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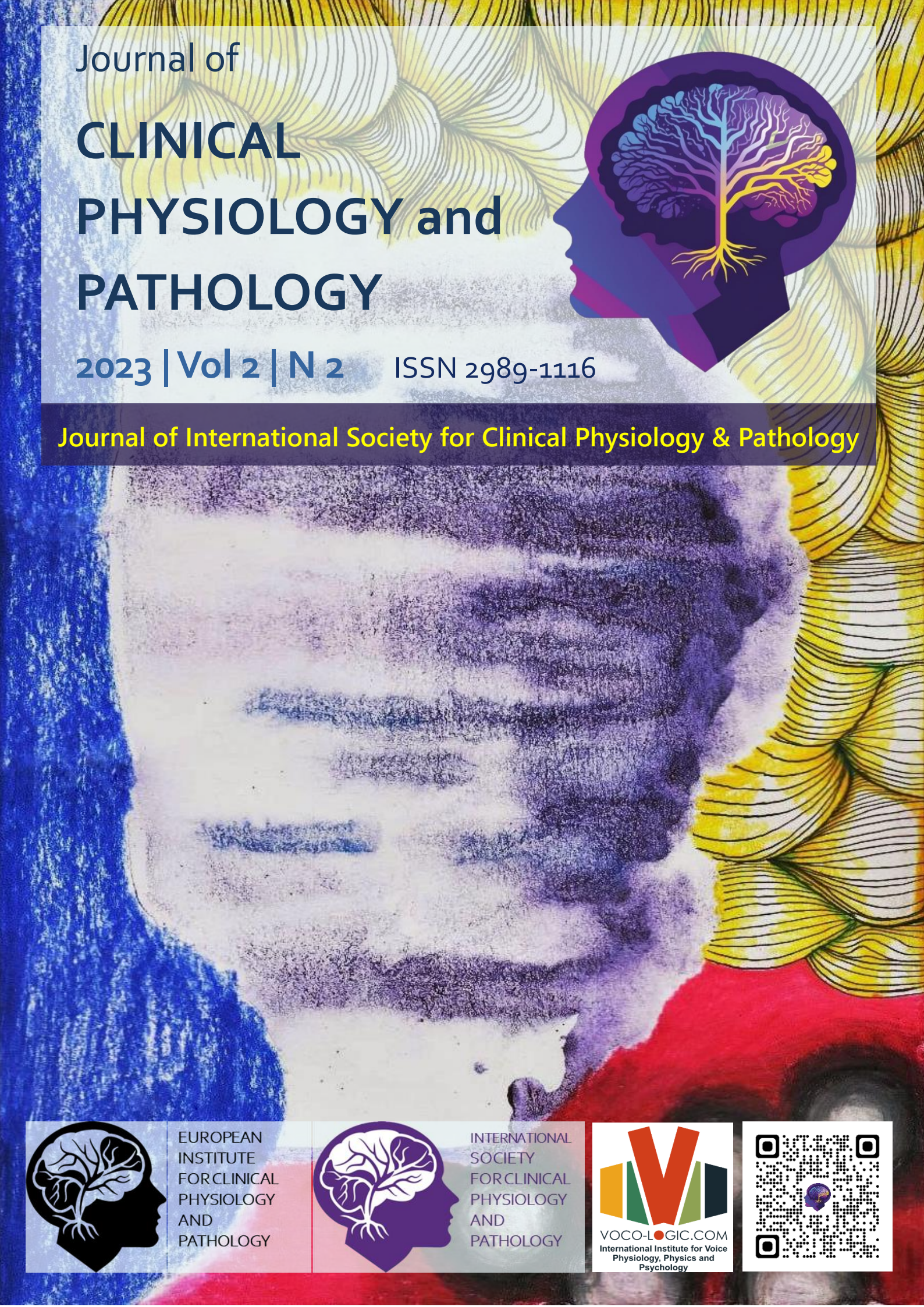

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Article

The Influence of the Relationship Between HRV Circadian Rhythms and Self-actualization on the Behavior of Skydivers During the Competitive Period

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Abstract: Human health, the development of social roles, inextricably linked with his behavior. Dissatisfaction with basic needs, such as the need for security, love, respect, self-respect, identity and self-actualization, leads to diseases and various disorders that affect the health of athletes and their sports achievements. During a competition, the effects of the circadian rhythms and the power of harmonics on the heart rate variability of skydivers were studied. People reveal the level and features of their self-actualization. The data obtained showed that during the acrophase of circadian rhythms in male skydivers, activation of mental processes is noted. This phenomenon is reliably associated with the need for cognition and spatial orientation. In the bathyphase of the competitive period, they showed a decrease in-group of synchronization, an increase in individual and cross-adaptive response. In female skydivers during the competitive period, according to the circadian rhythm indicators in the bathyphase, the need for protection and support revealed, which show psycho-emotional stress and a stable parasympathetic influence on the control of heart rhythm regulation. Group asymmetric synchronization of harmonic powers also noted. The results of the study of circadian rhythms showed a biorhythmological relationship between self-actualization of the personality of athletes and indicators of heart rate variability.

Keywords: circadian rhythm, heart rate variability, self-actualization, health, personality, skydivers.

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1. Introduction

The problem of studying the health of an athlete's personality is now again at the forefront of sports and psychological issues. The problem of socio-psychological optimization of interactions (interaction) of athletes occupied a special place in a team [1, 2]. Specialists are paying more and more attention to the mechanisms of "mastering roles" by athletes in the process of interaction. The influence of "role expectations" stimulates the athlete from the side of "significant" persons for him. Especially those with whom he comes into contact [3]. We know various examples of how the effectiveness of an athlete in a team decreases only because his "role expectations" did not coincide with his true capabilities, and, for example, leadership positions in one team came into conflict with the social positions that have developed in a new team [4]. Given that individuals interact in communication through their social roles, it is advisable to consider each act of communication as a socially modeled game [5]. The chain of such game models forms the integrity of communication as a system process.

In this regard, works in the field of humanistic psychology are of particular interest. Especially the concept of A. Maslow on the mental health of the individual. He inextricably linked the development of social roles with mental characteristics [6]. A distinctive feature of A. Maslow's concept is the constant emphasis on the relationship between the health of a self-actualizing personality and the basic (basic) needs and values inherent in human nature. He argued that the inability to satisfy basic psychological needs, such as the need for security, love, respect, self-esteem, identity and self-actualization, leads to diseases and various disorders, which are commonly called neuroses and psychoses. However, even self-actualized people who have a desire for truth, good-

ness, beauty, justice, order, law and other high values can experience derivation at the meta motivational level [7]. Dissatisfaction (frustration) of higher metaneeds (such as the need for perfection, justice, beauty, truth, authenticity) or a person's loss of fundamental value orientations leads to disorders that A. Maslow calls general and particular metapathology [8]. The highest values require from the individual, in addition to subjective experiences, also certain behavioral reactions [8, 9].

Researchers note the importance of self-actualization as one of the important criteria for assessing the health of a person (subject, personality), emphasizing the importance of harmony of the individual with their culture and maintaining internal independence [10]. It inextricably linked human health with natural and social rhythms, in the system of influence of which he is throughout his life [11, 12]. According to B.S. Alyakrinsky and O.G. Gazenko noted that the phase mismatch of the body's circadian rhythms with physical and social time sensors (in conditions, for example, evening and night work shifts) constantly accompanied by desynchronosis with disruption of the body's circadian system, designed for 24 hours of work [13, 14, 15, 16, 17].

The aim consists of studying of circadian rhythms and the relationship between some indicators of co-self-actualization and heart rate variability in the example of skydivers during the competitive period.

2. Methods

It examined the skydivers at rest (sitting). A total of 74 porters were examined (men - 37; women - 37). It conducted the measurements in the summer between jumps in natural conditions during the competition at the airfield. It held competitions in the territory of the temperate climate zone of Central Russia.

We studied circadian rhythms in terms of spectrum power (HF - total activity level of the parasympathetic link 0.40-0.15 Hz; LF - total level of activity of the vasomotor center 0.15-0.04 Hz; VLF - total level of activity of the sympathetic link of regulation 0, 04-0.0033 Hz, ULF - the total level of activity of higher autonomic centers less than 0.0033 Hz) of heart rate variability using the hardware-software complex "Varicard" in the statistical processing "ISCIM6.0". According to literature sources, HF reflects trophotropic influences on the regulation of the heart rhythm, LF - changes in the activity of baro- and chemoreceptors, VLF - ergotropic processes [18]. These indicators have a lognormal distribution.

The acrophase (the phase with maximum values) and bathyphase (the phase with minimum values) were calculated in circadian rhythms.

It studied self-actualization according to the methodology "Questionnaire of Personal Orientations by E. Shostrom" modified by L.Ya. Gozman and M.V. Kroz M.V. Shostrom".

The mean statistical indicators and their deviations (M±m), standard deviation (±σ), it calculated in the Microsoft Office Excel 2019 program. The significance of differences determined by the Student's t-test for parametric indicators by checking the equality of the average values in the two samples. The correlation was determined by r-Pearson, and by using the coefficient of determination (R2), showing the contribution of a particular parameter to the total value of the variables.

3. Results

Both men and women athletes-skydivers, because of the details of sports, have the right kind of personal qualities that propel them to achieve success in their undertakings, and satisfy the requirement for activity related to the obligation of making decisions in an extreme circumstance [19, 20, 21] Therefore, in the study of the personality psychology of skydivers, in order to substantiate the characteristics of the circadian rhythm, we turned to the concept of A. Maslow [8].

The results of the study showed the range of self-actualization in 25% of men and 41.6% of women, mental and statistical norm in 75% of men and 58.4% of women. Mental disorders and pseudo-self-actualization are not revealed. In general, their own beliefs, attitudes and principles guided skydivers, they are not conformal. They have internal support. Accept the values offered by society to the full, quickly respond to a changing situation. Deep enough and subtly to feel their feelings and needs. Respect themselves for the strength. Athletes are willing to take themselves in spite of their weakness. They see a person as good rather than bad; they easily recognize the truth, good, evil. They see opposites in nature and in life. The surrounding world perceived holistically. Skydivers are able to accept their aggression as a natural property. Easily and quickly encountered others try to play a significant role in the lives of their loved ones and friends. They have a high need to acquire knowledge about the world around them. They are individuals with a creative focus.

For men, creativity and the need for cognitive activity are important, and for women, flexibility of behavior. Both men and women do not need support.

A correlation analysis of the acrophase conducted in terms of frequency components of the heart rate variability spectrum with psychological indicators of self-actualization in men and women during the competition.

In men, found a positive relationship between the acrophase of the frequency components HF (ρ=0.482; P<0.05), LF (ρ=0.578; P<0.05), VLF (ρ=0.498; P<0.05) and time. Significant differences noted between HF bathyphase (ρ=0.65; P<0.01) with time orientation and VLF (ρ=0.498; P<0.05) with cognitive needs and creativity.

We can say that during the competitive period, during the acrophase of circadian rhythms, male skydivers show activation of mental processes. This phenomenon is reliably associated with the need for cognition and spatial orientation. In the bathyphase of the competitive period, there was a decrease in-group synchronization, an increase in individual and cross-adaptive response.

In female skydivers during the competitive period, it found a significant positive correlation between the bathyphase of the HF spectra (ρ=0.77; P <0.001) and the need for support, LF (ρ=0.74; P <0.001) - with time orientation (fig.).

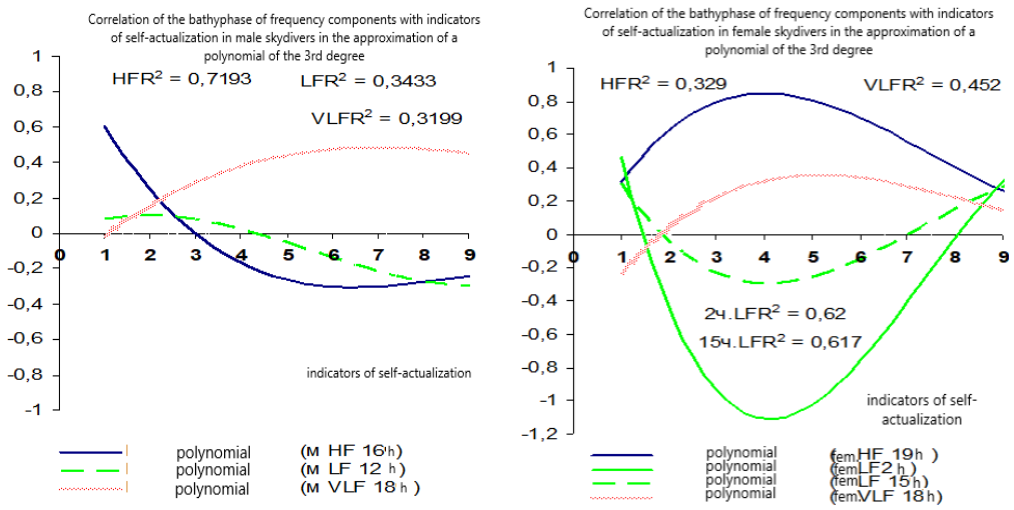

Figure. Correlation of the bathyphase of circadian rhythms of the frequency components of the HRV spectrum with the psychological indicators of self-actualization (SA) in male and female skydivers during the competition

In female skydivers during the competitive period, according to the circadian rhythm indicators in the bathyphase, there was a need for protection and support, which show psycho-emotional stress and a stable parasympathetic effect on the control of heart rhythm regulation. It observed a group asymmetric synchronization of harmonic powers.

4. Discussion

The study of the relationship of circadian rhythms [22] between heart rate variability and self-actualization in men revealed positive relationships with acrophase and bathyphase, and in women-only with bathyphase.

In male skydivers during the competitive period, the acrophase of circadian rhythms of the frequency components HF, LF, VLF shows an increase in the relationship with orientation in time. It can state that in male skydivers, the greatest activity of the power of parasympathetic and sympathetic influence on the control of the regulation of the heart rhythm enhances the ability to navigate in time. This indicates that they have a "biological clock" or sensitivity to biological rhythms, processes, and phenomena. In the bathyphase, the period of minimum HF values, sensitivity to orientation in time, remains. During the period of minimum VLF values, the need for creative knowledge, a critical analysis of one's actions, and the search for alternative solutions increases. It can conclude that in male skydivers in the acrophase of circadian rhythms, there is a close relationship and mutual influence between the biological and social response to the impact of a complex of factors of various nature. In the bathyphase, group synchronization decreases, and individual and cross-adaptive reactions increase.

In male skydivers, the need for cognition, which significantly affects the control of the heart rhythm, falls at 6.00 in the morning. This time can called the time-setter of the mental state and mental needs of men. The need for self-esteem performed correction of social behavior.

During the competitive period in female parachutists, there was evidence of a positive correlation between parasympathetic influence on heart rhythm regulation and the need for support in the bathyphase of circadian rhythms. Since the neurons of the parasympathetic nervous system are

cholinergic, it can assume that women show an increased sensitivity to the psychological and behavioral responses that accompany them. The cardiovascular center during periods of minimal activity in women is sensitive to rhythmic processes.

The largest number of high correlations of psychological characteristics, social behavior in female skydivers, causing circadian tension of regulatory systems, occurs at 8.00, 15.00 and 22.00 hours, this is due to the rhythm of reassessment of values, which can consider as the timing of the mental state and mental processes.

5. Conclusions

Thus, the results of the study of circadian rhythms showed a biorhythmological connection between the self-actualization of the personality of athletes and their mental processes, and the state during the competitive period. Evidence of circadian rhythms shows the correlation between heart rate variability and self-actualization. Self-actualization can considered as a criterion of social timing that affects the health and behavior of athletes during the competitive period. Important in the social life of the personality of athletes is productive longevity, which depends on the harmony they create between the resources of their body and the natural and social rhythms of the surrounding world.

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Article

The Use of Artificial Intelligence in the Diagnosis of Breast Cancer

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Abstract: The paper presents a brief overview of the tasks and methods of artificial intelligence, as well as a review of works devoted to its use in the field of diagnostics of oncological diseases, in particular, breast cancer. To reduce mortality and complications, it is necessary to conduct timely screening and improve methods of diagnosing the disease. It is especially important to diagnose and start treatment in the early stages. The goal is to study and summarize data on the use of various methods of artificial intelligence in the timely diagnosis of breast cancer. The analysis of scientific publications on this topic was carried out. The methods of Watson supercomputer, Microsoft Healthcare NExT, radiomics processes, automatic detection systems, Smart Detect for Breast are considered. The prospect of using artificial intelligence, as a screening method, it can allow for better detection of formations at an early stage, as well as lead to automation of this process, which entails a decrease in mortality from breast cancer. Comparing the performance of the artificial intelligence system in breast cancer screening with that of 101 individual radiologists, the researchers found that the former performed better than 61% of the radiologists. Currently, variations of artificial intelligence are presented. It is necessary to specify the methods and create a single program for use in the practice of a doctor.

Keywords: artificial intelligence, breast, screening, cancer, mammography, radiomics, diagnostics, automatic detection system, ultrasound, stages.

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1. Introduction

Currently, breast cancer occupies a leading position in statistics according to the World Health Organization. In 2020, over 2.2 million cases of this disease were registered. It is also noted that approximately every twelfth woman will suffer from breast cancer during her life. Breast cancer is the leading cause of cancer death in women. In 2020, approximately 685,000 women died from this disease.

To reduce mortality and complications, it is necessary to conduct timely screening and improve methods of diagnosing the disease. It is especially important to diagnose and start treatment in the early stages. According to the data for 2021 in Russia, breast cancer is diagnosed at the in-situ stage in only 0.2% of cases [1].

The need for early diagnosis also lies in the prevention and minimization of surgical intervention, which improves the quality of life of patients with breast cancer. Currently, for screening, the method of digital mammography is being widely introduced, which is performed for women aged 35 to 49 once every 1-2 years, for women over 50 every year. However, it should be noted that the mammography method has a variable sensitivity from 67.3% to 93.3% [2,3].

Also, in the diagnosis, additional methods are used, such as ultrasound and MRI of the breast. The combined approach makes it possible to more accurately determine the nature and prevalence of education [4-6].

Today, thanks to the development of computer technology and the digitization of mammography images, it has become possible to use artificial intelligence in breast cancer screening. Thanks to artificial intelligence, the detection of formations in the early stages is increased. In developed countries, it is becoming increasingly important to study this area for diagnosis, including cancer [7-9].

The aim of the work is to study the possibilities of timely diagnosis in the case of breast cancer using artificial intelligence methods.

2. Patients and Methods

The analysis of scientific literature on the topic of the possibilities and advantages of artificial intelligence in the diagnosis of formations was carried out. A variation of methods has been studied. The methods of Watson supercomputer, Microsoft Healthcare NExT, radiomics processes, automatic detection systems, Smart Detect for Breast are considered.

3. Results

AI data was first published in the 1950s, and application spread in the 1990s. Currently, global companies are developing their projects.

IBM has developed research projects using the Watson supercomputer to diagnose and improve treatment regimens for various diseases, including cancer. Also, Microsoft announced the launch of the Microsoft Healthcare NExT project, aimed at combating cancer. Google is implementing a number of diagnostic projects: "smart lenses", which will include a chip that analyzes the state of the environment and the wearer's body and provides information about health threats.

In 2017, British scientists published a report entitled "Artificial Intelligence in the UK National Health System", in the United States in December 2017, a group of leading American technology scientists JASON published a report "Artificial Intelligence for Health and Healthcare". These papers discuss the use of AI to provide highly qualified medical care to the population [10, 11].

Artificial intelligence includes machine learning and deep learning. The data obtained by the neural network is based on the processes of radiomics. Radiomics is the extraction of quantitative properties, named features from an image. Stages of radiomics: acquisition and reconstruction of images, selection of a zone and determination of its features, creation of a database [12].

This feature extraction operation is usually implemented using object recognition algorithms and results in a set of numbers, each of which represents a quantitative description of a particular geometric or physical property of the part of the image in question.

For oncological formations, the signs are size, shape, intensity and texture, which together provide a complex characteristic of the pathology, called the radiomic signature of the tumor. There is also a hypothesis that the selected features reflect the mechanisms that occur at the genetic and molecular levels [13, 14].

The first step involves image acquisition and reconstruction with loading of radiological images. After image adjustment, the second stage includes segmentation and feature extraction. The data is then sorted and collected in a database before analysis. After the segmentation is completed, the selected areas are converted to three dimensions to obtain volumetric images.

Special software then extracts the quantitative characteristics from the received data to create a report that is synchronized with a database based on various sample values.

The second stage in the implementation of artificial intelligence is machine learning, which includes a deep learning method. Deep learning allows you to train a model to predict an outcome given a set of input data.

Various deep irradiation architectures have been published in the literature, but most of these networks are based on some basic and similar neural network building blocks called "layers". The neural network consists of successive layers including an input layer (raw mammogram pixels), a hidden layer, and an output layer (prediction: benign/malignant) [15].

The earlier layers of deep irradiation act in a similar way to simple human brain cells that study low-level objects. Higher levels of abstraction are the result of layering multiple times. The information is propagated through the deep irradiation architecture and more complex features are extracted. These functions are then passed through the last layer of the network architecture for prediction and classification [16].

Automated detection systems can be used to provide second and follow-up opinions to radiologists for more accurate staging of breast cancer [17]. Ding et al proposed a new deep learning method for differentiating tumors into benign and malignant. The results of the experiment showed that the proposed method has an accuracy of 91%, high performance, and it can be useful for automatic irradiation systems in ultrasound examination of the mammary glands [18, 19].

Han et al used GoogLeNet to classify the breast image, with an accuracy of 90%. To train the deep neural network, the authors analyzed 4254 samples of benign tumors and 3154 samples of malignant tumors. The data obtained was sufficient to achieve acceptable performance.

Ultrasound manufacturers are introducing automated detection systems to assist clinicians. S-Detect Breast (Smart Detect for Breast) - a program for the automatic detection and analysis of breast formations in women, measurement and classification according to the BIRADS (Breast Imaging Reporting and Data System) system. The S-Detect™ technology showed agreement (91.2%) with the assessment of the breast radiologist in interpreting the nature of the formations in the mammary glands [20].

4. Discussion

Comparing the performance of the artificial intelligence system in breast cancer screening with that of 101 individual radiologists, the researchers found that the former performed better than 61% of the radiologists [21].

Kim et al used a dataset of over 4,000 cancer cases and nearly 25,000 normal cases, all without pixel-level annotations, to train, validate, and test deep learning of an ultra-precise neural network that could classify images as malignant or not, and generate heat maps highlighting the area that contributed the most to the final classification (Fig. 1) [22].

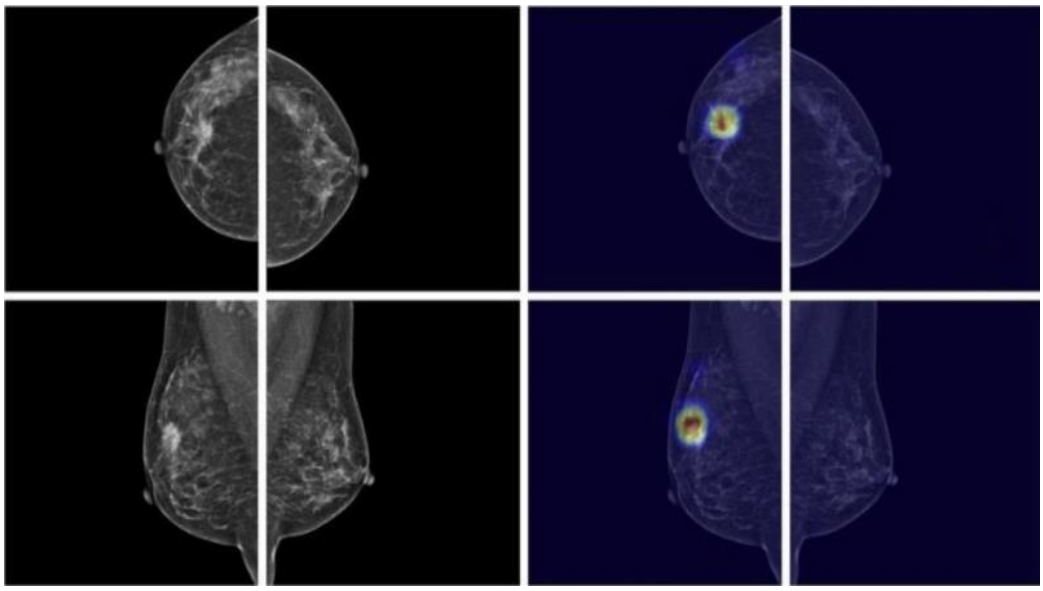

Figure 1. Digital mammography of a 44-year-old woman with invasive ductal carcinoma in the right breast (left), with a heat map overlay highlighting the area that most influenced the final classification decision (right). Application of data-driven imaging biomarker in mammography for breast cancer screening: a pilot study.

Published in the journal Nature, the results of an international study led by a research team led by McKinney in the US and UK demonstrate the advantages of an artificial intelligence model over a radiologist in both productivity and overall accuracy of screening mammography cases [23-26].

5. Conclusions

The prospect of using artificial intelligence as a screening method can make it possible to better detect formations at an early stage, as well as lead to automation of this process, which entails a decrease in mortality from breast cancer. Scientific literature data show that when comparing the work of diagnosticians and the capabilities of artificial intelligence, the prerogative is the use of artificial intelligence. Further research is needed in this area for standardized data sets and the creation of a single method with implementation for widespread use in medical practice.

Author Contributions: Conceptualization, Zakharova P. and Ibragimova N.; methodology, Tkebuchava T.; validation, Ibrokhimova P; writing—original draft preparation, Zakharova P., Ibragimova N., Tkebuchava T., Ibrokhimova P; project administration, Zakharova P. All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Article

Paradoxical Effect of Combined Exposure of Semax and Ammonium Molybdate on Learning and Memory of Rats

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Abstract: The combined effect of semax with aqueous solutions of lead diacetate (10-7 M) and ammonium molybdate (10-5 M) on the formation of a conditional two-way avoidance reaction in rats in a shuttle chamber was studied. It was found that both heavy metal salts inhibit learning and memory; lead diacetate caused greater depression. Semax slowed down the production of the conditional reaction, but counteracted the negative influence of both metals on this process. At the same time, the influence of semax on the formation of the avoidance reaction in the presence of ammonium molybdate, which in itself inhibited avoidance, paradoxically intensified. With the combined effect of the peptide and ammonium molybdate, the formation of a conditional reaction occurred much faster than against the background of semax without combination with molybdenum. In general, the data obtained indicate that semax counteracts the neurotoxic effect of lead and molybdenum salts. Since the main mechanism of the neurotoxic effect of heavy metals is oxidative stress, the indicated positive effect of semax can, in our opinion, serve as confirmation of the presence of antioxidant properties in the spectrum of pharmacological activity of the peptide.

Keywords: oxidative stress, semax, ammonium molybdate, lead acetate, learning, memory.

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1. Introduction

Endogenous peptide regulators, similar to adrenocorticotropic and melanocyte-stimulating hormones (melanocortins), play an important role in regulating the functions of the central nervous system. Currently, there is a lot of evidence of the positive effect of melanocortins on the development of conditioned reflexes. However, the nootropic effects of natural fragments of adrenocorticotropic hormone (ACTH) are short-lived [1]. This prompted the search for ways to increase the effectiveness of natural melanocortins by modifying their structure, which led to the creation of synthetic analogues with pronounced activity, but devoid of hormonal effects [2]. Among them, an important place is occupied by semax – a nootropic analogue of the ACTH fragment (4-10) of prolonged action, the structure of which includes the ACTH fragment (4-7) and the tripeptide Pro-Gly-Pro. Animal experiments have shown that this peptide, like natural melanocortins, has a wide spectrum of neurotropic activity [3]. Currently, it is used in the clinic as a nootropic and neuroprotective drug. Despite the fact that drugs developed on the basis of semax have been used in clinical practice for a long time, studies of its physiological effects continue. The relevance of such studies is determined by the need to clarify the mechanisms of action and the possibility of expanding the spectrum of clinical use of the drug.

Recently, the antioxidant activity of the peptide has been established, which significantly expands the spectrum of its action [4]. In particular, the ability of the peptide to resist the neurotoxic effect of heavy metals, the main mechanism of which is the induction of oxidative stress, is of great interest [5]. It is known that oxidative stress caused by heavy metals leads to neurodegenerative diseases, including Alzheimer's and Parkinson's diseases [6-9]. To date, separate studies have been carried out, which show the prospects of using antioxidants to counteract the neurotoxic effects of heavy metals [10-12]. This paper analyzes the possibility of using semax as a drug with antioxidant properties to counteract the inhibition of learning and memory in rats by molybdenum and lead salts.

2. Materials and methods

The experiments were conducted on six groups of male white mongrel rats (20 animals per group) at the age of 7-8 weeks. by the beginning of the experiment. The first group was injected with semax at a dose of 0.05 mg/kg; the 2nd and 3rd groups were injected with aqueous solutions of lead diacetate (10-7 M) and ammonium molybdate (10-5 M), respectively; the 4th and 5th groups

were injected with semax in combination with lead and molybdenum salts, respectively; 6-I group served as a control. Aqueous solutions of heavy metal salts were administered intraperitoneally by 2 ml 5 hours before the experiments, semax – 4 hours after the introduction of salt solutions. Control animals were injected with 2 ml of distilled water an hour before the experiment.

The experiments were carried out in a chamber divided into 2 equal halves by a partition with an opening. In animals, for 5 days (25 stimuli were presented daily), a conditional two-way avoidance reaction was developed, which serves as an experimental model of learning and memory. A sound conditional stimulus was turned on and after 10 seconds a current (0.5–0.7 mA) was applied to the floor wiring of the half of the chamber in which the rat was located. If the rat did not move to the safe half of the chamber, then after 10 seconds both stimuli were turned off; after 30 seconds, the stimuli were presented again. The transition of the animal to the safe half of the chamber, during the action of stimuli, led to their shutdown.

The study was conducted in accordance with the rules adopted by the European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986) and Directive 2010/63/EU of the European Parliament and of the Council of the European Union on the protection of animals used for scientific purposes.

The dynamics of learning in groups was assessed using a one–factor nonparametric Kraskel–Wallis analysis of variance; the difference between groups was assessed using the Wilcoxon criterion. The differences were considered statistically significant at $p<0.05$.

3. Results and discussion

The analysis of the graphs shown in Fig. 1 shows that both heavy metal salts inhibited the production of the avoidance reaction. Lead salt had a stronger depressing effect on learning, against the background of which animals, even at the final stage of training, received on average more than 20 shocks of current per experience out of 25 possible. The use of the Kraskel–Wallis analysis of variance showed that when exposed to lead diacetate, there was no statistically significant increase in the number of avoidance reactions, starting from the 2nd experiment, which indicates a deep inhibition of learning and memory. These data are consistent with those previously obtained by us [13]. The use of molybdenum caused a statistically significant decrease in the number of avoidance reactions relative to control only in the last three days of the experiment.

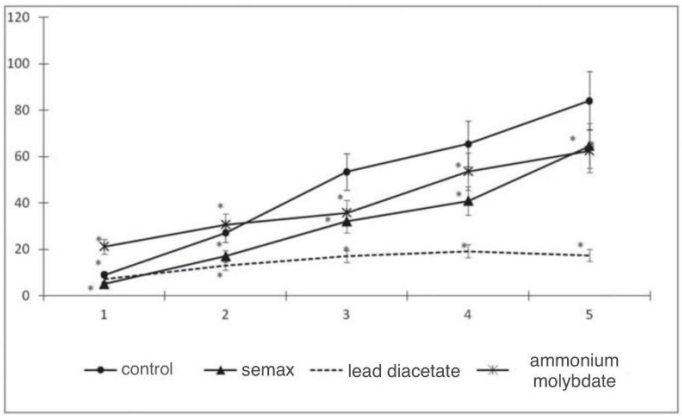

Figure 1. The influence of semax, lead diacetate and ammonium molybdate on the dynamics of the avoidance reaction. On the abscissa axis – the time of experiments, days; on the ordinate axis – the number of correct reactions as a percentage relative to all presentations. The data here and in Figures 2 and 3 are represented as the mean and the error of the mean. * – $p<0.05$ relative to control values.

Semax slowed down the development of the avoidance reaction. This is consistent with the data that the effect of the peptide depends on the methodological features of the experiments. In particular, it was shown that semax increases the number of conditional reactions of unilateral avoidance, but reduces the number of reactions of bilateral avoidance, while increasing, in comparison with control data, the number of these reactions in conditions of emotional stress and the need to learn a modified skill after functional disorders [14]. According to the results obtained in the present experiment, semax counteracts the neurotoxic effect of salts of both heavy metals on the formation of an avoidance reaction in animals, which confirms the above-mentioned ability of the peptide to have a positive effect in conditions that make learning difficult. The experimental results presented in Fig. 2 show that the levels of avoidance reactions with combined exposure to semax with salts of both lead and molybdenum exceed the corresponding indicators recorded when exposed to salts without a peptide. At the same time, the peptide's resistance to the inhibition of learning by lead and molybdenum salts manifests itself to varying degrees. The combined

effect of semax with lead accelerated the formation of an avoidance reaction with respect to animals that were injected only with metal, starting from the third day. The neuroprotective effect of the peptide increased in the course of the experiment. A statistically significant excess of the avoidance level in the combination of semax with molybdenum relative to the values observed when exposed to a salt of this metal without a peptide was noted throughout the experiment.

As mentioned above, both semax and molybdenum, introduced separately, slow down the learning of animals. In this regard, it is interesting to note that with combined exposure to peptide and ammonium molybdate, the formation of an avoidance reaction occurs statistically significantly faster than against the background of semax without combination with molybdenum salt (Fig. 3). On the first day of the experiment, the number of avoidance reactions with combined exposure was almost 7 times higher than the magnitude of the avoidance reaction in rats under by the influence of a single peptide. To a certain extent, this result looks paradoxical and requires explanation. It is known that the metal molybdenum is a part of the enzyme xanthine oxidase and can increase the activity of antioxidants [15]. In view of this, the specified feature of the combined effect of molybdenum and peptide can be explained by an increase in the antioxidant activity of the latter. In contrast, the combined effect of the peptide with lead diacetate leads to a decrease in the level of the avoidance reaction relative to this indicator when exposed only to semax. The latter means that exposure to lead salt weakens the activity of the peptide. A comparison of the combined effects on learning of semax with lead diacetate and semax with ammonium molybdate shows that the enhancement of the neuroprotective activity of the peptide is selective, since it occurs only in combination with molybdenum.

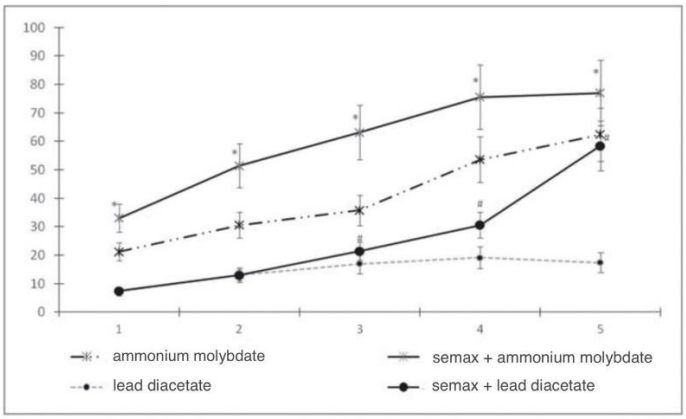

Figure 2. Semax's counteraction to the negative influence of lead diacetate and ammonium molybdate on the production of the reaction of the solution. The axis designations are as in Figure 1. * – p<0.05 relative to the values with a separate introduction of ammonium molybdate; # – p<0.05 relative to the values with a separate introduction of lead diacetate.

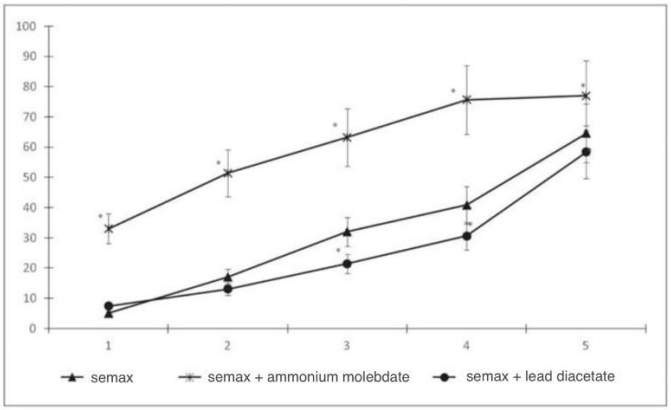

Figure 3. Comparison of the combined effect of semax and metal salts with the effect of one peptide on avoidance reactions. About the axis values – as in Figure 1. * – p<0.05 relative to the values with a separate introduction of semax.

Thus, it follows from the data obtained that the effect of semax on the formation of the avoidance reaction in rats in the presence of ammonium molybdate, which in itself inhibits learning,

paradoxically increases. In general, the data obtained indicate that semax counteracts the neurotoxic effect of lead and molybdenum salts. Since the main mechanism of the neurotoxic effect of heavy metals is oxidative stress, the positive effect of semax on the background of ammonium molybdate and lead diacetate can, in our opinion, serve as confirmation of the presence of antioxidant properties in the spectrum of pharmacological activity of the peptide.

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Conflicts of Interest: The authors declare no conflict of interest.

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Article

Changes in Expression of Chemokines, Cytokines and their Receptors under the Action of Selank and its Fragments

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Abstract: Currently, pharmacological preparations based on endogenous regulatory peptides are being actively studied as the most promising class of drugs that are practically devoid of side effects. This class of drugs includes a synthetic analogue of tuftsin - Selank. Selank, on the one hand, has an anxiolytic and nootropic effect, and on the other hand, it has pronounced antiviral properties. During the study of the immunomodulatory effect of Selank, we proved that both the whole peptide and its individual fragments can cause significant changes in the expression of genes of chemokines, cytokines, and their receptors in the mouse spleen 6 and 24 hours after a single injection. We also showed that a change in the mRNA level of most of the considered genes is observed after the introduction of Gly-Pro, previously proposed as a minimal fragment of Selank with antiviral activity - pharmacophore.

Keywords: Chemokine Gene, Single Intraperitoneal Injection, Relative Expression Soft Ware Tool.

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1. Introduction

Selank is a regulatory peptide, a synthetic analog of taftsin (a short fragment of Thr-Lys-Pro-Arg of the heavy chain of human immunoglobulin G), extended with a C-terminal part of the three Pro-Gly-Pro peptide to increase metabolic stability and increase the duration of action of the final peptide [1, 2]. Selank has a pronounced anxiolytic and nootropic effect and is highly effective in the treatment of anxiety and anxiety-asthenic disorders, leads to the activation and optimization of mnestic and cognitive functions of the brain, learning and memory processes[3, 4].

Along with the functions described above, Selank also has a pronounced immunotropic activity and is able to induce the secretion of interferons. The antiviral effect of Selank was found against influenza virus A/Aichi2/68 (strain H3N2) both in vivo and in vitro in experimental models [5]. In previous studies aimed at searching for genes that change their expression under the influence of Selank, we have shown that the introduction of Selank causes a transcriptomic response in rat hippocampus and spleen cells. At the same time, the most significant change in the mRNA level was noted for the Cx3cr1 gene in the rat spleen after a single injection of the drug [6].

Previous studies have shown that glyprolines are able to exert their own physiological effect, and synthetic peptides containing them can combine different physiological properties of their structural units [7].

In this regard, for a more detailed study of the immunomodulatory activity of Selank, we evaluated changes in the expression of chemokine and cytokine genes in the mouse spleen under the influence of both the whole Selank peptide Thr-Lys-Pro-Arg-Pro-Gly-Pro and three of its fragments: Gly-Pro (GP), Arg-Pro-Gly-Pro (RPGP), and taftsin Thr-Lys-Pro-Arg, 6 and 24 h after a single injection of the peptides.

2. Patients and Methods

A mouse was chosen as an experimental animal, since this species is the most suitable model object for immunological studies, and the spleen is one of the main organs of the immune system. In the experiment, male outbred mice were used, which were divided into 10 groups (10 individuals each with an average weight of 20 g). Of these, two control groups for two time points (6 and 24 h) and eight experimental groups, one for each peptide and corresponding time point. Animals from the control groups received saline intraperitoneally once. Animals from the experimental groups received a single intraperitoneal injection of Selank or its fragments (at a rate of 100 mcg/kg

of body weight). Animals from the control and experimental groups were decapitated after 6 or 24 h in accordance with their belonging to the selected time point, the spleen was immediately removed and frozen at –70°C. Total RNA was isolated from spleen tissues using the RNeasy® Mini Kit (Qiagen, Israel). On its basis, the first cDNA strand was synthesized using the RevertAid™ H Minus First Strand cDNA Synthesis Kit ("Fermentas", Lithuania).

25 genes from four groups were selected for analysis: chemokine genes (Ccl3, Ccl7, Ccl9, Ccl11, Ccl17, Ccl19, Ccl20, Cxcl10, Cxcl12, Cxcl15), chemokine receptor genes (Ccr2, Ccr4, Xcr1), cytokine genes (Il10, Il16, Il1f8, Il20, Ifng, Itgam, Itgb2, Scye1) and cytokine receptor genes (Il1r2, Il2rg, Il5ra, Il13ra1). These genes are involved in the cascade of immune responses that occur during inflammatory processes. Three housekeeping genes were selected as reference genes: Actb, Hprt1, and Hsp90ab1. Analysis of the effect of Selank and its three fragments on the expression of these genes in the mouse spleen was performed using real time PCR on an Mx3000P™ Real Time QPCR System (Stratagene Equipment, USA) using the SYBR Green I kit (Sintol, Russia) and commercial primers RT2 qPCR Primer Assay SYBR®Green (SABioscience, USA). The obtained values of reaction cycle thresholds (Ct) were normalized with respect to Ct of housekeeping genes and statistically processed using the Relative Expression Software Tool 384, version 2 [8].

3. Results

Quantitative evaluation performed during the study showed that the response of the largest number of genes upon administration of Selank is observed 24 h after the administration of the peptide (Table 1). The administration of GP, on the contrary, leads to a significant change in the level of mRNA of the largest number of genes 6 h after injection. Changes in the mRNA level of the largest number of chemokine genes were observed 6 h after the administration of GP and tuftsin, and also a day after the administration of Selank. A similar significant decrease in the mRNA level of the Cxcl12 gene was noted, by an average of 1.3 times 6 h after the administration of GP, RPGP, and tuftsin. There were no significant changes in the expression of this gene after the administration of Selank. The genes of chemokine receptors Ccr2 and Ccr4 were characterized by a significant increase in the expression level only after GP administration. A day after the administration of each of the peptides, a decrease in the level of mRNA of the Xcr1 gene encoding the receptor for the activator of the chemotactic activity of lymphocytes was observed. Six hours after the administration of GP, RPGR, and tuftsin, a significant decrease in the level of Itgam gene mRNA was observed, on average, by 50 times, and a twofold decrease in the level of mRNA of this gene a day after the administration of GP. A significant increase in the expression of the gene encoding gamma interferon (Ifng) by 1.2 times was also noted 6 h after administration of tuftsin and Selank. For the Il1r2 gene, a significant decrease in the mRNA level (by 14 times) was observed 6 h after the administration of Selank, and then an increase in the mRNA level of this gene by 4.5 times a day after the administration of the peptide. Also, a decrease in the level of expression of this gene by 11 times 6 hours after the administration of GP and its growth by 3 times a day after the administration of tuftsin was noted. The Il2rg gene, which encodes a common subunit of receptors for various interleukins, was characterized by a drop in the mRNA level 6 h after administration of each of the peptides.

4. Discussion

The results obtained showed that the administration of Selank and each of its fragments considered in this study has a significant effect on changes in the mRNA level of genes for chemokines, cytokines, and their receptors, and activation of some of them is observed even a day after a single administration of peptides. This suggests that Selank is involved in the regulation of inflammatory processes and is capable of inducing targeted changes in the expression of genes involved in the body's immune response.

5. Conclusions

A change in the mRNA level of a greater number of selected genes is observed after the introduction of GP, and the activation of most of them is noted as early as 6 h after the introduction of this peptide. Thus, we can assume that the minimal fragment of Selank that plays the role of a pharmacophore is the dipeptide Gly -Pro. To reveal a more detailed picture of the effect of Selank and its fragments on the expression of genes involved in inflammation processes, we will further study the temporal dynamics of changes in the mRNA level, as well as the dynamics of protein expression of the studied genes after the introduction of peptides. This study was supported by the programs of the Russian Academy of Sciences "Molecular and Cellular Biology", "Fundamental Sciences for Medicine"; State contracts No. 02 740 11 5084, P419; support programs for leading scientific schools (NSh 8418.2010.4, NSh 3438.2010.4).
Acknowledgments.

Table 1. Relative change in the mRNA level of genes of chemokines, cytokines and their receptors in the mouse spleen after 6 and 24 hours after the introduction of Selank or its fragments (the table shows only statistically significant results)
Note. The base expression level is 1. * p < 0.05; ** p < 0.01.

	Gene	Name of gene	Selank		GP		RPGP		Taftsin	
			6h	24h	6h	24h	6h	24h	6h	24h
chemokines	Ccl3	CC-chemokine ligand 3			1.42*				1.30**	
	Ccl7	CC-chemokine ligand 7		0.87**						
	Ccl9	CC-chemokine ligand 9							0.72*	
	Ccl11	CC-chemokine ligand 11				0.84*				
	Ccl17	CC-chemokine ligand 17	1.13**		1.63**					
	Ccl19	CC-chemokine ligand 19		0.64*						
	Ccl20	CC-chemokine ligand 20			1.38*			0.37**		
	Cxcl10	CXC-chemokine ligand 10			0.73**		0.79*			
	Cxcl12	CXC-chemokine ligand 12			0.81**		0.82**		0.87**	
	Cxcl15	CXC-chemokine ligand 15		0.74**						0.80**
chemokine receptors	Ccr2	CC-chemokine receptor 2			1.53*					
	Ccr4	CC-chemokine receptor 4			1.17*					
	Xcr1	XC-chemokine receptor 1		0.86*		0.80**		0.75**	0.81**	0.88**
cytokines	Il10	Interleukin 10			1.22*					0.69*
	Il16	Interleukin 16					0.77*			
	Il1f8	Interleukin 1-8		1.40**						
	Il20	Interleukin 20		0.76**		0.77*				
	Ifng	Gamma interferon	1.23*						1.25*	
	Itgam	Integrin alpha M			0.02**	0.47**	0.02**		0.02**	
	Itgb2	Integrin beta 2				0.81**		0.64**		
	Scye1	Small inflammatory cytokine E1			1.32*					
cytokine receptors	Il1r2	Interleukin 1 receptor type 2	0.08*	4.46**	0.09**					3.09*
	Il2rg	Interleukin 2 receptor gamma chain	0.57*		0.43**		0.63**		0.51**	
	Il5ra	Interleukin 5 receptor alpha		0.83*						
	Il13ra1	Interleukin 13 receptor alpha-1		0.82*						0.78*

Conflicts of Interest: The authors declare no conflict of interest.

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Clinical case

Optic Neuritis as Manifestation of Local Viral Encephalitis (Clinical Observation)

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Abstract: In the practice of an ophthalmologist and neurologist, the identification of relationship between optic neuritis and inflammation of the brain tissue is accompanied by significant diagnostic difficulties. In this regard, the role of interdisciplinary consultations is valuable, as an ophthalmologist knows the methods of ophthalmological diagnostics, which allow for topical diagnosis of the brain damage level, but for a neurologist, these methods are inaccessible. A clinical case of herpetic optoencephalitis (descending optic neuritis against the background of local encephalitis) in a teenager with a favorable outcome after conservative treatment is considered in the given paper. Conclusion: It is important to remember that during the optoencephalitis formation, its ophthalmic manifestations can remain not only the manifestation of this focal neurological pathology for a long time, but also require the timely appointment of appropriate routes of administration, doses and duration of etiotropic drugs use, therefore, the utmost diagnostic alertness regarding viral encephalitis (opticoencephalitis) is important at the slightest suspicion of a descending origin of the identified eye tissues inflammation.

Keywords: optic neuritis, viral encephalitis, diagnosis, treatment.

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1. Introduction

It is known that the incidence of encephalitis in the world is about 7-9 cases per 100,000 population and about 80% of encephalitis of infectious etiology is viral, among which the herpes simplex virus (HSV) is the most common [1].

There are also quite numerous descriptions in the literature of an increased risk of SARS-CoV-2 coinfection with neurotropic viruses such as Herpes Viridae [2], reactivation of herpes infection in immunocompromised patients after COVID-19, for example, in the form of retrobulbar neuritis, optoencephalitis, meningo-encephalitis. In 45-75% of cases, optic neuritis is accompanied by pathology of the central nervous system of varying severity.

Thus, it is obvious that the relevance of early diagnosis of these ophthalmic and neurological diseases in the current epidemiological situation will only increase.

A clinical case of herpetic optoencephalitis (descending optic neuritis against the background of local encephalitis) in a teenager with a favorable outcome after conservative treatment is considered in the given paper.

2. Purpose

Purpose to draw attention to the difficulties of diagnosing local optoencephalitis.

3. Methods

Methods of standard laboratory (general clinical blood and urine tests; methods of molecular genetic, serological blood tests) and ophthalmological (visometry, manual kinetic perimetry, color vision examination using polychromatic tables, biomicroscopy, ophthalmoscopy, tonometry) diagnostics were used.

4. Description of the Clinical Observation

Patient X (14 years old) was hospitalized in an ophthalmological clinic with a preliminary diagnosis of 'OU – Optic neuritis. Atrophy of the optic nerve'.

On examination within the framework of a medical consultation, he complained of a progressive deterioration in vision in both eyes ('blurred bright spot in the center').

Visus OD=0.02 was not corrected;

Visus OS=0.01 was not corrected.

By the decision of the medical council, the diagnosis was made: 'OU – Subacute descending optic neuritis with retinal arteritis (protracted course). Complete central, homonymous right-sided (lower quadrant) hemichromatopsia. Convergence paresis. Exacerbation of chronic viral conjunctivitis of herpetic etiology (Fig.1).

Figure 1. Medium-sized herpetic vesicles (indicated by an arrow) in the region of the lower transitional fold of the conjunctiva, identified by biomicroscopy of patient X.

Suspicion of reactivation of a herpes infection with damage to the central fibers of the optic pathway (Graziole's bundle, occipital cortex)' (Fig.2).

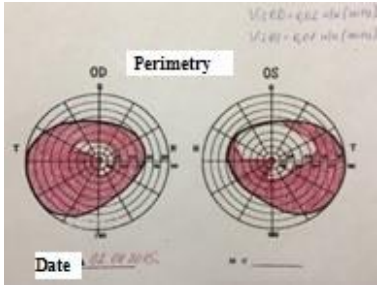

Figure 2. The result of kinetic manual perimetry of patient X using a red object (at the time of diagnosis).

The treatment included the systemic administration of antiviral, anti-inflammatory, decongestant drugs, nootropics, antioxidants and vitamins recommended by the council, against which visual acuity began to increase already on the third day. Improved vision made it possible to identify a new, previously undiagnosed and extremely important neurological symptom – dyslexia (according to the patient, reading the text was extremely difficult: 'I read like a first grader, spell it; it is difficult to combine letters into words'). At the same time, there was a complete regression of pathological changes in the visual field (Fig.3).

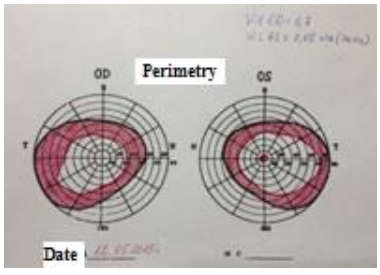

Figure 3. The result of kinetic manual perimetry of patient X using a red object (after 6 weeks of treatment).

At discharge, the visual acuity of patient X was:

Visus OD=1.0;
Visus OS=1.0.

All functions of the visual analyzer of this patient X, described in the paper, were fully restored. However, their complete recovery required a long-term multi-stage therapy using not only local, but also systemic routes of administration of antiviral, anti-inflammatory, decongestant, vitamin and antioxidant drugs.

5. Discussion

It is known that among all the etiological factors of optic neuritis, HSV dominates [3]. In this regard, an ophthalmologist should remember that the central nervous system (CNS) lesion area is primarily determined by this virus spreading pathways (hematogenous, lymphogenous, perineural): with hematogenous and lymphogenous pathways of damage, which is more common in young children and newborns, the development of diffuse lesions of brain structures is typical (with damage to the vascular endothelium, the development of thrombosis, ischemic disorders and hemorrhages in the central nervous system – the formation of a common variant of CNS damage occurs); with perineural pathway, more typical for adults and older children, the virus spreads along the axons of the cranial and spinal nerves (with damage to the CNS cells located in close proximity to the infected cells – a limited variant of CNS damage is formed).

6. Conclusions

The described clinical case demonstrates the manifestations variety of local encephalitis, which can occur not only in the presence, but also in the absence of cerebral, meningeal, general infectious symptoms. Thus, ophthalmic manifestations can remain the only manifestation of focal brain inflammation for a long time, so an ophthalmologist should be aware of the likelihood of a descending origin of the observed inflammatory changes in the eye tissues.

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Article

The Variation of Muscle Relaxant According to the Circadian Rhythm in Emergency Abdominal Surgery

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Abstract: In the contemporary anesthesiology services, muscle relaxation plays an integral role in emergency abdominal surgery in order to facilitate the work of the surgeons. Circadian rhythms control the behavioral, mental and physical changes of humans on a 24-hour cycle. The term circadian is originated from the Latin word "circa diem" meaning "around a day." They are regulated by the suprachiasmatic nucleus SCN in the hypothalamus which is the "master clock" of the brain and the body. A study was carried on 50 patients both male and female from eighteen to sixty years old undergoing emergency abdominal surgery. The level of muscle relaxation administered intravenously was monitored using a TOF Watch SX time 08:00 till 14:00 then from 15:00 -20:00. Two different muscle relaxants were used notably "atracurium benzilate and rocuronium bromide" each at a dose of 0.4 mg/kg and 0.5 mg/kg respectively. The time of action for endotracheal intubation, duration and extubation was recorded. As a result, it was demonstrated that there was a significant shorter time of action and shorter duration in surgeries taking place from 15:00 pm-20:00 as compared to 08:00 -14:00 with both relaxants. To conclude, according to the circadian rhythm, effects of muscle relaxants in the evening relatively differed from the morning by having a shorter duration bringing to the fact that the cholinergic system had a role to play.

Keywords: Muscle relaxant, Neuro-Muscular block, Emergency abdominal surgery, Circadian time, Residual Neuro-Muscular block.

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1. Introduction

Various studies have proven that muscle relaxants facilitate not only the work of the surgeons but also that of the anesthesiologists. They ease intubation, avoid vocal injury and involuntary muscle reflexes during surgery. With the evolution of time the method of accelerometry permitted anesthesiologists to understand their action and effect on human and its elimination. However, many cases of residual neuromuscular block had been reported with and without the use of antidotes notably: "proserine or sugammadex" for their reversal [19].

Additionally, some cases of allergic reactions were being identified with the use of muscle relaxants during surgery leading to anaphylactic shock [8]. An exactly adequate dosage shall be administered, whether it is short acting, intermediate or long acting, the anesthesiologists should take extra care in administering muscle relaxants. The main challenge now is to prevent residual

NMB [12,13,14], stop losing time on extubation, amplify the methods in NMB monitoring worldwide.

Since many unwanted cases in surgery due to residual NMB are present, a TOF watch and a BIS monitor is highly recommended in all anesthesiological care centers for NMB monitoring before, intra and post- surgery. Intrisinctly, the novelty of the study carried out denoted that time plays a key role on muscle relaxants. As the needle of the clock ticks evening time their duration is relatively shorter as compared to daylight [18] together with their frequency of elimination.

The circadian rhythm in our contemporary world plays a grand role in the process of a surgery where muscle relaxant is accountable. The usage of an appropriate dose, proper NMB monitoring in reliance to the circadian time decidedly is prioritized for zero residual NMB promoting quick recovery of the patient.

2. Patients and Methods

2.1. Materials of study:

The study consisted of 50 patients undergoing emergency abdominal surgery under combined endotracheal anesthesia using the following medications intravenously: phentanyl (30 mkg/ml) , propofol (200 mg), sevoran , either rocuronium bromide (0.5 mg/kg) or atracurium benzilate (0.4 mg/kg). The apparatus used for mechanical ventilation was drager fabius. A protocol of clinical research together with the protocol of anesthesia and the pre-anesthesiological interrogation protocol were utilized.The ecg of the patients was taken before start of the surgery.For monitoring of the depth of muscle relaxant a Tof Watch Sx was used. Results were recorded on Microsoft excel and further graphs,tables were designed according to the Tof results obtained.

2.2. Methods to implement:

The effect of non-depolarizing muscle relaxants including (aminosteroid and benzylisoquinoline composition) was determined on neuromuscular conduction throughout emergency abdominal surgeries by using TOF Watch Sx in accordance to daytime 08:00-14:00 and evening time at 15:00-20:00. “Rocuronium bromide” and “atracurium benzilate” were administerened intravenously in emergency abdominal surgery according to the following criteria: TOF 0, TOF 25 %, TOF 75 % and TOF 90 %. After administration of the 1st dose statistics were compiled on the result obtained. Two different muscle relaxants were used in to see how they react in different medical cases during emergency abdominal surgeries such as: laparoscopic appendectomy/cholecystectomy, hernia removal, relaparatomy sanitation and drainage of the abdominal cavity, dissection of intestinal adhesions, pancreatectomy. The blood pressure, the heart rate, the pulse -5 min after induction and after intubation, using capnometry, the ventilation parameters as follows :- PEEP, Tidal volume, PaCO2, Ti:Te, FiO2, sevoran and O2) were monitored. . An enquiry was conducted on the patients stating whether they took any medication in the anamnesis that can affect neuromuscular block. A query was being formulated on interrogation to the patients including the following: 1. They had a normal sleep or not- they slept normally 2. They did night shifts at work ?- none of them did 3. They did fly during the past few days – none of them flew anywhere recently [6,15].

2.3. Inclusion Criteria

- Adult male and female patients aged 18 to 60[21]
- Planned for a patient surgical intervention of medium duration (30–120 min)
- The severity of the condition before surgery according to the ASA classification (American Society of Anesthesiologists) - ASA Class I-III
- Patients with body mass index 18‹BMI‹30 kg/m2; Patients who have agreed to participate in the study, have read the Patient Information Sheet and signed the Informed Consent of the Patient, and are willing to cooperate in the course of the Study [21].
- Patients who are scheduled to undergo surgery using total intravenous anesthesia or combined endotracheal anesthesia (propofol, fentanyl, thiopental, midazolam, etc.) with an estimated duration of surgery of 30–120 minutes.

2.4. Exclusion Criteria

- Patients with significant disorders of neuromuscular conduction, neuromuscular diseases (including myasthenia gravis, Eaton-Lambert syndrome, a history of poliomyelitis, etc.) [22,23].
- Use in the perioperative period of drugs related to prohibited therapy in the study.
- Patients who have contraindications to the use of the TOF Watch device

(including Pacemaker, etc.);
● Acute infectious diseases.
● Patients with II-IV-degree burns.
● Patients with a history of hypersensitivity to drugs of the class used (pancuronium bromide, vecuronium bromide, atracurium benzilate, rocuronium bromide etc.)
● Patients with burdened allergic history (serious systemic manifestations of allergic reactions in history);
● Patients who participated in other clinical studies within the last 6 months. or currently participating in other clinical trials.
● Any other disease or condition that, in the opinion of the investigator, may confound the results of the study and limit the patient's participation in the study ASA IV.

A study was being carried out in the State Budgetary Healthcare Institution of the City of Moscow "City Clinical Hospital named after V.V. Vinogradov of the Moscow Healthcare Department"; (City Clinical Hospital No.64 of Moscow Department of Healthcare) situated in Moscow, Russia from the beginning of January 2023 to the end of February 2023 on 50 patients of the age of eighteen to sixty undergoing emergency abdominal surgery. They were classified into two groups; group 1 surgery which starts from 08:00 am till 14:00 pm then group 2 surgery which starts from 15:00 to 20:00. The TOF-reading demonstrates 4 phases or levels of muscular blockade:

1. Complete blockade
2. Deep blockade
3. Moderate blockade
4. Phase of recovery of neuromuscular block

Complete neuro muscular block happens after intravenous administration of muscle relaxant on intubation of the trachea, the rapidity of action and duration are related to the relaxant used [3]. This phase is known as TOF 0 period complete muscle paralysis where there is no result neither on TOF nor on post tetanic stimulation at PTC=0 according to the authors Wilson R.S, Savarese J.J, Kitz R.J 1975, Brand J.B, Cullen D.J 1977; Deep blocade is characterized by absence of answers on the muscle tone by one stimulation and by the TOF regime as compared to complete blockade in which pops up answers at the post tetanic stimulation (moderate phase).

All patients were under combined endotracheal anesthesia with the administration of propofol and phentanyl together with sevoran and oxygen (MAC ›1.0) supporting the anesthesia. Clinical monitoring was carried out using the international standards starting from the admissionvto the operation theatre till the implementation of anesthesia. Neuromuscular function was being measured each 15 seconds interval with the help of accelerometry all during the whole anesthesia with the help of the 4-x finger stimulation using the TOF Watch SX. The primary change of outcome at T1 was the time in minutes from the administration of the induction dose (0.5mkg/kg) of rocuronium bromide or 0.4mg/kg atracurium benzilate.

3. Results

3.1. Variation of muscle relaxants morning and evening

(Table 1) illustrates the variation of the time in seconds and in minutes once a first intubating dose of rocuronium bromide 0.5mg/kg and atracurium benzilate 0.4mg/kg were injected intravenously. The time of action in seconds at TOF 0 of both the non-depolarizing muscle relaxants from 15:00-20:00 were shorter as compared to 08:00-14:00. A standard dose of 0.6mg/kg rocuronium bromide normally took 60 seconds to act but in the study a dose of 0.5mg/kg was given which took a bit longer and the surgeries were mostly emergency massive open abdominal ones which could be another potential factor for the lag of muscle relaxant in action per seconds. A standard dose of atracurium benzilate ranges from 0.5-0.6mg/kg took 90seconds to act normally but a dose of 0.4mg/kg was used which also caused a little delay in the action time. Atracurium Benzilate duration basically is 15 to 35minutes however for emergency patients its duration was up to 87.4mins and 75.5mins.

4. Discussion

It was supported by Ismail Gogenur et al [1,9] that during laparoscopic cholecystectomy LC with evaluation to open massive abdominal surgery MAS together with the circadian activity parameters (IS, IV and AMP). Comparing MAS to LC, MAS metrics proved to be worse. The circadian activity was grossly altered demonstrating that MAS beared more drastic modifications. Circadian activity pattern measurements and postoperative subjective recovery metrics showed

strong correlation [20,21]. Melatonin plays an integral role in medicine and can be used as a supportive drug in the treatment of sleep disorders, CNS disorders, GIT and cardiovascular system [10] and many oncological diseases due to its anti-inflammatory effect on the body, anti-oxidative and anti-carcinogenic, regulating mitochondrial function even affecting homeostasis with substantially an affect in the normal circadian rhythm- the sleep/wake program supported by Alicja Baranovskaya et al [2,5,8,11,24].

Table 1. A first intubating dose using rocuronium bromide and atracurium benzilate from 08:00-14:00 and 15:00-20:00.

Muscle Relaxant and time Intubating Dose mg/kg	Rocuronium Bromide 08:00-14:00 0.5 n=11	Rocuronium Bromide 15:00-20:00 0.5 n=12	Atracurium Benzilate 08:00-14:00 0.4 n=14	Atracurium Benzilate 15:00-20:00 0.4 n=13
TOF 0/secs	193.5± 94.3	129.6± 54.9	303.9±153.8	273.5± 84.4
TOF 25%/mins	38.6 ±8.1	35.5±4.9	54±9.5	42.5 ±7.2
TOF 75%/mins	68.3± 16.8	54.8±10.8	73.8±10.8	63± 16.5
TOF 90%/mins	87.5± 21	75.8 ±10.7	87.4 ±14.4	75.5 ±16.5

Note: TOF - Train of Four; TOF 0- Complete M. R, TOF 25%- M.R starts to fade away TOF 75%- Average fading of M.R TOF 90%-Time of recovery from M.R (muscle relaxant)

Circadian rhythms are the typically 24-hour biological cycles that serve to get a living thing ready for everyday environmental changes. [24] They are regulated by the molecular clock, which in mammals is a transcriptional/ translational feedback process including the key clock genes Bmal1, Clock, Per1/2, and Cry1/2. Almost all an organism's cells include the molecular clock. While the suprachiasmatic nucleus' (SCN) central clock has received extensive research, little is known about the clocks in peripheral tissues like the heart and skeletal muscle. One of the major organs in the body, skeletal muscle makes up about 45% of body mass. More than 2300 genes, many of which were involved in myogenesis, transcription, and metabolism, are expressed in skeletal muscle in a circadian manner. Skeletal muscle's circadian rhythms can be influenced directly by the timing of activity and food as well as indirectly by light input to the SCN. The skeletal muscle molecular clock must not only be entrained to the environment but also in time with the rhythms of other tissues to function properly. The documented consequences on skeletal muscle when circadian rhythms were disturbed include fiber type changes, altered sarcomere structure, decreased mitochondrial respiration, and poorer muscle performance. Skeletal muscle certainly contributed to the negative impacts on metabolic health because it is an important metabolic tissue. These negative consequences including reduced glucose tolerance and insulin sensitivity. These findings suggested that skeletal muscle circadian rhythms are essential for the health of both the muscles and the systems. Further studies are required to understand how skeletal muscle's molecular clock functions, pinpoint the processes behind entrainment, and conduct a thorough analysis of circadian gene expression in skeletal muscle's heterogeneous tissue system supported by Harfmann BD, Schroder EA et al.

It was discovered that on mice and humans that the first exposure to light had a greater influence on circadian phase shifting than subsequent exposures. For flesh flies, mice, and people, phase response curves to light exposure intervals with a variety of durations were available as supported by the authors Beersma DG, Comas M et al [6]. The progression of phase across a long interval (hours) of light exposure was reconstructed for each of these 3 species by comparing the phase changes generated by pulses of different durations but beginning at the same circadian phase. According to the phase progression curves for flies, weak resetting resulted in the pacemaker stabilizing about InT18 (near subjective dusk) after enough light pulses. While delays could be as long as 18 h, the phase progression toward the end value never indicated advances longer than 7 h. It is possible to discern clearly between advances and delays in type-0 phase response curves by using the phase progression curve method. This split between delays and advances happened in Sarcophaga flesh flies when light exposure begins at InT0 (subjective midnight). Previous research in mice that showed phase shifts were more strongly produced at the start of a light pulse

than they were during subsequent light hours. Within one hour of exposure, the response had completely decreased. It is believed that response saturation, rather than mechanisms of light adaptation, was more responsible for the fluctuation. Response saturation, as opposed to light adaptation, was crucial to the circadian pacemaker's effective operation during natural entrainment. Phase progression curves with naturalistic light profiles could be a useful tool for comprehending pacemaker entrainment to natural light.

The circadian rhythms of salivary melatonin and cortisol were found to be disrupted in patients with allergic rhinitis. These results might also be contributive data to explain the pathogenesis of allergic rhinitis and they could be applicable as adjunctive therapeutic tools in the future and melatonin drugs might be an alternative in the therapy of resistant allergic rhinitis patients or allergic rhinitis patients who cannot use cortisol drugs. Patients with inflammatory illnesses of the upper airway tract, such as allergic rhinitis, rhinosinusitis, and nasal polyposis, might have sleep impairment. A disturbance was discovered in the levels of salivary cortisol and melatonin in those with allergic rhinitis. It's possible that allergic rhinitis-related sleep issues are what's causing the aberrant cortisol/melatonin ratio by Fidan P et al [8].

Chronic pain and sleep disruption are connected. Greater emotional distress, worse function, greater pain intensity, lower positive affect, and higher degrees of catastrophizing were all linked to more sleep disruption. According to cross-sectional mediation analyses, the significant direct effects of sleep disturbance on chronic pain intensity as well as the significant indirect effects of elevated emotional distress, lower positive affect, and greater catastrophizing associated with sleep disturbance both statistically contributed to the positive associations between sleep disturbance and chronic pain intensity. Similar to this, it was discovered that the associations between sleep disturbance and impaired function were statistically supported by both the significant direct effects of sleep disturbance on function as well as the elevated chronic pain intensity associated with these associations. Both direct and indirect pathways have shown a substantial relationship between chronic pain function and sleep disturbance. These findings were in line with a growing body of literature that discusses the potential importance of sleep disturbance in chronic pain sufferers and offered more evidence for including sleep disturbance in the diagnosis and treatment of chronic pain Burjes HJ, Burns JW et al [15, 16].

An emerging field of study known as chrono nutrition focuses on the close connection between endogenous circadian (24-hour) rhythms and metabolism. Circadian regulation of metabolic activity could be seen at all levels of an organism, including postprandial reactions and whole-organism physiology. Recent research has shown how circadian clocks regulated metabolism in important metabolic tissues as the liver, pancreas, white adipose, and skeletal muscle. One peripheral organ's tissue-specific clock disruption, for instance, could lead to obesity or interfered with the body's glucose balance. Insights into mechanistic processes gleaned from research on transgenic animals along with how these findings were being applied to the study of human genetics and physiology. The principles of chrono nutrition had already been shown to enhance human weight loss and were anticipated to improve both the general public's health and that of those suffering from metabolic disorders Johnston JD, Ordovás JM et al [21].

Numerous studies demonstrated the significance of circadian variation in the excretion of hormones, the sleep-wake cycle, the rhythm of the core body temperature, the tone of the autonomic nervous system, and the regularity of activity for both healthy and disease-causing processes Gögenur I [9]. The diurnal fluctuation in endogenous rhythms in connection to surgery is also receiving more study. The focus had been on the possibility that postoperative healing, morbidity, and mortality might be impacted by circadian variation in endogenous rhythms. Several research was carried out examining various endogenous rhythms and factors impacting these rhythms considering the paucity of studies that have examined these endogenous rhythms in connection to surgery. A series of research addressing various endogenous rhythms and factors impacting these rhythms. These different endogenous rhythms had been explored in relation to surgery. Additionally, it was analysed whether there was a relationship between postoperative circadian rhythm disruptions and recovery metrics and whether pharmacological administration of chronobiotics could hasten postoperative recovery. All the investigated endogenous rhythms showed irregular circadian cycles. The first night following both minor and major surgery, there was a delay in both the excretion of the melatonin metabolite (AMT6s) in urine and the endogenous rhythm of plasma melatonin. The length of the surgery was linked to this recovery time following major surgery. The first night after major surgery, the amplitude of the melatonin rhythm remained unchanged, but it grew the following night. The first night after minimally invasive surgery, the amplitude in AMT6s was decreased. Both major and small surgery resulted in a disruption of the rhythm of the core body temperature. After major surgery, the sleep-wake cycle changed, with REM-sleep lasting noticeably longer throughout the day and at night than it did before. After major surgery, the autonomic nervous system's balance was also altered, leading to a markedly higher number of myocardial ischemia events at night. Both mild and major surgery affected the circadian activity pattern. After major surgery, the amount of AMT6s excreted during the daytime rose on the fourth

postoperative day. The total amount of AMT6s excreted in urine related to sleep efficiency and wake time after sleep initiation, but not with the occurrence of postoperative cognitive dysfunction. After a laparoscopic cholecystectomy, it was demonstrated that the effects of melatonin replacement in patients who experienced less pain than the median level for three days. Systematically it was demonstrated that circadian disruptions are present in the release of hormones, the sleep-wake cycle, the rhythm of core body temperature, the tone of the autonomic nervous system, cardiac ischaemia, and the rhythm of activity after surgery. Circadian rhythm characteristics and indicators of the effectiveness of surgical sleep and recovery are correlated. Based on the current data, oral melatonin therapy during the first three nights following surgery cannot yet be universally advised for enhancement of sleep quality or other recovery characteristics. Future studies must look into whether it was warranted in subgroups or whether different perioperative treatment methods were utilized.

Moreover, the effect of muscle relaxants on emergency abdominal surgery patients with relation to the circadian rhythm proving that their frequency of elimination and duration evening time was lesser than during the morning indicating that a further approach on the assessment of melatonin release intra and post abdominal surgery from 18:00 to 24hr should be closely evaluated together with muscle relaxants. The use of atracurium benzilate is mostly effective in emergency abdominal surgery because by the mechanism of Hoffman it does not depend on whether the liver or the kidneys to get eliminated by the body and it can be alternative to rocuronium bromide which mechanism of elimination is through bile from the liver and urine by the kidneys post abdominal surgery for patients without regurgitation for the betterment of the temp of homeostasis in relation to any noticeable affect of the circadian rhythm on critically ill patients transported from surgery theatre to ICU on pro longed mechanical ventilation.

5. Conclusions

1. At TOF 75% using rocuronium bromide in the morning from 08:00am to 14:00pm a difference of 14mins was recorded as compared to the time interval of 15:00pm to 20:00pm for a first intubating dose of 0.4mg/kg.

2. At TOF 75% using atracurium bensilate in the morning from 08:00 to 14:00 a difference of 11mins was recorded as compared to the time interval of 14:00 to 20:00 for a first intubating dose of 0.4mg/kg.

3. It is clarified that the non-depolarizing muscle relaxants notably rocuronium bromide and atracurium benzilate in the evening time tend to be lesser in duration as compared to morning time under combined endotracheal anesthesia for emergency abdominal surgeries.

4. In emergency abdominal surgery patients the time of action of both atracurium benzilate with a difference of TOF 0 at 30.4 seconds and rocuronium bromide 63.9 seconds are higher than expected morning time from 08:00-14:00 and evening time from 15:00-20:00.

5. Circadian hours can indirectly react on the metabolism, medicines, neuro muscular function and on the expression of receptors, a big amount of rocuronium bromide (75%) absorbed by the liver and excreted without a change in bile and the rest is excreted through urine or turning into active metabolites.

6. Experimentally it can be that there is a circadian modulation of the hepatic circulation. It was demonstrated that melatonin a hormone secreted by the pineal gland responding to darkness is related to the regulation of circadian rhythms. The circadian clock functions by a 24hour rhythm that takes longer than 24 hours but resets every day by the sun's light/dark cycle [7]. By taking melatonin supplements can also shift the timing of the body's clock. Melatonin acts on the cholinergic system and can relatively be a matter of concern.

7. A severe anesthesiological protocol was maintained with high standards of control of temperature (especially the drugs which act on the neuro-muscular block), dosage and physiological monitoring [2].

8. We used only combined endotracheal anesthesia protocol together with sevoran and regardless of the fact that sevoran increases the duration of anesthesia.

9. It was also proven that propofol acts on the circadian hours and itself can be the reason of its changes. We demonstrated the clinical effect of evening hours in the duration of neuromuscular block of rocuronium bromide and atracurium benzilate.

10. Anesthesiologists must expect that the duration of muscle relaxants (rocuronii and atracurii) is lesser at evening after 14:00 as compared to morning hours also it was supported by the author Abasova.I.S that the duration of neuromuscular block rocuronium bromide will be 1/3 lesser during evening time as compared to morning and nighttime.

11. Importantly the pharmacodynamics and pharmacokinetics of rocuronium benzilate and Atracurium benzilate must be considered while used during night hours.

12. It is to be considered that due to some troubles of recovery from rocuronium benzilate in many patients, sugammadex is preferably used for its reversal [4,13,14].

13. Moreover, during evening time, the evaluation of the dose of rocuronium benzilate and Atracurium benzilate should be considered for security reasons.

14. Rocuronium bromide should be given a minimal dose to critically ill patients for there is residual neuromuscular block many hours after surgery or rocuronium benzilate can be replaced by atracurium benzilate because the later does not depend on any liver or kidney failure and is metabolized by the Hoffman mechanism.

15. An adequate dose of muscle relaxant should always be estimated for it is the first step for a smooth anesthesia [15,16,17].

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Review

The Relevance of the Use of NO-therapy in Traumatology and Rehabilitation Medicine

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Abstract: The purpose of this review is to familiarize with the possibilities of using NO-containing gas streams in traumatology and restorative medicine. It reflects the main mechanisms of action of nitric oxide, methods of exogenous delivery of NO and the clinical experience of Russian doctors on the use of NO therapy. The theoretical and clinical data presented in the review substantiate the effectiveness of the use of NO gas streams in injuries and their complications such as scarring processes and chronic osteoarthritis.
Nitric oxide is a gas molecule with a wide range of biological effects - bactericidal, vasodilating, pro- and anti-oxidative, pro- and anti-apoptotic and pro-proliferative. It also has the ability to activate neutrophils and macrophages, potentiate collagen synthesis, which significantly accelerates full-fledged regeneration.

Keywords: NO – therapy, rehabilitation therapy, nitric oxide, NO – containing gas flow.

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1. Introduction

According to data from (Sheu et al 2016) in the USA annually, in 4.3 million cases, injuries sustained at sports facilities or in places of active recreation required a doctor's consultation, while 3.2 million people repeatedly sought medical help. In approximately 230,000 cases, patients required hospitalization. Thus, athletes and people who lead an active lifestyle make up a fairly large part of the patients of traumatologists and sports doctors [1]. The need for daily training, a long period of rehabilitation, and high risks of post-traumatic complications require doctors to search for new methods of helping this group of patients.

Nitric oxide (NO) is a well–known gaseous molecule that regulates many physiological and pathophysiological processes in the body, which made it possible to single out a separate clinical direction – NO therapy. Currently, exogenous nitric oxide is used in surgery, oncology, dermatology, ophthalmology, otolaryngology and many other specialties (Huerta S., 2015, Shekhter A.B., 2020, Chernysheva M. M., 2018).

Currently, it is known that NO synthases are represented by three isoenzymes that are encoded by different genes, have different localization and are involved in a variety of physiological and pathological processes. Two isoenzymes, endothelial (eNOS) and neuronal (nNOS) are constitutive, they provide continuous formation of low concentrations of NO through cyclic guanosine monophosphate (cGMP) in vascular endothelial cells and neurons, respectively. Inducible NOS (iNOS) is produced only in response to the action of pathogens - lipopolysaccharides and proinflammatory cytokines (for example, interferon, INF-α, tumor necrosis factor (TNF)), etc.), which are generated by neutrophils and macrophages in response to damage [4, 5]. In the wound and in inflammatory processes, NO levels increase in the first hours after injury and reach a peak on day 2 [3, 6–9]. It is known that NO derivatives can play an anti-inflammatory role (Feelisch M., 2008, Hsu C. C. et al., 2017). Nitric oxide has direct and indirect effects, which is determined by its concentrations in tissues [2, 10, 11].

The main causes of nitric oxide deficiency in wounds are hyperglycemia, insufficiency of the synthetic cell system, weak or excessive exogenous stimulation of immune system cells, which is accompanied by impaired function of chemokines and cytokines necessary for leukocyte and macrophage migration, synthesis of regenerative factors, angiogenesis and fibroblast activation [12-14]. In view of this, the study of exogenous ways to increase the concentration of NO in wounds is an effective and promising direction in medicine.

The purpose of this review is to analyze the works devoted to the problem of treatment of traumatic injuries, including those related to sports with the help of exogenous NO.

2. Experience

Experience of practical application of exogenous NO-therapy for injuries:

The use of NO-therapy has already been studied in patients with moderate to severe rheumatoid arthritis (n =76), in whom traditional treatment was insufficiently ineffective. The course of therapy using the plasma-chemical device "Plason", which generates high concentrations of nitric oxide (500 ppm), included 10-12 daily procedures, for 5-8 minutes for each affected joint. The treatment was carried out through intact skin. Most patients repeated the same course after 3-4 months. As a result, patients noted the complete disappearance of pain, edema, hyperemia, restoration of joint mobility after 5-8 procedures, laboratory parameters normalized in the same time period. The patients did not take anti-rheumatic drugs, they had no relapses a year after treatment. link.

The use of Plason in the same regimen was also successful in 83% of patients with various forms of osteoarthritis with synovitis of the knee, shoulder and hip joints. Patients (n = 43) noted a decrease in the severity of edema after 2-3 procedures and pain after 3-5 procedures. Joint mobility improved after 4-10 procedures. The positive effect persisted for a year after treatment, which made it possible to reduce the dose of drugs (Vasilets V. N. et al., 2015).

The technique was used in both football players with bruises (n = 19) and track and field runners with tendovaginitis (n = 12). Before that, athletes received traditional physiotherapy procedures for 2-6 weeks, but they did not always have a pronounced positive effect. Blowing of the NO-CGF grass area (containing gas flow) was carried out for 10 seconds per 1 cm2. The course of therapy was 6-8 days. As a result, pain intensity decreased statistically significantly after the first session. After the fourth session, the athletes were able to start full-fledged training [61].

NO-therapy was performed in patients with injuries and inflammatory changes in the ligaments and tendons of the knee and shoulder joints, feet, menisci of the knee joint; muscles of the lower leg, hips and shoulders. NO-CGF (containing gas flow) was used in the maximum mode, for 10-15 seconds per 1 cm2 of the affected area. The course of therapy included 8-12 sessions. Significant pain relief during movement and reduction of edema was observed after 2-3 sessions. After 4-6 sessions of NO-therapy, the range of motion in the joints was restored and athletes could resume training [66].

In patients with injuries to the tendons of the hand with an open fracture of the clavicle, an open fracture of the mandible, intraoperative tissue treatment with a Plason apparatus was performed in the mode of coagulation and stimulation. In the early postoperative period, the NO-therapy regimen was used. As a result, patients noted a decrease in soft tissue edema in the area of surgery and a decrease in the intensity of pain syndrome. The use of NO-CGF for wound treatment after removal of metal structures (8 patients) allowed to reduce the number of hematomas and seromas in the postoperative period [65].

NO-therapy was performed intraoperatively for 1-3 minutes with plastic surgery of the tendons of the hand (3 cases) and tendon transplantation from the forearm (2 cases). In the postoperative period, the Plason device was used in the mode of stimulation and NO-therapy for 2-3 minutes daily. As a result, in all cases, wound healing occurred by primary tension, the severity of edema and pain syndrome was moderate [46].

3. Discussion

The use of NO-therapy has shown its effectiveness in traumatological patients, including those with various forms of osteoarthritis, as well as patients with rheumatoid arthritis. At the same time, these nosologies have a high social significance, since they often occur in young patients, especially in athletes, which is manifested by pain, functional disorders and a decrease in physical activity. However, the role of nitric oxide in these diseases is not fully defined. At the cellular level, the manifestations of posttraumatic osteoarthritis are characterized by apoptosis of chondrocytes and osteoblasts, the release of a large number of pro-inflammatory mediators (IL-1, IL-6, TNF-I and others), changes in the extracellular matrix (decrease in glycosaminglycans, collagen, increased activity of matrix metalloproteinases) (Punzi L. et al., 2016, Sward P. et al., 2013, Golovach I. Yu., & Egudina E. D., 2019).

It is known that in the acute phase of the inflammatory process, surface zone chondrocytes actively express an enzyme involved in the synthesis of NO–inducible NO-synthase (iNOS). iNOS formation is also induced by mechanical and biochemical factors, including inflammatory mediators such as IL-1α and TNF-Ɩ. NF-κβ (Vuolteenaho K. et al., 2007). At the same time, specific inhibition of iNOS and nitric oxide synthesis reduces the intensity of catabolic processes implemented by IL-1a, matrix metalloproteinases and peroxynitrite.

At the same time, NO derivatives can play an anti-inflammatory role and, according to some authors, do not matter in the progression of joint lesions (Feelisch M., 2008, Hsu C. C. et al., 2017). In particular, the introduction of exogenous nitric oxide or activation of iNOS contributed to the

synthesis of collagen types I and II, an increase in proteoglycans in tissues (Xia W. et al., 2004, Shi H.P. et al., 2007, Abramson S., 2008).

Moreover, in most studies on the role of nitric oxide in the pathogenesis of osteoarthritis, we are talking about the primary etiology of the disease, and not about post-traumatic (Studer R. et al., 1999, Vuolteenaho K. et al., 2007, Leonidou A. et al., 2018). Studies on the effect of NO-containing gas flow to stimulate the regeneration of articular cartilage in post-traumatic osteoarthritis have not yet been conducted. It would be interesting to study the functional activity of joints before and after treatment with NO-containing gas streams (including long-term results of articular cartilage regeneration in an experiment) in experimental modeling of post-traumatic osteoarthritis. In addition, conducting a comprehensive morphological, morphometric and immunohistochemical study will allow us to study the possibilities of reducing inflammation and stimulating the regeneration of articular cartilage with NO-therapy, as well as to justify the effectiveness of NO-therapy in the treatment of knee joint and periarticular injuries.

The study of functional and subjective changes in the state, as well as the dynamics of interleukin levels IL-1, IL-6, IL-8, IL-10, C-reactive protein in patients with posttraumatic osteoarthritis before and after nitric oxide therapy can contribute to the development of practical recommendations for the use of nitric oxide in traumatology and rehabilitation medicine.

5. Conclusions

According to the literature, NO has a wide range of biological effects and can promote tissue regeneration in a short time. NO-therapy has found its application for the treatment of various pathological conditions and diseases. However, the possibility of using NO-therapy in restorative medicine is an urgent, but extremely poorly studied problem that requires comprehensive studies to determine the leading mechanisms of action of nitric oxide, optimal therapy regimens, and to determine indications and contraindications for its use.

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Article

Dynamic Changes Of Physiological And Psychological Parameters Of Young Persons As Asthenia Risk Factors

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Abstract: Asthenic syndrome is the most important problem of the modern stage of development of human society, which is the most important component of many pathological conditions or risk factors for diseases. The purpose of the study is to determine some physiological and psychological parameters in young people in dynamics at different levels of intellectual load and evaluate their role in the formation of asthenic syndrome.
Materials and Methods: The study involved 160 3rd year students of the Medical Institute of Moscow State University. N.P. Ogarev, divided into four groups according to the type of higher nervous activity (HNA), based on the indicators "Extraversion / Introversion" and "Neuroticism", determined by the Eysenck scale. We assessed the characteristics of emotional balance, functional parameters of autonomic regulation, features of cognitive functions in young people in different periods of training load.
Results: the indicator of neuroticism correlated with the severity of asthenic syndrome in young people. Persons with a high level of neuroticism more often revealed maladjustment of mental processes, a decrease in cognitive functions, and an increase in emotional instability during the period of intense intellectual loads. After a period of increased intellectual load, asthenia occurs significantly more often in females. Features of autonomic regulation have little effect on the development of asthenia. The exceptions were individuals with a high level of neuroticism. In these groups, the stress of hemodynamic mechanisms was occurred frequently.

Keywords: young people, cognitive functions, asthenic syndrome, autonomic regulation, risk factors, stress resistance.

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1. Introduction

Asthenic syndrome is the most important problem of the modern stage of development of human society. This is a state on the border between health and disease, depleting the functional and adaptive reserves of the body (factors of immunobiological resistance, the ability to perform intensive physical and intellectual labor, the general reactivity of the body), and it is also a risk factor for the development of organic pathology on the part of many organs and systems [1]. Basically, the etiological factor in the development of asthenia is long-term stress, which is most susceptible to young people, since an integral part of their lifestyle is training in educational institutions of higher and secondary vocational education. A particularly high level of stress in students is observed during the session, when assessing the knowledge they have gained and assessing their competence. To prevent complications of asthenia, it is necessary to diagnose its development in students in a timely manner, as well as to have an idea of the predisposition to it, depending on the type of higher nervous activity (HNA), psychological and functional individual characteristics. In recent years, a progressive direction of state policy in the field of education is the personification and development of individual training programs in accordance with the personal characteristics of students [2]. In this regard, the most important task is to determine the influence of physiological and psychological factors on the development of asthenia and stress resistance.

The goal of our study was to determine the risk factors for the development of asthenic syndrome based on the study of the characteristics of emotional balance, the functional parameters of autonomic regulation, and the characteristics of cognitive functions in young people with different types of higher nervous activity in different periods of academic load.

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The volume of original articles, literature reviews, and articles of the section "To Help a Practical Physician" should not be less than 7 pages and should not exceed 15 pages for original articles, from 10 pages to 25 for – review articles, and for notes from practice – from 5 to 10 pages. The article should have no more than 6 figures and / or 6 tables. The editors reserve the right to shorten articles.

Original articles should have the following sections: headnote, material and methods, research results and discussion, conclusion or inference.

Authors should use English-language scientific terminology and not use "tracing-paper" of terms transcribed from foreign words. The abbreviation of words and names, in addition to the generally accepted abbreviations of measures, physical and mathematical quantities and terms, is allowed only with the initial indication of the full name. Highly specialized terms should be deciphered. We do not recommend using abbreviations in the title of the article.

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The names of the microorganisms are written in Latin and in italics.

Requirements for the presentation of statistical analysis:

The methods of statistical analysis used in the study should be described in the subsection "Statistical analysis" at the end of the section "Materials and Methods". It is necessary to describe statistical methods in as much detail as is necessary to assess their adequacy and to confirm the results obtained by knowledgeable readers, subject to access to relevant data. Description and presentation of the results of statistical analysis should comply with the Guide "Statistical analysis and methods in the published literature"

The list of literature attached to the article should include the works of domestic and foreign authors over the past 5-15 years. At least 25 sources are cited in the original articles and at least 50 in the reviews. At the same time, more than 50% of the cited papers should be printed over the past 5 years. The list is compiled according to the rules for compiling bibliographic references (authors' bibliography), taking into account the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" manuscripts submitted to the biomedical journals (see Appendix).

Bibliographic references should be numbered, in the text they are given in square brackets in accordance with the list of references. The author is fully responsible for the accuracy of the references.

References to thesis and abstracts are not recognized by the international community, and therefore should not be given.

Tables should contain generalized and statistically processed data. Each table must have a number and a title. Units are given in the SI system.

Example: Surgical correction of the curved nasal septum (CNS), or septoplasty, is one of the most common rhinosurgical operations. Nosebleeds, nasal septum hematoma, acute rhinosinusitis and pain syndrome are considered the most frequent complications after septoplasty [1, 2]. Septoplasty consists of the muco-suprachondral and/or muco-periosteal leaves separation and curved areas of the cartilaginous and/or bony parts of the nasal septum removal. As a rule, smooth sections of the extracted cartilaginous part of the nasal septum are placed back between the two leaves of the epiglottis. At the same time, the nasal cavity is tamponed after surgery to avoid complications [2].

2. Material and methods

The study involved 160 3rd year students of the Medical Institute of Federal State Budgetary Educational Institution of Higher Education «National Research Ogarev Mordovia State University», divided into four groups according to the type of higher nervous activity (HNA), based on the indicators «Extraversion/Introversion» and «Neuroticism» determined on the Eysenck scale: group 1 (n=43) - high level of extraversion, low level - neuroticism, group 2 (n=35) - high level of extraversion, high level - neuroticism, group 3 (n=49) - high level of introversion, high level - neuroticism, group 4 (n=33) - high level of introversion, low level - neuroticism.

All groups were comparable in age composition, the average age in the groups was 20,12±0,19 years. Students underwent a survey conducted in 3 stages, under different conditions of basic study load and stress level (stage 1 - in the middle of the semester, stage 2 - during the session and stage 3 - after the session). The gender distribution is characterized by the predominance of women in all groups (in group 1 – 39.50% (17) men and 60,50% (26) women, in group 2 – 14,29% (5) men and 85,71% (30) women, in group 3 – 10,20% (5) men and 89,80% (44) women and in group 4 – 30,30% (20) men and 69,70% (23) women).

Spielberger's State-Trait Personality Inventory was used to assess emotional states. Indicators of attention were assessed according to the method "Proofreading test" in the letter version.

To assess the level of short-term memory, online tests "memory for numbers" and "memory for images" were used. Using traditional methods, anthropometric data of students were assessed: weight, height, blood pressure, heart rate. To determine the level of asthenia, a Multidimensional Fatigue Inventory (MFI-20) was used.

The obtained data were processed by methods of medical statistics (assessment of the normality of the distribution, parametric t-test, Mann–Whitney U test, $\chi 2$ – for assessing the distribution of relative values, r – correlation coefficient; descriptive statistics with calculation of mean values and confidence intervals). The differences were considered reliable with a probability of an error-free forecast of more than 95% ($p<0.05$).

3. Results and discussion

The study of asthenia indicators depending on the type of HNA in young people was carried out at the third stage of the study after a period of intense intellectual load. The following results were obtained. In all groups, after a period of intense intellectual load, average indicators of asthenia were recorded, exceeding the reference values of the physiological norm. The determination of the total percentage of asthenia showed its maximum value in group 3 (59,07±4,57), which indicates the presence of severe asthenia, and the minimum in group 1 (35,19±4,00), which indicates the presence of moderate asthenia. The use of a scoring system for assessing general asthenia showed that its maximum value was also determined in group 3 (16,88±1,64), and the minimum in group 4 (10,41±0,75). It was revealed that the value of this indicator was significantly lower in group 4 compared to groups 2 and 3 by 27,19% and 62,15%, respectively ($p<0.05$). It should be noted that groups 1 and 4 were characterized by a low level of neuroticism, which probably increases the student's stress resistance during a period of high intellectual stress and reduces the likelihood of developing asthenia.

The study of the indicator of reduced activity revealed that its maximum value was determined in group 3 (17,92±2,32), and the minimum in group 4 (9,95±0,79). In addition, it was determined that the value of this indicator is significantly higher in group 3 compared to groups 2 and 4 by 39,62% and 44,48%, respectively ($p<0,05$).

The definition of the indicator of reduced motivation showed that its maximum value is observed in group 1 (13,26±2,44), and the minimum in group 4 (8,55±0,69). It was also revealed that the value of this indicator was significantly higher in group 3 compared to groups 2 and 4 by 31,03% and 41,03%, respectively ($p<0,05$).

Evaluation of the indicator of physical asthenia revealed the following patterns: its maximum value is observed in group 3 (17,36±2,18), and the minimum in group 4 (8,09±0,59); The value of this indicator is significantly lower in group 4 compared to groups 1, 2 and 3 by 26,58%, 70,70% and 114,59%, respectively, and in group 3 it is significantly higher than in group 2 by 41,07% ($p<0,05$).

The study of the indicator of mental asthenia showed that its maximum value is observed in the 3rd group (14,58±2,01), and the minimum in the 4th group (8,09±0,77); The value of this indicator is significantly lower in the 4th group compared to the 1st and 3rd groups by 62,05% and 80,10%, respectively, and in the 3rd group it is significantly higher than in the 2nd group by 32,19% ($p<0,05$) (Figure 1).

Thus, the greatest severity of asthenia was observed in respondents with a high level of neuroticism (group 3), and the lowest in persons with a low level of neuroticism (group 4). The level of extra-/introversion was less important in the formation of asthenia. The data obtained were confirmed by correlation analysis. In addition, it was found that in females, a high level of neuroticism and asthenia are significantly more common, which was also noted by Royston AP, Rai M and others [3].

The main idea of the study was to determine the emotional, cognitive and physiological characteristics in individuals with a high level of neuroticism to determine the most significant factors in the formation of asthenia in a situation of stress.

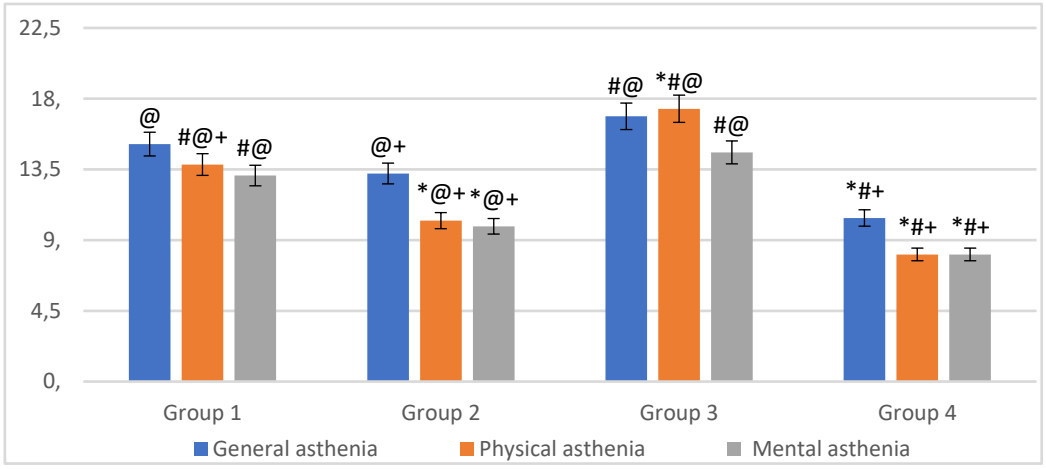

Figure 1. Indicators of general, physical and mental asthenia in young people with different types of HNA (hereinafter: * - the significance of the difference from group 1; # - the significance of the difference from group 2; + - the significance of the difference from group 3; @ - the significance of the difference from group 4; the statistical significance of the differences at p<0.05)

The study of anthropometric parameters showed some differences in height and weight indicators between groups, which is determined by the sexual heterogeneity of the groups. The estimated sample corresponded to the classical ideas about the anthropometric differences between female and male organisms.

A study of the mass index (BMI) showed higher values of this parameter in group 1 compared to group 3 by 8,73% (p<0,05). The highest index values were found in groups 1 and 4 (23,82±1,2 and 23,25±0,8 kg/m2, respectively), which is associated with a large number of men in these groups; The smallest – in groups 3 and 2 (21,74±1,0 and 21,78±0,9 kg/m2, respectively) – the greater number of women in these groups.

In the study group of young people, overweight was significantly more often noted in males. This indicator did not change in the dynamics of the study.

The determination of the duration of sleep demonstrated a slight lengthening of sleep at the second stage of the study (during the session) relative to the first in all groups, regardless of the characteristics of HNA. At the same time, sleep duration differed between groups: at the first stage of the study (in the middle of the semester), in group 1, sleep duration was longer compared to group 3 by 6,72% (p<0,05); At the second stage (during the session), there was a significant predominance of sleep duration in group 1 compared to group 2 by 16,06% (p<0,05), a longer sleep duration in group 1 compared to group 3 by 9,26% (p<0,05) and in group 4 compared to group 2 by 14,20% (p<0,05).

The study of the functional features of the cardiovascular system and its regulation showed significant differences in the studied characteristics in the groups.

The definition of the Kerdo Vegetative Index showed showed its maximum mean in group 2 and the minimum in group 4. Thus, in group 2, its value was significantly higher compared to groups 1, 3 and 4 by 48.83%, 49.66% and 71.25%, respectively (p<0.05), which is associated with the predominance of persons with predominant sympathetic influences in group 2. The percentage distribution of individuals with a predominance of activity of various parts of the autonomic nervous system is presented in Figure 2.

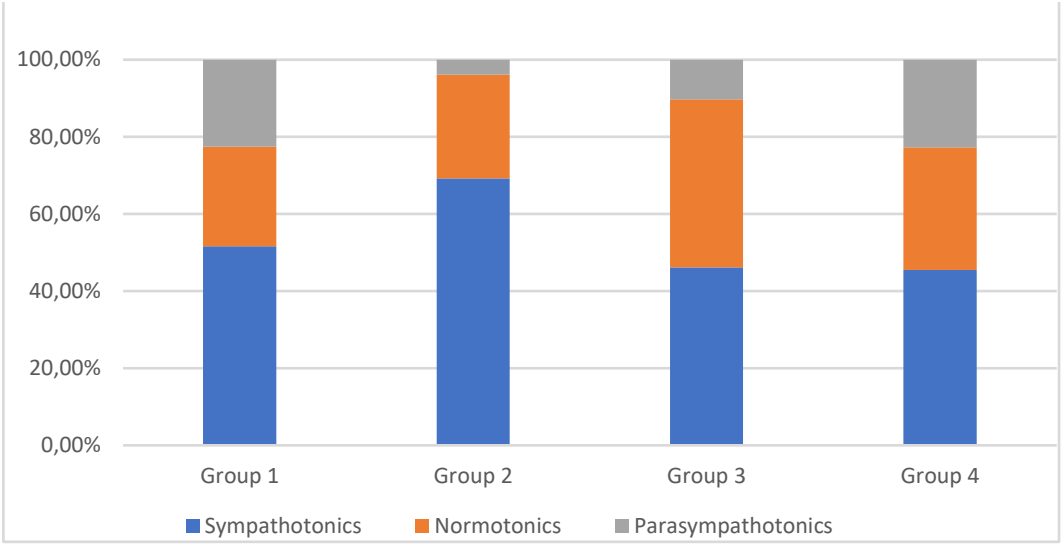

Figure 2. Percentage distribution of individuals with a predominance of activity of various parts of the autonomic nervous system

Measurement of systolic blood pressure (SBP) in the respondents of the study groups showed a normal average value of this indicator, however, in group 2 this indicator was significantly higher than in group 1 by 4,18% and comparable to group 3. It should be noted that groups 2 and 3 are characterized by a high level of neuroticism, which is probably due to the predominance of excitation processes in the central nervous system.

The determination of diastolic blood pressure (DBP) in the respondents of the study groups also revealed slight fluctuations in the values in all groups within the reference figures.

The calculation of pulse pressure (PP) showed its highest value in group 4, and the lowest in group 2. Thus, in group 4, its value is significantly higher compared to groups 1, 2 and 3 by 14,90%, 30,64% and 12,20%, respectively ($p<0,05$).

A study of cognitive functions showed the following results. The study of the volume of short-term memory did not reveal significant differences between the groups and dependence on the type of higher nervous activity at stage 1 (in the middle of the semester at the basic level of study load). The average value of short-term memory in all groups ranged from 86,31±2,13% to 89,06±1,97% of the amount of information provided.

At the second stage of the study, during the period of intense intellectual load (session), significant differences in the volume of short-term memory were revealed - the highest values were determined in groups 2 and 4 (87,75% and 84,27%, respectively), and the lowest indicator in group 3 (68,42%). When comparing the data of stages 1 and 2, a decrease in the amount of short-term memory in groups 1 and 3 by 10,38% and 21,56% ($p<0,05$), respectively, was revealed, as well as a slight increase in this indicator in group 2. It should be noted that individuals with high levels of introversion and neuroticism (group 3) are the least stress-resistant, which is probably reflected in a decrease in short-term memory during stress.

When assessing the indicators of attention, it was determined that the indicators of speed (productivity) of attention and accuracy of work (the third option, according to Whipp) were the same in all groups of respondents (there are no statistically significant differences) - the average values in all groups were from 4,13±0,23 c.u. to 4,61±0,17 c.u. and from 0,83±0,04 c.u. to 0,89±0,03 c.u., respectively. The study of the work accuracy index for the first and second options revealed a significant predominance of the index in group 1 compared to group 2 by 13,78% and 18,49% ($p<0,05$), respectively. Both groups are characterized by extroversion, but the level of neuroticism in the first group is significantly lower than in the second, which probably affects the accuracy of the work. This factor also showed its significance in the study of the coefficient of mental productivity, it was found that its value was significantly higher in group 1 compared to group 2 by 27,10% ($p<0,05$). Determination of the indicators of the volume of visual information and the speed of information processing revealed a significant predominance of these indicators in group 1 compared to group 2 by 11,38% and 18,36%, respectively ($p<0,05$). In groups 4 and 3, differing in the introversion of the respondents, the value of these indicators is approximately the same, which indicates the influence of the neuroticism index on the characteristics of attention only in conjunction with extra/introversion.

A study of procrastination at the first stage of the study revealed that its indicators were the same in all groups of respondents. Their average values in all groups ranged from 49,37±0,71% to 51,29±0,67%, which indicates a low level of procrastination in all groups.

The study of emotional balance revealed the conjugation of the dynamics of its indicators in different periods of intellectual load with the peculiarities of the HNA of young people. When assessing the respondents' reactive states, such as interest, aggression, anxiety and depression at different stages of the study at different levels of load, the following patterns were revealed: at the first stage of the study, respondents of groups 1 and 4 (with a low level of neuroticism) showed a higher level of interest than subjects from groups 2 and 3 (with a high level of neuroticism). The lowest value of this indicator was found in group 3 (19,04±0,78). Dynamic observation showed a decrease in the indicator of interest during the session in groups 1, 3 and 4 with its increase in group 2 by 8,41%.

Evaluation of the aggression indicator revealed that at the first stage of the study, respondents in groups 1 and 4 showed a lower level of aggression than those in groups 2 and 3. The highest level of this indicator was found in group 2 (14,37±1,24). The change in the dynamics by stages is characterized by a decrease in this indicator during the period of intense intellectual load and stress in groups 1 by 2,34%, 3 by 13,30% and 4 by 5,64% and its increase in group 2 by 7,83%.

The study of the anxiety indicator showed the following patterns: at the first stage of the study, respondents in groups 2 and 3 showed a higher level of anxiety than those belonging to groups 1 and 4. The highest level of this indicator was determined in group 3 (21,49±1,14). Dynamic observation showed a decrease in this indicator during the session in groups 1 – by 12,48% and 4 – by 12,83%, with a slight increase in groups 2 and 3.

When determining the depression index, its maximum level was found in group 3 (17,31±0,87). At stage 1 of the study, at the baseline level of study load, respondents in groups 1 and 4 demonstrated a significantly lower level of depression than those assigned to group 3 by 29,39% and 23,75%, respectively.

During the second stage, with an increased level of stress and stress, the difference in the depression index in the ratio of groups 1 and 4 to group 3 increased and amounted to 47,10% and 53,62%, respectively ($p<0,05$). This indicator remained the highest in the 3rd group (18,02±1,14). Dynamic observation showed a decrease in this indicator during the session in the 1st group by 9,14% ($p<0,05$), the 4th – by 19,35% ($p<0,05$) and its increase in the 3rd group by 4,16%. (Figure 3).

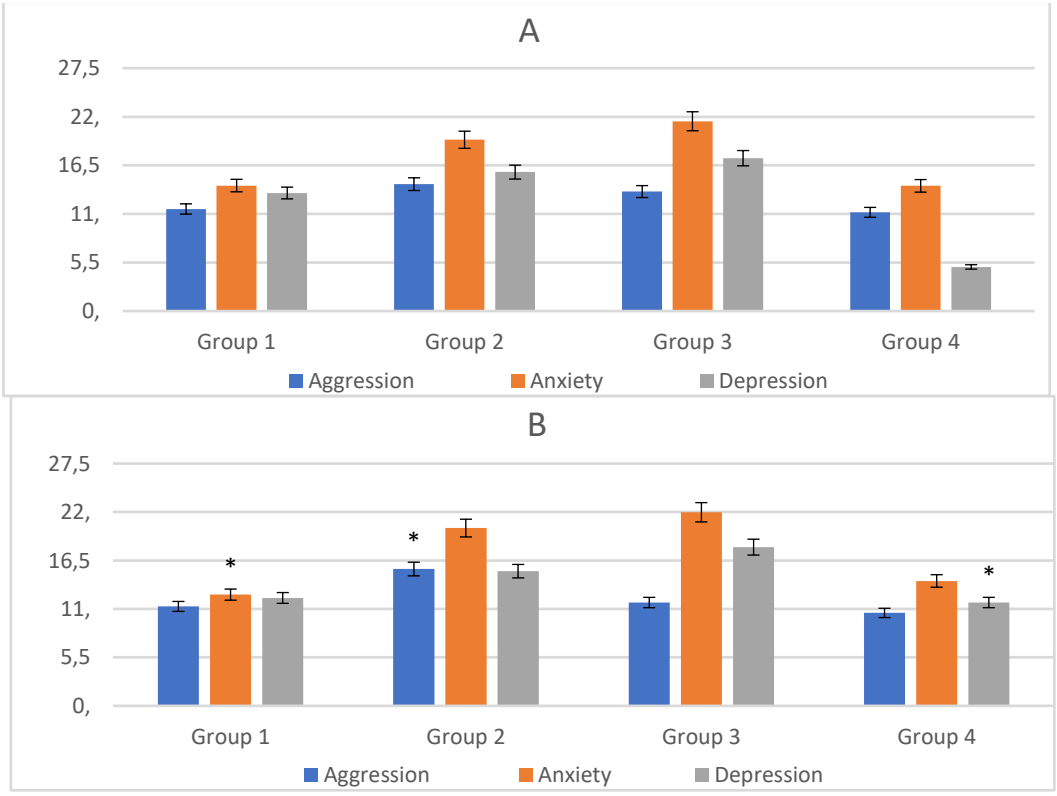

Figure 3. Indicators of aggression, anxiety, depression in young people with different types of GNI (A - during the period of basic intellectual load, B - during the period of intense intellectual load; * - the reliability of the difference between the observation periods at $p<0,05$)

Evaluation of individual personality characteristics, such as curiosity, aggressiveness, anxiety and depression, revealed generally similar patterns in the dynamics of these indicators and their differences between groups, as in similar reactive states.

Our data are consistent with the results of other researchers that an increase in depression and depressiveness during the session correlated with an increase in the level of asthenia, which was also noted in the study by Kraaij V, Bik J, Garnefski N. [3] and Milrad SF, Hall DL and others. [4,5] It was found that individuals with a high level of introversion and neuroticism are characterized by a high level of anxiety and depression, which was also established in the study by Shirahama M, Terao T et al. [6]

The calculation of the emotional balance indicator for groups of reactive states showed the following relationships: the emotional balance in terms of interest was approximately the same in all study groups at the first stage of the study (no statistical significance was revealed) - its average value ranged from 0,75±0,03 to 0,84±0,03 c.u. Dynamic observations revealed a decrease in this indicator in group 3 by 10,14% and an increase in group 2 by 8,54%. Interest characterizes the student's motivation for learning activities, a decrease in motivation during the period of knowledge control may indicate a maladaptation of mental processes against the background of stress.

The study of emotional balance in terms of aggressiveness both in the middle of the semester and during the session did not reveal significant differences between the groups. In general, this indicator was less than 1, which can be characterized as lower indicators of the reactive state relative to the basic characteristics of the individual, which indicates adequate psycho-emotional adaptation to the educational process.

The determination of emotional balance by the anxiety indicator also revealed that it was approximately the same in all study groups at the first stage of the study (no statistical significance was revealed) - its average value ranged from 1,11±0,05 to 1,19±0,06 c.u. Regardless of the period of the study, young people showed an increased value of this indicator as a reactive state, which indicates a certain level of stress even during a period of moderate academic load. Similar results were obtained in determining emotional balance in terms of depression.

5. Conclusions

Our results have revealed a direct correlation between asthenia and the level of neuroticism in young people. Asthenia is significantly more common in females. The level of asthenia does not depend on the predominance of the tone of various parts of the autonomic nervous system in the regulation of the cardiovascular system, but in individuals with a high level of neuroticism, the predominance of sympathetic adrenal influences is more often recorded. In persons with a high level of neuroticism during the period of intense intellectual stress, there is a maladaptation of mental processes, which is associated with a decrease in cognitive functions and an increase in emotional instability and correlates with the severity of asthenia after exercise.

Author Contributions: Conceptualization, T.V.; methodology, T.V. and N.M.; formal analysis, T.V., L.A., E.T, A.S.; investigation, L.A., E.T, A.S.; data curation, D.P.; writing—original draft preparation, L.A., N.M, T.V..; writing—review and editing, N.M.; visualization, L.A.; supervision, T.V.; project administration, T.V. All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Article

The Relationship of Disorders in the Hemostasis System with Changes in Homeostasis in Conditions of Progressive Inflammation

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Abstract: The urgency of the problem of acute peritonitis in surgical practice is due to the annual increase in morbidity, a high number of complications, therapeutic complexity and mortality. **Materials and methods**. The material of the study was 45 patients with acute peritonitis, who were divided into 3 groups depending on the course of pathology after surgery. The first group (n=15) – without complications, the second (n=15) – with wound complications, the third (n=15) – with tertiary peritonitis and sepsis. In addition to standard research methods, a number of laboratory tests are included to determine the severity of intoxication, oxidative activity, the state of the blood coagulation system, and the functional state of the liver. The study period is the 1st, 5th, 10th postoperative day. **Results**. The results showed that in the early period after surgery in patients with acute peritonitis, the state of hypercoagulemia, inhibition of fibrinolysis correlate with lipid peroxidation, endogenous intoxication, and violation of the functional status of the liver. With effective therapy, during the early postoperative period, the state of the hemostasis system and homeostasis indicators are corrected against the background of restoration of the functional status of the liver. With the aggravation of the phenomena of inflammation in the early postoperative period and the development of complications, there is a progression of changes in the studied indicators of homeostasis and hemostasis with further inhibition of the functional state of the liver. With the development of tertiary peritonitis and sepsis, the hemostasis system is modified in the form of hypocoagulemia and activation of fibrinolysis against the background of a sharp increase in endogenous intoxication, lipid peroxidation and greater inhibition of the functional status of the liver, including from its hemostasis-regulating component. **Conclusions**. The obtained results indicate the presence of a reliable correlation of disorders in the hemostasis system with changes in homeostasis in conditions of progressive inflammation.

Keywords: Peritonitis, liver, intoxication, lipoperoxidation, hemostasis.

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1. Introduction

By now acute peritonitis (AP) is considered one of the most life-threatening pathologies in emergency surgery. The relevance of AP lies in the high prevalence, polyetiology, complexity of the pathogenetic process, rapid progression, high mortality [1].

According to the literature, the death rate in acute peritonitis is 5–15%. However, with the progression of AP and the formation of complications (sepsis, shock), the mortality rate reaches 96–100 % [2].

Undoubtedly, the main reason for the decrease in the effectiveness of AP treatment seems to be insufficient knowledge of the mechanisms of its pathogenesis. Much attention has been paid to this issue recently. It was revealed that the basis of AP is: bacterial translocation, the development of endogenous intoxication, activation of proinflammatory cytokines, enteral distress syndrome,

vascular and hemostatic disorders (activation of platelet aggregation, increased vascular permeability, tissue hypoxia), the development of disseminated intravascular coagulation, etc. This can lead to multiple organ failure and death of patients [3, 4]. Modern data obtained by conducting in-depth studies have revealed a number of new pathogenetic mechanisms of the disease [5].

It should be noted that so far there has not been a significant breakthrough in understanding the role of the hemostasis system in the progression of the disease and homeostasis disorders in acute peritonitis. Therefore, the scientific search for an in-depth study of the pathogenesis of the disease with an emphasis on key mechanisms continues [6].

The purpose of the study. To establish the relationship of disorders in the hemostasis system with homeostatic modifications and the functional status of the liver with progressive acute inflammation.

2. Patients and Methods

2.1. General characteristics of patients

A clinical and laboratory study of 45 patients with acute peritonitis was conducted. The scientific work was carried out according to the ethical aspects of clinical research.

Inclusion criteria: clinical, laboratory and instrumental confirmation of the diagnosis; gender – female and male; age – 20 – 60 years; mild comorbidities; treatment – surgical.

Exclusion criteria: age – younger than 20 and older than 60 years; presence of severe concomitant diseases (infectious, oncological, somatic, mental).

The examined patients were divided into 3 groups depending on the course of pathology after surgical therapy. The first group (n=15) was without complications, the average age was 50.3±2.47 years, there were 9 men (60.0%) and 6 women (40.0%). The second (n=15) was with wound complications, the age was 60.5±3.81 years, there were 8 men (53.3%), and 7 women (46.7%). The third (n=15) – with tertiary peritonitis and sepsis, age – 66.8±3.72 years, men – 10 (66.7%), women - 5 (33.3%).

Causes of acute peritonitis: perforated appendicitis (12 (26.7%)), perforated gastric and duodenal ulcer (11 (24.4%)), perforated cholecystitis (5 (11.1%)), acute intestinal obstruction (13 (28.8%)), strangulated hernia (4 (8.9 %)).

Surgical intervention was performed for patients upon admission to the clinic and after preoperative preparation. It consisted in laparotomy, elimination of the cause of pathology, sanitation and drainage of the abdominal cavity and intestinal decompression (according to indications).

In the period before and after surgical treatment, patients were prescribed therapy, which was carried out according to clinical recommendations, which included antibacterial agents, infusion drugs, antispasmodics, painkillers, antihistamines, etc.

The study included relatively healthy people (n=15) of both sexes, aged 22-55 years.

2.2. Research methods.

Assessment of the severity of patients on the APACHE-II scale and the Mannheim Peritoneal Index (MPI). In addition to standard research methods, a number of biochemical analyses are included to determine toxemia (by the content of medium-weight molecules (MWM 280), toxicity index (TI)), oxidative stress (by the level of malondialdehyde (MDA) and diene (DC) conjugates), the state of the coagulation system (by the magnitude of the parameters of thromboelastography (TEG® 5000 Thrombelastograph® (USA)): reaction time (R), coagulation index (Cl)), liver function (by activity of alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT))in blood serum). The duration of the study is the 1st, 5th, 10th postoperative day.

2.3. Statistical analysis.

Statistical processing of the results was performed using Microsoft Office 2013, Excel Office 2013 and IBM SPSS Statistics 22 programs and using the Kraskel-Wallis and Fisher criterion.

3. Results

3.1. Analysis of indicators of endogenous intoxication.

Judging by the values of laboratory parameters, it has been recorded that patients with acute peritonitis develop endogenous intoxication syndrome.

In the first group, the content of MWM and the level of TI exceeded the normal level on the first day by 45.9 and 64.2% ($p<0.05$). On the next (5th) day after surgery against the background of drug therapy, the value of these parameters significantly decreased, but it exceeded the norm by 23.4 and 31.3% ($p<0.05$). By the final (10th) days, the level of molecules of average mass and the toxicity index for albumin were closely approaching the reference level (Fig. 1).

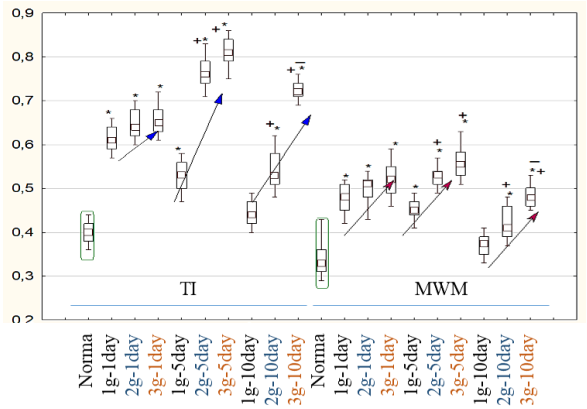

Figure 1. Dynamics of intoxication parameters. Notes here and further: * – statistically significant difference to the norm ($p<0.05$). + – statistically significant difference to the 1st group ($p<0.05$); - - statistically significant difference to the 2nd group ($p<0.05$).

In the second group, the indicators of endogenous intoxication (MWM and TI) exceeded the reference value on the first postoperative day by 49.5 and 68.7% ($p<0.05$), respectively. On the fifth day, there was an increase in the content of MWM and the level of TI, the value of which exceeded the norm by 55.3 and 74.3% ($p<0.05$), respectively. At the next stage of the follow-up period, the parameters of toxemia decreased significantly, but were higher than normal by 23.7 and 34.1% ($p<0.05$).

When analyzing the data of patients of the third group, it was found that the severity of intoxication was recorded to a high degree for all periods of the study: MWM – by 70.5 – 49.6% ($p<0.05$), TI – by 68.5 – 79.3% ($p<0.05$).

3.2. Analysis of indicators of oxidative stress.

The study of laboratory studies showed that the development of acute peritonitis is accompanied by pronounced phenomena of oxidative stress (Fig. 2).

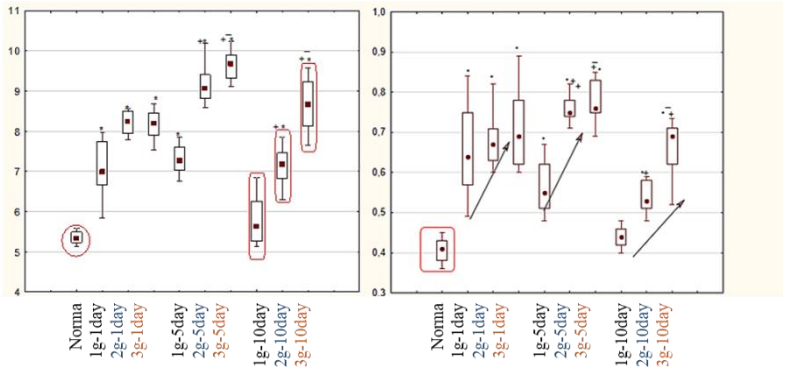

Figure 2. Dynamics of parameters of lipid peroxidation (right – MDA, left – DC).

It was demonstrated that in patients of the first group (without complications), the level of primary (DC) and secondary (MDA) lipid peroxidation products in the early stages (1st postoperative day) exceeded the norm by 63.5 and 50.0% ($p<0.05$), respectively. On the 5th day of the postoperative period, the content of DC and MDA against the background of drug postoperative support significantly decreased. Their value exceeded the norm group by 32.7 and 28.2% ($p<0.05$), respectively. 10 days after the operation, the values of the studied parameters of the floor closely approached the norm (Fig. 2).

When analyzing the activity of lipoperioxidation processes in the second and third groups, it was found that the plasma content of lipid peroxidation products was high at the first stage of observation: diene conjugates – by 65.8 and 68.0% ($p<0.05$), malonic dialdehyde – by 51.8 and 52.6% ($p<0.05$). At the second stage, the prolongation of lipid peroxidation (LPO) activity was recorded. The values of the indicators exceeded the norm. Thus, the content of DC increased by 75.3 and 68.2% ($p<0.05$), MDA – by 83.1 and 74.4% ($p<0.05$), respectively.

At the final stage of the study in the second group, the level of LPO metabolites decreased significantly, although the DC content in blood plasma exceeded the normal level by 17.9% ($p<0.05$,

and MDA – by 14.8% (p<0.05)). In the third group during this period, the level of DC and MDA remained high and exceeded the norm by 35.8 and 26.4%, respectively (Fig. 2).

3.3. Analysis of indicators of hepatic function.

Analysis of hepatic parameters in the dynamics of pathology showed the development of significant changes in the functional activity of the organ (Fig. 3).

It was found that the development of acute peritonitis in the early stages was characterized by hepatic dysfunction (Fig. 3). Thus, on the 1st day after surgical treatment, patients of the first group showed an increase in the activity of alanine aminotransferase and gamma-glutamyltransferase by 47.6 and 41.8% (p<0.05), respectively. After 5 days, a significant decrease in ALT and GGT activity was noted. However, their plasma activity exceeded the norm by 30.3 and 40.2% (p<0.05). At the final stage of the study (the 10th day after surgery), the activity of liver enzymes came close to the reference level (Fig. 3).

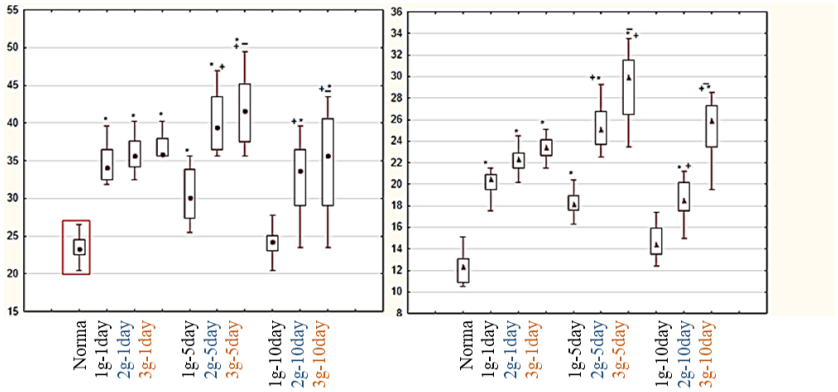

Figure 3. Dynamics of the parameters of the functions of the liver (right – GGT, left – ALT).

Patients in the second group demonstrated high activation of liver tests on the 1st and 5th days after surgery. This was evidenced by the increase in serum concentrations of ALT and GGT above the norm by 55.4 and 47.2% (p<0.05) at the first and 64.9 and 56.5% (p<0.05), respectively, at the second stage of the study. By the 9th day of observation, the activity of alanine aminotransferase and gamma-glutamyltransferase significantly decreased, but exceeded the norm by 25.6 and 19.2% (p<0.05).

In the third group, signs of hepatic depression remained at a high level at all stages of the study: on the 1st postoperative day by 56.7 and 48.1% (p<0.05), on the 5th - by 80.6 and 72.4% (p<0.05), and on the 10th – by 42.3 and 39.5% (p<0.05), respectively.

3.4. Analysis of indicators of hemostasis system.

In acute inflammation of the peritoneum, we found significant changes in the hemostasis system.

Thus, according to the TAG data, in patients of the first group (without complications), the phenomena of hypercoagulation and a decrease in fibrinolytic activity of the blood were recorded: on the first day, a decrease in R by 30.1% (p<0.05) and an elongation of Cl by 37.5% (p<0.05); after 5 days, the reaction time was below the normal level by 19.5 % (p<0.05), and the coagulation index increased by 24.1% (p<0.05). By the 10th day, coagulation and fibrinolytic activity of the blood was approaching normal (Fig. 4).

In the second group, hypercoagulation and hypofibrinolytic blood activity persisted on the first and fifth postoperative days: the R value was shortened by 40.1 and 48.9% (p<0.05), respectively, and Cl was lengthened by 33.7 and 35.1% (p<0.05), respectively. On the last day of the study, a significant restoration of the functional activity of the hemostasis system was recorded. However, the time R remained below the reference level by 21.1% (p<0.05), and the time of the coagulation index was longer by 26.9% (p<0.05).

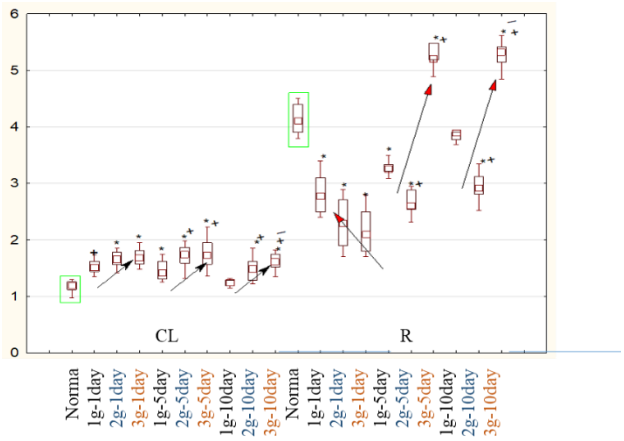

Figure 4. Dynamics of parameters of the hemostasis system.

In the third group, changes in the activity of the blood coagulation system in the form of hypercoagulation and hypofibrnolysis were detected on the first day. Thus, the R was crushed by 41.3%, and the Cl was lengthened by 52.6%. On the 5th and 10th days, the occurrence of significant changes in blood coagulation ability was demonstrated: the R exceeded the norm by 23.6 and 21.4% ($p<0.05$); the Cl became shorter by 70.1 and 56.7% ($p<0.05$), respectively.

3.5. Analysis of severity assessment.

In the course of the study, it was revealed that the severity of the studied patients, determined by the APACHE II scale, changed significantly. In patients of the first group, the number of points a day after surgery was 15.6±0.56, which corresponded to a severe degree [7]. On the fifth day, their number decreased to 8.2± 0.34, (moderate degree), on the tenth – to 4.3± 0.12 (mild degree).

In the second group, the number of points on the first day was high, and then gradually decreased, amounting to 15.9±0.74, 17.6±0.69 and 9.8±0.24, respectively, at the stages of the observation period. In the third group, the severe condition of patients persisted at all stages of the follow-up period: the number of points was 16.1±0.87, 18.2±0.94 and 13.5±0.43, respectively (Fig. 5).

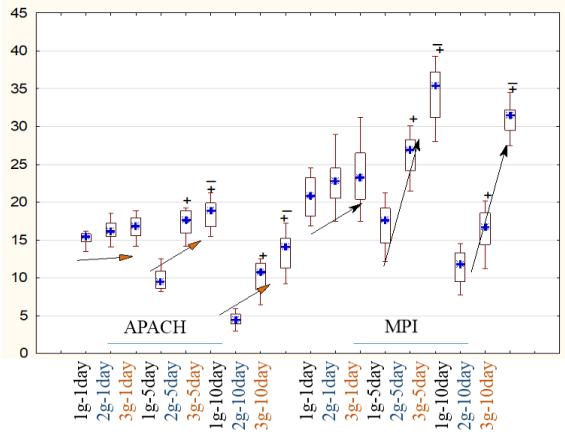

Figure 5. Dynamics of ARASNE II and MPI results.

The results of forecasting peritonitis according to the Mannheim peritoneal index showed that in the first group on the first day it was 20.4± 1.97, on the fifth – 15.6± 0.56 and on the tenth – 11.8± 0.34 (first degree of severity [8]). In the second group, the second degree of severity was recorded at the first two stages - 23.7 ±2.78 and 26.1±2.94. By the 10th day after surgery, the value of the Mannheim index decreased to 16.7±0.75. In the third group, the severity assessment on this scale showed that after the 1st day the number of points was 27.4±2.41 (second degree) and on the 5th and 10th days - 35.4±3.92 and 31.7±2.85, respectively (third degree).

When analyzing the results of surgical treatment of patients with acute peritonitis and the risk of postoperative complications, it was found that the development of postoperative negative consequences was not detected among the patients of the first group. In the second group, the formation of wound complications was noted, while three developed deep vein thrombosis of the lower limb. The latter were operated with a favorable outcome. In the third group, the observation showed the development of fatal complications: 3 had tertiary peritonitis, and 2 had sepsis. Two patients of this group died.

4. Discussion

According to modern concepts, it is shown that one of the main manifestations of disorders of the functional activity of the homeostasis system in the early stages of acute peritonitis is endotoxicosis. The latter is accompanied by the accumulation of intermediate and final toxins in the tissues and important organs (liver, kidneys, brain, etc.) of the body, leading to their functional changes [9].

In acute peritonitis, significant oxidative stress phenomena occur. A high level of toxemia, activation of lipoperoxidation processes lead to damage to various organs and systems of the body, especially the liver [10].

There is evidence that the development of dysfunction of various organs, especially the liver, in the early stages of acute peritonitis leads to a violation of the state of the blood coagulation system, which, in turn, may be a factor in the progression of the disease, the development of complications and mortality [11].

The results of the study confirmed the above. It has been established that the development of acute peritonitis is accompanied by the formation of pronounced endotoxemia, activation of lipid-modifying processes and oxidative stress, leading to serious violations of the functional status of the liver. This was accompanied by significant changes in coagulation and fibrinolytic activity of the blood. In patients of the first group, the registered changes in homeostasis indicators were reversible and were accompanied by transient phenomena of hypercoagulation and hypofibrinolysis. Moreover, by the final stage of the observation period, the state of the blood coagulation system was restored. In the second group, whose patients had various kinds of wound complications in the early postoperative period, significant violations of homeostasis persisted until 5 days after surgery, and by the 10th day there was a significant positive dynamics in their recovery. In this group, significant phenomena of hypercoagulation and inhibition of fibrinolysis were recorded in the first 5 days.. In the third group, in whose patients the progression of the disease with the formation of sepsis and tertiary peritonitis was noted, significant phenomena of intoxication, oxidative stress and liver failure were recorded during the entire follow-up period. At the same time, the state of the hemostasis system was characterized by paradoxical transformations: hypercoagulation and hypofibrinolysis – on the first day, and hypocoagulation and hypofibrinolysis – on the 5th and 10th days.

5. Conclusions

In acute peritonitis, the phenomena of hypercoagulemia, inhibition of fibrinolysis correlate with the phenomena of oxidative stress ($r=0.762-0.911$, $p<0.05$), endogenous intoxication ($r=0.812-0.955$, $p<0.05$) and impaired liver functional status ($r=0.785-0.908$, $p<0.05$). With effective therapy and improvement of the clinical and laboratory condition of patients, correction of homeostatic parameters, including hemostasis, is noted against the background of restoration of the functional status of the liver.

During the aggravation of the phenomena of peritoneal inflammation and the development of complications in the early postoperative period, there is a progression of changes in the studied indicators of homeostasis and hemostasis against the background of maintaining the depressed functional state of the liver.

With the development of tertiary peritonitis and sepsis, the hemostasis system is modified in the form of hypocoagulemia and activation of fibrinolysis against the background of a sharp increase in endogenous intoxication, oxidative stress and greater inhibition of the functional status of the liver, including from its hemostasis-regulating component.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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Article

Polymorphism of Genes of Platelets` Integrins and Fibrinogen as a Risk Factor for Homeostatic Disorders in Preeclampsia

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Abstract: The development of perinatal obstetrics is associated with the need for a detailed study of the pathophysiological mechanisms of preeclampsia (PE).

Materials and methods. A prospective cohort study included 173 patients aged 18-45 years with a singleton pregnancy at a gestational age of 22-41 weeks at the Mordovian Republican Central Clinical Hospital. There were 3 groups: group I (n=63) - pregnant women with moderate PE, group II (n=58) - patients with severe PE, group III (control) (n=52) - pregnant women with physiological pregnancy. The assessment of the prevalence of polymorphic variants of genes was by PCR diagnostics. A laboratory study of hemostasis, microcirculation and thromboelastography (TEG) parameters was performed.

Results. In patients with severe preeclampsia, there is a high prevalence of homozygous C/C variants (46.5%) of the ITGB3 gene and heterozygous C/T variants (55.5%) of the ITGA2 gene, hetero- (G/A) and homozygous (A/A) variants of the fibrinogen gene (FGB) - 48.3 and 36.2%, respectively. It is associated with such hemocoagulation disorders as an increase in the prothrombogenic potential of the blood based on a decrease in the number of platelets, prothrombin time and antithrombin III against the background of an increase in fibrinogen and an increase in the strength and volume of the blood clot according to TEG.

Conclusions. The severity of thrombophilia is associated with the severity of preeclampsia; pathological alleles of the studied genes are most often recorded in patients with severe PE and severe hemostasis disorders.

Keywords: Preeclampsia, hemostasis system, polymorphism, genotype, lipid peroxidation.

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1. Introduction

One of the most severe complications in the group of hypertensive disorders of pregnancy is preeclampsia, the frequency of which ranges from 2 to 8%. The classic criteria for the condition is the Zangemeister's triad, which includes increased blood pressure (›140/90 mm Hg), edema, and proteinuria in the second half of pregnancy [1, 2]. However, preeclampsia causes a lot of damage to other organs and organ systems, involving the cardiovascular, central nervous system, kidneys, liver, etc.

It has been established that preeclampsia is a significant risk factor for metabolic, cardiovascular and cerebrovascular complications. According to the American Heart Association, the occurrence of cardiovascular complications increases significantly in the group of women who have had preeclampsia. Thus, the risk of developing chronic arterial hypertension is three to four times higher, and the risk of heart disease and stroke is two times higher than in women with normal gestation. Moreover, early onset and severe course of preeclampsia is associated with a significantly higher incidence of cardiovascular pathology [3]. Therefore, hypertensive disorders of pregnancy are an important predictor of cardiovascular and cerebrovascular complications.

Despite the relevance of the problem, the issues of the etiology of preeclampsia and its complications are still insufficiently studied. The variety of symptoms and clinical manifestations of preeclampsia suggests heterogeneous pathophysiological pathways of its occurrence.

Currently, in the literature, one of the pathogenetic mechanisms for the development of preeclampsia is impaired remodeling of the spiral arteries. Its result is an increase in the sensitivity of blood vessels to vasoconstrictors, which negatively affects the uteroplacental blood flow, leading to hypoxia and ischemia. Endothelial dysfunction arising in response to hypoxic and ischemic processes in the placenta causes the release of inflammatory factors and triggers a cascade of hypercoagulable disorders, including local microthrombosis, which further impairs tissue microcirculation [4].

In addition, endothelial dysfunction leads to a decrease in vasorelaxant factors such as nitric oxide (NO) and an increase in lipid peroxidation activity and, as a result, reactive oxygen species, which exacerbate oxidative stress during pregnancy [5].

The presence of similar pathophysiological aspects of cardiovascular disease and preeclampsia suggests the presence of a genetic predisposition to the hemocoagulation disorders and related complications.

Purpose of the study. To study the contribution of polymorphism of some genes to the occurrence of hemostatic disorders in preeclampsia.

2. Patients and Methods

A prospective cohort study of 173 patients delivered on the basis of the Mordovian Republican Central Clinical Hospital was carried out. Patients were included in the study based on the clinical recommendations “Hypertensive disorders during pregnancy, childbirth and the postpartum period. Preeclampsia. Eclampsia" (2020). The inclusion criteria were the patient's voluntary informed consent to participate in the study, the age of pregnant women from 18 to 45 years, singleton pregnancy, gestational age of 22-41 weeks, and the absence of severe somatic pathology. In accordance with the purpose and objectives of the study, all pregnant women were divided into 3 groups. The first group consisted of 63 patients with moderate preeclampsia. The second group - 58 pregnant women with severe preeclampsia. The third group (control) included 52 patients with a physiological course of gestation. The parameters of the basical blood test and hemostasiogram were evaluated (analyzers "AutomaticAnalyzer 912" (Hitachi, Japan), "CR-10" (Amelung, Germany), "EsyLyte AVL-9180" (AVL, USA), "SYSMEX KX-21N" (Roch, Germany-France)), the level of malondialdehyde, products of nitric oxide metabolism, enzyme activity was determined by standard biochemical methods. We performed thromboelastography (TEG) (TEG® 5000 (USA)), assessment of microcirculation (LAKK - 02 (Russia)), PCR study of some genes of the hemostatic system (CFX96 Touch™ Real-Time PCR DetectionSystem (USA)). All received data were processed by methods of medical statistics Statistics 13.0.

3. Results

We have studied the main indicators of blood coagulation characteristics in pregnant women with preeclampsia of varying severity. The results demonstrate significant changes in the hemostasis system (Fig. 1).

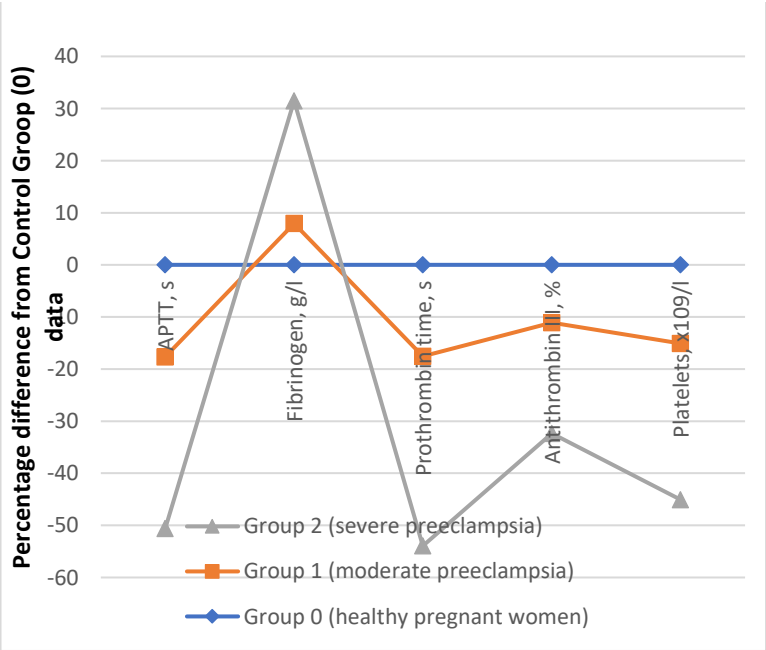

Figure 1. Some indicators difference of hemostasis in pregnant women with PE (M±m)

In the group of pregnant women with moderate preeclampsia, it is recorded a shortening of prothrombin time and aPTT by 17.52% (p<0.05) and 17.65% (p<0.05), relative to the control group. Similar disorders are observed in severe preeclampsia - prothrombin time and APTT are decreased by 36.42% (p<0.05) and 32.98% (p<0.05), relative to the control group and by 22.91% (p<0.05) and 18.62% (p<0.05) relative to similar indicators in moderate PE. At the same time, there is a decrease in the level of antithrombin III and the quantity of platelets in the group of pregnant women with moderate preeclampsia by 11.10% (p<0.05) and 15.11% (p<0.05), respectively, relative to the control group. In second group the level of fibrinogen exceeds that of the control group by 7.94% (p<0.05). In the group of pregnant women with severe preeclampsia, antithrombin III and the quantity of platelet are significantly lower than in the control group by 21.28% (p<0.05) and 29.94% (p<0.05), respectively, and similar indicators in moderate PE by 11.46% (p<0.05) and 17.48% (p<0.05), respectively. Reliably significant changes in hemostatic parameters are indicated by thromboelastography (TEG) (Fig. 2).

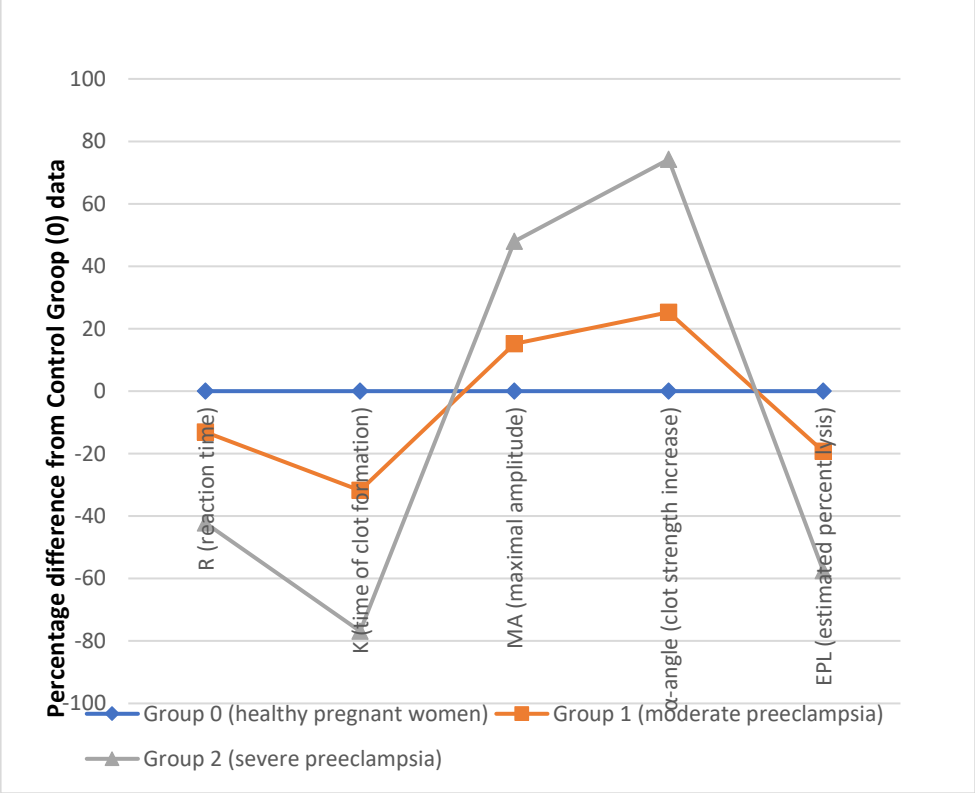

Figure 2. Some indicators of hemostasis in pregnant women with PE according to thromboelatography (M±)

In the group of pregnant women with a moderate course of preeclampsia, it is indicated a decrease in microcirculation, neurogenic tone and index of microcirculation efficiency by 11.97% (p<0.05), 19.66% (p<0.05) and 14.78% (p<0.05) relative to the control group. There is a statistically significant increase in the bypass rate by 25.23% (p<0.05) relative to group 3. In a severe course of preeclampsia, more pronounced changes in the above indicators are most specific against the background of an increase in the activity of myogenic mechanisms of regulation of vascular tone and a decrease in the influence of the neurogenic component.

We analyzed the molecular polymorphisms of the genes of the hemostasis system ((T1565C) ITGB3, (C807T) ITGA2, (G(-455) A) FGB) in pregnant women with varying degrees of preeclampsia.

In the group of women with moderate preeclampsia, the distribution of beta-3 integrin gene (ITGB3) genotypes is: TT genotype - 42.9%, TC genotype - 34.9%, CC genotype - 22.2% ($\chi 2$ = 4.21, p=0.04 and OR=3.0 (1.0–8.7)). Polymorphic variants (C/C, C/T, T/T) of the integrin alpha gene -2 (ITGA2) distributed as follows – 55,5, 27,0 и 17,5% ($\chi 2$=3,4, p=0,06 и OR=2,83 (0,91–8,77)) respectively, and genotype (G/G, G/A, A/A) fibrinogen gene (FGB) – 50,8, 31,7 и 17,5% ($\chi 2$=8,04, p=0,05 и OR=4,43 (1,53–12,8)).

There is a high prevalence of polymorphic variants of the genes of the hemostasis system in case of aggravation of the pathology. Thus, polymorphic variants of the beta-3 integrin gene (T1565T, T1565C and C1565C) account for 20.7%, 32.8% and 46.6% at $\chi 2$=5.84, p=0.01, OR=5.29 (1 .26–22.25), respectively. The prevalence of genetic variants (C807C, C807T and T807T) of the alpha-2 integrin gene is 20.7, 44.8 and 34.5% ($\chi 2$=20.0, p=0.001, OR=12.5 (3.82–42 ,45)) respectively, fibrinogen gene (G(-455) G, G(-455)A and A(-455)A) - 15.5, 48.3 and 36.2% ($\chi 2$=24.3, p=0.001, OR=42.0 (5.1–357.1)). Thus, in the group of patients with pregnancy complicated by preeclampsia, there is an increase in the frequency of occurrence of pathological alleles of the genes of the hemostasis system. Moreover, the maximum frequency of pathological alleles is associated with the aggravation of the pathology.

4. Discussion

It is known that a normal pregnancy is characterized by a hypercoagulable state of the blood, due to an increase in the procoagulant potential, suppression of endogenous anticoagulants and inhibition of the fibrinolytic system. These changes during normal gestation provide a low risk of blood loss during a cytotrophoblast invasion, a childbirth and a postpartum period. [6]. The risk of thrombotic complications increases with the addition of complications in the form of preeclampsia. We note a statistically significant decreasing of prothrombin time and aPTT. Thus, the average prothrombin time in a physiologically proceeding pregnancy, moderate and severe preeclampsia is 15.98±0.87, 13.18±0.54 and 10.16±0.49 sec. respectively. The APTT is shortening to 28.14±1.38 and 22.90±1.41 sec in groups 2 and 3, respectively, in contrast to the normal values in the control group (34.17±1.55). Our data are consistent with the results of the BhutaniN and others study, which shows a shortening of the prothrombin time as the pathology worsens (10.9 s, 10.1 s and 9.8 s, respectively), while the average APTT in the control group and in preeclampsia of varying severity was 26.68 s, 26.71 and 26.25 s. respectively. A decrease in the quantity of platelets, a shortening of the prothrombin time and aPTT indicate significant violations of the coagulation cascade. Moreover, similar changes in the above hemostasiological parameters are characteristic of DIC.

In our study, laboratory changes in hemostasis are confirmed by TEG. The clot formation time (K), α-angle and maximum amplitude (MA) reflect the physical properties of the blood clot - its relative density and size - and correlate with the level of fibrinogen and the quantity of platelets. In the group of pregnant women with moderate preeclampsia, there is a statistically significant decrease in clot formation time (K) and reaction time (R) compared with the control group - by 31.79% ($p<0.05$) and 13.11% ($p<0.05$), respectively. At the same time, α-angle, maximum amplitude (MA) and clot strength (G) are increased by 25.26% ($p<0.05$), 15.17% ($p<0.05$) and 30.72 % ($p<0.05$), respectively.

The data obtained, together with a laboratory-recorded increase in the level of fibrinogen and a decrease in the quantity of platelets, suggest the presence of significant hypercoagulable changes, as well as an increase in the size and density of the blood clot in women with preeclampsia of varying severity. Our study is consistent with the results of other studies [7, 8, 9]. However, in the work of Wang, M. et al. opposite results of studies are showed - in pregnant women with preeclampsia, the average values of R and K were higher than in the control group, at the same time, there was a decrease in the average values of MA and α-angle [10]. Thus, pathophysiological changes in hemostasis in preeclampsia require further research.

The deterioration of microcirculation closes the vicious circle of pathogenesis. In the study, there is an increase in the myogenic component of regulation against the background of a decrease in neurogenic tone with a decrease in the index and the efficiency of microcirculation, which ultimately leads to a deterioration in uteroplacental blood flow. In our study, the genetic aspects of the development of preeclampsia are studied too. It is known that the receptor responsible for platelet adhesion to the surface of subendothelial collagen is alpha-2 integrin (ITGA2). Polymorphism of the C807T gene of the ITGA2 gene causes structural changes in the above receptor, which leads to an increase in the platelet adhesion rate and, as a result, the development of thrombotic complications [11]. In the group of pregnant women with moderate and severe preeclampsia, there is a high frequency of prothrombogenic alleles of the genes of the hemostasis system affecting plasmic and platelet hemostasis, which is consistent with the study by Borodina I. E. et al. [12]. In addition, our results are consistent with the studies of Bakirov B. A. et al., and confirm the increase in the adhesive properties of platelets in patients with mutations in the ITGA2 and ITGB3 genes [13]. Moreover, in modern literature there is information that the presence of a homo- or heterozygous mutation of the ITGB3 gene is associated with resistance to the antiplatelet effect of aspirin [14].

5. Conclusions

Preeclampsia is characterized by pronounced changes in the coagulation properties of blood, which leads to disruption of microcirculation in tissues and deterioration of uteroplacental blood flow. Moreover, the aggravation of the pathology is associated with more pronounced changes in these disorders. The degree of changes in these pathophysiological components is associated with polymorphism of the genes of the hemostasis system. Thus, a comprehensive assessment of hemostatic factors in the carriage of mutant alleles of the (T1565C) ITGB3, (C807T) ITGA2, (G(-455) A) FGB) genes can be an effective predictor of adverse obstetric and perinatal outcomes.

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