCREATORAGIA	1831
Halyna V. Bilavych, Nataliia M. Blahun, Oktaviia J. Fizeshi, Svitlana J. Dovbenko, Olena M. Shapoval, Nadiya O. Fedchyshyn, Borys P. Savchuk CURRENT PROBLEMS IN COMMUNICATIVE DEVELOPMENT OF CHILDREN WITH SPECIAL EDUCATIONAL NEEDS: UKRAINIAN AND EUROPEAN SCIENTIFIC CONTEXTS	1838
Anatolii V. Vykhrushch, Nadiia A. Danik, Nadiya O. Fedchyshyn, Larysa Ya. Fedoniuk, Tetiana I. Khvalyboha, Solomiia I. Hnatyshyn, Olha M. Khrystenko DIDACTIC CULTURE OF MEDICAL UNIVERSITY TEACHERS AND STUDENTS IN THE CONDITIONS OF WAR	1846

CASE STUDIES	
Mykhailo D. Protsailo, Olga Ye. Fedortsiv, Volodymyr G. Dzhyvak, Ihor O. Krycky, Pavlo V. Hoshchynskyi, Ihor M. Horishnyi,	
Iryna B. Chornomydz, Yana V. Rohalska, Vira O. Synytska, Andrii M. Prodan, Iryna M. Nikitina	
CLINICAL FEATURES OF CONNECTIVE TISSUE DYSPLASIA, OSGOOD-SCHLATTER DISEASE AND MULTIPLE CORTICAL	1054
DISORDERS IN A CHILD	1854
Yulia A. Tkachenko, Yuriy V. Shkatula, Svitlana N. Kasyan, Yuriy O. Badion	
MANAGEMENT OF COMPLICATIONS FOLLOWING BUTTON BATTERY INGESTION	1861
VARIA	
Tetiana Danylova, Anatoliy Vovk, Ihor Hoian, Svitlana Kholodynska, Kateryna Honcharenko, Olena Ishchenko, Anna Bezhnar	
PHILOSOPHY AND MENTAL HEALTH	1866
Svitlana Storozhuk, Andrii Petraniuk, Nataliia Kryvda, Dmytro Iovmash, Iryna Matviienko, Yevhenii Shushkevych, Ali Hamaidia	107 <i>1</i>
TOWARD A HEALINT SOCIELL, WHEN TRAOMA AFFECTS GROOF IDENTITY	10/4
Ivan S. Myronyuk, Gennadiy O. Slabkiy, Victoria J. Bilak-Lukianchuk, Valeria V. Brych, Vitalii I. Kondratskyi	
THE ATTITUDE OF CERTAIN CATEGORIES OF THE POPULATION OF UKRAINE TO PERSONAL HEALTH DURING THE WAR AGAINST	
RUSSIAN AGGRESSION	1883

HISTOULTRASTRUCTURAL FEATURES OF THYMOCYTES DUE TO THE IMPACT OF THE EXPERIMENTAL GENERAL DEHYDRATION OF A MILD DEGREE

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ABSTRACT

The aim: The objective of the current study was to reveal ultrastructural changes in rats' thymocytes in experimental data in conditions of mild general dehydration. Materials and methods: The study was conducted on 20 non-linear adult male laboratory rats weighing 150-170 g. Histological and semi-thin slides of the thymus were prepared according to the required guidelines.

Results: On average, in the cortical zone of the thymus, there was decreased cellularity by 13.4% (p<0.001), while in the medulla zone this indicator turned out to be unreliable - 5.5% (p=0.19), compared to the indicators in animals of the control group. The study showed that a slight degree of general dehydration of the body causes ultrastructural changes in the thymus and is accompanied by a cell-mediated response of the central link of immunogenesis and results in morphological changes in the thymus, which are atrophic in nature with a typical pattern of remodeling of the organ's microstructure, which corresponds to cellular aging and the associated sign of accelerated involution.

Conclusions: General dehydration of a mild degree in the experiment is accompanied by a cell-mediated response of the central link of immunogenesis and results in morphological changes in the thymus, which are atrophic in nature with a typical pattern of remodeling of the organ's microstructure, which corresponds to cellular aging and the associated sign of accelerated involution.

KEY WORDS: Rat, thymus gland, histology, ultrastructure, experiment

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INTRODUCTION

The state of water homeostasis of the organism is crucial for maintaining its structures and the appropriate level of physiological functions. Mild dehydration can lead to several side effects that can occur covertly or with little manifestation. The problem of dehydration is expected to become increasingly relevant in connection with climate change, where more and more people will face the need to prevent and overcome the effects of heat stress, the emergence of new diseases, prevention, and treatment of which will require special attention to adequate hydration [1-5].

Maintaining the optimal hydration status of the body throughout life is a prophylaxis measure to prevent the development of age-related degenerative disease and a necessary condition for the normal functioning of the immune system. Hypohydration is known to increase plasma sodium concentrations and increase the expression of Nuclear Factor of Activated T-cells 5 (NFAT5) in many tissues, including the liver, thymus, spleen, and kidneys. NFAT5, originally identified as a key transcription factor involved in maintaining cellular homeostasis in hypertensive and hyperosmotic environments, in response to hyperosmotic stress induces the generation of TH17 cells and proinflammatory macrophages, thus, contributing to the development of autoimmune and inflammatory diseases [6]. Current experimental studies show that chronic hypohydration accelerates age-related pro- inflammatory changes, which along with coagulation changes are well-knownmodifiers of the aging rate [7].

Based on a comparative analysis of neuroendocrine regulation in conditions of low and high-water consumption, Armstrong et al proposed a theoretical model of the differential risk of chronic diseases and reduced life expectancy associated with insufficient hydration. The model is based on a homeostatic neuroendocrine response to mild dehydration, the central mechanism of which is increased secretion of vasopressin, a known neuropeptide produced by neurons of the supraoptic and paraventricular nuclei of the hypothalamus [8]. Vasopressin is found in various tissues of the body, including the thymus and, according to recent data, is an important immunoregulatory peptide for innate and adaptive immunity, the effect of which is associated with the ability to stimulate the hypothalamic-pituitary-adrenal axis and prolactin production [9,10]. Vasopressin stimulates the release of glucocorticoids, which increase the concentration of serum Glucocorticoid-inducible Kinase 1 (SGK1), the expression of which is increased due to dehydration-activated transcription of NFAT5. Increased SGK1 activity promotes the development of a number of diseases, including modeling immune responses (SGK1 is involved in regulating inflammation, activating CD4 + helper T cells that produce proinflammatory cytokines) and promoting the development of fibrous and calcified tissue under decompensated cellular stress associated, for example, with the depletion of the energy potential of cells [11,12].

Hydration parameters affect the morphofunctional features of regional lymph nodes, determining the variations for their structure and functional specialization [13].

Adequate hydration of the body is necessary to maintain adequate mucociliary clearance of the respiratory system. According to the latest experimental, clinical, and epidemiological data, chronic suboptimal hydration a fewweeks before the infection is associated with an increased risk of death from COVID-19. Regarding the mechanism, the hypothesis is that suboptimal hydration-related increase of Angiotensin Converting Enzyme 2 (ACE2) receptors in the lungsincreases the likelihood of infection, as ACE2 is a known site of coronavirus intrusion into alveolocytes [14,15]

Given this, further studies of the effects of hypo- and dehydration of various degrees on the immune system, in particular on the morphology of the thymus as a central organ of immunogenesis, will contribute to a better understanding of the structural basis of adaptive mechanisms and pathological processes in water deficiency.

THE AIM

The aim of this study was to establish the features of ultrastructural changes n thymocytes in conditions of mild general dehydration of the organism in the experiment.

MATERIALS AND METHODS

The study was conducted on 20 non-linear adult male laboratory rats weighing 150-170 g. The animals were kept in standard vivarium conditions in accordance with the international principles of the European Convention "About the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes" (Strasbourg, 1986) and " General ethical principles of experiments on animals", adopted by the First National Congress on Bioethics (Kyiv, 2001). 10 animals of the experimental group were fed by dry granulated combined feed with complete restriction of water intake. Thus, on the 3rd day of the experiment, the animals were put into a state of mild general dehydration, which was ascertained by the loss of body weight and thymus weight. 10 animals of the control group were on the usual drinking regime (had free access to water) and food ration. The animals were removed from the experiment by euthanasia with carbon dioxide. The thymus was selected for research.

Histological preparations were made according to the generally accepted method using a sled microtome MS-2 (Ukraine). Hematoxylin-eosin staining was used. To conduct an electron microscopic study, parts of the thymus with a size of 1mm³ were separated, which were first treated for 24 hours in glutaraldehyde according to Karnovsky, then kept in 1% osmium tetroxide according to Palade for 1 hour [1]. After that, the samples were dehydrated in ethanol of increasing concentration, followed by pouring the material into a mixture of epoxy resins (epon-araldite). Polymerization was carried out for 36 hours at a temperature of 600°C. Semi-thin sections with a thickness of 1-2 µm and ultrathin sections with a thickness of 0.5-1 µm were made on an ultramicrotomeUMTP-6m (Ukraine). Semi-thin sections were stained with 1% methylene blue in 1% sodium tetraborate. Ultrathin sections were contrasted with a Reynolds solution of uranyl acetate and lead citrate. Visual evaluation of electron micrographs was carried out on a PEM- 125K electron microscope (Ukraine) at an increasing voltage of 75 kV.

The study of semi-thin sections was carried out on an Olympus light microscope (Japan) with photographic documentation of the morphological picture by a video camera Baumer/optronicTyp: CX05c (USA).

On semi-thin sections in the cortical and medulla of the thymus, the absolutenumber of lymphoid cells in the field of view corresponding to an area of 0.009 mm² (magnification x1000) was determined using the program "ImageJ" (USA).

For conducting an immunohistochemical study, sections with a thickness of 5×10^{-6} m were made, which were subjected to standard deparaffinization and dehydration in xylene and alcohols of increasing concentration. Unmasking of antigens was carried out in a water bath "VB-4" (Ukraine) at a temperature of 97- 980C. The antigen-antibody reaction was visualized using the "UltraVision Quanto Detection System HRP DAB Chromogen" detection system (USA), which

Parameter, units of measurement	A group	o of animals
	Control	Experimental (3 days)
Thymus weight, mg	298,76 <u>+</u> 22,84	$286,85 \pm 35,50$ p = 0,68
Quantity of the lymphoid cells in the cortical zone of the thymus, visual field 0,009 mm ²	253,46 <u>+</u> 20,72	219,83 <u>+</u> 16,11 p<0.001
Quantity of the lymphoid cells in the medulla zone, visual field 0,009 mm ²	133,83 <u>+</u> 11,72	126,48 ± 12,24 p=0.19

Table 1. Dynamics of the parameters changes of the male rats thymus of in control and experimental groups
--

included blocking of endogenous peroxidase activity with hydrogen peroxide, blocking of non-specific background staining using "Ultra V block", amplification of the "Primary Antibody Amplifier" reaction Quanto" and final visualization with diaminobenzidine (DAB) with additional staining of nuclei with Mayer's hematoxylin.

Statistical processing of quantitative data was carried out using the Statistica v.10 program (StatSoft Inc., USA). Descriptive analysis of each sample was performed with calculation of Mean (M) and Standard Deviation (SD). The non- parametric Mann-Whitney U-test was used to assess the differences between the two samples according to the studied indicators. A difference of $p \le 0.05$ was considered significant.

RESULTS

According to the organometric study data, at the time of the introduction of the experiment, no reliable reduction of the thymus was found in the research groupanimals, which can be explained by specific compensatory processes aimed at maintaining the degree of hydration of the organ under conditions of generaldehydration.

According to the results of the histomorphometric analysis, in the animals that were in a state of dehydration, compared to the animals of the control group, no significant changes were found in the ratio of the cortex and medulla zones of the thymus (cortex:medulla ratio), which in both groups of animals was close to 2:1. However, mainly in the cortical zone of the gland, a decrease in the density of thymocytes is observed during dehydration. On average, in the cortical zone of the thymus, there was decreased cellularity by 13.4% (p<0.001), while in the medulla zone this indicator turned out to be unreliable - 5.5% (p=0.19), compared to the indicators in animals of the control group (Table I).

The cortical zone of the animals' thymus in a state of dehydration is formed mainly by thymocytes, among which there are cells with signs of karyopyknosis and compaction of the cytoplasm, epithelial reticulocytes with large light nuclei and long processes of the cytoplasm, and macrophages (Fig. 1A). The medulla zone of the thymus is formed by sufficiently differentiated lymphocytes, contains epithelial reticulocytes and Hassal's bodies in a small amount. Some of the lymphocytes of the cortical and medullary zones of the rodents' thymus in a state of dehydration have relatively large nuclei and a narrow cytoplasm. The ratio of CD3+ thymocytes of both zones of the thymus, in the presence of morphological signs of focal delymphatization, indicates more in favor of comparatively compensated thymopoiesis (Fig. 1B).

The subcapsular zone of an organ in a state of dehydration is expanded and formed by epithelial reticulocytes, lymphoblasts, prethymocytes, and also contains macrophages in a small amount.

Nuclei of lymphoblasts are typically round or oval in shape, large, with one or two nucleoli. Heterochromatin is located in the form of small pits mainly on the periphery of the nucleus, it is quantitatively inferior to euchromatin. The contours of the karyolemma are of increased osmiophility, loose, with multiple intussusceptions and protrusions, sometimes with areas of lysis.

The perinuclear space is well defined, in some cells it has condensed cytoplasm or is significantly expanded and filled with structureless amorphous masses. In the cytoplasm of individual lymphoblasts, there are vacuoles with electron-transparent contents and areas of cytolysis in the form of lightening. The Golgi complex is surrounded by multiple vesicles. Mitochondria in small numbers, increased in size, have an electron-bright matrix, and sometimes reduced disoriented cristae (Fig. 2). Figures of mitosis of different stages were found for individual prethymocytes.

On the background of a decrease in the thymocytes number in the animals' thymus in conditions of dehydration, an increase in the number of small lymphocytes is observed, compared to such data in animals of the



Fig. 1. A: Focal accumulation of thymocytes with signs of karyopyknosis and cytoplasmic thickening (marked 1). Semi-thin slice. Methylene blue stain. B: CD3+ thymus cortical substance. Reaction with MKAT to CD3 (P7), x200.

control group. Small lymphocytes have a nucleus with compact chromatin, an eccentrically located nucleolus, and a fairly narrow cytoplasm rim, which contains single rounded mitochondria and ribosomes (Fig. 3).

The majority of thymocytes of the cortical and medullary zones of the organ that were in a state of general dehydration of a mild degree have a typical structure. But, among them, there are cells with pronounced structural changes. Euchromatin predominates in the karyoplasm of such cells, but it is significantly less than in thymocytes of the control group animals. Heterochromatin is contoured in the form of small blocks. In some thymocytes, there is a violation of the structure of the karyolem. It has areas of lysis, which in places are replaced by vague wavy contours and intussusceptions. Areas of condensed chromatin and signs of karyolysis are present in the predominantly rounded nuclei. The perinuclear space of such cells is expanded, electron bright, sometimes filled with structureless amorphous masses. The cytoplasm has electron-illuminated areas, which can be regarded as signs of cytolysis. Such areas alternate with condensed cytoplasm, which has the appearance of a structureless mass of uneven electron density with remnants of destroyed organelles (Fig. 4).

There are thymocytes that obtain electron-dense mitochondria in their cytoplasm. Most of these organelles have a typical structure but differ in shape and size. Some of the mitochondria are damaged: the cristae are arranged irregularly, without a clearly defined orientation, some undergo reduction, the matrix is heterogeneous, and mostly electron-light. Similar ultrastructural features of mitochondria are characteristic of thymocytes, both cortical and medullary zones of the thymus (Fig. 5).

Along with the morphological features described above, there are signs of cell apoptosis. Thymocytes

often have pyknotically altered nuclei of an irregular shape due to chromatin aggregation into electron-dense pits. The karyolem of such cells mostly has uneven, discontinuous contours and a large number of bay-like intussusceptions. The perinuclear space is expanded, and a thin electron-light rim surrounds the compacted nucleus. Cytoplasm also undergoes densification or cytolysis: in many cases it is vacuolated or filled with fine granular material forming clusters of rounded and polygonal shapes. Mitochondria have a lighted matrix containing dense osmiophilic inclusions or multilamellar bodies, cristae and the inner membrane of organelles are often destroyed. The nuclei of apoptotically changed epithelial reticulocytes have deep intussusceptions and constrictions, which are also found in the nuclei of apoptotic thymocytes. However, the latter is characterized by an extremely high degree of chromatin condensation. At the same time, supercondensed chromatin forms clusters in the form of characteristic crescents, or completely fills the karyoplasm. In the latter case, the nucleus of an apoptotic thymocyte is practically not identified against the background of a narrow border of electron-dense cytoplasm, while the thymocyte itself takes on the appearance of an "ink spot". Apoptotic bodies containing separate fragments of nuclei preserve the characteristic structural organization of chromatin (Fig. 2).

DISCUSSION

This study showed that a slight degree of general dehydration of the body causes ultrastructural changes in the thymus, corresponding to the picture of the accidental transformation of the organ.

According to our data, the influence of a mild degree of general dehydration did not affect the cortex:



Fig. 2. Ultrastructural organization of the cortical substance of the rat's thymus. General dehydration, 3rd day. Electronic photography. Magnification: ×5000.

Designation: 1 – lymphoblast nucleus; 2 – lymphoblast cytoplasm; 3 – apoptotic thymocyte; 4 – thymocyte nucleus; 5 – narrow rim of thymocyte cytoplasm; 6 – vacuoles; 7- small lymphocyte.



Fig. 4. Ultrastructural organization of rat's cortical substances. Thymocytes. General dehydration, 3rd day. Electronic photography. Magnification: ×8000. Designation: 1- nucleus 2-mitochondria 3-karyolem with intussusceptions.

medulla ratio of the thymus. A decrease in the value of this ratio is a recognized, quite sensitive histological marker of negative effects, in particular toxic, infectious, etc. of a nature that causes the involution of the organ [16-18]. The normal cortex: medulla ratio noted by us in the thymus of animals that were in a state of a mild degree of general dehydration indicates that the functional microenvironment of thymocytes is preserved in general and there is a sufficient possibility of releasing their mature forms from the thymus.

At the same time, we found signs of initial cortical atrophy: focal delymphatization, decrease in the density of thymocytes in the cortical zone, cells with signs of karyopyknosis, karyolysis and cytoplasmic compaction,



Fig. 3. Ultrastructural organization of the cortical substance of the rat thymus. General dehydration, 3rd day. Electronic photography. Magnification: ×5000.

Designation: 1 – deformed nucleus of a lymphoblast; 2 – lymphoblast mitochondria; 3 – thymocyte nucleus; 4 – thymocyte mitochondria; 5 – cellular detritus.



Fig. 5. Ultrastructural organization of rat cortical substances. Karyorrhexis. General dehydration, 3rd day. Electronic photography. Magnification: ×8000.

violation of the nuclear-cytoplasmic ratio. Morphological signs of increasing thymocyte apoptosis processes are also quite indicative, although it should be noted that many cortical thymocytes are immature, shortlived, and subject to apoptosis and phagocytosis by macrophages in normal conditions [19]. One way or another, the loss of cellularity by the thymus, with a disturbed or preserved microarchitecture of the organ, is a sign of atrophy. The latter leads to a decrease in the elimination of naïve T-lymphocytes and a decrease in the expression ofT-cell receptors, which are an integral part of the processes of positive selection (recognition of "own" ligands, development of T cells) and negative selection (induction of cell death), and therefore changes the further fate of T-lymphocytes, associating it with autoimmunity [20, 21]. In general, autoimmunity develops as a consequence of cortical atrophy, when positive selection, which is autoimmune in nature, is supplemented by violations of negative selection and selection of regulatory T cells [22]. In our opinion, atrophic changes in the thymus in conditions of a mild degree of general dehydration of the body can be associated, as a cause, with the development of accelerated immunological aging, the consequences of which will be a decrease in anti-infective and post-vaccination immunity, suppression of immune surveillance of tumors, development of autoimmune processes, chronic systemic inflammation, which in turn will contribute to many degenerative diseases, metabolic disorders and cardiovascular pathology [23,24].

An important structural component of the thymus is the subcapsular zone, quite noticeable at later stages of embryonic development, but weakly expressed in the postnatal thymus of rats. This zone ensures the creation of a kind of gradient that determines the direction of migration of T-lymphocytes in the process of their maturation. After all, it is known that precursor cells of T-lymphocytes migrate to the thymus in a wave-like manner, so that the successful maturation and exit of one group of cells provides space for the next [25, 26].

Subcapsular epithelial cells produce thymic hormones, cytokines, chemokines, neuropeptides and extracellular matrix components. Also, in the thymus of rats, there are areas free of subcapsular epithelium, which contain immature T-lymphocytes and are considered an alternative route for such cells, moving along which immature T-lymphocytes do not come into contact with stromal elements, and therefore to some extent avoid the influence of positive and negative se-

lection [27,28]. The expansion of the subcapsular zone of the thymus of rats in the experimental group due to areas free of stromal elements that we discovered may be accompanied by an increase in the number of potentially autoreactive T-lymphocytes that do not die in the thymus and enter the pool of peripheral lymphocytes, increasing the risk of developing autoimmune processes in the body. An increase in the number of small lymphocytes in the expanded subcapsular zone probably illustrates the acceleration of the processes of proliferation and maturation of thymocytes with an earlier entry into the peripheral blood flow of immunocompetent cells. This occurs together with a decrease in transcriptional activity, as evidenced by a lower amount of euchromatin in lymphocytes of the thymus of animals under conditions of a mild degree of general dehydration.

Ultrastructural changes in the thymus under the influence of dehydration, in particular, such as intussusception and partial lysis of the karyolem of lymphoblasts, swelling of mitochondria, disorientation, and reduction of their cristae, are signs of the cellular aging process, which is essentially associated with the involution of the thymus [29].

CONCLUSIONS

General dehydration of a mild degree in the experiment is accompanied by a cell- mediated response of the central link of immunogenesis and results in morphological changes in the thymus, which are atrophic in nature with a typical pattern of remodeling of the organ's microstructure, which corresponds to cellular aging and the associated sign of accelerated involution.

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ORIGINAL ARTICLE

MICROBIOLOGICAL ANALYSIS OF ABDOMINAL CAVITY EXUDATE, BLOOD AND AFFECTED TISSUES SAMPLES FROM PATIENTS WITH INTRA-ABDOMINAL ABSCESSES IN COMPLICATED INFECTION OF ABDOMINAL CAVITY

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ABSTRACT

The aim: To conduct an analysis of the results of a microbiological examination of biological samples taken from patients with intra-abdominal abscesses. Materials and methods: Material for microbiological examination was collected from 60 patients during surgery and transported to laboratory at the same day. Isolation and identification of microbial pure cultures were performed by standard microbiological methods. Statistical analysis was performed using Statistica software.

Results: Analyzing the microbiological research results indicated importance of the sample collecting time (first or repeated surgery). In patient's blood taken during first surgery it was found a statistically significant predominance of no growth of microflora. In abdominal cavity exudates anaerobic cultures increased statistically significantly in repeated surgery. It was noted that in samples taken during first surgery mixed pathogens were represented mainly by facultative anaerobic cocci, then in repeated surgery anaerobic microorganisms were predominant. Examination of liver abscess content found that monoculture was isolated in 85.7 %. Blood and affected tissue samples in such patients were sterile. Investigation of samples from patients with multiple abdominal cavity abscesses revealed anaerobic microorganisms in 16.7 %. Blood samples of that patients in 40 % were sterile.

Conclusions: An analysis showed that in appendicular abscesses content gram-negatives were predominant. Gram-positive bacteria dominated in paravesical abscesses with 65 % isolates from gallbladder and 66.7 % from the affected tissue samples. In liver abscesses gram-positive cocci were isolated in 57.1 %. In multiple abdominal abscesses due to bowel perforation rod-shaped microflora was predominant (76 %) and represented by either obligate aerobes or obligate and facultative anaerobes.

KEY WORDS: microorganisms, liver abscess, paravesical abscess, gram-negatives, anaerobes

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INTRODUCTION

Intra-abdominal abscesses (IA) are considered to be one among serious problems in abdominal surgery [1]. The frequency of IA in the overall structure of surgical diseases is high. Among the many causes of IA, the main is hematogenous deposition of the pathogen from primary inflammatory focus, frequently from an inflamed abdominal organ [2]. Currently, due to the significant increase in the incidence of inflammatory diseases of the gallbladder and biliary tract, a significant amount in the overall structure of IA are liver abscesses and paravesical abscesses [3]. It is not always possible to establish the exact time of appearing of liver and paravesical abscesses, as they are usually preceded by long-term, often recurrent purulent cholangitis [4]. Abscesses that develop due to the transition of inflammation from the gallbladder to the liver, also usually appear on the background of prolonged cholecystitis [5].

Increasing in the frequency of surgeries on abdominal cavity with leaving drainages and stents for a long time also contributes to the rise in the number of IA [6].

Among the reasons for hematogenous IA are septic conditions of various genesis, acute purulent inflammatory diseases of the abdominal cavity, less often - infectious foci of other localization, including furuncules, hydradenitis, infected wounds that lead to rapid formation of abscesses in the abdominal cavity. In some cases, the direct cause of IA may not be reliably established [7].

Reseach data are unsystematic and sometimes contradictory, so microbiological analysis of samples from IA will not only help in qualitive study of the microflora, also in de-



Fig. 1. The range of etiological factors (absolute number of strains) isolated from the samples of patients with appendicular abscesses.

tecting unusual pathogens such as *Streptococcus mitis* and *Streptococcus oralis*, which can cause severe complications.

THE AIM

The aim of research was to conduct an analysis of the results of a microbiological examination of biological samples taken from patients with intra-abdominal abscesses in complicated infection of abdominal cavity.

MATERIALS AND METHODS

Material for microbiological examination was collected from patients with intra-abdominal abscesses in complicated infection of abdominal cavity that were treated in the surgical department of Kharkiv City Hospital № 18 during period from 2015 to 2020. 60 patients with intra-abdominal abscesses were included in analysis and divided into 4 groups. 20 patients with appendicular abscesses formed group I;25 patients with ruptured gallbladder, paravesical abscesses were in group II; 10 patients with liver abscess were in group III; 5 patients with multiple abdominal abscesses due to bowel perforation formed group IV. Material such as abscess content, abdominal exudate, affected tissues samples and blood was taken during surgery in patients and transported to laboratory at the same day. Isolation and identification of microbial pure cultures were performed by standard microbiological methods using Micro-la-tests (Czech Republic). Statistical analysis was performed using Statistica Software (StatSoft Inc., version 9, 2009 USA). All groups undergone the Gaussian distribution model. We established that the distribution in each group was abnormal. Methods of nonparametric statistics were used.

RESULTS

It was found that in samples from group I patients with appendicular abscesses (abdominal cavity exudate, af-



Fig. 2. The range of etiological factors (absolute number of strains) isolated from gallbladder content of patients with paravesical abscesses.



Fig. 3. The range of etiological factors (absolute number of strains) isolated from abscess content of patients with liver abscesses.

fected tissues and blood received within 24 hours after surgery) 48 strains of microorganisms were isolated (Fig. 1). From abdominal exudate predominantly (55 %) mixed cultures of *Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Enterococcus faecium, Streptococcus constellatus* and *Escherichia coli, Pseudomonas aeruginosa, Enterobacter cloacae/aerogenes, Proteus vulgaris* together with *Porphyromonas* asaccharolytica, Fusobacterium necrophorum, Bacteroides ovatus, Bacteroides vulgatus, Bacteroides fragilis, Eubacterium limosum, Veillonella parvula were detected. From affected tissues Streptococcus constellatus, Escherichia coli, Klebsiella oxytoca and Bacteroides caccae, Bacteroides fragilis, Bacteroides ovatus were isolated. It should be noted that only from one sample pathogens were not isolated. From blood of two patients (10 % of



Fig. 4. The range of etiological factors (absolute number of strains) isolated from patients with multiple abdominal abscesses during investigation of blood, exudates and affected tissue samples.

cases) facultative anaerobic gram-positive cocci were identified such as *Streptococcus constellatus* in monoculture and mixture of *Streptococcus mitis*, *Staphylococcus epidermidis* and *Staphylococcus hominis*.

Control analysis on second day after surgery did not reveal microorganisms in blood of group I patients (sterile blood).

Only in one case in female that underwent surgery due to abscess on the 15th day after surgery mixed culture was identified in abdominal cavity exudate consisting of facultative anaerobic gram-positive cocci (*Streptococcus constellatus*) and anaerobic gram-negative rods (*Porphyromonas asaccharolytica, Fusobacterium necrophorum, Bacteroides ovatus*).

On the 4th day after repeated surgery in this patient from the abdominal cavity exudate facultative anaerobic gram-positive cocci (*Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis*) were isolated.

Therefore, 37 strains of microorganisms were isolated from abdominal exudates. In 5% of samples microorganisms were not detected. Cocci were isolated in 45.9%, rod-shaped microorganisms were detected in 54.1% of samples. In 21.6% anaerobes were cultured. From samples of affected abdominal tissue gram-positive cocci were revealed in 14.3%; anaerobic cocci and rods were detected in 42.9% of cases.

Investigation of group I patients blood samples found that growth of microorganisms was not observed in 18 (90%) cases. In two patients, 4 microorganisms belonging to the facultative anaerobic cocci were detected in blood samples. Therefore, *Streptococcus mitis* is a typical pathogen of oral cavity, and its isolation from blood may be recognized as transitory bacteremia after tracheal intubation of the patient.

Investigation of abscess content from patients with gall bladder perforation, paravesical abscesses (group II) revealed 23 strains of microorganisms (Fig. 2). Gram-positive cocci were representatives of genera *Streptococcus*, *Staphylococcus*, *Enterococcus* and *Micrococcus*. This samples contained cocci in both mono (in 7 patients out of 12) and mixed culture, which was represented by both cocci and rods (in 3 patients). Rods predominantly were facultative anaerobes from family

Microorganisms (n=103 bacteri strain of yeasts)	al strains and 1	1 st group (n=48)	2 nd group (n=23)	3 rd group (n=7)	4 th group (n=25)
	blood	4	-	-	4
isolated from	exudate	37	20	8	12
	tissue	7	3	-	9
	blood	4	-	-	3
gram-positive cocci	exudate	17	13	4	3
	tissue	1	1	-	1
	blood	-	-	-	1
gram-positive rods	exudate	1	-	-	1
	tissue	-	-	-	1
	blood	-	-	-	1
gram-negative rods	exudate	20	7	3	8
	tissue	6	2	-	7
	blood	-	-	-	-
obligate anaerobes	exudate	5	1	-	2
	tissue	3	2	-	2
Candida albicans	abscess content	-	-	1	-
	blood	1	-	-	2
mono-culture	exudate	7	12	6	1
	tissue	-	-	-	-
	blood	1	-	-	1
mixed culture	exudate	12	3	1	3
	tissue	2	2		2
				blood (n=0)	blood (n=4)
Total (103 bacterial strains) exudate (n=37)		gall bladder content (n=20)	abscess content (n=7)	exudate (n=12)	
		tissue (n=3)	tissue (n=0)	tissue (n=9)	

Table I. Distribution of isolated microbial stains

Enterobacteriaceae (Escherichia coli, Klebsiella oxytoca). The growth of representatives of Pseudomonadaceae and Lactobacillaceae families was also obtained. It was found that representatives of all families mostly were isolated in a mixed culture in the amount of 1x107 CFU and were represented by facultative anaerobic gram-positive cocci (Streptococcus constellatus, Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Streptococcus viridans), anaerobic gram-positive cocci (Peptostreptococcus spp.), anaerobic gram-negative rods (Prevotella melaninogenica/oralis) and facultative anaerobic gram-negative rods (Escherichia coli, Enterobacter cloacae/aerogenes). 40 % of gallbladder samples were sterile, in other samples in 65 % cocci were detected. Obligatory anaerobic microorganisms were revealed in 5 % of cases.

The results of inoculation of affected tissues samples showed that in one case gram-negative anaerobic *Prevotella melaninogenica/oralis* in the amount of 1x10³ CFU in monoculture was detected. In two cases mixture of facultative-anaerobic gram-positive cocci (*Strep-tococcus constellatus*) and anaerobic gram-negative rods (*Prevotella melaninogenica*/oralis) in the quantity of 1x10⁷ CFU were isolated. It should be noted that in 92 % of cases pathogens were not revealed from the mentioned samples. All tested blood samples of group II patients were sterile.

Examination of liver abscess content in group III patients revealed 7 strains of bacteria (Fig. 3) and 1 strain of *Candida albicans* (1x10⁶ CFU). Also it was found that in 30 % of cases the growth of microorganisms was not observed. Monoculture was isolated in 85.7 % of cases and represented by facultative anaerobic gram-negative rods *Escherichia coli* (2 strains in 1x10⁸ CFU) and *Klebsiella pneumoniae* (1 strain in 1x10⁵ CFU), gram-positive cocci *Staphylococcus epidermidis* (1 strain in 1x10⁸ CFU) and *Enterococcus faecium* (3 strains in 1x10⁸ CFU). Blood and affected tissue samples of group III patients were sterile.

Investigation of samples from patients with multiple

abdominal cavity abscesses (group IV) identified 25 strains of microorganisms (Fig. 4). From abdominal cavity exudates 12 strains of bacteria were isolated and in 20 % of cases the growth of microorganisms was not detected. Anaerobic microorganisms were found in 16.7 % and for the first time in the mixed culture obligate aerobic microorganism *Acinetobacter baumannii* (in 1x10³ CFU), a gram-negative proteobacteria of the family *Moraxellaceae* was found.

Gram-positive facultative anaerobic microflora was represented by *Staphylococcus aureus* (1x10²⁻³ CFU), *Enterococcus faecalis* (1x10⁶ CFU) and anaerobic bacteria *Lactococcus lactis* (1x10⁶ CFU). Gram-negative facultative anaerobic bacteria included *Escherichia coli* (1x10³ CFU and 1x10⁶ CFU), *Klebsiella pneumoniae* (1x10⁶ CFU), *Citrobacter freundii* (1x10⁶ CFU), *Enterobacter cloacae* (1x10⁸ CFU). Also non-fermentive gram-negative aerobic rods *Pseudomonas aeruginosa* (1x10³ CFU) and gram-negative anaerobic rods *Bacteroides ovatus* (1x10⁶ CFU) were isolated.

From affected tissue samples of two group IV patients 9 strains of bacteria in mixed culture were revealed. It was found that the main etiological factors were gram-negative facultative anaerobic rods (2 strains of *Escherichia coli* in 1x10³ CFU and 1x10⁸ CFU; 1 strain of *Klebsiella pneumoniae* in 1x10⁸ CFU; 1 strain of *Citrobacter freundii* in 1x10⁶ CFU; 1 strain of *Proteus vulgaris* in 1x10⁵ CFU); gram-negative anaerobic rod-shaped bacteria *Bacteroides vulgatus* (1x10⁶ CFU) and *Bacteroides ovatus* (1x10⁶ CFU) and gram-positive obligate anaerobic rods *Clostridium ramosum* (1x10⁶ CFU). Gram-positive facultative anaerobic cocci were represented by *Enterococcus durans* (1x10⁷ CFU).

In blood samples of group IV patients 4 strains of bacteria were identified (table I), and it was found that in 40 % it was sterile. Isolated bacteria were 3 strains of *Staphylococcus epidermidis and 1 strain of Klebsiella pneumoniae*.

DISCUSSION

There are research data about determination of intra-abdominal abscesses etiological factors, which indicates that the main causative agents are purulent microbes - streptococci, staphylococci and rarely anaerobic microorganisms. IA can also been as the result of infecting with enterobacteria, enterococci and gram-negative flora [8-10]. According to data of recent years *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumani* and *Proteus spp*. are frequently isolated from patients with IA.

The growth of microorganisms in the bacteriological study of IA content is detected according to various

authors in most patients, but seriously depends on the timing and rational use of antibacterial therapy [11]. In addition, the spectrum of microorganisms that cause purulent lesions in the abdominal organs depends on the way of pathogen's penetration. Thus, in liver abscesses gram-negative microorganisms with a predominance *Escherichia coli* up to 24 % and gram-positive cocci with a predominance of *Enterococcus spp.* up to 17 % are on the first place. The frequency of detection of non-clostridial anaerobic flora in patients with liver abscesses can reach, according to experts, up to 41.8 %. There are reports indicating that approximately in a half of patients, especially those who undergo antitumor chemotherapy, staphylococci with multi-drug resistance are isolated [12].

The microflora in acute appendicitis complicated by abscess is represented by mixed cultures of facultative aerobes and obligate anaerobes [13]. And the most common are gram-negative bacteria, *Escherichia coli* and *Bacteroides fragilis* [14]. Our research showed that gram-positive flora, most often *Enterococcus faecalis* was predominant and found in 65 % of the abscess content and 66.7 % of the affected tissues. Gram-positive cocci, mainly *Enterococcus faecium*, were isolated in 57.1 % of liver abscesses. In multiple abdominal abscesses due to intestinal perforation, the rod-shaped flora was predominant (76 %) and represented by both aerobes (*Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae*) and obligate aerobes (*Bacteroides ovatus*).

Ratio M. and others [15] showed in their research data about 14 isolated microorganisms. In our research gram-negatives (mainly *Escherichia coli*) and gram-positive cocci (*Enterococcus spp., Staphylococcus spp.*) were predominant.

The fact that needs further analysis is the isolation from the blood (in two cases) of facultative anaerobic gram-positive cocci (*Streptococcus constellatus* in monoculture and *Streptococcus mitis*, *Staphylococcus epidermidis* and *Staphylococcus hominis* in mixed culture). On our opinion, it can be explained by the fact that blood for microbiological examination was collected after tracheal intubation during surgery.

Analyzing the results of microbiological research indicated importance of the sample collecting time (first or repeated surgery). In patient's blood taken during first surgery it was found no growth of microflora in most of all seedings.

In abdominal cavity exudates the number of cultures of anaerobic microflora and mixed culture seriously increased in repeated surgery.

It was noted that in samples taken during first surgery mixed pathogens were represented mainly by facultative anaerobic cocci, then in repeated surgery samples anaerobic microorganisms were predominant, and rod-shaped pathogens have always been a part of mixed cultures.

CONCLUSIONS

Bacteriological analysis of intra-abdominal abscesses content in patients with acute abdominal infection showed that gram-negatives (54.1 %), most often *Escherichia coli*, were predominant in appendicular abscesses. Gram-positive bacteria dominated in paravesical abscesses with 65 % isolates from gallbladder and 66.7 % from the affected tissue samples, most often it was *Enterococcus faecalis*. In liver abscesses also gram-positive microorganisms were predominant (57.1 %), but *Enterococcus faecium* was most often. In multiple abdominal abscesses due to bowel perforation rod-shaped microflora was predominant (76 %) and represented by either obligate aerobes or obligate and facultative anaerobes.

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ORIGINAL ARTICLE

TREATMENT OF COMBINED ACNE AND GENITOURINARY INFECTIONS CAUSED BY CHLAMYDIA AND MYCOPLASMAS

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ABSTRACT

The aim: To substantiate, develop and apply in clinical practice a method for the treatment of combined acne and genitourinary infections caused by *chlamydia* and *mycoplasmas*.

Materials and methods: Acne was diagnosed clinically. *Chlamydia trachomatis; Mycoplasma genitalium; Mycoplasma hominis; Ureaplasma urealyticum* were identified using polymerase chain reaction. 30 patients with combined acne and urogenital *chlamydia* and/or *mycoplasmas* received sequential oral antibiotic therapy with josamycin (1500 mg daily) and gatifloxacin (400 mg daily) for 10 days each. Simultaneously with antibiotic therapy, concomitant symptomatic and topical treatment was provided.

Results: The elimination of pathogens of urogenital *chlamydia* and/or *mycoplasmas* was achieved with 29 out of 30 patients (93.3%). At the same time a complete regression of facial rash inflammatory elements was detected at 18 (60%) treated patients, while with the remaining 12 (40%) the regression was significant. **Conclusions:** Antibiotic therapy was used in the treatment for both acne and urogenital *chlamydia* and/or *mycoplasmas*. An original method of complex treatment of combined acne and urogenital *chlamydia* and/or *mycoplasmas* was substantiated, developed and successfully applied. The offered method of treatment can be considered as a proof of high effectiveness both for elimination of pathogens from the genitourinary system of patients, and for complete or significant elimination of inflammatory facial rash.

KEY WORDS: antibiotic therapy, acne, chlamydia, mycoplasmas

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INTRODUCTION

Acne is an inflammatory disease of hair follicles and sebaceous glands of the skin [1]. As a rule, areas with high counts of sebaceous glands are affected, i.e. face, chest, and back [2,3].

Acne is one of the most common chronic recurrent skin diseases ranked first in the structure of cosmetic pathology and third in the frequency of visits to dermatovenereological facilities [2]. An analysis of age and gender peculiarities of acne showed that this state affects 70 to 80% of adolescents and young adults and about 11% of the population aged over 25, besides boys and men often suffer from severer dermatosis. The presence of rash on exposed skin areas contributes to significant decrease in self-esteem of patients with acne, development of anxiety, depression, and dysmorphophobia [4]. Social adaptation seems rather complicated for such individuals, the percentage of unemployed and single persons is rather significant among them [1].

Four main factors are important in the pathogenesis of acne: pathological follicular hyperkeratosis, hyper-

function and hypersecretion of the sebaceous glands, replication of *Prorpionibacterium acnae* on the skin and in hair follicles, and inflammatory reactions of surrounding tissues [5]. Furthermore, the level of sex hormones, androgens in particular, significantly affects the nature and volume of secretion of the sebaceous glands. As a rule, acne is diagnosed considering the clinical pattern and past history and does not require additional laboratory or instrumental diagnostic methods [1].

In modern dermatovenereological practice, the generally accepted and widespread acne treatment method is systemic antibiotic therapy [3] which can significantly reduce the severity of inflammation and thus provides an opportunity for using highly effective topical agents and procedures [6].

Antibacterial agents for systemic use relate to the standard of care in the treatment of moderate to severe acne, as well as resistant forms of acne. Considering the severity of the state topical therapy is supplemented by systemic antibiotic therapy, mainly tetracycline and macrolide agents. The main advantage of the systemic antibiotic therapy is the ability to significantly reduce the population of *Prorpionibacterium acnae* and the inability to generate inflammatory agents [4].

Antibiotics are also the mainstay in the treatment of sexually transmitted infections (STI) [7].

The recent years are characterized by an extremely unfavorable epidemiological situation regarding the incidence of STIs among the population, which in most countries belonged to the most common infectious diseases subject to registration [8]. One of the main reasons of the wide occurrence is considered wide liberalization of sexual relations, popularity of commercial sexual services, oralgenital and anal-genital contacts without using condoms, early sexual intercourses among adolescents with insufficient awareness of barrier contraceptives. Socioeconomic, demographic, medical and cultural factors play an important role in spreading sexually transmitted infections. Ongoing increase in the incidence of STIs, variety of their clinical manifestations and rather a high rate of complications, both with men and women is rather a serious threat to the reproductive health of a modern individual [9,10]. According to the World Health Organization over 330 million patients with urogenital infections are registered annually in the world whilst the most common pathogens are urogenital chlamydiosis (UGC) - Chlamydia trachomatis and urogenital mycoplasmosis (UGM) – Mycoplasma genitalium, Ureaplasma urealyticum, Mycoplasma hominis [11].

Despite the debate about the pathogenicity of *Ureaplasma urealyticum* and *Mycoplasma hominis* these microorganisms can enter the pathological microbiocenoses of the vagina in bacterial vaginosis in women and the equivalent of this condition in men [13]. Thus, these microorganisms should be diagnosed in the human genitourinary system and eliminated subsequently.

Up to date over 20 nosological forms associated with chlamydial infection are known. Susceptibility to urogenital chlamydia reaches 100% especially with immunocompromised individuals. The ratio of infected males to females is approximately 5:2. This infection can be found in every second woman with chronic genitourinary inflammation, in 57% of females with infertility, and in 87% of those after miscarriage [9].

Currently UGM account for up to 50% of STIs. At the present stage mixed chlamydial-mycoplasmal and other types of infections are common. Their treatment often comes amid resistance to antibiotics. Chlamydial infection is often combined with ureaplasmosis (13-15%), mycoplasmosis (9-10%). A significant proportion of patients with chlamydia also have bacterial vaginosis (26-29%) or candidosis of the genitourinary system (23-26%). Mostly often UGC and UGM develop during the most sexually active age (20-40 years) [8,11].

Thus, systemic antibiotics are often used in everyday dermatovenerological practice. They are prescribed both for the treatment of skin inflammatory diseases such as acne, and for STIs, in particular those caused by UGC and/or UGM pathogens [12].

Given the above, there is a certain need to develop and implement in everyday dermatovenerological practice methods for simultaneous treatment of combined inflammatory diseases of the skin (acne) and the genitourinary system, in particular of chlamydial and/ or mycoplasmal etiology.

THE AIM

The aim was to substantiate, develop and apply in clinical practice the method for the treatment of combined acne and genitourinary infections caused by *chlamydia* and *mycoplasmas*.

MATERIALS AND METHODS

72 patients with acne, who applied to a dermatovenereologist in 2018-2021 and had complains of pathological discharge from the external genitalia, underwent complex examinations for STI. 34 had UGC and/or UGM pathogens. We monitored 30 of them: 18 male patients (60%) and 12 female patients (40%) aged between 20 and 42. The mean age was 28 ± 2.5 years.

Each of the patients was notified about the purpose and methods of the study, possibility of side effects as a result of the therapy and signed the appropriate informed consent form. This study was approved by the Ethical Commission of the Ukrainian Military Medical Academy.

Acne was diagnosed according to clinical manifestations of this disease. UGC and UGM pathogens (*Chlamydia trachomatis; Mycoplasma genitalium; Mycoplasma hominis; Ureaplasma urealyticum*) were identified by using one of the most informative up-todate diagnostic methods: polymerase chain reaction (PCR) [14]. From men scrapings from the urethra and samples of prostate secretion after finger massage were taken. From women vaginal discharge, scrapings of the urethra and cervical canal were taken. Test samples after being registered were accumulated and, if necessary, stored frozen at a temperature of -10°C until PCR was carried out [15].

The patients with combined acne and genitourinary system infections caused by chlamydia and mycoplasmas received the outpatient treatment which included sequential oral antibiotic therapy with Josamycin (1500 mg daily) and Gatifloxacin (400 mg daily) for 10 days each. In addition, LIDOSE isotretinoin was pre-

		То	Total		Males		Females	
No.	STI pathogen	n	%	n	%	n	%	
		30	100	18	60	12	40	
1.	Chlamydia trachomatis	16	53.3	10	55.6	6	50	
2.	Micoplasma genitalium	6	20	8	22.2	2	16.7	
3.	Micoplasma hominis	10	33.3	6	33.3	4	33.3	
4.	Ureaplasma urealyticum	16	53.3	10	55.6	6	50	

scribed (course dose of 100–120 mg/kg). Simultaneously with general therapy, topical treatment was also provided, depending on the severity and prevalence of inflammatory or non-inflammatory elements of skin rash and their counts: Duac cream, Skinoren cream, Curiosin gel were prescribed. At the end of antibiotic therapy, Acnesept lotion was administered topically BID and Isotrexin gel OD at night for 3-4 weeks.

In addition, recombinant interferon 1,000,000 IU OD (after emptying) was administered rectally during the first 10 days of treatment. To prevent the activation of fungal microflora, oral Fluconazole 100 mg e. o. d. (10 doses) was also prescribed.

In addition, where necessary, the male patients received finger prostate massage and rectal suppositories containing ichthyol and chamomile extract. The female patients respectively received daily vaginal douching with Citeal and vaginal suppositories containing (per suppository) osarsol 0.25 g; boric acid 0.3 g; glucose 0.3 g. Suppositories were administered intravaginally overnight, 1 suppository OD for 10 days [6].

RESULTS

Table I presents data on the rate of identification of each of the pathogens in patients of the group under study. Notably, *Chlamydia trachomatis* (53.3% of patients) and *Ureaplasma urealyticum* –16 (53.3% of patients) were the most common. *Micoplasma hominis* and *Micoplasma genitalium* were somewhat less common in 10 and 6 (33.3% and 20%) of the examined patients respectively.

There were no significant differences in the rate of identification of UGC and UGM pathogens with male and female patients. It should be noted that a combination of all four pathogens was not found in any of the patients. Three pathogens were simultaneously found in 4 (13.3%) patients, two pathogens - in 18 (60%) patients, monoinfection was observed in 8 (26.7%) patients.

The treatment was provided simultaneously to the permanent sexual partner of each of the monitored patients. A prerequisite for achieving a recovery from STIs was the patients' abstinence from sexual activity during the entire course of treatment and a prohibition to have sexual intercourse without barrier contraceptives in order to prevent their reinfection until they had the laboratory confirmation of complete recovery. Also, the patients were prescribed Pevzner diet No 5, the goal of which was to ensure a liver-sparing regimen, normalization of bile secretion and intestinal activity.

At the end of antibiotic therapy, all patients were prescribed probiotics to restore normal intestinal microbiocenosis, and the female patients were additionally prescribed vaginal suppositories with lactobacteria.

The endpoints of recovery from STIs were analyzed three times: at months 1, 2 and 3 after completion of antibiotic therapy [8]. During the first follow-up partial recovery was confirmed with one patient, who did not have *Chlamydia trachomatis*, but had *Ureaplasma urealyticum*. This patient underwent an additional special examination and an additional course of therapy using other drugs. During the second and third follow-up none of the pathogens investigated was found in all 29 patients (93.3%) who remained in the monitoring group.

All patients with acne experienced the marked improvement in the condition of the skin, namely the significant quantity decrease of papulopustular inflammatory elements of rash. Thus, they were prepared (if necessary) for the subsequent stage of acne therapy involving the use of median peeling, mesotherapy and physiotherapy. Complete regression of inflammatory elements of facial rash was observed in 18 (60%) patients. In the remaining 12 (40%) patients, the regression of inflammatory elements of the skin rash was considered as significant.

Treating the patients with acne and STIs according to the proposed scheme there no clinically significant cases of side effects associated with antibacterial therapy were identified, i.e. there was no prerequisite for the withdrawal of antibacterial drugs in the monitored patients group and/or additional drug correction due to possible adverse effects.

DISCUSSION

Some literature sources indicate that it is not necessary to eliminate *Ureaplasma urealyticum* and *Micoplasma*

hominis from the genitourinary system of patients [4]. We consider these pathogens in the context of their potential to become the cause of bacterial vaginosis, a disease that is now extremely common [1], so it gives us the full right to eliminate them.

In addition, the existence of some pathological condition of the male genitourinary system which is the equivalent to bacterial vaginosis in women, has been shown [13]. In the occurrence of which an essential role is played by Ureaplasma urealyticum and Micoplasma hominis. And this fact in addition to epidemiological factors, gives us the reason to carry out the elimination of these microorganisms from the male genitourinary system.

The timing of antibiotic therapy for acne and STI often do not coincide [2,9]. Therefore, in the treatment of combined acne and STI, it is necessary to focus on the timing of acne treatment, because in the vast majority of cases the acne treatment takes more time.

Sometimes, it occurs difficult to explain patients with acne the necessity and/or possibility to be tested for STI, especially taking into consideration the fact that services for this group of diseases in our country, with rare exceptions, are not covered by medical insurance.

However, we believe that the benefits from the simultaneous treatment of combined acne and STI are much greater. Thus, our findings indicate the feasibility and high efficacy of the proposed complex treatment of UGC and UGM in patients with acne, both in terms of eliminating these pathogens from the genitourinary system, and in terms of relief of facial skin inflammations.

It should be noted that simultaneous treatment of combined inflammatory diseases of facial skin and the genitourinary system allows our patients to achieve significant savings compared to costs that would have been expected if these important medical issues were addressed separately.

In addition, by reducing the course of antibiotic therapy that would be required to address both medical issues separately, it is possible to significantly decrease the likelihood of developing side effects associated with antibiotic therapy, as well as their severity.

CONCLUSIONS

- 1. Antibiotics are used in the treatment of both acne and urogenital chlamydia and/or mycoplasmas.
- An original method of complex treatment of combined acne and urogenital chlamydia and/or mycoplasmas was developed and successfully applied in 30 patients.
- 3. The proposed method of complex treatment of urogenital chlamydia and/or mycoplasmas in patients with acne proved highly efficacious, both in terms of eliminating these pathogens from the genitourinary system, and in terms of relief of facial skin inflammations.

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ORIGINAL ARTICLE

CHANGES IN ARTICULAR CARTILAGE OF THE HIP JOINT INDUCED BY ACETABULAR LABRUM DAMAGE

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ABSTRACT

The aim: Histological studies of hip joint cartilage after articular labrum resection.

Materials and methods: Articular labrum of hip joint was excised in adult rabbits. In 1,5 and 4 months, the histology of the joint was studied. The condition of the cartilage after reverse fixation of labrum was separately investigated. The morphology of the joint was assessed according to the OARSI scale and morphometric measurements.

Results: The morphology of hip joint cartilage was changed after labrum resection including chondrocyte injury, cell heterogeneity and chondrocyte clustering, less signs of fibrosis. Cartilage erosion was correlated with grade of OARSI scale, but not necessarily with cartilage thickness. The extracellular matrix / chondrocyte ratio was more significant indicator of cartilage condition than multipoint analysis of cartilage thickness.

Conclusions: Injury of acetabular labrum cause change morphology of joint cartilage, which observed in the dynamics. In animal model the cartilage injury scoring scales are more accurate in long term studies while early changes can be interpreted with limitations.

KEY WORDS: trauma, morphology, hip joint, acetabular labrum

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INTRODUCTION

In recent years, interest in studying the role of the acetabular labrum in hip joint stability has increased. Changes in the acetabulum affect the biomechanics of the joint and the friction of the joint surfaces. This process negatively affects the condition of the cartilage and leads to osteoarthritis [1]. The relationship between the loss of joint stability through damage of the labrum and subsequent degenerative changes within the joint requires investigation. Presumably, the changed biomechanics induce displacement of the cartilage layers [2]. Other works partially describe histological changes in articular cartilage, inflammatory changes and vascularization of the labrum, changes in the cartilage matrix [3] and synovitis in the late stages of femoroacetabular impingement [4]. Animal models can aid researchers in studying the predictors of osteoarthritis. There are several animal models of hip joint osteoarthritis, for example, the methylprednisolone model [5]. It is known that articular cartilage damage is evident four months after osteotomy and bone rotation to create femoroacetabular impingement [6]. Spontaneous arthrosis of knee and hip joints can occur in rabbits older than one year [7]. The goal of creating animal models is to reproduce cartilage changes in vivo in a manner that most closely resembles clinical cases and allows the investigation of disease pathogenesis and the evaluation of the effects of medicines and other agents. We believe that the development of hip osteoarthritis is associated with changes in and damage to the joint capsule. Appropriate assessment of the state of the cartilage and stage of arthritis is quite difficult and depends on the degree and type of changes detected.

THE AIM

In this article, we aimed to examine the condition of joint cartilage after labrum resection and evaluate structural changes after its reattached.

MATERIALS AND METHODS

Experiments were carried out on 13 Chinchilla rabbits weighing 4,5-5,0 kg. Animals were anesthetized using a 60 mg/kg dose of sodium thiopental. In the projection of the hip joint along the dorsal surface, a 3 cm access was made. The skin and subcutaneous fatty tissue were dissected. Next, the muscles were separated from the greater trochanter, the capsule was dissected, and the head of the femur was dislocated. The articular labrum was exposed along the anterior-dorsal surface.

Articular labrum was: 1) excised (n=7); 2) excised and reattached transosseously with a non-absorbable braided thread N^o2-0 (n=3)

The femur has been repositioned. The capsule was sutured with a non-absorbable braided thread N $^{\circ}2$ -0. The muscles were transosseously reattached with non-absorbable braided thread N $^{\circ}2$ -0 to the greater trochanter. The wound was sutured layer-by-layer. Intact animals were used as controls (n=3).

After 1.5 months, 3 rabbits from the first group were removed from the experiment. 4 months after the operation, 4 rabbits from the first group and 3 rabbits from the group after reattachment of the labrum were removed from the experiment. We hypothesized that changes in the joint after surgery would not occur quickly, but at least after several months. The experimental period of 1.5 months in this work was considered as an analogue of the revision of the condition of the cartilage, since macroscopically the changes were not obvious and repeated suturing of the wound could have its consequences on the tissues in the operated area of the limb.

The articular complex was fixated using a 10% formalin solution. Strips of the joint about 2 cm thick were sawed off. Decalcification was carried out in OsteoFast 1, BioGnost, Croatia. Samples were embedded in paraffin through isopropanol. Paraffin sections were made on a Thermo Microm HM 360 microtome. The sections were stained with hematoxylin and eosin (H&E), picro-sirius red (PSR), and safranin O with fast green (SOFG). Microsections were examined on an Olympus BX51 microscope. Every standard block/section was evaluated using scale and morphometry methods (ImageJ) to determine the stage or quantifiable changes in articular cartilage. We assessed the changes over the entire joint surface and divided it into 4 segments: 2 central and 2 peripheral (according to the longitudinal plane of the section). Namely, the grade of cartilage is an average number from 4 fields of vision. To assess the joint according to the scale slices were studied at low magnification, with ×4 and ×10 microscope lenses.

We used the above-mentioned path and applied the OARSI scale as the most appropriate for our tasks (sam-

ples) [8]. We did not limit ourselves to the gradation of each sample and conducted a morphometric analysis. Morphometry of the cartilage tissue, especially of the articular surface, is a distinct method of assessing the state of the joint because, in cases of significant damage, data collected via morphometry can somewhat reflect the subjective assessment given by a researcher. Morphometry also has advantages regarding the assessment of early changes in the cartilage tissue, when a defect in the cartilage is not observable. Three indicators were calculated using ImageJ: cartilage thickness (µm), rate erosion of cartilage surface (%), extracellular matrix/ chondrocyte (ECM/Ch) ratio. Osteoarthritis Research Society International (OARSI) grading scale was used to determine the stage of articular cartilage changes. The "Chondrocyte clustering" indicator in Table I is presented as an independent indicator in order to better detail cellular reactions in cartilage. Statistical data analysis was carried out using one-way ANOVA, Bonferroni post hoc test, and Spearman's Rho correlation.

All experimental procedures on animals performed following the "European Convention for the protection of vertebrate animals used for experimental and other scientific purposes" and "Guide for the care and use of Laboratory Animals" (Strasbourg, 1986).

RESULTS

We have carefully studied specimens of the hip joint of rabbits that underwent resection of the acetabular labrum and after attempting to suture it to the joint tissues. Various histological methods of cartilage staining had different advantages for studying the structural changes. When H&E made it possible to obtain data regarding general changes in the cartilage tissue and to detect clear degenerative changes, SOFG staining made it possible to detect changes in cartilage biochemistry (loss of positive staining for Safranin indicates a decrease in proteoglycans in the ECM), and PSR staining showed the appearance of collagen and fibrosis. Table I shows the results of the evaluation and analysis of the articular surface of the femoral head for each animal. Figure 1 illustrates distinct structural changes in the articular surface of the femoral head.

The results of histological examination were as follows:

a) animals 1,5 months after surgery: in 2 samples articular cartilage did not have any defects, macroscopically had no observable changes, and death of chondrocytes and swelling of cellular lacunae were noted only in the superficial zone in 1 sample, there was a cartilage defect, as well as changes in cartilage surface and chondrocyte clustering.

Nº	Sample	OARSI o sca	grading ale	Cartilage thickness, µm		Rate erosion of cartilage surface	ECM/cho rat	ndrocyte io#	Chondrocyte clustering
1	Control	0		1066.7±222.5		0	8.1±1.59		0
2	Control	0	0	1173.2±175.9	1110.8±314.9	0	7.5±0.15	7.9±0.4	0
3	Control	0		1102.2±347.4	-	0	7.3±0.68		0
4	Exp-1.5 month	2.75±0.9		434.9±103.5		<25%	5.7±0.88		++
5	Exp-1.5 month	0.75±0.5	1.2±1.3	669.6±127.2	623.5±230.7†	0	6.1±0.80	5.9±0.2†	0
6	Exp-1.5 month	0.25±0.5		718.8±61.3	-	0	5.8±0.22		0
7	Exp-4 month	0.25±0.5		638.1±61.3		0	5.7±0.44		0
8	Exp-4 month	1.25±0.5	16112	604.0±171.2		0	5.9±0.56		0
9	Exp-4 month	1.5±0.5	1.0±1.3	508.2±61.9	508.5±175.0T+	0	5.8±0.41	- 5.0±0.3T+ -	+
10	Exp-4 month	3.5±0.5*		518.8±61.9	-	30-50%	5.1±0.17		+
11	Exp+suture-4 month	2.5±0.5		664.0±452.3		<25%	4.9±0.49		+
12	Exp+suture-4 month	3.5±0.5*	2.3±1.2	842.2±354.7	838.1±363.8†‡*	30-50%	3.9±0.12	4.7±0.6†*	++
13	Exp+suture-4 month	1.0±0.0		960.2±210.0		0	5.1±2.21	·	0

Note: all data presented as Mean±SD

Note: all data presented as Mean \pm SD

* synovitis. Intense fibrous tissue formation with PSR-positive areas

chondrocyte clusters / isogenous groups

 \pm p< 0.05, compared with the control group

‡ p< 0.05, compared with the experimental group on 1.5 month after operation

* p< 0.05, compared with the experimental group on 4 month after operation

b) animals 4 months after surgery: in 1 sample the cartilage condition was close to intact, although locally chondrocytes were hypertrophied or dead; in 2 samples heterogeneous cartilage staining was noted; in 1 sample heterogeneous staining, surface defects, and signs of fibrosis were observed.

c) animals 4 months after surgery and suturing: in 1 sample only damage to chondrocytes was detected; in 2 samples staining and heterogeneity of cellular composition on 1/2-2/3 of the cartilage thickness, cellular clustering, and the appearance of collagen were detected.

Morphology interpretation according to the OARSI scale was as follows:

Grade-0 – cartilage morphology is approaching an intact state, or chondrocyte changes are only local, 1 out of 3 animals after 1,5 months and 1 out of 7 animals after 4 months (group without reattachment of the labrum);

Grade-1 – damaged cells in the superficial zone of the cartilage, cellular heterogeneity, cell death, loss of the surface cell layer, 1 out of 3 animals after 1,5 month and 3 out of 7 animals after 4 months;

Grade-2 – cartilage displays heterogeneous staining in the upper 1/3 part of the cartilage, clustering of cells

in the cartilage, 1 out of 3 animals after 1,5 months and 1 out of 7 animals after 4 months;

Grade-3 – heterogeneous staining progressed to 1/2-2/3 of the thickness of the cartilage, change in cell density, cellular clustering, signs of fibrosis in the surface layer, PSR-positive staining surrounding cell clusters, in 2 out of 7 animals after 4 months. The loss of staining homogeneity, "gaps" in safranin O staining and the appearance of positive fast green reaction in these regions indicates changes in matrix histochemistry, loss of proteoglycans.

The grade of change in each animal can be seen in Table I.

To verify the validity of our research, 2 samples that could theoretically be classified as Grade-4, were instead assigned a Grade-3, as we made a correction for the number serial sections. Importantly, these changes were found in joint samples that expressed signs of inflammation, and leukocyte infiltration of the capsule (which was combined with synovial villi dysfunction). This is indicated in Table I. At the same time, there was always the tidemark between the cartilage and the calcified cartilage tissue. Average values according to the scale in different groups were



Fig. 1. Cartilage of the Femur head. a – cartilage without any defects, homogeneous staining (grade 0); b – cartilage defect, chondrocyte swelling, the appearance of «empty» lacunae (grade 3); c and d – cartilage defect, vertical «stripes» of heterogeneous staining, chondrocyte clustering (grade 2); e and f – cartilage defect replaced by fibrous tissue (grade 3). Studied groups: a,b – experimental group on 1.5 month; c,d,f – experimental group on 1.5 month after reattachment of the labrum. Stains: SOFG (a,c,d), PSR (b,e,f); magnification: a,c,e ×40; b,d,f ×100.

as follows: in the experiment group - 1.5 months 1.2 ± 1.3 ; in the experiment group - 4 months 1.6 ± 1.3 ; in the experiment + suture group - 4 months 2.3 ± 1.2 . The vertical linear measurements of the cartilage given in Table I (although debatable) are appropriate if there is no local defect in the cartilage. A decrease in cartilage thickness was noted in some specimens, but even in the presence of erosion of the surface layer around the cartilage, the thickness could be unchanged.

Correlational analysis revealed an absence of a relationship between cartilage thickness, ECM/ch ratio, and erosion rate. A weak correlation between cartilage thickness and ECM/ch ratio, and a strong correlation between cartilage thickness and OARSI grade were confirmed. Cartilage condition indicators such as ratio ECM/chondrocyte ratio, erosion rate, chondrocyte clustering, and the OARSI scale grade had a strong correlation and, therefore, are reliable parameters of cartilage changes. Figure 2 depicts the value and strength of the correlation between parameters.

DISCUSSION

Changes discovered in the articular cartilage of the femoral head are sufficient to confirm the relationship between changes in the cartilage and joint capsule damage (resection, rupture), regardless of conclusions that were made about the limitations (validity) of use of grading scales for measuring histopathological changes in the cartilage. We had doubts about the validity of grading scales for evaluation of focal changes in the joint since the structure can be changed heterogeneously. For example, changes in joint surface without significant decrease in chondrocytes, or with chondrocyte pyknosis and little or no changes in chondromucoid staining. When studying early changes in the joint (as in our cases), the factor of influence of subchondral bone tissue on the measurement results is usually not taken into account, because microscopically the bone looks intact, and there are hematopoietic islands in the bone marrow. While these changes are important for practical medicine. Therefore, focusing on the assessment of chondrocyte and cellularity changes is

Spearman's rho R p	Grade OARSI	Cartilage thickness	Rate erosion of cartilage surface	ECM/chondrocyte ratio	Chondrocyte clustering			
OARSI grade	1							
Cartilage thickness	-0.68 0.01	1						
Rate erosion of cartilage surface	0.80 0.00	-0.30 0.32	1					
ECM/chondrocyte ratio	-0.85 0.00	0.46 0.12	-0.79 0.00	1				
Chondrocyte clustering	0.85 0.00	-0.55 0.05	0.85 0.00	-0.72 0.01	1			
-1.0 Blue $\leftarrow 0.0 \rightarrow \text{Red}$ 1.0								

Fig. 2. Correlation strength between parameters of damaged femoral articular cartilage

more appropriate. With that in mind, it is interesting to evaluate the clustering of chondrocytes, which can be observed in samples Grade-3 and Grade-4 according to the OARSI scale.

In the later stages (Grade-5 and Grade-6) lacunae become empty due to cell death [9]. 4 months after acetabular labrum resection cartilage changes did not surpass the Grade-3 level. Changes in ECM/ chondrocyte ratio are associated with several types of changes: focal proliferation, chondrocyte swelling within the isogenous groups, chondrocyte clustering, and chondrocyte death. These changes may occur simultaneously and/or sequentially, despite this ECM content remains unchanged. Chondrocyte clustering can be easily distinguished from normal cellularity, as the number of cells and their size increases drastically; these groups have a distinct appearance in cartilage. These morphological changes are explained by chondrocyte proliferation that happens in an attempt to restore damaged cartilage [10]. An increase in cell number within the isogenous groups and an increase in cell cluster sizes are features of cell damage and histological signs of osteoarthritis [8]. Chondrocyte clusters are often located both near the superficial zone of the cartilage [11], and near the subchondral bone [8], though in our study, we observed them in the middle part of the cartilage. Chondrocyte clustering correlates with the collagen appearance around chondrocyte groups. This was confirmed by PSR staining (borders around cell clusters and/or appearance of positive red-colored regions). There is an opinion that collagen expression by chondrocytes in damaged cartilage can be a manifestation of cartilage regeneration [12]. Later, chondrocytes within the isogenic groups become hypertrophied and die, calcification can occur. This is confirmed by similar localization of apoptotic cells and calcium deposits within the tissue [13]. Namely, during the development of arthrosis, two processes occur at the same time – cartilage destruction and regenerative chondrocyte reaction. Progressing changes are the result of the predominance of the former. Such abnormal chondrocyte activity remains poorly understood and requires further research.

More detailed cartilage morphometry can be applied, as we demonstrate through our personal experience in this article, to which the authors of the OARSI scale do not object [14]. We measured cartilage thickness, from the surface outline to tidemark, and concluded that thickness analysis is not objective, vertical linear cartilage morphometry does not necessarily correspond to cellular changes in the cartilage. As can be seen in Figure 2, there is no reliable linear correlation between cartilage thickness and cellular changes. Evaluation of changes is especially problematic in the presence of local cartilage defects, because summarizing linear measurements in the affected area and perifocal zone simply averages out the mathematical data. In this way arises a question about the rationality of measuring linear indicators in the defect area of the cartilage in case of fibrosis (these measurements have more to do with the thickness of the fibrosis area rather than with the cartilage itself). Either way, we still presented our results (averaged data) in Table I, there is a reliable difference between intact samples and samples with arthrosis (the difference was shown by a one-way ANOVA Bonferroni post hoc test). The relationship between cartilage matrix and cellular composition (and chondrocyte clustering) appears to be encouraging and may hold promise.

We recognize that in experimental joint damage models, histopathological change scales are more accurate in later stages of change development, whereas interpretation of early changes is limited [15]. Since early changes are detected only in certain areas of the cartilage surface, mathematical analysis of such changes (for example, cartilage thickness) does not give a reliable result. Therefore the method of evaluating histopathological changes that are interpreted through the usage of grading scales is more sensitive in cases of significant articular cartilage damage. In these cases, changes can be observed macroscopically and observation results correlate with histological changes. Early histological cartilage changes cannot be identified macroscopically. A completely different alternative - is cartilage morphometry, but this approach in linear cartilage measurement should be used appropriately. Compared sections should be taken on the same level so that ultimately linear measurements (such as cartilage thickness) are consistent with overall changes in cartilage morphology. This is the main criterion; otherwise, morphometry would be conducted for incomparable cartilage areas and/or samples.

Ponce MC et al, 2018 [8] attempted to improve the grading system by integrating several cartilage parameters (level of cartilage surface damage, intensity of ECM staining, typology of chondrocyte changes within the cartilage). In our opinion, the problem of adequate assessment of bilateral/unilateral changes is debatable. Therefore, the data obtained by us and presented in Table I are sufficient for the quantitative presentation of microscopic changes, since the purpose of this work was to establish the development of changes in the hip joint after resection of the joint capsule. Further or alternative studies could consider different scales of morphometric parameters to detect differences between samples/cases. Further validation of cartilage assessment methods should undoubtedly continue in the future.

CONCLUSIONS

- 1. Injury of acetabular labrum cause change morphology of joint cartilage, which observed in 1.5 and 4 month. In long term studies the changes of cartilage surface were achieved but interpretation the interpretation of the results should be based multiple assessment approaches.
- 2. Reattaching of acetabular labrum in hip joint did not have a positive effect on the changes of the cartilage of the femoral head, and 4 months after excision of the labrum, changes in the cartilage reached the point of focal erosions.
- 3. Linear morphometric changes do not necessarily correlate with histochemical changes in cartilage, while the relative density of chondrocytes, erosion rate, chondrocyte clustering, and the grade on the OARSI scale are characterized by a strong connection.

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THE ROLE OF NITRIC OXIDE AND PEROXYNITRITE IN THE ERYTHEMAL PERIOD OF ULTRAVIOLET-INDUCED SKIN DAMAGE

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ABSTRACT

The aim: To study the activity of inducible NO synthase in the blood, the content of NO metabolites and peroxynitrite in the skin and blood of guinea pigs during erythema periods after local ultraviolet skin irradiation.

Materials and methods: The studies were carried out on 24 guinea pigs, subjected to local ultraviolet irradiation. The control group consisted of intact guinea pigs (n=6). After 2, 4 hours, on the 3rd, 8th day, the activity of inducible NO synthase (in blood), the content of total NO metabolites, nitrite anion, nitrates, peroxynitrite (in blood and skin) were determined.

Results: An increase in the level of peroxynitrite in the blood and of all NO metabolites in the skin was noted 2 hours after irradiation. After 4 hours activation of inducible NO synthase in the blood was observed, accompanied by an increase in the content of all NO metabolites and peroxynitrite both in the blood and in the skin. On the 3rd day high levels of excessive synthesis of NO and peroxynitrite in the blood and skin were also revealed due to the induced expression of this enzyme in the blood. On the 8th day the activity of inducible NO synthase remained high in the blood, which led to the accumulation of all NO metabolites and peroxynitrite in the blood and skin.

Conclusions: Thus, local ultraviolet irradiation of the skin of guinea pigs leads to the activation of inducible NO synthase in the blood and an increase in NO synthesis and peroxynitrite in the blood and skin.

KEY WORDS: nitric oxide, peroxynitrite, local ultraviolet irradiation

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INTRODUCTION

The key link in the pathogenesis of ultraviolet irradiation is the activation of free radical oxidation processes, which is manifested by an increase in lipid peroxidation against the background of a decrease in antioxidant protection [1]. In recent years, increasing attention has been paid not only to the active forms of oxygen but also to the active forms of nitrogen, in particular nitric oxide (NO) and its active metabolites. [2-4]. NO plays an important role in the processes of vasodilation, respiration, immune response, cell apoptosis [5]. The damaging effect of NO is mediated through its reactive forms and manifests itself when its synthesis increases due to the induction of inducible NO-synthase (iNOS) which is observed in inflammatory processes of different etiology and is combined with increasing formation of active forms of oxygen [2,5]. Most cytotoxic NO effects belong to peroxynitrite formed by interaction with superoxide-anion,

which causes cell function disruption and tissue damage, activation of lipid peroxidation, collagenolysis processes, and depolymerization of proteoglycans in the skin [2,6,7].

THE AIM

The aim is to study the activity of inducible NO-synthase in the blood, the metabolite content of NO and peroxynitrite in the skin and blood of guinea pigs in erythemal period after local ultraviolet skin irradiation.

MATERIALS AND METHODS

The studies were carried out on 30 guinea pigs, divided into 2 groups: Group 1 involved intact animals (control group), Group 2 consisted of animals subjected to local ultraviolet irradiation (exposure group). Erythema was induced by irradiation of the shaved skin area with ultra-

Terms after irradiation				
2 hours	4 hours	3rd day	8th day	
4,8	9,2	7,7	0	
(4-6)	(8-10)	(7-8)	0	



Table I. Total intensity in scores of the erythema reaction of the skin of guinea pigs exposed to local ultraviolet radiation

Fig. 1. Activity of inducible NO-synthase (iNOS) in the blood of guinea pigs in local ultraviolet irradiation Note. * - significance of differences in comparison with control ($P \le 0.05$)

violet rays (with a predominance of UVB) using a mercury-guartz irradiator (OKN-11-M, UV wavelength 240-320 nm, capacity 25.8 Wt/m2) placed at a distance of 10 cm from the animal for 2 minutes During irradiation, the skin area was shielded with a plate with five holes 6 mm in diameter. The degree of reaction was assessed in points for each spot: 0 - no erythema, 1 - clear redness, 2 - intense erythema. The intensity of 5 spots was summarized [8]. Experiments on animals were carried out in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, the Law of Ukraine "On the Protection of Animals from Cruelty". Two, four hours, on the 3rd and 8th days after irradiation, the activity of inducible NO-synthase [9] in the blood, the content of total NO metabolites, nitrates [10], nitrite anion [11], peroxynitrite [12] in the blood and skin were determined by spectrophotometric method. Statistical processing of the obtained data was carried out using the "Statistica 6.0" program using the parametric and the non-parametric methods. The statistical result was considered significant when $p \le 0,05$ [13].

RESULTS

Erythema developed in all guinea pigs after local ultraviolet irradiation. Two hours after irradiation, the total erythema was 4.8 points. Four hours after irradiation, the maximum erythema was registered, when the total intensity increased to 9.2 points. On the 3rd day, the intensity of the total erythema was still expressed, amounting to 7.7 points (Table I). In the subsequent periods (4-7 days), the intensity of the erythema grad-ually decreased. Erythema disappeared on the 8th day.

A single ultraviolet irradiation of skin was shown to cause changes in the blood activity of iNOS for 4 hours-8 days without normalization until the end of the experiment. Activity of iNOS increased 2.1 times 4 hours after exposure and 3.1 times on the third day as compared to intact animals (Fig. 1). On the 8th day, the maximum increase in enzyme activity was observed, which was 4.4 times higher than the control group.

A study of NO metabolites in the blood of guinea pigs showed levels above the norm for 4 h-8 days (Fig. 2). The total metabolite content increased 1.6 times after 4 hours, doubled on the 3rd day, and 1.9 times on the 8th day compared to the indices of the control group (Fig. 2, a).

In the study of nitrates, a similar dynamics was noted: their content was increased by 1.5 times after 4 hours, by 1.9 times on the 3rd day, by 1.4 times on the eighth dayas compared to the control group (Fig. 2, b).As for nitrite anion, there was an increase in its level by 2.1 times after 4 hours, by 3.1 times on the 3rd day, by 3.4 times on the 8th day relative to the control group (Fig. 2, c).

During the entire study period, an increase in the level of peroxynitrite in the blood was noted with a maximum increase in the indicator on the 8th day (Fig. 2, d). As early as after 2 hours, it was observed to increase 1.9 times



Fig. 2. The content of total metabolites of NO (a), nitrates (b), nitrite anion (c) and peroxynitrite (d) in the blood of guinea pigs in local ultraviolet irradiation Note. * - significance of differences in comparison with control ($P \le 0.05$)



Fig. 3. The content of total NO metabolites (a), nitrates (b), nitrite anion (c) and peroxynitrite (d) in the skin of guinea pigs in local ultraviolet irradiation Note. * - significance of differences in comparison with control ($P \le 0.05$)

relative to the control group. After 4 hours, the level of peroxynitrite remained high, exceeding the norm by 2.1 times. Further on, there was a progressive increase in the level of peroxynitrite, which exceeded the norm by 3.4 times on the 3rd day and 4.4 times on the 8th day.

During the entire experiment, an increase in the content of total NO metabolites in the skin was also determined (Fig. 3, a).

Thus, they increased 1.7 times 2 hours after irradiation, 1.8 times 4 hours after irradiation as compared to the control group. The maximum increase in the concentration of total NO metabolites was observed on the 3rd day after irradiation: 2.3 times relative to intact guinea pigs and 1.3 times compared to previous periods. Further on, there was a decrease, but on the 8th day this indicator remained 1.9 times higher than the norm.

The level of nitrates in the skin also increased (Fig. 3, b). Thus, 2 and 4 hours after irradiation, the level of nitrates increased by 1.7 and 1.8 times in relation to the control group. In the follow-up, on the 3rd day after irradiation, the level of this metabolite increased even more (by 2.3 times) compared with the indicators of the control group. In the subsequent period (on the 8th day), there was a tendency to a decrease in the content of nitrates relative to the previous period, however, their level remained high, exceeding the norm by 1.9 times.

An increase in the production of nitrite anion in the skin of animals was revealed during the entire study period (Fig. 3, c). Thus, the content of this metabolite in the skin increasesd 1.5 times (2 and 4 hours after irradiation) and 2.1 times (on the 3rd day) relative to the control group. Even after disappearance of erythema on the 8th day, the level of nitrite anion remained high (1.8 times) as compared to the control group.

Changes in the content of peroxynitrite in the skin were observed 4 hours to 8 days after irradiation (Fig. 3, d). After 4 hours, there was an increase in the content of this indicator by 1.2 times relative to the control group. On the 3rd and 8th days, peroxynitrite content exceeded the value of intact animals by 1.6 times and 1.9 times, respectively.

The data obtained indicate a significant accumulation in the blood and skin of the concentration of all NO metabolites and peroxynitrite under conditions of ultraviolet-induced stress.

DISCUSSION

Consequently, even a single ultraviolet irradiation of the skin increases the activity of inducible NO synthase in the blood and causes an intensification of NO synthesis, which is confirmed by an increase in all its metabolites in the blood. Normally, iNOS, as is known, is not synthesized, but under the influence of superoxide and cytokines, iNOS is induced and NO synthesis is produced in quantities several orders of magnitude higher than when cNOS is working [2,5]. Therefore, an excessive level of nitrite anion and nitrates indicates a high intensity of NO synthesis by the iNOS enzyme. Particular attention is paid to excessively high concentrations of nitrite anion, the most toxic metabolite. Parallel to the accumulation of NO metabolites in the blood, their content in the skin increased throughout the experiment. The increase in the content of peroxynitrite in the blood and skin in local ultraviolet irradiation is consistent with the evidence on its participation in the processes of free radical oxidation through the effect on the oxidative-antioxidant balance [2,6]. The sharp increase in the activity of iNOS, which results in the accumulation of NO metabolites and peroxynitrite in the blood, indicates serious immunological changes due to the impact of local UV irradiation of the skin.

Thus, immune disorders are observed in the erythemal period after ultraviolet irradiation of the skin of guinea pigs (2,4, hours, 3 days) and even after disappearance of erythema (8th day), which is confirmed by an increase in the activity of inducible NO synthase in the blood, the content of all nitric oxide metabolites (total, nitrite anion, nitrates) and peroxynitrite in blood and skin.

CONCLUSIONS

- 1. Local ultraviolet irradiation of the skin of guinea pigs results in increased inducible NO synthase activity in the blood during the erythemal period.
- 2. In parallel with the activation of inducible NO synthase in the blood, the concentration of all nitric oxide metabolites (total, nitrite anion, nitrates) increases during the erythemal period.
- 3. The development of ultraviolet erythema is characterized by the accumulation of nitric oxide metabolites (total, nitrite anion, nitrates) in the skin and peroxynitrite in the blood and skin.

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ORIGINAL ARTICLE

CHANGES IN THE SERUM LEVEL OF LEPTIN AND TRANSFORMING GROWTH FACTOR-B1 IN PATIENTS WITH ARTERIAL HYPERTENSION ON A BACKGROUND OF ABDOMINAL OBESITY

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ABSTRACT

The aim: Study of the levels of leptin and the growth modulator TGF-β1 in the blood serum of patients with hypertension, which occurs on the background of AO and without it.

Materials and methods: Carbohydrate metabolism was studied by the enzymatic method, the level of insulin in the blood (by the enzyme immunoassay method), the oral glucose tolerance test and the calculation of the NOMA index.

Results: The data obtained in the work indicate a significant role of leptin in the formation of hypertension itself and the development of obesity, carbohydrate and lipid metabolism disorders. The increased level of transforming growth factor- β 1 in the blood of such patients can be used as a fairly informative marker of the unfavorable prognosis of these diseases.

Conclusions: 1. In the control group, there was a significant increase in the initial values of heart rate, average levels of SBP and DBP, the frequency of hypercholesterolemia and insulin resistance was established. 2. Significant disorders of lipid and carbohydrate metabolism and leptin synthesis were found in patients with hypertension, which occurs against the background of AO. 3. When analyzing the level of leptin depending on gender, a statistically significant increase in the level of blood leptin was found in the group of women with AH with AO compared to women with AH without AO and the control group. 4. A significant increase in the level of transforming growth factor- β 1 in blood serum of patients with hypertension was established.

KEY WORDS: arterial hypertension, abdominal obesity, transforming growth factor- β 1, leptin levels

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INTRODUCTION

The problem of concomitant arterial hypertension (AH) and abdominal obesity (AB) is one of the most important for contemporary medical science [1, 2]. Such a combination is a very serious medico-social and economic problem of modern society, as the general risk of the patients increases significantly and there is an increase in the development of cardiovascular complications, which significantly increase mortality among this category of patients [3-5]. According to the WHO estimates, there are more than 1 billion overweight adults in the world, of them 300 million are obese. In European countries, 10 to 30% of the population suffer from obesity [6-8].

When AH is combined with AO, there is a marked increase in the frequency of prognostically unfavorable metabolic disorders (hyperlipidemia, insulin resistance, hyperuricemia), activation of subclinical inflammation, progression of endothelial dysfunction, which leads to the acceleration of development of atherosclerosis, type 2 diabetes mellitus and a significant increase in cardiovascular risk [1, 14-16].

In the recent years, investigation of AO pathogenesis has drawn attention to the role of leptin and transforming growth factor- β 1 in development of metabolic changes in AH. Leptin, protein identified in the mid-90s; is secreted by adipose tissue, the rate and volume of its secretion is closely related to the body weight. Hyperleptinemia is often combined with dyslipidemia, hyperglycemia, and arterial hypertension [17-19]. In the majority of obesity cases, resistance to leptin is found. In addition, there are controversial data on the relationship between the level of leptin in the blood and blood pressure indicators [20-22]. The role of leptin in the development and progression of AH, insulin resistance, abdominal obesity, and atherogenic dyslipidemia remains unclear.

Activation of proliferative and profibrotic factors, among which one of the most powerful is transforming growth factor- β 1 (TGF- β 1)[23,24], occupies a special place in the mechanisms of forming prognostically unfavorable metabolic disorders and complications. It is known that TGF- β 1 is a key profibrogenic factor both in the myocardium and in the vascular wall. This cytokine induces proliferation of fibroblasts and stimulates collagen production with subsequent development of tissue fibrosis [25-27].

It has been established that TGF- β 1 plays a major role in all the variants of fibrosis and sclerosis at chronic inflammatory processes, mechanical and other processes that lead to tissue damage [28, 29].

Thus, the study of serum leptin and transforming growth factor- β 1 in hypertension, against a background of AO and without its manifestations, is important.

THE AIM

The purpose of this work was to study the levels of leptin and growth modulator TGF- β 1 in the blood serum of patients with hypertension, which occurs against a background of AO and without it.

MATERIALS AND METHODS

The study involved 85 patients (45 men and 40 women), aged from 28 to 72 years (mean age 51.1 ± 0.7 years). The patients underwent a clinical examination using clinical, laboratory and instrumental methods in the conditions of inpatient treatment at Internal Diseases Department of Kharkiv City Clinical Hospital No. 2 named after prof. A.A. Shalimov.

All patients were diagnosed with hypertension, which in 45 patients occurred against a background of AO (group 1), and in 40 patients, hypertension occurred without AO (group 2). Among the examined patients, grade 2 hypertension was found in 44 (52%) persons, grade 3 – in 41 (48%) persons, grade I AO was found in 54 (63.5%) persons grade 2 – in 31 (36.5%)) persons. In the group of patients who were included in the study, burdened heredity for hypertension was found in 68 patients (80%). The duration of hypertension was from 5 to 15 years.

The control group consisted of 25 healthy (according to the results of clinical and additional studies) agematched subjects with a normal body weight. The mean age of the subjects in the control group was 48.9 \pm 1.1 years.

The patients with symptomatic hypertension, diabetes, diseases of the endocrine organs and blood, acute cardiovascular diseases, angina, heart failure, acute and chronic inflammatory processes, kidney, liver and bronchopulmonary diseases were excluded from the study.

The diagnosis of AH, assessment of its grade, diagnosis of AO, disorders of carbohydrate and lipid metabolism, asymptomatic lesions of the target organs was made in accordance with the Recommendations of the European Society of Hypertension and the European Society of Cardiologists (2018) [1].

The state of lipid metabolism was analyzed using enzyme method with Humareazer 2106 - 1709 (Germany) analyzer. The state of carbohydrate metabolism was investigated by determining their levels using enzyme method with Humareazer 2000 (Germany) analyzer, blood insulin levels were determined by immunoenzyme method using standard kits of DRG company (Germany) on an empty stomach and after a standard glucose load (oral glucose tolerance test) and by calculating IR indicator (NOMA index).

Blood leptin level was determined by the method of two-way enzyme immunoassay using DRG (USA) Leptin-ELISA kits on Humareazer 2000 analyzer. Blood serum TGF- β 1 was determined using kits of standard test systems TGF- β 1 ELISA manufactured by DRG Instruments (Germany). The level of native TGF- β 1 in the blood serum was determined by solid-phase immunoenzyme method.

Statistical data processing was carried out using Statistika 6.0 (StatSoft Inc, USA), Microsoft Excel 2007 on a personal computer and with the help of statistical methods (descriptive statistics, criteria for checking the probability of differences between groups, assessment of the probability of the obtained results).

RESULTS

Hemodynamic indicators between the groups of patients with AH with AO, AH without AO and the control group were compared. The data on hemodynamic changes in the examined persons are presented in Table I.

The levels of SBP and DBP, heart rate in patients with hypertension with AO were significantly higher than those in the control group and the group with AH without AO. Meanwhile, the levels of SBP and DBP, heart rate in patients with AH without AO were also significantly higher compared to those in healthy subjects.

Analyzing the obtained data, we found a statistically significant difference in the indicators of lipid metabolism: an increase in the mean level of blood triglycerides was established in the group of patients with AH with

	Groups of the patients				
Indices	AH with AO n = 45	AH without AO n = 40	Controls n = 25		
SBP (mm Hg)	168.2 ± 1.56 */**	155.2 ± 3.7 ***	122.3 ± 1.35		
DBP (mm Hg)	104.8 ± 1.5 */**	97.1 ± 1.79 ***	74.4 ± 2.17		
HR (per min)	87.9 ± 1.26*/**	76.5 ± 1.81	75.2 ± 1.34		

Table I. Hemodynamic indicators in the groups of patients with AH with AO, AH without AO and in the control group

Note.*

* - probability of the difference between the indicators in the group of AH with AO and in the control group is significant p<0.001;

** - probability of the difference between the indicators in the group of AH with AO and AH without AO is significant p<0.05;

*** - probability of the difference between the indicators in the group of AH without AO and the control group is significant p<0.001.

Table II. Blood leptin levels in patients with AH with AO, AH without AO and in the control group

Parameter	AH with AO	AH without AO	Controls
	n = 25	n = 20	n = 25
Leptin, (ng/ml)	13.9 ± 1.2*/**	7.8 ± 1.5 ***	2.4 ± 1.2

Note. *

1.* - probability of the difference between the indicators in the group of AH with AO and in the control group is significant (p<0.001)

2.** - probability of the difference between the indicators in the group of AH with AO and in the group of patients with AH without AO is significant (p<0.05)

3. *** - probability of the difference between the indicators in the group of AH without AO and in the control group is significant (p<0.01).

Table III. Blood serum TGF-B1 levels in patients with AH with and without AO, ng/ml

Controls	AH with AO	AH without AO
(n=25)	(n=25)	(n = 20)
6.80±0.06	13.79±0.57*/**	10.36±0.53***

Note.*

1.* - probability of the difference between the indicators in the group of AH with AO and in the control group is significant (p<0.05);

2.** - probability of the difference between the indicators in the group of AH with AO and in the group of patients with AH without AO is significant (p<0.05);

3. *** - probability of the difference between the indicators in the group with AH without AO and in the control group is significant (p<0.05).

AO (by 1.12 mmol/l (49.3%) compared to patients with AH without AO and by 0.98 mmol/l (43.5%) compared to the control group (p<0.001); a significant decrease in the average level of HDL cholesterol (by 0.4 mmol/l compared to patients with AH without AO (32.2%) and by 0.44 mmol/l compared to the control group (35.4%); a significant increase in the average level of total cholesterol (CHL) in the group of patients with AH with AO (by 0.79 mmol/l (13.1%) compared to the group of patients with AH without AO and by 1.55 mmol/l (25 .6%) compared to the control group).

Insulin resistance (NOMA index \geq 2.77) in patients with AH with AO occurred in a significantly higher number of cases (48.7% more often) than in the group of patients with AH without AO, p<0.001.

In the control group, NOMA index did not exceed the value of 2.77 in any of the cases. Analyzing the changes in the mean index of insulin resistance, we established that, in general, in the group of patients with AH with AO, NOMA index was significantly higher than that in the group of patients with AH without AO by 3.5 (47.9%) (p< 0.001), as well as in the group of healthy persons

by 5.76 (78.9%) (p<0.001). In the group of patients with AH without AO, the index of insulin resistance was 2.3 (60.5%) higher than in the control group (p<0.05).

The analysis of the results of blood leptin levels in patients with AH with AO, patients with AH without AO and healthy individuals of the control group (Table II) revealed a statistically significant increase in the level of blood leptin in the group of patients with AH with AO ($13.9 \pm 1, 2$ ng/ml), when compared to the patients with AH without AO (7.8 ± 1.5 ng/ml), (p<0.05), on an average this difference was 6.1 ng/ml and compared with healthy individuals of the control group (2.4 ± 1.2 ng/ml), p<0.001.

In the group of patients with AH without AO, the blood leptin level was significantly higher than that of healthy individuals of the control group (p<0.01), and on an average this difference was 5.4 ng/ml (table II).

Mean value of blood leptin level in women $(17.9 \pm 1.4 \text{ ng/ml})$ was significantly higher (by 5.8 ng/ml) than that in men $(12.1 \pm 1.8 \text{ ng/ml})$, (p < 0.01). And in persons with AH without AO, blood leptin content did not related statistically significantly to the gender.

The obtained data indicate that leptin resistance is noted in patients with AH and AO, which is the cause of a significant increase in the level of leptin in the blood of these patients. Similar correlations were found in other studies that studied leptin activity in a group of healthy young people without carbohydrate and lipid metabolism disorders and with increased blood pressure [21-23].

When studying the nature of the changes in serum TFR- β 1 levels in patients with hypertension, depending on the presence or absence of AO, it was established that in patients with AH with AO, as a whole, the level of TFR- β 1 was (13.79±0.57) ng/ ml and was significantly (p<0.05) higher (by 103%) than that in healthy individuals - (6.80±0.06) ng/ml and significantly (p<0.05) higher, (by 33%) than in patients with hypertension without AO - (10.36±0.53) ng/ml. Meanwhile, the level of TGF- β 1 in the blood serum in patients with AH without AO was also probably higher than that in the group of healthy individuals (Table III).

The analysis of the nature of changes in blood serum TGF- β 1 levels in the investigated patients with AH with AO and AH without AO, depending on the gender, did not reveal any significant differences. It was found that in both men and women of these groups, TGF- β 1 serum levels were significantly higher than similar levels in healthy individuals. Meanwhile, the index of TGF- β 1 in patients with AH with AO in both men and women was also significantly higher than in men and women with AH without AO.

Analyzing the data obtained in the work, first of all it is necessary to note the established significant increase in the levels of transforming growth factor- β 1 in the blood serum of patients with AH, which was more pronounced when AH was combined with AO. Activation of the whole series of powerful vasopressor factors, which simultaneously possess proliferative and profibrogenic properties, can be attributed to the mechanisms of increased formation of TGF- β 1 in patients with AH [29, 30]. The adverse effect of the activation of TGF- β 1 formation in AH with AO and the detection of an elevated level of this factor in the blood can be of great prognostic value for determining the nature of the further course of these diseases and development of their complications.

DISCUSSION

Obesity contributes to deterioration of the quality of life, as well as emergence of social, psychological and economic problems [9]. It was established that abdominal obesity itself (waist circumference > 88 cm in women and > 102 cm in men), aggravated by smoking, increases the risk of cardiovascular events by 5.5 times [10].

Obesity and excess body weight significantly increase the risk of developing such unfavorable prognostic diseases as type 2 diabetes, cardiovascular diseases (hypertension and stroke), arthritis, bronchial asthma and some forms of cancer [11-13].

It was established that patients with arterial hypertension on the background of obesity had significantly higher levels of systolic and diastolic blood pressure, heart rate, significant disorders of lipid, purine, carbohydrate metabolism, leptin synthesis, leptin resistance, insulin resistance occurred in significantly more cases than in the group patients with arterial hypertension and normal body weight [5].

The obtained data indicate that leptin resistance is noted in hypertensive patients with AO, which is the reason for a significant increase in the level of leptin in the blood of such patients. Similar correlations were found in other studies that studied leptin activity in a group of practically healthy young people without carbohydrate and lipid metabolism disorders and with increased blood pressure [15, 16].

Thus, the data obtained in the work testify to the significant role of leptin in formation of AH itself and development of such metabolic disorders as obesity, disorders of carbohydrate and lipid metabolism. The increased level of transforming growth factor- β 1 in the blood of such patients can be used as a fairly informative marker of unfavorable prognosis of these diseases [15].

CONCLUSIONS

- 1. Our findings indicate that in patients with AH and AO, when compared to the patients with AH without AO and healthy individuals of the control group, a significant increase in the initial values of the heart rate, mean levels of SBP and DBP, frequency of hypercholesterolemia and insulin resistance was established.
- 2. Significant disorders of lipid, carbohydrate metabolism and leptin synthesis were found in patients with AH, which occurs against a background of AO. Blood leptin levels in patients with AH and AO were found to be significantly higher than in healthy individuals; resistance to leptin was also noted, which is the cause for a significant increase in the level of leptin in the blood of such patients.
- 3. When analyzing leptin levels depending on the gender, a statistically significant increase in the level of blood leptin was found in the group of women with AH with AO, compared with the women with AH without AO and the control group.
- 4. A significant increase in the levels of transforming growth factor- β 1 in the blood serum of AH was established, which was more pronounced when AH was combined with AO, which can be used as a fairly informative marker of an unfavorable prognosis of these diseases.

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RELATIONSHIP BETWEEN THE DYSTROPHIC MANIFESTATIONS IN THE PERIODONTIUM AND INTESTINAL DYSBACTERIOSIS

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ABSTRACT

The aim: of our work was investigation of dystrophy in periodontal tissues and an attempt to establish the correlation between dystrophy in the periodontium and presence of intestinal disbacteriosis.

Materials and methods: Clinical-radiological examination was carried out in 146 patients with generalized periodontal pathology at the age from 26 to 59 years old. Among them in 92 persons generalized periodontitis was diagnosed and in 54 – periodontosis. The first stage of heaviness of the pathological process in the periodontium was revealed in 50 patients with generalized periodontitis and 28 persons with periodontosis. Other patients suffered from heavier forms of periodontal pathology (II and III stages), 42 persons with generalized periodontitis and 28 persons with periodontosis accordingly. Bacteriological analysis of feces for disbacteriosis was carried out in all patients.

Results: Changes in the physiological contour of the gums (that is macro relief of marginal periodontium) were found in the majority of examined patients. Because of the development of pathological gingival contour and recession of the gums, 72,5% of examined patients suffered from root denudation and different pathological conditions of roots cement structure – pigmentation, demineralization, wedge-shaped defects, caries. According to our clinical investigations it was found out that in majority of patients (83%) both inflammatory and dystophic changes were present, only 17% of patients had purely atrophic process in the periodontium without inflammation. In patients with GP and periodontosis, in whom dystrophic changes were accompanied by inflammation, clinical appearance was more expressed with redness, bleeding and suppuration from the pockets, thus hiding dystrophic signs.

Conclusions: According to clinical and radiological findings numerous dystrophic changes were found in all structures of the periodontium and teeth of patients with periodontosis and generalized periodontitis. Changes intensify in disease progressing into the II-III stages. In patients with periodontosis clinical- radiological peculiarities of dystrophy were revealed in early stages of disease progression, while in generalized periodontitis dystrophic changes become apparent in late stages of disease. The presence of colon disbacteriosis was established in patients with periodontosis and generalized periodontitis. Disbacteriosis intensifies when diseases progress into II-III stages of heaviness. These data indicates to possible correlation between the development of dystrophic changes in periodontal tissues and the presence of intestinal disbacteriosis.

KEY WORDS: intestinal disbacteriosis, generalized periodontitis, periodontosis, dystrophy, gingival contour

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INTRODUCTION

Dystrophy of the periodontium is presented in clinical manifestation of two main diseases – generalized periodontitis and periodontosis. Clinical symptoms of these diseases differ in the expression of dystrophic changes in periodontal tissues, their peculiarities and extend.

Three dental terms, namely "gingivitis", "periodontitis", and "periodontosis" predominate in the world practice for the last decades. They are also approved for the general use in the medical practice and studies. The Ukrainian dentists use the terms "gingivitis" and "periodontitis" to indicate the inflammatory process (in the gums and in periodontium, accordingly), while the term "periodontosis" is applied for the dystrophic process. Though, these definitions may, to some extent, suit the dentists , they do not fully reflect the entire complexity of the periodontal pathology, that is why the appearance of a larg'e number of new terms in literature is quite logical. In modern literature, and especially in the English one, all the generalized processes in the periodontium, both of inflammatory and dystrophic character are more frequently united under one definition – "periodontitis".

Periodontosis is considered to be a generalized dystrophic process in periodontal tissues. Periodontosis (dystrophy of the periodontium) is a damage of periodontium, in the basis of its development lies the disturbances of tissue (cellular)metabolism, which leads to the structural changes and functions of various manifestations; in the level (stage) of the pronounced damage of periodontium the chronic periodontosis occurs in the form of the gingival atrophy, resorption of the alveolar bone and the pathologic mobility of teeth.

Etiology of periodontosis, associated with neurotrophic changes (Danilevskyj's, theory) and changes in blood vessels of periodontium leading to reduced vascularization and thus to dystrophic changes in the tissues (Evdokimov's, theory) are well known.

It is known that the metabolism and structural organization of tissues (cells) provides the mechanisms, the total number of which is united under the definition "trophicity" [(Gr.trophikos) or pertaining to nutrition]. There are cellular and extracellular mechanisms of trophicity. The cellular mechanisms are provided with the structural organization of the cells & their autoregulation. It means that the cellular trophicity to an even greater degree is the property of the cell itself as the complex system that is selfregulated.

The extracellular mechanisms of trophicity are represented by the transport systems (blood, lymphatic and microcirculatory) and the integrative (endocrine, neurohumoral) mechanisms of regulation.

It has been determined that the disturbances of one of any other mechanisms of the trophicity (cellular or extracellular) create a higher risk for the developing of organ dystrophy, including the periodontium (periodontosis). If these disturbances are not caused by the intensification of coagulation process, than the developed dystrophies belong to the non-causative dystrophies (periodontoses).

In the cellular mechanism disturbances of trophicity, the main chain of the dystrophic pathogenesis is the fermentative process disturbances in the cell. The disturbances of autoregulation with the appearance of the enzymopathy and the development of dystrophy may be caused by various factors: hyperfunction, toxic substances, radiation, hereditary insufficiency or the absence of the enzyme and others.

Dystrophic changes of the periodontium can be formed as the result of the functional disturbances in the transport systems (blood circulation, microcirculation, ultracirculation), which provide the metabolism and the preservation of the cellular structure (cells) [1, 2]. The main chain of its pathogenesis is the hypoxia (dyscirculatory hypoxia). They can develop in cases of disturbances of the endocrine regulation of the trophicity (diabetes, thyrotoxicosis, hyper- parathyroidism, etc.) or as the result of the disturbances of the nervous regulation of the trophicity of the periodontium (the disturbances of the innervation, the tumour of the brain and others).

One more mechanism of the development of dystrophy in the organism, which often is not taken into account, is intestinal dysbacteriosis (ID). But investigations of intestinal disbacteriosis as the pathogenetic factor in the development of periodontal dystrophy were not carried out by now.

THE AIM

The aim of our work was investigation of dystrophy in periodontal tissues and an attempt to establish the correlation between dystrophy in the periodontium and presence of intestinal disbacteriosis.

MATERIALS AND METHODS

Clinical-radiological examination was carried out in 146 patients with generalized periodontal pathology at the age from 26 to 59 years old. Among them in 92 persons generalized periodontitis was diagnosed and in 54 – periodontosis. The first stage of heaviness of the pathological process in the periodontium was revealed in 50 patients with generalized periodontitis and 28 persons with periodontosis. Other patients suffered from heavier forms of periodontal pathology (II and III stages), 42 persons with generalized periodontitis and 28 persons with periodontosis accordingly.

Bacteriological analysis of feces for disbacteriosis was carried out in all patients. ID was characterized by the high titers of conditional pathogenic microorganisms (CPM) and their associations with the background of normal intestinal microbiota changes. The light stage of heaviness of ID (I-II) was diagnosed in case of lowering of the quantity of Bifido- and Lacto- bacteria, Escherichia Coli in the feces and presence of Escherichia species with reduced enzyme properties. ID of I-II degree was not often revealed in patients with GP.

It is known that intestinal disbacteriosis is a clinical sign of secondary immunodeficiency syndrome. In that case, profound immunological investigation in the dynamics of ID correction is necessary to reveal the role of intestinal disbacteriosis in general disbalance of immune system and importance of immunomodulatory therapy.

The level of ID was estimated according to G. Kuzniecova [3], taking into consideration species and populations of feces microbiota. To simplify the results of investigations and make them more objective, patients with GP who had only changes of obligative microbiota were unified in the ID group of I-II stages of heaviness, patients who, except changes of colon microbiocenosis, had been diagnosed the growth of quantity of conditional-pathogenic microorganisms (CPM) and their associations were taken to ID group of III-IV stages of heaviness.

Type of	Number of	Patients with changed	Patients with con	Patients with different types of pathological gingival contour (gingivoglyphics) (%)				
pathology	patients	gingival contour (%)	strenuously arcade type	flat type	balloon- like type	combined type	teeth roots (%)	
Periodontosis I stage	28	57,1	14,3	32,1	3,6	7,1	100,0	
Periodontosis II-III stages	26	69,2	11,5	34,7	7,6	15,4	100,0	
Generalized Periodotitis I stage	50	66,0	12,0	16,0	20,0	18,0	22,0	
Generalized Periodotitis II-III stages	42	85,7	21,4	16,7	11,9	35,7	73,8	

Table I. The frequency of pathological gingival contour and teeth root denudation in examined patients

Table II. State of microbiocenosis in the colon of patients with Generalized Periodontitis (GP) and Periodontosis.

			Patients with periodontal dystrophy, with revealed					
Groups of patients with periodontal dystrophy	Number of patients	Eubiosis		Intestinal disbacteriosis of I-II degree		Intestinal disbacteriosis of III-IV degree		
		absolute number	%	absolute number	%	absolute number	%	
Generalized Periodotitis I stage	50	14	28	30	60	6	12	
Generalized Periodotitis II-III stages	42	_	_	18	42,9	24	57,1	
Periodontosis I stage	28	5	17,9	19	67,8	4	14,3	
Periodontosis II-III stages	26	_	_	14	53,8	12	46,2	

RESULTS AND DISCUSSION

Changes in the physiological contour of the gums (that is macro relief of marginal periodontium) were found in the majority of examined patients. According to the data presented in the table I, in patients with periodontosis flat type of gingival relief prevailed in I stage as well as in II-III stages of disease, two-three times rarely strenuously arcade type of gingival contour was observed. In patients with I stage of periodontitis all three types of pathological gingival contour (gingivoglyphics) were observed with the same frequency: flat, balloon-like, and combined, while in II-III stages of generalized periodontitis combined and strenuously arcade type of gingival contour dominated. Because of the development of pathological gingival contour and recession of the gums, 72,5% of examined patients suffered from root denudation and different pathological conditions of roots cement structure - pigmentation, demineralization, wedge-shaped defects, caries. According to our clinical investigations it was found out that in majority of patients (83%) both inflammatory and dystophic changes were present, only 17% of patients had purely atrophic process in the periodontium without inflammation. In patients with GP and periodontosis, in whom dystrophic changes were accompanied by inflammation, clinical appearance was more expressed with redness, bleeding and suppuration from the pockets, thus hiding dystrophic signs.

Periodontal dystrophy was observed in number of signs: recession of the gums (lowering of the level of marginal gingival), atrophy of interdental papilla with formation of pathological spaces between adjacent teeth, thinning, flattering paleness of the gums (Fig.1, 2). Patients complained on gums tightening, itching, increase sensibility to thermal, mechanical and chemical irritants. Because of large interdental spaces, lot of plaque and calculus accumulated on teeth surfaces. We observed Stilman's clefts from 1`-2 to 5-6mm long. In the bone of alveolar process pronounced dystrophic changes were found, which were probably caused by changes in blood and nervous supply. Radiographic examination of the bone of alveolar process showed horizontal bone loss and osteosclerosis but in deep parts of the bone osteoporosis and osteosclerosis alter-



Fig.1. Slowly progressing periodontitis, lInd-IIIrd stage of heaviness with changes of gingival contour and gums recession in patient S. 45-year-old female. Note the traumatic occlusion.



Fig. 2. Dystrophic changes in patient K., 37-year-old male. Note the prominent gingival recession.

nated with each other. Cortical plate of alveolar bone was preserved, in some places we observed its thickening. Narrowing of periodontal spaces and sometimes their complete absence (what testified to the presence of hypercementosis) were revealed. Abovementioned changes were present already in early stage of periodontosis, being more pronounced in II and III stages of the disease.

In patients with periodontosis with developed inflammation, radiographic examination besides dystrophic changes of alveolar process showed thinning and destruction of cortical plate of alveolar crests and foci of osteoporosis.

In patients with generalized periodontitis with presence of dystrophic component X-ray showed only single zones of osteosclerosis in different parts of interdental septa, which interchange with osteoporosis, prevailing in bone structure. These manifestatios of dystrophy was observed in 62,5% of patients only. It is important that number of interdental septa with vertical bone destruction in patients with periodontitis with clinical signs of dystrophy was less than in patients without dystrophic component. Thus, it is difficult to differentiate in X-ray patients with periodontosis, having inflammatory process and periodontitis patients with dystrophic component. This fact demands detail and precise radiographic estimations.

According to bacteriological investigations of feces of examined patients changes of intestinal microbiota have been detected in the majority of them. As it is shown in table II, in persons with I stage of GP normal condition of colon microbiocenosis was detected only in 28% of patients, in most patients ID of the I-II stages prevailed. It is characterized by lowering of the quantity of Bifido- and Lacto- bacteria, Escherichia Coli in the feces and presence of Escherichia species with reduced enzyme properties. Patients with I stage of periodontosis have similar changes of colon microbiocenosis, but number of patients with eubiosis (normal condition of colon microbiota) was 1,5 times lower when compared with periodontitis patients. In II-III stages of periodontosis as well as in II-III stages of periodontitis we didn't find patients with normal colon microbiocenosis. ID of III-IV stages were diagnosed 3-5 times more often in these patients, characterized by the high titers of conditional pathogenic microorganisms (CPM) and their associations with the background of normal intestinal microbiota changes. More pronounced these changes were in periodontitis patients of II-III degree of heaviness. Probably it is due to re-infection while swallowing contents of periodontal pockets. Hence, investigations of colon microbiocenosis in patients with periodontosis and generalized periodontitis revealed that development of both of these dystrophic-inflammatory diseases proceed against a background of existing and aggravation of colon disbacteriosis.

Some researchers pay attention to the importance of dysbacteriosis in the oral cavity for the development and treatment of periodontitis [4-6]. Number of investi-

gations [7 - 11] point out that presence of intestinal disbacteriosis (ID) leads to serious changes in the absorption of important nutrients in human organism (amino acids, vitamins, microelements, et al.), has negative influence on local and general immunity, many types of metabolic processes, change of the homeostasis. That is why lingering state of intestinal disbacteriosis (ID) should have an effect on the nutrition of periodontal tissues.

CONCLUSIONS

- 1. According to clinical and radiological findings numerous dystrophic changes were found in all structures of the periodontium and teeth of patients with periodontosis and generalized periodontitis. Changes intensify in disease progressing into the II-III stages.
- Characteristic signs of pathological gingival contour (gingivoglyphics) as well as other clinical-radiological peculiarities of dystrophy are different in patients with periodontosis and periodontitis and help to improve their differential diagnosis.
- In patients with periodontosis clinical- radiological peculiarities of dystrophy were revealed in early stages of disease progression, while in generalized periodontitis dystrophic changes become apparent in late stages of disease.
- 4. The presence of colon disbacteriosis was established in patients with periodontosis and generalized periodontitis. Disbacteriosis intensifies when diseases progress into II-III stages of heaviness. These data indicates to possible correlation between the development of dystrophic changes in periodontal tissues and the presence of intestinal disbacteriosis.

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INFECTIOUS MONONUCLEOSIS DURING THE WAR AND COVID INFECTION PANDEMIC IN UKRAINE

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ABSTRACT

The aim: To analyze the current views on diagnosis and management of infectious mononucleosis in children. The purpose of our work is also a comparative characteristic of the incidence of infectious mononucleosis in Ukraine and the city of Poltava (2006-2022).

Materials and methods: The data of scientific literature have been analyzed, using the bibliosemantic method of study. We used a retrospective analysis of statistical data on the incidence of infectious mononucleosis 2006-2022 and the most frequent cases of infectious pathology in children in the period 2019-2022, and also conducted an analysis of the percentage of those vaccinated according to the vaccination calendar.

Results: We had an increase in the incidence in 2009, but in subsequent years it was in the range of 23-25.2 per 100.000 children. The incidence of patients diagnosed with infectious mononucleosis per 100.000 of the children population in the Poltava region is one of the lowest in Ukraine, accounting for 8.1 - 10.1% over the past 3 years, which can be explained by the decrease in visits by parents and their children to the hospital to avoid contact with patients with the coronavirus disease and the fact that our region also had rather lower rates of children with Covid-19 compared in Ukraine.

Conclusions: the situation with the spread of infectious mononucleosis in children in Ukraine is such that it causes concern, and when comparing the incidence in 2009 and 2022, the authors noted an increase in the overall incidence of this nosology by 5%.

KEY WORDS: children, management, prophylaxis, infectious mononucleosis

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INTRODUCTION

Currently, the issue of infectious mononucleosis is relevant due to the following main factors: the rising incidence of morbidity in Ukraine over the past 3 years, the great variability of the clinical course of the disease and the complexity of specific diagnostics, which leads to a large percentage of diagnostic errors, the general infection with the Epstein-Barr virus (EBV), which can affect the immune system. Antibodies to EBV are detected in 15% of children under 1 year of age and 90% of adults.

All this is caused by a large number of risk factors: migration of the population from temporarily occupied territories, overcrowding of people in places of refuge from the war, changes in the quality of food, humanitarian difficulties, the action of chemicals, stress and immunosuppression. The war led to an increase in viral etiology and an increase in the share of children with secondary bacterial complications, a decrease in the percentage of vaccinated persons according to the vaccination calendar. We know that after such childhood infections as measles and chicken pox there is lifelong immunity, then infectious mononucleosis is a rather serious disease that affects the immune system, epitheliocytes of blood vessels, can turn into a chronic course and complicate the quality of life, causing concern to doctors.

THE AIM

The aim of the paper is to analyze the current views on diagnosis and management of infectious mononucleosis in children. The purpose of our work is also a comparative characterization of the incidence of infectious mononucleosis in Ukraine and the city of Poltava (2006-2022) against the background of an increase in infectious pathology in children and a decrease in the percentage of mandatory preventive vaccinations during the Covid-19 pandemic and martial law, as mediated factors affecting the increase of patients with the indicated nosology.

MATERIALS AND METHODS

We used a retrospective analysis of statistical data on the incidence of infectious mononucleosis 2006-2022 and the most frequent cases of infectious pathology in children in the period 2019-2022, as well as an analysis of the percentage of people vaccinated according to the vaccination calendar. The authors, as children's infectious disease specialists, cite one of the examples of a case from the history of the disease, which recently occurred in the children's infectious disease department of Poltava. The data of scientific literature have been analyzed, using the bibliosemantic method of study.

RESULTS

The disease was first described by N.F. Filatov in 1885 under the name "idiopathic lymphadenitis with fever". The causative agent of infectious mononucleosis is the Epstein-Barr virus (EBV), isolated in 1964 by Epstain and Barr from Burkitt lymphoma cells. It has been proven that EBV is widely disseminated and antibodies to the virus have been detected in all studied populations with the incidence rate of infection 80% to 90% of the population worldwide. The studies revealed great diversity in the time of primary infection and the stages of infection dissemination. Wealthy population of highly developed countries are most often infected at the age of 14-15 years, while the lower socioeconomic groups of population of developing countries is already infected in 70% -100% of cases by the age of 3-5 years. However, despite the general prevalence and contagion, there is a clinical diversity of diseases caused by the virus in different regions: infectious mononucleosis, nasopharyngeal carcinoma and Burkitt lymphoma predominate in Europe, Asian countries, and Africa, respectively. A detailed description of the symptoms of the disease and their combination refers to 1970-1975. Treatment of infectious mononucleosis remains symptomatic until now. Acyclovir, which has been successfully used for the treatment of other herpes infections, is ineffective. The appropriateness of antibiotic therapy is denied by a number of contemporary domestic and foreign authors.

EBV belongs to the herpesvirus family, genus γ-herpesvirus type 4. It is a DNA-containing virus. A mature virus has a spherical shape, contains a double-stranded DNA genome, a capsid, a protein, and a lipid outer shell. EBV has specific antigens: capsid (VCA), nuclear (EBNA), early (diffuse EAD and localized EAR), membrane (MA). During the acute infection, first, antibodies to early antigens (EA, VCA) appear, and then to nuclear ones (EBNA). Detection of antibodies to capsid (VCA) and nuclear (EBNA) antigens in the absence of antibodies to early antigens (EA) is the marker of persistent infection: latent infection. The spectrum of antibodies differs significantly in different diseases associated with EBV. Thus, patients with IM develop antibodies that belong to three classes of immunoglobulins, to various virus-specific antigens. Patients with Burkitt lymphoma have increased titers of IgG antibodies to EAR. Patients with nasopharyngeal carcinoma have increased titers of IgA antibodies to EAD and VCA. Antibody titers correlate with enlargement of the neoplasm and decrease in case of successful treatment.

The virus produces proteins that are analogs of interleukins that alter the immune response and suppress cellular immunity. There is a marker of the lymphoproliferative process on the X-chromosome, and the Epstein-Barr virus has a tropism for lymphoid tissue. An incorrect immune response due to abnormal genetic recombination can provoke an oncological process, Burkitt lymphoma, lymphogranulomatosis, etc. The DNA virus enters the cell, where the proliferation of lymphocytes occurs; this process is called immortalization (immortality of lymphocytes). In the acute phase, up to 20% of B-lymphocytes are affected. When the process is generalized and chronic, disturbances occur in T-lymphocytes, killer cells, and epitheliocytes of the vessels.

Ways of penetration into the child's body: airborne, sexual, vertical – from mother to child, hematogenous. The incubation period can range from several days to 1-2 months.

The following are the features of infectious mononucleosis in children:

- activation of the Epstein-Barr virus (EBV) can be caused by frequent acute respiratory infections, convulsive syndrome, neurological diseases, childhood infections [1];
- after the primary reaction, the diseases may not manifest itself and become chronic; it can be determined only by the markers;
- in the primary regional infection, lymphodenopathy, more often cervical and submandibular, is noted, and tonsillitis phenomena (from catarrhal to purulent inflammation) are apparent. Notably, tonsillitis without lymphadenopathy can be confused with infectious mononucleosis, although such cases could be possible;
- parenchymal dissemination is noted at the end of the 1st week: splenomegaly is less prominent compared to liver enlargement, as well as possible alterations in the myocardium, blood vessels, kidneys, lungs, and nervous system. Timing is crucial only for 30% of children;
- in young children, the disease may proceed as a respiratory disease;
- when the clinical picture is similar, but there is no serological confirmation, then infectious mononucleosis syndrome is possible, the causative agent of which can be measles, rubella, toxoplasmosis,

No.	Year	Number of cases	Morbidity per 100.000 of children population
1.	2006	50	23.71
2.	2007	58	28.39
3.	2008	54	27.18
4.	2009	69	35.17
5.	2010	63	28.47

Table I. Incidence of infectious mononucleosis in children of the Poltava region.

Table II. Vaccination coverage 2020-2022 in the Poltava Region and Ukraine

	2020) year	2021	2021 year		9 months 2022 year	
The name of the vaccination (revaccination)	Region %	Ukraine %	Region %	Ukraine %	Region %	Ukraine %	
Tuberculosis up to 1 year	95,6	88,8	88,7	88,8	71,4	43,0	
Whooping cough, diphtheria, tetanus under 1 year	89,8	80,1	90,6	80,1	72,5	46,9	
Whooping cough, diphtheria, tetanus in 18 months	92,1	78,1	91,6	78,1	72,7	46,1	
Diphtheria, tetanus of children in 6 year	58,7	59,7	83,8	59,7	69,3	46,6	
Diphtheria, tetanus of children in 16 year	90,4	73,6	92,2	73,6	65,8	43,4	
Diphtheria, tetanus in adults	76,6	47,0	75,0	47,0	52,3	24,2	
Poliomyelitis up to 1year	92,0	83,0	89,7	83,0	89,7	83,0	
Poliomyelitis at 18m.	92,7	83,0	91,5	83,0	91,5	83,0	
Poliomyelitis at 6 years	92,2	81,7	89,1	81,7	89,1	81,7	
Poliomyelitis at 14 years	92,5	81,8	91,2	81,8	91,2	81,8	
Measles, mumps, rubella 1 year	94,8	83,3	96,6	83,3	96,6	83,3	
Measles, mumps, rubella at the age of 6m.	92,0	83,4	92,8	83,4	92,8	83,4	
Hepatitis B-3 up to 1year	91,8	79,8	91,0	79,8	91,0	79,8	
Hemophilic infection of children up to 1 year	91,2	85,1	93,1	85,1	93,1	85,1	

hepatitis B virus, HIV infection, adenovirus infection, cytomegalovirus infection;

 it is also necessary to take into account the possibility of simultaneous human infection with several causative agents of the family of herpesviruses: coand superinfection. Among patients, in 2% of cases, the clinical course of the disease takes the form of combined EBV- and CMV-infectious mononucleosis.

Children with severe immune deficiency may develop generalized forms of EBV-infection with damage to the central and peripheral nervous system in the form of meningitis, encephalitis, and polyradiculoneuritis. Duncan syndrome belongs to a group of hereditary diseases that appear in men after EBV infection. The prognosis of the disease is very unfavorable, more than 70% of patients die before reaching 10 years of age. Survivors often develop severe hypogammaglobulinemia, lymphoblastic lymphoma, less commonly aplastic anemia, and necrotizing vasculitis with damage to arteries and large vessels [2].

Our attention was drawn to the problem of the increasing tendency of infectious mononucleosis among children in 2020-2022 in Ukraine. There are many scientific works and studies on the coronavirus disease, but the authors did not find publications about how often children get sick with infectious mononucleosis after suffering from Covid-19, so we share observations from our own experience of working as a pediatric infectious disease specialist.

Under the Covid-19 pandemic, coronavirus infection (pneumonia of a new type) was first diagnosed on March 3, 2020 in Chernivtsi. On March 13, the first death associated with coronavirus infection was recorded. As of October 24, 2022, there were 5,279,346 (12.8%) sick people in Ukraine, of which 109,819 (2.1%) died. Distribution of those infected with COVID-19 in Ukraine by the age of 0-17 years is 5.00%, 18-29 years is 11%, 30-49 years is 37%, 50-69 years is 38%, 70 years and older is 9%.

In April 2020, several European countries reported an increase in cases of Kawasaki-like syndrome among children. Kawasaki syndrome is a disease that is diagnosed mainly in infants and children under the age of five. However, the new multisystem inflammatory syndrome, which the experts have linked to COVID-19, also occurs in older children, accompanied by high fever, rash, swelling, inflammation affecting the eyes, blood vessels and heart, as well as infectious-toxic shock [3].

A recent study of 186 children with multisystem inflammatory syndrome showed that the average age of patients was 8.3 years; 73% of children were previously healthy, the rest had laboratory evidence of SARS-CoV-2 infection (PCR and/or antibodies). Gastrointestinal (92%), cardiovascular (80%), hematological (76%), skin-mucosal (74%) and respiratory (70%) symptoms were observed in children [4]. But these complications are minor in Ukraine. The coronavirus in children most often occurs in a mild form or without symptoms, but it still leads to a decrease in the body's resistance to other infections for a certain time [5].

According to the authors, this can be material for further research by scientists on the incidence of infectious mononucleosis after a history of coronovirus disease, as a pathological chain is observed - "virus-immune system-vascular epitheliocytes-cells-RNA".

Scientists have investigated:gene polymorphism, coding the host proteases, which are involved in the virus entry into the cells can influence the susceptibility to and mortality from coronavirus disease 19 (COVID-19). Our study indicated the presence of an association between the tmprss2 rs12329760 polymorphism and the severity of COVID-19 in the Ukrainian population [6].

Activation of the infection, infectious mononucleosis, is facilitated by the factors that reduce general and local immunity. The authors drew attention to statistical data on the incidence of infectious mononucleosis among children in previous years (Table I).

We had an increase in the incidence in 2009, but in subsequent years it was in the range of 23-25.2 per 100.000 children (Table I). In January 2021, the incidence was 28.1 per 100.000, and in January 2022 it was 29.2. We noted an increase by 5% in the incidence of infectious mononucleosis in Ukraine. The findings can be useful for further research on the relationship of the activation of the above infection in individuals who were sick or had an asymptomatic course of Covid-19. The incidence of patients diagnosed with infectious mononucleosis per 100.000 of the children population in the Poltava region is one of the lowest in Ukraine, accounting for 8.1 - 10.1% over the past 3 years, which can be explained by the decrease in visits by parents and their children to the hospital to avoid contact with patients with the coronavirus disease and the fact that our region also had rather lower rates of children with Covid-19 compared to other regions of the country.

The authors noted that 8 children in 2022, who had a previous diagnosis of infectious mononucleosis, were

transferred to other specialized departments with multiple complications, pneumonia, coronavirus disease, diabetes, which can be explained by a decrease in immunity due to the stressful situation in the population in the last year. In 2022, the number of refusals from hospitalization for 1-3 days increased due to the complications of the war and the fear of parents for the life of the child when staying in institutions with increased crowding. The number of children discharged with improvement due to parents' desire to continue treatment in outpatient settings has increased. Scientists know that an increase in the incidence of infectious mononucleosis can also be caused by other commonly transmitted infectious diseases. In 2018, we had a measles outbreak due to a decrease in the number of people vaccinated.

The authors state that children whose parents refused vaccinations according to the calendar had a history of measles, chicken pox, and frequent colds. They were more often infected with infectious mononucleosis due to triggered immunity.

According to official data, that the increase in the incidence of measles in the Poltava region [7] and in Ukraine as a whole was preceded by years with a rather low coverage of the population with vaccination against this disease.

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 [8].

New challenges have arisen today due to stress, nutritional disorders during military operations. The authors are concerned that we are observing a tendency towards a decrease in preventive vaccinations during 2020-2022, in particular against diphtheria, poliomyelitis, and tuberculosis [9].

We have come across reports of a fiery outbreak of diphtheria in September 2022 in one of the western regions of Ukraine. The authors indicate these data to emphasize that even among controlled infections with the help of vaccinations, fiery outbreaks were observed in Ukraine during the specified period. But serious concern is caused by adverse trends in the health of children among the incidence of uncontrolled infection - infectious mononucleosis.

Specific prevention has not been developed against infectious mononucleosis, but we have a decrease in the percentage of vaccinations in Ukraine due to the war, covid disease (Table II).

It is known that, in most cases, the disease is caused

by specific causes (causing agents) independent of the person, but a certain proportion of this disease occurs due to non-compliance with the correct lifestyle and neglect of the principles of hygiene (after all, this is also a disease of kisses), vaccination, as a way of protection against controlled infections and prevention of immunodeficiency and probable infection of this not highly contagious infectious mononucleosis. In this regard, special attention should be paid to the problem of preventive measures and recommendations for indirect prevention of the development of this pathology. The authors present the data in Table II, where we clearly observe a decrease in the percentage of vaccinations among the child population during the last 2 years, which may cause an increase in the incidence of these diseases, according to immunodeficiency and the mediated occurrence of infectious mononucleosis. Scientists know that up to 90% of people become infected with viruses of the herpes family (which includes the Ebstein-Barr virus) during their lifetime, but 15%, who probably have reduced immune resistance, get sick (Table II). So, this is another reason for concern and further study of the trend towards an indirect increase in the incidence of infectious mononucleosis in 2020-22 by 5% in Ukraine.

DISCUSSION

We present a clinical case of a young female patient with a diagnosis of infectious mononucleosis who received treatment at the children's infectious unit in Poltava city. On August 17, 2022, the 15-year-old female patient S. was admitted to the First City Clinical Hospital with complaints of an increase in body temperature to 37.8, sore throat, difficulty breathing through the nose, general weakness, and loss of appetite. From the past medical history, it is known that she has been ill since 08/12/22, when the fever and sore throat appeared and nasal breathing became difficult. It is also known that it grew and developed according to age. The child had infectious diseases often. It is known that the parents have had coronavirus infection six months ago. Vaccinations according to the calendar were carried out only at 1 year of life, the parents refused the following ones.

The girl received outpatient treatment (symptomatically) that was not successful. During the examination, the child's condition was moderate due to intoxication syndrome. Body temperature was 37.8, clear consciousness, moderately lethargic. Bed status was active. Normosthenic physique. Nutrition was satisfactory. Soft tissue turgor was preserved. The skin was pale, clean. Visible mucous membranes were clean, normal color. The mucous membrane of the oropharynx was

hyperemic, the tonsils were enlarged, purulent masses in the lacunae were removed with a spatula, no bleeding. No swellings were noted. Swallowing was not impaired. Enlarged lymph nodes: submandibular - 2.0 x 1.5 cm, painless, mobile, not fused to the skin and surrounding tissues; posterior-cervical - 1.0 cm, in the form of a "chain", the rest were small. The skin over them was not changed. Breathing through the nose was difficult. The respiration rate was 18 breaths per minute. Over the lungs: percussion-pulmonary sound; auscultatory: breathing was vesicular, no wheezes. The boundaries of the heart were not changed. Auscultation revealed clear heart sounds, the rhythm was normal. The heart rate was 90 beats per minute. The tongue was wet with a white coating. The abdomen was soft, painless on palpation, involved in the act of breathing. Liver +1.0 cm, spleen -. Feces were normal. Urination was painless, diuresis was sufficient. Pasternatsky's symptom was negative on both sides. Meningeal signs were negative. No focal neurological symptoms were detected. Laboratory tests (made on 17/08/22) showed: CBC: RBC=4.42x10¹²/L, Hb=129g/L, WBC=9.2x10⁹/L, ESR=40mm/h, eosinophils=1%, stab=2%, segmental=26%, lymphocytes=49%, monocytes=7%, atypical mononuclear cells=14%, platelets= 328x10³/L. Blood biochemical tests (made on 18/08/22) showed: total bilirubin=10.1µmol/L, direct bilirubin:=3.110¹²/L, indirect bilirubin=7.0x10¹²/L, AIAT=265 units, AsAT=145 units, urea= 3.1g/L, total nitrogen=20g/L, creatinine=20 µg/l, glucose=5.0 mmol/l. Urinalysis (made on 17/08/22) showed: light yellow color, clear, density=1020, acid reaction, RBC= 2-6 FOV, WBC= 0-1 FOV, few epithelia, mucus, no salt; Tests for viruses of the herpes-group (made on 18/08/22) showed: ELISA IgM VCA EBV: positive. Nasal smear for eterobiosis (made on 17/08/22): not detected. Fecal worm egg counts (made on 17/08/22): not detected. Nasal and oropharynx smear for BL No.73-74 (made on 17/08/22): negative. Oropharynx smear for microflora and sensitivity to antibiotics No. 948 (made on 17/08/22): Citrobacter freundi. ECG (made on 19/08/22) showed: sinus arrhythmia, heart rate was 57-100 beats per minute. Vertical position of the electrical axis of the heart. Violation of the processes of repolarization of the apical-lateral area of the left ventricle. The treatment was provided: 1000 mg ceftriaxone twice a day No. 7, herpevir, probiz, loratadine, chlorophyllipt, nasal irrigation with saline solutions, intravenous drip: 0.9% sodium chloride solution, dexamethasone, 4% glutargin solution, 5% glucose solution. She was discharged with improvement on 08/25/2022 at her mother's insistence with the follow-up treatment recommendations: supervision of a pediatrician for 12 months; adherence to the diet No.5 for 6 months, exclusion of the physical activity and insolation for 12 months; home stay for 1 month; continue treatment with: probiz 1c twice No.15, 400 mg lipster 4 times for 7 days, 500 mg/day ukrliv for 1 month. Blood biochemistry test, blood test (liver and kidney tests) after 1 month and if necessary. PCR blood DNA EBV after 1 month, once in 3 months up to 12 months. Scheduled abdominal ultrasound and ECG. Examination by a pediatrician (infectiologist) after 1 month, once in 3 months up to 12 months. Scheduled examination by a cardiologist.

CONCLUSIONS

Therefore, there are many indirect risks that increase the possibility of contracting infectious mononucleosis - frequent infectious diseases, due to refusal of vaccination, stress, immunodeficient state, which will reduce the resistance of the body against the Ebstein-Barr virus. The situation with the spread of infectious mononucleosis in children in Ukraine is such that it causes concern, and when comparing the incidence in 2009 and 2022, the authors noted an increase in the overall incidence of this nosology by 5%. Preventive measures are very important to prevent the development of this category of disease. Vaccination against other viral diseases refers to secondary prevention factors that can be influenced by preventing immunosuppression and reducing the risk of infection with the Ebstein-Barr virus.

The development of a vaccine against infectious mononucleosis is a promising direction to overcome this problem as a necessary motivator to maintain health at a young age. Thus, pediatricians, family doctors, infectiologists should carry out prophylaxis among the population regarding infectious mononucleosis, coronavirus infection as it is a reliable measure of preventing morbidity and reduction.

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ORIGINAL ARTICLE

CARBOHYDRATES METABOLISM IN THE BLOOD OF RATS WITH IMPAIRED GLUCOSE TOLERANCE UNDER LONG TERM MELATONIN INJECTIONS

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ABSTRACT

The aim: To determine the influence of melatonin on the glucose level and content of malondialdehyde, activities of pyruvate kinase and glucose-6-phosphate dehydrogenase enzymes in the blood; histochemical features of glycogen distribution in liver of rats with impaired glucose tolerance.

Materials and methods: Diabetes in rats was induced by intra-abdominal injection of a 5% solution of alloxan monohydrate at the rate of 170 mg/kg of body weight. Four days after animals were divided into rats with impaired glucose tolerance and melatonin-group with impaired glucose tolerance (5 mg/ kg «Sigma» USA, daily and intraperitoneal for 42 days starting from 5th day). Impaired glucose tolerance was determined by measurement of glucose profiles - fasting <5.6 mmol/l; postprandial (2h post-load) 7.8 – 11.0 mmol/l. Histochemical examination of the liver was performed according to the standard method of PAS-reaction staining. Statistical analysis was performed using Statistica 10 StatSoft Inc.

Results: Pyruvate kinase activity in erythrocytes and optical density of glycogen in hepatocytes of animals with impaired glucose tolerance decreased on 18% and 11%, activity of glucose-6-phosphate dehydrogenase and content of malondialdehyde increased on 35% and 23%, respectively compared with the control. We have reached the recovery of the pyruvate kinase and normalization of glucose-6-phosphate dehydrogenase activities, malondialdehyde levels, glucose profiles in the blood as well as glycogen distribution in the liver caused by melatonin injections.

Conclusions: We have determined that long term melatonin injections did better glucose tolerance in rats.

KEY WORDS: alloxan-induced diabetes mellitus, antioxidant, glucose concentration

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INTRODUCTION

There are evidences that impaired glucose tolerance (IGT) is a risk factor for cardiovascular disease [1]. Melatonin has potent antioxidant properties, and it has proven to be highly effective in a variety of disorders linked to inflammation and oxidative stress.

Hyperglycemia-mediated oxidative stress plays a key role in diabetic complications [2].

In the presence of intracellular thiols, especially glutathione, alloxan generates reactive oxygen species in a cyclic redox reaction with its reduction product, dialuric acid. Autoxidation of dialuric acid generates superoxide radicals, hydrogen peroxide and, in a final iron-catalysed reaction step, hydroxyl radicals. These hydroxyl radicals are ultimately responsible for the death of the beta cells. [3].

To prevent complications in patients with diabetes mellitus blood glucose concentration should be taken under control [4]. This is possible by the investigation of glucose degradation pathways. The main are glycolytic and pentose phosphate pathways of glucose-6-phosphate oxidation. Here are some enzymes: pyruvate kinase and glucose-6-phosphate dehydrogenase, which are regulatory in both ways respectively. Pyruvate kinase enzyme is controlling the reaction of substrate level phosphorylation, while glucose-6-phosphate dehydrogenase enzyme is responsible for NADPH₂ generation. This processes of carbohydrates metabolism have to be corrected in condition of oxidant stress under diabetes mellitus conditions. Malondialdehyde is one of the main indicator of oxidant stress in the blood and tissues because it is one of several end products formed through the decomposition of lipid peroxidation products.

THE AIM

The aim was to determine the influence of melatonin on the glucose level and content of malondialdehyde, activities of pyruvate kinase and glucose-6-phosphate dehydrogenase enzymes in the blood; histochemical features of glycogen distribution in liver of rats with impaired glucose tolerance.

MATERIALS AND METHODS

Research performed in compliance with the Rules of the work using experimental animals (1977) and the Council of Europe Convention on the Protection of Vertebrate Animals used in experiments and other scientific purposes (Strasbourg, 1986), according to directions of International Committee of Medical Journals Editors (ICMJE), as well as "Bioethical expertise of preclinical and other scientific research conducted on animals" (Kyiv, 2006). Experiments were conducted on 50 sexually mature male rats with a body weight of 0.18 - 0.20 kg. Diabetes was induced by intra-abdominal injection of a 5% solution of alloxan monohydrate at the rate of 170 mg/kg of body weight [3]. The GTT (glucose tolerance test) measures changes in blood glucose concentration over a 2-h period following the administration of a bolus of glucose. Animals were divided into 3 groups: 1) control group; 2) group with IGT (fasting plasma glucose (FPG) <5.6 mmol/l; postprandial glycemia (2-h post-load) 7.8 - 11.0 mmol/l)); 3) animals with IGT, which were injected with melatonin. Melatonin (Sigma, USA) was injected intraperitoneally at the rate of 5 mg/kg of body weight daily for 42 days, starting on the 5th day after the injection of alloxan. Blood was taken from the tail vein to assess glycemia level using OneTouchUltra (LifeScan, USA). Rats were sacrificed on the 47th day of experiments. Blood was taken to determine the activity of the enzymes glucose-6-phosphate dehydrogenase (G6PD), pyruvate kinase (PK) by standard methods [4]. The method of malondialdehyde (MDA) investigation [5] is based on a spectrophotometric determination of the trimetinic colored complex formed from the malonic aldehyde interaction with thiobarbituric acid.

The liver was fixed in a 10% neutral buffer solution of formalin. Next, the pieces of tissue were dehydrated and embedded in paraffin according to standard methods. Tissue sections 5 µm thick were obtained on a sled microtome. Histochemical examination of the liver was performed according to the standard method of PAS-reaction staining (with amylase control), additional staining of cell nuclei was not performed to ensure the purity of specific staining [6]. In order to objectify quantitative studies of glycogen concentration, computer microdensitometry was performed in histochemical preparations. To do this, digital copies of the optical image of the sections of the microscopic preparations were first obtained in TIFF graphic format using an Olympus C740UZ digital camera using a 40x objective and a 10x microscope eyepiece.

Statistical analysis was performed using Statistica 10 StatSoft Inc. To determine an adequate method of statistical estimation of the average difference between the study groups held preliminary check distribution quantities in samples. According to the criteria Shapiro-Wilk, which is used to assess the normality of distribution in the sample volume $n \le 50$, all samples not received data on deviation of the distribution of samples from normal (P>0.05). Given these data, the use of Mann-Whitney test was considered sufficient for valid conclusions. Differences were considered to be statistically significant at P ≤ 0.05 .

RESULTS

In accordance with results rats were classified into two groups according to the glucose tolerance status as having normal glucose tolerance when FPG was < 7.0 mmol/L (120 mg/dL) and 2-h post-load < 7.8 mmol/L (140 mg/dL) – to these group belong rats without alloxan injection; IGT when FPG was < 5.6 mmol/L (100 mg/dL) and 2-h post-load was 7.8–11.0 mmol/L (140–199 mg/ dL). These was estimated in accordance to the American Diabetes Association criteria [7]. In group of IGT rats: 2-h post-load plasma glucose level was higher on 28% in comparison to respective index of control. Impaired glucose tolerance in the blood of alloxan diabetic rats under long term melatonin injections on 47th day was stabilized (Fig 1.), glucose levels did not differ from control.

Melatonin injections caused a sharp decrease in average by 52% and normalization (on 47th day) in the elevated serum glucose levels (2-h and 3-h post-load) in IGT group of rats compared with respective glucose levels before treatment.

The decrease in the optical density (Table I) of glycogen in hepatocytes and cytoplasm of Kupffer cells in the group of animals with IGT was somewhat less pronounced and was 10% and 18% lower, respectively, than in control rats.

Characteristic for this group of animals was an increase in the deviation of the brightness of glycogen in hepatocytes compared to the control by 30%, a redistribution of glycogen (Figure 2) in the cytoplasm of hepatocytes into large grains was observed. The last indicator in the cytoplasm of Kupffer cells showed a probable tendency to decrease by 5%, compared to the indicator of control animals.

During the histological examination (Table I) on the 47th day after the introduction of alloxan in the liver of animals with IGT (Fig. 2), changes in the distribution of glycogen due to vacuolization of the cytoplasm of hepatocytes (although not everywhere) and large granularity (in a small amount) are observed, compared to the control indicators (Fig 4).



Fig. 1. Glucose tolerance profiles in rats with impaired glucose tolerance under long term melatonin injections on 47^{th} day. Blood plasma glucose, mmol/L (n=6, x±Sx) :

1. Changes are reliable ($p \le 0,05$).

2. a - concerning intact rats (control); b - concerning IGT.

Table I. Quantitative indices of glycogen distribution in rat liver cells in different groups under study (n=6, x±Sx).

	Hepat	ocytes	Kupffe	Kupffer cells		
Indexes Groups	Optical density (Units of Optical density)	Brightness deviation (unites)	Optical density (Units of Optical density)	Brightness deviation (unites)		
Control	0,302±0,0038	3,2±0,06	0,336±0,0043	3,9±0,05		
IGT	0,271±0,0035ª	4,2±0,08ª	0,278±0,0039ª	3,7±0,06ª		
IGT + melatonin	0,293±0,0044 ^b	4,1±0,08ª	0,271±0,0043ª	3,4±0,08ª		

Glycogen distribution in rat liver cells (n=6, $x\pm Sx$):

1. a, b - changes are reliable ($p \le 0,05$).

2. a - concerning control rats; b - concerning rats with IGT.

In a group of animals with IGT, under the influence of exogenous melatonin administration, the optical density of glycogen in hepatocytes was normalized (this indicator exceeded the corresponding index of IGT group of rats by 8%) (Fig 3). Whereas the brightness deviation was significantly unchanged compared to untreated animals and remained significantly higher by 28% compared to control, respectively.

The optical density of glycogen in the cytoplasm of Kupffer cells, in this group of animals, did not differ from the indicators of the untreated rats and remained lower by 19% in comparison with the indicators of control animals. The brightness deviation decreased by 12% compared to the values of control rats.

PK is an enzyme of glycolytic cleavage of glucose with the formation of pyruvate and synthesis of ATP. Under conditions of physiological norm, pyruvate goes further into the process of pyruvate dehydrogenase complex, but under conditions of insulin deficiency, it is transformed into lactate.

According to results (Fig 5), we've got, the activity of PK in blood of IGT group was 18% less than in control group. The activity of this enzyme was recovered by

melatonin action, it went higher on 15% and was not differ from control.

As we have mentioned before (Fig 5) the activity of PK in erythrocytes of animals with IGT decreased by 18% and same time activity of G6PD (Fig 6) increased on 35% respectively compared with the control. The changes may be the result of less insulin production due to disturbances in free radical mechanisms caused by alloxan monohydrate injection and an inhibition of pyruvate dehydrogenase activity. We have reached the recovery of the PK and normalization of the G6PD activities in the blood of diabetic rats by melatonin injections compared to control. Impaired glucose tolerance in the blood of alloxan diabetic rats under long term melatonin injections was stabilized and blood glucose levels did not differ from control.

The level of MDA (Fig. 7) was found to be higher on 23% in IGT group than in control. So, the lipid peroxidation was increased in diabetic rats with IGT. Melatonin prevented diabetes-induced increase in MDA levels in blood of IGT rats compared with control. It may be explained by powerful antioxidant function of melatonin.



Fig. 2. Liver of a rat with IGT.





Fig. 4. Liver of a control rat. PAS reaction. Lens $40.\times$ Eyepiece $10\times$.

DISSCUSION

We have found a hypoglycemic effect of melatonin. It can be associated with the ability to activate glucose transporters in peripheral tissues. Moreover, there are known studies where the relationship between circadian rhythm disturbances (disorder of melatonin secretion) and the occurrence of metabolic syndrome are established [8]. It means hyperglucemia conditions and loss sensitivity to insulin.

The effects of melatonin on insulin secretion are mediated through the melatonin receptors (MT1 and MT2). It is possible that melatonin increases the secretion of



Fig. 5. Pyruvate kinase, mkmol/min×mg in blood (n=6, x±Sx):

- 1. a, b changes are reliable ($p \le 0,05$).
- 2. a concerning control rats;
- b concerning rats with diabetes mellitus.



Fig. 6. Glucose-6-phosphate dehydrogenase, nmol/min×mg (n=6, x±Sx): 1. a, b - changes are reliable (p \leq 0,05). 2. a - concerning intact rats; b - concerning rats with diabetes mellitus.





x±Sx): 1. a, b - changes are reliable (p≤0,05).

2. a - concerning intact rats;

b - concerning rats with diabetes mellitus.

insulin and restores the supply of glucose to the cells acting through calcium ions [9].

The positive effect of exogenous melatonin on the state of hepatocytes and the content of glycogen is probably due to its antioxidant properties and ability to stimulate the absorption of glucose by tissues, increase the concentration of ATP and stimulate the deposition of glycogen in tissues.

It is well known that PK enzyme activity is up regulated by insulin. Decrease in activity of PK, that we have determined, can be explained by insufficiency of insulin action. The introduction of melatonin normalized the enzyme activity. The increase of PK function can be explained by enhancing mitochondrial function (including of activation of pyruvate dehydrogenase complex) and protecting nuclear and mitochondrial DNA caused by melatonin injections [10].

Melatonin often function by inhibiting hypoxia-inducible factor-1a leading to pyruvate dehydrogenase complex disinhibition allowing for intramitochondrial conversion of pyruvate into acetyl coenzyme A. Melatonin is a glycolytic which converts diseased cells to the healthier phenotype [11]. Thus, melatonin has potential to regulate glucose homeostasis through activation of glycolysis in blood of diabetic rats.

Our results have shown that activity of G6PD is increased under condition of impaired glucose tolerance. This is happened because in condition of high glucose consumption cell is producing energy through aerobic glycolysis in cytosol without mitochondrial reactions of pyruvate dehydrogenase complex and citric acid cycle. This way is resulted in formation of lactic acid. It provides advantages because of the rapid production of ATP and the activation of pentose phosphate pathway which provides nucleotides required for elevated cellular metabolism. Moreover, this pathway is needed for recovery of glutathione that uses NADPH, taken from G6PD reaction. Under melatonin action the activity of G6PD is normalized. Possible this is because the pro- and antioxidant components as well as glucose concentration in the blood get balanced after melatonin treatment: glucose enters peripheral tissues through opened glucose channels, damage of β -cells of Langergans islets are stopped by activation of glutathione system of antioxidant defense.

Diabetes mellitus produces disturbances in the lipid profile of body making the cells more susceptible to lipid peroxidation. Experimental studies show that polyunsaturated fatty acids in cell membrane are extremely prone to attack by free radicals due to the presence of multiple bonds. Lipid hyperperoxides through intermediate radical reactions produce such fatty acids that generate highly reactive and toxic lipid radicals that form new lipid hyperperoxides (Matough et al., 2012). A critical biomarker of oxidative stress is Lipid peroxidation which is the most explored area of research when it comes to reactive oxygen species (Hatice et al., 2004). MDA are formed as a result of lipid peroxidation that can be used to measure lipid peroxides after reacting it with thiobarbituric acid [12].

We have estimated that the lipid peroxidation was increased in diabetic rats with IGT by the increase level of MDA in blood.

Diabetes may cause myocardial cell damage and eventually lead to the development of diabetic cardiomyopathy [1]. It is a disease caused by diabetes that is independent of coronary artery disease, hypertension and heart valve disease. The main characteristics caused by oxidative stress, cardiac hypertrophy, apoptosis, myocardial fibrosis and impaired cardiac function. Melatonin, a potent antioxidant agent, is essential for glucose homeostasis and regulation.

Melatonin prevented diabetes-induced increase in MDA levels in blood of IGT rats compared with control. It may be explained by powerful antioxidant function of melatonin.

As an antioxidant, melatonin exhibits several unique features which differ from the classic antioxidants. These include its cascade reaction with free radicals and its capacity to be induced under moderate oxidative stress. The antioxidant capacity of melatonin has been compared with other antioxidants including vitamin C, vitamin E, glutathione and NADH in both in vitro and in vivo conditions. In most cases, melatonin is superior to these molecules. Of particular note is the ability of melatonin to protect cells against oxidative stress more efficiently than other antioxidants under in vivo conditions [13]. An important reason for this is its cascade reaction with reactive oxygen and nitrogen species. Thus, the products (or metabolites) of melatonin following its interaction with reactive oxygen and nitrogen species retain the ability to scavenge free radicals. In this respect, one melatonin molecule has a capacity to detoxify numerous toxic reactive oxygen or nitrogen species. In contrast, the scavenging ratio of other antioxidants with reactive oxygen or nitrogen species is 1:1 or less.

Possible link between melatonin and insulin interaction may be in its protective effect against free radical attack of β -cells Langergans islets in pancreas [14].

Melatonin has been effectively used to combat oxidative stress, inflammation and cellular apoptosis and to restore tissue function in a number of human trials; its efficacy supports its more extensive use in a wider variety of human studies [10].

CONCLUSIONS

We found the changes in glucose tolerance profiles and pyruvate kinase and glucose-6-phosphate dehydrogenase activities in the blood of rats with impaired glucose tolerance. These show impairments in glycolytic and pentose phosphate pathways of glucose-6-phosphate oxidation in rats with impaired glucose tolerance. These was accompanied by increased lipid peroxidation processes which resulted in accumulation of malondialdehyde in the blood of diabetic rats.

In rats with impaired glucose tolerance, we observed a decrease in the optical density of glycogen in hepatocytes and the cytoplasm of Kupffer cells.

We have determined that long term melatonin injections did better glucose tolerance in rats with impaired glucose tolerance by maintaining the carbohydrate metabolism in the blood and glycogen in the liver. These may be useful evidence in protection against diabetic complication such as cardiovascular diseases or others.

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BIOMECHANICAL STUDY OF MINIMALLY INVASIVE TECHNIQUES IN SURGICAL TREATMENT OF THE TIBIA PROXIMAL EPIMETAPHYSIS FRACTURES

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ABSTRACT

The aim: Improving efficiency of the tibia proximal epimetaphysis fractures treatment by introducing minimally invasive techniques using the up-to-date metallic constructions

Materials and methods: The study is based on the results of examination and treatment of 119 patients, using arthroscopic technique. The results were evaluated regarding the P. Rasmussen scheme, post-traumatic arthrosis – Kellgren – Lawrence, life quality - «SF-36 Health Status Survey»

Results: The offered treatment method provided for the following: good outcomes in BI– 94.1%, satisfactory ones – 5.9%; respectively in BII – 91.7%, 8.3%; BIII – 92.9%, 7.1%; CI- 87.5%, 12.5%; CII – 91.7%, 8.3%; CIII – 88.9%, 7.4%, unsatisfactory outcomes – 3.7%

Conclusions: The tibia proximal epimetaphysis fractures make up from 8.9% to 11% of all lower leg fractures and up to 87% of the knee joint fractures. Such fractures are accompanied with the knee joint soft tissue injuries in up to 56% of cases. The meniscus injury is diagnosed in 50-94% of the patients; collateral ligament injury: 20% - 83%; anterior cruciate ligament injury : 20% - 69%, femoral muscle ligament injury – up to 47%, joint capsule ruptures – up to 75%, fibular nerve injury – 3% of cases. The treatment fails in 24.2-50% of cases. Operative treatment of such injuries using arthroscopic method provides for mini-invasive intervention character, visualizing and splint reposition control; the opposite compression screw provides for strong fixation.

KEY WORDS: tibia proximal epimetaphysis fractures, arthroscopic method, study of biomechanica

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INTRODUCTION

The tibia proximal epimetaphysis fractures make up from 8.9% to 11% of the lower leg fractures and up to 87% of the knee joint fractures. In this group, lateral process fractures make up from 52% to 80% of cases, medial process fractures – up to 7% and multifragmental fractures – 41% of cases. The incidence of such fractures abruptly increases with age of the patients – 1% of all factures in the young patients and 8% in the elderly ones[1, 2].

Such fractures are accompanied with the knee joint soft tissue injuries in up to 56% of cases. The meniscus injury is diagnosed in 50-94% of the patients; collateral ligament injury: 20% - 83%; anterior cruciate ligament injury : 20% - 69%, femoral muscle ligament injury– up to 47%, joint capsule ruptures – up to 75%, fibular nerve injury – 3% of cases[3, 4].

The treatment of the tibia proximal epimetaphysis fractures fails in 24.2-50% of cases [4,5].

The treatment of the tibia proximal epimetaphysis fractures, particularly of the intra-articular ones, despite some positive tendencies, still makes a relevant issue, as early resuming movements in the joint, which will not be complicated with secondary dislocation, is possible only with sufficient attachment and fixation of the joint surface fragments. In case of the fracture types A, B1, C1, B2 and C2 by AO classification the steady bone fragment osteosynthesis is rather efficient for providing early motion in the joint, but in case of B3 and C3 fracture types the recalled treatment principles are hard to implement with traditional techniques of external osteosynthesis, and even harder- with conservative treatment. In multifragmental fractures with affected joint surface, the small fragment size doesn't always provide for steady osteosynthesis with external constructions. In such case, early motions are contraindicated, and, as a rule, there arises necessity of additional external immobilizing, which leads to functional deterioration [5, 6].

Apart from this, the intra-articular injuries present a significant factor of the knee joint osteoarthrosis. The expressed pain syndrome, joint functional capacity restrictions and often exacerbations provide for the decreased workability (on average, in 60% of cases), leading to disability (11.5%) [1, 7].

So, despite achievements in the tibia proximal epimetaphysis fractures treatment by modern conservative and operative methods, the remote results don't satisfy patients and orthopedic traumatologists, so further studies are required, making the issue one of the most significant medical and social problems.

THE AIM

The aim was to improving efficiency of the tibia proximal epimetaphysis fractures treatment by introducing minimally invasive techniques using the up-to-date metallic constructions.

MATERIALS AND METHODS

The study includes 119 patients with the tibia proximal epimetaphysis fractures: 36 females (30.3%) and 83 males (69.7%), with average age 49±3 years. The proximal epimetaphysis fractures due to high-impact trauma were observed after road accidents in 50.4% of cases (60 patients), after falling from a height – in 24.4% (29), due to low-impact trauma – 25.2% (30). The skin traumas (of various severity) were stated in 15.0% of cases (19 patients), knee joint ligament traumas – in 40.3% (48), meniscus traumas – in 73.9% (88), vascular-nervous structure injuries - in 2,4% (2), compartment- syndrome – in 5.9%.

AO/ASIF classification was used for the data analysis [7, 9]. The STORZ apparatus was used for arthroscopic diagnostics and treatment, with its basic components: Halogen 250 twin 201133 20, EndovisionXL 202800 20, Multidrivell 207121 20, Arthropump 283300 20, ColourvideomonitorTM-1700 PN, as well as required instruments.

Clinical, general laboratory and roentgenological (traditional, if necessary- CT, MRI) examination procedures were conducted. The remote results were evaluated regarding the P. Rasmussen scheme, post-traumatic arthrosis –Kellgren – Lawrence, life quality - «SF-36 Health Status Survey».

The aim of the anatomic-biomechanical experiment was defining validity of the tibia proximal epimetaphysis fractures attachment using standard and opposite compression screws designed by the authors. Testing of the bone-attachment system was done using the universal testing machine TIRAtest-2151, which is shown in Fig. 1.

The universal testing machine TIRAtest-2151 was used by the authors to detect firmness and material deformation parameters when stretching, pressing and bending them. The advantages of the facility are as follows:

- Microprocessor registering and processing the results;
- Cyclic load regimen testing which is regulated by the microprocessor; automatic detection of the characteristics registered in printed testing protocol and confirmed by statistical data;
- Easy data introduction which is corrected by the operator using keyboards with light diodes;
- Automatic regaining primary position after destruction of the specimen;
- Possibility of attaching the external self-recording devices;
- Module machine system with individual opportunities of extension for force sensors and length control sensors, facilities for attachment and testing operating system;

Opinion of the Ethics Commission of the National Medical University dated 23.04.2017, protocol №79: research methods do not involve increased risk for research subjects and comply with existing ethical norms and standards for research.

RESULTS

Using arithmetical calculations, the authors have studied laws of high- and small-diameter screw thread interaxial forces in the opposite compression screw, defined optimum areas of the screw thread bearing area, optimum number of turns of a thread and their width, necessary length of the high- and small-diameter screw thread and of all opposite-compression screw in order to create compression and prevent stripping of a small-diameter screw thread during screwing into the bone. Besides, they studied the "bone-splint-screw" system reliability margin with static dosed loading as well as calculated the time which is required for creating axial force from complete opposite compression screw tightening in order to detect the compression direction and parameter.

Basing on physical and arithmetical calculations using technical formulae for estimating the bearing capacity of the screw thread attachments, the authors offered technical construction parameters (Table I).

Fig. 2 shows general image of the opposite compression screw.

To check for arithmetical calculations and detect reliability of the tibia proximal epimetaphysis fractures two

Characteristics	Unit	Small-diameter thread	High-diameter thread
External thread diameter	mm	d=5	d'=7
Internal thread diameter	mm	d ₁ =3,0	d' ₁ =5
Mean thread diameter	mm	d _{cep} =4	d' _{cep} =6
Winding pitch	mm	S=3,5	S'=3
Winding height	mm	h=1	h'=1
Screw pitch angle	0	ψ = 15°33'28''	ψ = 9°2'35''





Fig. 1. Universal testing machine TIRAtest-2151

Fig. 2. Opposite compression screw (a) screw scheme, b) screw general image (3D - model)



Fig. 3. Testing with transmitting the load onto the process



Fig. 4. Photocopy of X-ray image (B2 fracture of external process)

Fig. 5. MRI fragments. B2fracture of the external process without disintegration of meniscus and ligaments

types fixation (standard spongy and self-compressing) there was held anatomical-biomechanical experiment, the scheme of which is represented in Fig. 3.

Due to anatomical-biochemical studies it was established that when transmitting pressing effort onto all surface of the knee joint the fixating screw type almost doesn't affect osteosynthesis system rigidity. When increasing the speed by 25 times the rigidity figure C increases from 977 to 1050 N/mm (attachment with standard screws) and from 1050 to 1130 N/mm (at-



A - fracture region after correcting the interposition

B – fracture region after reposition and attachment with self-compressing screw



Fig. 7. X-ray image of the patient after operative intervention (fragment attaching using the opposite compression screws)

tachment with self-compressing screws), which made up 7 and 8 % respectively; the rigidity of the system with self-compressing screws when increasing the load also increases, thus ranging within 0.74 – 0.75% of rigidity of the healthy joint (which is considered equal to 1); while transmitting the oppressing effort onto the splint, the attaching screw type significantly affects deformation of the osteosynthesis system with all load types. The residual deformation of the self-compressing screw systems is significantly lower than the residual deformations of the standard screw systems, which evidences about increased deformation reliability of attaching the bone fractures with the self-compressing screws.

Basing on the anatomical-biomechanical experiment, the authors introduced an opposite-compressing screw for attachment of the bone fragments (Patent of Ukraine, № 76760, MПК A61 B17/22. Opposite-compression screw for attachment of the bone fragments / Burjanov O.A., Kvasha V.P., Skobenko Ye.O., Sobolevskiy **Fig. 6.** Intra-operation arthroscopic image of the knee joint

Yu.L., Yarmoliuk Yu.O., the applying institution and patent holder –O.Bogomolets National medical university -№ u 201208938; applic. 20.07.2012; published 10.01.2013, Bulletin №1). The opposite-compression screw use with the tibia proximal epimetaphysis fractures is supported by the following clinical case.

A patient K., aged 33 years old (case history № 2654), was hospitalized into an orthopedic-traumatology unit with tibia lateral process fracture and the B2 fragment dislocation (trauma which is characterized as an isolated fracture of external process with the bone tissue compression area, usually with integrated cortical layer), Fig. 4 shows X-ray image of the injury.

The intraarticular structures may be viewed in Fig 5.

After an appropriate pre-operational preparation on the second day the patient was performed arthroscopic revision of the knee joint, reposition and attachment of the fragments with the offered construction screws. Fig. 6 represents the intra-operation arthroscopic image of the knee joint (A- region of the fracture after interposition correction, B – region of the fracture after reposition and attachment with the self-compression screw).

Fig. 7 represents the X-ray photoimages in post-operative period.

On the 3rd day, after reducing pain, the patient started regular passive and active movements in the knee joint. Fracture union was stated in 7 weeks after the operation, the knee joint resumed its functional capacity completely.

A significant advantage in treatment of the intra-articular fractures of tibia proximal epimetaphysis was introduction of the arthroscopic method which allows to avoid arthrotomy, completely visualize the knee joint structures(meniscus, ligaments), hold an adequate control of reposition and combine the fragments metal osteosynthesis with operative interventions.

Arthroscopy should be conducted during the first or in 7 days after the injury, which is related to the hema-
toma stages. The decrease of the operative intervention injury rate is related to decrease in post-operative complications, provides for quick recovery of motion functions and volume, and, consequently, decreased disability term.

The differentiated treatment strategy which included metal osteosynthesis, arthroscopic method and prevention of deforming arthritis, provided for the following results with the BI: good – 94.1%, satisfactory – 5.9%; respectively BII – 91.7%, 8.3%; BIII – 92.9%, 7.1%; Cl-87.5%, 12.5%; CII – 91.7%, 8.3%; CIII – good – 88.9%, satisfactory – 7.4%, unsatisfactory – 3.7%.

DISCUSSION

The prevailing fracture types among the tibial proximal epimetaphysis fractures are those of type BII, which are observed in 21.6% of all cases, and the CII-III, which evidences about quite high occurrence of high-energy fractures [2]. The most frequently used classification of the tibial proximal epimetaphysis fractures is the Schatzker's, which represents six types of traumas and, as many specialists consider, is significantly advantageous over the AO/ASIF. Along with it, it has several critical drawbacks, as according to high variety of such injuries, the Schatzker classification does not completely answer modern requirements, and needs improvement [9].

These fractures are accompanied by traumas of the knee joint soft tissues – in up to 56% of cases. The meniscal injuries are diagnosed in 50% to 94% of patients, collateral ligaments injuries – in 20% to 83%, anterior cruciate ligament in 20% to 69%, hip muscle ligaments – in up to 47%, the joint capsule rupture - in up to 75%, injuries of the fibial nerve in 3% of all cases [2], so, complex instrumental examination (X-Ray, CT, MRI) will provide for complete pre-operative planning, to avoid intra-operational errors (7.5% of such fractures stay unrecognized) [10].

Quite disputable is the issue of splinters fixation facilities, which include various plates, intramedullary pins and external fixation apparatuses [11-13]. Numerous advantages of the facilities are recalled, but the results are analyzed for the defined fracture type, not by the tibial proximal epimetaphysis fracture in the whole. The modern intramedullary pins may be used with the A fractures, while they cannot stabilize the splinters in the C fractures [14].

The external fixation apparatuses are well-recognized for treatment of intraarticular fractures of the tibial proximal epimetaphysis. Though, their use for osteosynthesis is associated with infection risk (osteomyelitis – 2.7%-6.4% of cases) and certain physical inconveniences for the patient. Most specialists consider the facility as a choice method for complicated high-energy fractures of types CII and CIII by the AO classification, associated with injuries of soft tissues in the knee joint region and open fractures, when all other joint surface reconstruction methods are impossible or quite risky. In many cases it is applied combined with supraosseous osteosynthesis [15].

A positive step in the tibial proximal epimetaphysis fractures operative treatment is the use of various constructions of the T- and F- shaped plates AO, special growth plate LC-DCP, and mini-invasive system LISS. The studies of this direction provided for practical implementation of the minimally invasive surgery concept (Minimally invasive surgery - MIS): Minimally Invasive Plate Osteosynthesis (MIPO) (AO Manual of fracture management: Minimally Invasive Plate Osteosynthesis) [16].

For the last century the method of tibial intra-articular process fractures treatment has significantly changed due to the use of mini-invasive technologies, the so-called arthroscopy-associated methods [17]. The authors positively regard this method [18].

As for the above-mentioned discussion, the authors suppose that various methods of the splinter fixation may be widely used, but positive treatment outcome depends on the distinct indications(fracture type) for their use.

An important aspect of the tibial proximal epimetaphysis fractures is filling bone defects which develop in subchondral region, particularly with the impression fractures.

A traditional method of the bone tissue substitution is the use of autograft, obtained from the ilium wing, though, some disadvantages, which were defined in the 90s [19], lead to studies and implementation of other substitution methods (porous nickel titanium, trabecular metal, calcium phosphate, bioglass) [20].

CONCLUSIONS

- 1. Arthroscopic method is useful in the operative treatment of tibia proximal epimetaphysis fractures as it allows to avoid arthrotomy, helps to visualize the knee joint structures(meniscus, ligaments), control adequately reposition and combine metal osteosynthesis of fragments with operative interventions for the soft tissue intra-articular structure injuries.
- 2. Due to arithmetical calculations and anatomical-biomechanical experiment results, the authors introduced an opposite-compression screw which provides for reliable attachment of the fragments and mini-invasive character of the procedures.

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DYNAMICS OF TOBACCO SMOKING PREVALENCE AMONG STUDENTS AND DIRECTIONS OF ITS PREVENTION

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ABSTRACT

The aim: To study the dynamics of tobacco smoking prevalence among students and to find out the main directions of its prevention. Materials and methods: The research involved 647 students (men and women) of the first – fourth instructional years of pedagogical specialties. The research was conducted during 2020-2022. The research methods included analysis and generalization of literary source on the research topic, documentary method,

questionnaires, pedagogical observation and statistical methods.

Results: It was found that the phenomenon of tobacco smoking has long historical roots and is widespread in all countries of the world. It was found that 32.4 % of male students and 14.9 % of female ones smoke; herewith, 16.0 % of male and 8.3 % of female students smoke up to 10 cigarettes per day. It is established that a number of normative legal documents have been adopted and a system of preventive measures has been developed in order to counteract smoking among students.

Conclusions: Smoking is a significant health and social problem the solution of which requires significant human and financial resources. Despite some achievements in this area, the active involvement of not only men, but also women, mainly students, in smoking is of particular concern. The use of tobacco products provokes a threat to the health of students and the population as a whole, which requires additional efforts on the part of society, government agencies and non-governmental organizations to prevent this addiction.

KEY WORDS: students, prevention, smoking, health, vicious habit

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INTRODUCTION

Students' attitude to a healthy lifestyle as the highest value is associated with understanding the uniqueness of their own life and the lives of others. Awareness of the value of life necessarily involves understanding its opposite – death. Depression, fear of death is one of the factors that causes the monotony, poverty of the individual's experiences, as well as hisor her pursuit of illusory pleasures of life. Quite often, such illusory pleasures are vicious habits: smoking, alcohol consumption, drug addiction, substance abuse, gambling, Internet addiction, etc. Therefore, quite often such social phenomena as drug addiction, alcoholism, unwillingness to live with the lack of meaning in life and its devaluation, non-compliance with all other principles of a healthy lifestyle and health preservation in general are inherent in a large number of students today. Tobacco smoking is one of the most common vicious habits among students [1-3].

According to the World Health Organization (WHO), smoking causes up to 8 million deaths annually, including almost 1.2 million among people who do not smoke but are exposed to secondhand smoke [4]. There are two types of smoking: active smoking is the direct process of actively smoking tobacco products by the smoker, while passive smoking involves the process of inhaling secondhand smoke (smoke emitted from a cigarette or exhaled directly by the smoker). In addition, the smoke that settles on the hair and clothes of people around during smoking is also harmful to health [5]. Tobacco smoking among students and its prevention is an urgent problem today and requires further research.

THE AIM

The aim is to study the dynamics of tobacco smoking prevalence among students and to find out the main directions of its prevention.

Tasks: 1) to study the historical aspects of the emergence and spread of tobacco smoking; 2) to investigate the attitude of students to smoking and to find out the main directions of tobacco smoking prevention among students.

MATERIALS AND METHODS

The work was performed at a higher education institution during the 2020-2022 academic years. 647 students (boys and girls) of the first, second, third, and fourth years of pedagogical specialties, who studied at a higher education institution, took part in the study.

Research methods: analysis and generalization of literary sources on the research topic, documentary method, questionnaires, pedagogical observation, statistical methods. Analysis and generalization of literary sources and documentary method were used to find out the current state of the researched problem, systematize and generalize information to achieve the aim and solve the tasks of the article (22 sources on the topic of the article from the scientometric databases Scopus, PubMed, Web of Science Core Collection, Index Copernicus, Google Scholar, J-Gate and others were investigated). The survey was conducted according to the authors' questionnaire, which was designed to study the attitude of students of different sexes and instructional years to smoking (it consist of 10 questions). The questionnaire was assessed by the experts in this field (3 professors and 5 associate professors) and was approved by the Academic Council of ZhSU (Protocol No. 17 dated 25.08.2020). The survey was anonymous. Pedagogical observation was used to assess students' adherence to healthy lifestyle norms, frequency of use of tobacco products, and their attitude to preventive measures to stop smoking. Statistical methods were used to check, systematize and summarize the received data. All calculations were performed in Microsoft Excel software.

The subject of our research, which is based on the generalization of statistical facts, is a regularity that does not require the detection of the reliability of the difference between students of different years of studying, but only indicates the dynamics of growth or decrease in the number of students who smoke in different years of studying.

This research followed the regulations of the World Medical Association Declaration of Helsinki. Informed consent was received from all students who took part in this research.

RESULTS

The use of tobacco products in Europe has an ancient history, which contains records dating back 500 years since the discovery of America in 1492, where tobacco was found. The use of this plant became popular in Europe in the XVII-XVIII centuries [6]. Historical data on the use of tobacco products by the peoples of the world were found in Indian temples, which depicted the inhalation of aromatic smoke by priests. Smoking pipes were found in the tombs of the ancient Egyptian nobility. Scythians inhaled smoke from burning leaves. Identical descriptions were found in ancient Chinese chronicles. Mayan Indians were the first to chew and smoke tobacco leaves. Thanks to them, tobacco plants spread throughout the Americas [7]. The passion for tobacco was so powerful that this plant began to be assigned medicinal properties, considering it a panacea. However, in 1828, harmful substance i. e. nicotine was found in tobacco leaves. In small doses, it acts stimulatingly, which encourages people to smoke, but gradually nicotine accumulates in the smoker's body and poisons it [8].

In order to prevent the spread of tobacco products in the nineteenth century in Europe, attempts were made to restrict the import and smoking of tobacco, to impose taxes on trade in its products. Despite such restrictions, smoking actively gained momentum around the world. The number of smokers increased during the two world wars. Preventive mailings (brochures, booklets) about the dangers of smoking first appeared in 1950. At the same time, the first filter cigarettes and the first warning labels on cigarette packs about the dangers of smoking appeared in 1960. During this period, tobacco companies focused their attention on "new" consumers of their products - women. Women were attracted to smoking through cigarette advertising. The production of cigarettes directly for women was started. "Philip Morris" was the first of the tobacco companies, which in 1968 released thin cigarettes, which were created specifically for women. Advertisements for this brand of cigarettes showed independent and at the same time successful women who smoke. In the 1970s, the movement against women smoking as a risk factor for the development of a number of non-communicable diseases spread. Then trading companies, in order not to lose consumers, resorted to another marketing measure - they began to offer women "light" and "soft" cigarettes as a much "safer" option [9]. Recently, against the backdrop of a global decrease in demand for cigarettes and a decline in the prestige of smoking, the global tobacco industry has developed a fundamentally new way of consuming tobacco products i. e. new electronic gadgets, without smoke and ash. British

			,			
Assistuale de analytica	Condon	Instructional year				la total
Attitude to smoking	Gender	1 st	2 nd	3 rd	4 th	în totai
	male	63.8	57.9	54.3	55.9	59.6
Do not smoke	female	79.2	79.5	74.5	81.2	79.2
	total	70.6	74.1	66.3	74.0	72.1
	male	6.7	9.3	5.7	8.8	8.0
Quit smoking	female	4.9	5.8	11.8	3.5	5.9
	total	5.9	6.7	9.3	5.0	6.6
Smoke:	male	29.5	32.8	40.0	35.3	32.4
	female	15.9	14.7	13.7	15.3	14.9
	total	23.5	19.2	24.4	21.0	21.3
up to 10 cigarettes per day	male	12.3	20.3	20.0	20.6	16.0
	female	9.8	6.9	9.8	9.4	8.3
	total	11.2	10.1	13.9	12.6	11.1
up to 15 cigarettes per day	male	8.6	7.8	20.0	8.8	10.5
	female	4.9	7.3	3.9	4.7	5.9
	total	7.0	7.5	10.5	5.9	7.6
more than 20 cigarettes per day	male	8.6	4.7	-	5.9	5.9
	female	1.2	0.5	-	1.2	0.7
	total	5.3	1.6	-	2.5	2.6

Table I. Attitude of students of different gender and different instructional year to smoking (in %, n = 647)

Table II. Attitude of students of different gender and different instructional year to smoking depending on the place of their residence (in %, n = 647)

Attitude to emoking	Condor	Place of residence		
Attitude to smoking	Gender	village (n = 341)	town / city(n = 306)	
	male	68.5	60.2	
Do not smoke	female	84.9	74.7	
	total	78.5	69.6	
	male	9.2	10.2	
Quit smoking	female	4.7	7.6	
	total	6.5	8.5	
Smoke:	male	22.3	29.6	
	female	10.4	17.7	
	total	15.0	21.9	
up to 10 cigarettes per day	male	12.3	12.0	
	female	6.6	8.6	
	total	8.8	9.8	
up to 15 cigarettes per day	male	7.7	10.2	
	female	3.3	7.1	
	total	5.0	8.2	
more than 20 cigarettes per day	male	2.3	7.4	
	female	0.5	2.0	
	total	1.2	3.9	

American Tobacco became one of the leading companies in the world that has developed and implemented these innovative technologies in the tobacco industry [10]. "New" smoking products are actively promoted through marketing and are represented on the market by electronic cigarettes and tobacco heating systems. E-cigarettes are electronic portable devices for heating liquid and generating vapor, which is inhaled by the smoker. The liquid can be with or without nicotine, but mostly it contains flavors and colors that make it pleasant to taste and "attract" users with its appearance. Tobacco heating systems are portable devices that use special sticks similar to cigarettes. Due to heating, an aerosol is released, which is inhaled by the smoker. Unlike e-cigarettes, tobacco heating systems always contain tobacco. The promotion of the products' "reduced risk" by the developers misleads consumers and endangers their health, as according to recent data, such tobacco products, like the previous ones, contain about 8 thousand different chemical compounds [11].

According to the scientists [12], in recent years there is a tendency to increase the intensity of daily smoking in Ukraine. According to their research, 24.2 % of adult Ukrainians (42.2 % of men and 9.4 % of women) smoke daily; 1.7 % of adults use tobacco heating systems. Women are joining the smoking habit at a rapid pace. Every third female smoker is under the age of 20, which within Ukraine reflects the global trend of girls starting to smoke in adolescence. In 2005, the prevalence of smoking by women was 20 %, and today the number of female smokers has tripled. The high prevalence of smoking among women of reproductive age is of particular concern [13].

Due to mass marketing, the prevalence of e-cigarette smoking increased significantly in 2020 (compared to the previous year). This indicator increased from 5.8 % to 13.2 % among women. The number of female smokers of electronically heated tobacco products also increased from 3.4 % to 10.5 % in 2019-2020 [14].

Recently, the popularity of hookah smoking has been gaining momentum, due to the misconception that smoking it is not harmful to health compared to other tobacco products. The number of hookah supporters today is 9.2 % (among which the majority are women), and 49.2 % have tried to smoke hookah at least once. According to WHO, one hour of hookah smoking is equal to 100 cigarettes smoked [15].

Nowadays, 51 % of men of working age in urban and 60 % in rural areas smoke. As for women, this figure has increased from 5 to 20 % over the 20-year period. It is important that the age of 75 % of women who smoke is from 17 to 22 years [16]. Scientific evidence shows that tobacco dependence occurs faster in women than in men. The first signs of "nicotine dependence" are detected if a woman smokes one cigarette a day (5 cigarettes a week) [17].

Our research among students of ZhSU shows that 32.4 % of men and 14.9 % of women smoke. If 29.5 % of male students smoked during the first instructional year, then later this indicator increased significantly and amounted to 40.0 % during the third instructional year. Among women, the most abusive smokers are first-year female students (15.9 %) and fourth-year female students (15.3 %) (Table I).

It is important to note that 16.0 % of male and 8.3 % of female students smoke up to 10 cigarettes per day; 10.5 % of men and 5.9 % of women – up to 15 cigarettes per day; 5.9 % of men and 0.7 % of women – more than 20 cigarettes per day.

A characteristic feature is also that students who entered higher educational institutions from rural schools and lived in rural areas smoke less – 15.0 % (22.3 % – men and 10.4 % – women), 29.6 % of men and 17.7 % of women smoke among people from the city (Table II).

It is known that cigarette smoke is harmful not only for those who smoke, it is dangerous for everyone around. Cigarette smoke contains benzene, which is a source of ionizing radiation. Smoking causes lung cancer, it is associated with more than 80 % of cases of chronic bronchitis and eczema of the lungs, more than 25 %– coronary heart disease, complicates the course of respiratory diseases, stomach ulcers. Smoking is especially dangerous for pregnant women.

In order to prevent smoking in the world, the WHO has developed four effective strategies (MPOWER), which were aimed to help countries in combating tobacco smoking among the population [1]: MONITORING - monitoring of tobacco consumption and preventive measures; PROTECTION - protection of people from exposure to tobacco smoke (smoke-free public places); OFFERING assistance in the direction of cessation of tobacco use (today, comprehensive services for the treatment of tobacco dependence are available only for 5 % of the world's population); WARNING - warning about the dangers associated with tobacco use (such methods include graphic images on cigarette packs, which are mandatory today in only 42 countries); ENFORCING - strict control over compliance with legislative regulations on bans on advertising, promotion and sponsorship of tobacco products; RAISING - increasing taxes on tobacco products. Primary and secondary prevention of tobacco smoking is distinguished. Primary prevention involves the application of a set of measures aimed at preventing the use of tobacco products. Secondary prevention involves working with the population to inform about the harmful effects of nicotine as a psychologically active substance. Secondary prevention is aimed at those people who already smoke. Its main goal is early detection of tobacco dependence among the population and avoidance of mental and physical dependence on tobacco products.

It was found that social advertising about the harm of smoking in Ukraine is supported by 82 % of students surveyed. In addition to such advertising activities, anti-tobacco promotion during festivals, conferences, etc. is also effective.

Ukraine's health policy is implemented in the European policy under the slogan referred to as "Health for All", which is directly aimed at improving the quality of life of the population, including by overcoming such harmful habits as smoking. In combating tobacco smoking, the WHO uses a gender approach, focusing on the differences between all aspects of physiology, psychology and social roles of men and women. Tobacco control is one of the priority tasks in many countries of the world. The main principles of tobacco control are set out in the WHO Framework Convention on Tobacco Control (FCTC), which was adopted in 2003 with the support of 168 countries. Since 2005, this document has been binding on its signatory states [1].

In order to combat tobacco smoking in the period from 2005 to 2021, a number of regulatory documents (Laws of Ukraine) were adopted in Ukraine, which: provide for the gradual introduction of effective measures aimed at reducing the level of tobacco use among the population, including students, restricting access to them for children, public health, etc.; regulate the levels of tar and nicotine content in tobacco products, the mechanism of their retail price, confirmation of product conformity through certification; determine the prohibited places provided by law: premises and territories of health care facilities, educational institutions, public places, etc.; establish requirements for the prohibition of advertising and sponsorship of tobacco products. In 2017, the Verkhovna Rada of Ukraine adopted a seven-year "Excise Tax Increase Plan" for tobacco products, according to which the excise tax will increase by 20 % by 2025 (the average price of a pack of 20 cigarettes increased by almost 70 %). In addition, anti-tobacco legislation has been updated in Ukraine, namely the Comprehensive Anti-Tobacco Bill No. 4358 of November 10, 2020"On Amendments to Certain Laws of Ukraine on the Protection of Public Health from the Harmful Effects of Tobacco", namely the Law of Ukraine No. 1978-IX which was adopted by the Verkhovna Rada of Ukraine on December 16, 2021, which amended the laws that were adopted earlier. The innovations are aimed at preserving a smoke-free environment; reducing the attractiveness of tobacco products by prohibiting advertising, sponsorship and promotion of such products and the use of flavor additives; protection from exposure to secondhand smoke, emissions from e-cigarettes and aerosol tobacco products for heating in public places, prohibition of their sale to minors; increasing the size of the health warning (up to 65 % of the area) on the health hazards of smoking on tobacco packs.

Ukraine's compliance with the WHO FCTC requirements will further contribute to the prevention and reduction of tobacco use. These requirements include:

- Inclusion of questions on tobacco smoking in population surveys, which will help to supplement information on all forms of tobacco use, including new types of tobacco products.
- 2. Ensuring access to free or affordable services in terms of assistance provision in case of smoking quitting at both national and local levels.
- 3. Strengthening measures aimed at informing the population about the risks of tobacco products use by placing graphic and text warnings on cigarette packs about the negative impact on health, which occupy more than 50 % of the surface area of the pack, as well as their rotation (i.e. their regular change).
- 4. Increase the price of tobacco products and eliminate illegal trade in tobacco products.

- 5. Conducting information campaigns to raise public awareness about the dangers of tobacco use, aimed at changing risky behavior and creating professional assistance services for smokers.
- 6. Evaluating the effectiveness of bans and strengthening control over the implementation of current legislation.

These measures will contribute to the gradual reduction of smoking among the population of Ukraine, including among students.

DISCUSSION

According to scientists, tobacco smoking is not only a global medical, social and economic problem of society, this vicious habit harms the health of the smoker and his or her environment, which often destroys social ties and breaks up families [18]. States spend up to 200 billion dollars annually on the treatment of non-communicable diseases dependent on tobacco smoking, in Ukraine – 2 billion. Quitting smoking and other forms of tobacco consumption is a significant problem for smokers, especially women, due to the addictive properties of nicotine. According to the scientists [8], dependence on nicotine is stronger even than on heroin.

According to the data of the scientists [19], Ukraine occupies the 17th place among the world's countries in absolute terms of tobacco consumption. In the world there are approximately 870 cigarettes smoked by a person per year, while in Ukraine – 1500-1800 (about 4.5 cigarettes per day), which is almost twice as much as the global average.

Public health professionals play an important role in the prevention of this addiction. In this context, the Ministry of Health of Ukraine together with public organizations encourage the implementation of social advertising in Ukraine in the areas of public prevention and suppression of smoking [20]. Ukraine has joined the creation of anti-tobacco social videos with the participation of active and passive smokers who share their personal experiences about the terrible consequences of tobacco products [12]. The heroes of the social videos are smokers with many years of experience, including women. This project was supported by the World Lung Health Foundation in 2003 as part of the implementation of the WHO FCTC. Article 12 of the FCTC states the need to inform the public about the health hazards of tobacco and the effects of tobacco smoke [19].

It is established that the state policy of tobacco control in Ukraine is implemented in the context of: the WHO FCTC; the Association Agreement between Ukraine and the European Union on the control of non-communicable diseases (Article 427); the National Action Plan on non-communicable diseases, which provides for information campaigns, monitoring of compliance with the requirements of the legislation, qualified assistance to the population in case of smoking cessation. The WHO FCTC emphasizes the importance of systematic monitoring of the situation in the field of tobacco control, which is crucial for understanding and overcoming the prevalence of tobacco smoking in Ukraine.

According to the scientists [21, 22], the increasing trend towards a healthy lifestyle, the demand for tobacco products may decrease as a result of systematic pressure on the global tobacco market by government organizations and society. This may be facilitated by the new taxation system, which provides for a systematic increase in indirect taxes on tobacco products, which will not only reduce demand for them, but also lead to a decrease in their production.

CONCLUSIONS

It was found that tobacco smoking as a phenomenon formed for a long time is widespread in all countries of the world. Smoking is a significant medical and social problem the solution of which requires significant human and financial resources. Despite certain achievements on this way, the active involvement of not only men but also women, mainly of student age, in smoking is of particular concern. It was found that 32.4 % of male students and 14.9 % of female students smoke; 16.0 % of male students and 8.3 % of female students smoke up to 10 cigarettes per day. Students who live in rural areas smoke less – 15.0 % (22.3 % – men and 10.4 % – women), 29.6 % of men and 17.7 % of women smoke among people from the city. Therefore, counteracting smoking among students remains a priority for society. The use of tobacco products provokes a threat to the health of students and the population as a whole, which requires additional efforts on the part of society, government agencies and non-governmental organizations to prevent this addiction.

A system of preventive measures has been developed, including: surveys of the population on the consumption of tobacco products, prohibition of tobacco advertising, smoking in public places, warnings about the dangers of smoking on tobacco products, increasing taxes on tobacco products, promotion of a healthy lifestyle.

Prospects for further research are aimed at studying the motivation of Ukrainian students to use tobacco products.

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ORIGINAL ARTICLE

INFLUENCE OF THE AMOUNT OF COMPRESSION ON VENOUS AND ARTERIAL BLOOD FLOW VELOCITY AND SKIN MICROCIRCULATION OF THE LOWER EXTREMITY

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ABSTRACT

The aim: To determine the effect of compression on the venous and arterial velocity of the main blood flow of the lower limb and the skin microcirculation of the rear part of the foot.

Materials and methods: 20 healthy subjects participated in this study: 11 men 11 (55%) men and 9 (45%) girls. The ankle brachial index (ABI), femoropopliteal index, femoral arterial blood flow velocity (AFV), venous blood flow velocity (VFV), transcutaneous oxygen pressure (tcPO2) and carbon dioxide pressure (tcPCO2) were measured. After the general measurements were taken, the tire was inflated to 10 mm Hg under general basic conditions and kept for three minutes. The experiment ended when no decrease in tcPO2 was observed between two consecutive pressure levels.

Results: The average tire pressure to reach physiological zero was 80 mm Hg. for all participants. At 10 mmHg significant changes in indicators were found by 19% (p=0.0001). tcPCO2 values increased significantly at 10 mmHg (p=0.0319) and continued to increase until the end of the study. It was established that its values increased by 14% compared to the input data (p=0.0005).

Conclusions: At the maximum compression of 60 mmHg the arterial blood flow rate decreased by 5.5 times (p=0.0001). TcPC02 increases significantly when compressed by 10 mm Hg also in parallel with the decrease in the regional perfusion index, which begins at an external compression of 40 mm Hg, which is evidence of the deterioration of the perfusion of the skin of the anterior part of the foot in healthy subjects.

KEY WORDS: microcirculation, tcp02, tcpC02, blood velocity, angiosom

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INTRODUCTION

External compression on the lower extremities is mostly implemented by elastic compression and is used to prevent or limit the formation of edema of various origins, and in case of chronic venous insufficiency in the stage of decompensation, as a proven treatment procedure with the class of evidence «B» [1-3].

The pressure created by medical elastic products should decrease from the distal to the proximal parts, requiring a vertical position of the patient, and for chronic venous insufficiency in the stage of decompensation, it was recommended to use III class compression, where the pressure level at the level of the ankle is >35 mmHg. In an attempt to find an explanation for the beneficial effect of compression on venous function due to the improvement of the pumping function of the calf muscle with an increase in the venous blood flow rate and a decrease in venous reflux, the researchers focused the main attention on the blood flow in the deep and superficial venous system, not

taking into account the changes in the microcirculation of the skin of the lower leg and foot [2].

Although it is known for certain that a local external pressure of 20 mm Hg leads to a decrease in blood circulation in the skin, where in the stage of decompensation with chronic venous insufficiency, we already have a trophic disorder in the form of an open trophic ulcer [3, 4].

Therefore, it should be expected that the imbalance between the beneficial effect on venous blood circulation and the risk of progression of tissue ischemia must be evaluated in each specific case.

THE AIM

The aim of the study was to determine the effect of compression on the venous and arterial velocity of the main blood flow of the lower limb and the skin microcirculation of the rear part of the foot.



Table I. Average values of IRP indicators in different areas of angiosomes (n=20)

Angiosome	RPI (M±sd)
ATA	1.50±0.14
PTA	1.85±0.20
PA	1.70±0.15
Back surface of the foot	1.40±0.16
Sole	1.10±0.11
Lateral bone	1.4±0.31
Medial bone	1.3±0.04

MATERIALS AND METHODS

20 healthy subjects participated in this study. Among them were 11 (55%) men aged 24 (22-27), weight 66 (62-80) kg and height 175 (169-182) cm and 9 (45%) girls, whose average age was 23 (20 -26) years old, weight 58 (47-72) kg, height 165 (160-178) cm. All volunteers gave their written consent to participate in the experimental protocol, which meets all the requirements for conducting research according to the Declaration of Helsinki. All participants underwent a general physical examination.

trating branch of the peroneal artery.

Fig.1. Simplified illustration of angiosomes of the foot: 1- medial calcaneal; 2- medial plantar; 3 - lateral plantar; 4 - dorsal angiosome of the foot; 5 - lateral calcaneal artery; 6 - angiosome of the anterior pene-

In all subjects of the study, the ankle brachial index (ABI) was measured, which is the ratio of the systolic

Table II.	ífects of positive compression on both venous and arterial femoral blood flow velocities and dor	sal foot skin microcirculation in young healthy
subjects (I	=20).	

Pressure (mm Hg)	0	10	20	40	60	80	100
VFV m/s -1 (M±sd)	0.13±0.041	0.10±0.074	0.09±0.03 **	0.07±0.041 ***	0.05±0.025 ***	0.4±0.0011 ***	0.1±0.009 **
AFV m/s -1 (M±sd)	0.22±0.019	0.18±0.013 ***	0.15±0.009 ***	0.11±0.007 ***	0.07±0.004 ***	0.05±0.005 ***	0.04±0.01 ***
tcPO2 (mm Hg) (M±sd)	76.8±15.4	75.3±16.1	71.9±11.4	72.6±9.7	63.7±11.2 **	40.5±8.8 ***	16.9±12.1 ***
tcPCO2 (mm Hg) (M±sd)	38.6±2.7	40.4±2.4*	42.0±5.7 *	42.8±6.4 **	44.1±6.2 ***	44.7±6.6 ***	44.7±12.1 *

Note: * - p<0.05, ** - p<0.01, *** - p<0.0001





Fig. 3. Comparison of changes in AFV and changes in IPR depending on the degree of limb compression

arterial pressure on the anterior or posterior tibial artery to this indicator on the brachial artery. An ABI value of less than 0.9 indicates the presence of stenosis in the arteries of the lower extremities. To determine the functionality of the deep femoral artery, the deep femoral-popliteal index was determined, which is the ratio of the difference between the regional systolic pressure in the popliteal artery above the knee and below the knee to the regional systolic pressure above the knee. All these indicators were measured during selection for the study.

Ultrasound examination of the femoral vessels was performed using a 7 MHz linear sensor. Femoral arterial blood flow velocity (AFV) and venous blood flow velocity (VFV) distal to the saphenofemoral junction were measured. We performed a study of the microcirculation of the skin of the lower extremities taking into account the angiosomal approach using the TCM 400 Radiometer device (Denmark). Transcutaneous oxygen pressure (tcPO2) was measured using a Clark type electrode. Transcutaneous carbon dioxide pressure (tcPCO2) was measured using a Severinhaus type carbon dioxide electrode. A combined transcutaneous oxygen and carbon dioxide pressure electrode was used, which was placed distally from the cuff. The electrode was attached to the skin of the back of the foot with adhesive tape. All measurements were carried out in room air conditions.

In order to achieve statistically reliable results, not absolute values were used, but the ratio of the obtained value in the first interdigital space of the investigated lower limb to the same value in the chest area. The norm of oxygen tension for the skin of the chest is 85 mm Hg, for the interdigital space 60 mm Hg. The resulting index of two values was called the regional perfusion index (RPI). Further, RPI was calculated in relation to the value of perfusion in the studied angiosome to the same in a normal point of a specific patient (ulnar fossa).

The regional perfusion index is used to exclude the influence of cardiopulmonary disorders and simplify the interpretation of tcPO2, which is correlated with the values obtained on the chest.

To determine tcPO2, angiosomes of the anterior tibial artery (ATA), posterior tibial artery (PTA), and peroneal artery (PA) were used, since the corresponding arteries participate in the perfusion of the corresponding skin-muscle flaps (Fig. 1).

As can be seen from the given illustration, the medial calcaneal angiosome, medial plantar and lateral plantar angiosome correspond to PTA. ATA is responsible for the dorsal angiosome of the foot. In the blood supply of the lateral calcaneal angiosome and the angiosome of the anterior penetrating branch of the peroneal artery, mainly PA.

Heart rate and systolic and diastolic blood pressure on the arm were also measured throughout the study usingautomatic cuff inflation system with a diameter of 16 cm to control the general hemodynamic parameters of the study subjects. All subjects were in a horizontal position in the same climatic conditions with the exception of the previous load.

After the general measurements were taken, the tire was inflated to 10 mm Hg under general basic conditions and kept for three minutes. Sonographic parameters were measured in the last two minutes. The total duration of each subsequent approach was 3 minutes. After the first approach, the pressure in the tire was increased to 20 mm Hg, then the pressure was gradually increased in steps of 20 mm Hg. The experiment ended when no decrease in tcPO2 was observed between two consecutive pressure levels. The minimum values were defined as the physiological zero of the participant, which was observed when the individual maximum value of the tire pressure was reached.

The criteria for inclusion in the study were: the absence of any cardiovascular pathology, the absence of any concomitant diseases on the part of other organs and systems, written consent to conduct the study, ankle-brachial pressure index >1.1, femoral-popliteal index < 0.35.

Results are shown as mean and standard deviation. Analysis of differences between paired values was performed using a one-sample Student's T test to determine differences within subjects. The p-values were calculated taking into account the number of participants at each pressure, significant results were registered at a value of p<0.05. Correlation analysis was performed using the Pearson correlation test. Statistical processing and analysis of the obtained results was performed using Jamovi and Exel2019.

RESULTS

Each subject had a stable heart rate and systolic and diastolic blood pressure on the arm throughout the experiment. These indicators did not change significantly and averaged 62 ± 13.0 per minute and 106 ± 15.0 mm Hg, 60 ± 7.0 mm Hg.

Before conducting the study, tcPO2 norms were measured in healthy subjects depending on the angiosomes of the foot (Table I).

According to the resultsshown in table 1, it can be stated that each angiosome has its own level of blood supply depending on the atria and its diameter.

To investigate the statistical hypothesis that when the positive pressure in the cuff increases, the transcutaneous oxygen tension in the limb will decrease and, conversely, the transcutaneous carbon dioxide tension will increase, a statistical comparison of the tcpO2, tcpCO2, AFV and VFV indicators, which characterize the blood supply and microcirculation of the limb between the norm, when the pressure of the cuff is equal to zero and indicators at each subsequent increase in pressure.

The results of the tcpO2, tcpCO2, AFV and VFV measurements and their statistical comparison are presented in Table II.

As can be seen from Table II, the minimum values were reached at 80 mm Hg. in 12 subjects. Therefore, further measurements with a pressure of 100 mm Hg. was conducted only in 8 subjects. The average tire pressure to reach physiological zero was 80 mm Hg for all participants.

Studying the speed of femoral arterial blood flow already at 10 mmHg. significant changes in indicators were found by 19% (p=0.0001). The higher the tire pressure, the more the AFV value decreased with each step. The arterial blood flow rate decreased by 5.5 times compared to the input data at the maximum pressure in the tire (p=0.0001).

No significant changes in VFV were registered at a tire pressure of 10 mm Hg. Compression at 20 mm Hg caused a decrease in VFV relative to the initial level (p=0.0011). Venous femoral blood flow velocity decreased significantly, on average by 31% compared to baseline conditions. At individual maximum tire pressure, the maximum decrease in venous velocity compared to the resting value was 83.8% (p=0.0028).

Turning to tcPO2, although it tended to decrease, no significant changes were detected until the tire pressure reached 60 mmHg. (p=0.0039). The value of transcutaneous oxygen pressure further decreased with increasing pressure in the tire. The lowest value registered in the subjects was 16.9 ± 12.1 mm Hg which means a decrease in tcPO2 by 4.5 times (p=0.0001).

When checking statistical indicators according to FDR and FWER, statistically significant results can be considered those with p<0.0001, other indicators, despite their values, did not pass statistical verification.

To establish the influence of the level of external compression on changes in the main blood flow and microcirculation, a Pearson correlation test was performed. A strong inverse correlation was established between the increase in pressure in the cuff and the change in the transcutaneous pressure tension in the limb (r= -0.9, p=0.0002), when analyzing the correlation between the cuff pressure and the change in the transcutaneous tension of carbon dioxide, a direct strong correlation was established connection (r= 0.9, p=0.0001). According to the data of the correlation test, it can be concluded that when the pressure in the cuff increases, there are changes in the microcirculation in the limb in the form of an increase in carbon dioxide pressure and a decrease in oxygen tension in the tissues, which subsequently leads to ischemia of the limb. When analyzing the correlation, the indicator of 100 mmHg was not taken into account, since at this value there is practically no blood flow in the limb.

On the other hand, tcPCO2 values increased significantly at 10 mmHg (p=0.0319) and continued to increase until the end of the study. Analyzing changes in the transcutaneous pressure of carbon dioxide, it was established that its values increased by 14% compared to the input data (p=0.0005).

To compare the changes in tcPO2, the value of RPI was calculated, which normally ranges from 0.8 to 1.4 for the back of the foot. The results of the changes are shown in Fig. 2.

As can be seen from the graph shown, similarly, the RPI values significantly decrease starting from a pressure level of 40 mmHg. as well as the tcPO2 indicator, therefore, the use of RPI can serve as a criterion of choice for diagnosing the degree of ischemia.

The dependence of AVF and RPI changes on the degree of compression is shown in fig. 3.

Analyzing the changes in AFV and RPI, we came to the conclusion that tissue oxygen saturation does not change as dramatically as the degree of arterial blood flow speed, because AFV changed sharply with each step of increasing the pressure in the tire, and as you can see RPI, it decreased smoothly, and its sharp decrease is noted at 60 mm Hg (p<0.01).

If we analyze the obtained results, the first indicators that respond to the degree of compression were AFV and tcPCO2, which already at a value of 10 mmHg. varied significantly with a significant difference.

DISCUSSION

The results of this study demonstrate significant deterioration of AFV, tcPCO2 with a compression value of only 10 mmHg. Art., although VFV and tcPO2 did not decrease. On the other hand, in our experimental conditions, tcPO2 seems to be less relevant than tcPCO2 for the assessment of local microcirculation impairment.

Very little information is known about the effect of external compression on general venous blood flow [5]. On the other hand, few results are available on the effect of uniform limb compression and the effect on arterial blood flow [6]. Even less is known about the influence of external pressure on venous and arterial blood flow and distal microcirculation.

The pressure created by elastic compression or bandages can be classified according to the amount of compression [7]. But on the other hand, the pressure values used in the management of patients are in the range from 14 to 17 mmHg. for light compression bandages, and for moderate ones, these values are from 25 to 35 mmHg and can even be 60 mmHg, but as can be seen from the results of our research, even at a pressure of 10 mmHg there are changes in microcirculation in the lower limb.

A 2009 Cochrane review comparing compression with primary bandaging (non-compression bandages) in usual care concluded that venous ulcers healed faster with any form of compression therapy than without. It is better to give the patient knitwear of a deliberately lower compression class or one that does not correspond to the scale of the lesion (for example, stockings instead of pantyhose), than to leave it without elastic compression at all.

Studies have shown that selective compression improves the results of sclerotherapy. E. Berliner and co-authors [8] analyzed eight studies, three of which showed that compression stockings can alleviate the symptoms of chronic venous insufficiency and help heal long-standing chronic ulcers (level of evidence A). However, changes in microcirculation in these studies were not described, and what effect does the different type of jersey and pressure have in a specific case, resulting from the study conducted. Our research is consistent with the research of such scientists as Sabri and Berengere Fromy, since we showed that the femoral venous blood flow rate decreases significantly at a limb pressure of 20 mmHg [9].

Halperin and the authors drew the attention of scientists that an external pressure of 10 mm Hg. is sufficient to decrease the arterial blood flow rate in normal limbs, which fully corresponds to our research results, and is explained by a decrease in arteriovenous pressure gradients and a decrease in the caliber of small vessels in the compression zone, which causes an increase in flow resistance [10].

Also, analyzing the data of other authors, it was established that the decrease in tcPO2 with increasing pressure is consistent with the study of Silva H et al., who noted that compression of the lower limb when the subject is lying down leads to a drop in transcutaneous oxygen pressure in the tissues [11].

On the other hand, our results suggest that tcO2 alone does not interpret arterial hemodynamics adequately under our experimental conditions. It is possible that the blood flow of the skin is disturbed due to pressure on the tire up to 60 mm Hg. was not high enough.

However, for pressures as low as 10 mmHg, tcPO2 increased significantly. We assume that the pH increased and distal microcirculation was observed in the forefoot. Andreozzi and his co-authors have already demonstrated that there is a discrepancy between tcPO2 and tcPCO2 [12]. In a follow-up study, they noted that «in some cases, tsPO2 cannot provide a correct assessment of the risk of skin necrosis, whereas tsPCO2 measurement can» [13].

Therefore, the measurement of tsPO2 by itself may not be an adequate tool in our experimental conditions to control the distal microcirculation.

From this study, it can be seen that positive pressure on the entire leg did not provide a significant beneficial effect on the velocity of blood flow in the femoral veins. While we have shown that at uniform external pressure up to 10 mm Hg. in healthy young people, significant violations of both the arterial blood flow of the lower limb and the microcirculation of the front part of the foot were observed. Although this result was found in healthy volunteers, the technique used in this work is an interesting approach to understanding the effects of compression.

Compression therapy is the basis of treatment of venous trophic ulcers of the lower extremities. Most authors are of the opinion that compression of the lower extremities is one of the main pathogenetically justified methods of conservative treatment chronic venous insufficiency. At the same time, the effect of compression treatment is determined due to a decrease in the pathological venous capacity of the lower extremities. This happens in connection with the coming compression of venous intermuscular plexuses, superficial and penetrating veins, improvement in the functional activity of the valvular apparatus and in connection with a decrease in the diameter of the veins.

There is also an increase in reverse absorption of tissue fluid in the venous knee of the capillary and a decrease in its filtration in the arterial - due to an increase in tissue pressure. As a result, a reduction in swelling and an increase in the fibrinolytic activity of the blood is achieved, as the tissue activator (plasminogen) is produced more intensively and the rheology of the blood improves due to the reduction of the stagnation of the latter in the venous channel [12, 13].

According to some authors, good wound care and the use of compression therapy are sufficient to cure most short-lived and small venous ulcers [14], however, taking into account the results of various researchers that correlate with our data, we can conclude that not everything is so clear-cut and changes in perfusion should be evaluated tissue and microcirculation changes, which are accompanied by trophic disorders.

The question of conducting a study of patients with vascular diseases, both with arterial and venous pathology, is relevant. This may lead to a better understanding of the potential beneficial and harmful effects of compression in such patient populations.

CONCLUSIONS

- 1. At a maximum compression of 60 mmHg the arterial blood flow rate decreased by 5.5 times (p=0.0001).
- 2. Venous velocity of blood flow in the femoral vein at compression of 20 mmHg was 0.09±0.03 m/s⁻¹, which is 31% less than the initial data, and at the maximum pressure of the cuff, the decrease in venous velocity compared to the initial value was 0.1±0.009 m/s⁻¹ (83, 8%) (p=0.0028).
- 3. tcpCO2 increases significantly when compressed by 10 mmHg. also in parallel with the decrease in the regional perfusion index, which begins at an external compression of 40 mm Hg, which is evidence of the deterioration of the perfusion of the skin of the back of the foot in healthy subjects.
- 4. A strong inverse correlation was established between the increase in pressure in the cuff and the change in the transcutaneous pressure tension in the limb (r= -0.9, p=0.0002), when analyzing the correlation between the cuff pressure and the change in the transcutaneous tension of carbon dioxide, a direct correlation was established strong correlation (r= 0.9, p=0.0001).

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FEATURES OF BONE REMODELING AROUND SURFACE-MODIFIED TITANIUM AND TANTALUM IMPLANTS

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ABSTRACT

The aim: To study the osseointegrative properties of titanium and tantalum implants with different surface structures in animal experiments. **Materials and methods:** The histological and morphometric study was carried out on 60 male white rats after titanium implants with different surface structures made by 3D printed technology were inserted in the distal femur bone: presented by the multilayered layers of interlacing pores of 300 microns (series 1); rough (> 2 microns) (series 2); and tantalum implants with 300 microns pores and 80% porosity (series 3) as control material.

Results: On the 30 days we found statistically significant differences in the bone-implant contact rate between the 2^{nd} experiment series (44.77 ± 1.86)% and 1st (59.91 ± 2.86)% (p=0.000047) and 3rd (53.89 ± 2.11)% (p=0.000065), on the 90 days between the 2^{nd} experiment series (51.26 ± 2.7)% and 1st (66.84 ± 2.63)% (p=0.000187) and 3rd (70.35 ± 4.32)% (p=0.000349). There was a difference between the indices of the bone-implant volume at day 90 between the 1st (48.43 ± 2.2)% and 2nd (36.88 ± 2.56)% series (p=0.000919), between the 2nd and 3rd series (51.2 ± 3.06)% (p=0.000107). There were no significant differences between the studied indices in the 1st and 3rd series of the experiment.

Conclusions: Titanium implants with multilayered interlaced pore layers of 300 microns and tantalum with 300 microns pore size and 80% porosity may be promising. Rough-surface titanium also has osseointegrative qualities, but they are lower compared to other materials.

KEY WORDS: Titanium, Tantalum, Bone-to-implant contact, Bone-implant volume

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INTRODUCTION

Titanium (Ti) and its alloys have excellent corrosion resistance and high biocompatibility, which has led to their wide use as a material for orthopedic and dental implants. In recent years, along with titanium, tantalum implants have taken a leading position in orthopedics [1]. Despite the widespread use of these biomaterials, work on the improvement of implants continues. One of the directions is to modify the implant surface (roughness, porosity, etc.) and create porous frameworks, which contributes to early mechanical stability due to the possibility of direct contact of the implant with the bone, close adhesion and ingrowth of cells and vessels into the pores [2, 3]. Significant progress has been achieved by using materials with predetermined properties and surface characteristics, on which biologically active substrates can be formed. When developing implants and introducing them into clinical practice, the main evaluation criterion is osseointegration.

Osseointegration is a key concept in orthopedics and traumatology, as various non-natural biomaterials

are widely used in the surgical treatment of patients. Osseointegration is viewed as a structural, mechanical, and functional relationship. which is defined as a time-dependent healing process leading to rigid fixation of alloplastic materials in bone with their capacity for functional loading [4]. Currently, the notion of osseointegration has expanded. The term has been interpreted from a new perspective, i.e., osseointegration can be seen as a demarcation reaction to a foreign body caused by immunity and classified as delayed type (type IV) hypersensitivity, which manifests itself as a reaction to drugs and foreign bodies [5, 6]. That is, the authors consider osseointegration as an immunomodulated inflammatory process, which at an early stage promotes the attraction of cells to the implant surface.

Osseointegration is a complex process that can be influenced by many factors, the osseointegration process includes material biocompatibility, implant design with particular attention to its surface and internal structure, biomechanical characteristics of the



Fig. 1. Areas of morphometric study: thickened line - bone-implant contact (BIC), square –region of interest (ROI).

bone-implant interface, material quality and loading conditions. In recent years, due to the introduction of 3D-printers, the possibilities of creating implants with different qualities, including a given surface structure, have expanded. It is the modified surfaces that are considered as a way to improve the osseointegrative qualities of implants [7, 8]. This is a promising area for future research, since surface topography and its biochemical modification may be key factors in the cytocompatibility and osseoinductive qualities of the biomaterial [2, 9, 10].

THE AIM

To study osseointegrative properties of titanium and tantalum implants with different surface structures in animal experiments.

MATERIALS AND METHODS

CHARACTERISTICS OF THE IMPLANTS

Samples of titanium implants were printed on the Arcam EBM Q20 plus 3D printer (Arcam a CE Additive Company, Sweden) from titanium powder of Ti6Ai4V grade (manufacturer: DEBORA-ELECTRO Production Enterprise LLC, Dnipro, Ukraine). The implants differed in the structural organization of the surface. Some titanium samples had a rough surface. Out of 4 surface categories (according to Albrektsson T., Wennerberg A. scale [11]) our samples were referred to the 4th, that is the surface roughness was within more than 2.0 µm. The surface of the other titanium samples exhibited multi-layered layers of interlaced pores of 300 µm. The tantalum sample was porous, with an average pore diameter of 300 µm and a porosity of 80%.

EXPERIMENTAL ANIMAL STUDIES

The study was conducted in the operating room of the experimental-biological clinic of the State Institution "Sytenko Institute of Spine and Joint Pathology of the National Academy of Medical Sciences of Ukraine". Sixty white male laboratory rats (age 6 months, mean weight 401.6 ± 6.87 g) were included in the experiment. The metaphyseal defect (3 mm) was reproduced in the distal femur with a dental bur in the anterior access, followed by the introduction of implants $(3 \times 2 \text{ mm})$. The operations were performed under general intramuscular anesthesia by injecting the animals with ketamine 50 mg/kg under aseptic and antiseptic conditions. In the course of the study the requirements of the European Convention for the Protection of Vertebrate Animals Used for Research and Other Scientific Purposes were observed as well as the study design was approved by the Bioethics Commit-



Fig. 2. Stages of surgery. Implantation into the distal femur of rats. A. Implant with a rough surface. B. Implant with the surface represented by multilayered layers of interwoven 300 µm pores. C. Implant made of tantalum, 300 µm pores, 80 % porosity.



Fig. 3. Newly formed bone trabeculae adjacent to the implant. A. Titanium implant with a rough surface. B. Titanium implant with a surface composed of layers of interlaced 300 µm pores. C. Tantalum implant with a porous surface. 30 days. Hematoxylin and eosin. X100.



Fig. 4. Newly formed bone trabeculae adjacent to the implant. A. Titanium implant with a rough surface. B. Titanium implant with a surface composed of layers of interlaced 300 μm pores. C. Tantalum implant with a porous surface. 90 days. Hematoxylin and eosin. X100.

tee at the Sytenko Institute of Spine and Joint Pathology of the National Academy of Medical Sciences of Ukraine (protocol No 191 from 2019/04/22).

Three series of experiments were performed (Fig 1 A. B. C): series 1 – implantation of titanium pins with a rough surface (> 2 microns); series 2 – implantation of pins with a surface represented by multilevel layers of interwoven pores of 300 μ m; series 3 – implantation of tantalum pins with a porous surface (average pore diameter 300 μ m, porosity 80%). Twenty animals were included in each series, five for each study period. Rats were euthanized from the experiment on days 7, 14, 30, and 90 by overdosing on ketamine.

HISTOLOGICAL PROCEDURES

The distal sections of the femur with implants after the animals were removed from the experiment were isolated and placed in a 10% solution of neutral formalin. After decalcification in 10% formic acid, implants were sparingly removed, samples were dehydrated in successive concentrations of ethyl alcohol (50% to 100%), ethyl alcohol + ether mixture (1:1), and encased in celloidin. Sections were made on a Reichert microtome (Austria), stained with hematoxylin and eosin, and with van Gieson's picrofuchsin.

The histomorphometric study was performed according to the standard approach to the evaluation of osseointe-

gration by the bone-implant contact index (BIC, %) and the bone-implant volume (BIV, %) was evaluated in a standardized region of interest (ROI) [12,13]. The BIC was calculated based on an estimate of the proportion of bone tissue among other tissues on the surface of the 1.5 mm implant in the ROI and cortex area. The BIV was assessed in rectangles (1.3 mm \times 0.5 mm) in the cancellous bone in the ROI area at a distance of 0.5 mm from the implant over 1.3 mm (Fig 2). The BIV is the area of bone trabeculae in relation to the total tissue area in the ROI. According to the available recommendations, three central sections from each animal were examined to standardize the experiment [12]. Morphometric studies were performed using a Micros microscope (Austria) (\times 100) and DSM 800 camera software (Ukraine) with image output to a computer.

Statistical analysis. The numerical values were checked for normality of distribution using the Kolmogorov-Smirnov criterion, and the data are presented as the mean (M) and standard error (m). Student's t-test was used to assess the reliability of values in two independent samples. At a significance level of $p \le 0.05$ the null hypothesis was rejected with 95% probability.

RESULTS

On the 7th day there were no differences between the tissues around the three types of implants studied. They were surrounded throughout by granulation tissue









Fig. 6. Indicators (%) of bone tissue on the implant surface. Bone-implant contact (BIC). 90 days after implantation.

Fig. 7. Bone tissue area indices (%) in the examined area. 90 days after implantation.

interspersed with connective tissue. Maternal bone trabeculae with signs of destructive changes were located around the implants in the areas of cancellous bone. They had irregular margins, there were no osteocytes in the marginal parts. In the intertrabecular spaces there was red bone marrow with foci of cellular detritus as well as newly formed granulation tissue with signs of edema containing fibroblasts, lymphocytes and single macrophages. Dilated sinusoids and capillary vessels were present. Single maternal bone trabeculae showed formation of woven bone overlayers and narrow single newly formed bone trabeculae located in the intertrabecular spaces. In the areas of contact with the cortex, the implants adhered tightly to the bone without formation of intermediate tissues. There were destructive abnormalities in the cortex, the matrix was irregularly stained, empty osteocyte lacunae, microcracks and small resorption cavities were present.

In the trabecular bone area on the 14th day the surface of three implant types showed connective tissue in the form of bands of different width with collagen fibers running parallel to the implant and small areas of immature bone tissue deposited on the bone trabeculae. In small areas, the formation of woven thin bone trabeculae was detected mainly in the areas of cancellous bone adjacent to the cortex. The woven bone trabeculae had a high cell density and were in contact with the maternal bone trabeculae and the implant surface. The intertrabecular spaces contained red bone marrow, and the areas near the implant contained loose connective tissue. In the cortex areas at the "implant-bone" interface we recorded compact bone remodeling with the formation of a narrow layer of osteogenic connective tissue with the presence of osteoblasts. Small resorption cavities were revealed in the cortex area, as on the previous day, and areas without osteocytes were preserved.

On the 30th day the newly formed thin bone trabeculae intertwined with each other were found on the surface of all examined implants in their areas located in the area of cancellous bone (Fig. 3 A. B. C). The density of newly formed bone trabeculae adjacent to the implant was in the areas adjacent to the cortex. Red bone marrow was located in the intertrabecular spaces. Due to the unevenness of implant surfaces, areas with a protruding location of newly formed bone or connective tissue were found. Intertrabecular spaces were narrowed, bone trabeculae at the sites formed a network, intertwined with maternal bone trabeculae. A lamellar bone was formed around the implant sites located in the cortex area.

At day 90th no peculiarities in the organization of the tissues surrounding the examined implants were revealed as well. Bone tissue with areas of red bone marrow was adjacent to the implant surfaces from the intertrabecular spaces open towards the implant (Fig. 4 A. B. C). Small interlayers of connective tissue were detected. Thickened bone trabeculae forming a network were noted. The inter-trabecular spaces were filled with red bone marrow. Newly formed lamellar bone was fixed in the cortex areas between implants and compact bone. Small fields without osteocytes and disordered layers of bone tissue were present in the cortex.

Descriptive histological studies were complemented with morphometric analysis to reveal the peculiarities

of the bone tissue remodeling around three implant types. On the 30th day we registered the formation of the bone tissue on the implant surface, demonstrated the difference of BIC between the 1^{st} (59.91 ± 2.86)% and 2^{nd} $(44.77 \pm 1.86)\%$ series of the experiment, (p=0.000047); also, between the 2^{nd} (44.77 ± 1,86)% and the 3^{rd} (53.89 $\pm 2,11$)% series (p=0.000065) (Figure 5). A similar pattern of change persisted at day 90, with differences between the 1st (66.84 ± 2.69)% and 2nd (51.26 ± 2.7)% series (p=0.000187), and between the 2^{nd} (51.26 ± 2.7)% and 3^{rd} (70.35 ± 4.32)% series (p=0.000349) (Figure 6). The differences in ROI when evaluating the bone implant volume (BIV, %) at day 90 showed that the BIV was $(48.43 \pm 2.2)\%$ in the 1st series of experiments, while it was significantly lower in the 2^{nd} series (36.88 ± 2.56)% (p=0.000919) (Fig. 7). There were also significant differences between series 2 (36.88±2.53)% and series 3 (51.2±3.06)% (p=0.000107). No significant differences were found between the BIC and BIV indices in the 1st and 3rd series of the experiment.

DISCUSSION

From a clinical point of view, titanium and its alloys as well as tantalum are the preferred materials in orthopedics and traumatology because of their high biocompatibility, and in some studies have been shown to have similar osseointegrative and biomechanical properties [14, 15]. The surface organization and topography of the implant determine its ultimate ability to integrate with the surrounding bone tissue [16]. Migration, adhesion and proliferation of cells to the implant surface, tissue formation are important prerequisites for the initiation of bone regeneration process and formation of bone-implant interface [17]. Most of the implants undergoing experimental studies and used in clinical settings have a porous structure, as the pore size and total percentage of porosity are the determining factors of osteogenesis. In addition, porous implants provide an opportunity to use antibiotics and biologically active substances to saturate the pores and prevent inflammation and stimulate peri-implantation osteogenesis. Based on the analysis of dental implants incorporating porous materials with pore sizes of 100 µm, 150 µm, it was recognized that pores of this size are acceptable for bone tissue ingrowth, but in other studies pores of 300 µm were presented as ideal for supporting both bone tissue and vessel ingrowth inside the material [18]. We studied tantalum with a pore size of a rounded configuration of 300 µm and titanium with a pore size of 300 µm, but partially merging with each other. On the basis of the study no differences in BIC and BIV were found between these biomaterials at 30th and 90th days of study. Implants made of titanium with a rough surface had lower values, which may be related to the degree of roughness. Various modifications are used to create titanium surface with a combination of osteogenic properties, but there is still no consensus on the optimal implant roughness that stimulates osseointegration. However, it has been established that rougher surfaces can stimulate attachment, differentiation and proliferation of bone cells, thereby increasing bone growth and mineralization [19], which we observed on the titanium surface represented by multilayered layers of interwoven 300 µm pores. Positive manifestations of osteogenesis were also recorded around a macroporous tantalum specimen with a pore diameter of 300 µm and 80% porosity.

The course of the osseointegration process is interpreted in several aspects, contact and distance osteogenesis are considered, as well as the prediction of long-term implant stability based on the BIV study [20]. While the initial stage of osseointegration provides a link in the implant-bone interface, the long-term prognosis of implantation, implant stability, depends on the success of bone remodeling around the implant in the long term. Histological studies are considered as the gold standard in experimental studies, as they give an opportunity to assess the contact and distant osseointegration, as well as to give a prognosis of the implant stability [12]. The results of our study showed that around the three specimens we studied in the early period distant osteogenesis is characteristic, that is connective tissue is formed directly on the implant surface with its subsequent reorganization into bone tissue, and osteogenesis takes place at a distance and acts as an inducer of bone formation in the direction of the implant. On the 30th day most of the implant surfaces were in contact with the bone tissue, and the BIC of all the examined implants increased by the 90th day. The differences were revealed between the titanium samples, the implants with rough surface significantly differed from the samples with macroporous surface

in terms of BIC index. High indices were also recorded for the implants made of porous tantalum, BIC with the surface represented by the multilayered layers of interlaced pores of 300 microns and the implants made of porous tantalum were different only in comparison with the rough implants. No differences with tantalum and titanium implants with the surface represented by multilayered layers of interwoven 300 µm pores were found. As for the long-term stability prognosis, all the implants studied showed high BIV values in ROI. In terms of this index, of the three samples with different surfaces studied, lower values were recorded for the titanium implants with rough surfaces, but the BIC and BIV values were over 50%, which can also be considered as a positive result. So, the implant surface is an important prerequisite for initiation of tissue regeneration process and implant stabilization.

Our study has certain limitations: it was performed using animals with normal bone tissue. Peri-implantation bone remodeling in osteoporosis with these implants needs further research.

CONCLUSIONS

The implants with a rough surface and the surface with multilayered interlaced 300 microns pore layers made of Ti6Ai4V titanium powder by 3D printed technology, according to the manufacturer's technology, differed in the osseointegration qualities; BIC and BIV were higher with the implants with multilayered interlaced 300 microns pore structure at day 30 and day 90.

Tantalum implants with porous surfaces were characterized by pronounced osseointegrative qualities. There were no differences in BIC and BIV indices between the implants made of porous tantalum and the implants made of titanium with multilevel interlaced layers.

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ORIGINAL ARTICLE

FEATURES OF THE FUNCTIONAL MORPHOLOGY OF THE FULL-TERM PLACENTA IN WOMEN WITH THREATENED ABORTION WITH BLEEDING IN THE FIRST TRIMESTER OF GESTATION

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ABSTRACT

The aim: To examine the morphology regarding the term placentas in pregnancies with threatened abortion with bleeding in the first trimester **Materials and methods:** 118 term placentas were selected, of which 40 placentas with the physiological course of pregnancy. 78 placentas were from women with threatened abortion with bleeding in the first trimester, of which 37 patients received hormonal therapy (group I), 41 women were prescribed symptomatic therapy (group II). Placentas were investigatedaccording to the protocol, which includes organometric, macroscopic and microscopic studies. **Results:** In the placentas of group II is a significant increase of the area of terminal villi compared due to the stroma against the background of a deficit of fetal capillaries. In group I have revealed that the specific weight of the vascular bed of the terminal villi was 1.5 times higher compared to the control (P=0.031) and 2.7 times higher than the group II (P=0.022) and dominates the share of the stroma. The weight of the epithelium of the terminal villi in all groups is approximately the same (P=0.042), but the ratio of the epithelium to the stroma is higher in the group I (0.63) than in the control (0.43). **Conclusions:** In women with a pathological course of the first trimester of pregnancy the compensatory mechanisms in full-term placentas are morphologically represented by an increase in the number of terminal villi, syncytio-capillary membranes, intensification of angiogenesis. In the placentas of women who received hormonal therapy adaptive reactions are most effective and able to compensate for the gestational immaturity of the chorion.

KEY WORDS: complicated I trimester of gestation, threat of abortion, bleeding, functional morphology of the full-term placenta, chorion

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INTRODUCTION

By the end of the first trimester of pregnancy, the main structural elements of the placenta are formed, placentation is completed, utero-placental and feto-placental blood flow is established, the placenta remains immature only in terms of morphology and function [1]. The stages of placental morphogenesis are fairly well studied – three periods can be distinguished in the formation of the chorion: I - pre-villous (7-8th day of embryonic development); II – formation of villi (9-49th day of embryonic development); III – formation of cotyledons (50-90th day) [2].

As is known, the utero-placental complex is capable of dynamic adaptation in the conditions of the mother's homeostasis, which changes during gestation. However, due to various reasons, the compensatory and adaptive mechanisms of the placenta at various levels are exhausted, which is primarily associated with a violation of the morphology and functional failure of the structures of the placenta [3-5].

Today, thanks to numerous studies, a large amount of factual material has been accumulated regarding the morphology of the placenta and the features of compensatory reactions in the utero-placental complex in extragenital pathology, complications of the second half of pregnancy, etc. [6-8].

However, there is no unified view of the issues regarding the peculiarities and morpho-functional interpretation of the complex of adaptive changes in the full-term placenta in the presence of complications in the early stages of pregnancy in the literature.

THE AIM

To study the macroscopic and microscopic morphological findings regarding the full-term placentas in pregnancies with threatened abortion with bleeding in the first trimester of gestation.

MATERIALS AND METHODS

For analysis, 118 placentas were selected for term deliveries at 39-40 weeks of gestation, of which 40 placentas made up the control group – observation with the physiological course of early pregnancy. A study was conducted of 78 placentas from women with pathology in the first trimester of pregnancy (a threatened abortion with bleeding), of which 37 patients received hormonal therapy in the early stages (group I), 41 women were prescribed only symptomatic therapy (group II).

The diagnosis of threatened abortion with bleeding was established based on the clinical laboratory and ultrasound examinations. Exclusion criteria from the study were pregnancies that occurred as a result of assisted reproductive technologies, multiple pregnancies, anomalies of the development of female genital organs, severe extragenital pathology in the mother, congenital anomalies of the fetus.

Placentas were studied according to the protocol, which includes data from organometric, macroscopic and microscopic studies (form No. 013-2/0, approved by the order of the Ministry of Health of Ukraine No. 417 dated 19.08.04). The study was conducted in full compliance with the ethical principles contained in the "Human Rights Declaration" adopted in Helsinki, which follows the Good Practice Rules in the Clinical Study and Legal Regulations.

The macroscopic examination consisted in determining the main organometric parameters of the placenta, umbilical cord and free fetal membranes, evaluating the option of attaching the umbilical cord to the placenta, the type of branching of the vessels of the chorionic plate and assessing their diameter, descriptive characteristics of the maternal surface of the placenta and the features of the structure of the cotyledons.

For the histological study of the placentas of the relevant observations, 6-8 pieces of tissue were taken from the central, paracentral and peripheral zones, with capture of the fetal and maternal surfaces of the organ.

The material was fixed for 48 hours in a 10% solution of neutral buffered formalin, after which dehydration was carried out in an ascending battery of alcohols and paraffin embedding at a temperature of 64° C. Serial histological sections with a thickness of 5 µm were made on a sledge microtome, on which after deparaffinization general histological and specific histochemical reactions. Staining of the preparations with hematoxylin and eosin for inspection purposes was carried out according to the generally accepted method. For the histochemical study, the technique according to N.Z.Slinchenko with the chromotrope water blue was used to identify fibrin, vessels and the fibrous component of the stroma of chorionic villi [9].

In order to objectify quantitative studies, computer morphometry and histostereometry of objects in histological and histochemical preparations were performed on digital copies of microscopic preparations using different microscope lenses depending on the goals of the analysis. Digital copies of images were analyzed using a licensed copy of the computer program ImageJ (1.48, W. Rasband, National Institutes of Health, USA) in accordance with the stated purpose.

Statistical processing of digital data was carried out in accordance with the specific tasks of a certain fragment of the study. The planning of the necessary number of observations in each research group was determined on the basis of calculations of a sufficient number for the specific applied statistical method at a sensitivity level of 0.80 and a significance level of p=0.05. For parametric data, testing of the hypothesis about the normality of the distribution of quantitative characteristics in groups was carried out using the Shapiro-Wilk's test. If the hypothesis was not rejected, parametric methods of statistical analysis were used: two-sided Student's t-test (for equal and unequal variances tested by Levene's and Fisher's tests). To establish discrepancies between the percentage display of the frequency of a certain characteristic among two statistical samples, a special statistical method was used the Fisher transformation method [10].

The main statistical characteristics which are given in the description of the research results in the tables include: the number of observations (n), the arithmetic mean (M), the standard error of the mean value (m), the level of statistical significance (p). Statistical calculations were performed in the environment of a free-to-use licensed copy of the computer program Paleontological Statistics (PAST) v4.05. (Hammer Ø. PAST: Paleontological Statistics, Version 4.05. 2021) [10].

RESULTS

Carrying out macroscopic studies we established that the shape of placentas in both study groups with complications of the first trimester of pregnancy was oval in 66%, and circular in 39.5% of observations, in the control group with a physiological course of pregnancy the oval shape was found in only 34% of placentas.

At the same time, the frequency of abnormal configurations of placentas was significantly higher among women with pathology in the 1st trimester of pregnancy who received hormone therapy (P=0.028) and who



Fig. 1. View of the maternal surface of a full-term placenta: 1 – during physiological pregnancy, distinct cotyledons; 2 – with a complicated course of the first trimester of pregnancy, incomplete formation of the furrows that separate the cotyledons.



Fig. 2. The chorionic tree of the full-term placenta: 1 – the physiological course of pregnancy, the structure of the chorionic tree corresponds to the gestation period; 2 – complicated course of the first trimester of pregnancy, insufficient number of terminal villi and villi with syncytio-capillary membranes. Chromotrope - water blue according to N.Z. Slinchenko.

received symptomatic treatment (P=0.006). Difference from control was calculated by Fisher's transformation method (Table I).

The percentage ratio of umbilical cord attachment variants in all three groups of studied placentas was approximately the same with an obvious predominance of lateral umbilical cord attachment (P=0.012) and rare marginal variant (P=0.006). The difference between indicators of umbilical cord attachment options within each study group according to Fisher's transformation method p<0.05.

These features are important regarding the point of view of evaluating the blood circulation of the placenta because the type of attachment of the umbilical cord to the placenta largely determines the type of vascular branching in the chorionic plate. During a visual inspection of the fetal surface of the placentas we noted that the amnion in all cases was transparent, smooth, and the vessels departing from the umbilical cord were well contoured. As shown in Table I, the type of vascular branching in the placentas of all studied groups was mainly intermediate (P=0.018), the friable type was slightly less common (P=0.028) and the percentage of the trunk type was the lowest (P=0.005) (the difference between the percentages of types vascular branching within each study group according to Fisher's transformation method p<0.05).

The study of placentas from the maternal surface let to establish the incomplete formation of furrows that separate cotyledons in 90.7% of observations of the group II (with a complicated course of the first trimester

Macroscopic sign	Placentas of control group women (n=40)	Placentas of women with a complicated first trimester of pregnancy who received hormone therapy (I group) (n=37)	Placentas of women with a complicated first trimester of pregnancy who did not receive hormone therapy (Il group) (n=41)
Abnormal forms, %	2,5±2,4	5,4±3,7 P=0,028	9,7±4,6 P=0,006
	Options	for attaching the umbilical cord,	%
central	35,0±7,5	37,8±7,9 P=0,026	34,1±7,4 P=0,034
lateral	52,5±7,8	54,1±8,1 P=0,022	51,2±7,8 P=0,037
marginal	9,5±4,6	5,4±3,7 P=0,016	7,3±4,0 P=0,032
	Т	ype of vascular branching, %	
friable	35,0±7,5	37,8±7,9 P=0,024	34,1±7,4 P=0,034
intermediate	52,5±7,8	54,1±8,1 P=0,024	51,2±7,8 P=0,033
trunk	12,5±5,2	10,8±5,1 P=0,031	14,6±5,5 P=0,029

Table I. Macroscopic characteristics of placentas at 39-40 weeks of gestation (M±m).

Note: The probability of P differences between study groups was calculated using the Fisher transformation method.

Table II. Morphometric	parameters of the termina	I villi of the chorion of the	placenta at 39-40 weeks of	gestation (M±m)
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Morphometric indicators	Placentas of control group women (n=40)	Placentas of women with a complicated first trimester of pregnancy who received hormone therapy (I group) (n=37)	Placentas of women with a complicated first trimester of pregnancy who did not receive hormone therapy (II group) (n=41)
Total area of terminal villi, %	48,8±7,5	53,9±6,3 P=0,037	60,0±5,4 P=0,022
	Specific	weight in the total area of the chori	on, %
Stroma	53,8±4,5	38,5±6,7 P=0,024	60,2±6,1 P=0,038
Epithelium	23,4 ±3,2	24,4±5,1 P=0,042	26,0±4,8 P=0,039
Vessels	22,8±5,4	37,1±2,7 P=0,031	13,6±3,8 P=0,002

Note: The probability of P differences between study groups was calculated using the Fisher transformation method.

of pregnancy who did not receive hormone therapy), which is significantly higher than in placentas with a physiological course of pregnancy (5.5%, p<0.001), as well as compared with the placentas of the group I of women with a complicated course of the first trimester of pregnancy who received hormone therapy (64.7%, p=0.038, according to Fisher's transformation method). A typical view of the maternal surface of the placenta of full-term pregnancy is shown in Fig 1.

The number of calcifications was moderate and practically did not differ in the placentas of women with a pathological course of the first trimester of pregnancy and the control group. Only isolated calcifications were found in the placentas of women who did not receive hormone therapy in the early stages of gestation, which in our opinion is a certain sign of immaturity of the placental tissue.

Analyzing the weight of the placentas it should be noted that it did not differ reliably in the three studied groups. So in the control the weight ranged from 392.0 g to 520.0 g and averaged 452.2 \pm 22.0 g, in women of the group I it was 436.5 \pm 24.0 g and in the group II – 421,4 \pm 31.0 g. It should be noted that in separate observations only a tendency to decrease the weight of the placenta was recorded in pregnant women with a pathological course of the first trimester of pregnancy

Indicators	Control	Complicated course of the first trimester of pregnancy		
		l group	ll group	
Terminal villi, %	64,5±1,0	69,6±1,1*#	60,5±1,3*	
Villi with syncytio-capillary membranes, %	48,5±2,2	63,1±2,5*#	44,5±4,0	
Villi with the number of vessels > 3, %	22,1±0,7	29,2±0,6#	10,4±0,8*	
Villi with syncytial nodules, %	49,0±1,8	60,4±2,2*#	50,4±3,3	
Number of intervillous fibrinoid (points)	1,4±0,05	1,7±0,11*	2,0±0,08*	

Table III. Histostereometri	parameters of term	placentas in women	with a complicated	I trimester of pregnancy	(M±ṁ)
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Note: the symbol * means the probability of withdrawal at the level of P<0.05 in comparison with the control group; the symbol # means the probability of difference at the level of P<0.05 in the comparison of indicators of the I and II groups. P differences was calculated using the Fisher transformation method.

who did not receive hormone therapy (group II). Differences between the arithmetic means of the study groups calculated according to the two-sided unpaired Student's t-test and the Mann-Whitney's test p<0.05.

The results of comparative morphometric and histostereometric studies of the terminal villi of the chorion in women with a complicated course of the first trimester of pregnancy depending on the received treatment give an idea of the implementation of compensatory mechanisms in the full-term placenta at the tissue level (Table II).

As can be seen from the Table 2, in the placentas of women with a complicated course of the first trimester of pregnancy who did not receive hormone therapy (group II), there is a significant increase in the total area of the terminal villi of the chorion compared to the control (P=0.022). It is worth noting that this is mainly due to the stromal component (P=0.038) against the background of a pronounced deficit of fetal capillaries (P=0.002).

Observations of the placentas of women who received hormone therapy in the 1st trimester (group I) revealed a completely different picture: the specific weight of the vascular bed of the terminal villi was 1.5 times higher compared to the control (P=0.031) and 2.7 times higher than the group II (P=0.022) and significantly dominates the share of the stromal component. The specific weight of the epithelium of the terminal villi in all studied groups is approximately the same (P=0.042), but the ratio of the epithelium to the stroma is higher in the group of women who received progestogens in the 1st trimester (0.63) than in the control group (0.43).

For the most complete assessment of the manifestations of the compensatory capabilities of the tissue of full-term placentas in women with a complicated Ist trimester of pregnancy we also examined villi with the same morphofunctional characteristics (Table III).

From the data in the Table 3 we can see that the number of terminal villi in the groups differs significantly. In the placentas of women with a complicated course of the first trimester of pregnancy their number increases to $69.6\pm1.1\%$ compared to the control ($64.5\pm1.0\%$) P<0.05, which also characterizes a high level of adaptive changes. In women who did not receive gestagenotherapy (group II) the number of terminal villi significantly decreases, and the level of villi containing 3 or more vessels remains low in this group ($10.4\pm0.8\%$). In the control group this the indicator is 2 times higher and in group I placentas is higher almost 3 times. As for the percentage of syncytio-capillary membranes, in women who received hormone therapy this indicator was significantly higher compared to the group I and the control respectively 63.1 ± 2.5 and 48.5 ± 2.2 (P<0.05).

In patients who underwent only hemostatic therapy in the early stages of pregnancy (group II) the number of villi with syncytio-capillary membranes and the number of vessels more than 3 was lower in relation to both the group I and the control group (P<0.05). The number of villi with syncytial nodules was significantly higher in patients of the group I compared to the group II of subjects. In women who did not receive hormonal therapy in the early stages of pregnancy the percentage of these villi was almost the same as in a physiological pregnancy. The level of intervillous fibrinoid was higher than the norm in both women of the I and II groups.

A typical histological picture of the chorionic tree of the studied placentas is shown in Fig 2.

When studying histological preparations of full-term placentas from women with a complicated course of the first trimester of pregnancy we paid attention to significant microscopic polymorphism of the structure of the villous chorion.

Against the background of an increase in villi number, in some places groups of terminal villi are closely adjacent to each other which leads to a narrowing of the intervillous space. The stroma of the villi is loose, in some places swollen with a different number of cellular elements among which Hofbauer's cells are found. The number of capillaries in one villus varies from 1 to 8. In histological preparations avascular villi with a dense stroma and large fibroblasts are also found. Capillaries are located both in the center and closer to the periphery forming syncytio-capillary membranes. There are villi with the absence of an epithelial layer walled up by masses of fibrinoid.

DISCUSSION

This study has evaluated the morphological features of the full-term placenta in women with threatened abortion with bleeding in the 1st trimester of pregnancy depending on the treatment provided – hormone therapy or symptomatic (hemostatic) therapy.

Among the macroscopic findings in placentas with a complicated first trimester of pregnancy a higher frequency of incomplete formation of the furrows separating the cotyledons was determined, compared to full-term placentas during a physiological pregnancy. This important macroscopic feature of the placenta is one of the signs of immaturity of the placenta and is used in the classification of ultrasonographic stages of placenta maturity according to Grannum [11, 12].

At the histological level of the examination of placentas during the complicated course of the first trimester of pregnancy signs of inhibition of the development of the chorionic tree were found. They are manifested by a higher percentage of gestationally less mature chorionic villi and a violation of the transition of terminal villi into terminal "specialized" forms, the main criterion of which is the presence of syncytio-capillary membranes [13].

To assess the maturity of the chorionic tree by determining the correspondence of the percentage of certain types of chorionic villi to a certain period of gestation there is a classification based on Gastelucci M. (1982) improved by Kaufmann R. (1982-1996) and Davydenko I. S. (2005) [14].

A number of fundamental studies of the morphology of the placenta, carried out by Benirschke K. (2012),

Benton S. J., McCowan L. M., (2016), Burton G. J. (2015), have shown that a decrease in the specific volume of fetal capillaries, the average number of capillaries in the profile of the terminal villus, disruption of angiogenesis in chorion in the form of a spatial distribution of capillaries mainly in the central parts of the villi, the excessive development of collagen in the stroma of the chorionic villi with sclerosis are direct morphological prerequisites for the deterioration of the perfusion of substances from the blood of the mother to the blood of the fetus and vice versa, and in addition, it can cause disorders reconstruction of the microcirculatory channel which occurs during the transition of terminal villi into terminal "specialized" ones [1, 4, 5, 15].

CONCLUSIONS

- 1. It has been established that in pregnant women with a pathological course of the first trimester of pregnancy the peculiarities of the functional morphology of the full-term placenta are noted, which are caused by a violation of the maturation of the chorionic tree.
- 2. The implementation of compensatory and adaptive mechanisms in placentas at the end of pregnancy is morphologically represented by an increase in the number of terminal villi, the specific weight of the vascular component in them (intensification of angiogenesis), the number of syncytio-capillary membranes and syncytial nodules.
- 3. The type of the treatment of bleeding in the first trimester of pregnancy affects the further development of the placental system. Adaptive reactions at the end of pregnancy are most effective in the placentas of women who received hormonal therapy and able to compensate for the gestational immaturity of the chorion.

Prospects for further research consist in the study of pathomorphological changes in placentas in pregnant women with a complicated course of the first trimester of pregnancy depending on the date of delivery.

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THE BIOMECHANICAL ANALYSIS OF PELVIC OSTEOTOMIES APPLIED FOR DDH TREATMENT IN PEDIATRIC PATIENTS

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ABSTRACT

The aim: This article aimed to evaluate biomechanical changes during the most commonly used pelvic osteotomies (Salter, Dega, Pemberton) for DDH treatment in pediatric patients.

Materials and methods: Virtual pelvic models of 2- and 6-years old patients were created, material properties were assigned, pelvic osteotomies were simulated and biomechanical changes were evaluated using finite element analysis (FEA).

Results: It was revealed that the patient's age impacts pelvic bones and cartilage density (in younger patients the pelvic elements are more pliable - p < 0.05). Stress distribution after each of the abovementioned pelvic osteotomy was assessed in 2- and 6-year-old patients' pelvic models. The new term "restriction point" was introduced, which means a place where restriction of acetabular deformity correction occurs.

Conclusions: It was found that there are no purely reshaping and reorientation pelvic osteotomies as previously believed; the pelvic ring acts as a unit in carrying out the applied load. Biomechanical overload of triradiate cartilage during Salter osteotomy in 2-year-old patients and in 2- and 6-year-old patients during Pemberton osteotomy was revealed; overload of the posterior cortical layer in the greater sciatic notch in 2-years old patient during Dega osteotomy was revealed.

KEY WORDS: Developmental Dysplasia of the Hip, pelvic osteotomy, finite element analysis, hinge point, biomechanics

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INTRODUCTION

Developmental Dysplasia of the Hip (DDH) is a common hip disorder in neonates [1]. Without treatment, DDH leads to early-onset hip arthritis [2]. Early detected DDH may be successfully treated non-operatively while surgery is necessary in neglected cases or after failed non-operative treatment [3]. Among surgical options, pelvic osteotomies are deemed to play a key role in acetabular deformity correction [4].

Three reconstructive pelvic osteotomies (Salter, Pemberton, and Dega) are widely used in patients under 6 years old, when the most active acetabulum development occurs [5-6]; these osteotomies are further divided on reorientation and reshaping [7-8]. Correction of acetabular deformity during pelvic osteotomies occurs due to the distal iliac bone fragment reorientation. "Hinge points" are those anatomical structures where plastic changes take place during fragments' reorientation [9] (in this paper "plasticity" was defined as "the ability to retain a shape attained by pressure deformation" according to Merriam-Webster dictionary).

It is suggested that symphysis pubis cartilage is the hinge point during Salter osteotomy, triradiate cartilage - during Pemberton osteotomy, posterior-medial cortical layer in the greater sciatic notch – during Dega osteotomy [10-12]. The number and location of hinge points are important for the surgeon in terms of their possible damage during surgery and of possible pelvic osteotomies combinations.

To the best of the authors' knowledge, there are no biomechanical investigations to identify the number and location of hinge points during pelvic osteotomies for DDH treatment in pediatric patients. Moreover, some inconsistencies exist about hinge points' number and locations and further division of pelvic osteotomies on reorientation and reshaping is under question [13-14].

Another shortcoming of current research is the absence of ligaments' role during pelvic osteotomies. However, the authors of this article believe that pelvic ligaments will play a major role as restrictors during acetabular reorientation.

The last question that is not covered in the literature is the patients' age impact on biomechanical changes during pelvic osteotomies; however, different results previously were described in younger and older patients [15-17].







Fig. 2. Pelvic model with simulated Pemberton osteotomy and assigned materials.

Fig. 3. Mesh-model of Pemberton pelvic osteotomy with pelvic ligaments.

Finite Element Analysis (FEA) is a reliable method for the simulation of load application in biological models. There are some FEA investigations dedicated to the load distribution in the human pelvis in different conditions [18-20].

2) To reveal load distribution during pelvic osteotomies

- using these models.3) To investigate pelvic ligaments' role during pelvic osteotomies.
- 4) To find out the impact of patient's age on biome-
- chanical changes during pelvic osteotomies.

MATERIALS AND METHODS

PELVIC MESH MODELS

Pelvic CT scans of 2-years old (y.o.) and 6-y.o. patients without hip joint pathologies were obtained from the

THE AIM

The aims of this paper were:

 To create reliable models of human pelvises of 2- and 6-years old patients; to simulate the abovementioned pelvic osteotomies on these models.



Fig. 4. Distribution of von Mises stress during Salter pelvic osteotomy. In the upper row, it is 2-y.o. patients' pelvic model; in the lower row – 6-y.o. patients' pelvic model. White spirals represent spring elements of pelvic ligaments.



Fig. 5. Distribution of von Mises stress during Pemberton pelvic osteotomy. In the upper row, it is 2-y.o. patients' pelvic model; in the lower row - 6-y.o. patients' pelvic model.

hospital database. CT scans were performed on spiral CT-scanner "Siemens somatom definition as, USA" with slice thickness 0.8 mm. in 2-y.o. patient and 1.5 mm. in 6-y.o. patient. For reviewing CT-scans software "Medixant. RadiAnt DICOM Viewer [Software]. Version 2020.1. Mar 9, 2020" was used.

CT scans of both patients were transported into Mimics 20.0 (Materialise Inc., Leuven, Belgium), where pelvic bones and sacrum automatic segmentation was performed. Pelvic cartilages were added manually according to the anatomical landmarks [21]. Three pelvic osteotomies (Salter, Dega, Pemberton) were simulated manually on both pelvic models (of 2y.o. and 6-y.o. patients) according to their descriptions in the literature [7-8]. Finally, 6 pelvic models with simulated pelvic osteotomies were available for further work.

Voxel-based mesh models [22] were created for the simulation of load distribution during pelvic osteotomies (due to the variable cortical bone thickness in different pelvic regions [23]). Tetrahedral 4-point node mesh models of each pelvic osteotomy were created with XY resolution = 2 pixels (P) *0.50P and

Ligament	Stiffness (N/mm)	Number of elements
sacroiliac	5000	45
sacrospinous	1500	12
sacrotuberous	1500	30
superior pubic	500	10
arcuate pubic	500	15

Table I. Pelvic ligaments and their mechanical properties.



Fig. 6. Distribution of von Mises stress during Dega pelvic osteotomy. In the upper row, it is 2-y.o. patients' pelvic model; in the lower row - 6-y.o. patients' pelvic model.

Z resolution = 1P*0.70P for 2-y.o. patients' pelvic models; XY resolution = 2P*0.57P and Z resolution = 1P*1.20P for 6-y.o. patients' pelvic models. Mesh density was calculated accordingly to the minimally possible elements' size. The edge length of tetrahedral elements was 0.99 mm in all 2-y.o. patients' pelvic models, the number of elements in these models was 9 485 028; Edge length of tetrahedral elements was 1.15 mm in all 6-y.o. patients' pelvic models, the number of elements in these models was 10 467 600.

MATERIAL PROPERTIES

Material density was calculated according to Sun W. [24]: *Eq. 1* for Hounsfield units (Hu) \leq 816; *Eq. 2* for Hu > 816. Pelvic models (both bone and cartilage

elements) were divided into 10 different materials according to Hounsfield units values [25] as proposed by Zhixiu Hao et al. [26]. The value of each material was equal to the mean Hu values of all elements included in this group whether the material was bone or cartilage (Fig. 1). Material density for pelvic bones and cartilages ranged from 0.13 to 1.82 in 2-y.o. patients' pelvic models and from 0.06 to 2.3 in 6-y.o. patients' pelvic models.

Young's modulus (*E*) was calculated according to Carter and Hayes [27] (Eq. 3). Young's modulus ranged from 7.73 MPa to 17488 MPa in 2-y.o. patients' pelvic models and from 0.53 MPa to 35257 MPa in 6-y.o. patients' pelvic models.

Poison's ratio (\mathbf{v}) was assigned according to Shen, M. et al. [20] (0.2 for cartilage and for trabecular bone, 0.3 – for cortical bone). For material with E>12240 MPa (cortical bone) Poison's ratio was assigned as 0.3; for material with $E \le 12240$ MPa Poison's ratio was assigned as 0.2 (without further separation on trabecular bone and cartilage because γ is the same for these tissues).

Example of 6-y.o. patient's pelvic model with simulated Pemberton osteotomy and assigned materials is presented in Fig. 2.

PELVIC LIGAMENTS

Pelvic models with simulated osteotomies and assigned materials properties were transported into ABAQUS v6.14-2 (Dassault Systemes Simulia Corp., Providence, RI, USA).

Pelvis ligaments were added manually as spring elements with a polyaxial degree of freedom. The number of ligaments was in concordance with their number in the native pelvis; ligaments were added manually according to the anatomical landmarks [28-29]. The number of elements in pelvic ligaments and their material properties was set according to the literature data [26] (Table I). Other pelvic girdle restrictors (muscles, hip joint capsule) were not added due to the authors' belief that pelvic ligaments are the main restrictors during pelvic osteotomies.

Pelvic mesh-model with simulated Pemberton osteotomy and added ligaments is presented in Fig. 3.

Table II. Biomechanical changes during Salter, Pemberton and Dega pelvic osteotomies.

2 y.o. patients' pelvic model		6 y.o. patients' pelvic mode	I
	Salter osteotom	У	
Hinge points	v.M stress	Hinge points	v.M stress
Triradiate cartilage posterior arm	1.9e+01	Pubic bone symphysis	6.1e+01
Contralateral pubic bone metaphysis	1.7e+01	Ipsilateral and contralateral pubic bone	450101
lpsilateral pubic bone metaphysis	1.3e+01	metaphyses	4.50+01
Diffuse points at contralateral and ipsilateral pubic and ischium bones; anterior and posterior limbs of the contralateral triradiate cartilage	9.9e+00	Diffuse points at contralateral and ipsilateral pubic and ischium bones	2.3e+00
Restriction points	v.M stress	Restriction points	v.M stress
Sacrospinous and sacrotuberous ligaments attachment point to the ipsilateral sacrum	3.9e+01	Sacrospinous and sacrotuberous ligaments attachment point to the ipsilateral sacrum	1.3e+02
Sacrotuberous ligament attachment point at the ipsilateral ischial tuberosity	1.7e+01	Sacrospinous and sacrotuberous	450+01
Contralateral sacroiliac ligament attachment points contralateral	1.1e+01	ipsilateral ischial spine and tuberosity	4.50+01
Sacrotuberous ligament attachment points to contralateral ischial tuberosity	1.5e+00	Sacrospinous and sacrotuberous ligaments attachment point to the contralateral sacrum	2.8e+01
Sacrospinous and sacrotuberous ligaments attachment point to contralateral sacrum; sacrospinous ligaments	8.3e+00	Sacrotuberous ligament attachment points to the contralateral ischial tuberosity	1.7e+01
attachment point to the contralateral ischial tuberosity		Contralateral sacroiliac ligament attachment points	2.8e+00
Pe	mberton osteoto	omy	
Hinge points	v.M stress	Hinge points	v.M stress
Triradiate cartilage posterior arm	6.1e+01	Triradiate cartilage posterior arm	3.8e+01
Triradiate cartilage anterior arm	2.0e+01	Triradiate cartilage anterior arm	7.9e+00
Triradiate cartilage inferior arm	1.0e+00	Triradiate cartilage inferior arm	7.9e+00
Contralateral and ipsilateral pubic bone metaphysis	1.0e+00	lpsilateral pubic bone metaphysis	6.3e+00
Ipsilateral pubic and ischium bones diffuse points	7.7e+00	lpsilateral pubic and ischium bones diffuse points	6.3e+00
Restriction points	v.M stress	Restriction points	v.M stress
Sacrospinous and sacrotuberous ligaments attachment point to the ipsilateral sacrum	1.3e+01	Sacrospinous and sacrotuberous ligaments attachment point to the ipsilateral sacrum	1.7e+01
Sacrospinous and sacrotuberous ligaments attachment point to the ipsilateral ischial spine and ischial tuberosity	1.0e+01	Sacrospinous and sacrotuberous _ ligaments attachment point to the	1 30+01
Sacrospinous and sacrotuberous ligaments attachment point to the contralateral sacrum	7.7e+00	ipsilateral ischial spine and ischial tuberosity	1.56401
	Dega osteotom	У	
Hinge points	v.M stress	Hinge points	v.M stress
Posterior iliac cortical layer in the greater sciatic notch region	6.6e+01	Posterior iliac cortical layer in the greater sciatic notch region	1.1e+01
Medial cortical layer of the uncut iliac bone	1.4e+01	Medial cortical layer of the uncut iliac	3 1e+00
Triradiate cartilage posterior arm	1.1e+01	bone	5.10+00
Restriction points	v.M stress	Restriction points	v.M stress
Sacrospinous and sacrotuberous ligaments attachment point to the ipsilateral sacrum	2.8e+01	Sacrospinous and sacrotuberous ligaments attachment point to the ipsilateral sacrum	3.5e+00
Sacrospinous and sacrotuberous ligaments attachment point to the ipsilateral ischial spine and ischial tuberosity	1.4e+01	Sacrospinous and sacrotuberous _ ligaments attachment point to the	2 60±00
Sacrospinous and sacrotuberous ligaments attachment point to the contralateral sacrum	1.1e+01	ipsilateral ischial spine and ischial tuberosity	2.00100
BIOMECHANICAL CHANGES ASSESSMENT

First of all, auto-computed von Mises (v.M.) stress was encountered. Then, we observed the same v.M. stress distribution after establishing the upper limit manually as half of the upper auto-computed limit. It was made to reveal more points where stress is generated that may be overlooked using auto-computed values. It was set as 1.9e+01 and 6.7e+01 for Salter osteotomy pelvic models (2-y.o. and 6-y.o.); 3.3e+01and 5.3e+00 for Dega osteotomy pelvic models (2-y.o. and 6-y.o.); 3.1e+01 and 1.9e+01 for Pemberton osteotomy pelvic models (2-y.o. and 6-y.o.).

Data of von Mises stress with manually established upper limit were taken for further analysis.

STATISTICAL VALIDITY

The results were considered statistically significant with p<0.05. To perform statistics calculations JASP Team (2020). JASP (Version 0.11.1.0)[Computer software] was used.

RESULTS

After performed CT-scans segmentation it was revealed that 2-y.o. patients' pelvic model has a lower element density than 6-y.o. model according to gray-value-based scale (p<0.05). This difference reflects a different proportion of bone and cartilage tissues and different plasticity and pliability of these tissues during surgeries in 2-y.o. and 6- y.o. patients. Thus, in younger patients it may be a larger potential for deformity correction due to greater plasticity of pelvic elements.

After pelvic osteotomies, FEA von Mises stress was assessed. Those areas distally to the lower iliac bone fragment where the stress was generated during load application, which further led to acetabular deformity correction were named "hinge points". Those areas where the stress was generated during load application, which led to the restriction of acetabular deformity correction were named as "restriction points". This term is new and was not coined previously. In this paper hinge points in the upper iliac bone fragments were not encountered for the following reason: deformity in a sacroiliac joint doesn't lead to acetabular deformity correction.

The biomechanical changes that occur during Salter, Pemberton and Dega pelvic osteotomies in 2- and 6-years old patients' pelvic models are presented in Table 2 and in Figures 4-6. After the performed FEA it was revealed that there is no single hinge point during Salter, Dega and Pemberton osteotomies in 2- and 6-years old patients (contrary to the previously established opinion). Stress generation was revealed in the contralateral hemipelvis during Salter pelvic osteotomy in both pelvic models and in 2-y.o. patient's pelvic model during Pemberton osteotomy.

The main hinge point during the abovementioned pelvic osteotomies was the following: Salter osteotomy - ipsilateral triradiate cartilage posterior limb in 2-y.o. patient's pelvic model and pubic bone symphysis in 6-y.o. patient's pelvic model; Pemberton osteotomy the posterior triradiate cartilage limb in both 2- and 6-y.o. patient's pelvic models; Dega osteotomy - the posterior iliac cortical layer in a greater sciatic notch region in both 2- and 6-y.o. patient's pelvic models.

Restriction points presented themselves the attachment points of ligaments, which are connected with a stable point (sacrum): sacrotuberous, sacrospinous, sacroiliac. Sacrospinous and sacrotuberous ligaments were found to be the most reasonable restrictors of acetabulum reorientation in all the cases.

DISCUSSION

Two commonly accepted theories applied for pelvic osteotomies for DDH treatment in pediatric patients are 1) the location of hinge points during each osteotomy and 2) the division of pelvic osteotomies on reorientation and reshaping [7-8]. In this work, the simulation of three pelvic osteotomies (Salter, Dega, Pemberton) according to their descriptions in the literature was performed on 2 and 6 years old children's pelvic digital models. Mesh models of these pelvises with simulated surgeries were created; material properties were assigned according to the voxel-based method; pelvic ligaments were added as main movement restrictors (according to authors' belief); boundary conditions were set and the load was applied.

After performing FEA, it was revealed that there is no single hinge point during pelvic osteotomies, applied load "moves" circumferentially from the applied place and causes stress generation in different pelvic areas. This fact puts under question the traditional division of pelvic osteotomies on reorientation and reshaping; each osteotomy may become reshaping due to the plastic changes that take place in triradiate cartilage.

It was found out that during Salter osteotomy there is a possibility of triradiate cartilage injury in 2-y.o. patient (due to triradiate cartilage overloading). Also, we've found that in 2-y.o. patient contralateral pubic bone metaphysis is mainly loaded rather than symphysis pubis cartilage which proves Thompson A. [13] results and contradicts the accepted theory about hinge point location [7].

During Pemberton osteotomy anterior and posterior triradiate cartilage limbs are mainly loaded; this may lead

to damage and further triradiate cartilage closure (as described previously [11]). In 2-y.o. patient contralateral hemipelvis was loaded that put under question the possibility of simultaneous bilateral application of this technique or its' combination with other osteotomies (contrary to others [12]). However, in 6-y.o. patients, the bilateral application of Pemberton osteotomy or its combination with other osteotomies is biomechanically possible.

During Dega osteotomy, the main stress was generated in the posterior iliac cortical layer in a greater sciatic notch (that proves "traditional" hinge point location [15]). Excessive pressure during surgery may potentially lead to fracture in this region. Simultaneous bilateral application of Dega osteotomy is biomechanically possible due to absent stress generation in the contralateral hemipelvis.

In this work, it was revealed that pelvic ligaments play a major role as restrictors during pelvic osteotomies; this issue is not covered in current literature. Authors called ligaments'attachment points" restriction points". Sacrospinous and sacrotuberous ligaments were found to be the main restrictors during lower iliac bone fragment movement.

In this work, it was observed the influence of patients' age on biomechanical changes during pelvic osteotomies. Two reasons may explain this: 1) different pelvic elements' density and 2) different biomechanics in younger and older patients during pelvic osteotomies. It was revealed that pelvic elements in 2-y.o. patients' pelvic model are much "softer" (p<0.05) than in 6-y.o. one; so, hypothetically, less load may cause more acetabular deformity correction. Also, more cartilaginous hinge points were revealed in 2-y.o. patients' pelvic models; this allows more acetabular deformity correction too. Thus, the patient's age may have an impact on results (as described by others [15-17]).

CONCLUSIONS

- 1) There is no single hinge point during Salter, Dega and Pemberton osteotomies.
- 2) During Salter osteotomy, the ipsilateral triradiate cartilage posterior limb was mainly loaded in 2-y.o. patient's pelvic model. The contralateral hemipelvis was heavily loaded during this technique in both pelvic models.
- During Pemberton osteotomy, the anterior and posterior triradiate cartilage limbs were mainly loaded. The contralateral pubic bone was loaded in 2-y.o. patient's pelvic model.
- In Dega osteotomy, the posterior iliac cortical layer in a greater sciatic notch region was mainly loaded. The contralateral hemipelvis wasn't loaded.

APPENDICES

Eq. 1: $g(g/cm^3) = 1.9 \cdot 10^{-3} QCT+0.105;$ Eq. 2: $g(g/cm^3) = 7.69 \cdot 10^{-4} QCT+1.028;$ g-density (g/cm^3); QCT - quantitative computed tomography number, the value of QCT is equal to Hu;

Eq. 3: $E = E_c \cdot \varepsilon^{0.06} \cdot (\rho/\rho_c)^3$;

E – Young's modulus (MPa), ϵ – the strain rate (/s), ϱ – density (g\cm³); E_c and ρ_c – Young's modulus and density under the strain rate ϵ =1.0/s (22,100 MPa and 1.8 g\ cm³ respectively).

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ORIGINAL ARTICLE

COPING STRATEGIES AND PSYCHOLOGICAL ADJUSTMENT TO THE COVID-19 PANDEMIC AMONG THE UKRAINIAN STUDENTS' YOUTH

DOI: 10.36740/WLek202308116

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ABSTRACT

The aim: Establishment of emotional and behavioral ways of student response to the coronavirus pandemic, the assessment of dominant coping strategies, and the prevalence of neurotic states and stress among students.

Materials and methods: The research used a specially developed questionnaire and a block of psychodiagnostic methods for diagnosing manifestations of neurotic conditions in students (Clinical questionnaire for the detection and assessment of neurotic conditions by K.K. Yakhin, D.M. Mendelevich), the level of psychological stress (Psychological Stress Scale PSM-25) and basic coping strategies (R. Lazarus'"Coping Strategies" questionnaire). The sample consisted of 213 respondents (119 girls, and 94 boys).

Results: Among Ukrainian students, the dominant reactions to the pandemic are depressive disorders, anxiety, and fears, a third of students self-reported autonomic disorders. The stress level is moderate. Girls react to the pandemic situation with more serious mental health disorders compared to boys. The use of all coping strategies was recorded at a high level of stress, which suggests that students have already exhausted their adaptation potential and are maladapted to the current conditions.

Conclusions: The study confirms the negative impact of the pandemic on the mental health of young people. The relationship between the type of response to the pandemic and the severity of neurotic disorders and stress was established. Available mental resources to cope with a difficult situation are exhausted, so students prefer to avoid and ignore stressful information. This creates the need for psychological support and educational activities regarding healthcare techniques.

KEY WORDS: pandemic, COVID-19, youth, mental health, coping

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INTRODUCTION

During the coronavirus pandemic, there is a deterioration in the mental health of the population, especially among patients with the coronavirus, their relatives, and medical workers who constantly work under stressful conditions. The coronavirus affects the mental state of patients in two ways: it directly affects the nervous system [1], causing disorders of the psyche, emotions, cognition, and consciousness, as well as indirectly through the influence of stressful information about the spread of coronavirus disease, mortality, complications, thus causing psychogenic disorders [2-6].

Of course, most of the attention during the coronavirus pandemic is on physical health and the negative consequences of the disease for the body. However, over time, there are more and more studies of mental and emotional states that occur during self-isolation, negative reactions to quarantine restrictions, fear of getting sick, and the consequences of illness on mental health [7, 8].

The COVID-19 pandemic and quarantine in many countries led to intense and general distress, and the development of several mental disorders: anxiety, depression, burnout [7, 9], acute stress disorder, post-traumatic stress disorder [10, 11], obsessive-compulsive disorder [10]. In Italy, negative consequences for mental health among the population were found 3 weeks after the adoption of isolation measures against COVID-19: signs of post-traumatic stress disorder were found in 37%, depression in 17.3%, increased anxiety in 20.8%, impaired sleep in 7.3%, severe stress in 21.8% and adaptation disorders in 22.9% [11].

Even before the pandemic, high baseline levels of stress and mental health problems among students at higher education institutions were demonstrated. [12]. William E. Copeland from the University of Vermont found that college freshmen during the COVID-19 pandemic had an increase in "externalizing problems" (aggression or behavior that affects others), and attention deficit disorder [13].

A relatively new concept is deprivation stress, which occurs in response to self-isolation and quarantine restrictions introduced by the governments of various countries given the seriousness of the situation [2]. Quarantine measures can vary from minor (closing entertainment facilities or limiting the number of people in them) to stopping traffic and banning people from leaving the house. A remote form of work or study also leads to a change in the daily routine, nutrition, and a decrease in physical activity and social interaction. Although various online platforms are coming as a substitute for direct personal communication, they are only temporary and imperfect surrogates that cannot compensate for the lack of "live" communication.

Also, isolation at home increases anxiety and depression and can provoke physical violence. As reported by French researchers [14], the psychological consequences of self-isolation include mood disorders, anxiety, panic disorders, addictive behavior, and suicide attempts.

THE AIM

The purpose of the study was to establish the emotional and behavioral ways students respond to the coronavirus pandemic and to diagnose dominant coping strategies and the prevalence of neurotic states and stress among students.

MATERIALS AND METHODS

With the help of psychodiagnostic methods, the level of severity of neurotic states in students was investigated (Clinical questionnaire for the detection and assessment of neurotic states by K.K. Yakhin, D.M. Mendelevich), the level of psychological stress (Psychological Stress Scale PSM-25) and the main coping strategies, which were used by respondents (R. Lazarus" Coping Strategy" questionnaire).

Research progress: 1. using a questionnaire to diagnose the type of response to the pandemic (indifference, anger, helplessness, fear). 2. using psychodiagnostic techniques to establish the level of neurotic states, stress, and dominant coping strategies among students during the pandemic. 3. to establish the severity of stress and neurotic disorders in students depending on their type of response to the pandemic (one-factor variance analysis). 4. establish connections between coping strategies and neurotic states and stress levels (correlation analysis).

Correlation analysis (Pearson's test), comparison of groups using univariate variance analysis, and Student's t-test were used to process the obtained results.

Sample: 213 people took part in the research, of which 44.1% were men, 55.9% were women, aged 17 to 23, students of the 1st-4th year of the NAU (specialty Aerospace faculty and Psychology), Taras Shevchenko Kyiv National University (specialty "Psychology" and "Military Service"), National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute".

RESULTS

The use of psychodiagnostic methods allowed us to assess the manifestations of neurotic disorders in young people (anxiety, depression, asthenia, hysterical type of response, obsessive-phobic states, and autonomic disorders) as well as the level of stress.

Analyzing empirical data, let us characterize the mental reactions of Ukrainian students to the coronavirus pandemic. Thus, 34.5% of respondents demonstrated a fairly high level of anxiety, which can be interpreted as a neurotic disorder. 45.5% responded with a depressive disorder, 41% had a phobic type of response, and 35.5% of respondents noted a high level of vegetative disorders. Similar results are presented in studies by authors from different countries [10, 11]. Instead, the majority were found to have a low level of stress (64%), an average level of stress 30.5% and a high level of stress only 5.5%. Perhaps this is because, at the time of testing, there were no strict quarantine restrictions, and most students adapted to all changes in social activity, including online learning.

It is worth noting that the sample as a whole showed a high intensity of all coping strategies. The tension is recorded in the range of 50-66%, which indicates a significant amount of effort that students spend on them for the active application. Young people spend a maximum of mental energy using coping mechanisms that the latter cease to be adaptive. Thus, being in the conditions of a pandemic for more than a year, students have already exhausted their adaptation potential and are maladapted to the current conditions. Data on maladaptation are consistent with data presented in studies [11].

It is important to note that, based on the results of comparing the data of boys and girls using the Student's t-test, we can say that girls have a significantly higher level of stress than boys (Table I). In girls, symptoms of

Table 1. Comparison of the level of stress and neurotic disorders among boys and qu	able I. Comparisor	of the level of stress a	and neurotic disorders	among boys and gi
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Indexes	Aver	Significance			
indexes	Girls, n=119 Boys, n=94		of the Student criterion		
Stress	102,7	71,4	0,001		
Anxiety	-0,8	3,33	0,001		
Neurotic depression	-2,4	1,16	0,001		
Asthenia	0,33	5,07	0,001		
Hysteria	-1,3	2,6	0,001		
Obsessive-phobic states	-1,9	1,5	0,001		
Vegetative disorders	-2,06	7,4	0,001		

Table II. Indicators of neurotic disorders in groups of students with different types of emotional response to the pandemic

	Group 1 (indifference)	Group 2 (malice)	Group 3 (impotence)	Group 4 (fear)
Stress	74,38	91,34	105,08	90,74
Anxiety	3,47	0,37	-1,22	0,19
Neurotic depression	1,62	-1,69	-3,72	-0,72
Asthenia	4,91	2,09	-0,63	1,85
Hysteria	2,78	-0,01	-2,36	-0,33
Obsessive-phobic states	1,60	-0,58	-2,14	-1,78
Vegetative disorders	6,87	1,52	-3,02	0,05

Table III. Significant correlation between coping strategies, stress and neurotic disorders in student youth

Scales	Anxiety	Neurotic depression	Asthenia	Hysterical type of reaction	Obsessive-phobic states	Vegetative disorders	Stress
Confrontational coping	-0,254**	-0,214**	-0,203**	-0,299**	-0,219**	-0,225**	0,351**
Distancing	-0,156*	-0,184*	-	-0,213**	-0,211**	-0,232**	0,306**
Self-control		-0,165*	-0,182**		-0,193**	-0,181**	0,214**
Avoidance	-0,509**	-0,524**	-0,514**	-0,537**	-0,466**	-0,525**	0,657**
Planning problem solving	-	0,205**	-	-	-	-	-
Positive reassessment	-	-	-	-0,170*	-0,183**	-0,167*	0,198**
Acceptance of responsibility	-0,356**	-0,298**	-0,420**	-0,294**	-0,364**	-0,361**	0,411**

*- Correlation relevant for level 0.05 (2-side)

**- Correlation relevant for level 0.01 (2-side)

anxiety and neurotic depression are also significantly more pronounced, as well as hysterical reactions and asthenia. Girls also more often notice obsessive-phobic and vegetative disorders in themselves compared to boys. The fact that the pandemic situation has a worse effect on women's mental health is confirmed by research [15].

To establish the type of response of students to the pandemic, they were offered a questionnaire. To the question "What feelings does the pandemic situation cause you?" we received the following distribution of answers: 28.8% - indifference; 27.4% - anger, irritation due to restrictions; 17.2% - helplessness, depressed mood; 17.2 – fear, anxiety, concern. The other 9.4% gave the following answers: anxiety for close elderly

relatives, upset, anger at people who ignore quarantine restrictions, etc.

Based on the answer to this question, the respondents were divided into four groups. Using univariate analysis of variance (ANOVA), it was established which neurotic disorders prevail in each of them (Table II). We immediately note that the most psychologically healthy group was the group of respondents who answered that the situation of the pandemic causes them indifference, in this group no pronounced neurotic disorders were recorded.

In the group of respondents who named anger as the dominant emotion, violations on the scale of neurotic depression were the most pronounced, and manifestations of asthenia were the least characteristic of them. Neurotic disorders on almost all scales were found in the group of "helpless respondents". They showed symptoms of depression, and hysteria and confirmed the most autonomic disorders (sleep disorders, heart pain, etc.). For the group of respondents who answered that they feel fear, obsessive-phobic disorders were the most pronounced.

With the help of correlation analysis using Pearson and Spearman criteria, we planned to find out the relationship between coping strategies with neurotic disorders and stress in students during the pandemic. It was established that the coping strategies used by young people are associated with the development of neurotic disorders (Table II). When analyzing these data, it is worth taking into account the peculiarities of the calculation of points according to the method of assessment of neurotic states by K.K. Yakhina, D.M. Mendelevich (the higher the score on the scales, the higher the level of mental health, the lower the score, the more pronounced the corresponding disorder).

While analyzing correlations, we are taking into account the maladaptive level of coping. Judging by the inverse correlations presented in the table, we can say that the more mental health deteriorates, anxiety, depression, and fears increase and autonomic disorders manifest, the more young people try to apply various coping strategies with greater or lesser effectiveness. We would like to pay special attention to the fact that the strongest connection is manifested between the avoidance strategy and all types of neurotic disorders. In order not to worry, and to protect themselves from fears and depression, young people choose to deny the seriousness of the problem of the disease, to divert their attention to other matters, etc. Neurotic disorders are exacerbated by the use of confrontational coping and distancing. Also, significant relationships were established between neurotic disorders and the strategy of accepting responsibility. Excessive responsibility can likely cause feelings of guilt, increase anxiety and cause neurotic disorders.

Let us analyze the correlations between coping strategies and the level of stress. The more students are under the influence of stressful factors, the more they resort to various coping strategies. It is obvious to pay attention to the fact that to overcome stress, they may resort to impulsive reactions, conflicts, or manifestations of hostility. In the conditions of a pandemic, the Internet and social networks, where one can engage in verbal disputes with other users, can become a platform for confrontation. Also, students use avoidance and acceptance of responsibility as effective coping methods. Summarizing the results of the correlation analysis, it can be said that young people resort to various coping strategies to improve their mental state, but the high level of intensity of coping indicates their maladaptive nature.

DISCUSSION

Even at the beginning of the coronavirus pandemic, surveys showed the deterioration of the mental health of the population and the appearance of clinically significant symptoms of anxiety and depression [16]. However, the situation with mental disorders is complicated by the duration of the pandemic and its uncertainty: the population is tired of fearing for their health and the safety of their relatives, fatigue accumulates over time, and irritation increases due to guarantine restrictions and distance education. Studies indicate the predominance of a negative assessment of the pandemic and its consequences and the prevalence of depressive, anxious, hysterical-phobic reactions among students. Even though the vast majority of our respondents did not suffer from coronavirus or suffered from the disease in a mild form, the level of neurotic disorders in them is guite high. If Rettie, & Daniels report that about a quarter of the study participants showed significantly increased anxiety and depression, with 14.8% reaching the clinical threshold of health anxiety [10], then in our sample 34.5% of respondents showed a level of anxiety, which can be interpreted as a neurotic disorder. Numerous studies have confirmed the impact of the coronavirus pandemic on distress, the development of several mental disorders, mood deterioration [10], increased anxiety [10, 11], and depression [8, 10, 11].

The results of our study indicate higher rates of stress and neuropsychological disorders in girls, which is consistent with Kecojevic's data [15]. Rossi et al. indicate that women and youth were one of the most vulnerable population groups [11]. Women report significantly higher levels of fear related to COVID-19, more severe depressive symptoms, sleep disturbances, and higher levels of intolerance of uncertainty [8].

28.8% of students marked indifference as the main reaction to the situation with the coronavirus pandemic, which, in our opinion, may indicate denial of the existing problem and indicates an avoidance reaction quite typical for youth. Most respondents experience expressed negative emotions: anger, irritation, fear, anxiety, helplessness, and low mood. As noted by Sandín et al, the high level of the emotional impact of the pandemic is reflected in fear of the coronavirus, sleep problems, and emotional symptoms (worry, distress, hopelessness, depression, nervousness, and anxiety) [6].

CONCLUSIONS

The study of the reaction of student youth to the COVID-19 pandemic established the most common emotional and behavioral reactions, the severity of stress, neurotic disorders, and coping strategies. It has been established that the experience of helplessness provokes the most pronounced neurotic disorders, while an indifferent attitude to the threats of the pandemic preserves mental health and reduces the level of stress. The high

level of intensity of coping strategies determines their close connection with neurotic disorders: a long period of the pandemic leads to exhaustion of the ability to cope with problems, ineffective coping, and maladaptation. The significant prevalence of anxiety, depressive, and hysterical-phobic disorders indicates the need to pay more attention to their prevention and to develop adaptive coping strategies in students, to provide them with psychological support during the pandemic.

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REVIEW ARTICLE

APPLICATION OF SURROGACY TECHNOLOGY BY FOREIGNERS IN UKRAINE (LEGAL CONFLICT)

DOI: 10.36740/WLek202308117

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ABSTRACT

The aim: To establish legal conflicts between the use of surrogacy technology by foreigners in Ukraine, to develop mechanisms to overcome them. Materials and methods: The study used a methodology that embodies an interdisciplinary approach that allows systematic analysis of theoretical and

practical aspects of legal conflicts in the use of surrogacy technology by foreigners in Ukraine, as well as develop proposals for their elimination. **Conclusions:** It is proposed to adopt at the level of an international act unified approaches to determining the origin of a child born as a result of the use of surrogate motherhood technology to eliminate legal conflicts. The need to amend the legislation of Ukraine and the establishment of a ban on unilateral refusal from the surrogacy agreement after the embryo has been implemented is argued. Based on the analysis of judicial practice, it was established what problems may arise in the registration of paternity and maternity by foreign genetic parents in connection with the application of the surrogacy procedure by foreigners in Ukraine in cases where their native legislation does not permit or restricts surrogacy.

KEY WORDS: Assisted reproductive technologies, surrogacy, procedure, embryo

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INTRODUCTION

In Ukraine, the procedure of full surrogacy is currently allowed (a surrogate mother should not have a genetic link with the child). At the same time, the lack of clear legal requirements for the procedure of surrogacy, the relatively low cost of its implementation in Ukraine leads to significant demand among foreigners for the use of this reproductive technology.

Experts note that after the ban on surrogacy for foreigners in India, Ukraine has only increased demand for surrogacy, which has become an additional factor in transforming our country into one of the centers of surrogacy at the world level [1]. Given that more than 80% of couples who have used the services of surrogate mothers in Ukraine are foreign nationals, the issue of banning foreigners from using this method of assisted reproductive technologies has been repeatedly raised. At the same time, different legal regulation of surrogacy in Ukraine and abroad leads to legal conflicts over the use of this assisted reproductive technology by foreign nationals, creates additional obstacles in determining the origin of the child and further registration of his birth.

The relevance of the study is confirmed by the fact that in December 2021 and January 2022, four bills

on the legal regulation of assisted reproductive technologies were submitted to the Verkhovna Rada of Ukraine. Undoubtedly important is the desire of the Parliament of Ukraine to legislate the legal aspects of the use of various assisted reproductive technologies, which include surrogacy. Despite criticism in the press and public statements by some politicians, the bills do not propose to ban the use of surrogacy technology in Ukraine. That is, such reproductive technology will remain available to foreigners. At the same time, the government and three alternative projects have different, sometimes even opposite approaches to the legal regulation of surrogacy, different requirements for surrogate mothers, no equality and balance of interests in regulating the rights and responsibilities of genetic parents and surrogate mothers. requirements for the form of the surrogacy agreement and its essential conditions. There are no single approaches to resolving the legal consequences of force majeure. Yes, there are still many unresolved issues regarding the legal consequences of multiple pregnancies, the birth of a child with illness or the death of a child or the death of a surrogate mother. All bills require such a surrogate mother as having a child. However, there

are no guarantees for the child in the event of the death of the surrogate mother. Currently, there is a public and expert discussion of the bills, which shows a number of unresolved issues. This confirms the need for thorough research that would solve a number of practical problems and create the preconditions for the development of quality legislation in the field of regulating the use of all possible reproductive technologies.

Among scientists, the problem of legal regulation of various assisted reproductive technologies is of considerable interest, and the subject of most scientific papers is the analysis of the legal basis of surrogacy [2], the nature, conclusion and elements of surrogacy [3], clarifying the features of legal the status of the parties to the surrogacy agreement [4], protection of the rights of surrogate mothers [5] and children [6]. In addition, scientists have analyzed in a comparative aspect of the problem of legal regulation of the use of surrogacy technology in Ukraine and some foreign countries, including the United States [7, 8] and European countries. At the same time, in these works, the problems of legal regulation of surrogacy are not comprehensively clarified, which did not allow to develop common approaches to the use of such important assisted reproductive technology, taking into account a number of ethical, legal and religious aspects.

Scientists also substantiate the peculiarities of legal relations in the field of such ART as surrogacy, in particular the combination of public and private legal aspects, their regulation by the system of civil, medical and family law [9]. At the same time, in our opinion, the wording is more correct that in the relationship of surrogacy not only public and private legal aspects are combined, but a balance of public and private interests should be ensured. It is the guarantee of such a balance of interests that should be the basic value that will become the basis of the legislative act that will regulate the use of assisted reproductive technologies. Moreover, the regulation should have a clear legal definition of the possibility of surrogacy by foreigners and establish special legal protection for children born to surrogate mothers. Ensuring the best interests of the child in the use of surrogacy should be key to regulating the legal relationship between the genetic parents, the surrogate mother and the medical institution.

THE AIM

This article is for installation to establish legal conflicts between the use of surrogacy technology by foreigners in Ukraine, to develop mechanisms to overcome them.

MATERIALS AND METHODS

The study used a methodology that embodies an interdisciplinary approach that allows systematic analysis of theoretical and practical aspects of legal conflicts in the use of surrogacy technology by foreigners in Ukraine, as well as develop proposals for their elimination. The specified system of methodology included: the historical method which is applied at the analysis of transformation of legislative approaches to regulation of technology of surrogacy; systemic to determine and clarify the legal nature of surrogacy; the formal-legal method was used in the analysis of the texts of current domestic regulations, the legislation of the Member States of the European Union governing surrogacy, as well as case law; legal hermeneutics was used to clarify the content of regulations governing the procedure for the use of surrogacy; the comparative legal method was used to clarify the differences in the legal regulation of the procedure of surrogacy in Ukraine and abroad; the forecasting method provided an opportunity to develop proposals for resolving legal conflicts that occur when using the method of surrogacy by foreigners in Ukraine; The dialectical method has helped to clarify the possibility of protecting the rights of genetic parents and children born to surrogate mothers. Methods of critical analysis have become the basis for clarifying the positions of scientists. This methodology allowed a thorough study of empirical data, statistics, case law of Ukrainian courts, as well as the case law of the European Court of Human Rights.

Scientific researches, international conventions, national legislation of Ukraine, judicial practice, legal and ethical issues were used in the research.

The research work included three main stages. At the first stage of the work, the analysis of doctrinal sources, analytical materials, legislation and case law on the use of surrogacy in Ukraine was carried out. The essence of such assisted reproductive technology as surrogacy, as well as the types and legal basis for its use were clarified.

At the second stage of the research the working hypotheses were tested, the peculiarities of the conclusion, form and content of surrogacy agreements were investigated at the theoretical and practical levels. The importance of informing the genetic parents and the surrogate mother about the essential terms of the contract, the consequences of refusing to perform the contract, the legal consequences of the surrogate mother's failure to follow the doctor's instructions during pregnancy. In addition, they analyzed the legal positions of the European Court of Human Rights on the possibility of using surrogacy technology, legal certainty in the use of assisted reproductive technologies. Investigated the threats posed by the COVID-19 pandemic in the use of surrogacy technology by foreigners, as well as the protection of the rights and interests of children born to surrogate mothers. Legal conflicts were also revealed over the use of surrogacy technology by foreigners in Ukraine.

The third stage of the study included an analysis of possible ways to overcome the identified legal conflicts with the use of surrogacy technology by foreigners in Ukraine. At this stage, a scheme of the legal mechanism for registering the birth of a child by a surrogate mother and its export abroad by foreign genetic parents was formed. This scheme provides for two variable algorithms: 1) in the case where the genetic parents are citizens of a foreign state, which does not restrict the use of surrogacy; 2) in the case where the genetic parents are citizens of a foreign state that prohibits or restricts the use of surrogacy. It was established that with the second variable algorithm there is an additional stage - the court decision in Ukraine to establish the fact of family ties between the child and genetic parents. In addition, theoretical conclusions were substantiated and ways to improve the legal regulation of surrogacy were developed.

REVIEW AND DISCUSSION

Demand among foreigners for the services of surrogate mothers in Ukraine has led to the division of politicians, experts and citizens into two groups. Proponents of the ban on surrogacy in Ukraine refer to the provisions of Article 21 of the Convention for the Protection of Human Rights and Dignity of Human Rights in connection with the use of biology and medicine: the Convention on Human Rights and Biomedicine, which prohibits financial gain from the human body and its parts [8]. Emphasis is placed on the biotic aspects, the disruption of the emotional connection between mother and child in the perinatal period. In addition, it is noted that the amount of compensation for surrogate mothers contributes to the orientation of these medical services for foreign nationals and may worsen the demographic crisis in Ukraine and even threatens the nation's gene pool.

The Presidential Commissioner for Children's Rights Mykola Kuleba noted in 2020 that surrogacy in Ukraine is not regulated and leads to violations of children's rights, is a form of exploitation of women to earn income by private business [9]. In this regard, there are often suggestions that if not ban, then at least prevent the development of "surrogate tourism" [10]. The COVID-19 pandemic and the closure of borders have further drawn attention to the issue of surrogacy, when as of June 18, 2020, foreign parents who were citizens of 27 different foreign countries could not enter Ukraine and reunite with their 161 genetically related children. A total of 149 pairs of foreigners applied for permission to enter Ukraine [11].

Opponents of banning surrogacy by foreigners in Ukraine, including the Ukrainian Association of Reproductive Medicine, argue that restricting the use of surrogacy for foreigners is unacceptable, as it will not promote the development of reproductive medicine in Ukraine and significantly reduce financial revenues of clinics [12].

At present, Ukrainian legislation does not contain restrictions on the use of ART by foreigners, including the provisions of Article 123 of the Family Code, if an embryo conceived by a spouse who is a foreign citizen is transferred to a Ukrainian citizen, they are recognized as the child's parents [13].

In addition, the surrogacy procedure is regulated by the Order of the Ministry of Health of September 9, 2013 № 787, which stipulates that this method is used in the presence of medical indications and the necessary list of documents (surrogate mother's application, copy of passport, marriage certificate or on the divorce of a surrogate mother (except single women), a copy of the birth certificate of the child (children), the consent of the surrogate mother's husband to participate in the program, patient applications for ART, copies of their passports, marriage certificates, notarized copies of written contracts which is the surrogate mother and the genetic parents of the child) [14, 15].

In practice, the use of surrogacy in Ukraine is regulated by treaties. In the absence of legislation, there are many practical problems that can result in litigation, namely in cases where the surrogate mother does not want to give up the child or the future parents officially divorce, or the child is born with defects and so on.

The surrogacy agreement must contain the following conditions:

1) the subject of the contract (services provided by the surrogate mother for childbirth, childbirth and transfer to the genetic parents);

2) conditions and procedure for performance of the contract by the parties, conditions and procedure for the procedure, provision of necessary medical care and medical services to ensure the physical and psychological health of the surrogate mother, her place of residence during pregnancy, and household and other living conditions, the procedure for providing genetic parents with information about the health of the surrogate mother during pregnancy, etc.);

3) the procedure for settlements between the parties (the amount of compensation for childbirth, compensation for medical care, life and health insurance, daily expenses during pregnancy, including meals for surrogate mothers, household expenses, transportation costs, other costs agreed parties);

4) the rights and responsibilities of both surrogate mothers and genetic parents include: the right to information about the health of the fetus and surrogate mother, as well as her age, nationality, level of education, pregnancy, the right to be present at ultrasound; research and other important medical procedures, etc. The surrogate mother has the right to information about the child's genetic parents, the course of pregnancy, compensation for childbirth, reimbursement of personal and household expenses.

The duties of a surrogate mother include the following: to register for medical treatment; regularly visit a medical institution; monitor the progress of pregnancy, monitor health, follow the advice of a doctor, inform genetic parents about their health and the health of the child, transfer the child after it

5) liability of the parties for non-compliance with the terms of the contract. Given a number of practical problems in the implementation of surrogacy agreements, including failure to perform their duties, both surrogate mothers and genetic parents, it is necessary to clearly define the responsibilities of the parties, to provide for penalties [17]. The surrogacy agreement may provide for additional (optional) conditions, including the confidentiality of the terms of the agreement.

The unresolved problem is the lack of legal regulation of unilateral waiver of the surrogacy agreement. We are convinced that unilateral refusal is possible only before the implementation of the embryo in the body of a surrogate mother. After implementation, there should be a strict legislative ban on unilateral waiver of the surrogacy agreement, which must be established in the Law of Ukraine "On the use of assisted reproductive technologies", which is before parliament or, according to today's realities, prescribed in the agreement.

As a general rule, the surrogacy agreement must be terminated by its proper performance and the achievement of the desired result. At the same time, early termination of the contract is possible due to other circumstances: termination by mutual consent of the parties (it should be emphasized that both unilateral refusal and termination by agreement of the parties is possible only before the embryo is implemented in the woman); termination due to unforeseen circumstances (for example, termination of pregnancy for reasons beyond the control of the parties or due to threat to the life of the surrogate mother, death of the surrogate mother, death of the child during childbirth, etc.).

To register the birth of a child, the surrogate mother submits an application for the surrogate mother's consent to the spouse's consent to the spouse's registration of the child's parents, the signature of which must be certified by a notary, and a certificate of genetic relatedness of the parents (mother or father).) with baby [18].

Foreign citizens apply to embassies to bring their children to their country of origin. Parents from the United States and Canada apply for an average of three weeks, from Ireland for two to three weeks, from Australia for seven to eight weeks, and longer from the United Kingdom for about four months [19].

At the same time, problems may arise from the registration of paternity and maternity by foreign genetic parents due to different legislative regulations on the procedure of surrogacy in Ukraine and their country of origin. If surrogacy is prohibited in the country of origin, there is a risk of non-recognition of the paternity and maternity of a child born to a surrogate mother.

In addition, in some European countries (Germany, Spain, Great Britain) the law requires that a court decision issued in the country of birth of the child to confirm the family ties between the child and parents [20]. Without such a decision, the biological parents will not be able to legalize the fact of their paternity in the state of citizenship.

The Unified State Register of Judgments of Ukraine contains many examples of judgments in favor of genetic parents to establish the fact of kinship with a child. Thus, in the decision of the Solomyansky District Court of Kyiv of July 15, 2020, it was established that a child born in Kyiv through the use of assisted reproductive technologies is the son of Spanish citizens. The court decision states that the appeal to the court is conditioned by a special procedure for Spain to register paternity of children born by surrogacy abroad. In particular, according to paragraph 2 of the Instruction of the Main Directorate of Registers and Notaries of Spain of 18 February 2019 № 2367 on updating the registration of paternity of persons born by surrogacy, application for registration in the Consular Register of Civil Status on paternity of children born after publication orders are not subject to review, except when there are decisions of the judicial authorities of the country concerned, which are final and have entered into force [21]. Thus, the legislation of Spain establishes an imperative requirement for spouses to register in Spain the paternity of a child born to a surrogate mother - to obtain in Ukraine a relevant court decision confirming their family relationship.

In the decision of the Kupyansk District Court of the Kharkiv region of April 3, 2018, a German citizen was recognized as the father of two children (twins) born to a surrogate mother in Ukraine. Despite the fact that on February 2, 2018, the Kharkiv City Department of Civil Status Registration issued birth certificates of children,



Fig. 1. Legal mechanism for registration of the birth of a child by a surrogate mother and its export abroad by foreign genetic parents

which indicate the parents of German citizens. At the same time, the German embassy does not issue passports to children without a court decision establishing paternity, and in addition, a man who is married to a surrogate mother must be involved in the trial. This situation is due to the fact that German law prohibits surrogacy. The legal mother of children under German law is the woman who gave birth, ie the surrogate mother [22]. The possibility of acknowledging paternity of children exists only when the surrogate mother is not married. If the surrogate mother is married, the presumption of paternity of the surrogate mother's husband must also be rebutted in the court decision.

Litigation can be heard for more than one month, which entails additional financial costs for foreign nationals, related to both litigation and transport and other costs.

There is a well-known situation when in 2011 Italian citizens used the services of surrogacy in Ukraine. Despite the fact that the spouses were not provided with genetic material, the child, born to a surrogate mother, was registered as descended from Italian parents on the basis of documents issued by a medical institution. In October 2011, the child was transported to Italy, but after the Italian authorities established that there was no genetic link between the child and the parents, she was selected and transferred to a children's institution [23].

In dealing with the seizure of children from parents born to surrogate mothers, the ECHR proceeds from the protection of the right to privacy and the principle of the best interests of the child. In particular, in Paradiso and Campanelli v Italy (2017), the Grand Chamber emphasized the State's discretion in recognizing the right to use surrogacy and, given the facts, acknowledged the impact of the decision on the applicants, but concluded that there had been no violation of Article 8. Convention for the Protection of Human Rights and Fundamental Freedoms [24].

In the case of Mennesson v. France, the applicants traveled to California to use the services of an egg donor and a surrogate mother who gave birth to twins in March 2000. However, the French embassy refused to register the fact of birth due to lack of genetic connection of one of the parents, despite the decision of the California court. The applicants lived in France and challenged the refusal to register the birth with the ECHR, which found no violation of Article 8 of the Convention on Parents and admitted a violation of Article 8 on children (applicants 3 and 4) as the latter were in a state of legal uncertainty and: "... the consequences of non-recognition in French law of the legal relationship between parents and children are not limited to parents who have chosen a certain method of ART, prohibited in France. They also affect children themselves, whose right to respect for private life, which means that everyone should be able to establish the components of their personality, including the legal relationship between parents and children, is significantly violated. Accordingly, there is a serious question about the compatibility of this situation with the best interests of children"[25]. Thus, regardless of the prohibition or restriction of the use of certain ARTs in a foreign country, if the child was born to citizens of such parents abroad, the European Court of Human Rights proceeds from the position of protecting the child's rights and best interests.

CONCLUSIONS

In Ukraine, there is no proper legislative regulation of the use of surrogacy, as well as other assisted reproductive technologies. That is why it is time to adopt a law that would establish legal certainty in the use of assisted reproductive technologies, would be high quality and effective in regulating surrogacy. Improving the current Ukrainian legislation by adopting a high-quality, clear and predictable law is in line with the case law of the European Court of Human Rights and meets international standards.

There are legal conflicts in connection with the application of surrogacy by foreigners in Ukraine in cases where their legislation of their country of origin does not allow or restrict surrogacy. Hundreds of cases are heard by the courts of Ukraine every year on the basis of applications from citizens of Great Britain, Spain and Germany to confirm their family ties with children born to surrogate mothers. This is due to the requirements of foreign law, not Ukraine.

Analysis of the legal mechanism of registration of the birth of a child by a surrogate mother and its export abroad by foreign genetic parents allowed to identify two variable algorithms: in the case where the genetic parents are citizens of a foreign state, which does not restrict the use of surrogacy; in the case where the genetic parents are citizens of a foreign state that prohibits or restricts the use of surrogacy. It was established that the second variable algorithm has an additional stage - a court decision in Ukraine to establish the fact of family ties between the child and genetic parents.

In order to eliminate such legal conflicts, it is necessary to establish common approaches at the level of an international act to determine the origin of a child born as a result of surrogacy technology, which in our opinion will be in the best interests of children and relevant ECHR practice.

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PREECLAMPSIA AND ITS EFFECT ON THE STATE OF CARDIOVASCULAR SYSTEM IN WOMEN

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ABSTRACT

The aim: To determine the features of the impact of preeclampsia on the development of cardiovascular disorders in women in the future. Materials and methods: The study involved an assessment of literary sources, which were published mainly in the last five years, using scientometric and specialized databases Pubmed, Science direct, Scopus, Web of Science, Google Scholar and V.I. Vernadskyi NLU "Scientific Periodicals of Ukraine". Conclusions: Cardiovascular disorders are not only a medical problem, but also a social one. Preeclampsia is a dangerous condition that contributes to the development of CVDs, increases the rate of mortality and disability among women. All this makes it absolutely necessary to study the features of the pathogenesis in detail, to understand exactly how, through which mechanisms, the preeclamptic state affects the woman's body, and this will allow doctors to indirectly influence its pathogenesis and reduce negative consequences and improve the quality of life.

KEY WORDS: preeclampsia, cardiovascular diseases, risk of development, pathogenic links, cardiovascular biomarkers

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INTRODUCTION

Cardiovascular diseases rank first among all causes of disability and mortality of the population. Arterial hypertension (AH), as the most common representative of this cohort of diseases, occupies a special place among the most pressing issues of medicine in general and the medico-social well-being of mankind. To date, an increase in the mortality rate from cardiovascular diseases (CVDs) has been noted in women, both individually and in comparison with men. Cases of cardiovascular impairments have become more frequent among women of young age (from 25 to 35 years), but the causes of their development are at the stage of consideration [1]. An opinion is expressed about the connection of CVDs in women with pregnancy and its pathological conditions [2]. Since pregnancy is a special stage of a woman's life and is a "stress test" for all body systems, its complications can become powerful inducers of the development of various somatic diseases, even in healthy young women [3].

THE AIM

To determine the features of the impact of preeclampsia on the development of cardiovascular disorders in women in the future.

MATERIALS AND METHODS

The study involved an assessment of literary sources, which were published mainly in the last five years, using scientometric and specialized databases Pubmed, Science direct, Scopus, Web of Science, Google Scholar and V.I. Vernadskyi NLU "Scientific Periodicals of Ukraine".

REVIEW AND DISCUSSION

Preeclampsia (PE) is a complication of pregnancy, which is considered a multisystem abnormal process with characteristic manifestations in the form of arterial hypertension (an increase in arterial systolic pressure \geq 140 mmHg and diastolic pressure \geq 90 mmHg) and proteinuria (significant \geq 0.3 g per day), developing after the 20th week of pregnancy. PE has a complex pathophysiological mechanism, and is currently not fully understood. Currently, the main links of the pathogenesis of this abnormality are considered to be as follows: endothelial dysfunction, changes in the reactivity of the immune system, metabolic transformations with the formation of oxidative stress, features of lipid metabolism, changes in the concentration of cytokine components, activation of the primary links of inflammation, etc. [4-7].

Why is preeclampsia of interest not only to obstetricians and gynecologists, but also to related specialists? Because it is characterized by the development of very serious complications, such as eclampsia (E), acute renal failure (ARF), HELLP syndrome, malignant arterial hypertension. But doctors do not always pay timely attention to the first manifestations of this grave disorder, which can rightfully be considered an inducer of the development of cardiovascular diseases [8].

The opinions of advanced obstetric schools, foreign and domestic scientists, and the European Society of Cardiology agree that the course of preeclampsia provokes the development of cardiovascular diseases, and subsequently chronic diseases of other organs and systems. [9-11].

In this regard, the American Heart Association included PE among the risk factors for the development of cardiovascular diseases (CVDs) in women [12-14].

CVD development is underlain by common pathogenic links of PE advancement, therefore, it is necessary to specify their definition, which will make it possible to prevent their occurrence and reduce the risk of CVD in a specific woman and in the population as a whole [15].

It is well known that pregnancy is stressful for the mother's body, and the development of obstetric complications in the future can increase the risk of developing CVDs. Research in recent years confirms the presence of long-term cardiovascular complications in women who had preeclampsia during pregnancy. Thus, women with a history of preeclampsia have an increased risk of such future CVDs as chronic hypertension, heart failure, stroke, coronary heart disease, and cardiovascular mortality [16-17]. Yes, according to A. I. Lokki et al. [18], women with preeclampsia without CVD risk factors 90 days postpartum had twice the risk of CVDs as manifested by coronary artery revascularization, cerebrovascular disease, or peripheral artery disease. At the same time, in women with a history of preeclampsia and metabolic syndrome, this risk increased almost 12 times. According to the results of a study by British scientists, in women with preeclampsia, the overall frequency of the first cardiovascular events within nine years after childbirth was 2.77% compared to women after an uncomplicated pregnancy (1.4%) [19]. Another evidence of such a relationship is that, according to current recommendations, pregnancy history is part of the routine assessment of CVD risk in women [20]. Therefore, maladaptation of the cardiovascular system during pregnancy increases the tendency to develop CVDs in the postpartum period.

Currently, several pathways are known regarding the etiological relationship between preeclampsia and CVDs. On the one hand, it has been suggested that preeclampsia can be a predictor of cardiovascular events through various pathways [21]. On the other hand, the relationship between future CVDs and preeclampsia is partially explained by the common risk factors: dyslipidemia, insulin resistance, diabetes, obesity, endothelial dysfunction, increased inflammatory reactions, hypercoagulation states [22].

According to modern concepts, preeclampsia results from hypoperfusion and hypoxia of the placenta, occurring due to the improper development of the uterine placental spiral arteries. These conditions trigger an inflammatory reaction, which can cause endothelial dysfunction and vasoconstriction, mediating the risk of future CVDs [23-24].

According to G. Kalapotharakos et al. [25], it is vascular mechanisms, as opposed to cardiac hypertrophy, that may cause increased long-term cardiovascular risk after preeclampsia. A. R. Markovitz et al. [26] showed the etiological relationship between the development of pregnancy complications and disorders of the functioning of the cardiovascular system, manifested by metabolic syndrome, vascular dysfunction or inflammation.

Preeclampsia is characterized by an abnormal rearrangement of placental vessels, causing uteroplacental ischemia. Under such conditions, spiral arteries do not undergo physiological transformation, maintaining thick walls with a narrow lumen. Such remodeling of spiral arteries accelerates maternal blood flow in the intervillous space. Maternal blood flow, which speed is approximately 1–2 m/s, is characterized by a strong impulse, resulting in destruction of villi and formation of an echogenic cystic lesion lined with blood clots, which can enter the mother's body [27]. At the same time, the failure of remodeling leads to a repeated cycle of placental ischemia/reperfusion and causes endothelial dysfunction, changes vascular tone, increases the formation of reactive oxygen species (ROS), the release of inflammatory cytokines, antiangiogenic factors, as well as an imbalance of maternal immune cells [28]. ROS reduce the bioavailability of nitric oxide, which is a proangiogenic factor, as a result of which vasodilation and angiogenesis are disturbed, and the bioavailability of antiangiogenic factors — soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) — increases [29]. sFlt-1 through binding of vascular endothelial growth factor and placental growth factor is associated with defective angiogenesis and endothelial dysfunction, sEng initiates proliferation and migration of endothelial cells. Researchers believe that these antiangiogenic biomarkers significantly contribute to endothelial damage during pregnancy in the case of preeclampsia, but do not remain elevated after delivery [27]. A. E. Stanhewicz [30] suggests that vascular

damage during preeclampsia persists and contributes to the cascade of CVD development.

Endothelial dysfunction is associated with inflammation, the consequence of which is atherosclerosis. Lipids are deposited in the walls of the spiral arteries of the uterus, which is similar to the early stages of atherosclerosis [31]. According to S. C. A. de Jager et al. [28], in women with preeclampsia, the endothelium does not completely recover, remaining more sensitive to inflammation, as is observed in the case of atherosclerosis. C. Anthoulakis and A. Mamopoulos [32] found that the pulse wave speed and the augmentation index at a heart rate of 75 beats per minute are higher in pregnancies complicated by preeclampsia. The authors believe that assessment of arterial stiffness is a promising tool for risk stratification of cardiovascular complications in the future.

Thus, three important stages of the pathophysiology of preeclampsia have been identified: placental hypoxia and oxidative stress, excessive release of antiangiogenic and proinflammatory factors, and widespread systemic endothelial dysfunction and vasoconstriction [33-34]. There is evidence to suggest that suboptimal trophoblastic invasion causes an imbalance of angiogenic and antiangiogenic proteins, ultimately causing widespread inflammation and endothelial damage, increased platelet aggregation, and thrombotic events with placental infarctions [35].

S. Sławek-Szmyt et al. [36], having conducted a review of studies on the relationship between preeclampsia and the long-term risk of CVDs in mothers, concluded that there are common pathophysiological pathways between them. At the same time, scientists drew attention to insufficient study of intermediate mechanisms (chronic bacterial infections, TNF α) responsible for this association. Pregnancy often occurs at an early stage of a woman's life, when usually CVDs have not yet been detected. Therefore, the issue of screening and prevention of CVDs in women with preeclampsia arises. In this case, determining the level of cardiovascular biomarkers may be useful for predicting the risk of developing CVDs. Biomarkers such as sFlt-1, placental growth factor, interleukin (IL)-6, IL-6/IL-10 ratio, high-sensitivity cardiac troponin I, activin A, soluble human leukocyte antigen G, pregnancy-associated plasma protein A, and norepinephrine can be potentially suitable for cardiovascular risk stratification after preeclampsia and contribute to the development of prevention strategies [37].

Although a history of preeclampsia is recognized as a specific risk factor for CVDs later in life, it is still unclear how to improve the cardiovascular health of these women. Currently, some guidelines suggest monitoring for hypertension, hyperlipidemia, and diabetes, as well as providing advice on a healthy lifestyle for women with a history of preeclampsia [38]. Further research is needed to determine appropriate monitoring strategies for such women.

CONCLUSIONS

Cardiovascular disorders are not only a medical problem, but also a social one. Preeclampsia is a dangerous condition that contributes to the development of CVDs, increases the rate of mortality and disability among women. All this makes it absolutely necessary to study the features of the pathogenesis in detail, to understand exactly how, through which mechanisms, the preeclamptic state affects the woman's body, and this will allow doctors to indirectly influence its pathogenesis and reduce negative consequences and improve the quality of life.

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TREATMENT OF PATIENTS WITH CHRONIC PANCREATITIS COMPLICATED BY PANCREATORAGIA

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ABSTRACT

The aim: To present and share our experience in the treatment of pancreatoragia which could help to prevent pancreatoragia in patients with chronic pancreatitis in the pre- and postoperative period.

Materials and methods: Surgical treatment of complicated chronic pancreatitis (CP) was performed on 249 patients in the surgical clinic of the medical faculty N²2 of National Pirogov Memorial Medical University of Vinnytsia during 2000 - 2021. Pancreatorrhagia occurred in 6 (2.4%) patients, group A – 3 (1.2%) - as disease manifestation, group B – 3 (1.2%) – as complication after surgery.

In group A the source of bleeding was the lower pancreato-duodenal artery: 2 (0.8%) had lower pancreaticoduodenal artery aneurysms with bleeding into the cyst, 1 (0.4%) - a year after previously performed pancreato-duodenal resection. In group B pancreatorrhagia developed in 3 (1.2%) patients after the Frey-Izbitsky local resection of the pancreas: 2 (0.8%) - from pancreato-jejuno anastomosis, 1(0.4%) - from pancreatopleural fistula.

Conclusions: Pancreatoragia, as a manifestation of chronic pancreatitis, occurred in 6 (2.4%) patients. Bleeding occurred as a manifestation of the disease in 3 (1.2%) patients and in 3 (1.2%) patients - in the postoperative period. It is possible to use fibrin or cyanoacrylate glue to filling the defect of the pancreatic duct or to suture vessels in the parenchyma of the pancreas by PDS for the prevention of pancreatoragia in the postoperative period.

KEY WORDS: chronic pancreatitis, pancreatoragia, complications

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INTRODUCTION

Chronic pancreatitis (CP) is a polyetiological disease wich has a number of pathogenetic pathways of the pancreatic glandular tissue fibrotization. Clinical manifestations of classical CP are belt-like abdominal persistent pain, exo- and endocrine insufficiency; pathomorphological signs are atrophy and fibrosis of the pancreas with dilation of the main pancreatic duct and calculosis. Pancreatoragia is a bleeding from the Fater's papilla, where the source of bleeding is in the pancreas or in adjacent structures [1,2]. Pancreatoragia is an extremely rare manifestation of the chronic pancreatitis. The pancreatoragia may occur in ruptured aneurysm or pseudoaneurysm of the pancreatoduodenal, gastroduodenal, hepatic arteries into pseudocyst cavity. Such cases are unusual, but according to some studies, the incidence of bleeding into the pseudocyst cavity ranges from 6 till 17%. The cause of pancreatoragia can be a tumor of the pancreas, for example: adenocarcinoma of the pancreas, serous cystadenoma, mucinous cystic pancreatic neoplasms, neuroendocrine tumors. Bleeding from the pancreas can be also as the result of iatrogenic trauma after medical manipulations, such as biopsy of the pancreas during endoscopic ultrasound, stenting, etc. [3]. Often, pancreatoragia complicates the postoperative period after surgery on the pancreas. According to the recommendations of the International Study Group of Pancreatic Surgery (ISGPS) for bleeding after pancreatectomy, there are three degree of bleeding: degree A, B, C. According to the time of onset divide early (up to 24 hours after surgery) and late (later 24 hours after surgery) bleeding. The source of bleeding can be intraductal, extraductal. According to the severity it can be mild or severe [4,5].

THE AIM

The aim of our study was to present and share our experience in the treatment of pancreatoragia which could help to prevent pancreatoragia in patients with chronic pancreatitis in the pre- and postoperative period.

MATERIALS AND METHODS

Surgical treatment of complicated chronic pancreatitis (CP) was performed on 249 patients in the surgical

department of the medical faculty N°2 of National Pirogov Memorial Medical University, Vinnytsya., Vinnytsia, Ukraine during 2000 - 2021. There were 187 men (74.8%) and 62 women (25.2%), the average age were 51.25 \pm 13.7 years.

According to the TIGAR-O classification 193 (77.6%) patients with CP had preveously attack of acute pancreatitis, 176 (71.1%) patients were alcohol abused. Calcifying form of CP had 28 patients, obstructive form - 30, fibrosis - 55, inflammatory - 5, pancreatic cysts was detected in 119 patients. According to the Büchler classification "B" stage of chronic pancreatitis was observed in 38.2% (n = 96) patients, "C" stage - 61.8% (n = 153) patients. Pancreatogenic diabetes was observed in 101 (41,06%) patients. All patients underwent transabdominal surgery. Pancreatic resection was performed in 58 patients (23%), internal and external drainage – 109 patients (43%), symptomatic procedures - 82 patients (32%).

REVIEW

Pancreatoragia is a bleeding from the main duct of the pancreas, which occurred in 6 (2.4%) out of 249 patients. Moreover, in 3 (1.2%) patients bleeding occurred as a manifestation of the disease, and in other 3 (1.2%) patients - in the postoperative period.

Two patients had an aneurysm of the lower pancreaticoduodenal artery out of patients wich had pancreatoragia as the main manifestation of the disease. There was a cyst of the pancreas, which had no connection with the main pancreatic duct (type VI by Nealon), where was detected active blood flow. Both patients had elective surgery to treat CP. Bleeding was stopped by suturing the pancreatoduodenal artery. One patient was admitted to hospital with manifestations of profuse gastrointestinal bleeding (case I).

CASE I

Patient M., 45 years old, was admitted to surgical department on November 2018 with active gastrointestinal bleeding with signs of hemmorhagic shock. In anamnesis the pancreatoduodenal resection was performed for chronic fibro-degenerative calculous pancreatitis in the 2014. Pancreaticojejunostomy was performed by a combined method: formed by a two-row duct-to-mucosa pancreaticojejunostomy with additional Blumgart type protective mattress sutures(Fig 1 A,B)

The patient was urgently performed fibrogastroduodenoscopy - the source of bleeding in the upper gastrointestinal tract was not detected. Laboratory tests: complete blood count: Hb-52 g/l, erythrocytes - 1,85 * 10¹²/l, leukocytes -8,2*10⁹/l, erythrocyte sedimentation rate (ESR) -37mm/h, blood glucose 8,3 mmol/l, total protein - 70 g/l, bilirubin total 0.5 mg/dL, direct - 0, urea - 5.4, creatine - 0.02, prothrombin index - 80%, prothrombin time - 14', fibrinogen - 3.2 g/l. Medications include fresh-frozen plasma, erythrocytes, tranexamic acid, etamsylate, omeprazole 120 mg, octreotide. The volume of intravenous therapy was up to 3 liters per day.

The conservative treatment helped to stop bleeding. The next day, fibrocolonoscopy was performed: no pathology of the colon was detected. However, after the procedure, the patient had a recurrence of bleeding in the hospital.

In the state of severe hemorrhagic shock the patient underwent urgent surgical treatment. During the operative exploration the entire small intestine was filled with blood above the entero-entero anastomosis. Fibrogastroduodenoscopy was performed intraoperatively, no sources of bleeding in the upper gastrointestinal tract (upper ligament of Treitz) were found. It was decided to continue the Fibrogastroduodenoscopy with manual assistance to the level of entero-entero anastomosis where was no source of bleeding also. When the endoscope approached the pancreaticojejunostomy, a large amount of fresh blood suddenly had appeared in the lumen of the afferent loop. Enterotomy was made below the functional choledochojejunostomy up to 4 cm and during the operative exploration from the area of pancreaticojejunostomy the pulsating bleeding appeared, bllod stream was up to 0.3 cm, the vessel was sutured, the bleeding was stopped. A ligature impregnated with bile salts was found in the lumen of the anastomosis on the surface of the intestine, which was removed. The enterotomy incision was sutured with a double-row suture.

The postoperative period passed without complications. The patient was discharged on the 10th day after surgery.

CASE II

Patient N., 51 years old, was admitted to surgical department on January 23, 2017 with complaints on severe pain in the upper abdomen, nausea, repeated vomiting of undigested food, abdominal swelling, weight loss, severe general weakness.

According to his medical history he has been ill for two years, from the moment of acute destructive pancreatitis occuring caused by alcohol consumption.

At the time of admission diagnosis was chronic fibrous-degenerative calculous pancreatitis, with persistent pain syndrome, external and internal secretory insufficiency.



Fig. 1. A: Modified type of pancreato-jejuno anastomosis. B: Modified type of pancreato-jejuno anastomosis



Fig. 2. Boders of Frey-Izbicki local resection of the pancreas

The patient underwent surgery - combined Frey-Izbickiy local pancreatic resection with longitudinal Roux-en-Y pancreaticojejunostomy with entero-enteroanastomosis. The technique of the surgery was in the following way: there was performed U-shaped excision of the pancreas tissue throughout all pancreas parenchyma and the boundaries of the excision were 5 mm on the upper and lower border of the body and tail of the pancreas. The boundary of the depth is the cut of a back wall of the pancreatic main duct. The next stage was excavation in the head of the pancreas. The cutout border was about 5 mm along the upper, lateral and lower borders of the pancreatic head. The depth cut of removal is the posterior wall of the Virsung duct, the duct of the uncinate process, which was excised, and the common bile duct. The Santorini duct was excised in one block with the upper part of the pancreatic parenchyma. Excision of the pancreatic tissue was performed with an electrocautery, there

was performed additional electrocoagulation of small pancreatic vessels and the arteries of the parenchyma were additionally sutured with separate ligatures. Therefore, in the area of a pancreatic gland`s head there was a thin rim of thickness approximately 5 mm. This operation was supplemented by transpancreatic papillosphincterotomy to restore the physiological passage of pancreatic juice into the duodenum (patent of Ukraine №115291 from 10.10.2017). (Fig 2)

Then a pancreaticojejunostomy was performed on the Roux-en-Y intestinal loop (40 cm) with the Brown entero-entero anastomosis. In the postoperative period, the patient had a small amount (up to 10-15 ml) of fresh blood discharge from drainages in the lesser sac. Furthermore, after the restoration of the natural intestinal passage, a melena stool was noticed. The level of HB was - 110 g / l, er - 3,1*10¹²/ l. The patient underwent standard postoperative medication plus additionally heamostatic therapy was prescribed.



Fig. 3. Protective jejunostomy on the same loop of intestine with pancreato-jejunoanastomosis after Frey-Izbicki local resection of the pancreas in patient with pancreato-pleural fistula.



Fig. 4. The branch of inferior posterior pancreato-duodenal artery involved in pancreato-je-juno anastomosis.



Fig. 5. Possible sourse of bleeding from pancreato-jejuno anastomosis after Frey-Izbicki local resection of the pancreas. On the 7th day of the postoperative period patient had reccurents of bleeding.

The patient underwent urgent relaparotomy: during the operative exploration of the abdominal cavity - the lumen of the pancreaticojejunostomy, the Roux-en-Y intestinal loop, the entero-entero anastomosis, the afferent intestinal loop of the small intestine, including the duodenum and part of the stomach were tightly swabbed with a single clot. The volume of blood clot was up to 200 ml in the lesser sac. The clot were removed from the lesser sac. The pancreatic jejunal anastomosis was separated on his upper part, clots were removed from the intestinal lumen. The intestinal lumen was processing by antiseptics, but a detailed inspection did not reveal the source of the bleeding. Additional coagulation of the pancreas resection area was performed. A jejunostomy was formed on the previously formed Roux-en-Y intestinal loop to control hemostasis, and a pancreaticojejunostomy anastomosis was formed on the same Roux-en-Y intestinal loop. (Fig 3) Sanation and drainage of the abdominal cavity was done.

The postoperative period passed with supuration of the laparotomy wound, severe hypochromic anemia. The patient was discharged on the 20th days after surgery.

CASE III

Patient K., 41 years old, was admitted to surgical department on February 17, 2020. According to his medical history he had an attack of acute pancreatitis 1 year before, then was treated three times because of diffuse pleural fibrosis and underwent surgical procedure - decortication of the left lung 4 months ago.

During the examination: Ps - 92 beats / min. Blood pressure was = 90/60 mm Hg. Sa O2 = 93%. Weakened vesicular breathing with moist rales is heard in the lower parts of the right lung. The abdomen was painful in the upper part of abdomen, bloated. During rectal exam were not found any changes. Hb-83 g/l, erythrocytes - $2.77*10^{12}$ /l, leukocytes - $6.4*10^9$ /l, ESR -40 mm/h, blood glucose 3.9 mmol/l, total protein - 47 g/l, albumin 24 g/l, total bilirubin 0.94 mg/dL, direct - 0, indirect - 0.94 mg/dL, urea - 4.8, creatine - 0.062 mmol/l, prothrombin index - 89%, fibrinogen - 4.2 g / l. The patient had CT scan where detected pancreato-pleural and pancreato-mediastinal fistula.

The patient was prescribed medication therapy: hemostatic, antibiotic therapy, fresh-frozen plasma, erythrocytes, proton pump inhibitors, nonsteroid anti-inflammatory drugs.

The patient underwent surgical treatment. During the operative exploration of the pancreas: head 6 cm, body – 2 cm, tail 2 cm, all structures were fibrous changed. In

the caudal part of the pancreas fistula was detected: up to 1 cm in diameter, which begins on the posterior surface of the pancreatic body and run to the left adrenal gland. Spleen-preserving corporo-caudal resection of the pancreas was made. The fistula was cut out. During inspection of a stump of a pancreas - the pancreatic duct was being expanded to 1 cm. The pancreatic duct is dissected throughout to the head of the pancreas. Local resection of the pancreas by Frey-Izbitsky with subsequent revision of the duct was made.

In the area of the pancreatic head on the posterior surface was found another fistula, which run from the main pancreatic duct into the retroperitoneal space and spread to the mediastinum along the v.porta and v.cava. Due to the absent of possibility of resection of the fistula or its excision decided to make external drainage of the fistula through a suspended jejunostomy on the excluded loop on Roux-en-Y loop (fig 5). On the same intestinal loop, a Duval pancreatojejunostomy was formed with a double-row suture with a entero-entero anastomosis.

The postoperative period passed with complications. On the 7th day after surgery patient had fresh blood discharge from a fistula, which had drained through an enterostomy. Furthermore, there was a secretion of fresh blood in the drainage from the abdominal cavity. The patient had hemorrhagic shock. Hemostatic therapy was performed the bleeding was stopped by medication. According to computed tomography, there was a retroperitoneal hematoma in the area of the portal vein. The patient's condition stabilized. The patient was discharged on the 21st day. However, on the 40th day of the postoperative period, at home the patient had a recurrence of profuse bleeding which caused the patient death.

DISCUSSION

Following literature analysis there are no statistical data that can show the actual incidence of late pancreatoragia. Among the possible reasons it can be the erosion of pseudoaneurysms of the pancreaticoduodenal vessels [5].

Following the case I, that was happening to this patient, we can suggest that the bleeding arose from the lower pancreaticoduodenal artery, which was cut out through the mattress suture because of heavy physical activity which this patient had and it could cause severe pancreatoragia. The case belongs to a series of casuistry. Based on our sample data, late pancreatoragia was recorded in one patient out of 249, which set 0.4% [6,7].

Acording to the case II the literature rewiev about early pancreatoragia showed that this complication occurs in 2-3% of cases. The common cause II of bleeding is ligature eruption or vascular erosion in the area of pancreaticojejunostomy [9].

Among patients presenting with pancreatoragia in our sample, postoperative bleeding from pancreaticojejunostomy occurred in 2 (0.8%) patients. Bleeding occurred in patients which had been undergoing Frey-lzbitsky combined surgery in the early postoperative period, which is probably occurred due to the larger volume of pancreatic resection.

In this case II, massive bleeding occurred in the early postoperative period, on the seventh day, probably from the artery after eruption by ligature. The source of bleeding could be multiple branches of the anterior pancreatoduodenal artery, its prepancreatic arcade or branches of the splenic artery and pancreatic arteries of the pancreatic body and tail. (Fig 5)

The bleeding occurred in two stages. The first stage, when there was leakage of blood through the drainage, in a volume up to 20 ml. The second stage was after eruption of the ligature, when began massive bleeding which caused hemorrhagic shock. It didn't notice intraoperative, during the primary operation, when hemostasis was achieved by electrocoagulation and additional suturing of the vessel. Obviously, the cause of ligature eruption may be the case of excessive pulling of the node, with eruption of the parenchyma by a thread or tying a ligature at the site of excessive tissue coagulation, which eventually is weakened and rejected after some period of a time. The third probable cause is the erosion of the stitched vessel by pancreatic juice.

To prevent this type of bleeding in postoperative period, the hemostasis must be performed extremely by suturing blood vessels in the parenchyma of the pancreas with S-shaped sutures. PDS 3/0 or 4/0 were used for hemostasis.

The data analysis of pancreaticopleural fistula showed that pancreaticopleural fistula occurs in 0.4% of patients

with chronic pancreatitis. The level of complications that accompany the course of pancreaticopleural fistula is indicated at 10%, but the details of complications in the literature were not specified. [10]

The clinical case was published in 2007 where chronic pancreatitis was complicated by pancreaticopleural fistula and hemotorax, which required surgical treatment. However, the authors did not prove that the bleeding arose from the lumen of the pancreatic-pleural fistula. [11]

Acording to the cause III of pancreatoragia, there was vascular erosion in the lumen of the pancreaticopleural fistula. Erosion probably was occurred before surgery, which was impossible to recognise during the operation. The cause of erosion is difficult to analyze, because after surgery, the ingress of pancreatic juice into the lumen of the fistula was interrupted, i.e. the main factor in the occurrence of bleeding was removed. However, this clinical case indicates that any defect in the lumen of the Virsung duct, even when the outflow of pancreatic juice into the intestine must be closed, either by stitching or by filling with fibrin or cyanoacrylate glue.

Postoperative mortality among patients with pancreatorgia was 16.7% (1 patient), who died 40 days after surgery.

CONCLUSIONS

- 1. Pancreatoragia, as a manifestation of chronic pancreatitis, occurred in 6 (2.4%) patients. Bleeding occurred as a manifestation of the disease in 3 (1.2%) patients and in 3 (1.2%) patients - in the postoperative period.
- 2. It is possible to use fibrin or cyanoacrylate glue to filling the defect of the pancreatic duct or to suture vessels in the parenchyma of the pancreas by PDS for the prevention of pancreatoragia in the postoperative period.

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CURRENT PROBLEMS IN COMMUNICATIVE DEVELOPMENT OF CHILDREN WITH SPECIAL EDUCATIONAL NEEDS: UKRAINIAN AND EUROPEAN SCIENTIFIC CONTEXTS

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ABSTRACT

The aim is to analyze the current problems in communicative development of children with special educational needs.

Materials and methods: The research used a number of scientific methods: general scientific (analysis, synthesis, generalization), historical, specific research, comparative-historical, and others, which ensured the selection and analysis of the source base, made it possible to determine the general trends in the study of the problem of the communicative development of the child, the achievements of Ukrainian and foreign scientists in the field of research on the language of children with special educational needs, to distinguish the common and the different in the scientific research of scientists.

Conclusions: Updated studies of scientists from Ukraine, Poland, Sweden, Britain and other countries testify that communication skills are key in the language development of a preschool child, they form the basis without which the child's further education, socialization, etc. are impossible. Meanwhile, there is no unity among scientists in their views on the nature of language disorders and their classification. The contribution of domestic and foreign authors to the study of the communicative development of a child with speech difficulties is singled out.

KEY WORDS: communicative development, preschool children, special educational needs, general underdevelopment of speech, inclusion, speech therapy, diagnosis, speech defects

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INTRODUCTION

Ensuring the realization of the right to education of children with special educational needs (SEN) in Ukraine is currently considered a major task of state policy not only in the field of education, but also in terms of demographic and social and economic development [1]. From this point of view, it seems appropriate to use productive experience abroad in the process of working out the methods of development of communication skills for students with peculiarities of language development.

Despite the fact that the issue of the development of communicative activity of children with SEN, in particular, the peculiarities of language development, is widely covered in numerous foreign works (F. Armstrong, D. Anderson, M. Davis, J. Bellow, K. Jenks, X. Kerbo, S. Corlett, M. Crozier, F. Crosby, D. Cooper, T. Newman, H. Silver, P. Silver, V. Schmidt, J. Shane, K. Taylor, A. Hodkinson, etc.) and Ukrainian scientists (N. Bazima, O. Belova, L. Vavina, I. Vdovichenko, A. Vysotska, T. Ilyashenko, I. Kolesnyk, I. Marchenko, I. Martynenko, V. Labunska, E. Sobotovych, L. Trofymenko, N. Cherednichenko, M. Sheremet, etc.), however, the problem stated in the title of the article was not deeply studied by the scientists.

THE AIM

The aim is to analyze the current problems in communicative development of children with special educational needs.

MATERIALS AND METHODS

The research used a number of scientific methods: general scientific (analysis, synthesis, generalization), historical, specific research, comparative-historical, and others, which ensured the selection and analysis of the source base, made it possible to determine the general trends in the study of the problem of the communicative development of the child, the achievements of Ukrainian and foreign scientists in the field of research on the language of children with special educational needs, to distinguish the common and the different in the scientific research of scientists.

REVIEW

Communicative personality development of a preschool child is the subject of interest of many scientific disciplines, therefore it is understood in different ways. Having carried out the interdisciplinary nature of research, Ukrainian science offers different perspectives for considering this problem [1; 2; 3; etc.]. Linguistics defines language as a natural system of sound signs subject to the rules of their combination and use [4]. Foreign scientists (linguists, psychologists, teachers) (L. Vygotskyi [5], J. Wood [6], M. Grokhovalska [7], I. Kurch [8], J. Piaget [9], I. Smolka [10], etc.), as well as Ukrainian scientists N. Bazim [2], I. Martynenko [11], M. Sheremet [12], etc.) single out three groups of factors that determine the communicative development of the individual. These are, for example, innate factors that are considered fundamental in the concept of N. Chomsky [13]; environmental factors, which are decisive components, for example, in the concept of B. Bernstein; factors related to the child's own language activity and activity when he learns language programs, that is, in the course of his actions, he discovers its functions [14].

A well-known British scientist J. Wood [6, pp. 1-14] once rightly emphasized that in the field of language acquisition, «the achievements of preschool children are truly impressive.» It really is. Language «arises in a person's consciousness without the participation of consciousness, functions imperceptibly», humanity uses language as a tool, and «you need to thinkreally deeply to notice that there are mechanisms of its functioning» [15, p. 324].

The process of learning a language is quite complex. Many researchers, creating new theories of language acquisition, base them on the data of psychological science, primarily N. Chomsky's theory of innate linguistic abilities [13]. Foreign scientists [5; 6; 7; 8; 9; 10; 13; 14; 15; and others], presenting the achievements and perspectives of the psychology of children's language, emphasize that a communicative approach prevails in a child's acquisition of language, according to which language learning is considered through the prism of the individual's presence in society, communication with others. This process occurs in the process of communication with the environment (L. Vygotsky [5]). According to J. Bruner (2006) [16], under such conditions, the language development of a child is socially dynamic: language develops under the conditions of an environment where there is «a lot of language and communication», the child learns and discovers generally accepted ways of using language in the context of interaction with other people, «who in the field of language are more mature than her» [16]. The scientist notes, that to learn a language means to learn how «our compatriots do it and learn to do it yourself» [16]. The author considers «compatriots» primarily parents, who are the first to provide a child with natural support for learning. Another social group is educators, teachers who, together with other children, create a new social context for language development.

We completely agree with the opinion of some researchers (for example, G.-R. Shaffer, the author of books devoted to child psychology and child development) that «the main necessary element of language acquisition is initially the interaction of the mother with the child» [17, p. 319-329], with other adults. The language environment of the kindergarten is important, where there is a specific language used by educators, this is a kind of «child-directed speech», which is significantly different from the language of adults. Environment adapted to the child's cognitive abilities will help him improve his language skills [17, p. 1-17]. Mothers have a natural tendency to monitor the child's attention in their speech, demonstrating patterns during speech, monitoring the child's ability to perform specific communication roles. To establish communication, they respond to a nonverbal communication code, signals that mothers interpret as sufficiently communicative expressions of their children. Studies have shown that a child learns language through participation in certain specific interactions [18].

There is a lot of literature, the authors of which trace the stages of development of a child's communication skills. Let us mention, among other sources, the psycholinguistic study of the communicative competence of preschool children, but «with a distinct linguistic bias», the author of which is a well-known Polish scientist, the author of numerous works on speech therapy, J. Porayski-Pomsta (1994) [19], and a thorough monographic the research of the authoritative scientist L. Smolka (2004) [10], who presented the properties and conditions of the formation of this competence with a special emphasis on 6-7-year-old children.

DISCUSSION

The concept of «a child with special educational needs» is quite complex, Ukrainian and foreign scientists under-

stand it differently. The study of the sources in the field of inclusive education, speech therapy gave grounds for the conclusion that there is still no unanimity in the views of scientists regarding the conceptual and terminological apparatus in relation to the term system in the area of inclusive education. With proper educational documents of Ukraine, persons with special needs are those people who need «additional permanent or temporary support in the educational process» in order to ensure their rights to education [20]. In the National Strategy for the Development of Inclusive Education for 2020-2030 [21] the circle of persons to whom the provisions on inclusive education apply is outlined: disabled children, other persons who are not recognized as disabled children in the established order, but have temporary or permanent health limitations and require the creation of special conditions for education (upbringing), disabled persons and other persons with limited health opportunities over the age of 18 who are studying under basic professional educational programs of primary professional, secondary professional and higher professional education.

It should be noted that in the foreign theory and practice of inclusive education, children with special educational needs and those who have difficulties in fulfilling the standards of program educational requirements are usually included as children with SEN, which is a consequence of the specificity of their cognitive and perceptual functioning (such children have lower than average intellectual abilities, as well as dyslexia, dysgraphia, dysorthography, dyscalculia), health (chronically ill children) and environment limits (children of immigrants, children from educationally ineffective families) . This understanding of special educational needs is aimed at the implementation and implementation of the idea of equalizing educational opportunities for all students [1].

Both Ukrainian and foreign experts claim that the basis for making decisions about the place in the education system of a child with a certain type of disability should be a reliable and comprehensive diagnosis, carried out as early as possible and repeated at different periods of its development [3; 4; 5; 7; 8; 9; 19 and others]. It is also important to provide each child with multidisciplinary and competent counseling, as well as psychological and pedagogical assistance (taking into account his needs). The education of a child with special needs (with a disability) should be possible both in a mass school and in an integrated school and a special school. The education system should be accessible and flexible, i.e. provide the possibility of a child's transition from a general institution to a special institution and vice versa. The main criteria for determining the optimal form of education at a certain educational stage should be: the current level of development and the result of the realization of the child's educational needs, the opportunities determined by his intellectual level and the functioning of the senses, sight and hearing, as well as the didactic progress of the student up to this time [2;4;11;12].

In the situation where the child's capabilities are limited, the educator/teacher has a particularly important task. All forms of individualization for children with special needs, including children with specific learning disabilities (in our case - speech difficulties, in particular, its underdevelopment) should be based on recognition and use of the child's potential to overcome shortcomings. A thorough acquaintance with the child will make it possible to determine his real needs and capabilities, and then to formulate requirements that meet them, at the same time, are consistent with the current basic curriculum [11; 12].

Today, the number of children with a history of delayed language development is noticeably increasing. Usually, motor and psychomotor development disorders are added to the structure of the ontogenesis of such children. Historically, the term «developmental delay» was used to single out a special group of children in terms of their assessment of readiness for schooling. Today, this term is more often used to describe the state of higher mental functions in children with various organic, genetic and psychological developmental pathologies [3; 4; 12]. In our opinion, the term «delayed language development» is not completely a diagnosis but a fact of ascertaining the need for medical and pedagogical intervention in the child's development. In most cases, a pronounced delay in language development is accompanied by a violation of visual-spatial skills and/or motor discomfort. Language development usually improves as a child grows up, but a mild lack of language development often remains throughout life.

Scientists note that delay in language development is several times more common for boys than for girls [4]. Developmental delay is characterized by a hereditary burden of similar or related disorders, which implies an important role of genetic factors in the etiology of many (but not all) cases. Environmental factors often cause developmental delay, but most often they are not of primary importance. Most often, the etiology of developmental delay is unknown, therefore, without constant dynamic monitoring, it is impossible to predict the possibilities of its further development. Two types of developmental delay are usually distinguished. First, these are disorders where there was an undeniable phase of previous normal development, such as childhood disintegrative disorder, Landau-Kleffner syndrome, and some cases of autism. These conditions are assigned to the 1st type, because although their onset and course are different, the characteristic features are preserved and are similar in many respects to the group of disorders of language development; moreover, they may have a similar etiology. Secondly, there are disorders primarily caused as a deviation or as a delay in the development of functions; this especially applies to autism. Although autistic disorders are defined as deviations, developmental delay to a certain extent is almost always found out, therefore language development in autism has its own characteristics [3; 4; 7; 11; 12].

Delay in language development is one of the types of delay of psycholinguistic development. When it comes to the «normal course of development», it is necessary to specify whether a stage was formed when the language function of the child carried a social load. If the child simply repeated individual syllables or even phrases and sentences, but did not fill them with social content i.e. did not address the addressee of the speech, did not use speech in relation to some specific life situation, we cannot talk about a delay in language development. Rather, it is possible to state here a deviant way of formation of higher mental functions, since the main function of speech is symbolic support of mental processes and its social implementation [11].

Scientists distinguish the delay of psycholinguistic development as primary and secondary. Primary delay is formed in the case of structural damage to the brain or disruption of its function for various reasons. Secondary delay occurs against the background of a primarily intact brain in chronic somatic diseases (heart disease, etc.) accompanied by cerebral insufficiency [11]. Usually, such a delay has a systemic nature and is distinguished by an algorithm: the norm minus 1 or in minor cases minus 2 - epicrisis terms, while the primary delay is characterized by irregular development [12].

There are terms like general and systemic underdevelopment of language. Under the general underdevelopment of the language, scientists mean a delay in speech development in a child with normal intelligence. Systemic underdevelopment of language is a language disorder against the background of underdevelopment of other higher mental functions. In the first years of life, due to the immaturity of the nervous system in children, the peculiarities of the maturation of motor and psycholinguistic functions are more often traced. Therefore, usually in early childhood it is possible to talk about a general delay in psychomotor development with greater severity of psychoemotional or psycholinguistic retardation [4; 12]. In children older than 3 years, the clinical picture becomes more obvious. The main clinical signs of mental retardation are delayed development of basic psychophysical functions (motor skills, speech, social behavior); emotional immaturity; uneven development of individual mental functions; functional, reversible nature of violations [3; 4; 12]. If intellectual disability in preschool age is masked by language disorders, then at school age it manifests itself clearly and shows itself up in a poor supply of information about the world, slow formation of concepts about the shape and size of objects, difficulties in calculations, retelling what is read, in misunderstanding of what is read, difficulties in coherent speech etc. Concrete-figurative type of thinking prevails among such children. Mental processes are inert. It is observed pronounced exhaustion. The behavior is immature. The level of visual and figurative thinking is guite high, and abstract -logical thinking, inextricably linked with inner language, is insufficient [11].

Speech delay is formed in a neurologically healthy child with a normal perinatal history. The child has no hearing or vision defects. Heis brought up in a normal environment. A child may be able to communicate in certain, well-known situations, perceive and understand everything, but the language is impaired. As with other developmental disorders, the first difficulty in diagnosis lies in differentiating general language delay from normal developmental variants. The rate of development and the pace of solid assimilation of speech skills is a very broad concept (from 1 year to 3 years). Such variations in the timing of language acquisition are of little or no clinical significance, as most children are «late talkers» but continue to develop quite normally. Unlike them, children with specific disorders of speech development retain the features of the original language personality in adulthood: delay in speech development is often accompanied by difficulties in reading and writing, violations of interpersonal relationships, emotional and behavioral disorders [3]. Therefore, early and thorough diagnosis of specific disorders in language development is very important.

Diagnosing general language delay in preschool children is quite difficult. When diagnosing a delay in language development, certain criteria should be followed: severity, course, type and accompanying problems. Speech delay is considered pathological when a delay of 2 standard deviations is detected. There are usually associated problems with this level of delay. However, the older the child, the less the degree of delay, as language improves with natural human development. In the case of pathological speech delay, it is useful to take into account the criterion of the course. If the current level of impairment is relatively mild, but there is a history of severe impairment, it is more likely that the current development is the result of a major disorder rather than a variant of the norm. It is necessary to pay attention to the type of language functioning. Language can be simply delayed, as in a child of a younger age, or it can be pathologically delayed, if it is qualitatively different from normal. For example, the speech of such a child contains echolalia, perseverations or stamps. Furthermore, if a delay in some specific aspects of language development is accompanied by future school-related deficits (specific reading and writing delays), impairments in interpersonal relationships, and/or emotional or behavioral disorders, it is unlikely that this is a variant of the norm. There is another difficulty in diagnosis i.e.distinguishing delayed language development from mental retardation or delayed development of mental disorders. With mental retardation, speech is impaired in the same way as other mental functions. And with a specific developmental disorder, language and intelligence can be sufficiently developed, but behavior and communication disorders come to the fore [3; 11; 12].

Thus, under general or specific mental development delay it is not possible to diagnose language retardation F80. An appropriate diagnosis of mental retardation (F70-F79) must be made; from the diagnoses included in F80-F89, speech conditions characteristic of children with hearing impairment should be excluded, since the regularity of their language development has a specific character [12].

We agree with the opinion of scientists that it is impossible to distinguish diagnosesclearly, especially at an early age. A similar principle applies to neurological pathology and anatomical defects. Thus, articulation pathology due to palatal pathology or dysarthria due to cerebral palsy should be excluded from this section. In addition, there are numerous types of dysarthria (violation of the tone of speech and motor muscles), which are characterized by the presence of articulation disorders. For example, depending on the type of predominant muscle tone, spastic, hyperkinetic, hypotonic, etc. dysarthria are distinguished [12]. All the listed types of dysarthria are part of the symptom complex of bulbar or pseudobulbar syndrome [12]. With dysarthria, the child uses an insufficient number of sounds in speech for his age, but the level of language development (skills) corresponds to his age. Anyway, normally at the age of 4, errors in the pronunciation of speech sounds are common, but the child's speech is understandable to strangers. A child masters most speech sounds by the age of 6-7. Although difficulties with certain sound combinations may remain, they do not lead to communication problems. By the age of 11-12, almost all speech sounds should be mastered. With pathological development, the child's mastery of speech sounds is delayed and/ or deviated, and difficulties arise when communicating with people because they do not understand the child's speech. Omissions, distortions or substitutions of speech sounds are observed; the pronunciation of sounds is disturbed depending on the combination of sounds (in some words, the child can pronounce phonemes correctly, and in others – can not). In such a case, the diagnosis can be made only when the severity of the articulation disorder is beyond the normal variations corresponding to the mental age of the child, the non-verbal intellectual level is within normal limits, expressive and receptive language skills are also within normal limits, articulation pathology cannot be explained by a sensory abnormality, incorrect pronunciation is definitely abnormal, given the peculiarities of language use in the different conditions in which the child is.

Speech therapists use the classification of all types of speech disorders, taking into account the nature and peculiarities of the pathology. For the most part, specialists use the clinical-pedagogical classification of language disorders, distinguishing several types of pathology associated with impaired pronunciation or writing. There is a psychological and pedagogical classification in science [11]. According to it, scientists group disorders in language development from partial to general, at the same time taking into account a set of different psychological and linguistic criteria, under such conditions they single out manifestations of the disorder in various variations of the child's improper development. According to the psychological and pedagogical classification, any speech disorders are divided into changes in the means of communication and disorders in the use of means for communication. Factors that cause these pathologies include the following: disorders of intrauterine development due to severe toxicosis, intoxication, various diseases of a woman, Rhesus conflict of mother and fetus (the period from 4 weeks to 4 months of pregnancy is considered especially dangerous, when the speech apparatus is formed and under the influence of unfavorable factors, various pathologies may appear (split lip, cleft palate, etc.); if unfavorable factors appear in the last stages of pregnancy, there may be a delay in development, which will also negatively affect the child's language); asphyxia or other birth injuries that can cause bleeding in the brain; the transfer of certain diseases in childhood, which can provoke a slowdown in the development of the brain; heredity; under the influence of this factor is possible only in the presence of other criteria for the development of the violation; unfavorable factors of the social environment, which include an unfavorable environment, deafness or speech impairment in parents, psychotraumatic situations, etc. [11].

There are also changes in the child's oral speech, which are manifested in such speech disorders as intonation disorders, voice formation disorders or phonemes; violation of the pace of pronunciation. Problems related to language disorders can appear individually or in combination with something else. Among the disorders of oral speech is dysphonia (a pathology where speech is completely absent or severely impaired due to irreversible changes in the structure or functioning of the vocal apparatus; the voice may be absent or its timbre changes, as well as strength, other parameters; such disorders of associated with an organic or functional lesion of the vocal apparatus); bradylalia (slowing of speech of a pathological nature, it develops in a situation when the process of inhibition is more pronounced than excitement, the child's speech becomes too slow and unclear, he stretches the words during pronunciation); tachylalia (disruption of oral speech, which is associated with pathological acceleration of speech; grammatical, phonetic, lexical aspects of speech are unchanged; if the child often pauses or stops during speech, this pathology is called poltern); from stuttering (logoneurosis) (manifested in a violation of the rhythm and tempo of speech due to convulsive contraction of the muscles of the speech apparatus; stuttering is functional and organic, most often its development is associated with critical periods in the child's development); dyslalia (this problem of oral speech is associated with the incorrect pronunciation of sounds against the background of normal hearing and innervation of the child's speech apparatus; the pathology is manifested in the distortion of sounds or a change in their sequence; the cause of development is incorrect formation of the articulation apparatus or violation of articulation positions due to a defect of the articulation apparatus; experts also single out the psycholinguistic aspect of dyslalia, which is associated with impaired perception of sounds); rhinolalia(the pathology is accompanied by a change in the tone of the voice due to anatomical damage to the child's speech apparatus, as a result of which resonance occurs, and speech becomes humming, indistinct and monotonous; this speech disorder also includes congenital cleft palate, in which this disorder is also observed); dysarthria (a disorder of the child's oral speech associated with minimal innervation of the speech apparatus or damage to the central nervous system; dysarthria usually occurs in patients with cerebral palsy); alalia (disorder of oral speech, which is associated with insufficient development or complete absence of speech; the cause is organic damage to certain areas in the brain; the pathology is formed at the stage of intrauterine development or in childhood; this speech defect is the most complex, since the speech system is not formed at all); and phasia (these disorders are associated with the loss of the ability to use the means of speech, the cause of this critical condition may be an infectious lesion of the nervous system or a suffered craniocerebral injury) [2; 3; 11; 12; 22].

CONCLUSIONS

The problem of communicative development of preschool children with SEN is relevant, but not fully studied. Ukraine's attention to persons with disabilities is evidenced by, among other things, the European-oriented social educational policy, the dynamics of the inclusion of children with disabilities in inclusive preschools, the activities of inclusive rehabilitation centers, etc. Communicative personality development of a preschool child is the subject of interest of many scientific disciplines, whose representatives understand it in different ways. Given the interdisciplinary nature of research, Ukrainian science offers different perspectives for considering this problem. According to the results of the analysis of the basic foundations of the development of communicative skills of preschool children, which are presented in modern psychological and pedagogical literature, the contribution of Ukrainian and foreign scientists in the field of pedagogy, speech therapy, psychology, and linguistic didactics to the study of certain aspects of the child's language development has been clarified. Numerous sources have been updated, the authors of which trace the stages of development of a child's communication skills. The studies of both Ukrainian scientists and scientists from Poland, Great Britain, Switzerland, etc. seem interesting, the authors are unanimous in the opinion that communication skills are key in the language development of a preschool child, they form the basis without which further education of the child is impossible, as well as socialization, etc. A conclusion is made about the lack of unity of scientists in their views on the nature of language disorders, their classification, the conceptual and terminological apparatus of the scientific problem is clarified, the contribution of national and foreign scientists to the study of the language development of the child's personality is highlighted. The factors that cause difficulties in the language development of preschoolers with limited health opportunities are singled out. Different types of speech disorders in children are characterized.

The direction of further scientific research will be the problem of the development of communication skills of preschoolers with severe speech disorders.

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DIDACTIC CULTURE OF MEDICAL UNIVERSITY TEACHERS AND STUDENTS IN THE CONDITIONS OF WAR

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ABSTRACT

The aim: To analyse the essence of the concept of "didactic culture", to outline its structure, to describe the peculiarities of the development of the didactic culture of teachers and students in the conditions of war, to characterize the role of information technologies in its formation.

Materials and methods: A number of scientific methods were used in the research: a comparative-historical method to consider retrospectively the concept of didactic culture; bibliographic method to identify the existing source base; content analysis for analytical processing of literature; chronological method to analyse the study of didactic culture in a time sequence; structural and systemic analysis to clarify its specifics at different levels; comparative analysis to establish common and specific features in the system of didactic culture development in different countries; a questionnaire method for studying students' opinions about the structure of speech culture as a component of didactic culture; a method of generalization and specification that contributes to the formulation of conclusions and recommendations on the didactic culture development.

Conclusions: The didactic culture is considered as a socio-pedagogical phenomenon and an important component of professional and pedagogical culture. The didactic culture development in wartime conditions should be based on the principles of humanism, praxeology and acmeology, with the account of the challenges and features of the information society and the globalized world. In this context, systematic comparative studies will contribute to the use of the experience of other countries, and the development of psychodidactics will allow to approach the understanding of the deep patterns of the process of didactic culture development.

KEY WORDS: didactic culture, students, war, teaching, learning, value, information culture

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INTRODUCTION

In modern conditions, the significance of personality is growing both for the person and for the society, the development of culture, economy, and defence capability. Higher medical educational institutions of Ukraine gain invaluable experience of professional training of specialists in war conditions. These tragic circumstances made it necessary to review the established methods, organizational principles of the educational process, and raised the requirements for teachers' culture. After all, among the students there are those whose parents died in the war, there are young people resettled from temporarily occupied territories, and young people with experience of participating in military operations. Obviously, this problem requires a series of monographic studies. In the article, we will try to outline only the most important aspects.

Medical universities play an important role in this complex and controversial process. These educational

institutions are exactly those developing the elite of the nation, those training the "intellectual capital" of the country.

Attention to the organization of the educational process in medical universities is growing every year. This is proved by numerous scientific papers [1-8]. Among the numerous issues of the organization of the educational process, we single out a new problem, which has been termed as "didactic culture".

THE AIM

To analyse the essence of the concept of "didactic culture", to outline its structure, to describe the peculiarities of the development of the didactic culture of teachers and students in the conditions of war, to characterize the role of information technologies in its formation.

MATERIALS AND METHODS

A number of scientific methods were used in the research: a comparative-historical method that provides an opportunity to consider retrospectively the concept of didactic culture; bibliographic method that helps to identify the existing source base; content analysis for analytical processing of literature; chronological, which allows to analyse the study of didactic culture in a time sequence; structural and systemic analysis of the process of didactic culture formation to clarify its specifics at different levels; comparative analysis to establish common and specific features in the system of didactic culture development in different countries; a questionnaire method for studying students' opinions about the structure of speech culture as a component of didactic culture; a method of generalization and specification that contributes to the formulation of conclusions and recommendations on the didactic culture development.

REVIEW AND DISCUSSION

Didactic culture involves the understanding and application in the process of teaching and learning of the laws of human intellectual development. An important element of the didactic culture development in wartime is deepening of students' moral values. In particular, one of the elements of work in this direction is the systematic writing of creative essays by students, which serve primarily as a means of self-reflection, of the formation of students' creative abilities, and the development of their professional, critical thinking. It is the actualization of the value system that should become the basis for the activation of educational work, the transition to a new level of didactic culture. An important element of the didactic culture development is overcoming the harmful informational influence, which is one of the features of the wartime, and to produce positive impact on young people through informational resources, in particular through blogs. They can simultaneously serve as a means of educational influence and a method of forming critical, analytical thinking, and media literacy.

Analysing the problem of didactic culture, the authors cannot definitively determine the origin of this concept. Currently, the conclusion is confirmed that this concept was used by the famous writer John Fowles in the controversial paper "Aristos", which was published in 1964. It should be noted that the book has many interesting educational and didactic aspects. In the context of the research topic, specific attention should be paid to the author's conclusions about the mass media, "standardizing technologies, the replacement by the didactic culture of the twentieth century of the didactic morality of the nineteenth century as proof that the organ of propaganda "serves" the public, the spread of museums and art galleries, the book sea of information – all this forces us, fundamentally modern beings, to see the world through an unrelated way" [9]. As we can see, the statement is not directly related to the educational process. But it turned out to be quite effective for characterizing the development of didactic systems and for corresponding changes in pedagogy.

In our opinion, this problem requires additional research by specialists in comparative studies. Moreover, the appearance of the name itself does not mean that the problem had not beenanalysed on essential grounds before.

Traditionally, difficulties arise when defining the concept. Domestic experts often use the definitions of representatives of other countries, in particular T. Berezina, who states that "the didactic culture of the head of a higher education institution is an integrative quality of the personality, which is expressed in a set of competencies in the pedagogical, psychological and didactic fields of knowledge, the ability to actively influence the setting and development of the educational process of a higher educational institution, which allow to guarantee high quality of education" [10]. This definition has several drawbacks. Each pedagogical phenomenon has "integrative" features. The set of competencies in the combination of pedagogy and psychology raises more questions than answers. These same drawbacks are inherent in the active influence on the "establishment and development of the educational process of a higher education institution" and on the assurance of high guality of education.

Analysing the didactic culture of the future university teacher, A. A. Plaksin suggests to consider this concept as "an integral property of the teacher's personality, which ensures effective pedagogical activity regarding the development of the professional culture of the future specialist and contributes to the creation and mastering by the teacher of new pedagogical values and technologies, the self-development of their personality, didactic cultural creativity. At the same time, didactic culture is a component of pedagogical culture as a social phenomenon. The didactic culture of a future university teacher is based on the teacher's clear and comprehensive knowledge of the discipline they teach, professional competence, a humanistic system of values and beliefs, modern pedagogical thinking, didactic cultural creativity" [10]. This definition is much better. Its disadvantage is a violation of the requirements of logic, i.e., the requirement about the impracticality of repeating the basic concept (definiendum) through similar concepts. We have a peculiar list: didactic culture

 professional culture – pedagogical culture – cultural creativity. At the same time, we consider attention to values and self-development as a positive aspect.

A. A. Plaksin's proposal to structure didactic culture into different components deserves specific attention. Thus, the author singles out a value-motivational component, which consists in "the development in the future teacher a set of pedagogical values as norms that regulate their educational activity (goals, means, relationships, qualities) and generates in the teacher's mind a personal system of value orientations and a positive motivation for educational activity"; cognitive component as "a set of methodological, general theoretical, didactic, methodical knowledge that provides the basis for the didactic competence of the future teacher. At the same time, the core of the cognitive component is didactic knowledge reflecting modern theories, concepts, regularities, principles, forms and methods of organizing the educational process"; the technological component as "didactic conditions (gnostic, projective, constructive, organizational, communicative), the possession of which allows the future teacher to carry out the process of teaching, modelling the optimal forms, methods, techniques and methods of interaction with the ones they teach"; the personal-creative component as "the formation of the author's own innovative elements of the didactic process, a high degree of personal creativity in mastering innovative teaching methods and techniques, the constant development of creative pedagogical thinking" [11].

The paradox is that the authors, using the experience of teachers from other countries, offering their definitions of the concept of "didactic culture" do not sufficiently appreciate the best definition suggested in the dissertation of V.Y. Hryniov (2003). According to the author of the dissertation, this concept should be considered as "personal formation that determines the effectiveness of the educational and cognitive activity of students, contributes to the creation and mastering of pedagogical values and technologies by the student, stimulates them to self-development and creativity" [12]. Let us emphasize several important aspects. Firstly, V.Y. Hryniov considers the problem in the context of cognitive activity of students. That is, we are talking about the interaction of a teacher and a student, or a teacher and a pupil. Secondly, the issue of values is singled out. Thirdly, the prioritization of self-development and creativity indicates an understanding of promising tasks for many years ahead.

We tried to expand this problem. The development of society allows one to consider didactic culture at the level of participants of the educational process: teachers, lecturers, educators, parents, pupils, students, people of any age who are engaged in self-improvement.

In our opinion, didactic culture is the understanding and use in the process of teaching and learning of the laws of human intellectual development. Understanding involves an informational component, while application emphasizes the need for practical activity. Teaching and learning distinguish the subjectivity of the process. Teaching is the teacher's activity. Learning is a student's activity. Awareness of regularities emphasizes a higher level of didactic culture compared to chaotic actions. It would be possible not to differentiate teaching and learning, since this is the essence of modern didactics, but at this stage we considered it necessary to emphasize these two processes, which in particular are a good illustration of the philosophical law of unity and struggle of opposites. It is enough to mention the interaction between Plato and Aristotle. In modern conditions, the heads of scientific schools could say a lot about this. Regarding creativity and self-improvement, we consider these phenomena in the context of the transition to the level of personality. The problem of didactic culture turned out to be so deep and promising that a series of monographic studies should be expected. The need for differentiation is obvious, which can be achieved by clarifying the name of one of the subjects of the educational process: didactic culture of a school teacher, didactic culture of a university teacher, didactic culture of parents (debatable, but promising, because parents with the appropriate level of education participate in the education of children). Moreover, manuals will be written with the account of the specifics of disciplines and educational institutions.

Let us consider how Polish experts solve the issue of didactic culture. The author of many books on didactics, Dorota Klus-Stańska, in 2011 published an article with the controversial title "Why school didactic culture does not change". Three aspects are important in the article. First, the author suggests the definition of theconcept of didactic culture: "beliefs, values, norms and models of behaviour combined with methods of knowledge creation recognized in the school". Secondly, domestic experience is critically evaluated: a critical assessment of an attempt to use the solution of a mathematical problem in a way that has not yet been studied in the classroom; negative reaction of the teacher on the offer to use a problem task for independent solution of the task; during the training, teachers single out such advantages of active learning methods as the development of readiness for cooperation and better memorization of the content, and at the same time there is no time for such methods; critical evaluation of such methods due to the large number of students in the class. It is obvious that such isolated examples cannot characterize the didactic system as a whole. At the same time, such examples characterize the understanding of the essence of didactic culture. Thirdly, the education system of British educational institutions is positively evaluated: the encouragement of parents to educate their children; solving tasks of various levels of complexity; student activity as a priority task; preference and priority of learning in small groups; the use of essays in teaching with anideaof avoiding banality, to write as if they wanted to "cause a storm in the media" [13].

An interesting approach was proposed by M. Wiśniewska. The author examines, in particular, the significance of the organizational culture of the educational institution at the level of the teacher, student, head of the institution, and administrative staff [14]. Let us emphasize that Polish experts in didactics increasingly consider didactics as a science of the laws of teaching and learning, that is, the interconnected activities of the teacher and the student.

The transition to the information society in a new way raises questions about the role of information in the didactic culture of the teacher and student, especially in the conditions of information war.Let us summarize the experience of Ternopil National Medical University regarding the education of students in wartime conditions.

At the practical classes, teachers discuss important state documents, addresses of political leaders, moral authorities. As an example, let us cite Olena Zelenska's greetings on the occasion of International Nurses' Day: "Today the world is celebrating Nurses' Day. Since February 24, this profession has gained special significance in Ukraine. After all, the war turned our nurses into brave fighters of the medical front, who every day in the hottest spots, risking their own lives, save Ukrainians... Midwife Vira Tselyk from the first day of the war assisted in child birth in the bomb shelter of the Chernihiv maternity hospital. For 46 days under constant bombardment, the midwife lived with mothers and babies, taking care of them as if they were family members. Nurse Alla Chernets organized the work of the Trostianets city hospital from the first shelling until the building was completely destroyed. Under the targeted fire of tanks, she saved people, organizing the evacuation of the wounded and sick. Nurse Oksana Balandina was returning from night duty at the Lysychansk hospital when she and her husband came under aerial bombardment. She covered her husband and lost two legs, saving him. Nurse Svitlana Klymenko lost her son near Mariupol, her husband, a doctor, went missing during the war. Despite the pain, she continued to work at the Ivankiv hospital during the occupation... And these are just some of the stories: thousands of nurses remained

on duty in Ukrainian hospitals. They apply dressings, assist, care, treat, comfort, evacuate, seek medicine. To be not only a nurse, but also a mother or daughter to patients. We all bow low to you for this" [15]. On May 7, 2022, the Minister of Health of Ukraine V. Liashko stated that since the beginning of the war in Ukraine, 10 medical workers have died, and more than 40 have been injured. Such facts should be analysed in classes, influence the value system of young people, and form a sense of professional responsibility and patriotism in future doctors [15].

The authors of an interesting study with the eloquent title "Fundamental values of academic integrity" emphasize the importance of six values, such as: honesty, trust, justice, respect, responsibility, courage, and also substantiate an important conclusion for Ukrainian universities: "Academic communities flourish when their members 'live' by fundamental values. This requires constant reminders of these values and conversations around them to show students, faculty, and administration the effectiveness and efficiency of such dialogues in spreading the word about academic integrity and improving various aspects of life on and off campus. Integrity is strengthened in academic communities when moral and so the overall norms of this community coincide with fundamental values and are supported by institutional principles and practices. When public educational institutions are 'imbued' with integrity, they help create a stronger civic culture of society as a whole" [16].

In the conditions of war, the system of values needs clarification, in-depth systemic evaluation, as significant changes are taking place, especially in the youth environment. From the first day of the war (February 24, 2022), students of Ternopil Medical University wrote creative papers, which will be the subject of a separate study. We will offer a few creative works from hundreds written by future doctors. According to the results of the content analysis of the creative papersby the students of I. Horbachevsky Ternopil National Medical University, which we conducted [17], when a month had passed since the beginning of the full-scale war, we can state that today for young people priority is given to national and family values, as well as peace, faith, freedom, dignity, unity, benevolence as fundamental values, which are especially relevant in the conditions of modern military realities. Future doctors, among other things, explain the importance of family comfort and communication, which became disrupted during the war (author's style preserved):

"In my opinion, nowadays it is necessary to appreciate every moment together with relatives and friends. There is no need to quarrel in a difficult time that has developed for our people. Only when you lose, you have to consider that everyday things,routine is very important to us. Morning coffee with the family, smiling grandmother and little sister, peaceful nights and peaceful skies. When you understand the seriousness of war and human losses, you learn to appreciate what you used to consider ordinary";

"...in my opinion, the war made me rethink my values and my life in general. Now, for the majority of Ukrainians, the main value and treasure is life, family and relatives, we also began to value our home, whatever it is, our House! Boundless respect for the Armed Forces of Ukraine and the President of Ukraine has increased, even outside the borders of our State. And how valuable the peaceful sky became; we didn't even notice it before! We have become an even bigger nation, even stronger, even more united, united as never before. We help each other, people in the east and in the centre of Ukraine. The whole world is proud of us. Because we are Ukrainians, and this is the most important value".

Almost all authors of the essays pointed out national unity as the most important value and prerequisite for victory in the war with the enemy. They justify their position in the following way: "One of the most important values of Ukrainian society during the war is the unity of the people. Only if we work together will we be able to achieve victory and overcome any enemy, even the strongest. Unity is our true strength. The war showed how united, strong and indivisible we can be. It is something that cannot be broken". Students claim that Ukrainian heroic history as spiritualethnogenetic heritage belong to the fundamental values that are particularly relevant today and motivate, equip, and keep Ukrainians strong inwar.It can be proved by the quotes from student essays:

"...the spirit of Ukrainians is indomitable. This is our foundation, the stone of invincibility. This is what has been carried down through the years from our ancestors who fought bravely for our existence. The history of Ukraine proves more than once that Ukrainians never give up and always fight to the end. And no matter how much the enemies wanted to destroy this spirit, how much they sought to suppress the desire of Ukrainians to be completely independent, destroying our culture and national identity, they would still not be able to do it";

"...my value and pride are that I was born in Ukraine. In a country that has been fighting for its freedom and independence for so many years and centuries. I am lucky to be Ukrainian, we are an extremely strong and loyal people. All Ukrainians unite and help previously unknown people. This is our value";

"...what is our superpower? The fact that we are Ukrainians! The eternal enemy stole our peace, but not our

freedom, not our dream. Millions of Ukrainians aspire to live in a free, democratic, successful, highly developed country. Freedom and dignity are the most important values for Ukrainians today. Without exaggeration, we have a sacred duty to defend the independence of our state, in which every person, their life and dignity are values. During the war, I and every Ukrainian man or woman rethought our beliefs, views and values. We understood that the real meaning of life is to be grateful and do good deeds. We are convinced that the most important things are the life and health of our relatives and loved ones. After all, there is nothing more valuable than them. Now, I will say "I love you" to my dear people more often. War teaches that you should not postpone life for later, but live every moment. On the day of Ukrainian victory, we will be the happiest people on the planet! And now we are strong, because we have Heroes who sacrifice their lives - the only most valuable thing they have is our peaceful sky. And this conscious civic position of theirs is evidence of the greatest love a person is capable of in order to protect their Motherland, parents, spouses, children, just people! We will not be able to bring back our fallen soldiers and civilians, children... But we will definitely remember them in our hearts and all the events that changed us, that confirmed that Ukrainians are the strongest, noblest, best nation! A nation for which freedom and justice, humanity and mercy are not just words, but values for which every conscious Ukrainian man and woman lives. Values that really united the Ukrainian nation. I believe that God is with Ukraine, who always calls people to be dignified, kind, and merciful. Therefore, we will definitely win!".

The dynamics of changes in value orientations of Ukrainians in connection with the war which can be traced in student essays – namely, from the shift of priorities from material values to spiritual ones – should become the basis for the activation of educational work, the transition to a new level of didactic culture [17].

Using the advantages of content analysis, you can get the information necessary to assess the level of development of values, making the necessary changes in the educational process. The main challenges of today are the war, which at the preparatory stage had the character of an information confrontation. Under these conditions, it is important to evaluate the blogosphere of the young generation. Let us consider the bloggers' assessment of the changes that took place in 2022 [18]. S. Bezverkha claims: "I consider blogging as a cultural and educational activity. Social networks provide an opportunity to share one's creativity with the audience, to communicate with subscribers... I can be read by fellow citizens who serve, who have lost a loved one, who are under occupation. You should understand that a cup of coffee described in "stories" will inspire someone, and someone will be offended or outraged. In general, during the first month of the fullscale invasion, most of the content was related to war news. In addition, bloggers often made reposts about collecting funds for the military, searching for transport to evacuate civilians, etc". According to M. Raschupkina, all people have changed in recent months."For the first few days, everyone tried to recover, then they thought about what to do next... Now, in the third month of the war, bloggers are more united than ever before. Interesting patriotic solutions are generated, and the trends of social networks are now getting straight to the heart. The war did what the enemy did not expect - it strengthened our faith and love for Ukraine" [19].

It is necessary to pay attention to one more promising direction of research. We mean changes in speech culture. In particular, researchers, analysing "hate speech", emphasize that this is a problem for decades.

In the pilot study conducted by us [18], qualities unacceptable for specialists working in the mass media were studied. These data are also important for medical publications. Survey participants (162 persons) chose the following: unreliability of information – 74; corruption – 63; incompetence–49; non-objectivity – 42; bias – 28; indifference – 27; engagement – 23; illiteracy – 21; irresponsibility – 19; rudeness – 17; emotionality – 17; laziness – 17; plagiarism – 16; supremacy – 11; selfishness – 7; frivolity – 5 [18]. The unreliability of information, language illiteracy and too much surzhykin the texts, lack of normal education – basic and professional – is a big problem, especially in Internet publications and the blogosphere.

The survey participants were asked the open question "What qualities should a successful blogger possess?". Respondents indicated that creativity of bloggers is important (37 students), their level of education (31 students), expertise in the chosen topic – 27, charisma – 22, 21 people voted for efficiency. A sense of humour is also important for the audience, as indicated by 21 participants, personal work style – 20, relevance – 18, objectivity – 18, benevolence – 9, determination – 4, media literacy – 2, no answer – 9 [18].

We would like to draw the attention to the peculiarities of the results in different regions and cities of Ukraine. Thus, the students of the western cities of Ukraine singled out fakes, information warfare and corruption as the main threat to the information environment. Instead, students from the centre and east of the country put the information war, Russification, war with Russia and corruption in first place. In our opinion, there is currently a new direction "Blogology", which we consider as a science of the regularities of the creation, distribution and influence of author's texts in electronic media [20].

CONCLUSIONS

To summarize let us consider the promising directions for further research. A systematic assessment of the quality of the educational process in new historical conditions is essential. After all, the war in Ukraine, millions of refugees who ended up in other countries require a reassessment of traditional forms, methods, and means of education. The requirements for distance learning, for the preparation of medical video materials, which must be standardized and accessible to students teachers, specialists in the process of their professional development, are changing. As an example, we can name the new simulation centres, which in the conditions of international cooperation allow to achieve much better results, especially in the training of paramedics.

The educational process simulation, expert evaluation, studying the opinion of teachers and students will allow to achievequalitatively new learning and teaching results. Praxeology has significant untapped potential, which in combination with acmeology will allow us to move tointegral thinking, which, according to the experts of the Club of Rome, will provide optimal answers to the challenges of the globalized world.

Systematic comparative studies will contribute to the use of the experience of other countries. The development of psychodidactics will allow us to get closer to understanding of deep regularities of the educational process. Modern specialists are beginning to develop a relatively new direction of research, regarding the scientific substantiation of the logic of questions, which plays an important role in certain types of professional activity (such as the anamnesis and iatrogeny in medicine). Monographs devoted to systematization, classification, dynamics of erroneous actions of participants in the educational process, the basics of editing scientific texts will be interesting and promising. Further differentiation, with the account of the specifics of the activities of the medical staff is appropriate. Therefore, in the near future, we can expect the appearance of new papers on the issues of regularities in the didactics of higher education, regularities of the educational process in higher education institutions, and hence the patterns of specialization. The logical conclusion of this stage will be textbooks of a new generation, which will combine the experience of past years with the capabilities of electronic means, will take into account the achievements of pedagogical personology, thus, contributing to the development of integral thinking of the individual.

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CASE STUDY

CLINICAL FEATURES OF CONNECTIVE TISSUE DYSPLASIA, OSGOOD-SCHLATTER DISEASE AND MULTIPLE CORTICAL DISORDERS IN A CHILD

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ABSTRACT

The aim: To analyze scientific data on the problems of disorders of bone morphogenesis in children, in particular, non-ossifying fibroma. To analyze modern methods of diagnosis and treatment of this disease in the context of the latest scientific achievements.

Materials and methods: The latest data of scientists from the world's leading clinics describing various forms of fibrous skeletal lesions in children of different ages were analyzed. We examined a boy with fibrous lesions of the cortical layer of the knee joint bones and a girl with a large fibrous focus of the distal femoral metaphysis, which resulted in a closed pathological bone fracture. Surgical treatment, osteosynthesis, marginal resection of the tumor, bone grafting and histological examination were conducted.

Conclusions: Despite numerous studies of this disease, the etiopathogenesis of this disease has not been studied. There are no early symptoms of fibrous bone lesions in children. Diagnosis is possible only when a pathological fracture of the affected bone occurs due to extensive growth of fibrous tissue and a significant decrease in the mechanical strength of the bone. Most cases of recognition of such a disease occur accidentally when performing X-ray examinations for other reasons - bruises, sprains, arthralgias, osteochondropathy, infectious diseases, etc. It is known that boys are more mobile and require more frequent X-ray examinations for limb injuries than girls, so the likelihood of accidental detection of such changes increases significantly. Thus, long-term observations of children with fibrous bone lesions have shown that after 40 years, patients rarely developed malignant tumors - osteogenic sarcoma, fibrosarcoma, malignant fibroma of tubular bones, pelvic bones.

There are no early symptoms of fibrous bone lesions in children. Recognition of such a disease occurs by chance when X-ray examinations are performed for other reasons.

KEY WORDS: unsyphilitic fibrous bone, pathological fracture, cortical defect, osteochondropathy, features, radiograph, tomography

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INTRODUCTION

The formation of the child's skeleton is a complex and poorly understood process. Various genetic and external embryotoxic factors can cause an imbalance in this complex process. Long tubular bones are formed as a result of enchondral calcification - cartilaginous, fibrous tissue is gradually replaced by bone. Sometimes such replacement does not occur and the bone has foci of this embryonic fibrous tissue. Most often, such inclusions of cartilage and embryonic fibrous tissue are located in the metaphyses of long tubular bones of various sizes and shapes [1,2].

Fibrous dysplasia is the least studied section of childhood bone pathology, although it is common. It is

formed during the intrauterine development of bones, although it does not appear immediately after birth. There is no clear boundary between the concepts of benign tumor-like formation and tumor. Most people consider this disease to be similar to a tumor [3-5].

Malignant transformation in Non-Ossifying Fibroma (NOF) is rare, and mostly in older age. The most common type of malignant transformation is osteosarcoma (70%), followed by fibrosarcoma (20%) and chondrosarcoma (10%). The mechanism of malignant transformation of fibrous dysplasia is not entirely clear. One such mechanism is the activation of a mutation in the GNAS gene located on chromosome 20q13 [6-8]. Most non-ossifying fibroma do not need treatment. They usually disappear on their own when the child's bones stop growing. In some instances, treatment may be advised to stabilise the affected bone after a fracture. There are many options for treating bone and soft tissue tumours, and some children need combined treatment. At CHOP, the specialists of the Bone and Soft Tissue Tumour Programme use a team approach to treatment [9].

There are several different treatments for this pathology. The dominant treatment method for Non-Ossifying Fibroma is conservative, but there are also options for continuation in case of negative results of the conservative method. The main ones are when non-ossifying fibroids are surgically removed using a simple surgical procedure called curettage. Surgeons scrape the tumour out of the bone with special instruments. They then fill the hole with a bone graft taken from the child's own body or from a donor. Sometimes a bone substitute may be used [10]. This type of treatment has an excellent recovery rate. The child patient will be able to return to his or her normal lifestyle within three to six months. To monitor and evaluate the quality of treatment in the hospital, periodic X-rays are required to see how the bone is fusing and to make sure that the tumour does not grow back in the area. There are also contemporary treatments that have prospects for development in the future of medicine: platelet-rich plasma and mesenchymal stem cells. In the first case, their advantage is the simplicity of the method and blood sampling, as the patient's material is used [11]. In the case of stem cells, the method's peculiarity is their ability to migrate to the place of inflammation and speed up the recovery period [12].

THE AIM

The aim of the study is to analyze the literature data for the purpose of timely diagnosis, treatment and prevention of fibrous dysplasia, which is the least studied section of bone pathology of childhood and occurs quite often. Also to demonstrate two clinical cases related to these diseases.

MATERIALS AND METHODS

The latest data from scientists of the world's leading clinics describing various forms of fibrous skeletal lesions in children of different age groups were analyzed. The long-term results of observations, according to the literature, of such patients after 40 years of age who had fibrous lesions of the skeleton bones in childhood were studied.

A boy with fibrous lesions of the cortical layer of the knee joint bones and a girl with a large fibrous focus of the distal femoral metaphysis were examined at the regional children's clinical hospital, which resulted in a closed pathological bone fracture.

The examinations were performed using standard X-ray equipment and a computed tomography scanner. Histological examination - microscope, hematoxy-lin-eosin stain, eyepiece x 300.

REVIEW AND DISCUSSION

Non-Ossifying Fibroma is classified as a benign tumor-like mass grouped according to the World Health Organization (WHO) histological classification of bone tumors. According to the literature, NOF is predominantly located in the metaphyses of long tubular bones and occurs frequently in 30-40% of children aged 4 to 8 years . As the bone grows, the focus of NOF moves away from the epiphyseal cartilage plate towards the diaphysis. NOF is localized eccentrically in the bone metaphysis without involvement of pathological changes in the periosteum. Some scientists believe that boys suffer from this disease twice as often as girls, others - on the contrary, more often than girls, and others - almost equally. As a rule, NOF is diagnosed by chance when an X-ray is taken for another reason. Usually, NOF does not occur after the age of 30 [13,14].

Most scientists believe that NOF has a benign course, and in the process of child growth, these foci gradually regress and are replaced by full-fledged bone tissue spontaneous recovery occurs [15]. According to Ritchl et al, a classification scheme was created that distinguishes between four different stages of nonosseous fibroids [16]. (Table I)

Surgical treatment was performed in cases of large foci, namely more than half of the bone perimeter, to prevent pathological fractures or when such a fracture has already occurred [17]. The fracture is repositioned, the tumor is curetted, and the cavity is then filled with a bone allograft (donor bone) or an autograft taken from another bone of the same patient [18]. Fracture fixation is performed individually depending on the amount of displacement of the fragments and the fracture line. For this purpose, various onlay plates (implants) with angular stability are selected.

Malignant transformation in NOF is rare, and mostly in older age. The most common type of malignant transformation is osteosarcoma (70%), followed by fibrosarcoma (20%) and chondrosarcoma (10%) [19].

Based on a comprehensive examination - radiography, CT, MRI, clinical data, such changes were most often observed in the distal femoral metaphysis, proximal

Table I. Four different stages of Non-Ossifying Fibroma (NOF) according to Ritchl et al.

Stage A	A small oval lumen with a thin, clear rim adjacent to the growth zone.
Stage B	A grape-like lumen that has moved with bone growth into the metaphysis and increased in size.
Stage C	The mineralization phase, the beginning of bone replacement starting from the diaphyseal part towards the growth zone.
Stage D	Complete bone replacement of the fibrous lesion.



Fig. 1. Patient U., 13 years old. Frontal projection of the knee joints. Suspected foci of enlightenment of the cortical layer of the femoral and tibial metaphyses.

tibia metaphysis, humerus metaphysis, and less often in the pelvic bones. The mechanism of malignant transformation of fibrous dysplasia is not entirely clear. One such mechanism is the activation of a mutation in the GNAS gene located on chromosome 20q13. Mutated skeletal stem cells lose the ability to maintain a normal histological environment, cause an imbalance of phosphate-regulating hormone (FGF-23), which leads to osteomalacia and bone deformation and indicates that bones are an active participant in the body's endocrine metabolism. It is believed that skeletal stem cells have a huge osteogenic potential in the development of bone, cartilage, fibers and other connective tissues [20-22].

The radiographic picture of NOF is very characteristic. As a rule, in the metaphysis of long tubular bones, there is a spindle-shaped lucency of various sizes, sometimes capturing more than half of the bone perimeter. The contours of the lumen are clear, without periosteal reaction, bone destruction [23]. Such changes are diagnosed accidentally as a result of examination of a child for other reasons. If the cortical defect is large, more than half the perimeter of the bone, then a pathological fracture may be observed at this site with the corresponding fracture clinic - pain, swelling, bone deformation, limb dysfunction. The dominant method of NOF treatment is conservative. According to various authors, small cortical defects are not treated by adhering to the slogan «Don't touch me and leave me alone,» i.e., only dynamic observation is performed [24,25].

CLINICAL CASE 1

Patient U, boy, 13 years old. A week ago, after physical activity on the legs, he felt pain in the left shin. Sports activities in rowing only increased the pain. He did not undergo treatment. The pain intensified, lameness and limitation of movements in the knee joint appeared.

On examination, he limps on the left leg. Atrophy of the left thigh muscles up to 1 cm at the level of the middle third, of the lower leg - 1 cm. Movement in the left knee joint is limited, with bending pain in the lower leg. The length of the legs is the same. The apophysis of



Fig. 2. Patient U. 13 years old. Direct tomography clearly shows cortical defects of the distal metaphysis of the right femur and proximal metaphysis of the left tibia.

the left tibia is swollen, hot, painful when pressed. With forced flexion of the left knee joint, the pain increases, with extension, it decreases. The skin on the tibia apophysis is unchanged. Muscle tone is reduced. The feet are flattened, the height of the longitudinal arch of both feet is reduced. Osteochondropathy of the left tibia apophysis (Osgood-Schlatter disease) was suspected. In order to clarify the diagnosis, an X-ray of the left knee joint in 2 projections was performed. The examination radiographs revealed osteoporosis, fragmentation of the apophysis of the left tibia, and the diagnosis was confirmed. A detailed evaluation of the obtained radiological data revealed fuzzy foci of spindle-shaped lucency of the distal femoral metaphysis (Fig. 1).

The resolution of classical X-ray equipment could not provide clear information about bone changes, so an additional examination was performed - a computed tomography scan of both knee joints. Two defects of the cortical layer were found on the posterior plane of the distal metaphysis of the right femur: a spindle-shaped defect of 0.5×1.5 cm with clear contours, the depth of which did not exceed the thickness of the cortical layer. On the posterior-internal plane of the proximal metaphysis of the left tibia, there was a spindle-shaped defect of the cortical layer of 0.4×1.5 cm with clear contours, two linear cortical defects of 1×0.1 cm somewhat distal (Fig. 2). Transverse sections revealed three cortical defects of the distal metaphysis of the right femur and a cortical defect of the proximal metaphysis of the left tibia (Fig. 3).

Clinical diagnosis. Left-sided osteochondropathy of the left tibial apophysis (Osgood-Schlatter disease). Coracoid defects of the distal metaphysis of the right thigh, proximal metaphysis of the left tibia. Bilateral flat feet.

The peculiarity of the first case is that the boy was accidentally diagnosed with two diseases that require completely opposite methods of treatment - Osgood-Schlatter disease and cortical defects of the metaphysis of the thigh and tibia. Thus, osteochondropathy is subject to powerful physiotherapeutic treatment - lower leg massage, thermal procedures (ozokerite, paraffin, solux), electrophoresis with salt solutions, balneotherapy, peloid therapy, vitamin therapy. Prohibition of physical activity on the legs. Such treatment would be carried out for several years both in a hospital and in a sanatorium. Since malignant transformation of fibrous foci into osteogenic sarcoma is possible, such treatment is not suitable for those bone changes that were diagnosed by chance - cortical bone defects (he has been ill since birth). The child was forbidden any physiotherapeutic procedures on the limb - heat, microwave, massage, artificial vitamins, hydrogen sulfide, radon baths, etc. Dynamic X-ray (or CT) observation, significant reduc-



Fig. 3. Patient U., 13 years old. Transverse sections of tomography show cortical defects of the distal metaphysis of the right femur and proximal metaphysis of the left tibia.

tion of physical activity on the limbs, and temporary cessation of rowing were recommended. In the long run, the bone defects should completely disappear by the time the child's growth is complete. However, there are isolated observations that state that such bone remodeling is not always favorable and can be observed at an older age (over 40 years) with degeneration into a malignant tumor. That is, optimistic views on this disease are not always realized [20]. The mechanism of such transformations has not been fully studied, so such patients are subject to mandatory X-ray, magnetic resonance or tomographic observation in the dynamics. If the defects increase and exceed the diameter of the bone, there are signs of bone destruction, periosteum, then it is recommended to immediately seek further in-depth examination of the patient at any age.

CLINICAL CASE 2

A girl, 6 years old. She fell on the street. Complaints of severe pain in the lower third of the left thigh, limitation of movement of the leg, unable to step on the leg independently. On examination, there is a pronounced edema of the lower third of the left thigh, movements in the knee joints are sharply limited and cause severe pain. An X-ray of the left thigh in 2 projections accidentally revealed a large center of lucency in the distal metaphysis 3 x 3 cm with clear contours, located eccentrically, the fracture line

is helical through the entire focus of the disease, slight displacement of the fragments. There is no periosteal reaction. Fibrous dysplasia of the hip was suspected. She was operated on for a pathological fracture of the lower third of the left thigh with displacement of the fragments. The operation revealed a helical fracture at the site of the lesion, the cavity of which was filled with yellowish fibrous tissue with blood streaks. An edge resection of the tumor was performed with its subsequent replacement with bone chips from an allograft. The fragments are aligned, fixed with a titanium plate with angular stability and screws (ChLP. Distal lateral fibula plate). The wound healed with primary tension, sutures were removed on the 8th day after surgery. She was discharged in satisfactory condition at her place of residence. Walking with crutches with partial load on the left leg.

Histologic examination (soft part) - fibrous tissue with severe edema, massive hemorrhages, angiofibrosis, mitotic multinucleated cells, single giant multinucleated cells. Hematoxylin and eosin stain, objective x 300. Bone histology - multiple fibrous fibers with numerous hemorrhages, single giant cells, multinucleated cells. Hematoxylin and eosin stain, objective x 300. Histologic conclusion: Fibrous dysplasia of the left thigh.

Conclusive clinical diagnosis. Pathological, screwshaped, fracture of the lower third of the left thigh on the basis of non-syphilitic bone fibrosis (NOF) with displacement of fragments. As a result of a pathological hip fracture, NOF of the left hip was accidentally diagnosed. NOF was asymptomatic, but the fracture with its pronounced clinical manifestations helped to identify this disease. The focus of fibrous lesion was localized in a classic place with a pronounced radiological picture. If the fracture had not occurred, the girl would not have known about the presence of this disease.

CONCLUSIONS

- 1. NOF is a disease that occurs from birth, starting with intrauterine development and is asymptomatic.
- 2. The disease is diagnosed incidentally as a result of an X-ray examination for other diseases.

- 3. Treatment of NOF at this stage of medical development has not been developed, in most cases only observation.
- 4. Surgical treatment is carried out in case of pathological bone fractures or for their prevention, when the size of the NOF focus is larger than the diameter of the bone.

Prospects for further research include the development of the latest early diagnostic criteria based on genetic, biochemical and other markers of this disease for the timely diagnosis, treatment and prevention of NOF. The etiopathogenetic treatment is the introduction of the genome editing method in the GNAS gene located on chromosome 20q13 with «genetic scissors» - CRISPR-Cas9.

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MANAGEMENT OF COMPLICATIONS FOLLOWING BUTTON BATTERY INGESTION

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ABSTRACT

Ingestion of button batteries by children is increasing every year, which is becoming a clinical problem for pediatricians. The number of complications and mortality when using batteries exceeds similar indicators when accidentally swallowing other foreign bodies. This is due to the electrochemical and mechanical effect of the battery on the mucous membrane of the gastrointestinal tract and especially the esophagus. With a late diagnosis, an ordinary battery leads to the development of fatal complications. In modern literature, there are no protocols that would relate to the treatment of similar situations, in particular, in the development of a tracheoesophageal fistula. The article describes a case of successful treatment of a tracheoesophageal fistula due to a long-term stay of a battery in the esophagus. This condition was also complicated by the development of bilateral tension pneumothorax. The dilemma in such cases is always difficult: to choose operative or conservative treatment. Both methods have their advantages and disadvantages. In this clinical case, preference was given to conservative treatment, which ended quite successfully. But the main goal is to prevent such situations. This can be achieved by raising parents' awareness of the risks of battery ingestion. Also, the efforts of a doctor who is faced with a similar situation should be directed to the fastest possible diagnosis and removal of such a foreign body as a battery.

KEY WORDS: foreign bodies, tracheoesophageal fistula, conservative treatment, tension pneumothorax

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INTRODUCTION

Every year the number of cases related to the use of foreign objects such as batteries by children is increasing. This is due to the development of science and technology, which leads to the appearance of a large variety of gadgets that are powered by compact batteries. These are calculators, scales, hearing aids, key chains, and, what is especially dangerous, children's toys. Low-quality samples of the latter include batteries with a thin metal shell, which corrode very quickly with the release of aggressive electrolyte content in heavy metals such as mercury, zinc, lead and lithium. They have both local and general effects on the body due to intoxication through absorption. In addition, physical stretching of the wall of the esophagus by a foreign body of more than 15 mm in a young child has an ischemic effect with a violation of microcirculation in the wall of the esophagus and the subsequent development of necrosis. But the greatest harm is caused by electrical damage to the mucous membrane of the esophagus when it comes into contact with the poles of the battery [1-3].

Due to the residual voltage even discharged batteries have a detrimental effect on the mucous membrane

of the esophagus, and complications such as necrotic esophagitis with the risk of perforation or stenosis of the esophagus, tracheoesophageal fistula, mediastinitis, hemo- and pneumothorax, etc. are possible after only 2 hours of exposure. [4].

Among all complications, tracheoesophageal fistula is the most dangerous fatal consequence. Traditionally a surgical tactic is chosen for this type of complication. It consists in disconnecting the joint, which is aggressive and threatening in terms of complications and intraand postoperative mortality. Methods of conservative treatment of this pathology are also described, but this problem remains insufficiently studied due to the small number of registered and published cases. [6].

Conservative treatment requires close monitoring of the progression of mediastinitis and aspiration pneumonia and readiness to switch to operative treatment in case of failure of the latter. [4, 6, 7].

CASE REPORT

This article presents an example of conservative treatment of a complicated long-term finding of a battery in the esophagus in a 2-year-old child. The girl was admitted 20 hours after the onset of the following complaints: dysphagia, refusal to eat, restlessness, and increased salivation. The parents denied the possibility of the child using a foreign body. A foreign body battery in the first narrowing of the esophagus was detected during the chest X-ray examination. (Fig.1). A diagnostic fibroesophagoscopy was performed, which revealed a button lithium battery with a diameter of 20 mm, 3V in the middle part of the esophagus. After removing the battery an erosive ulcerated defect covered by fibrin remained on the mucosa. No tracheoesophageal fistula was detected. On the second day nutrition was started through a nasogastric tube. On the fifth day, the child's condition worsened due to the increase in fever and respiratory failure. The patient was intubated and transferred to mechanical ventilation. X-ray examination revealed bilateral lower lobe pneumonia. Antibiotic therapy with broad-spectrum drugs (cefotaxime, amikacin), antisecretory therapy, and parenteral nutrition were started. A nasogastric tube was again installed for stomach decompression. On the 6th day, the child's condition worsened due to increased respiratory and heart failure manifestations. Bilateral tension pneumothorax was clinically diagnosed, which was also confirmed by X-ray examination.

The rapid development of this complication led to cardiac arrest in the child. Resuscitation measures were started immediately simultaneously with the puncture and subsequent drainage of the pleural cavities according to Bülau. Clinical death lasted 10 minutes, after which cardiac activity resumed. Treatment of post-resuscitation disease has begun.

After the stabilization of the condition, a rigid diagnostic and remedial bronchoscopy was performed, which revealed a tracheoesophageal fistula of 0.5 x 0.5 cm with fibrinous layering along the edges and with prolapse of the esophageal mucosa into the tracheal lumen on the back wall on the left. In the subligamentous space of the trachea, there was a circular layering of fibrin. According to computer tomography focal pneumomediastinum and bilateral lower lobe bronchopneumonia, bilateral drained pneumothorax were diagnosed.

Taking into account the seriousness of the child's condition, a conservative treatment strategy using massive antibiotic therapy (meropenem, vancomycin, metronidazole) was chosen for the treatment of tracheoesophageal fistula. For decompression of the stomach and enteral feeding, fundoplication according to Nissen, gastrostomy according to Kader was performed and a food probe was additionally inserted through the gastrostomy opening into the small intestine. Enteral nutrition with «Rehydron Optim» was

started, then the mixture «Nutricia Infatrini Peptisorb» was added with a slow expansion of the daily volume to the age norm. The caloric deficit was compensated by parenteral nutrition. The child's condition remained severe, but with gradual improvement in the form of a decrease in oxygen dependence, febrile fever, and positive X-ray changes. In the neurological status, hypertonicity of the extensor muscles and periodic tremors of the lower limbs remained. Control bronchoscopy on the 14th day demonstrated the beginning of the healing process of the fistula. (Fig 2). On the 30th day after the removal of the foreign body repeated esophagoscopy was performed and a complete healing of the tracheoesophageal fistula with the formation of esophageal stenosis was diagnosed. The child is extubated. Spontaneous breathing was adequate. Enteral nutrition was carried out for two months, after which esophagocolonoplasty was performed. Currently, the child is undergoing rehabilitation therapy for mild post-hypoxic encephalopathy. She is conscious, receives oral nutrition, digests food, started talking, sits, and walks with support. Attacks of headache, dizziness and capricious behavior are also periodically disturbing.

This clinical case demonstrates the need for immediate measures if there is information in the anamnesis about the use of batteries by a child due to the risk of developing life-threatening complications. The severity of the complications depends on the duration of the stay (more than 2-3 hours), the size of the battery (more than 20 mm), and its voltage [8]. But often the episode of foreign body ingestion remains unnoticed by parents, and clinical signs can be nonspecific and resemble colds[9]. Therefore physicians should be especially alert for symptoms such as dysphagia, refusal to eat, cough, repeated vomiting, fever, chest and abdominal pain, wheezing, and respiratory distress [9, 10].

With a late diagnosis, the risk of complications increases. These may be symptoms similar to those described in the clinical case, namely, associated with the development of perforation of the esophagus, the formation of a tracheoesophageal fistula, aspiration pneumonia and the occurrence of tension pneumothorax. It is also possible to develop mediastinitis, pleural empyema, lung abscess and aortoesophageal fistula. To determine the location of a battery-type foreign body, the first diagnostic method is an X-ray of the neck, chest and abdomen, if necessary. This method also allows you to distinguish button batteries from other metal foreign objects by the presence of a «double ring» (anterior-posterior projection) or «steps off» on the side projection. [10-12].

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and



Fig. 1. Antero-posterior X-ray of the chest demonstrates the presence of a metallic foreign body with a «double-ring" sign in the esophagus.

the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESGHAN) have issued clinical guidelines for the management of children who have ingested a battery. According to these recommendations, the removal of button batteries from the esophagus is recommended within 2 hours from the moment of ingestion both in patients with clinical signs and in patients with no symptoms of a foreign body entering the gastrointestinal tract. If during X-ray control it becomes clear that the battery remains in the stomach for more than 48 hours, then ESPGHAN offers its endoscopic removal. NASPGHAN recommends elective endoscopic removal of gastric batteries within 24 hours if the battery does not progress on radiographic examination or if certain signs appear in a previously asymptomatic patient. [10, 11]. The National Capital Poison Center (NCPC) also recommends removing the battery within 2 hours of ingestion. The only exception is patients older than 12 years who swallowed a battery with a diameter smaller than 12 mm. Such patients can be observed on an outpatient basis, but the exit of the battery with a stool should be monitored for 10-14



Fig. 2. Flexible bronchoscopy 14 days after retrieval revealed tracheoesophageal fistula (TEF) formation, 5 mm in diameter.

days. If this did not happen, such patients undergo radiography to determine the location of the foreign body. But even if the battery is removed, it is necessary to remember the risk of perforation of the esophagus with the formation of a tracheoesophageal fistula (98% of such complications develop within 48 hours after battery removal). [12].

Currently, there are no recommendations for the treatment of acquired tracheoesophageal fistula in the case of ingestion of a lithium battery. Surgical treatment with fistula closure is radical. This can be a one-time restoration of the trachea and esophagus with small fistulas (up to 5 mm). At the same time, tracheal resection with tracheoplasty is recommended for defects larger than 10 mm. or tracheotomy with tracheoplasty and partial esophagectomy and gastrostomy. But such interventions require equipment for extracorporeal circulation and can be accompanied by a large number of complications, the rate of which, according to some authors, is about 64%. [13-15].

An alternative is a conservative treatment aimed at involuntary closure of the fistula. Similar fistula treatment with esophageal rest, gastric decompression, antibiotic therapy, and antisecretory therapy is recommended by some authors to continue for 4-8 weeks in clinically stable patients, and the state of healing is to be monitored by repeated endoscopies. On average, the closure of a fistula without surgery varies between 28 and 77 days. [16]. Surgical treatment is indicated only in the absence of signs of healing. Conservative treatment reduces the risk of postoperative complications and recurrences. But at the same time, such waiting tactics are dangerous due to the risk of aspiration pneumonia due to reflux and the development of respiratory disorders. [5, 17].

In our case conservative treatment was chosen for the patient. No fistula was detected during the initial examination. Respiratory disorders, which were regarded as manifestations of aspiration bronchopneumonia, required mechanical ventilation of the lungs. It is possible that the increase in pressure in the respiratory tract led to the release of air from the tracheoesophageal fistula, which was complicated by a bilateral tension pneumothorax with the development of clinical death. Resuscitation measures with simultaneous decompression of the pleural cavities made it possible to restore cardiac activity. Due to the unstable condition of the patient, it was decided to continue the conservative treatment of the fistula. Operative delivery was carried out in a minimal volume to enable enteral nutrition and decompression of the stomach. Healing of the fistula occurred within a month from the moment of ingestion,

which made it possible to later perform reconstructive surgery on the esophagus.

CONCLUSIONS

This clinical case demonstrates the risk of life-threatening delayed complications in case of battery use. Clinicians must be aware of the main symptoms and be prepared to provide care for a sudden deterioration in a previously healthy patient. Also this situation makes it possible to focus the attention of doctors on the fastest possible diagnosis and removal of such a foreign body as a button battery. This will reduce the number of serious complications and mortality in pediatric patients. In addition, serious measures should be taken to prevent the ingestion of batteries by providing sufficient information to parents and children regarding the danger of batteries entering the respiratory tract or gastrointestinal tract.

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PHILOSOPHY AND MENTAL HEALTH

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ABSTRACT

The aim: The paper aims to examine the relationship between philosophy and mental health.

Materials and methods: The authors used integrative anthropological approach, interpretive research paradigm, hermeneutical approach. The data collection was carried out using Scopus, Web of Science, PubMed, Google Scholar databases. Research papers were identified according to search terms: "mental health", "philosophy", "Ancient philosophy", "Epicureanism", "Stoicism", "Eastern philosophy", "Buddhism", "Taoism", "psychology", "psychotherapy", "anxiety", "depression", "happiness", "mindfulness", "meaning in life".

Conclusions: Attempts to cope with life challenges, frustration, fear, anxiety, stress should not be isolated endeavors, but they need to be placed in a wider philosophical context, as far as every issue, including mental health issues, has a philosophical perspective at its core. Such experience can cultivate human strength, self-confidence, awareness, empathy. In times of uncertainty, when we do not know where to go, when we do not understand who we are and what is our purpose on earth, philosophy helps us to find our way. In the most difficult times, philosophy acts as a guiding star and consolation reconciling us with what we are unable to change.

KEY WORDS: philosophy; mental health; Ancient philosophy; Eastern philosophy; psychology; psychotherapy

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INTRODUCTION

In 2020, the World Health Organization, together with United for Global Mental Health and the World Federation for Mental Health, encouraged world population to support a global movement calling for greater investment in mental health. The Director-General of the World Health Organization T.A. Ghebreyesus notes that this movement is more important today than it has ever been before: "We need to move for our own mental health, the mental health of our families, friends and colleagues, and more importantly, so that there is a massive increase in investment for mental health services at national and international levels" [1]. Nowadays, mental and substance use disorders are the leading causes of disability worldwide [2]. Studies conducted in low- and middle-income countries have demonstrated the effectiveness of both psychopharmacological treatment and evidence-based psychotherapy for the treatment of mental disorders [3-8]. Research on economic efficiency of mental health care highlights the economic value of disease prevention [9, 10].

However, the reality is different. Despite the validity of the effectiveness of measures to support mental health, there is a huge gap between their real application and the needs of any given society [11, 12]; and large-scale improvements in mental health are far from desirable. The costs of mental health care include social services, primary, secondary, and tertiary care. Financial resources are needed for treatment facilities, staff, administration, training, supervision, media, etc. Given the enormous burden of mental disorders, the available treatments are not enough to improve the mental health situation in low- and middle-income countries. With the COVID-19 pandemic, the situation has become even more acute exacerbating mental health problems. The global health care system has already faced with the need to solve psychological problems and provide psychosocial support related to COVID-19. In Ukraine, the war unleashed by russia made the situation even worse causing anxiety, depression, post-traumatic stress disorder, not to mention serious physical consequences. Such a situation in the world and in Ukraine in particular marks a turning point in which mental health must become a priority for the public health sector. The governments of all countries must recognize the tangible and intangible consequences of mental health issues and invest in this area.

Although funds are limited and the time frame for addressing these issues successfully is becoming ever tighter, the door of opportunity, which has existed since ancient times, is open for those who are looking for a way out. We mean philosophy and its practical implications. It is about balancing our mental and, accordingly, physical state, reducing anxiety and depression, realizing our delusions and false concepts, and regaining meanings of life in the ocean of uncertainty [13].

THE AIM

The paper aims to examine the relationship between philosophy and mental health.

MATERIALS AND METHODS

The authors used integrative anthropological approach, interpretive research paradigm, hermeneutical approach.

The data collection was carried out using Scopus, Web of Science, PubMed, Google Scholar databases. Research papers were identified according to search terms: "mental health", "philosophy", "Ancient philosophy", "Epicureanism", "Stoicism", "Eastern philosophy", "Buddhism", "Taoism", "psychology", "psychotherapy", "anxiety", "depression", "happiness", "mindfulness", "meaning in life".

REVIEW AND DISCUSSION

In the ancient world, philosophy was a fairly common practice of social recovery, which helped people maintain mental health, relieve stress, and get rid of fears. The ancient Greeks were the first to take care of social health of fellow citizens at the state level. They developed special health rituals based on the principle "Pan Metron Ariston", which means "Moderation in All Things". The responsibility for taking care of one's own health was considered as the honorable civic duty. Moderation was interpreted as the ability to control oneself, one's feelings and thoughts; as the culmination of the path of knowledge and self-formation, in fact, as the ideal of ancient philosophy.

For the great Greek philosopher Socrates, a person who does not follow the doctrine of moderation is weak, unable to control himself/herself and actually an unhappy person, since he/she cannot achieve the pleasure that he/she desperately seeks [14]. Moderation is of great value for the distinguished Greek philosopher Aristotle; this idea was reflected in his rationalistic ethics [15]. To achieve pleasure and happiness, a wise person strives for harmony of reason and desires [16]. "Ancient philosophers often acted as a kind of private consultants who served as advisers in everyday affairs and at the same time contributed to the establishment of social equilibrium resolving disputes, leading politicians to balanced decisions, etc. But one of the most important functions of philosophy, in addition to searching for truth and justice, was concern for the human soul. Epictetus, for example, considered his school as a kind of psychological clinic, in which all students had to realize their mental state as pathological in order to "heal mental ulcers by bringing the mind to rest". Plutarch believed that "a doctor made a mistake if he thought that he could neglect philosophy; it would also be a mistake to reproach a philosopher for the fact that, going beyond the boundaries allotted to him, he addressed the issue of health" [17]. As I. Andreev and L. Nazarova emphasize, the field of medicine closest to philosophy is precisely the science of the soul, that is, psychiatry [18]. Contemporary psychology and psychiatry should embrace the phenomenon of a human being including body, soul, spirit, and their synthesis. This is a difficult task, and philosophy can provide invaluable assistance elaborating the "holistic approach, according to which a human is an undivided, alive and organic, ideal and material being" [19].

Modern psychology, psychotherapy and psychiatry are increasingly moving into the field of evidence-based medicine and evidence-based practices, which sounds quite contradictory when it comes to such a phenomenon as a human, each of whom has his/her own existential experience and is in some way unique. As the result, a mental health professional perceives his/her patient as a typical representative of some general norm or pathology, i.e., he/she misses the understanding of this person as a unique individuality, unique personality, which often leads to difficulties in the specific diagnosis and treatment. In addition, their adherence to guidelines and protocols largely determines the diagnosis and course of treatment. Unfortunately, many medical specialists, as well as the representatives of other branches of knowledge, overlook the best evidence, especially if it is beyond the established scientific paradigm and, by doing so, they do not allow any room for alternative viewpoints, which can be more effective in this or that particular case [20, 21].

People do not question that the one who has good training and experience succeeds in treatment, rather than the one who has abstract knowledge. However, let's turn to Aristotle who said: "the physician does not cure man, except in an incidental way, but Callias or Socrates or some other called by some such individual name, who happens to be a man. If, then, a man has the theory without the experience, and recognizes the universal but does not know the individual included in this, he will often fail to cure; for it is the individual that is to be cured. But yet we think that knowledge and understanding belong to art rather than to experience, and we suppose artists to be wiser than men of experience (which implies that Wisdom depends in all cases rather on knowledge); and this because the former know the cause, but the latter do not" [22].

Being at the intersection of science and art, philosophy has great potential. It is the basis of all knowledge, and only philosophy can answer the fundamental guestions of human beings, explain, console, create meanings which is absolutely necessary for our mental health. That is, philosophy answers questions about the ultimate foundations of existence. But this is not one protocol answer intended for everyone. This answer varies and depends on the degree of destruction of the personal worldview, on the level which S. Kierkegaard called "despair": "A person, who claims that life is the path of sorrow and that human's destiny on earth is to grieve, has joy outside himself/herself, just as a person who sees the meaning of life in pleasure and joy has sorrow outside himself/herself; joy can, therefore, unexpectedly overtake the former, like sorrow - the latter. Both beliefs are based on external conditions that are beyond a person and his/her will, and sorrows and joys are equally beyond control of a person; any worldview based on external, independent of a person, conditions is... despair" [23]. The answer depends on the "depth" of human "I", at which individuals are forced to look for the foundations of their existence that through their lens they perceive as the general foundations of the universe. It is philosophy that can help in understanding individuals as complex dynamic systems, as well as their feelings, interests, sociocultural mechanisms underlying their development, the multifaceted relationship between social, cultural, spiritual processes that shaped them; it is philosophy that can reveal their existential core.

Very often, traumatic events and their psychological consequences lead to the loss of self and, ultimately, to the loss of the meaning in life. This is one of the most dangerous "non-protocol" situations, in which the very existence of a person becomes really meaningless, with all the ensuing negative outcomes. Philosophy addresses this acute problem enabling the individuals to create new meanings. F. Nietzsche said: "If you have your why for life, you can get by with almost any how" [24]. It is the meaning of life that has become the cornerstone of logotherapy - a therapeutic approach developed by the psychiatrist and psychotherapist V. Frankl. Believing that it was possible to turn suffering into self-development, V. Frankl helped clients to struggle with existential vacuum and uncover their true meanings. V. Frankl himself was a clear example of the effectiveness of his theory: his ideas helped him survive in the concentration camp and motivate other prisoners to continue living in inhuman conditions, in which their strength was running out and death seemed the easiest way out. According to V. Franks, the purpose of logotherapy is to cope with the suffering caused by the philosophical problems posed by life [25]. Thus, philosophy carries out the function of intellectual therapy, which is especially important in situations of instability, social explosions, wars, when a person is in a borderline situation, on the verge of being and non-being.

Modern people live in the era of upheaval. However, there is nothing new under the sun, and our ancestors went through the same existential challenges. For example, the Hellenistic period brought much to the table giving rise to Cynicism, Epicureanism, Stoicism, Skepticism. These schools of philosophy oriented the ancient Greeks and Romans in the world of turmoil and uncertainty trying to provide individuals with peace of mind and happiness. Getting rid of all misfortunes was seen primarily in autarchy (human self-sufficiency), adiaphora (indifference), ataraxia (equanimity). Of course, painful, destructive mental states cannot be eradicated as they are a part of human life. However, humans can turn them into something more bearable and even overcome a fear of death, one of the basic human fears. In his letter to Menoeceus, Epicurus addressed this issue: "Become accustomed to the belief that death is nothing to us. For all good and evil consists in sensation, but death is deprivation of sensation. And therefore, a right understanding that death is nothing to us makes the mortality of life enjoyable, not because it adds to it an infinite span of time, but because it takes away the craving for immortality. For there is nothing terrible in life for the man who has truly comprehended that there is nothing terrible in not living. So that the man speaks but idly who says that he fears death not because it will be painful when it comes, but because it is painful in anticipation. For that which gives no trouble when it comes, is but an empty pain in anticipation. So, death, the most terrifying of ills, is nothing to us, since so long as we exist, death is not with us; but when death comes, then we do not exist. It does not then concern either the living or the dead, since for the former it is not, and the latter are no more" [26]. Inner balance, self-control, restraint of emotions and desires – this is the path of the sage striving to live a serene, healthy, stress-free life. This is a kind of victory over oneself, which makes it possible to overcome all difficulties and hardships.

The representatives of Stoicism argue that some things are in our control and others not. For example, Epictetus said: "Things in our control are opinion, pursuit, desire, aversion, and, in a word, whatever are our own actions. Things not in our control are body, property, reputation, command, and, in one word, whatever are not our actions. The things in our control are by nature free, unrestrained, unhindered; but those not in our control are weak, slavish, restrained, belonging to others. Remember, then, that if you suppose that things which are slavish by nature are also free, and that what belongs to others is your own, then you will be hindered. You will lament, you will be disturbed, and you will find fault both with gods and men. But if you suppose that only to be your own which is your own, and what belongs to others such as it really is, then no one will ever compel you or restrain you. Further, you will find fault with no one or accuse no one. You will do nothing against your will. No one will hurt you, you will have no enemies, and you not be harmed" [27]. In fact, the only thing we can control in this world is our attitude to the situation. It is our attitude towards it that causes our poor mental health and well-being. Emotions are the result of our judgment, while things/ situations themselves are neutral. They become positive or negative after we have thought about them in a certain way, i.e., have attributed certain value characteristics to them.

These ideas became inspirational to the development of cognitive-behavioral therapy [28]. The Stoic belief that not things make us happy or unhappy, but only the idea of them, became the background of rational emotive behavioral therapy founded by A. Ellis [29]. A recent study conducted at Birkbeck University of London indicates that cognitive trainings based on the ideas of Stoicism have a positive impact on the individuals with emotion regulation disorders [30]. One of the researchers A. MacLellan stated: "Our findings demonstrate potential for supporting emotional wellbeing through the practice of Stoicism which can be combined with other established cognitive interventions. Our study has implications for augmenting and supporting existing therapies, as well as providing a promising solution to bolster resilience in those at risk of anxiety and depression in an accessible and cost-effective way" [31]. Another study shows a positive effect of Stoic trainings on resilience and empathy of medical students [32]. In this way, in times of turmoil and uncertainty, ancient philosophy comes back into our life offering centuries-old recipes for overcoming crisis situations, thereby expanding the psychotherapist's toolkit.

In Eastern cultures, significant attention was paid to physical and mental health. Eastern philosophical traditions have greatly enriched humanity by providing methods for dealing with difficult life situations. Therefore, it is no coincidence that the spiritual heritage of the East attracts close attention and arouses keen interest of psychologists and psychiatrists, not to mention philosophers, religious and cultural scholars. For instance, Taoism, which has become increasingly popular, includes three relatively autonomous, but deeply interconnected levels - philosophical discourse, religious doctrine, and psycho-techniques. "Taoism is perhaps the only one religious and philosophical system that encourages its adherents to live a happy, long, healthy life in this (not in the transcendent) world. For Taoists, life is the highest value... Taoism has contributed to the development of science and medicine in China. Many herbs, minerals were discovered in the search for extraordinary means to prolong life or achieve immortality. Taiwanese say: "Confucianism is a food store, Buddhism is a department store, and Taoism is a drug store". Nowadays, Taoist practices of physical and spiritual healing, universal human development are well known outside of China" [33].

The Taoist worldview is based on the idea of qi – the grand vital force that permeates everything in the world; and the world exists due to its transformations. When something blocks the flow of qi in human body, an imbalance occurs and symptoms of disease are manifested. The experienced physicians can help to regulate the normal flow of qi and accordingly restore the balance that leads to healthy life. This is the basis of traditional Chinese medicine, which is closely connected to the practice of Taoism.

In contrast to the Western thought, which cut the world into material and ideal components, the Chinese philosophical tradition proposed the "third way" thereby overcoming the insurmountable boundary between matter and spirit: they are the different modes of one unified Qi. These ideas were manifested in the interpretation of the "mind-body" problem. According to Y. Lee and colleagues [34], Qi (Gih) is not static potential, but activation without a goal. Qi (Gih) defines a two-way interaction between subject and object and is seen as a psychosomatic phenomenon that connects the mind and body. Y. Lee et al. distinguish between blood-Qi (Gih) and mind-Qi (Gih): "Blood-Gih denotes passion and intention and represents the activation from body (blood) to mind (emotion). By contrast, mind-Gih corresponds to the health and physical conditions as instances of activation from mind to body. Therefore, blood-Gih and mind-Gih possess features that can be characterized as activation and together represent a bi-direction of Gih, mind-to-body and body-to-mind. The question arises regarding how the blood or mind is compounded with Gih to direct the other. Both the blood and the mind are hypothesized to attain their relative properties. It is through psychosomatics that the body (blood) works with the mind" [34]. From the standpoint of Eastern philosophy and Eastern medical science, Gih (Qi) attempts to incorporate mental and biological processes by performing psychosomatic work [35]. Gih (Qi) has "the potential to activate and influence both the mind and the body, and its function is mediated by the hormonal metabolic and automatic nervous systems" [34]. Thus, Eastern philosophy laid the foundation of Eastern medical science, which is based on the control of the balanced circulation of Qi and aimed at harmonizing physical states and mental processes.

The philosophical ideas of the East have gradually evolved into practices that are now available throughout the world. Mind-body practices have attracted attention as useful complementary methods for dealing with chronic pain and distress associated with noncommunicable diseases. Although this approach alone cannot completely eradicate diseases, it can significantly improve psychological well-being and guality of life by reducing relevant symptoms along with physiological consequences of distress [36]. Mind-body practices may be seen as a fruitful strategy of complementary, holistic and integrative medicine that "focuses on the interactions among the brain, mind, body, and behavior, and the powerful ways in which emotional, mental, social, spiritual, and behavioral factors can directly affect health" [37]. These include Eastern physical, spiritual and intellectual practices such as yoga, tai chi, qigong, meditation, and mindfulness.

The practice of mindfulness is inextricably linked to psychological well-being. Awareness and non-judgmental acceptance of our experience are "regarded as potentially effective antidotes against common forms of psychological distress –rumination, anxiety, worry, fear, anger, and so on..." [38]. Mindfulness is the way of attentive living, attentive presence, attentive mind; this is the way to full human flourishing. The lesson we can learn from it is how to balance our actions with contemplation, which is to a large extent the task of philosophy.

Meditation, according to K. Wilber, is a "sustained instrumental path of transcendence" [39]. It is the deepest personal spiritual experience that can completely change the state of our mind. The goal of meditation techniques is to give our consciousness positive directions [40]. Mindfulness meditation is most systematically conceptualized in Buddhism; it is the method of dealing with consciousness, which has a philosophical and conceptual background and should be applied in accordance with special instructions. Buddhism as a universal theory of reality elaborated a concept of void - the ontological basis of freedom. "Modern psychotherapists often turn to the practice of meditation, because it leads to the true source of human beings, their true essence. A state of relaxation and an altered state of consciousness are both achieved through meditation that is especially effective in psychotherapy. But more than that, meditation is used as a method of personal growth so that a person can develop a more positive attitude towards life in general" [41]. The growth of interest in Zen Buddhist philosophy in the last third of the 20th century contributed to the popularity of meditative techniques and to their use in psychotherapy [42-46].

In the late 1970s, the practical implications of Eastern philosophy began to be studied as a method of improving psychological well-being. J. Kabat-Zinn [47] explored the use of mindfulness meditation in the treatment of patients with chronic pain that led to the development of Mindfulness-Based Stress Reduction (MBSR). Mindfulness-Based Cognitive Therapy (MBCT), Dialectical Behavior Therapy (DBT) and Acceptance and Commitment Therapy (ACT) were established on the basis of mindfulness-related principles and practices [48-50]. Mindfulness meditation practices are associated with higher levels of positive emotions, optimism, life satisfaction, adequate self-esteem, empathy, autonomy, competence [51-55]. Mindfulness develops the ability to "detach" from one's thoughts and emotions and perceive them as transient mental "events" [48]. This helps to break the chain of negative thoughts, which is a risk factor for a number of mental disorders [56].

Practices based on Eastern philosophical traditions teach us to be "here and now" [57, 58], be at peace with ourselves and the world around us; they pave the way to a harmonious, balanced, and happy life.

CONCLUSIONS

It is no wonder that the influential Roman philosopher Boethius named his book "The Consolation of Philosophy". This book was written while Boethius was imprisoned and was waiting to be executed; and this activity helped him to come to terms with the tragic situation.

Attempts to cope with life challenges, frustration, fear, anxiety, stress should not be isolated endeavors, but they need to be placed in a wider philosophical context, as far as every issue, including mental health issues, has a philosophical perspective at its core. Such experience can cultivate human strength, self-confidence, awareness, empathy. In times of uncertainty, when we do not know where to go, when we do not understand who we are and what is our purpose on earth, philosophy helps us to find our way. In the most difficult times, philosophy acts as a guiding star and consolation reconciling us with what we are unable to change.

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VARIA

TOWARD A HEALTHY SOCIETY: WHEN TRAUMA AFFECTS GROUP IDENTITY

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ABSTRACT

The aim: The purpose of the article is to identify the essence and causes of collective trauma and reveal its consequences for group identity.

Materials and methods: The authors used an interdisciplinary approach along with the principles of objectivity, tolerance, and impartiality. The analysis of the texts was conducted according to the basic principles of hermeneutics, namely the inexhaustibility of the authentic text and immanent critique. In addition, the method of conceptual and categorical analysis was applied, as well as induction, deduction, generalization, etc. The data collection was carried out using PubMed, Scopus, Google Scholar databases. Research papers were identified according to search terms: "trauma", "traumatic experience", "collective trauma", "traumatization", "stress", "historical trauma", "defeat", "the Holocaust", etc.

Conclusions: Collective trauma is a mental wound caused by the direct or indirect traumatic experience – a stressful situation that becomes a source of emotional tension due to an unexpected threat to the life of a group of people. Collective trauma occurs, on the one hand, due to the awareness of helplessness in the face of danger and, on the other hand, due to the excessiveness of traumatic experience, which turns it into the eternal present and destroys identity. Historical traumas arise in the process of conscious exploitation of traumatic experience by political or other leaders in order to achieve emotional unity and group consolidation. Without appropriate processing, they can cause antisocial behavior of the traumatized persons that manifests in seeking revenge. Social partnership can help us to avoid the negative consequences of collective trauma and achieve social consensus.

KEY WORDS: trauma; traumatic experience; collective trauma; traumatization; stress; historical trauma; identity; group identity; social partnership

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INTRODUCTION

Nowadays, it is becoming increasingly difficult to define socio-cultural, economic and political transformations of the contemporary world through the lens of established concepts of "evolution" and "revolution". This is due to the fact that modern civilization finds itself in a zone of permanent turbulence, which causes social instability and loss of control over the situation. Social instability has an extremely negative impact on the psycho-emotional state of the individuals and at the same time causes an increase in scientific interest in practices that can contribute to the balancing of the social system and ensure the healthy and harmonious development of both an individual and a group.

A growing interest in mental health brings many new concepts and categories into the field of public attention. One of the concepts that was "introduced" to the active glossary of both analysts and lay persons is the concept of "trauma", which is used together with the concepts derived from it, such as "traumatization", "traumatic experience", "collective trauma", "historical trauma", etc. In social networks, mass media, public speeches, these terms are often used without proper scientific interpretation that does not contribute to the meaningful explanation and description of the past, rational perception of the present, and constructive elaboration of the future. This is partly due to the fact that even within the scientific community [1-9] there is still no unified understanding of what community mental health is and how to understand the phenomenon of "collective trauma". Instead, the uncritical use of the understudied concept contributes to the strengthening of victimhood and sense of helplessness in society, which, as Arnold Toynbee put it in his book "A Study of History", can lead to the destruction of a community or even an entire civilization [10].

The problem of a traumatized society was posed in the fundamental scientific work of A. Toynbee, but the scientist had not focused on the problem of trauma in his research. First of all, he was interested in the problem situations or challenges, the solution of which could affect the future of the human society. A case in point, according to the scientist, can be a defeat which under certain circumstances turns into a test that can mobilize the internal forces and potential of society and stimulate it to revenge. Of course, A. Toynbee was aware that challenges caused by unexpected and powerful natural or social upheavals are not always possible for communities to overcome, which ultimately leads them to gradual death or transformation into marginal communities subordinated to other internally stimulated societies [10]. Thus, the scientist, whether consciously or not, defines two types of challenges, or traumatic situations, - defeats that mobilize the internal resources of communities and can become a powerful stimulus for future cultural uplift and traumas which cause the death of the community.

As we can see, despite the insufficiently developed conceptual apparatus, A. Toynbee's conclusions and theoretical remarks are not devoid of the rational core and can serve as the theoretical and methodological basis for philosophical-historical research and social analytics, at least within the context of their verification by the consequences of the Buffalo Creek flood. An expert witness of this event was K. Erikson, an American sociologist who published his fundamental work "Everything in Its Path: Destruction of Community in the Buffalo Creek Flood" (1978) soon after the catastrophe [11]. Revealing the social consequences of the natural disaster, the scientist for the first time clearly distinguished between individual and collective trauma and showed that the latter could have catastrophic consequences for the community leading to worldview disorientation, which could generate not only migration, but also the decline in moral values and the increase in crime.

The conclusions and theoretical generalizations proposed by K. Erikson were further developed in the works of A. Neal. In his book "National Trauma and Collective Memory: Major Events in the American Century" published in 1998, the scientist offered a thorough study of national trauma. According to the researcher, it appears as a set of individual and collective reactions to events that resembles the eruption of a volcano and affects the foundations of the entire social world [12]. Such events are always exceptional, they have the incredibly explosive "power" and, therefore, generate chaos and subsequent rapid and radical social transformations. These shifts attract the attention of all social groups and arose the specific emotional reactions of the community. The community usually fails to reject or ignore the traumatic experience, as well as to demonstrate benevolent contempt or cynical indifference [12]. People cannot take easy the fact that a traumatic event has already occurred and the established and familiar world of their lives has been destroyed – in the future, we should expect social changes that will open up many new opportunities [12]. According to A. Neal, the vicissitudes that took place in American society after the Civil War, the Great Depression, and the Second World War are illustrative examples in this context [12].

Despite the potential of the traumatic experience to change society, A. Neal is not inclined to idealize trauma. He believes that a stressful situation under certain conditions can contribute to social cohesion, however, it often causes disorganization, anxiety, anger, fear, sadness, depression in both an individual and entire community. Confusion and social chaos, according to A. Neal, can be avoided in the process of returning to trauma through its representation, which is designed to get repressed trauma memories back [12]. Thus, the traumatic experience gradually turns into a flashback that can define the identity and life of the community, but only as the tragic past.

Ambiguous, but fateful, social consequences of trauma are of great importance to the scientific community; and the trauma of Holocaust survivors has been the center of their attention for a long time. The genocide of European Jews gave rise to multiple studies that embrace various aspects of the tragedy itself, as well as its impact on the further development of the entire European community. We can mention the works of C. Caruth [2, 13, 14], in which the researcher, using the example of the Holocaust trauma, tries to reveal the essence of individual and collective traumas and investigate their impact on individuals and entire generations. For example, in her well-known work"Trauma: Explorations in Memory" [13], the researcher claims that trauma, within the psychological framework, is an excessive experience that society cannot immediately process in order to give an answer. This leads to a delayed reaction – the traumatic experience is repeated as a return of the past in various everyday practices, as a search for similar circumstances, as pseudophobias or dreams not only in the members of the group that suffered trauma, but also in their descendants even decades later.

It should be noted that researchers have paid a lot of attention to the study of transgenerational transmis-

sion of traumatic experiences. In this context, we can mention N. Kellermann [7] who analyzed secondary, visible and invisible, imprints of the Holocaust trauma on survivors and their descendants; E. Lishner Freud and E. Berant who studied the transmission of the Holocaust trauma by women from generation to generation, from survivors to their descendants [15] or V. Volkan [16] who examined the characteristics of the transmission of traumatic stress to the next generations.

The abovementioned studies, as well as many others aimed at understanding individual and collective trauma, indicate trauma-induced enslavement by excessive experience and emphasize the inseparable unity of trauma and identity. In most cases, according to C. Caruth [2], researchers find the destruction of the foundations for self-awareness skills, orientations, and mental characteristics. At the same time, there are traumas [9, 16] that political leaders deliberately use to strengthen the emotional unity of the community in order to achieve certain individual or group goals. As the example of the russian federation demonstrates, these, at first glance, completely "harmless practices" can lead to tragic results - misuse of trauma can generate new traumas that will contribute to an even greater exacerbation of the international situation.

THE AIM

Given the lack of a generally accepted understanding of the phenomenon of "collective trauma", the purpose of the article is to identify the essence and causes of collective trauma and reveal its consequences for group identity.

MATERIALS AND METHODS

The authors used an interdisciplinary approach along with the principles of objectivity, tolerance, and impartiality. The analysis of the texts was conducted according to the basic principles of hermeneutics, namely the inexhaustibility of the authentic text and immanent critique. In addition, the method of conceptual and categorical analysis was applied, as well as induction, deduction, generalization, etc. The data collection was carried out using PubMed, Scopus, Google Scholar databases. Research papers were identified according to search terms: "trauma", "traumatic experience", "collective trauma", "traumatization", "stress", "historical trauma", "defeat", "the Holocaust", etc.

REVIEW AND DISCUSSION

Within contemporary intellectual discourse, it is customary to consider trauma as damage that leads to the

destruction of certain structures or to their change, so that "they cannot be immediately restored after the termination of the traumatic action. For this, additional restorative processes are required, which should not occur in the case of the normal, non-traumatic development" [17]. Rehabilitation can occur relatively independently in the process of gradual regeneration, however, in some cases, it is necessary to resort to external means and therapy. Sometimes we deal with traumas, after which full recovery is impossible. However, even in such severe cases, it is necessary to transfer the system from an acute, unstable state to a stabilized one with the minimization of the negative consequences of traumatization. Within this context, traumas that lead to disability can serve as an illustrative example [17]. On the other hand, it is completely impossible to deal with traumas that are incompatible with life.

Given that trauma is a wound that causes destruction, mental trauma is considered as "the emotional reaction of the psyche to mental, physical or cultural violence", which leads to the destruction of an individual's basic ideas about her/himself and the world [9]. Trauma usually appears as the reaction to a life-threatening event and occurs not as much due to the experience of the threat itself, as because this threat was perceived by consciousness a moment later than the traumatic event occurred. In other words, trauma arises not only out of the incomprehensibility of a near-death experience, but also out of the incomprehensibility of survival. It is survival that gives rise to trauma in the sense that "the surprise or accident of death becomes the surprise or accident of life" [14].

Mental trauma that occurs in a group of people or in the entire society as a result of some catastrophic events or criminal actions conducted by political or other social subjects is called collective trauma [17]. Unlike personal trauma, collective trauma is formed slowly and, therefore, it is usually devoid of suddenness, although it remains a kind of shock [11]. A distinctive feature of collective trauma is not the number of traumatized people, but the fact that, in addition to direct participants, it affects people who are not directly involved in the traumatic events. Sometimes, it has an impact on those who were not personally affected by the tragedy or on the whole society. That is, collective trauma is not limited in space and time. For example, these are the traumas of the Holocaust and the genocide of Ukrainians in 1932-1933, the consequences of which are felt not only by people who were directly affected by these horrible situations, but also by their descendants.

As V. Volkan showed in the article "Traumatized Societies and Psychological Care: Expanding the Concept

of Preventive Medicine", the essential characteristic of trauma to be prolonged in space and time is caused by the specifics of transferring traumatic experience to the next generation [16]. In the process of examining former concentration camp prisoners, including children, the researcher discovered that something more essential was transmitted from parents to children than just anxiety or other mental health issues. Children of survivors identify themselves much more deeply with their parents and show signs and symptoms related to the past mental content of their parents and, in general, to the past which they did not and could not witness. This is due to the fact that traumatized adults unconsciously "imprint" their own traumatized image into the identity of their children in the process of upbringing. As a result, children become carriers of a traumatic parental image, although this image can vary significantly depending on accompanying economic, social or other conditions. In such manner, "secondary traumatization" occurs. It generates a cumulative effect that determines the psychic content of the identity of a large group. Therefore, all "embedded images" are associatively connected with the same traumatic event [16].

As a result of the cumulative effect, every child – a representative of the second generation after mass trauma - develops connections with the mental representation of the trauma, as well as unconscious tasks related to the need to cope with this representation. They seek to preserve the memory of their parents' trauma, to mourn their losses, to react to their humiliation or to avenge parents' suffering. The descendants' responses to the traumas of ancestors can be manifested in different forms and be realized in special social and economic achievements as it happened in Israel, in mourning the dead and acknowledging their national guilt as it was in Germany after the Second World War, in an attempt at revenge as it was observed in the Caucasian peoples enslaved by russia, an example of which was the russian-Chechen wars.

If the second generation cannot fulfill their tasks and react to the trauma – express grief or sorrow, get rid of the feeling of shame, etc., – they, according to V. Volkan, pass it on to the third generation. Intergenerational transmission of trauma creates a powerful unconscious bond between all members of a larger group (nation or ethnos). Depending on external circumstances – economic, social or political – this general task may also be transformed from generation to generation. For example, one generation may manifest traumatic grief, feel ashamed, be aware of the sacrifice. The representatives of the next generation may recognize their own inescapable duty – to avenge losses and sacrifices. Regardless of how the memory of trauma manifests itself in subsequent generations, the main task of the descendants of the traumatized persons is to preserve the mental image of the tragedy, which for decades and centuries will strengthen specific identity of a certain large group [16].

It should be noted that in the situations, in which a traumatized group is threatened with a new ethnic, national, economic, political or religious crisis, leaders, whether consciously or not, appeal to the so-called "chosen trauma" to strengthen the emotional consolidation of their group [16]. According to V. Volkan, the events in Yugoslavia may serve as the example. During the period of instability, the Serbian authorities began to actively exploit the historical memory of the Battle of Kosovo (1389), as well as the death of Lazar Hrebelianović, the medieval Serbian ruler, who was killed at this battle. His remains were exhumed, and the coffin had been transported from one Serbian village to another during a year. In every village, a kind of a burial ceremony was performed. As V. Volkan stressed, this seemingly harmless ritual caused a kind of a "shift in time", which resulted in the shift in the Serbs' behavior and attitude: they began to act as if Lazar was killed vesterday that entailed a "condensation" of feelings and time combined with a regression to more primitive types of response. As a result, Serbs began to perceive Bosnian and Albanian Muslims as the cause of their historical misfortune that justified revenge. The Serbs began to kill, rob, and rape "their offenders" demonstrating medieval cruelty [16].

A similar, however not identical, situation is observed in contemporary Ukraine. Since the very beginning of the full-scale invasion of russian troops, whose gualified hallmark is the intolerable cruelty against the peaceful Ukrainian citizens, the seemingly forgotten, but in most cases repressed memories of the numerous atrocities of the russians in the past have been revived in the Ukrainian historical memory. It is necessary to mention the revival of the Baturyn tragedy of 1708, during which all "residents of Baturyn, regardless of age and gender, were massacred according to the inhuman traditions of Muscovites" [18], the famine of 1932–1933 (Holodomor), during which the soviet government condemned to death from hunger more than 3 million Ukrainians [19], the Executed Renaissance, and the Great Terror of 1937 in general. These and many other tragic pages of Ukrainian history arose in collective memory as clearly as if they happened recently or even simultaneously with the tragic events in Bucha, Irpin, Hostomel, Mariupol and other Ukrainian cities and villages. Memories of these tragic events were revived spontaneously, without the conscious and purposeful activity of political leaders. They contributed to the

concentration of national feelings and intensified the desire to resist the aggressor and dissociate from everything russian through opposition. Obviously, this was the reason why, despite the unbelievable cruelty of the russians, Ukrainians did not demonstrate antisocial behavior, but, on the contrary, tried to show the best human qualities – they contrasted russian atrocities with mercy and humanity and began to seek retribution in the manner determined by international law.

We believe that the reaction of Ukrainian people to russian crimes against humanity does not refute V. Volkan's conclusions, but only complements and clarifies his theoretical generalizations. In particular, there is no doubt that historical memory can be imposed, but it can also impose itself on society, opinion leaders, and officials through narratives and social practices that arise in the process of traumatization [9]. To represent them in historical memory, we have to give convincing answers to the questions concerning the nature of the pain experienced by individuals (or their ancestors) and the nature of the victims themselves. Comprehensive explanations for the relationship between trauma victims (sometimes rather few) and a wider audience must also be elaborated and developed. The last, however, mandatory condition for creating a convincing memory narrative should be social stigmatization [20].

If a real traumatic experience does not go through a process of institutionalization, then, most likely, it is impossible to turn it into a collective trauma narrative. An example is the Baturyn tragedy that for more than three centuries had been a poorly articulated historical trauma of Ukrainians, even despite the efforts of some politicians to present this tragic page of Ukrainian history in the form of a heroic narrative [9]. Meanwhile, after the russian invasion, this event became a significant part of self-determination of the majority of Ukrainians and transformed into historical trauma. This, in turn, gives reason to assume that political support and ritualization are important, but not decisive factors in the formation of historical trauma.

At the same time, it is necessary to pay attention to the fact that russia's military aggression is an unimaginable stress factor for the entire Ukrainian society. The war caused anxiety and tension, which manifested in the fight-or-flight response [21]. This response is a universal human reaction to something new, unexpected and, most importantly, unpleasant. Being in a state of emotional and physical tension that arises under dangerous conditions, the Ukrainians were forced to make decisions quickly and independently, to respond to threats and unexpected, dangerous, and cruel acts on the part of the enemy group. To put it differently, despite the unexpectedness of the life-threatening situation, the Ukrainians at the beginning of the fullscale invasion, as well as throughout the war, have not been helpless and defenseless victims; on the contrary, they found the strength to mobilize the resources and stood up for their state and identity.

The ability of Ukrainians to fight back suggests that russia's invasion is a stressful situation and even a traumatic event, but it cannot be defined as collective trauma. Of course, this does not mean that during the war and especially after the war there will be no signs of collective trauma among the military personnel, prisoners of the war, numerous witnesses of russian atrocities in Ukraine, volunteers, displaced persons, etc. All these people have often become completely helpless in the face of mortal danger, have experienced events that without further ado can be called traumatic. All of them clearly understood that they could die at any moment; they felt defenseless and experienced horrors that C. Caruth coined as "an excess of what has been seen" [14]. According to S. Freud, many of these people will not be able to let go of these traumatic memories for many years to come. These events will recur in dreams, obsessions, despair, etc.. The loss of control over the environment, destruction of will and self-confidence reduce and sometimes undermine the perception of themselves thereby destroying the personal identity of many Ukrainians [22]. Thus, it is very likely that the incredibly large number of traumatized people in Ukraine will make it possible to talk about the collective trauma caused by russian aggression.

An analysis of the modern Ukrainian experience indicates the need for a clear distinction between traumatic experience, that is, a traumatic situation that arises unexpectedly and threatens the life of an individual or a group, and trauma (including collective trauma). The latter manifests itself as an emotional reaction of a group of people to unexpected and exceptional events imprinted in memory that destroys the established ideas of an individual or the whole community about the world and themselves and changes individual or collective identity [23]. In other words, a traumatic situation is stress that, under certain conditions, can mobilize defensive reactions and, as the Ukrainian experience shows, even crystallize identity, while trauma, including collective trauma, is closely related to the destruction of group identity as a result of disorganization and confusion caused by trauma.

The destructive impact of trauma on group identity requires additional clarification of the well-known statement of the French philosopher E. Renan. He wrote that "common patience unites more than common joys. In national memoirs, sadness is more important than triumph, sadness imposes duties, sadness induces common efforts" [24]. This widely known idea of the scientist has a significant history, however, it can cause contradictions due to the uncertainty of the conceptual apparatus. The sadness caused by grief and failure can be interpreted as trauma that destroys our identity and does not contribute to the consolidation of the group. However, in cases, in which it is seen as the defeat, the situation takes on a completely different meaning, because, as history shows, defeats often bring community together and create a vision for the future. Through this lens, let us recall the history of the formation of Ukrainian statehood in 1917-1920. Despite the fact that the Conciliar Independent Ukrainian State failed to stay on the political map of the world, the historical memory of this heroic period activated and crystallized the feeling of national unity many decades later. In addition, it legitimized the political claims of Ukrainians and mobilized their resistance under extremely unfavorable political conditions for the development of the national struggle.

The mechanism of transformation of defeat into a heroic narrative of collective memory is quite simple peoples/nations who failed to win on the battlefield invariably strive to win the battle on a "white field of paper" [25]. In their works, they try to devalue the enemy's victory while emphasizing their own dignity, honor, and humanity. Thus, on the one hand, the losers crystallize their own identity and, on the other hand, they devalue the defeat, moral qualities, and moral superiority of the winners. Quite often, the losers "win" by making the winners believe in their moral superiority. One of the brightest examples is the story of the crucifixion of Christ, which, as the Gospel Story testifies, marks the defeat of the Christ's teaching. However, when the Gospels were written, Christianity won, because the letters appeared to be "sharper" than a spear and nails.

An equally typical example is the image of Cossack Mamay - the Ukrainian folk hero. Folk paintings devoted to him became very popular in the 18th century, that is, during the period of the consistent destruction of the remnants of Cossack autonomy by the russian imperial authorities. The images of the "Cossack Mamay" in Ukrainian houses, together with the folk legends and traditions common at that time, served the Ukrainians as a reminder of the glorious Cossack past, of the invincibility of the will in the fight against the enslavers and gradually transformed into a spiritual portrait of the suffering and courageous Ukrainian people. This idea was firmly rooted in the consciousness of Ukrainians. It was transformed into a narrative of collective memory, as well as into a mental portrait of Ukrainians. This can be evidenced by the very eloquent portrayal of Cossack Mamay in the novel "There Is No End for the Cossack Family, or Cossack Mamay and a Stranger Young Woman" (1958) authored by O. Ilchenko. Revealing the image of Mamay, the writer remarked: "Cossack Mamay sharpened his saber every day. He sharpened it every day, because he dulled it every day fighting off all sorts of Cains... <> Although, it must be said, he did not like that business: neither sharpening, nor dulling. But he breathed hell against all lordship, against wrongdoing, against human misery, against all the impertinent ones who dared to encroach on Ukraine, and the Cossack had to fight with them. Thus, he was a peaceful man with a gentle disposition, a victorious, cunning, and clever warrior - a true Cossack soul! - so clever that neither a saber, nor a bullet, nor a sword could hit him, - they didn't hit him, even Lady Death herself gave him up so long ago that he didn't even know how many years he had spent in the world: two hundred? three hundred? although he was forty and forty all the time - no more, no less" [26].

Another eloquent Ukrainian attempt to become winners in "the battlefield of blank paper sheets" was the activation of the Ukrainian cultural and literary life in the 1920s. In our opinion, this cultural upsurge was a kind of response to the defeat of the state competitions of 1917-1920. Unfortunately, it resulted in incredibly tragic destruction of about 5 thousand Ukrainian writers [27]. This period of Ukrainian history later acquired enormous consolidating potential primarily due to the active work of the authors of the 1960s. With the beginning of the Khrushchev Thaw, they turned to the Soviet authorities with the demand for the rehabilitation of those repressed in the 1920-30s and contributed to the popularization of their writings among Ukrainians. Due to their active position, memories of the mass destruction of the Ukrainian intelligentsia (the brain of the nation) by the stalinist regime were brought back to the Ukrainian mind. They were inscribed in the narrative of collective memory and transformed into historical trauma that consolidated society [28].

The abovementioned situation gives grounds to state that only some group traumas entail destruction and disorganization. We have already noted that leaders could appeal to "chosen trauma" for the sake of strengthening the emotional consolidation of an ethnic group, in order to confront another hostile group, in order to strengthen group identity. Most likely, it is the purpose of addressing the "chosen trauma" that determines the social reaction – the desire for revenge and antisocial behavior or mourning rituals and ceremonies that bring people together. Ritualization of traumatic memories provides a link to the past and at the same time sets perspectives and challenges for the future. In other words, the ultimate goal of all remembrance ceremonies is to "overcome" the past, that is, to develop strategies that secure the community from all traumatic events that led to clashes and trauma in the past. This, in turn, requires a search (including historical experience) for healthy consolidating ideas and ways of mutual understanding. The greatest success is achieved by those communities that do not hide their "dark" pages of history, but consider them in the context, in accordance with the legal and moral norms prevailing at that time, admit their guilt for the crimes and take responsibility for it. The experience of the European Union is the case: European nations in their pursuit of social partnership and peace have invested a lot of time and efforts to reach a consensus and avoid rehashing the painful past. Their conscious focus on social partnership contributes to the harmonization of social, national, and international relations, as well as to the sustainable development of the entire European society.

CONCLUSIONS

Recently, politicians, analysts, various experts and even lay persons have been actively using the concepts of "trauma" and "collective trauma" without proper scientific understanding. This seemingly harmless practice may have unpredictable and even traumatic results for both an individual and the entire society. Such a situation causes the growth of scientific interest in the topic of trauma, which has a multidisciplinary nature, but is reflected in disciplinary organized studies that usually highlight a specific side of the phenomenon. This lays the ground for various misunderstandings and speculations. An important condition for avoiding political manipulations and social conflicts is the development of a generally accepted understanding of the essence, causes, and consequences of trauma, as well as its complex and ambiguous varieties such as "collective trauma" and "historical trauma". Despite the conceptual similarity, content unity, and common source - a traumatic experience, i.e., a stressful situation that causes emotional tension due to unexpectedness and threat

to life, - all the traumas mentioned by us have somewhat different and usually threatening consequences. This is because trauma is a wound that puts survival on the brink of death and necessarily leaves visible or invisible scars. By analogy, we propose to consider mental trauma as an emotional reaction of the psyche to mental, physical or cultural violence, which destroys an individual's basic ideas about her/himself and the world and ultimately about her/his identity. In cases, in which any traumatic situation (disaster, violence, criminal acts, etc.) has been experienced by a group of people and this has led to the destruction of group identity, we can speak of collective trauma. It arises from both the direct traumatic experience and the victims' unconscious transference of their traumatic images to their descendants.

The source of any trauma is a traumatic experience – stress that causes fight-or-flight response. If individuals have the ability to respond to stress in this way, the traumatic experience does not necessarily lead to trauma, which occurs as a reaction to an unexpected life-threatening situation. Strictly speaking, mental trauma including collective trauma occurs when a person or a group cannot fight back, react to violence, and feel helpless.

Historical trauma is a rather specific type of collective trauma that arises in the process of conscious exploitation of traumatic experience or "chosen trauma" by political or other leaders in order to achieve emotional unity and consolidation of the group; it is devoid of identity-destructive potential; however, it can cause antisocial behavior of the traumatized persons who seek revenge. To prevent this, historical traumas are usually "enveloped" in rich ceremonies, which provide a connection with the past and the ancestors' experiences, while at the same time contribute to their "overcoming" through the development of the strategies that may protect the community from the future conflicts and traumas. Social partnership in the broadest sense of the word can be seen as an equally important aspect of overcoming trauma.

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THE ATTITUDE OF CERTAIN CATEGORIES OF THE POPULATION OF UKRAINE TO PERSONAL HEALTH DURING THE WAR AGAINST RUSSIAN AGGRESSION

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ABSTRACT

The aim: To study the self-assessment of personal social and medical well-being by certain categories of the population of Ukraine in the conditions of war. Materials and methods: The results of a sociological survey among 127 internally displaced persons from the war zone and the territory temporary occupied by the Russian invaders, as well as 122 permanent residents of the Transcarpathian region were used as the materials of the study. Bibliosemantic, sociological, medico-statistical methods and the method of structural and logical analysis were applied.

Results: It was determined that personal health, as a priority, takes the fifth position among the surveyed population with a score of 9.0 points in the group of surveyed internally displaced persons and 9.2 points in the group of interviewed permanent residents of Transcarpathian region. At the same time, 66.2% of the surveyed internally displaced persons and 71.4% of permanent residents of the Transcarpathian region during the war of Ukraine against Russian aggression noted a decrease in attitude to their own health as a personal priority.

Conclusions: The results of the study indicate a low level of health-preserving behavior of the surveyed population during Ukraine's war against Russian aggression. This situation in the future may lead to a deterioration in public health and an increase in the need for medical services.

KEY WORDS: Ukraine, war, population, personal health, attitude, sociological survey, results

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INTRODUCTION

In contrast to traditional armed conflicts, in modern wars a constant disregard of International Humanitarian Law and the Geneva Convention by the parts of the conflicts is detected [1]. The scale of losses on both sides is already much higher than in the typical war of the modern era. Analysis of available information sources indicates that armed conflicts, forced displacement of people and related problems, such as unemployment, poverty and social isolation, significantly increase vulnerability to psychosocial stress and the prevalence of mental and behavioral disorders among the population affected by the military conflict by more than 20% [2-5]. Thus, the war also affects the health of citizens and these are not only the wounds, contusions and injuries, but also long-term consequences. It is noted that in the future, many Ukrainians may face psychological and mental problems, increased addictions and exacerbation of some diseases [6]. The analysis of the situation experienced by Ukrainian society in the context of a hybrid war with Russian federation in post-COVID period shows an increase in the burden due to mental and behavioral disorders [7,8]. Researchers point to a significant deterioration in the state of civilian population of Ukraine as a result of the war [9,10]. In these conditions, it is important to have a motivated attitude of the population to the preservation and strengthening of personal health, which led to the relevance of this study.

THE AIM

The aim was to study the self-assessment of personal social and medical well-being by certain categories of the population of Ukraine in the conditions of war.

MATERIALS AND METHODS

The results of a sociological survey among 127 internally displaced persons from the war zone and the territory temporary occupied by the Russian invaders, as well as 122 permanent residents of the Transcarpathian region were used as the materials of the study. The survey was conducted according to a specially developed questionnaire. The attitude to health in the system of personal priorities was assessed by the respondents on a 10-point scale. 10 points determined the highest level of priority. Participation in the study was voluntary. The activity of the respondents composed 83.0% (300 questionnaires were distributed). The study was conducted in February 2023. The study preserved the confidentiality of information about respondents. Bibliosemantic, sociological, medico-statistical methods and the method of structural and logical analysis were applied in the course of study.

For the application of these materials and methods during the study, permission was obtained from the ethical commission of Uzhhorod National University. Protocol dated 08.02. 2023 № 6/2.

RESULTS

The results of the sociological survey were summarized in a table, statistically processed and analyzed. Table I provides data from the results of the study on determining personal priorities for the surveyed population and the place of personal health in these priorities.

The analysis of the results obtained during the sociological survey showed that during the war economic and security priorities are among the personal priorities for the surveyed category of the population. At the same time, for internally displaced persons, the leading positions belong to security priorities, and for permanent residents of Transcarpathian region to ones of economic nature.

Personal health, as a priority, takes the fifth position in both groups of the surveyed population with a score of 9.0 points in the group of surveyed internally displaced persons and 9.2 points in the group of interviewed permanent residents of Transcarpathian region.

It should be noted that 66.2% of the polled internally displaced persons and 71.4% of permanent residents of Transcarpathian region during the war of Ukraine against Russian aggression pointed out a decrease in attitude to their own health as a personal priority, and only 9.4% and 17.1% respectively indicated its increase.

Next the data on the presence of certain harmful habits in the studied groups of respondents were statistically processed and analyzed. The results are given in Table II.

The analysis of the results of study given in Table II indicates an increase in the level of all identified harmful habits among the surveyed population. It is alarming to have a conceiving increase in the proportion of the population with alcohol abuse and the use of psychoactive substances. Thus, among internally displaced persons, the share of those who abuse alcoholic beverages increased 2.1 times and amounted to 18.1%, and such, respectively, among permanent residents of the Transcarpathian region increased 1.6 times and amounted to 17.2%.

Next the level of health-preserving behavior of the

	Table I. The level	of attitude to	health in the s	ystem of person	al priorities
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Personal priorities	Internally displaced persons		Permanent residents of Transcarpathian region	
	Points	Rank	Points	Rank
Personal health	9.0	V	9.2	V
Children's health	9.5	I	9.4	III
Health of family members	9.2	IV	9.3	IV
Economic well-being of the family	9.5	Ι	9.6	I
Ensuring decent living conditions	8.9	VI	9.5	II
Family safety	9.3	III	9.3	IV
Personal safety	9.0	V	9.1	VI
The presence of a permanent job	8.8	VII	9.6	I
Constant communication with relatives who are in the zone of hostilities / occupation	9.4	II	8.7	VII
Providing the family with food	8.2	VIII	8.4	VIII
	Share of responde	ents, %		
Reducing during the war the level of attitude to one's own health, as a personal priority	66.2		71.4	
Raising during the war the level of attitude to one's own health as a personal priority	9.4		17.1	
Could not answer the question	24.4		11.5	

Table II. Presence of harmful habits, %

Harmful habits	Internally displaced persons		Permanent residents of Transcarpathian region	
	Before the war	During the war	Before the war	During the war
Tobacco smoking	24.4	38.6	27.9	34.4
Frequent alcohol consumption	11.8	21.3	13.9	19.7
Alcohol abuse	8.7	18.1	10.6	17.2
The use of psychoactive substances	3.5	7.1	5.7	8.2

Table III. The level of health-preserving behavior of the polled population during the war of Ukraine against Russian aggression, %

	Internally displaced persons		Permanent residents of Transcarpathian region	
Indicator	Practically healthy (n-52)	Individuals with chronic diseases (n-75)	Practically healthy (n-69)	Individuals with chronic diseases (n-53)
Consulted a doctor for preventive purposes	-	-	30.4	32.0
Wages a healthy lifestyle	5.8	9.3	30.4	35.8
Adheres to preventive behavior when staying in crowded places	17.3	14.7	36.2	45.3
When the state of health worsens, self- medication is carried out	71.2	52.0	31.9	35.8
Performs the doctor's prescriptions of therapeutic nature	-	16.0	-	54.7
Partially performs the doctor's prescriptions of therapeutic nature	-	49.3	-	35.8
Performs the doctor's prescriptions of preventive nature	-	10.7	-	30.2
The maximum possible adheres to the rules of sanitary culture	40.4	45.3	69.6	77.4
The maximum possible adheres to the rules of personal hygiene	59.6	54.7	82.6	90.6

surveyed population during Ukraine's war against Russian aggression was studied. The results obtained are presented in Table III.

The analysis of the results of study given in Table III indicates a low level of health-preserving behavior of the surveyed population during the war of Ukraine against Russian aggression. At the same time, among internally displaced persons, it is much lower than among the permanent population of Transcarpathian region. In general, the surveyed contingents of the population are mostly not prone to the prevention of diseases and the preservation of personal health. This situation is facilitated by both psychological and socio-economic and living conditions of internally displaced persons.

DISCUSSION

In the course of the study, the results of which are presented in this article, the goal was achieved and the attitude of certain categories of the population of Ukraine to personal health during the war against Russian aggression was studied. Organizational and methodological restrictions arose in the course of the study, that are associated with the psychological state of internally displaced persons and the lack of their motivation to participate in a sociological survey.

The results of the study are original. They point to a decrease in the attitude of the population to their own health as a personal priority and a low level of health-saving behavior.

At the same time, the publication within the framework of the "National Program of Mental Health and Psychosocial Support" on the initiative of the First Lady of Ukraine Olena Zelenska indicates that part of the country's population is in some uncertainty. They are sure that they have no control over anything in their lives, and therefore, they as if put it on pause, postponed it indefinitely "after the victory". The result is self-doubt; lack of understanding in the new layout; uncontrollable panic, fear and anxiety; constant depression; loss of identity; complete misunderstanding of how to get out of this state and where to start. In psychology, this condition is called fading [11]. Chaban O.S., Khaustova O.O. [12] note that for the population of Ukraine in the current conditions of fullscale Russian military aggression, a parallel formation of both individual and collective traumatization is registered, which, accordingly, negatively affects the level of both individual psychosomatic and public health. The management of conditions associated with acute stress and grief in non-specialized health care facilities is carried out in accordance with the special manual (Assessment and Management of Conditions Specifically Related to Stress: mhGAP Intervention Guide Module, v. 1.0), [13] developed under the

The Ministry of Health predicts that about 15 million Ukrainians will need psychological support because of the war. At the same time: people with mental disorders are more prone to smoking, guit harder and, on average, smoke more; in general, visiting the doctors, attention to one's own health and the frequency of routine examinations decreases in the presence of mental diseases, which leads to late diagnosis of diseases and less success of their treatment; the risk of death from cancer in the presence of depressive disorders increases by 50%, and from heart diseases – by 67%; in people with post-traumatic stress syndrome, hypertension, angina pectoris, tachycardia, other heart diseases, gastric ulcer, gastritis and arthritis are more common; PTSD often encourages risky behaviors that lead to alcohol, drug abuse [14]. This in general confirms the data we have obtained on the attitude of certain categories of the population of Ukraine to personal health during the war against Russian aggression.

The problem described above was not covered in the foreign and domestic scientific literature available during the last decade. In the future, it is planned to conduct a comprehensive study of the impact of Russian aggression on the health of the population of Ukraine in three zones: temporary occupation, active hostilities and a zone that is remote from active hostilities.

CONCLUSIONS

The attitude of certain categories of the population of Ukraine to personal health during the war against Russian aggression is studied. It was established that personal health, as a priority, takes the fifth position among the surveyed population with a score of 9.0 points in the group of surveyed internally displaced persons and 9.2 points in the group of interviewed permanent residents of Transcarpathian region. At the same time, 66.2% of the polled internally displaced persons and 71.4% of permanent residents of Transcarpathian region during the war of Ukraine against Russian aggression noted a decrease in attitude to their own health as a personal priority. The results of the study indicate a low level of health-preserving behavior of the surveyed population during Ukraine's war against Russian aggression. The situation described may in the future lead to deterioration in public health and an increase in the need for medical services.

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