

Dear Colleagues,



We are happy to present you the first issue of electronic scientific journal of the Kharkiv National Medical University "Inter collegas". The edition is published on the eve of the 210th anniversary of alma mater, and its main objective is to present scientific achievements of the staff and students of our university, as well as our

colleagues from other educational and scientific institutions.

The language of the new edition is English. This is due to the fact that internationalization and mobility in science and education are now the most pressing than ever.

The special background for the advent of our magazine is the coming into force of the revolutionary Law of Ukraine "On Higher Education". This law opens new prospects not only in education and science, but also in the successful implementation of all plans for the development of our country.

To start something new is always gratifying and exciting. I hope your participation in the life of the magazine will be a reliable guarantee of our mutual success.

**Rector of the Kharkiv National Medical University, corresponding member of National Academy of Medical Sciences of Ukraine,
Doctor of Medical Sciences,
Professor Vladimir Lesovoy**

ACADEMICIAN L.T. MALAYA - AN OUTSTANDING SCIENTIST OF MODERN TIMES

Dedicated to the 95th Anniversary

Abstract. *Present review is dedicated to the memory of the outstanding scientist, gifted manager, founder of therapeutic and cardiology schools as well as understanding and sincere person, who is well-known not only in Ukraine, but also far beyond the borders – Lyubov Trofimovna Malaya. The whole professional life of L. T. Malaya is connected with Kharkiv National Medical University. A heightened sense of the new was always inherent in Lyubov Trofimovna. On the initiative and under the guidance of L. T. Malaya, a whole range of new high-tech methods of diagnosis and treatment of cardiac disease was developed and implemented in practice, as well as new highly efficient and economical hospital-substituting technologies. Lyubov Trofimovna's natural talent combined with passionate love for her profession. She was all focused and striving to help the patient, it was the meaning of her life. The life of Lyubov Trofimovna is a vivid example of selfless service to science, extraordinary versatility of interests and depth of knowledge. .” Undoubtedly, L. T. Malaya rightfully belongs to the galaxy of famous Ukrainian therapists. I would like to believe that the doctors who have been lucky enough to work and learn from L. T. Malaya will pass to new generations a particle of their professionalism and humanity, and this thread will never stop running.*

On January 13, 2014 the scientific medical community and physicians of different specialties of Ukraine celebrated a glorious anniversary of the Hero of Socialist Labor, Hero of Ukraine, Academician of National Academy of Sciences, National Academy of Medical Sciences (NAMS) of Ukraine and Russian Academy of Medical Sciences, Honored Scientist and Technician of Ukraine, Laureate of State Prize of USSR and State Prize of Ukraine in the fields of science and technology, laureate of awards at the AMS of Ukraine, Doctor of Medical Sciences, Professor Lyubov Trofimovna Malaya. We, disciples and followers of Lyubov Trofimovna Malaya, who worked hand in hand with her for many years, are especially acutely aware today of how much her personal contribution to the development of the national cardiology, therapy and medicine is in general [1,2].

It is a hard task to highlight L. T. Malaya's creative activity because of its versatility. One thing is clear: Lyubov Trofimovna is a talented organizer; on her initiative, the Research Institute was established in Kharkiv in 1986, where she became the first director and worked until her last days because she did not imagine her life without beloved work. Now the Institute of Therapy of National Academy of Medical Sciences of Ukraine bears her name. Speaking about the contribution of L. T. Malaya in the development of medical science, President of NAMS, Academician A. M. Serdyuk said that it was thanks to her that the Institute was established, and, in a short time, became a powerful scientific and medical complex [3].

During the Great Patriotic War, more than 200,000 doctors and about 500,000 health care workers were employed in the military medical services. The proportion of women among all health care workers was 46%. Among front-line physicians, women accounted for 41%, among military surgeons — 45%, among nurses — 100% [4]. L. T. Malaya went all the way from a doctor in front-line hospitals of South, North Caucasian, Transcaucasian fronts up to the Deputy Head of the Medical Department of the Kharkiv military district. After the war, a famous military leader, Marshal of the Soviet Union I. Kh. Bagramyan, wrote: "What the Soviet military medicine did during the past war can be justly defined as a feat. For us, the veterans of the Great Patriotic War, the image of a military medic will remain the embodiment of high humanism, courage and selflessness." That is probably why Lyubov Trofimovna said: "My dream is that succeeding generations would live peacefully, amicably and happily. I hope this will come true." [5] Years of harsh war left Lyubov Trofimovna with the rank of medical service major, Medal for Battle Merit, Medal for Taking Part in the Heroic Defense of the Caucasus," Medal "For the Victory over Germany in the Great Patriotic War 1941–1945" as well as huge medical and organizational experience, professional skills, a sense of the enormous responsibility for the assigned work and subordinates, and firing shrapnel wound in the left leg [6].

In the glorious galaxy of luminaries of the Ukrainian medicine, the name of Academician L. T. Malaya shines with special, inimitable brilliance. Her curious

mind, phenomenal diligence and sense of the new formed the basis for early expressed interest in scientific work, in which she took a great interest while still at residency under the supervision of Prof. S. Y. Steinberg — a prominent physician and former student of N. D. Strazhesko. Watch hours at the bedside of patients, work in the laboratory, night reading of medical books, hard work on a dissertation became new pages in the biography of the young scientist. It should be emphasized that Lyubov Malaya carried the memory about her teacher through all her life. “He was strict, talented and extremely friendly. He modeled out of me not only a physician, but also a personality”, remembered Academician Malaya with great respect [7].

Her dissertation “Tuberculin diagnosis in clinic of internal diseases”, brilliantly defended in 1950, demonstrated the diagnostic value of tuberculin reactions in the clinic of internal diseases and raised a number of issues which contributed to the development of a whole branch of new research. In 1954 L. T. Malaya defended her doctor’s dissertation “On changes of cardiovascular system in tuberculosis”, which laid the foundation for the further study of the whole complex of clinical and fundamental problems of internal medicine. Her scientific work was described by an outstanding world-class scientist Academician A. L. Myasnikov as follows: “One can definitely tell that neither in domestic nor in foreign literature there is a similar work done so carefully and widely” [8].

The whole professional life of L. T. Malaya is connected with Kharkiv National Medical University. Lyubov Trofimovna passed all stages of the hierarchy from clinical intern (1946) to assistant (1954), assistant professor (1954), full professor (1955) and head of the department. From a talented but young scientist, she became a mentor, pedagogue, teacher. A brilliant lecturer and promoter of knowledge in the field of internal medicine, Lyubov Trofimovna was the founder of the modern Ukrainian therapeutic school. It is her textbooks that taught many generations of physicians. Lyubov Trofimovna was personally acquainted with many cardiologists and therapists in all corners of Ukraine, where she visited with lectures, presentations and performances, taking part in national and interregional conferences and congresses with brilliant clinical analyses. For many years she was the head of

the specialized Scientific Council for defense of dissertations for a scientific degree of Candidate and Doctor of Medical Sciences D 64.600.04, which now bears her name.

A great place in L. T. Malaya's research work took theoretical and practical issues in areas such as cardiology, atherosclerosis, coronary heart disease, arterial hypertension, and their clinical manifestations and complications such as myocardial infarction, heart failure, heart rhythm disorders, rehabilitation treatment, and study of the therapeutic effectiveness of new medicines.

A heightened sense of the new was always inherent in Lyubov Trofimovna. On the initiative and under the guidance of L. T. Malaya, a whole range of new high-tech methods of diagnosis and treatment of cardiac disease was developed and implemented in practice, as well as new highly efficient and economical hospital-substituting technologies. Thus, the introduction of the concept of phased system of rehabilitation of patients with myocardial infarction in Ukraine, of course, is owned by L. T. Malaya. Under her guidance, a specialized cardiology intensive care unit at the 27th Kharkiv Municipal Clinical Hospital was established for treatment of patients with myocardial infarction. Implementation of the system of phased treatment of patients with myocardial infarction allows every year to return hundreds of thousands of such patients to productive professional work. For the first time in Ukraine, L. T. Malaya initiated fundamental research in the field of integrated prevention of major noncommunicable diseases, which are an integral part of the corresponding WHO program "Health for All".

On the initiative and under the guidance of Lyubov Trofimovna, in-depth studying of microcirculation of myocardial infarction and its complications, including using radioactive isotopes, liquid crystal thermal indication and thermal imaging technology, allowed to provide an original scheme of drug correction of microcirculation. Of particular note is the study of hemostasis in myocardial infarct. The Clinic's Infarct Department and cardiological problem lab carefully studied the pathogenesis and treatment of cardiogenic shock in patients with myocardial

infarction, its complications, myocardial healing processes and, especially, hemostasis in myocardial infarct.

Working out the problem of neurohumoral regulation of homeostasis in cardiovascular diseases progressed considerably in the works of L. T. Malaya and her colleagues. For the first time in Ukraine, L. T. Malaya's team thoroughly studied the metabolism of biologically active polypeptides as components of the kallikrein-kinin system of blood and prostaglandins, effectively proving the most important role of local hormones in the formation and progression of cardiovascular pathology. Developing the concept of the leading role of atherosclerosis in evolution of coronary heart disease, L. T. Malaya studied the features of protein-lipid metabolism abnormalities in atherosclerosis and, by means of immunoelectrophoresis, found in the blood of patients the protein-lipid complex acting as antigen. The study of pathogenetic mechanisms of atherosclerosis and its complications, the therapeutic value of humoral and cellular factors of atherogenesis in coronary heart disease was significantly developed in the works of L. T. Malaya and her colleagues. On the basis of examination of the role of biologically active substances in the occurrence and course of cardiac pathology, complex pharmacological correction of hypertension depending on the activity of renin was implemented in clinical practice, antibradykinin preparations for ischemic heart disease and hypolipidemic drugs for atherosclerosis were applied.

When examining the problems of heart failure, it was shown by Lyubov Trofimovna and her school that the clinical manifestations of this syndrome are accompanied not only by disordered intracardiac, peripheral hemodynamic and metabolic disorders, but also by disorders of neurohumoral regulation as well as adaptive and compensatory mechanisms. It was demonstrated that the leading factor of the pathogenesis of chronic heart failure is disordered neurohumoral mechanisms of vasoregulation in the form of insufficient activity of vasodilating systems (endothelial factors, atrial natriuretic peptide, kallikrein-kinin system) against the background of hyperactivity of vasoconstrictive (endothelin-1, vasopressin, renin-angiotensin, sympatico-adrenal) systems of regulation. It was demonstrated that the

implementation of the therapeutic potential of various groups of medications used in patients with heart failure, depends on the fundamentally different ratios of activity indicators of neurohumoral systems of vascular tone regulation, which was the theoretical basis for the ability to forecast the effectiveness of treatment in this cohort of patients. The effectiveness of neurohumoral modulators, including ACE inhibitors, AT1-angiotensin receptor antagonists, blockers of mineralocorticoid receptors and α -adrenergic blockers was studied in patients with chronic heart failure. Lyubov Trofimovna's works confirmed the concept of individualized treatment for patients with chronic heart failure, which is particularly important at the present time.

The life of Lyubov Trofimovna is a vivid example of selfless service to science, extraordinary versatility of interests and depth of knowledge. Although L. T. Malaya was, according to E. M. Tareev, "a first rank cardiologist," she did not focus on cardiology only [9]. Almost all the articles on the biography of Academician of NAS and NAMS of Ukraine and Russian Academy of Medical Sciences L. T. Malaya list the achievements of her and her students in various sections of the internal diseases. Actually, there is no area of multifaceted medical science, where Lyubov Trofimovna and her school would not make a huge contribution. The wide range of L. T. Malaya's scientific and practical interests also included such clinical aspects of internal medicine as the study of the causes of chronicity of internal diseases, the development of methods for early detection, optimal drug therapy and prevention of the most common diseases of the circulatory system, respiratory organs, diseases of the gastrointestinal tract and kidneys with the implementation of research results into health care practice. Lyubov Trofimovna said: "What gives me the strength to live and work is the love of the chosen specialty, awareness that my life and work are for the benefit of mankind, boundless thirst for knowledge, high responsibility, and exceptionally kind attitude of those whom I truly love, who helps me in the difficult days of my life" [10].

Lyubov Trofimovna's natural talent combined with passionate love for her profession. She was all focused and striving to help the patient, it was the meaning of her life. Lyubov Trofimovna possessed clinical thinking of a broad therapist, in

connection with which she was often invited to participate in consultations of specialist doctors and analyses of the most sophisticated diagnostic patients. Staff rounds with subsequent analyses of clinical features of disease were real school for practicing physicians. Each diagnosing made by L. T. Malaya was always the result of a thoughtful examination of the condition of the patient; the treatment prescribed by her was always based on the individual and personal characteristics of the patient, a profound knowledge of the pathogenesis of disease and clinical pharmacology. With a phenomenal memory, even many years after the first meeting with patient, she remembered the details of his/her medical history and taught the younger generation of doctors how to conduct a diagnostic search. L. T. Malaya loved to repeat: “The main thing is to be a good doctor. If at least one mother does not lose her son or one father or husband returns to his family after illness, our work is not in vain” [3]. Undoubtedly, L. T. Malaya rightfully belongs to the galaxy of famous Ukrainian therapists.

I would like to believe that the doctors who have been lucky enough to work and learn from L. T. Malaya will pass to new generations a particle of their professionalism and humanity, and this thread will never stop running.

Professor I. I. Knyazkova

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Syrovaya A.O., Bachinskiy R.O., Grabovetskaya E.R.

CREATION OF NEW DRUG COMPOSITIONS AND PHARMACOLOGICAL SUBSTANTIATION OF THEIR SUITABILITY FOR PAIN SYNDROMES AND INFLAMMATIONS IN EXPERIMENTAL RATS

Kharkov National Medical University, Ukraine

Abstract. *Creation of combined drugs whose pharmacological effects are due to the rational combination of ingredients is the urgent problem of modern medicine. Combination of several components in one drug expands its pharmacological range and promotes polytropic activity. The advantage of combined drugs compared with pure drugs is that they more effectively eliminate pain and inflammation than each individual component.*

Combined analgesics often include caffeine. According to literature data caffeine enhances analgesic effect of nonsteroidal anti-inflammatory drugs (NSAIDs) and nonnarcotic analgesics (NNA). However, there are no data on the composition of diclofenac sodium (D-Na), ibuprofen (Ib) with caffeine in the literature. This fact caused experimental studies of influence of caffeine on the analgesic and anti-exudative effects of D-Na and Ib. Experimental studies have been conducted on laboratory animals (white adult rats of the WAG strain) by intragastric administration. Analysis of experimental results clearly indicates that caffeine potentiates analgesic and anti-exudative effects of D-Na and Ib.

Thus, compositions of D-Na and Ib with caffeine were experimentally studied for the first time. Suitability of compositions is proved and application in inflammation and pain of various origins is demonstrated. Results can serve as foundation for development of new domestic combined drugs with analgesic and anti-inflammatory effects.

Keywords: *non-steroidal anti-inflammatory drugs, ibuprofen, diclofenac sodium, caffeine, analgesic activity, anti-inflammatory activity, CNS.*

Combination drug therapy is often used in medical practice. Caffeine (1,3,7-trimethylxanthine) is often introduced to the combined analgesic drugs for enhancing of their pharmacological activity [1, 2]. Derivative of acetic acid – diclofenac sodium

(D-Na) is one of the most effective non-steroidal anti-inflammatory drugs (NSAIDs). It possesses both analgesic and anti-inflammatory effects and also is well tolerated. It has stronger anti-inflammatory and analgesic effects than acetylsalicylic acid, butadion, and others. D-Na serves as the modern world "gold standard" of treatment [3–5]. Propionic acid derivative –Ibuprofen (Ib) also belongs to safe NSAIDs along with D-Na [6–9]. There are many known combinations of NSAIDs and nonnarcotic analgesics (NNA) with caffeine, but there are no compositions Ib + caffeine, D-Na + caffeine in pharmaceutical practice.

The purpose of our study was to create and investigate new compositions comprising caffeine and NSAIDs of different chemical structure and to substantiate pharmacologically their suitability for pain syndromes and inflammatory processes. An opportunity to achieve a stronger pharmacological activity (analgesic and anti-inflammatory) of the composition compared with individual drug was the basis of our study.

Materials and Methods. Effect on the nociceptive system was determined by the influence on the central and peripheral components of the pain response.

Analgesic effect of peripheral origin is studied on peripheral component of the nociceptive response. Comparative characteristics of the analgesic effect of the drug D-Na and pharmacological combination D-Na with caffeine, as well as drug Ib and its pharmacological composition with caffeine was carried out using the screening model "acetic acid-induced cramps". The mechanism of pathology under the influence of acetic acid includes activation of kallikrein-kinin system, prostaglandins, biogenic amines, and leukotrienes which are endogenous mediators of inflammation and contribute to the development of abdominal muscles cramps, accompanied by stretching of hind limbs and arching of the back. The rats were observed for 20 minutes after administration of acetic acid and number of cramps in rats was counted. Cramps were induced by single intraperitoneal administration of 0.6 % acetic acid at the rate of 1 ml per 100 g weight of the animal. Animals were divided into 5 groups, 6 animals in each group. First group was the control one, 3% starch mucilage was once orally intragastrically administered to animals of this group (2 ml per 200 g of

rat). Investigated NSAIDs and their compositions with caffeine in the form of 3% starch mucilage suspension were once intragastrically administered to animals of groups 2nd – 5th. D-Na (5 mg per 1 kg of body weight of the animal) was administered to the animals of 2nd group. Composition of D-Na (5 mg per 1 kg of body weight of the animal) with caffeine (0.6 mg per 1 kg of body weight of the animal) was administered to the animals of 3rd group. Ib (6 mg per 1 kg of body weight of the animal) was administered to the animals of 4th group. Composition of Ib (6 mg per 1 kg of body weight of the animal) with caffeine (0.6 mg per 1 kg of body weight of the animal) was administered to the animals of 5th group. Examined NSAIDs and their compositions with caffeine as well as 3 % starch mucilage were administered 1 hour before administration of algogenic agent. The animals were observed for 20 minutes and number of cramps was counted. Analgesic activity was estimated by the ability of NSAIDs and their compositions with caffeine to reduce the number of cramps in the experimental groups in comparison with control animals and expressed in percents. Analgesic activities of pure Ib and D-Na were also compared with analgesic activities of their compositions with caffeine.

Analgesic activity of central origin was studied on central component of the nociceptive response. Analgesic effect of investigated NSAIDs and their compositions was studied on influence on the central component of pain response using summation-threshold index (STI) which reflects the functional state of the CNS. STI was determined by the criterion of unconditioned-reflex motor reaction of animals in response to electric stimulation with frequency of 2 impulses per second with increasing voltage 1 V per second by S.V. Speranskiy. Impulse stimulator was employed for this purpose. The distribution of animals in groups and doses of drugs and their combinations with caffeine were similar to research study of analgesic activity of peripheral origin. STI was determined at the beginning of the experiment (initial pain threshold), in 30, 60 and 90 minutes after administration of suspensions of investigated substances D-Na and Ib and their compositions.

The effect on the inflammatory process. Anti-exudative effect of the examined compounds and their compositions was studied using an experimental model of

formalin edema. NSAIDs, their combinations with caffeine, and starch mucilage (control group) were administered 1 hour before the maximum experimental edema. Exudative inflammation was modeled by subplantar injection of 0.1 ml of 2% formalin solution in the rat hind paw. Paw volume was measured using oncometer before the experiment and at the moment of maximal swelling i.e. 4 hours after administration of flogogenic agent. Increasing of edema was expressed in reference units. The percent of inhibition of inflammation was calculated by the formula [10]:

$$\% \text{ inhibition of inflammation} = \frac{(V_k - V_r)}{V_k} \cdot 100\%, \quad \text{where:}$$

V_k – volume of paw in control less the initial volume of this paw before swelling;

V_r – volume of swelled paw in research less the initial volume of this paw.

Animals were divided into 5 groups, 6 animals in each group. First group was the control one, 3% starch mucilage was once orally intragastrically administered to animals of this group (2 ml per 200 g of rat). Investigated NSAIDs and their compositions with caffeine in the form of 3% starch mucilage suspension were once intragastrically administered to animals of groups 2nd – 5th. D-Na (8 mg per 1 kg of body weight of the animal) was administered to the animals of 2nd group. Composition of D-Na (8 mg per 1 kg of body weight of the animal) with caffeine (0,6 mg per 1 kg of body weight of the animal) was administered to the animals of 3rd group. Ib (6 mg per 1 kg of body weight of the animal) was administered to the animals of 4th group. Composition of Ib (6 mg per 1 kg of body weight of the animal) with caffeine (0,6 mg per 1 kg of body weight of the animal) was administered to the animals of 5th group.

The study was carried out in accordance with the methodological recommendations of the State Pharmacological Center MoH Ukraine [10]. Number of animals and their distribution in groups were in accordance with economical approach, bioethical rules and statistics requirements. Recalculation of the human

doses for rats was done by using the ratio of species sensitivity by Rybolovlev Yu. R. [10]. Statistical calculations were performed by conventional methods [11].

Laboratory animals employed in the study were kept in experimental biological clinic of KhNMU following the norms of the storage, care and feeding approved by the principles of "European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes" (Strasbourg, 1986) [12] and the decision of the First national Congress on Bioethics (Kyiv, 2007) [13]. Experiments were carried out in the morning, which according to the literature data corresponds to the dependence of the main pharmacological parameters and pharmacological activity of investigated drugs on circadian rhythms [14, 15].

Results and Discussion. Effect on the nociceptive system. Studying of peripheral component of analgesic activity.

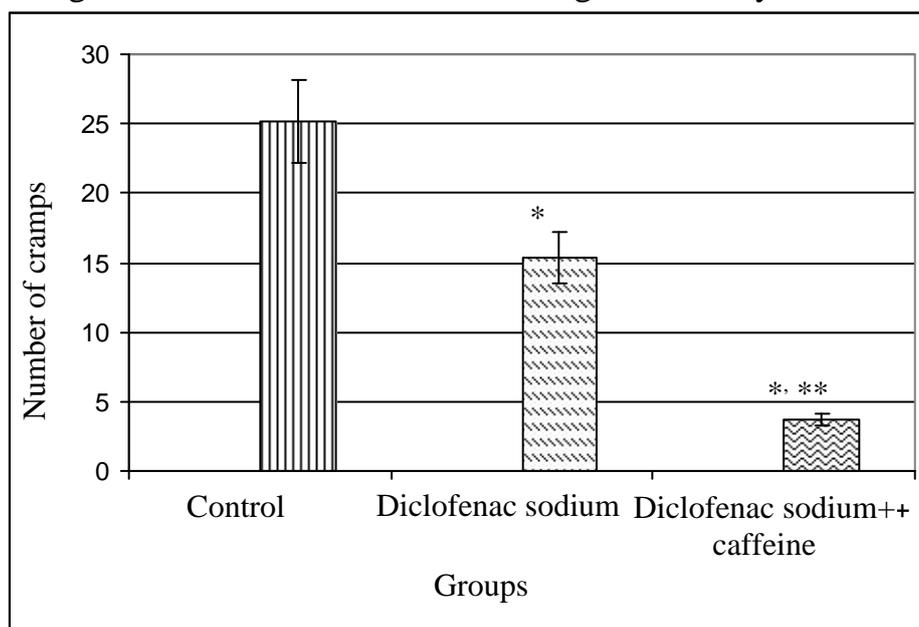
Experimental studies have shown that administration of pure D-Na significantly reduces the number of cramps to $15,33 \pm 0,21$ as compared to the control group ($25,17 \pm 0,17$), ($P < 0,001$). Analgesic potential is 39 %. Administration of pharmacological composition of D-Na with caffeine significantly reduces the number of cramps to $3,67 \pm 0,61$ as compared to the control group ($25,17 \pm 0,17$), ($P < 0,001$), as well as compared to the group with administration of pure drug ($15,33 \pm 0,21$), ($P < 0,001$). Analgesic potential is 85 % (Fig 1).

Administration of pure Ib also significantly reduces the number of cramps to $10,83 \pm 0,31$ as compared to the control group ($25,17 \pm 0,17$), ($P < 0,001$). Analgesic activity is 57%.

Addition of caffeine to Ib leads to significant reduce of cramps to $7,5 \pm 0,34$ as compared to the control group ($25,17 \pm 0,17$), ($P < 0,001$), as well as compared to the group with administration of pure drug ($10,83 \pm 0,31$), ($P < 0,001$). Analgesic activity is 70% (Fig 2).

Analysis of experimental results indicates that caffeine potentiates analgesic activity of NSAIDs of different chemical structure – D-Na (phenylacetic acid derivative) and Ib (propionic acid derivative).

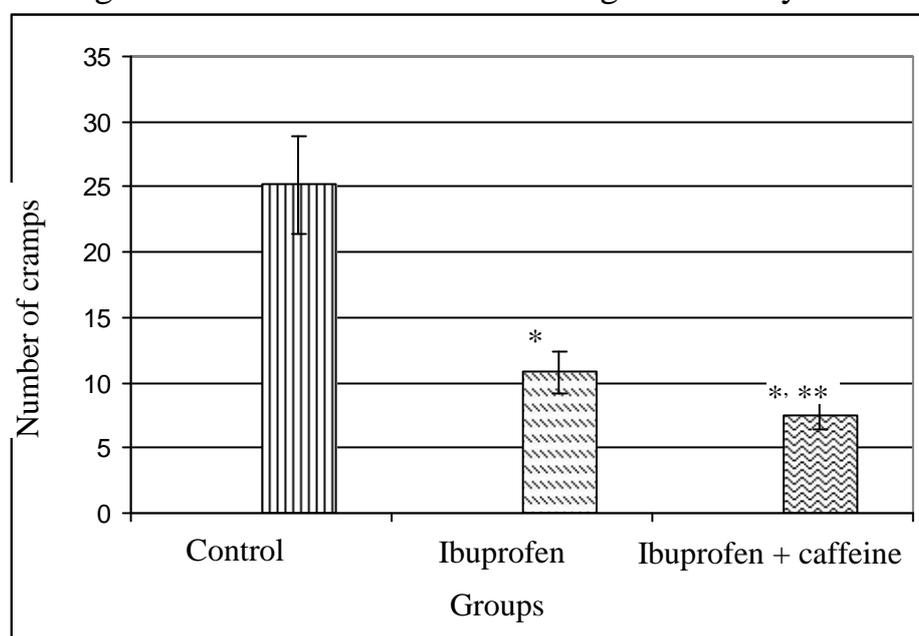
Fig. 1. Influence of caffeine on analgesic activity of D-Na



Note: * – difference is statistically significant versus control

** – difference is statistically significant versus pure D-Na

Fig. 2. Influence of caffeine on analgesic activity of Ib



Note: * – difference is statistically significant versus control

** – difference is statistically significant versus pure Ib

Research of the central component of the analgesic activity. Analysis of the results of center link of analgesic activity research indicates that administration of

pure Ib does not cause significant difference between the derived parameters compared with the control and the initial level that does not correspond to the central mechanism of the analgesic activity of the drug (Table 1). Administration of pharmacological composition of Ib with caffeine causes significant decrease in the summation ability of CNS in rats as compared to the initial level as well as compared to the group of pure drug administration in 30 and 60 minutes. This fact confirms the central mechanism of analgesic activity of pharmacological composition (Table 1). Pure D-Na as well in a pharmacological composition with caffeine does not cause significant shift of studied parameter (Table 1.).

able 1.

Parameters of STI (sec) in case of administration of pure D-Na and Ib and pharmacological compositions with caffeine (n=6)

gr.	Research conditions	Initial level	30 min	60 min	90 min
1.	Control	8,62±0,20	8,58±0,18	8,60±0,21	8,65±0,24
2.	D-Na	8,17±0,24	9,58±0,47	9,30±0,49	9,57±0,38
3.	D-Na+ caffeine	8,17±0,24	9,68±0,45	8,88±0,39	9,27±0,28
4.	Ib	8,75±0,17	8,92±0,25	8,73±0,26	8,28±0,20
5.	Ib+ caffeine	8,75±0,17	8,03±0,27***,***	7,90±0,26***,***	8,43±0,27

Note: difference is statistically significant: * – versus control; ** – versus initial level; *** – versus administration of pure NSAID.

Influence on the process of exudation. Analysis of experimental results shows that D-Na and Ib reduce swelling by 33% and 37 % respectively. The compositions of NSAIDs with caffeine show more intense anti-exudative activity: D-Na + caffeine significantly reduces the formalin edema as compared with control group ($P < 0,01$). Activity of D-Na composition with caffeine is 47%, which is significantly different from the activity of pure D-Na ($P < 0.05$ – 33%). This result allows making conclusion that caffeine is able to potentiate anti-exudative activity of D-Na (Table 2).

Composition of Ib with caffeine appears to be the most effective among the studied compositions. This combination significantly reduces development of formalin edema ($P < 0,001$), as testified by paw volume which almost coincides with the initial volume (inhibition – 95%). Pure Ib reduces edema by 37% (the difference between activity of pure Ib and its combination with caffeine is statistically significant – $P < 0,001$) (Table 3).

Table 2.

Anti-exudative activity of D-Na and its compositions with caffeine (n=6)

Parameters	Control		D-Na		D-Na + caffeine	
	Initial volume of paw (mm)	Volume of paw in 4 hours after edema inducing (mm)	Initial volume of paw (mm)	Volume of paw in 4 hours after edema inducing (mm)	Initial volume of paw (mm)	Volume of paw in 4 hours after edema inducing (mm)
X±Sx	17,75±1,03	30,5±1,19	19,25±0,85	27,75±0,85 *	17,00±0,32	23,8±1,20 *. **
Inhibition of edema, %				33		47

Note: * – difference is statistically significant: D-Na versus control;

** – difference is statistically significant: pure D-Na versus composition with caffeine

Table 3.

Anti-exudative activity of Ib and its compositions with caffeine (n=6)

Parameters	Control		Ib		Ib + caffeine	
	Initial volume of paw (mm)	Volume of paw in 4 hours after edema inducing (mm)	Initial volume of paw (mm)	Volume of paw in 4 hours after edema inducing (mm)	Initial volume of paw (mm)	Volume of paw in 4 hours after edema inducing (mm)
X±Sx	17,75±1,03	30,5±1,19	18,75±1,31	26,75±1,03 *	17,8±0,2	18,4±0,51 *. **
Inhibition of edema, %				37		95

Note: * – difference is statistically significant: Ib versus control;

** – difference is statistically significant: pure Ib versus composition with caffeine.

Thus, the compositions of the investigated NSAIDs with caffeine have pronounced anti-exudative activity, so caffeine potentiates anti-exudative activity of the studied NSAIDs – D-Na and Ib. The composition of caffeine with Ib shows more intensive anti-exudative effect than composition of caffeine with D-Na (Table 2 and 3).

Conclusions. 1. Compositions of studied NSAIDs with caffeine affect the peripheral component of pain reaction and have pronounced analgesic activity of peripheral origin, thus caffeine potentiates the analgesic activity of D-Na and Ib. As for analgesic activity of central origin it is found that caffeine potentiates the central mechanism of analgesic activity of Ib only [16].

2. Compositions of studied NSAIDs with caffeine have pronounced anti-exudative activity, so caffeine potentiates anti-exudative activity of D-Na and Ib. The composition of caffeine with propionic acid derivative (Ib) has more intense anti-exudative effect than caffeine composition with phenylacetic acid derivative (D-Na) [17].

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WOUND HEALING EFFECT TIOTRIZOLINE OINTMENT FOR ACTION ON SKIN IONIZING RADIATION IN RATS

Kharkov National Medical University, Ukraine

Abstract. *The wound healing effect "Unguentum Thiotriazolini 2%" (JSC "chemical-pharmaceutical plant" Red Star ", Ukraine) was studied in rats with local radiation skin lesions. The rats were divided into four groups, each comprised of six rats: intact (group 1), radiation injuries of the skin (group 2), radiation injuries of the skin + ointment: methyluracil (group 3) and Thiotriazoline (group 4). Rats of 2, 3 and 4 groups were exposed to X-rays of the hip (80 Gy). In Group 3 and 4 the ointments were applied on the skin 1 hour before exposure and for 10 days after it once a day. On the 35th day of experiment immunomorphological study of focus of exposure (macrophages, cells are producers of interleukins IL-1 and IL-10) was performed. The results showed that the ointment Thiotriazoline (group 4) caused a more pronounced wound healing effect, manifested increased macrophage reaction, restoration of cytokine balance, compared with group 2 and 3.*

Key words: *Thiotriazoline ointment, wound healing effect, ionizing irradiation of the skin*

Ionizing radiation is a widely used in the treatment of various types of cancer and radiation skin injury is a significant problem. This injury occurs in about 95% of patients receiving radiation therapy for cancer [1]. For many years, radiation burns have been treated like thermal burns, in spite of differences in their pathogenesis [2]. Radiation burns have a dose-dependent clinical manifestation, which includes dry desquamation at 12–20Gy, moist desquamation at 20Gy, and necrosis at >35Gy [3].

Radiation burns associate with violation of skin immunity. Ionizing radiation causes degranulation of mast cells in the dermis. Mast cell–derived histamine, serotonin, tumor necrosis factor- α , and tryptase significantly alter the release of chemokins by dermal fibroblasts [4]. The features of radiation injuries to the skin are suppression of

repair processes, expressed chronic inflammation and low efficacy of therapeutic interventions, in large part due to a violation of the immunological mechanisms [4, 5]. Management of skin radiation injury includes mainly local conservative treatment with ointments, gels, liniments, creams, containing corticosteroids and nonsteroidal agents [6], lanolin-free, water-based moisturizing cream [7], local bone marrow-derived stem cells [2] and other medications. The application of ointments that have a complex multi-directional effect on the wound process is the most promising. In this connection, our attention was attracted by drug of polytropic actions, thiotriazoline ointment "Unguentum Thiotriazolini 2%" (JSC "chemical-pharmaceutical plant" Red Star – “”, Ukraine) with the membrane stabilizing, antioxidant, and anti-inflammatory properties. This determines the expediency of study of this drug efficacy in the skin damage caused by ionizing radiation.

Purpose: to study the wound healing effect "Unguentum Thiotriazolini 2%" in a single local ionizing irradiation of rat skin.

Materials and methods. The study was conducted on 4 groups of WAG rats: Group 1 - intact (n=6), Group 2 - radiation damage to the skin - control (n=6), group 3 (comparator drug) - radiation damage to the skin+methyluracil ointment (n=6), group 4 (main) - radiation damage to the skin+thiotriazoline ointment (n=6). In rats of the 2nd, 3rd, and 4th groups local radiation damage to the skin was caused by a single local action of X-rays radiation at the thigh area of animals in the exposure dose of 80 Gy (irradiator Tur-60, 5 mA, 50 kV, filter 0.3 mm Al, dose 80.2 Gy / min, irradiation area 20mm²) [8]. In Group 3 and 4 one hour before irradiation and after it for 10 days once a day the ointment of thiotriazoline and methyluracil respectively were applied on the surface of skin. The severity of skin reactions to radiation exposure was evaluated by clinical manifestations, duration and timing of the healing of radiation damage. All groups of animals were taken out of the experiment at 35 days after irradiation in accordance with the requirements of the European Convention for the Protection of Vertebrate Animals. For objectification of healing morphological and immunohistochemical (quantification of macrophages, cells-producer of

interleukin IL-1 and IL-10) studies of the skin in the area of exposure were carried out [9,10]. The data obtained were analyzed by standard method of variation statistics. **Results.** All rats in group 2 at 24 hours after irradiation developed primary erythema. On the third day true bright erythema appeared and remained until the 7th day. Reaction of wet and dry desquamation developed sequentially from the 7th day after irradiation. On 7-9 day dry epitheliitis, that is, the appearance of dry yellow crusts and marked desquamation, were observed in all rats. Dry desquamation lasts for 8 days. In some animals during this period already the integrity of the skin was violated, and epithelium exfoliation occurred. Moist desquamation developed on day 15 after exposure and its duration was on average 17 days. Thus the large areas of weeping surface appeared followed by the formation of brown crusts and ulcer. Ulcers with purulent necrotic manifestations that was persisting to the end of the observation period, developed in 83% of animals. According to immunohistological studies this group developed severe ulcerative destructive changes with signs of chronic radiation ulcers, degenerative changes in fibrous stroma accompanied by macrophages deficiency, 2.8-fold increase in cells-producers of proinflammatory interleukin IL-1 and 1.8 times decrease in cells-producers of anti-inflammatory interleukin IL-10 as compared with intact rats (Table 1).

Reduced the number of macrophages that regulate the proliferation of fibroblasts and provide a link between the inflammatory and reparative response, confirms the absence of repair processes in animals of this group. In addition, lack of anti-inflammatory cytokines contributes to the development of immune deficiency and the formation of chronic inflammation [11].

In the third group of animals (radiation skin damage methyluracil ointment+) radiation reactions proceeded more easily than in the controls. Pronounced erythema developed in 83% of the exposed rats lasted for 6 days. Dry epidermitis, characterized by the appearance of yellow crusts on the background of hyperemia with further development expressed peeling, lasted 7 days. Moist desquamation, which was observed for 15 days, was characterized by the emergence of sites weeping surface followed by the formation of brown crusts with skin cracks.

Table 1

The relative amount of macrophages and cells-producers of interleukins in the skin of rats on 35 day after radiation

Groups	Macrophages	Cells-producers of interleukin	
		IL-1	IL-10
Group 1 - intact	8,33±0,55	2,50±0,42	1,33±0,21
Group 2 - radiation damage to the skin	8,83±0,31	7,00±0,36 ^{###}	0,75±0,11 [#]
Group 3 - radiation damage to the skin + methyluracil ointment	8,83±0,31	3,17±0,31 ^{***}	1,42±0,37 [*]
Group 4 - radiation damage to the skin +thiotriazoline ointment	11,17±0,31 ^{**}	4,67±0,42 ^{***}	3,33±0,33 ^{***}

Notes:

1.Significance of differences comparing to group 1(# – 0,05; ## – 0,01; ### – 0,001)

2.Significance of differences comparing to group 2 (* – 0,05; ** – 0,01; *** – 0,001)

In 67% of the rats irradiation led to the formation of a surface covered with sores. The disappearance of the radial change began on 28 day after exposure. At the stage of healing the irradiated area of the skin was a glossy surface with traces of peeled crusts. Immunomofrologic data confirmed the improved course of healing in comparison with the control, but severe destructive processes with reduced regenerative activity, as well as local immune processes (2.2-fold reduction in cells producing IL-1 and increase in cells producing IL-10 up to 1 9 times) reminded (Table 1). The amount of macrophages did not change.

Radiation damage in group 4 (radiation skin damage + thiotriazoline ointment) were less pronounced compared to the control group and group 3 (radiation skin damage + methyluracil ointment), and faster died down. So, erythema was observed for 5 days in 66% of rats. Dry desquamation accompanied by slight peeling lasted not more than 6 days. The duration of course of moist dermatitis was reduces to 11 days; its severity also was reduced. Ulcerative defect occurred only in 33% of the exposed rats. Restoration of the epithelium integrity and the healing was noted from 22nd day that is 6 days earlier than in the third group. In all rats the area of irradiation was epithelized completely, providing a surface that is completely healed. Thiotriazoline ointment showed more pronounced effect in contrast to the previous groups:

epithelialization of skin defects was associated with preservation vessels of microvascular circulation and appendices of the skin, increase in the number of macrophages by 26.5%, decrease in cells-producers IL-1 by 1.5 times with greater increase in cells producing IL-10 (4.4-fold) (Table 1). Apparently, marked macrophage reaction promoted rapid wound cleansing of cellular debris and, due to macrophage-fibroblast interaction it accelerated fibroblast proliferation, synthesis and secretion of collagen. Activation of cell-producers proinflammatory cytokine IL-1 promoted the development of an adequate inflammatory response, and growth of cells that produce anti-inflammatory cytokine IL-10 stimulated the production of macrophages, fibroblast growth factor, which is one of the links in the activation of healing processes that have been found in our histological studies.

Thus, thiotriazoline ointment reduces the intensity of development and decreases the time course of acute radiation damage to the skin of rats in the irradiation, as evidenced immunomorphologic data: increased macrophage reaction, restoring the cytokine balance.

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Ashcheulova T., Kovalyova O.

DISTANT APOPTOSIS BIOMARKERS IN HUMAN HYPERTENSION

Kharkov National Medical University, Ukraine

Abstract. *The aim was to study plasma apoptosis markers (TNF- α , sTNF-R1, sFasL) levels in patients with arterial hypertension (AH) depend on degree of blood pressure elevation.*

We examined 78 patients with AH, which were divided into 3 groups depend on AH degree: 1 group (n=18) – 1 degree AH, 2 group (n=25) – 2 degree AH, 3 group (n=35) – 3 degree AH. Plasma tumor necrosis factor- α (TNF- α), soluble TNF receptors type 1 (sTNF-R1), and soluble Fas ligand (sFasL) levels by ELISA were detected.

It was found that plasma TNF- α levels in all groups patients were higher than in healthy normotensives ($p < 0.05$). Maximum mean was detected in 2 degree AH patients. Circulating sTNF-R1 levels of all groups patients were elevated vs normal means ($p < 0.05$). In spite of detected increasing TNF-R1 concentration, natural TNF-inhibitor, and insignificant decreasing of TNF- α /sTNF-R1, cytokine level remained high, that confirm possibility of TNF-mediated apoptosis pathway in hypertensive patients. Obtained results indicate possibility of Fas-related apoptosis in patients with arterial hypertension.

Conclusion. *Result of our clinical study showed increased immuno-inflammatory and proapoptotic activity depends on presence and degree of arterial hypertension.*

Keywords: *apoptosis, circulating apoptosis biomarkers, arterial hypertension.*

Apoptosis, or programmed cell death, is a normal component of the development and health of multicellular organisms. Cells die in response to a variety of stimuli and during apoptosis they do so in a controlled, regulated fashion [1,2]. This makes apoptosis distinct from another form of cell death called necrosis in which uncontrolled cell death leads to lysis of cells, inflammatory responses and, potentially, to serious health problems. Apoptosis, by contrast, is a process in which

cells play an active role in their own death (which is why apoptosis is often referred to as cell suicide) [3,4].

The term programmed cell death was first introduced in 1964, proposing that cell death during development is not of accidental nature but follows a sequence of controlled steps leading to locally and temporally defined self-destruction [5].

Eventually, the term apoptosis had been coined in order to describe the morphological processes leading to controlled cellular self-destruction and was first introduced in a publication by Kerr, Wyllie and Currie [6]. Apoptosis is of greek origin, having the meaning "falling off or dropping off", in analogy to leaves falling off trees or petals dropping off flowers. This analogy emphasizes that the death of living matter is an integral and necessary part of the life cycle of organisms. The apoptotic mode of cell death is an active and defined process which plays an important role in the development of multicellular organisms and in the regulation and maintenance of the cell populations in tissues upon physiological and pathological conditions. It should be stressed that apoptosis is a well-defined and possibly the most frequent form of programmed cell death, but that other, non-apoptotic types of cell death also might be of biological significance [3,5].

There are a number of mechanisms through which apoptosis can be induced in cells. The sensitivity of cells to any of these stimuli can vary depending on a number of factors such as the expression of pro- and anti-apoptotic proteins (eg. the Bcl-2 proteins or the Inhibitor of Apoptosis Proteins), the severity of the stimulus and the stage of the cell cycle.

There are 3 different mechanisms by which a cell commits suicide by apoptosis.

1. Generated by signals arising within the cell;
2. Triggered by death activators binding to receptors at the cell surface:
 - Tumor necrosis factor- (TNF-)
 - Lymphotoxin
 - Fas ligand (FasL)
3. May be triggered by dangerous reactive oxygen species [7,8].

Apoptosis is an energy-dependent process by which a specific genetic program leads to the activation of molecular cascades that cause cell death. Apoptosis is marked by the involution of the cell, eventuating in phagocytosis by neighboring cells. By deleting cells, apoptosis plays a physiological role in controlling cell mass and architecture in many tissues, including the myocardium [9-11].

Under a pathophysiological point of view, hypertension affects the myocardium at two different stages. In both humans and animal models, pressure overload is characterized by a period of compensation in which left ventricular concentric hypertrophy normalizes systolic wall stress and contractile function is preserved. The period of adaptation, which may last for weeks in rodents and months to years in humans, is inexorably followed by a transition to cardiac failure. This transition is characterized by impaired survival, the onset of chamber dilatation with the failure of further concentric hypertrophic growth to normalize load, and progressive contractile dysfunction. A number of observations suggest that the transition to failure relates mainly to cardiomyocyte loss due to both apoptosis and necrosis, changes in the composition of motor unit and cytoskeleton of cardiomyocytes, and alterations in the metabolism of the extracellular matrix [12-16].

Apoptosis is recognized, increasingly, as a contributing cause of cardiomyocyte loss with important pathophysiological consequences. Recent evidence demonstrates that cardiomyocyte apoptosis is abnormally stimulated in the heart of animals and humans with arterial hypertension [17,18].

Cardiomyocyte apoptosis has been proposed to occur as a result of an imbalance among the factors that induce or block apoptosis. Alternatively, it is possible that apoptosis reflects some intrinsic abnormalities in those factors that act within the cardiomyocyte determining the resistance or the susceptibility of the cell to apoptosis [19].

In conclusion, much work is being carried out regarding the mechanisms and the extent of cardiomyocyte apoptosis in hypertensive heart disease, but many methodological and conceptual issues still remain unsolved. Clarification of these

unresolved issues will then allow an estimation of the role of apoptosis in the pathogenesis of heart failure associated with hypertensive heart disease.

Therefore, the aim of our clinical investigation was to study plasma apoptosis markers (TNF- α , sTNF-R1, sFasL) levels in patients with arterial hypertension depend on degree of blood pressure elevation.

Design and methods. We examined 78 patients with arterial hypertension, duration of the diseases in which was from one month to 40 years (10.09 ± 48 years). Duration of blood pressure (BP) elevation not more than 5 year was evaluated in 30.28%, from 5 to 10 years – 34.51%, and more than 10 years – in 35.21% of patients. Control group include 20 healthy persons.

BP levels vary: systolic BP (SBP) – from 134.70 mm Hg to 250.00 mm Hg (in average 170.96 ± 1.33 mm Hg); diastolic BP (DBP) – from 80.70 mm Hg to 160.00 mm Hg (in average 103.14 ± 0.63 mm Hg). Average mean of heart rate (HR) 80.32 ± 0.69 beats per minute were determined (from 50 to 120 b/min).

AH 1 degree were diagnosed in 35.01% patients (SBP – 149.39 ± 0.56 mm Hg, DBP – 95.96 ± 0.46 mm Hg); 2 degree – in 32.39 % patients (SBP – 166.33 ± 0.67 mm Hg, DBP – 102.53 ± 0.72 mm Hg); 3 degree AH was detected in 32.39 % patients (SBP – 196.54 ± 1.72 mm Hg, DBP – 111.46 ± 1.29 mm Hg) (Figure 1).

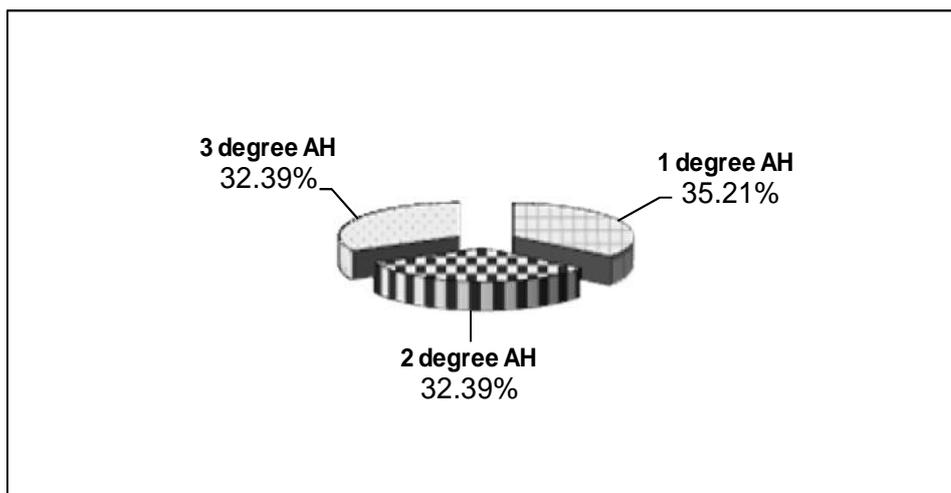


Figure 1. Patients division depend on arterial hypertension degree

Depend on degree of target-organs affection, I stage AH was determined in 8.45% patients, II stage AH in 81.69%, III stage – in 9.86% patients (Figure 2). In 3.17% examined persons, cerebral stroke was in anamnesis, in 6.69% patients – myocardial infarction.

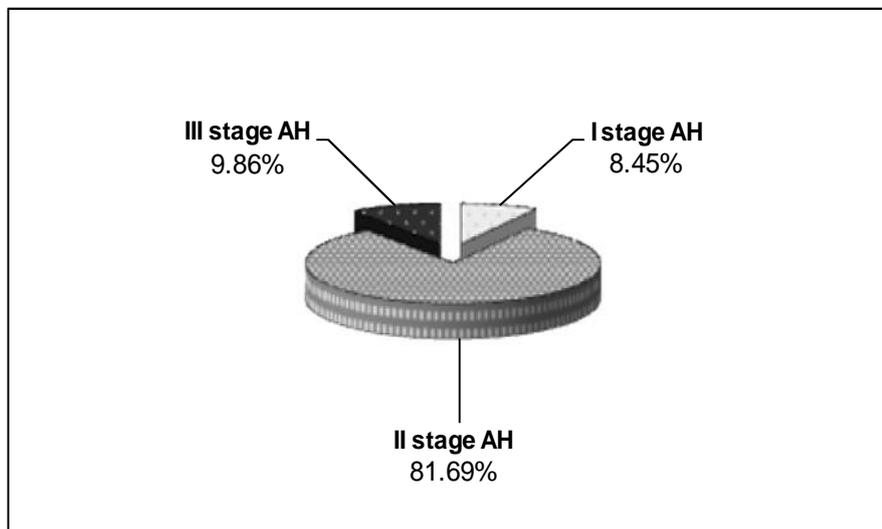


Figure 2.Patients division depend on arterial hypertension stage

In most patients (93.66%) hypertension was complicated by heart failure (HF): in 26.06% cases I degree HF, in 59.15% - IIA degree HF, and in 8.45% - IIB degree HF. 6.34% patients had no HF signs (Figure 3).

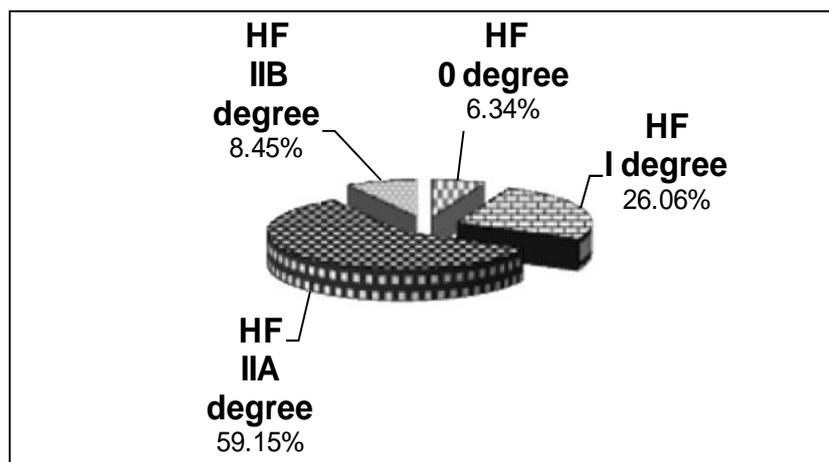


Figure 3.Patients division depend on heart failure degree

Division of the patients according to functional class (FC) New York Heart Association (NYHA) showed I NYHA functional class in 3.17% patients, II NYHA FC – in 45.452%, III NYHA FC – in 44.37%, and IV NYHA FC – in 7.04% (Figure 4).

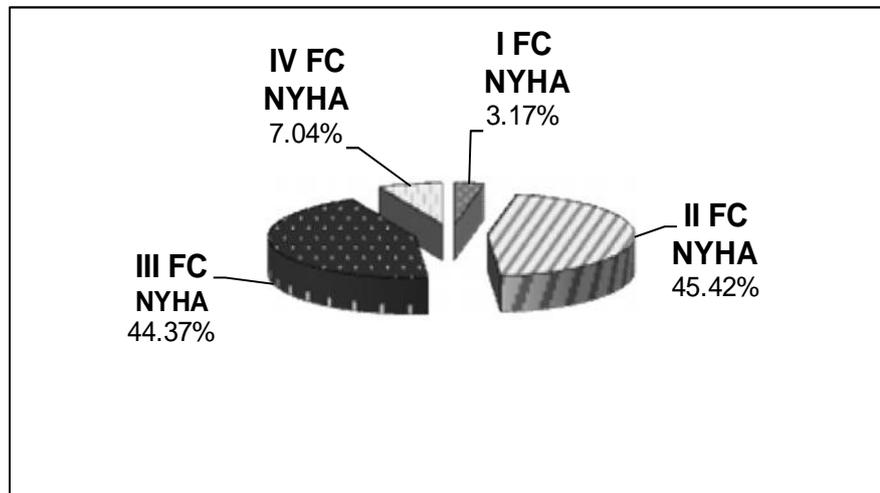


Figure 4. Patients division depend on functional class (NYHA)

Concomitant coronary heart disease (CHD) took place in 72.89% patients: among them in 1 degree AH presence of CHD was diagnosed in 57% patients, whereas in 2 degree AH – in 77.17% and in 3 degree – in 85.86% patients.

Exclusion criteria: secondary arterial hypertension, concomitant oncological pathology, acute and chronic inflammatory diseases, diabetes mellitus, significant alterations of heart rhythm and conductivity.

Tumor necrosis factor- plasma levels were determined by ELISA method (“ProCon TNF “Protein contour”, Saint Petersburg, Russia), which is used to quantitative determination of Human TNF- in plasma, serum, and cultural fluids in concentrations intervals 20-2000 pg/ml. According to this method normal serum blood TNF- levels usually don’t exceed 50 pg/ml.

Determination of tumor necrosis factor- soluble receptors type 1 (sTNF-R1) was done by ELISA (sTNF-R1EASIA, BioSource Europe S.A., Belgium). Reagents kit is used to human sTNF-R1 quantitative analysis in serum, plasma, cellular cultures and others biological fluids. According to this method normal sTNF-R1 level

that was assessed in 129 healthy persons vary from 0.3 ng/ml to 2.9 ng/ml, 1.2 ± 0.6 ng/ml in average.

Plasma sFasL levels were measured by test-system "humansFasLigandELISA" (BenderMedSystems, Vienna, Austria). Assay kit is used to human sFasL quantitative analysis in such solutions as supernatants or fluids of human organisms by **Enzyme-LinkedImmunosorbentAssay** – ELISA.

Statistical analysis was conducted according to rules of medico-biological information assessment after creation of data base in program Microsoft® Excel. Parametric and nonparametric statistical methods were used. Continuous variables are presented as average mean (M) and standard error (SE) and were tested using Student's t-test. To analyze relationships between examined parameters correlation analysis was conducted. All tests were two-sided and considered statistically significant at $p < 0.05$. Odds ratios are reported with 95% confidence intervals. Data analyses were performed using computer program „STATISTICA7.0" forWindows (StatSoftInc., USA).

Hemodynamic overload causes hyperactivity of proinflammatory cytokines that can initiate apoptosis cascade. In order to confirm this hypothesis, patients were divided into 3 groups depend on AH degree: 1 group (n=18) – 1 degree AH, 2 group (n=25) – 2 degree AH, 3 group (n=35) – 3 degree AH (Figure5).

Circulating sTNF-R1 levels of all groups hypertensive patients were elevated vs normal means ($p < 0.001$ in all cases) (Figure 6).

Analysis of plasma sTNF-R1 content dynamic showed tendency of its increasing parallel to BP level elevation (1 group vs 2 group $p = 0.59$; 1 group vs 3 group $p = 0.36$; 2 group vs 3 group $p = 0.75$).

Mean of TNF- /sTNF-R1 ratio that reflect relation ligand/receptor complex, of normotensive control group was 11.03 ± 2.84 . Study of this parameters changes shows its increasing in hypertensive patients with different degree of BP elevation as compared with normotensive persons (control vs 1 group $p = 0.0004$; vs 2 group $p = 0.0001$; vs 3 group $p = 0.0006$).

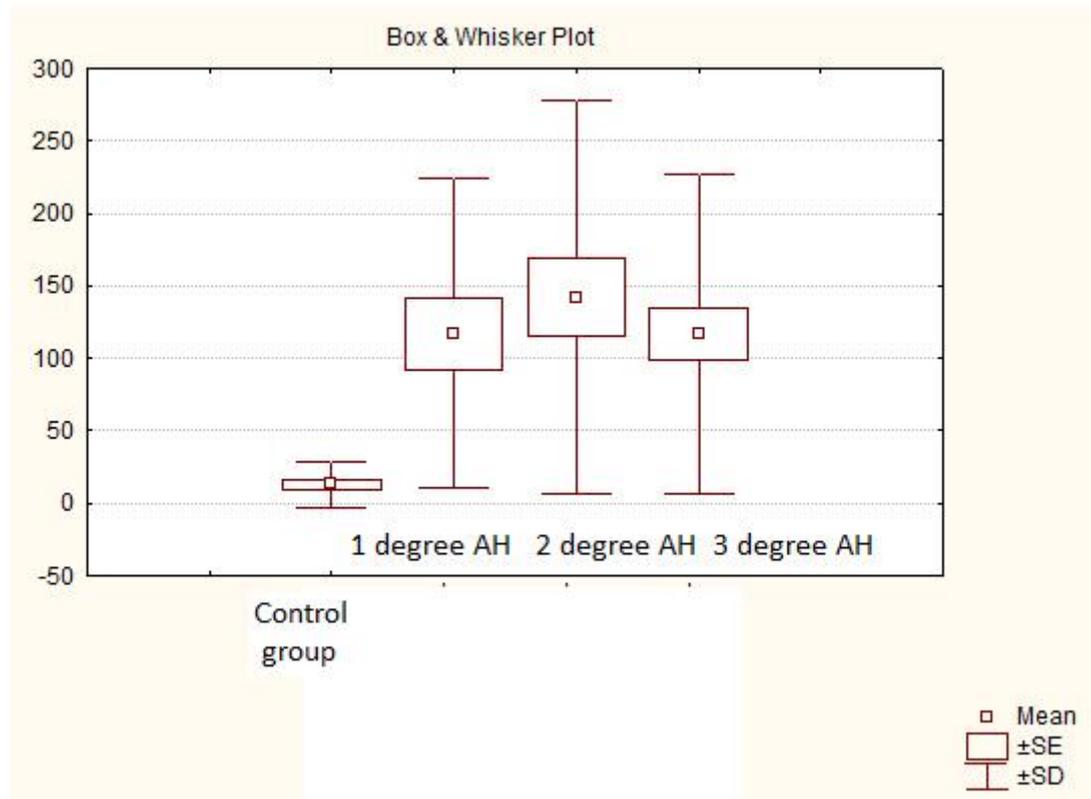


Figure 5. Plasma TNF-a levels in healthy persons and patients depend on AH degree

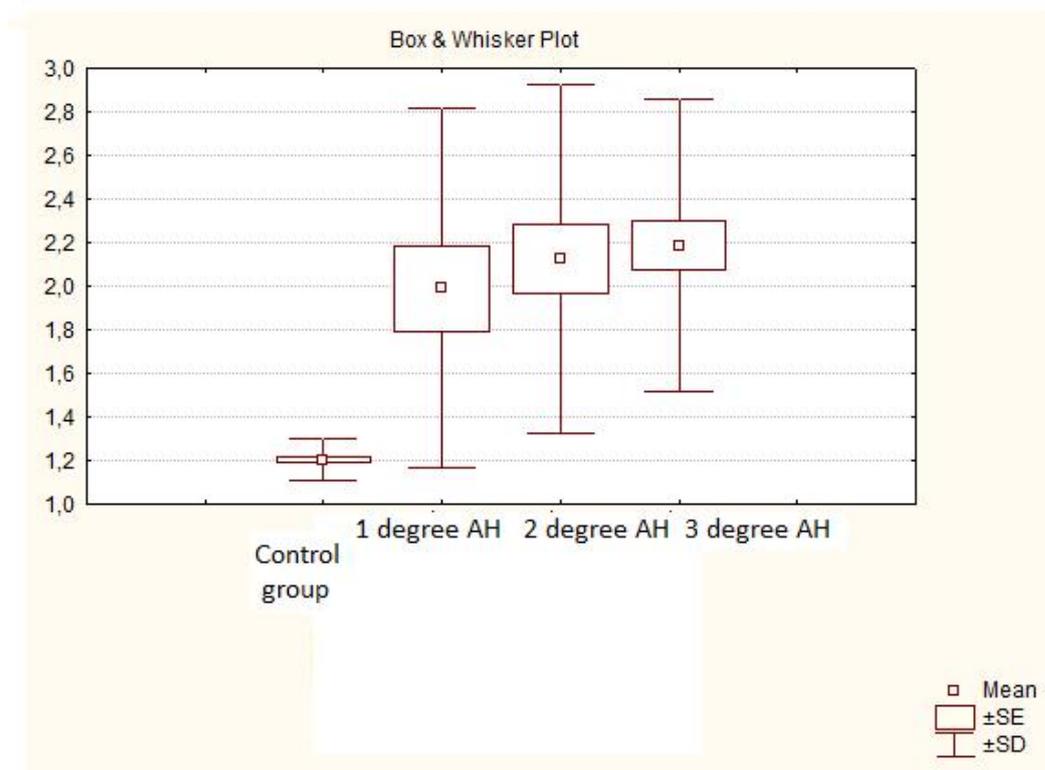


Figure 6. Plasma sTNF-R1 levels in healthy persons and patients depend on AH degree

Maximum mean was revealed in patients with 2 degree AH, that reflect more significant elevation of TNF- vs its natural antagonists – sTNF-R1 ($p=0.34$ vs 1 degree AH; $p=0.61$ vs 3 degree AH). Inpatients with 3 degree AH it was evaluated insignificant lowering TNF- /sTNF-R1 compared with 2 degree AH patients, but it was higher than in 1 degree AH ($p=0.59$) and normotensive subjects of control group.

Correlation analysis revealed positive relationships between SBP and sTNF-R1 ($r_s=0.41$; $p=0.040$) in patients with 2 degree AH; between DBP and TNF- ($r_s=0.51$; $p=0.002$), TNF- /sTNF-R1 ($r_s=0.49$; $p=0.003$).

Thus, in spite of detected increasing TNF-R1 concentration, natural TNF-inhibitor, and insignificant decreasing of TNF- /sTNF-R1, cytokine level remained high, that confirm possibility of TNF-mediated apoptosis pathway in hypertensive patients.

Alternative mechanism of apoptotic cellular death realization is binding of Fas receptor with corresponding ligand – Fas ligand (FasL). Apoptosis inductor rate in blood of hypertensive patients was $73\pm 5\%$, in average level 0.38 ± 0.03 ng/ml (concentration interval from 0 to 0.91 ng/ml).

We found significant sFasL detection rate in hypertensive patients depend on degree of BP elevation (Table 1).

Table 1

sFasL depend on level of blood pressure elevation

Parameters	1 degree H ($n=18$)	2 degree H ($n=25$)	3 degree H ($n=35$)
Age (years)	52.83 ± 1.46	53.40 ± 2.35	55.94 ± 1.56
AH duration (years)	5.51 ± 1.20	7.52 ± 1.36	13.20 ± 1.56
SBP (mm Hg)	149.08 ± 1.51	164.97 ± 1.13	196.40 ± 2.83
DBP (mm Hg)	96.04 ± 1.21	102.03 ± 1.53	113.52 ± 2.06
sFasL (ng/ml)	0.28 ± 0.07	0.40 ± 0.06	0.41 ± 0.04
Detection rate (%)	56 ± 12	76 ± 9	80 ± 7
Absolute patients amount (n)	10	19	28

In 1 degree AHsFasL presence was found approximately in one-half of patients; in 2 degree AHsFasL detection rate was higher ($p=0.082$ according ²); in 3 degree AH tendency of sFasL detection rate increasing was shown ($p=0.75$ vs 2 degree AH; $p=0.040$ vs 1 degree AH according ²). Assessment of average sFasL levels dynamics evaluated same tendency of its elevation (Figure 7).

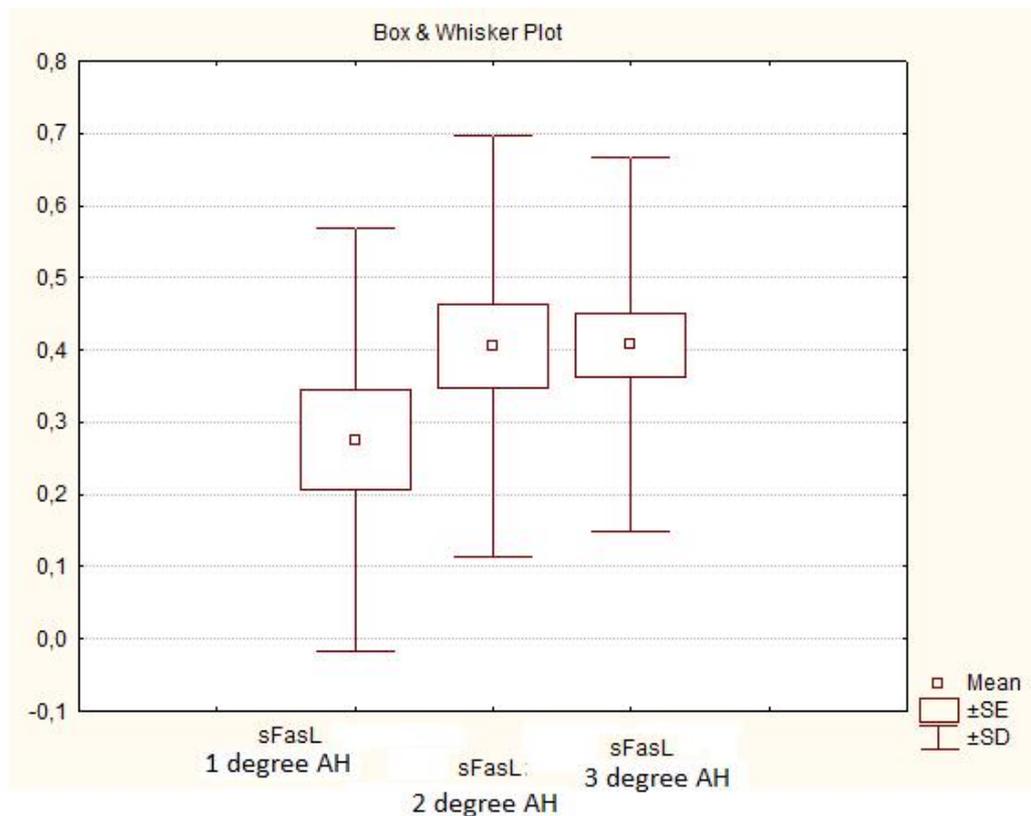


Figure 7. Plasma sFasL levels in hypertensive patients depend on blood pressure level elevation

There were no significant difference between average sFasL means in blood plasma of patients with 2 and 3 degree AH ($p=0.97$) and sFasL levels were some higher compared with 1 degree AH ($p=0.16$; $p=0.10$ correspondingly).

Positive correlation was found between age of hypertensives and plasma sFasL levels ($r=0.40$; $p=0.048$); negative – between sFasL and TNF- ($r=-0.55$; $p=0.005$), TNF- /sTNF-R1 ($r=-0.45$; $p=0.023$) in patients of 2 degree AH, between sFasL and TNF- ($r_s=-0.54$; $p=0.0008$), TNF- /sTNF-R1 ($r_s=-0.55$; $p=0.0006$) in 3 degree AH

patients. Obtained results indicate possibility of Fas-related apoptosis in patients with arterial hypertension.

Conclusion. Result of our clinical study showed increased immune-inflammatory and proapoptotic activity depends on presence and degree of arterial hypertension.

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THE LEVEL OF NEUROACTIVE AMINO ACIDS IN BLOOD PLASMA OF PSORIATIC PATIENTS

Kharkov National Medical University, Ukraine

Abstract. *Some amino acids neurotransmitters, such as glutamate, aspartate, glycine and -aminobutyric acid may be involved in the pathogenesis of psoriasis and hypertension. But their relationship with dermatosis severity and comorbidities are unclear. The aim of this study was to quantify level of activating and inhibitory amino acids in blood plasma of the patients suffering from isolated psoriasis and psoriasis combined with hypertension depending on severity of disease. The study was conducted on two groups of patients, first group consisted of 74 patients with isolated psoriasis, second group consisted of 48 patients with psoriasis combined with hypertension, control group comprised 30 practically healthy patients. Blood plasma level of glycine, glutamate, aspartate and -aminobutyric acid were defined by liquid chromatographic analysis.*

Severe course of psoriasis, especially combined with hypertension is characterized by excitatory and inhibitory mechanisms imbalance with signs of protective inhibition insufficiency; deficiency of GABAergic protective mechanisms along with increased release of excitatory amino acids determines the severity of psoriasis in this contingent of patients. Changes of the level of excitatory and inhibitory amino acids in blood plasma of psoriatic patients indicate their obvious participation in formation of cerebral circulation disturbance and autonomic regulation of peripheral vessels disorder.

ey words: *aspartate, GABA, glutamate, , glycine, neuroactive amino acids, psoriasis.*

This article is a fragment of the study “Diagnostic and prognostic aspects of cardio-metabolic disturbances in patients with systemic dermatoses” of the department of dermatology, venereology, medical cosmetology and the department of propaedeutic of internal medicine 1 of Kharkiv national medical university, state registration 0107U001393.

Introduction

Recently it has been prevailing view that psoriasis is a systemic disorder of multifactorial etiology with genetic and exogenous factors involvement, that results

in escalation of functional disorders, metabolic violation and launching of the mechanisms of pathological process formation [1-3].

The question of psoriatic patients' rehabilitation is very actual and socially significant. Treatment of this disorder has been difficult and controversial problem. Even initial and a fortiori prominent psoriatic manifestations often have complicated course, resistant to treatment, with predisposition to aggravation and relapses [4; 5]. In this regard, there is necessity to create a differentiated program of restorative treatment, aimed to boost functional reserves, development of compensatory mechanisms of the organism, prevention of aggravations and complications.

Despite fundamental studies of psoriasis, its many aspects remain poorly understood, especially regarding its combination with somatic diseases. These aspects include issues of cooperative interaction and the role of integrative systems of the body – neurological, endocrine and immunological [6-8].

Resolving of these allows in-depth approach to pathogenesis study from the perspective of multisystem evaluation of the homeostatic function based on the monitoring of metabolism indicators and on the condition of their regulating systems considering principal risk factors [9].

Amino acids glutamate and aspartate are widespread excitatory CNS neurotransmitters and play important role in homeostasis providing. GABAergic and Glutamatergic neurons are widespread in almost all brain structures that signifies undoubted importance of such type neurotransmission [10,11].

The goal of this study was to study the level of activating and inhibitory amino acids in blood plasma of the patients suffering from isolated psoriasis and psoriasis combined with hypertension depending on severity of disease.

The object and methods of the study.

The study was conducted on two groups of patients, age range from 40 to 65 having confirmed diagnosis of psoriasis, that were examined and treated in an outpatient dermatologic city clinic 5 in Kharkiv (Ukraine). The first group consisted of 74 patients with isolated psoriasis, 40 of which had mild course of disease, 24 – moderate, and 10 – severe course. The second group consisted of 48

patients with psoriasis combined with hypertension, 22 of which had mild course of disease, 16 - moderate and 10 - severe course. Precise anamnesis and laboratory examination were conducted, that consists of generalclinical and biochemical analysis of the peripheral blood. Control group comprised 30 practically healthy patients.

Blood plasma level of glycine, glutamate, and aspartate were defined by liquid chromatographic analysis with amino acidic analyzer AAA-339 (Czech Republic). For calibration tests and quantitative evaluation of chromatographs there were used standard technical solutions of amino acids (the firm "Lachema"), that accompanied the reagent kit of amino acid analyzer. The level of γ -Aminobutyric acid (GABA) was defined after its segregation by chromatographic analysis by Carmona et.al method [12]. To measure the level of GABA there was conducted the reaction with ninhydrin. Fluorescence was measured under the excitation wave length of 380 nm and fluorescence of 450 nm. For processing and analysis of statistical information a computer kit Statistica 6.0 was used for mathematical analysis of the obtained numeral material.

Results of the study and its discussion.

During the conducted study there were determined changes of the level of excitatory amino acids in blood plasma (Table 1). There was statistically reliable increase of the level of glutamate and aspartate in patients with isolated psoriasis of moderate and severe course in comparison to the control group.

The raise of the level of glutamate was 42% and 76 % respectively, of aspartate – 22% and 57%. In case of isolated psoriasis of mild severity these indicators practically did not differ from the control group. In case of psoriasis combined with hypertension there was significant raise of the level of glutamate and aspartate, 53% and 31% in the group of mild severity, 90% and 109% in the group of moderate severity, and 130% and 191% in the group of severe course. It should be noted that the level of excitatory amino acids was statistically higher in patients with moderate and severe course of psoriasis combined with hypertension, in comparison to patients with isolated psoriasis.

Table 1.

The level of glutamate and aspartate in blood plasma of patients with psoriasis depending on its severity (M m).

Indicator	Control group	Severity of disease		
		mild	moderate	severe
		isolated psoriasis		
glutamate	21,2 ± 1,9	24,3 ± 2,5	30,2 ± 3,0*	37,3 ± 3,6*
aspartate	5,23 ± 0,50	5,92 ± 0,53	6,36 ± 0,60*	8,23 ± 0,77*
		psoriasis combined with hypertension		
glutamate	21,2 ± 1,9	x32,4 ± 3,0*	x40,2 ± 3,7*	x48,7 ± 4,6*
aspartate	5,23 ± 0,50	6,86 ± 0,63*	x10,95 ± 0,97*	x15,21 ± 1,34*

Note: unit of measure is mmol/l; * - reliability in comparison to the control group ($p < 0,05$); x – reliability in comparison to isolated disease ($p < 0,05$).

Such results indicate that psoriasis, especially combined with hypertension, is accompanied by the release of excitatory mediators. As a consequence hyper stimulation of NMDA-receptors of N-metil-D-aspartate develops, that provokes dilatation of Ca-channels, massive entrance of Ca into the cell with consequent activation of proteases and phospholipase. Hyperenzymatic activity leads to interruption of integrity of the cell membrane and its organelles, first of all the internal membrane of mitochondria that significantly deepens energetic disturbances. Glutamate receptor activation leads to synthesis of free radicals by activation of Ca-dependent arachidonic acid cascade, nitric oxide synthesis [10]. As previous studies have showed, psoriasis is accompanied by activation of glutamate receptors, that is one of launching mechanisms of free radical generation [13].

It is proved that under the normal conditions, there is a stable equilibrium between activity of Glutamatergic and GABAergic neurotransmitter systems. But in case of increased release of glutamate and aspartate the protective inhibition of CNS

increases, that is provided by such neurotransmitter amino acids as GABA and glycine.

The level of GABA and glycine in patients from isolated psoriasis group of mild severity practically did not differ from the control group.(Table 2). Patients from the same group but of moderate severity had reliable increase of these indicators in comparison to the control group, 23% and 35% respectively, and in case of severe course the patients had 21% and 23% decrease in these indicators.

In the group of psoriasis combined with hypertension the dynamic of these indicators was a bit different. In case of mild severity the level of GABA and glycine in blood plasma was reliably higher (on average on 28%) in comparison to the control. In case of moderate and severe course the level of inhibitory amino acids declined: GABA on 23% and 16% respectively, glycine on 34% and 27%.

Such dynamic of the level of neuroactive amino acids in blood plasma in patients with isolated and combined with hypertension psoriasis envisions significant changes of the effect that they make on the organism.

Table 2.

The level of GABA (-Aminobutyric acid) and glycine in blood plasma of patients with psoriasis depending on its severity (M +_ m).

Indicator	Control group	Severity of disease		
		mild	moderate	severe
		isolated psoriasis		
GABA	46,8+_4,3	50,3+_4,9	57,5+_5,3*	37,1+_3,3*
glycine	5,23+_0,50	5,57+_0,52	7,06+_0,67*	4,03+_0,40*
		psoriasis combined with hypertension		
GABA	46,8+_4,3	59,7+_5,5*	x36,18+_3,8*	x30,9+_2,9*
glycine	5,23+_0,50	6,67+_0,63*	x4,38+_0,38*	3,84+_0,36*

Note: unit of measure is mmol/l; * - reliability in comparison to the control group (p < 0,05);

x – reliability in comparison to isolated disease (p < 0,05).

Thus, under the proper functioning of the cardiovascular system and metabolism, GABA concentration in the adrenal medulla is maintained on the constant level, that shows, on the one side, the high level of plasticity of the CNS metabolism, and, on the other side, it shows importance of the physiological role of GABA and its functions which are metabolic and transmitting. As a metabolic product of the adrenal medullar GABA has anti-hypoxic, vasodilating effect, under the normal conditions it almost does not go through the blood-brain barrier and acts mostly on the periphery.

During the compensation of disturbed cerebral circulatory dynamics the important role belongs to GABAergic system, that is one of the main elements of neuro-chemical regulation of cerebral blood flow under the normal and pathological conditions. Vascular effects of GABA are due to inhibition of sympathetic and activation of parasympathetic centers in the CNS, its effect on vascular GABA-receptors. Thanks to this GABA and its agonists decrease cerebro-vascular resistance, especially in case of increased arterial tonus [14 –16].

Concerning glycine, it is seen as possible regulator of autonomic nervous system disturbances [17]. There are data that glycine actively influences on hypothalamic mechanisms of vasomotor regulation. Moderate amount of glycine in autonomic ganglions and in tissues of some organs suggests the possibility of its participation in the peripheral regulatory mechanisms [18].

Having the results of decrease of the levels of GABA and glycine in blood plasma of psoriatic patients, especially in its severe course, allows us to make the conclusion about severe disturbance of the above mentioned effects of these mediators. We know that the main route of GABA synthesis in the cerebral tissue and in the walls of the cerebral arteries is its synthesis from glutamic acid. The increased glutamate level and decreased GABA level in blood plasma might show the inhibition of this metabolic route of glutamate and activation of others. Besides this, significant decrease of the level of inhibitory amino acids shoes ineffectiveness of inhibitory defense mechanisms. The raise of GABA and glycine levels in cases of

mild and moderate course of isolated psoriasis and mild course of psoriasis combined with hypertension indicates switching-on of the compensatory mechanisms of protectiveinhibition.

Conclusions

1. Severe course of psoriasis, especially combined with hypertension is characterized by excitatory and inhibitory mechanisms imbalance with signs of protective inhibition insufficiency; deficiency of GABAergic protective mechanisms along with increased release of excitatory amino acids determines the severity of psoriasis in this contingent of patients.
2. Psoriasis accompanied by Glutamate receptor activation, than is one of starters of free radical generation.
3. Changes of the level of excitatory and inhibitory amino acids in blood plasma of psoriatic patients indicate their obvious participation in formation of cerebral circulation disturbance and autonomic regulation of peripheral vessels disorder.
4. . Biochemical monitoring of the level of neuro active amino acids in blood plasma of psoriatic patients allows to monitor the effectiveness and validity of treatment.

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MORGELLONS DISEASE

Kharkov National Medical University, Ukraine

Abstract. *This article discusses Morgellons (Morgellons disease, unexplained dermatopathy) which is bad studied, and the article considers Morgellons history, possible Etiology and data pertaining of research and clinical picture. Also it shows own observations.*

Keywords: *Morgellons, fibers, «delusional infestation»*

Morgellons disease or Morgellons syndrome or unexplained dermatopathy is a name given to a condition in 2002 by Mary Leitaó in which sufferers have the delusional belief that they are infested with disease-causing agents described as things like insects, parasites, hairs or fibers, but in reality no such things are present. Most experts, including dermatologists and psychiatrists believe that Morgellons symptoms of known diseases is a Delusional parasitosis.

History

According to Mary Leitaó, her then two-year-old son developed sores under his lip and began to complain of "bugs". She chose the name Morgellons disease (with a hard g) from a description of an illness in the monograph *A Letter to a Friend* by Sir Thomas Browne, in 1690. The Morgellons Research Foundation of Mary Leitaó made the exploration of a new infectious disease from Congress and the Government of the United States. Then the scientists concluded that such diseases or infectious lesion does not exist and the reason is a mental disorder. No evidence was found or other evidence of infectious, parasitic or any other process.

Etiology and epidemiology.

The etiology of the disease is unknown. In the literature different authors claim parasitic disease (acariasis, èntomoz or worms), infectious (bacteriosis, possibly with transmissible through contamination), toxic or organic-the neurotic origin. A popular

version is a version of Parasitosis Psychogenic. It is also the most probable. It often finds its "victims" among the mentally ill or even just psychiatric patients.

However, patients continued to complain and their number was increasing. There were suggestions that the disease could be linked to the Morgellons genetically modified organisms (GMOs), modified by using *Agrobacterium* microorganisms. In addition, Lyme disease was considered, immune deficiency or Ecotoxicology (because of chemtrails).

Agrobacterium tumefaciens (Soil bacteria) can transform plant cells using a special plasmid. If you have seen growths on the trunk of the tree, so you saw crown-gall disease (tumors) caused by *Agrobacterium*. Therefore, these bacteria are often used in genetic engineering to modify products and GMOS.

According to researchers at the State University of New York, *Agrobacterium* is a universal machine for migrating genes and creating alien proteins. Therefore, they can also change human DNA. Thus, potentially *Agrobacterium* can implement a horizontal transfer of DNA that can be considered as one of the probable causes of Morgellons disease.

Finally, in January 2012 a new independent study clarifies some details. According to the publication in the journal of clinical and experimental Dermatology, Morgellons disease, in fact, is a real disease.

Based on extensive research, including micro-immuno fluorescence of skin, hair, tissue and other material from patients, researchers reported several interesting facts.

- Patients with Morgellons disease have abnormal functioning of follicular keratinocytes. Genetic errors of cells of hair follicles and skin in DNA were fixed.

- Fibre markets have unique floral arrangement and contain keratin (a structural protein of the skin), which means that the fibers were created by a human body. Thanks to immunohistological antibody, staining it became clear that the patient's threads are keratinocytes.

- Changes in keratinocytes (of skin) most likely caused by *Spirochaetes* - Lyme disease (Lyme borreliosis).

According to scientists, the fibers are clearly biological. They are not implanted in the skin. Perhaps, their origins because of cross-contamination of DNA of GMOS. This new study clarifies a recognition of the problem of Morgellons disease and may contribute to new studies of this disease.

Some scientists believe that Morgellons is a symptom which is a long known like diseases such as skin disorders including allergic dermatitis, allergic contact dermatitis, contact dermatitis, idiopathic urticaria and infestation with the parasite scabies.

The head of the research programme the Morgellons Research Foundation Professor Randy Wymore (site of the Morgellons Research Foundation: morgellons.org)

The first results of Wymore refuted a version about hallucinations. "General practitioners, dermatologists, and the results of laboratory studies have shown that these strands are textile fibers. However, "it's not true", said Wymore.



Morgellons skin disease photo taken from
<http://www.medem.kiev.ua/page.php?pid=1941>)

Wymore thinks this is neither textile fibers, nor worms, insects, fragments of human skin or hair. He says that these strands do not appear from the outside. In his view, this substance materialized within the body and possibly because of some kind of infection.



Morgellons strands visible by microscope (photo taken from <http://www.medem.kiev.ua/page.php?pid=1941>)

He also says that skin problems are not the worst symptoms. The neurotoxin or microorganism can affect muscles and memory.

Epidemiological data on Morgellons diseases is very incomplete and Morgellons Disease Research Foundation register includes over 12000 victims around the world.

The clinical finding

The main social registered people with the infection were nannies, nurses, and teachers with a threefold advantage in the number of first versus of infection in a teaching environment.

Patients experience:

- Uncontrolled muscle cramp,
- Presence of non-healing sores on the skin and small dark threads which are going out from wounds on the skin
- Sores on the skin accompanied by burning and itching
- feeling a crawling
- Joint pain
- An exhausting fatigue
- Changes in consciousness,
- Memory loss,
- Mood disorders
- Serious neurological manifestations.

Patients think that creeps or crawls or insect are inside them. Such things because of hallucination. Sometimes patients even demonstrate the "parasites" or "fibers" extracted under the skin, which in actual fact are hairs or exfoliated epidermis. In the research process which was in Northern California in 2006-2008, has revealed that skin clinical manifestations are vary widely: papules, patches and the macula. But none of the patient were not detected vesicles, bull or scabies.

In literature some authors suggest a version of psychogenic parasitic disease. In 2012, the CDC (United States) published results of a study without infectious or environmental causes of disease. Laboratory tests of participants of the study did not reveal anything but reveal strands of cotton and other materials that can be in clothes.

The researchers could not explain the feelings of participants. They suggested that it might be a "delusional disorders", when people mistakenly believe that their bodies are being invaded by small organisms. In Psychiatry this disease is diagnosed as Ekbom syndrome, which was described by German doctor T.Wittmaak, and then by the Swedish neurologist K.A.Ekbom (1907-1977).

Treatment and prognosis are unknown.

Because doctors and scientists do not know for sure whether this is an independent disease, and if it is, what causes this disease? It used different empirical methods of treatment (for example, antibiotics, de-worming, antifungal medication, psychoactive drugs to treat mental problems, etc.)

Here is our observation.

A sick A. is about 45 years old, married. Has 2 adult sons. They have higher education and work abroad.

From the history it is known that the patient is suffering from calculous cholecystitis for a long time (10 years). She had a conservative treatment in medical establishments in Kharkov city and she was in China (2012, 2013) in the clinic using unconventional Chinese medicine (acupuncture, moxibustion, vacuum massage) twice.

After a visit to Sri Lanka in 2013, she felt worse. She was bothered by pain in the right hypochondrium, diarrhoeal (Dyspepsia) phenomenon and diarrhea (or

diarrhoea). She applied to the District Hospital Center where she was advised to study clinical blood analysis, urine analysis and stool at the I/g.

In these studies there were detected no changes. It was recommended to try "Vormil" 400 mg 1 time per day (3 days). After taking the drug status of her health has been seemed better. The patient started feeling itchy skin.

From the words of the patient after scratching on the skin started to appear some hairs.

At the time of the survey, September 25, 2013: a sick above average growth, a few low power. Patient adequate, well oriented in time and space. Neurological status without conditions. Tendon reflexes are normal. No pathological reflexes.

Thyroid and peripheric lymph nodes are not palpated.

Pulm- vesicular breath

Cor-clean, rhythmic tones

BP 130/80 mmHg, Ps 76 beats per minute, satisfactory qualities.

The abdomen is soft, slightly painful in the right podreberie. The liver at the edge of costal arch.

Pasternackiy Symptom is negative on both sides.

Stools and diuresis without features.

Locus morbi

Leather trunk, upper and lower extremities somewhat dry, turgor and elasticity of the skin.

With rubbing skin, arms and lower legs for a few seconds in 10-15 min would appear dark "hairs" from hair follicles.

In the study of new hairs a laboratory doctor with 30 years of experience in dermatology and Venereology defines them as "textile yarn", i.e., the keratin in the product does not identify. The clinical blood test, urine and stool testes are without pathological changes.

Patient has to do an antipruritic therapy in the form of corticosteroid ointments.

The patient did not addressed to the Department of Dermatology, Venereology and AIDS.

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ANALYSIS OF CHANGES IN THE IMMUNOLOGICAL CHARACTERISTICS IN PATIENTS WITH PSORIASIS

Kharkov National Medical University, Ukraine

Abstract. *We studied the changes of immune status in 46 patients with psoriasis in the dynamics of complex treatment, which included the administration of dalargin and amizon. There have been studied and analyzed, some immunological parameters (cellular link CD3+, CD4+, CD8+, CD22, humoral link Ig , , G, CIC), which are integral reflection interrelationship and interdependence of individual components of immunity in patients treated with dalargin and amizon. Effectiveness analysis was carried out this treatment. After treatment there was a normalization of the level of cellular immunity. This testifies to the restoration of functional reserves of immunocompetent cells.*

Keywords: *psoriasis, immune system, immune modulators, mizon, Dalargin.*

Psoriasis is a multifactor skin disease affecting 1 % to 3 % of population worldwide [1]. Both Ukrainian and foreign researchers notice the following features of psoriasis: a chronic disease associated with characteristic skin rash in a form of epidermal and dermal papules considerable skin flaking. A psoriatic patch is formed on the basis of the impaired proliferation and differentiation of keratinocytes in combination with increases processes of angiogenesis and epidermal and dermal infiltration with mononuclear cells [2, 3].

In spite of numerous studies performed, pathogenesis of psoriasis and mechanisms of its onset have not been clarified yet. Therefore, therapy of psoriasis is a rather sophisticated task of dermatology today. Main current therapies include Methotrexate, Cyclosporine, retinoids, phototherapy and photochemotherapy. Such therapies are efficacious, however, they may cause a series of adverse events (hepato- and nephrotoxicity, myelosuppression and teratogenic effects etc.) [6]. Conventional methods of systemic therapy of psoriasis fail to cause a complete recovery and are

aimed on an alleviation of the severity of the disease and a prolongation of the remission period only. The aforementioned facts necessitate a search for new pathogenetic approaches to the treatment of psoriatic disease.

In recent years, agents modulating immune reactions in the skin have been used in the treatment of patients with psoriasis. The use of such agents is substantiated with the data on the features of the interaction of cells of the skin and immune system. The onset of an inflammatory process is known to make the skin a part of the immune system without the central analytical link. In particular, in patients with psoriasis, activated antigen-presenting cells migrate to regional lymph nodes to trigger a pathway followed with the activation and proliferation of lymphocytes - cells of the immune system. Before the activation of antigen-presenting cells and lymphocytes, a pathogen introduction causes reactions by keratinocytes, tissue basophils, macrophages and vascular endothelial cells to produce various mediators, including anti-inflammatory tumour necrosis factor alpha [5, 4].

Impaired immune response is another element of pathogenesis of psoriasis. Numerous studies of the immune system status in patients with psoriasis have revealed a reduction of the absolute and relative levels of circulating T-lymphocytes as a result of the prevailing reduction of T-suppressor subpopulation as compared with T-helper subpopulation manifested through the changes in immunoregulatory index TH/TS (helper-suppressor cell ratio). Certain authors consider such immune dysfunctions an important element of pathogenesis of psoriatic disease. The levels of B-lymphocytes decrease in the blood of patients with psoriasis, and the levels of IgA, IgM and IgG also turn changed [7, 8].

Subjects and methods of examination. Immunological characteristics were analysed in 46 patients with psoriasis of 21 to 58 years of age staying on an in-patient treatment at the Dermatologic Department of the 5th Kharkiv City Clinical Dermatovenerologic Dispensary. Patients were divided into 3 groups:

Group 1 comprised 20 patients treated basic therapy for psoriasis;

Group 2a comprised 14 patients treated basic therapy with Dalargin;

Group 2b comprised 12 patients with psoriasis treated with basic therapy plus Dalargin and Amizonum.

In patients with psoriasis, immune status changes manifested in an impaired interaction of immune competent cells – suppression of T- and B-mediated immunity, increase in the levels of circulating immune complexes (CIC) and activation of the antibody-mediated immunity – are noticed. Regulatory and effector cell imbalance causes an inadequate immune response in patients with psoriasis, which is the core element of the pathogenesis of this disease. Regulatory T-cells are a subpopulation of T-lymphocytes playing an important role in the maintenance of the immune tolerance in the organism. Such cells control the intensity and duration of an immune response via a suppression of the activity of T-helpers and T-cytotoxic cells. An inflammatory process in a psoriatic patch is supported on account of T-cell immune mechanisms. Activation of T-lymphocytes in the affected skin is accompanied with the production of anti-inflammatory cytokines and growth factors causing the proliferation of keratinocytes and an impairment of their differentiation.

A study of the immune status of patients has revealed the excessive formation of CIC – natural components of complex immunopathological processes – in the blood. The study subjects showed a significant increase in the serum levels of IgG, which was particularly marked during psoriasis progression. Such antibodies are responsible for the formation of CIC in patients with psoriasis above all. We believe that a reduction of serum levels of IgG in patients after treatment with a combination of Dalargin and Amizonum is associated with a reduced IgG production owing to the alleviation of the pathological process (Table 1).

Increase in the blood levels of T-suppressors after basic treatment of patients was not significant and could be associated with the lack of mechanisms favouring the inhibition of autoimmune reactions in such patients. Such opinion was confirmed with a reduction of blood levels of CIC and increase in the blood levels of IgG in patients after the basic therapy.

Table 1.

Dynamics of the immune system characteristics of patients with psoriasis in a course of treatment

Immunological characteristic	Before treatment n = 46	After treatment		
		Group 2a n = 14	Group 2b n = 12	Group 1 n = 20
D3+, %	48.0±2.2 ¹	54.1±0.43 ¹	57.0±2.7 ¹	59.6±1.3
D4+, %	22.5±1.0	24.3±1.0	26.4±1.0	29.4±0.9
D8+, %	23.1±1.7 ¹	21.0±2.2 ¹	20.8±2.4	16.6±0.3
D22+, %	8.5±0.8	9.7±1.6	10.1±0.9	10.6±0.3
IgA, g/L	2.2±0.2 ¹	1.9±0.2 ¹	2.0±0.1 ¹	3.3±0.3
IgM, g/L	1.7±0.4	1.5±0.05	1.4±1.2	1.4±0.2
IgG, g/L	14.2±1.6 ¹	14.4±1.3 ¹	12.2±0.8	10.6±0.7
Circulating immune complex, U	94.2±10.0 ¹	100.0±12.6 ¹	111.2±12.8 ¹	56.2±5.0

¹p < 0.05

An analysis of the immunological characteristics of patients with psoriasis has revealed the correlation between the changes in such characteristics as CD4+, CD3+, CD8+, CD22+, IgA and IgM in the course of treatment of patients of all study groups. Such characteristics have shown the same trends of changes in all treatment groups. We believe this is quite natural, since patients with psoriasis treated with Dalargin and Amizonum plus basic therapy have shown normalisation of their immunological characteristics and different extent of improvement of the process of recovery.

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POSSIBILITIES OF DOPPLER ULTRASONOGRAPHY IN VALUING OF MORFOFUNCTIONAL CONDITION OF LIVER FOR PATIENTS WITH VIRAL HEPATITIS AND HEPATOCIRRHOSIS

¹*Kharkov National Medical University, Ukraine*

²*LTD Medical Diagnostic Center «Expert-Kharkov», Ukraine*

Abstract. Objective: *To study possibilities of dopplerography in the estimation of progress and gravity of chronic viral hepatitis and cirrhosis of liver, and also to define possibilities of dopplerography in the estimation of degree of expression of inflammatory process in a liver from data of ultrasonography.*

Materials and methods: *50 patients were inspected with the chronic diffuse diseases of liver (34 patients with chronic viral hepatitis and 16 patients with a hepatocirrhosis), and also 15 patients of group of control. The following Doppler indexes were measured: hepatic artery resistive index, hepatic artery pulsativity index, portal vein velocity, modified hepatic index, hepatic vascular index and diameters of hepatic and splenic veins, sizes of spleen, velocity of blood flow in a portal vein, velocity of volume blood flow in a portal vein. These indexes were compared between 3 groups on the degree of inflammation.*

Results: *velocity of blood flow in portal vein, hepatic vascular index and modified hepatic index were the most informative for differential diagnostics of cirrhosis and hepatitis.*

Conclusions: *Doppler ultrasonography is a highly sensitive method for diagnostics of changes of parameters of blood flow at an inflammatory process and fibrosis of liver.*

Key words: *chronic hepatitis, hepatocirrhosis, portal vein, hepatic artery.*

Chronic viral hepatitis (CVH) is one of the most widespread diseases in the world and is the predictor of such dangerous pathological states such as cirrhosis and hepatocellular carcinoma. A hepatocirrhosis is very dangerous from such

complications as ascites, portal hypertension, bleeding from varicose extended veins of esophagus [1, 2].

Any chronic process in a liver is accompanied by activating of fibrogenesis that results in violation of structure of conjunctive tissue framework of liver, the degree of which determines functional inability of subsequent processes of regeneration. [3]. Exactly rates of fibrogenesis and determine speed of progress of chronic diffuse diseases of liver and forming them in cirrhosis.

Growth of actuality of problem of fibrosis of liver in the last years is linked with data about convertibility of cirrhotic changes in a liver and researches of efficiency of different variants of therapy, that would allow promoting efficiency of treatment and improving the prognosis of patients with CDDL [4,5] Forming of fibrosis of liver is not a linear, slowly progressing process [6, 7], and influence of a few damaging factors considerably accelerates it [8]. Determination of the stage of fibrosis of liver and possibility of estimation of rates of its progress is extraordinarily important, as it will allow forecasting efficiency of antiviral therapy and developing strategy of management of patient with CDDL in every case.

Presently ultrasonography remains the most often used radiologic method of research due to the availability. Without regard to that for such patients changes in the parenchyma of liver, such as steatosis and periportal fibrosis in most cases can be revealed. At the use of only the two-dimensional mode sonographic data will be within the limits of norm [8,9]. Many authors proved that an inspection of patients with the diffuse damages of liver with a help only of the two dimensional mode is poor informative, especially on the early stages, and the revealed changes of parenchyma of liver are not specific [9, 10]. Therefore until now opened is a question of the use of the various Doppler methods with the calculation of indexes and measuring of velocities of blood flow in vessels [10]. Variability of histological picture at CDDL: unevenly located foci of inflammation, regeneration and normal parenchyma of liver can create complications at a biopsy on the early stages of disease (false-negative results), and because this method is an invasion and not always well carried by patients, and also dangerous is appearance of complications,

actual is a problem of non-invasive diagnostics of this state, especially on the early stages.

Materials and methods

We investigated 50 patients (37 men and 13 women in age from 18 to 70 years) with CDDL, and also 15 patients of control group which did not have diseases of GIT, and passed sonographic investigation on other reasons. The diagnosis of CVH was established serologically on 34 patients. Serologic investigations showed that in 16 patients hepatitis C was found out, hepatitis B was in 12 patients, both hepatitis B and C – in 6 patients. In 16 patients hepatocirrhosis was diagnosed.

The degree of activity of inflammatory process for patients was estimated on the level of aminotransferases (AST,ALT) - minimum activity was characterized by the increase of level of AST and ALT up to 1,5-2 norms, low – up to 3-5 norms, moderate – up to 9 norms, high – higher than 9 norms. Sonographic investigations were performed to the patients in the morning on an empty stomach. All studies were performed on a sonography system (Xario SSA 660, Toshiba Medical Systems) by a single experienced sonologist. The sizes of liver and spleen, diameters of portal and splenic veins, degree of steatosis, velocity of blood flow in portal vein (PVV) were measured. Volume velocity of blood flow in portal vein (VVPV) was calculated by multiplying of peak linear velocity of portal blood flow on square of cross-sectional area of portal vein. Hepatic artery resistive index (HARI), hepatic artery pulsativity index (HAPI), modified hepatic index (MHI) - PVV/HARI, hepatic vascular index (HVI) – PVV/HAPI were calculated.

The degree of steatosis was determined as follows: **soft**, insignificant increase of echogenicity of liver, when the walls of intrahepatic vessels and diaphragm are well visualized; **moderate** - moderate increasing of echogenicity of liver, when the walls of intrahepatic vessels and diaphragm are badly visualized; **expressed**, when it is impossible to see a diaphragm and walls of intrahepatic vessels due to the considerable increasing of liver echogenicity.

Results and discussion

Changes in a hepatic hemodynamics at CDDL are lighted up in many works, but information is a contradictory. Estimation of changes of hepatic blood flow only on the basis of change of portal blood flow velocity not always gives the possibility adequately estimate pathological processes, especially on the early stages, that is why for more objective estimation we decided to investigate the new indexes of changes of hepatic blood flow, such as modified hepatic index (MHI), hepatic artery resistive index (HARI), hepatic artery pulsativity index (HAPI), modified hepatic index(MHI), hepatic vascular index (HVI), and also diameters of hepatic and splenic veins, sizes of spleen, velocity of blood flow and volume blood flow in portal vein. In domestic works there is not the systematized information in relation to application of these indexes in practice. In this research we tried to define importance of Doppler ultrasonography in diagnostics and dynamic monitoring of patients with CDDL and role of the above-mentioned Doppler parameters for diagnostics and dynamic management of this group of patients, and also to compare findings with the changes of biochemical indexes (AST, ALT) which represent expression of syndrome of cytolysis and cholestasis, and also allow to estimate the degree of activity of inflammatory process in liver.

All patients were divided into 3 groups: 1 group (34 patients) with CVH, 2 group (16 patients) with cirrhosis and 3 group (15 patients) – control group.

HARI, HAPI, MHI, and HVI in all groups are presented in the table 1. In the group of cirrhosis the mean values of HARI and HAPI were considerably higher, than in the group of hepatitis and control group, those indexes in the group of hepatitis were considerably higher, than in the group of control. MHI and HVI in the group of hepatitis were considerably less than in the group of control, and in the group of cirrhosis these values were less than in the group of hepatitis and control group ($R < 0,001$).

Statistical discrepancies in the group of cirrhosis and other two groups are presented in the table 2.

Table 1.

Values of HARI, HAPI, MHI, HVI in all groups

Values in the group	HARI	HAPI	MHI cm/s	HVI cm/s
Control (n=15)				
<i>Minimal</i>	0,66	0,81	30,2	20,2
<i>Maximal</i>	0,76	1,39	57,3	39,1
<i>Medium</i>	0,71 ±0,05	1,1 ±0,1	43,8 ±7,2	28 ±5,5
CVH (n=34)				
<i>Minimal</i>	0,62	0,98	17,59	7,5
<i>Maximal</i>	0,91	3,13	47,8	26,2
<i>Medium</i>	0,76 ±0,01	2,06 ±0,5	32,5 ±0,9	16,9 ±0,01
Cirrhosis (n=16)				
<i>Minimal</i>	0,62	1,11	10,3	4,08
<i>Maximal</i>	0,99	3,12	42,52	20,19
<i>Medium</i>	0,8 ±0,03	2,1 ±0,3	26,4 ±7,3	11,5 ±4

Diameters of portal and splenic veins in patients with cirrhosis were considerably higher than in the group of hepatitis and control group. The mean value of PVPV in the group of cirrhosis was considerably less than in the group of control and group of hepatitis ($P < 0,001$). There was not a meaningful difference of this index between the group of hepatitis and control group. Velocity of volume blood flow in portal vein did not differentiate in all three groups. ($P > 0,05$).

Patients from the group of CVH depending on the level of activity of transaminasis were divided on 3 sub-groups: 1 sub-group (12 patients) – increasing of indexes up to 3-5 norms, 2 sub-group (13 patients) – up to 5-9 norms, 3 sub-group (9 patients) – more than 9 norms.

The values of the Doppler indexes depending on activity of inflammatory process in liver are indicated in the table 3.

HARI and HAPI in 2 groups were considerably higher, than in a group 1, and HARI in group 3, more than in group 1. MHI in group 1 was more than in group 3.

There were not found meaningful distinctions between PPVV and HVI in all three sub-groups.

Table 2.

Values of PPVV, diameters of portal and splenic veins, sizes of spleen in all groups as compared to the group of cirrhosis

Values in the group	PPVV, cm/s	Diameter of portal vein, mm	Diameter of splenic vein, mm	Length of spleen, mm
Control (n=15)				
<i>Minimum</i>	18	6,5	5	80
<i>Maximal</i>	35	12	9	128
<i>Medium</i>	26,5±4,5	9,3 ±1,3	7 ±1	104±12
CVH (n=34)				
<i>Minimum</i>	11	7,5	5	82
<i>Maximal</i>	29	14	11	149
<i>Medium</i>	20±4	10,8 ±1,2	8 ±1,5	115,5±11
Cirrhosis (n=16)				
<i>Minimum</i>	6	9	6	112
<i>Maximal</i>	25	18	21	245
<i>Medium</i>	15,5 ±3,5	13,5 ±2	13,5 ±3	178,5 ±34

The results of group of cirrhosis were compared separately to each of groups.

*P <0,001

Conclusions.

1. Pathological changes of hepatic hemodynamics at viral hepatitis and cirrhosis of liver depending on the degree of inflammation it is possible to estimate with the help of Doppler ultrasonography.
2. The most informative for determination of activity of inflammatory process in liver are hepatic artery resistive index and hepatic artery pulsativity index. Hepatic vascular index, velocity of blood flow in portal vein and modified hepatic index are informative at differential diagnostics of cirrhosis and hepatitis.

3. Doppler ultrasonography is highly sensitive method for diagnostics of changes of parameters of blood flow at inflammatory process and fibrosis of liver. Two-dimensional sonography does not allow estimating progress of chronic hepatitis and gravity of liver cirrhosis without the use of dopplerography.

Table 3.

Values of HARI, HAPI, MHI, HVI, PPVV depending on activity of inflammatory process in liver.

Index	Level of transaminasis		
	1 Low 3-5 norms (n=12)	2 Medium 5-9 norms (n=13)	3 High more than 9 norms(n=9)
HARI			
<i>Minimal</i>	0,71	0,7	0,55
<i>Maximal</i>	0,79	0,98	0,82
<i>Medium</i>	0,75 ±0,02	0,84 ±0,06	0,68 ±0,05
HAPI			
<i>Minimal</i>	0,98	1,1	1,03
<i>Maximal</i>	1,22	1,98	1,86
<i>Medium</i>	1,1 ±0,08	1,54 ±0,5	1,44 ±0,2
MHI			
<i>Minimal</i>	32	22	19
<i>Maximal</i>	39	38,5	49
<i>Medium</i>	35,5 ±2,5	30,25 ±3	34 ±7,4
HVI			
<i>Minimal</i>	19	8	6
<i>Maximal</i>	28	22	23
<i>Medium</i>	23,5 ±2	15 ±3	14,5 ±4
PPVV			
<i>Minimal</i>	19	16	10
<i>Maximal</i>	27	30	34
<i>Medium</i>	23 ±2	23 ±3	22 ±5,5

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SLING-THERAPY IN MEDICAL REHABILITATION

¹Kharkiv National Medical University, Ukraine,

Abstract. *This overview deals with new for Ukraine method of physical rehabilitation – sling therapy. The restoration of muscular-skeletal function is realized by physical excesses with or without special devices. But the limiting factor in many cases is severe pain that person should overcome while excesses. One of the peculiarities of the sling therapy is that the suspension by itself is an unstable support of the body. Such unstable support causes redistribution of muscular tone and activates the coordination of the movements thus contributing to the restoring the balance. Several places of support and using such elastic cords provide the painless performance of the exercise. Sling therapy can be used for diagnostic of «the weak link» in muscle-skeletal chain, correction the asymmetry of muscular tone, relief of pain while performing the exercise, and for improvement of the coordination of movements.*

Key words: *sling therapy, suspension therapy, physical rehabilitation, “weak links” testing, painless performance of the exercises.*

Muscular-skeletal disturbances are troubling not only sportsmen but many ordinary people that are not engaged in sports. The main approaches to restoration of muscular-skeletal function are realized by physical excesses with or without special devices. But the limiting factor in many cases is severe pain that person should overcome while excesses.

Sling-therapy or suspension therapy is the method of physical rehabilitation where the suspension of the body or limbs is used. Due to these suspensions the axial load on the joints is taken off and the body is supported in the space while doing the exercises. And so we can say that the method of sling therapy gives a possibility to facilitate exercising.

One of the peculiarities of the sling therapy is that the suspension by itself is an unstable support of the body. Such unstable support causes redistribution of muscular tone and activates the coordination of the movements thus contributing to the

restoring the balance [1,2,3,4]. As a result the misbalance in tone between the right part and the left part of the body and between the muscles-antagonists is removed.

Using of elastic cords in suspension system gives possibility to perform some exercises with resistance. It is important aspect of the equal muscles tone restoration [3,5,6,7]. These cords can be also used for facilitation of the some movements performing.

One of the main obstructions in physical rehabilitation is pain while moving. Several places of support and using such elastic cords provide the painless performance of the exercise. As follows, sling therapy is indicated to the people, who feel pain while doing certain exercises [4, 8].

Variable ways of suspension the limbs can exclude the strong muscles from performing the exercises. As the result we can use the groups of muscles that are needed training and form more rational patterns of motion [4, 9, 10, 11] .

Furthermore, the system of suspension therapy can be used in diagnostics «the weakest links» in muscle-skeletal system and to remove it successfully while training [9].

There are indications of using slung-therapy that are based on the peculiarities of this method that are mentioned above:

1. The diagnostic of «The weakest link» in muscle-skeletal chain
2. Correction the asymmetry of muscular tone
3. Pain while performing the exercise
4. Improvement of the coordination of moves.

One more peculiarity of sling therapy is that it is very comfortable in use for patient. It can be use individually, or in small groups in hospitals for in-patients or in rehabilitation centers. Also it can be used in groups is sport centers or fitness-centers. It can be used at home after passing the teaching course is special institutions.

Clinical studies showed the efficiency of using the sling therapy in treating different diseases and muscle dysfunctions [6], particularly in treating pain in the lower back [12, 13,14,15,], neck [16, 17], aftermaths of sport and ballet traumas [12], injures of knee joint [18], shoulder joint [19,20], after-pregnancy pelvis and spine

pain [21], fibromyalgia [8], chronic muscle-skeletal pain and other. Exercising using suspension system can be applied in aged patients [22].

Thus successful use the exercises with suspensions in rehabilitation of sportsmen is very promising, especially when the coordination and accuracy is needed [10,13,23,24,25]. Finally, in addition to the therapeutic results, using sling-therapy facilitates the work of doctor of rehabilitation and increases the effectiveness of the exercises.

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CHANGES OF MARKERS OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH VARIOUS TYPES OF HYPERTENSION UNDER THE THERAPY

Kharkov national medical university, Ukraine.

Abstracts. Background: *The multifactorial influence determines the complexity of the medical correction of high blood pressure in patients with CKD.*

Methods: *Plasma S-nitrozotriols, von Willebrand factor (vWF) levels were measured at start of the study t and in the end.*

Aim: *the assessment of the impact of antihypertensive therapy on markers of endothelial dysfunction in patients with hypertension only and in patients with high blood pressure comorbid with chronic kidney disease.*

Results: *It was found that therapy with lisinopril the vWF content decreased in 10.5 % ($p < 0.01$). After the treatment with candesartan the level of vWF decreased in 8.61 % ($p < 0.05$). Under the influence of lisinopril nitric oxide increased in 7.69 %, and reached in average $0,143 \pm 0,04$ mmol / l. After the treatment by candesartan the level of nitric oxide increased in 11.1 %, reaching an average of $0,16 \pm 0,04$ mmol / l.*

Conclusions: *The positive influence of renin-angiotensin-aldosterone system modulators on endothelial function was established in patients with different variants of hypertension.*

Key words: *hypertension, endothelial dysfunction, chronic kidney disease.*

The primary determinants of progression of arterial hypertension (AH) in the patients with chronic kidney disease (CKD) are an excess of sodium and water in the body, activation of the renin-angiotensin-aldosterone and sympathetic-adrenal systems, increased endothelial synthesis of vasoconstrictive substances, bivalent ions and parathyroid hormone. [1] The age over 50 years, hypertriglyceridemia, proteinuria and diabetes are among independent factors of progression of hypertension [2]. This multifactorial influence determines the complexity of the medical correction of high blood pressure in patients with CKD.

Hypertension is characterized by the development of functional changes in the endothelium, thrombogenicity of vascular wall; inflammatory reactions, vascular reactivity to vasoconstricting and vasodilating substances [3].

Von Willebrand factor and nitric oxide, which is formed from L-arginine, plays a role of particular importance for the assessment of endothelial function. It was demonstrated a direct correlation between the level of nitric oxide metabolites, blood pressure (BP) and increased cardiovascular morbidity and mortality, that means - endothelial damage was identified as one of the main risk factor for cardiovascular disease and as the subject of therapeutic interventions [4,5,].

In experimental and clinical studies (EUCLID, REIN, BRILLIANT) was demonstrated the ability of angiotensin-converting enzyme (ACE) inhibitors to cause significant antihypertensive and antiproteinuric effects, that is, to provide cardio- and renoprotection by restoring endothelial function [6].

At the same time the results of other randomized controlled trials have shown that angiotensin-receptor-blockers (ARBs) (losartan, telmisartan, irbesartan, candesartan, eprosartan) can also provide renoprotective and antihypertensive effects, which are not less effective than ACE inhibitors, causing correcting impact on glomerular filtration rate and proteinuritic function [7]. Nephroprotective effect of ARB II was studied mainly for losartan and irbesartan.

The study IRMA and IDNT showed that irbesartan reduced the degree of microalbuminuria and the risk of ESRD mortality. The study RENAAL demonstrated nephroprotective effect of losartan in patients with diabetes mellitus type 2. MARVAL, DROP, SMART trials, which included patients with diabetic microalbuminuria, evidenced the nephroprotective effect of valsartan [8]. In addition, there is no exact evidence of any particular drug or class preferred for the treatment of hypertension in patients with CKD. There is no clear data about what medicine is more effective in normalization of endothelial function in such cohort of patients.

There is a modern data which supports the idea of development of endothelial dysfunction while disease progression - endothelium-dependent vasodilation (EDVD) becomes reduced and content of endothelin-1 is being increased [9].

Based on the fact that the degree of endothelial dysfunction is important for the formation of this pathology, the development of the best management for endothelial function is an important clinical challenge.

Purpose - a comparative assessment of the impact of therapy with candesartan or lisinopril on indicators of endothelial dysfunction in CKD patients with hypertension.

Materials and Methods:

We examined 54 patients – 30 males (55.5 %) and 24 females (44.4 %) with age of 37 to 59 years (mean age $51,5 \pm 6,4$ years). The control group consisted of 20 healthy subjects (9 men and 11 women), comparable with the studied patients by age and sex.

Patients were divided into the following groups: 30 patients (55.5 %) with chronic kidney disease stages II-III and hypertension II stage, including 14 men and 16 women, the second group of 24 patients (44.4 %) patients with chronic kidney disease II-III stages without hypertension, including 11 men and 13 women. Patients were followed for 8 weeks.

Depending on the treatment, the patients were randomized into two groups. First subgroup consisted of 30 patients treated with basic therapy of lisinopril 10 mg/day. This subgroup included 9 (31.34 %) patients with CKD and hypertension, and 7 patients (23.88 %) with CKD without hypertension. The second subgroup consisted of 24 patients, which in addition to the primary therapy were assigned to use candesartan 32 mg/day. Inside this subgroup there were 12 (22.39 %) patients with CKD and hypertension, and 12 patients (22.39 %) with CKD only.

CKD diagnosis was established on the basis of various clinical and laboratory examinations. Inclusion criterias of patients in the study were that they have clinical signs of CKD, confirmed by results of additional tests. Patients with concomitant acute inflammatory, infectious disease, cancer, immune diseases and chronic diseases in the acute phase, rheumatic diseases were excluded. CKD stage was set on according to GFR formula Cockcroft - Gault.

The study protocol was approved by the Ethics Review Committee. All clinical work was conducted in compliance with Good Clinical Practice Rules (GCP) (ICH E6). All subjects signed an informed

Assessment of endothelial function state was performed by von Willebrand factor (Sigma chemical Co, USA) ristomycin aggregometry method (Biola, Russia). In addition, endothelial function was evaluated by studying the dynamics of blood flow in the brachial artery during reactive hyperemia on the ultrasound scanner HD11XE (Philips, USA) using linear 7.5 MHz probe (resolution 0.01 mm) by D. Celermajer et al., 1992. Determination of S-nitrosothiols was performed spectrophotometrically by Marzinzig M., et al., 1997 in modification of Kovaleva O. N. et al., 2007 [10].

Results and discussion. All patients from the both groups were characterized by the development of endothelial dysfunction before the treatment. It was confirmed by increased levels of von Willebrand factor and nitric oxide reduction in comparison with the control. During comparative study of the nature of endothelial dysfunction in patients of groups I and II, we have found that levels of von Willebrand factor had more pronounced increasing in the blood in patients with CKD associated with hypertension.

Before the initiating treatment with lisinopril in CKD patients with hypertension the systolic blood pressure (SBP) was elevated in comparison with the control group by 29.4 %, and diastolic blood pressure (DBP) - by 25.85 %. Under the influence of lisinopril (Table) the SBP decreased by 16.81 % (from $161,9 \pm 9,6$ mm Hg to $135,1 \pm 10,7$ mmHg , $p < 0.05$), and DBP - by 12.5 % (from $98,8 \pm 6,5$ mmHg to $86,4 \pm 4,1$ mm Hg.).

Before treatment with the candesartan SBP and DBP were also increased in CKD patients with hypertension in comparison with the control group at 31.15 % and 26.87 %. Under the influence of candesartan the systolic blood pressure decreased by 16.23 % from $164,9 \pm 12,5$ mmHg to $137,9 \pm 11,7$ mmHg ($p < 0.05$), and diastolic blood pressure by 11.95 % from $99,6 \pm 5,3$ mmHg to $87,7 \pm 4,9$ mmHg. Thus, the influence of candesartan and lisinopril on SBP and DBP decreasing was comparable.

It was found that on the background of lower blood pressure the contents of von Willebrand factor became decreased in patients of first subgroup. Thus, if the initial level of von Willebrand factor was increased in comparison with control by 43.32 % ($p < 0.01$) and averaged $158,37 \pm 6,79\%$, against after 8 weeks of therapy with lisinopril the vWF content decreased by 10.5 % and averaged $141,75 \pm 5,75\%$ ($p < 0.01$).

CKD patients with hypertension treated with candesartan were characterized by similar changes. Prior to the appointment of candesartan the levels of von Willebrand factor in patients averaged $165,57 \pm 6,57\%$, and were by 49.83 % higher than in the control group ($p < 0.01$). After the treatment with candesartan for 8 weeks the level of von Willebrand factor decreased by 8.61 % ($p < 0.05$) and averaged $151,33 \pm 5,12\%$ ($p < 0.05$).

The changes of other vasoactive substances in the patients' blood under the influence of treatment with either candesartan or lisinopril were characterized by the following. Content of nitric oxide (S-nitrosothiols) before the treatment with lisinopril was reduced by 40.91 % and averaged $0,13 \pm 0,038$ mg / dL. After treatment, this index increased by 7.69 %, and reached an average of $0,143 \pm 0,04$ mmol / l. In the subgroup of patients treated with candesartan the initial level of nitric oxide (S-nitrosothiols) was also reduced compared with control group by 34.56 % , and averaged $0,144 \pm 0,027$ mmol / l ($p < 0.05$). After the treatment, it rose by 11.1 %, reaching an average of $0,16 \pm 0,04$ mmol / l.

The reduction of von Willebrand factor that was discovered under the influence of lisinopril and candesartan leads to reducing of vasospastic condition of the endothelium. However, increasing of nitric oxide (S-nitrosothiol) level, as indicator of the vasodilator mechanisms of cellular interactions is noteworthy. It can be regarded as a compensatory increased vasodilator activity in response to the reduced action of von Willebrand factor.

In patients with CKD without hypertension, in a subgroup with lisinopril therapy the same dynamics of changes in the content of von Willebrand factor and nitric oxide (S-nitrosothiols) was defined.

There was a decreasing of von Willebrand factor content after treatment with lisinopril at 7.73 % to an average of $143,27 \pm 5,68\%$ and increasing of nitric oxide (S-nitrosothiols) by 9.7% to an average of $0,147 \pm 0,042$ mg/liter.

In patients with CKD without hypertension the therapy with candesartan lead to lowering the level of von Willebrand factor compared to baseline of 8.91 % ($p < 0.05$), reaching an average of $148,24 \pm 5,07\%$ and an increasing in nitric oxide metabolites (Snitrosothiols) to 10.06% , an average of $0,164 \pm 0,043$ mg / dL.

We can assume that activity of vasoconstriction mechanisms is predominant in patients with chronic kidney disease and is associated with endothelial dysfunction on background of sympathetic nervous system activation [11, 12]. At the same time a failure of physiological mechanisms takes place caused by decrease in activity of nitric oxide. Effects of ACE inhibitor (lisinopril) and ARB II (candesartan) primarily aimed at the normalization of endothelial function, which was evidenced by decreasing the blood content of von Willebrand factor and increasing of nitric oxide formation.

As it is considered that the changes of the content of von Willebrand factor is biochemical marker of endothelial involvement in the processes of regulation of vascular tone, it can be argued that the CKD with hypertension is accompanied by a more significant increasing of the formation of constrictive factors and insufficient production of relaxing factor, that is proved by lowering content of S-nitrosothiols.

Significant reduction of von Willebrand factor under the influence of lisinopril in CKD with hypertension, confirms a greater impact of the ACE inhibitor on synthesis of von Willebrand factor. A more significant reduction of the vWF in the blood under the influence of lisinopril probably depends on the increased local formation of angiotensin II.

This confirms the position that one of the action mechanisms of the renin-angiotensin-aldosterone system modulators is the ability to improve the endothelial function and to reduce the content of von Willebrand factor in the blood.

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COMPARATIVE STUDY OF THYROID STATE IN NEW CASES OF PULMONARY TUBERCULOSIS AND TUBERCULOSIS CASES TREATED PREVIOUSLY

Kharkov National Medical University, Ukraine

Abstract. *An epidemic situation on tuberculosis in Ukraine is characterized the height of relapses of the disease. Because tuberculosis shows an immune deficient disease, and a thyroid actively participates in forming of antituberculosis immunity, comparative study of thyroid state in new cases of tuberculosis and cases previously treated is of currency. In 60 patients (30 persons with new cases of tuberculosis and 30 persons previously treated) echostructure of thyroid is studied, and also the levels of free thyroxine, thyroid stimulating hormone and antibodies to thyroglobulin and thyreoperoxides are measured by immune-enzyme method in a blood stream. Pathology of echostructure of thyroid is diagnosed in 53, 33% of new cases of tuberculosis and in 60, 66% of cases previously treated. The level of free thyroxine was significantly lower and level of thyroid stimulating hormone was significantly higher in new cases comparing with persons previously treated. The percentage of autoimmune thyroiditis and the percentage subclinical hypothyroidism were higher in new cases comparing with persons previously treated. The changes found is the ground for recommendation to screen thyroid state persons with tuberculosis relapsed and treatment failure.*

Key words: *pulmonary tuberculosis, relapse, thyroid pathology.*

Regardless of the stabilization of the morbidity of tuberculosis epidemic situation in Ukraine in total remains to be strengthen. Nowadays the most threat is multidrug-resistant tuberculosis spreading [5] and as the result the increasing of rate of cases with relapsed tuberculosis and cases of treatment failure. Relapsed tuberculosis is characterized by more severe clinical and x-ray signs of the disease in compare with firstly diagnosed cases [3]. According to WHO data multidrug-resistant tuberculosis is diagnosed in 16% patients with firstly diagnosed tuberculosis and in 44% patients

with relapsed disease. The efficacy of treatment of patients with relapsed tuberculosis in Ukraine was 34,2% and 35% in treatment failure in 2012. The patients with relapsed pulmonary tuberculosis and treatment failure represent a great threat epidemic due to massiveness of bacilli expelling and drug-resistance of mycobacterium tuberculosis (MTB). The causes of relapses are still remaining insufficiency studied. At the same time it is known that concomitant diseases influence on the development of relapses playing the role of trigger mechanism in tuberculosis process reactivation [4]. Thyroid pathology with insufficiency of thyroid function affects on the reactivation any of immunodeficiency disease because thyroid hormones stimulate T-lymphocytes forming immune response of the body to tuberculosis infection [2,6,7,8]. That is why the study of thyroid state in previously treated tuberculosis (relapsed tuberculosis, treatment failure) is of currency.

Above mentioned is the ground of **the main goal of the research:** comparative study of thyroid state in patients with new cases of tuberculosis and previously treated tuberculosis (relapsed tuberculosis, treatment failure, treatment after interruption and other cases of revised treatment).

Materials and Methods: 60 patients treated in Kharkov region antituberculosis dispensary N1 during 2010-2014 years. 30 persons at the age of 18 to 58 years (in average - 35,18 years) composed the group of firstly diagnosed tuberculosis (FDTB). 30 persons at the age of 18 to 60 years (in average - 38, 81) composed the group with previously treated patients (PTTB). This group included 16 patients with relapsed tuberculosis, 9 patients with treatment failure, 3 patients with chronic case of tuberculosis («other TB») and 2 patients with treatment interruption. There were 18 men (60%) and 12 women (40%) in group FDTB and there were 20 men (66,66 %) and 10 women (33,33%) in group PTTB. Infiltrative pulmonary tuberculosis prevailed in both groups. Infiltrative tuberculosis was diagnosed in 26 patients (86,66%) in group FDTB. 3 patients of this group suffered with caseous pneumonia and 1 patient had disseminated pulmonary tuberculosis. Infiltrative tuberculosis was

diagnosed in 26 patients (86,66%), 2 patients suffered from fibrous-cavernous tuberculosis and 1 patient had infiltrative-ulcerous tuberculosis bronchitis in group PTTB. Every patient with pulmonary tuberculosis had a cavitation. Tuberculosis in all 60 patients followed by bacilli expelling. Thus, gender, age and structure of the morbidity were approximately equal in both groups.

Echostructure of thyroid was investigated in every patient. The levels of free thyroxine and thyroid stimulating hormone were measured in the bloodstream of everybody before starting of antituberculosis chemotherapy. Echostructure of thyroid was examined with diagnostic apparatus SSF-240A by Toshiba Medical Systems production and the hormone were measured by immune-enzyme method with the aid of «ALCOR BIO» (Saint-Petersburg, Russia) and spectrum-photometer Tecan Sunrise (Austria).

The Results and Discussion: as a result of the study the pathology of the volume and/or structure of the thyroid was diagnosed in 16 patients (53,33%) from group FDTB and in 20 patients (60,66%) from group PTTB. In FDTB patients pathological changes realized mainly in a changing of thyroid volume (more frequently in its hyperplasia than in hypoplasia. Euthyroid state was kept in most of patients. In group PTTB diffused pathology of thyroid like autoimmune type prevailed. Diffused pathology implies diffused decreasing of echogenicity of the thyroid with inclusions of more high echogenicity following by the picture of heterogenicity (“mosaic picture”) of a acoustic density of thyroid and also unequal its structure as moderate and large germicides (Table 1). Autoimmune thyroiditis (AIT) with subclinical hypothyroidism was diagnosed in 6,66% patients with FDTB and in 16,66% cases of PTTB. Besides in the group of PTTB in 2 patients nodular euthyroid goiter was diagnosed and 1 patient from this group had diffused toxic goiter of 4 degree (viscera pathology form). The parameters of hormone significance of this case were not included in group moderate significance of this case.

Within the investigation of hormone state reliable more low significance of free thyroxine ($12,06 \pm 1,78$ pmol/l) was established in group of PTTB comparing with the group of FDTB ($14,02 \pm 1,29$ pmol/l). The results of the study also demonstrated reliable more high significance of thyroxine stimulating hormone ($2,51 \pm 0,34$ mkIU/ml) in group of PTTB comparing with the group of FDTB ($1,27 \pm 0,51$ mkIU/ml)).

Table 1.

Pathological changes of thyroid, revealed by ultrasound scanning

Groups of patients	Changes of thyroid volume,	AIT, euthyreosis	Nodular euthyroid goiter	Diffused toxic goiter	AIT, subclinical hypothyroidism
FDTB	13 (43,33%)	1 (3,33%)	-	-	2(6,66%)
PTTB	5 (16,66%)	7 (23.33%)	2 (6,66%)	1 (3,33%)	5(16,66%)

The results of performed investigations reflects the decreasing of thyroid activity in persons previously treated for tuberculosis including relapses of the disease and treatment failure comparing with the persons with firstly diagnosed pulmonary tuberculosis. More high percentage of thyroid pathology found in patients previously treated for tuberculosis can partly explain treatment failure by concomitant disease – thyroid pathology. Besides, the decreasing of thyroid pathology in this group of patients, from one side, reflects inhibitory influence of antituberculosis drugs [1], from other side, is the ground for examination of the persons with relapsed tuberculosis, treatment failure and other groups of previously treated patients for thyroid pathology. Thus, such patients must undergo ultrasound examination of thyroid meaning to reveal morphological changes and also the level of thyroid stimulating hormone in the blood must be measured for timely diagnosis of thyroid

function changes. One of the cause of more low efficacy of chemotherapy of patients previously treated for tuberculosis may be the decreasing of thyroid activity supplying adequate immune response to tuberculosis infection.

Conclusions:

1. More than in half of tuberculosis patients changes of structure and volume of thyroid gland as its hypoplasia and hyperplasia.
2. In patients with relapsed tuberculosis, treatment failure, treatment after the interruption and other groups of patients previously treated for tuberculosis more high rate of pathological changes of structure and volume of thyroid gland (63,66%) comparing with the patients with firstly diagnosed pulmonary tuberculosis (53,33%).
3. High rate of autoimmune changes of thyroid gland (60%) and also subclinical hypothyroidism (16,66%) is the ground for necessity of the screening of thyroid state of previously treated patients. Ultrasound examination of thyroid gland and measurement of thyroxine stimulating hormone level in free blood storm is recommended for screening of previously treated tuberculosis patients.

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Ospanova T., Semydotska Zh., Bilchenko O.,

Veremeyenko O., Avdeyeva O., Bolokadze I.

CERTAIN CRITERIA OF RENAL AFFECTION IN CASE OF COPD.

Kharkov National Medical University, Ukraine

Abstract. *Chronic pulmonary problems belong to the group of leading diseases in modern society. Often the severity of the course and prognosis of chronic pathology of lungs are determined by extrapulmonary manifestations of the disease. Nephrological aspects of lung pathology are poorly studied.*

In this clinical research, we have examined 27 patients with COPD of the II-nd and III-rd stages of pulmonary insufficiency of the II-nd – III-rd degree. There were 20 (74%) males and 7 (26%) females. The average age of patients was $53 \pm 3,7$ years.

The severity of clinical picture in patients with COPD is increased while the progress of the pathological process occurs. The association of nephropathy at the early stages of its development does not worsen the clinical course. The diagnosis of microalbuminuria is the early marker of renal involvement in the pathological process.

The development of combined acidosis is distinctive for patients with COPD. Kidneys are actively involved in the compensation of these disorders by increasing the excretion of titrating acids, and at later stages the increased ammoniogenesis becomes evident.

Key words: *chronic obstructive pulmonary disease, nephropathy, microalbuminuria.*

In contemporary society, chronic pulmonary diseases are included in a group of leading diseases at the level of hypertension, ischemic heart disease, diabetes mellitus: over 30% for all other forms of human pathology. The World Health Organization refers COPD to the diseases having a high social burden. According to the prognosis for the period to 2020, made by the experts from the WHO, COPD will become one of the leading causes of death. [1, 2, 3]

The latest concept of medical science emphasizes not only on the efficiency of the processes of diagnosis and treatment, but also on the prevention of diseases. The severity of the course and the prognosis of chronic pneumopathies are frequently

determined by extrapulmonary manifestations of the disease. [3, 4] Therefore, preventive and treatment programs largely depend on comorbidities, against which they develop.

The presence of comorbidity modifies significantly the main clinical manifestations and requires the flexibility in determining therapeutic schemes. Deficient attention to extrapulmonary manifestations of diseases of the respiratory system and inadequate assessment of their impact cause diagnostic and therapeutic mistakes. In clinical studies an adverse prognosis has been demonstrated in combination of COPD with pathologies of the cardiovascular system, such as coronary heart disease, arrhythmia, hypertension. [3, 4, 5] This combination becomes particularly dangerous in case of the severe course of pneumopathy.

It is known that kidney is one of the main organs involved in maintaining the homeostasis of the organism. The state of renal functions, including the glomerular filtration mechanism, depends on the level of blood oxygenation. At the same time, bronchial obstruction, causing hypoxemia, is the pathophysiological basis of COPD. Renal hemodynamics, responding to changes in blood gas composition, is included in the mechanisms of the disease progression. In addition, the inflammatory process affects primarily the respiratory tracts and pulmonary parenchyma, but its systemic responses are manifested at certain stages of the disease: systemic oxidative stress, endothelial dysfunction, increased activity of pro-coagulating factors and others, also affecting the renal condition [4, 6, 7].

However, despite the importance and relevance, renal aspects of pulmonary pathologies are poorly studied. The least resolved issue includes the features of formation of changes in kidneys in case of chronic pulmonary diseases, the assessment of renal homeostatic functions.

Materials and Methods

In this clinical study, we have examined 82 patients who were hospitalized in the Pulmonology Department of Municipal Health Care Institution Regional Clinical Hospital – Center of Emergency Medical Care and Medicine of Catastrophes. They had the chronic obstructive pulmonary disease (COPD) of the II-nd and III-rd degrees

of severity, with the pulmonary insufficiency (PI) of the II-nd and III-rd degrees. There were 60 (74%) males and 22 (26%) females. The average age of patients was $53 \pm 3,7$ years (men – $54 \pm 2,6$ and women – $45 \pm 3,7$). The coronary heart disease and hypertension were the most frequent comorbidities.

All patients were divided into 3 groups :

I group – patients, diagnosed COPD of the II-nd degree, PI – the II-nd degree, totally 19 (24 %) patients, including 10 men and 9 women

II group – patients with COPD of the III-rd degree, PI – the II-nd degree, all together 41 (50%) patients, including 33 men and 8 women

III group – patients with COPD of the III-rd degree, PI – the III-rd degree, all together 22 (26%) patients, including 17 men and 5 women.

The physical examination and medical history were done for all patients in the in-patient department; they were undergone the following procedures: laboratory tests of clinical blood and urine analysis, biochemical blood tests (urea and creatinine levels), study of microalbuminuria (MAU) and proteinuria, determination of the external respiration function (ERF), study of indices of renal acid excretion – titrating acid excretion per day ($E_{t.ac.}$), ammonium excretion per day ($E_{NH_4^+}$) and excretion of water ions (E_{H^+}).

Mostly the patients of all groups complained of the cough associated with the discharge of poor amount of viscous sputum, asphyxia, tachycardia, dyspnea. The intensity and frequency of complaints depended directly on the stage of the disease and the degree of pulmonary insufficiency.

All patients participated in our research are smokers, but patients in group I have an average index – 15 pack/years, and patients from groups II-III – 30 pack/years.

The external examination has revealed acrocyanosis more in patients from groups II and III (11 cases), whereas only 5 cases was detected in the I-st group.

While examining the I-st group by auscultation, the rough respiration with solitary wheezing and whirring rales were heard over the entire surface of lungs, whereas in the patients from groups II and III, the rough respiration with multiple

wheezing and whirring cracklings were auscultatory heard over the entire surface of lungs.

No pathology was detected while auscultating the heart in patients of the I-st group, but in patients from groups II and III the cardiac examination revealed the occurrence of the accent of the second tone above the pulmonary artery in 80% of cases.

Results

While examining the functions of external respiration (FER) – in patients of the group I, it was found that respiratory volumes (RV) in men make on average ($74 \pm 3,7$), and in women – ($76 \pm 2,9$); FEV_1 in men is ($65 \pm 4,0$), in women – ($70 \pm 1,3$). At the same time in groups II and III, when examining the FER, it was found the significant deterioration of these indices – so RV in men make on average $43 (\pm 2,6)$, in women – ($57 \pm 1,4$), and FEV_1 in men is ($38 \pm 2,2$), in women – ($49 \pm 2,3$).

In the study of MAU in patients from the group I, the test was positive in 10 cases – the MAU level was 0,03 g/L, and the level of creatinine in the urine was 2,2 mmol/L. The patients of the II-nd and the III-rd groups had the significantly higher MAU level – from 0,15 to 0,3 g/L, the level of creatinine – 17,7-26,5 mmol/L in 18 cases. Proteinuria was found only in 11 men from the group III and was on average 0,5 g/L.

Biochemical analysis of blood in patients from groups I and II (the II-nd group had only MAU) did not show any pathological changes. While in patients of the group III with microalbuminuria and proteinuria, the levels of urea and creatinine was a little higher than the physiological norm – $9,3 \pm 0,7$ mmol/L, and $126 \pm 1,5$ mmol/L.

According to creatinine clearance and depending on its level in the blood plasma, the glomerular filtration rate (GFR) in patients of the III-rd group was on average $62 \pm 4,58$ ml/min, corresponding to the second stage of chronic kidney disease (CKD), whereas in patients from I-st and II-nd groups the GFR had no pathological changes.

Therefore, we have found correlations between parameters FER, FEV₁ and MAU, indicating the presence of direct dependence of pathological changes in lungs and kidneys.

In addition, acid-base balance of blood was studied in all patients. The obtained data are presented in Table 1.

Table 1.

Indicators of acid-base status in patients with COPD (M ± m)

Groups Indicators	I group	II group	III group
of blood	7,40±0,01	7,36±0,01	7,35±0,01
(mmol/L)	0,36±0,01	-4,04±1,09	-5,17±0,55*
₂ (mm Hg)	85,3±4,3	47,93±6,41	28,21±1,48*
₂ (mm Hg)	39,2±0,15	38,23±3,79	47,48±47,48*

Comments: * - p 0.01

Taking into consideration the detected changes in kidneys and combined acidosis in patients from the III-rd group, an additional testing of acid renal excretory function was carried out. The obtained results are presented in Table 2.

Table 2.

Indicators of acid renal excretory function.

Groups Indicators	I group	II group	III group
t.ac. mmol/d	32,56±2,62	35,77±2,75	39,83±0,38
NH ₄ mmol/d	75,84±5,21	77,62±7,17	87,77±1,09
E _{H+} mmol/d	110,314±5,11	113,39±4,25	127,70±1,35*

Comments: * - p 0.01

Thus, the involvement of renal tubules mechanisms into the process of compensation is distinctive for patients with COPD, who have acidosis as a result of ventilation disorders. The analysis of the data suggests that the excretion of titrating

acids is increased in patients with COPD of the III-rd degree. In patients with COPD, suffered from nephropathy, this index tends to increase, but the differences are not statistically significant. At the same time, the daily excretion of ammonium is statistically considerably increased throughout the entire period of the pathological process in the lungs, while the disease aggravates.

Analyzing the indices of the renal function of acid excretion in patients with COPD and nephropathy, their compensation abilities should be also regarded. The daily excretion of hydrogen ions in the patients from the third group was even higher than in other groups. This point indicates the high compensation abilities of kidneys. It is well known that in case of surgical removal of 5/6 – 7/8 of renal parenchyma, the supercompensation of hydrogen-ion excretion together with ammonium was observed. These phenomena suggest that so-called “intact or adaptive nephrons” have the ability to support the constant homeostasis of the organism, even if kidneys are wrinkled (M.Ratner, V.Serov, N.Tomylyna, 1977).

Hence, the analysis of all these indicators suggests that even in the most severe stages of COPD, the activity of acid-excretory function of kidneys is obvious and the involvement of renal mechanisms in the regulation of acid-base balance occurs.

Conclusions

Thus, our analysis suggests that the severity of the clinical picture in patients with COPD increases in the progression of the pathological process both in the case of isolated pulmonary affection, and in patients, suffered from COPD associated with nephropathy. Associated nephropathy at the early stages of its development does not worsen the clinical course. The diagnosis of microalbuminuria in the absence of other objective signs is the early index of renal involvement in the pathological process.

The malfunction of acid-base balance of the blood and the development of acidosis (first respiratory and later metabolic) are characteristic for patients with COPD. The role of kidneys in the regulation of acid-base balance of the blood in patients with COPD is the following: the first compensatory mechanism of the tubular apparatus is the increase of titrating acids, and at later stages the

augmentation of ammoniogenesis occurs. When comparing these parameters in patients with the isolated COPD and with the development of nephropathy, these indices were higher. This observation indicates the high compensation abilities of kidneys, and the possibility of “intact” nephrons to ensure compensatory functions in certain situations.

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QUALITY OF LIFE IN PATIENTS WITH DIABETIC NEPHROPATHY AND OVERWEIGHT

Kharkov National Medical University, Ukraine

Abstract. *Introduction.* Diabetes mellitus (DM) permanently changes person's life. The diabetic nephropathy has an impact so much physical as emotional status along the process of its progression, this process deteriorates the quality of patient's life (QOL). The purpose of the present investigation is to learn influence of the clinic-psychological factors on the quality of life of patients with diabetic nephropathy and overweight.

Methods. Short Form Health Survey-36 (SF-36) questionnaire, socio-demographics and clinical parameter characteristics were used.

Results. The study enrolled 78 patients with DM, chronic kidney disease (CKD): diabetic nephropathy (DN). 65% of the patients suffered from CKD 1, 25 % had 2 stage and 10% - 3 stage. We found the lowest level of QOL in patients with type 1 DM, with DN at 3 stage of CKD, hypertension, in patients older 45 years. Patients with type 1 DM 3 stage of CKD had strongly reduced general health perceptions, role physical functioning, and vitality.

Summary. Health-care professionals have the duty to monitor quality of patient's life, personal psychological pattern to prescribe the effective treatment to its full potential.

Key words: *quality of life, diabetes mellitus, overweight*

Introduction

Diabetes mellitus (DM) has become a serious society wide health problem regarding increasing prevalence. DM is a chronic disease associated with several potentially preventable disabilities such as neuropathy, nephropathy, cardiovascular disease, blindness, and amputation. Diabetes-related morbidity and mortality impose a sizeable burden on individuals with diabetes and on society, representing a major public health concern. DM is a chronic disorder that can limit a patient's life, physically, emotionally, socially and spiritually, and this has an impact on a patient's quality of life (QOL) [1, 2]. Diabetic nephropathy (DN) is the most severe complication of diabetes mellitus, which has an impact as on physical so on

emotional status during the process of its progression. Chronic kidney disease (CKD) is an important cause of hospitalization and morbidity in patients with DM. Data on the effect kidney problems have on quality of life among persons with diabetes are not available, nor are data on changes in quality of life experienced among persons treated for DM complicated by CKD [1, 2, 3]. Recent years have witnessed a dramatic rise in the prevalence of obesity worldwide, stimulating interest in the health and quality of life consequences of this phenomenon. Doctors and researchers have found that obesity and diabetes are connected. Persons who are obese are at high risk for developing Type 2 diabetes, particularly if a close family member is affected with diabetes. Obesity deteriorates the quality of patient's life too. Numerous studies have demonstrated that obese persons experience significant impairments in quality of life as a result of their obesity, with greater impairments associated with greater degrees of obesity. Weight loss has been shown to improve quality of life in obese persons undergoing a variety of treatments. Further research is needed to clarify whether quality of life differs among subsets of obese persons [4, 5, 6]. Until recently, there has been little standardization of quality of life measures in obesity. The SF-36 has been used in a number of studies of obese persons. Several obesity-specific instruments have also been developed and have shown great promise.

Diabetic patients need not only improvement of the symptoms, but also in improvement the well-being and life satisfaction. The quality of life of obese individuals is an important issue that should be included in weight management treatment and research [5, 7].

Therefore, the *purpose* of the current study is to learn influence of the clinic-psychological factors on the quality of life of patients with diabetic nephropathy and obesity.

Methods

We used Short Form Health Survey-36 (SF-36) questionnaire, psychological tests: Spielberg, EPI, Schmieschek, socio-demographics and clinical parameter characteristics for examination of the patients with DM complicated with DN and

obesity. The SF-36 includes one multi-item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions.

The study enrolled 78 patients with DM, chronic kidney disease (CKD): DN (M-59%, F-41%; mean age - 41.3 years): 40 pts with type 1 (DM 1) and 38 pts with type 2 (DM 2) diabetes mellitus, which were examined in Kharkiv Regional clinical hospital. 38% of diabetic patients had compensated DM and 68 % - subcompensated DM.

Socio-demographics and clinical parameter characteristics (the diagnosis, treatment management, sex, age, body mass index (BMI), and blood pressure (BP) were indicated. QOL results for people with DM were compared to the healthy person (n=20).

Results

Based on their BMI, 47% of patients were nonoverweight, 53% were overweight and obese (BMI 30,5 to 52 kg/m²). Blood pressure were elevated in 24% of patients, 65% of the patients suffered from CKD 1 stage (75.2% microalbuminuria, 24.8% macroalbuminuria), impaired renal function was found in 35% of patients (25 % had CKD 2nd stage and 10% - CKD 3rd stage).

Worsening of quality of life for people with diabetes mellitus and obesity found decreasing of role physical functioning and vitality, energy or fatigue.

Mean SF-36 scale scores were: Physical health (PH), 38.2±9.7 compare to 51.0±5.6 for control group; mental health (MH), 41.0±11.2 compare to 44.0±8.0.

We found the lowest level of QOL in patients with type 1 DM, with DN at 3 stage of CKD, hypertension, in patients older 45 years. Patients with impaired renal function scores significantly lower than those with normal renal function. Patients with type 1 DM 3 stage of CKD had strongly reduced general health perceptions, role physical

functioning, and vitality: Physical functioning (PF) – 41.85 ± 10 in CKD 1st stage and 35.9 ± 8.14 in CKD 3rd stage; General health (GH) - 32.94 ± 5.18 in CKD 1st stage compare to 29.87 ± 4.1 in CKD 3rd stage.

Lower level of QOL was found in patients with type 2 DM than patients with 1 type DM: PH - 33.4 ± 7.8 and 40.7 ± 9.9 ; MH – 34.7 ± 12.1 43.0 ± 9.9 .

Patients with good control of the glucose level had twice bigger level of social functioning, than persons with poor one.

Personal psychological status of the patients with DM and obesity had revealed diminished levels of the patients' health and activity, but much higher mood. PH and MH in patients with BMI < 30 kg/m² was higher than in persons with BMI > 30 kg/m² (PH: 42.4 ± 9.3 compare to 32.7 ± 7.5 ; MH: 44.0 ± 9.9 compare to 35.1 ± 11.2). It was shown more high level of introversion in DM and obesity, and high level of personal anxiety and situational anxiety. Choleric, phlegmatic, melancholic number of patients was the same as in obese and normal weight groups.

Summary

The SF-36 Health Survey is the most widely used self-report measure of functional health. It has a primary advantage of ease of administration which allows estimating a disease by the patient himself, to reveal «critical factors», influencing on QOL in each individual case, to establish the possible reasons for a low assessment the patient of the physical, mental, social possibilities. In addition, it provides a vehicle for quickly screening patients for readiness and specific treatment-related concerns. By consideration of the ethical problems arising at dialogue of the patient and the doctor, it is necessary to consider results of its research

QOLHealth-care professionals should monitor quality of patient's life, personal psychological pattern to prescribe the effective treatment and affect the social rehabilitation.

The clinical variables of obesity, impaired renal function, arterial hypertension were significantly associated with reduced QOL.

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DETERMINATION OF ADAPTIVE RESPONSES IN PATIENT WITH BRONCHIAL ASTHMA

Kharkov National Medical University, Ukraine

Abstract. *Observation of patients with progressing bronchial asthma (BA) showed that complications of BA depend not only on the reaction of the organism and treatment but also on the development of different adaptive responses (AR) of the organism.*

Keywords: *Bronchial asthma, adaptive responses, obesity.*

Bronchial asthma (BA) is one of the most widespread chronic diseases substantially influencing the patients' quality of life and being an economic and social burden for the society.

Observation of patients with progressing BA showed that complications of BA depend not only on the reaction of the organism and treatment but also on the development of different adaptive responses (AR) of the organism [1].

The aim of the research is to define the criteria of BA progression taking into account the features of lipid metabolism and adaptive responses in patient with BA and increased body weight and obesity [2].

The data got as a result of examination of 21 patients (13 women and 8 men at the age of 29-54) with increased body weight and obesity are used in the study. Verification if diagnosis was conducted by means of generally methods of patients' examination. Data of anamnesis, blood and urine tests results, daily diuresis, functional state of lungs - spirometry, peak flow monitoring, data of lipid spectrum were studied. A degree of obesity was determined according to the recommendations of WHO (2009) depending on BMI. The assessed level of total cholesterol (TC) and triglycerides (T) defined the state of lipid metabolism. Nonspecific AR were

determined on the basis of relative amount of lymphocytes and segmented neutrophils (index of adaption) and relative amount of lymphocytes in peripheral blood [3].

The conducted research demonstrated that BA course in patients with increased body weight and obesity has its features. In examined patients the level of cholesterol fluctuated from 2,80 mmol/l to 10,8 mmol/l that averaged $5,81 \pm 0,97$. Increased body weight was accompanied by the minimum level of cholesterol ($5,0 \pm 0,2$ mmol/l). In women the level of TC was higher than in men and made up $8,32 \pm 1,3$ and $6,97 \pm 1,01$ accordingly. The low level of TC was accompanied by worsening of clinical and functional indices. In patients of such a group was found elevated ESR $26 \pm 5,1$ mm/hour, reduced amount and the fall of FEV₁ to $54 \pm 3,5\%$ whereas at the high level of cholesterol that was $6,7 \pm 1,65$ mmol/l, ERS was $19,3 \pm 2,3$ mm/hour, the level of lymphocytes was $29,3 \pm 1,02\%$ and FEV₁ – $67,3\%$. The level triglycerides ranged from 0,5 mmol/l to 6,1 mmol/l and averaged $1,34 \pm 0,8$ mmol/l. The normal level was detected in 8 patients (38%), in the remaining patients hypertriglyceridemia was discovered. With the increase of BMI the number of patients with normal TG decreased and made up (23,8%). The number of patients with the high level of TG and obesity reached 6 people (28,6%) whereas with normal of increased body weight, respectively, two (9,5%) and one (4,8%) patients. In 3 patients with BA and elevated TG and obesity diabetes was diagnosed.

Analysis of adaptive responses showed that patients had different types of AR: stress (28,7%), exercise (40,7%), calm activation (18,9%), increased action (11%). In the group of patients characterized by FEV₁ less than 59,3%. The response to stress is more common than in patients of other groups. The formation of adaptive response was affected by patients' age. In young patients favourable AR training was created more often whereas in the age category – stress reaction.

Conducted research that obesity in combination with elevated TG in patients with asthma should be a predisposing factor that leads to impaired lung function and disease progression [4].

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Kirsanova T.A, Kuznetsov S.V.

CLINICAL AND LABORATORY- INSTRUMENTAL FEATURES OF MIXED HERPESVIRAL MENINGITES IN CHILDREN WHICH CAUSED BY COMBINATION OF HERPES SIMPLEX VIRUS AND CYTOMEGALOVIRUS

Kharkov National Medical University, Ukraine

Abstract. *The children of pre-school and school age with the burdened premorbid background, the average physical and physiological neuropsychic development more often have mixed herpesviral meningitis, caused by the combination of the virus of herpes simplex with the cytomegalovirus, somewhat more frequent in spring and in summer. The clinical picture was characterized by the symptoms of intoxication, catarrhal, general cerebral, gepato- or gepatolienal syndromes. In the peripheral blood of patients more there are found lymphocytosis, increase of ESR, anemia; in the urine of half of patients there is detected protein, of third part – acetone; in the liquor there is moderate lymphocytic cytositis, decrease of level of sodium and calcium. On electrocardiogram of children there are revealed sinus arrhythmia and disturbances of repolarization processes. On the echoencephalogram of the overwhelming majority of patients it is recorded normotension.*

Keywords: *children, virus meningitis, the virus of herpes simplex, cytomegalovirus, clinical picture.*

Viral meningites in children are some of the most severe neuroinfectious diseases according to frequency and evidence of severe consequences. In 15-60% of cases from the general morbidity by the viral affections of central nervous system viral meningitis finished by death of those patients [1,2]. In 85-96% of cases of herpesviral meningites take place neurologic deficiency [2,3]. All of them becomes to reason of invalidization and social disadaptation of reconvalescents. Among the

etiologic factors of viral meningites in the first place there are found the viruses of family Herpesviridae [1,6]. Some authors show that in 60-70% of cases herpesviral infection occurs not as mono- but mixed infectious pathology of nervous system caused more often by combination with virus of herpes simplex and other viruses of this family [1,2,6]. Detection of mixed affections of nervous system which caused by viruses of this family in the early stages of disease is important part of diagnostic process [3,6]. That is permit to quickly correction of therapy for decrease of severity and frequency of rezidual neurologic disturbances. Thus, the question of diagnostics of viral meningitis in children is one of the most prevalent problems of neuroinfectious pathology [4,5].

The aim of the research: improvement of diagnostics of meningites in children caused by the association of herpes simplex virus with cytomegalovirus, on basis of the study of their clinical picture, analysis of the results of standard laboratory and instrumental methods of diagnostics.

Materials and methods of the investigation

The clinical picture and the results of the standard laboratory-instrumental methods of diagnostics of 15 children with mixed herpesviral meningites which caused by association of herpes simplex virus and cytomegalovirus, who hospitalized into the regional children's infectious clinical hospital of Kharkov was analyzed.

The verification of diagnosis was accomplished by the founding of specific antibodies to viruses (IgM and IgG) by the method of immune-enzyme analysis (ELISA-test), DNA of viruses in the blood serum and the liquor by the polymerase chain reaction, specific cytomegaloviral cells in the liquor by microscopic method.

Results and discussion of investigation

Under the observation was 15 children in age 1 month - 15 years old with viral meningites, which caused by association of herpes simplex virus with cytomegalovirus: 2 (13,3%) - untill 1year old, 3 (20,0%) - 1-3 years old, 4 (26,7%) -

4-6 years old, 2 (13,3%) - 7-11 years old, 4 (26,7%) - 12-15 years old. Among of them was 7 boys and 8 girls (53,3%).

In winter 3 cases (20,0%) of disease was registered, in spring - 4 (26,7%), in summer - 5 (33,3%), in autumn - 3 (20,0%).

Analysis of anamnesis vitae of children of first three years old showed that in all cases pregnancy was complicated by gestosis I and/or II half pregnancy, and from early age has artificial feeding.

2 children (13,3%) in anamnesis vitae has manifestations of allergy. 11 children (73,3%) has experienced in the past one or more diseases: 9 (60,0%) - acute respiratory infections, 1 (6,7%) - bronchitis, 1 (6,7%) - pneumonia and in 2 children (13,3%) - intestinal infection. Neurologic-and-behavioral development in 14 patients (93,3%) conform to age, in 1 (6,7%) - was his delay.

In 3 children (20,0%) physical development was below average (<1), 9 (60,0%) - average (± 1), 3 (20,0%) - above average (> 1).

Children entered to hospital on first-second day of disease beginning.

General condition of 13 children (86,7%) was moderately severe, of 2 (13,3%) - severe.

The clinical picture of meningitis was characterized by symptoms of intoxication, catarrhal, general cerebral, gepato- or gepatolienal syndromes (Tab. 1).

Fever in the first three-five days were recorded in all patients, including 5 children (33,3%) - up to $38,0^{\circ}\text{C}$; 8 (53,3%) - up to $39,0^{\circ}\text{C}$; 2 (13,3%) - above $39,0^{\circ}\text{C}$.

In 11 patients (73,3%) revealed changes in the upper respiratory tract: discharge from the nose were recorded in 4 children (26,7%), hyperemia of the mucous membranes of the oropharynx - 11 (73,3%).

In 5 patients (33,3%) was observed moderate enlargement of the liver size, 1 (6,7%) - the liver and spleen.

8 patients (53,3%) at onset of the disease complained of intense headache.

In 3 children (20,0%) in the first day recorded short-term klonik-tonic convulsions.

In 5 patients (33,3%) during the first two days of the disease was observed vomiting: in 2 of them (40,0%) it was ones, 3 (60,0 %) - many times.

Table 1.

The principal clinical manifestations of mixed herpesviral meningites at onset of the disease

Clinical manifestations	Number of patients	
	abs.	%
Fever:	15	100
up to 38 ⁰	5	33,3
38,1-39 ⁰	8	53,3
39,1-40 ⁰	2	13,3
Mucous discharge from the nose	4	26,7
Hyperemia of mucous membranes of the oropharynx	11	73,3
Enlargement of the liver	6	40,0
Enlargement of the spleen	1	6,7
Headache	8	53,3
Convulsions	3	20,0
Vomiting:	5	33,3
single	2	40,0
multiple	3	60,0
Positive meningeal signs	4	26,7

Positive meningeal symptoms (rigidity of occipital muscles; upper, middle and lower Brudzinsky's symptoms; Kernig's symptom; Lessage's symptom in infants) found in 4 children (26,7 %).

In the peripheral blood in 10 children (66,7%) lymphocytosis was recorded, in 4 (26,7%) - acceleration of ESR, in 3 (20,0%) - anemia.

In the urine of 8 patients (53,3%) the protein is occurred, in 3 (20,0%) - acetone.

In the liquor of all patients pleocytosis (211±17,3 cells in 1 mkl) was registered. Biochemical indices of liquor characterized by decreased level of sodium and calcium and normal concentration of protein, glucose, potassium, chlorine.

On electrocardiogram of 3 children (20,0%) sinus arrhythmia and in 2 (13,3%) disorder of repolarization process was register. On echoencephalography in 11 children (73,3%) normotension, 4 (26,7%) - hypertension was revealed.

Conclusions:

1. Mixed herpesviral meningitis, which caused by combination of herpes simplex virus and cytomegalovirus, occurs more frequently at children of 1-3 years old (20%), 4-6 years old (27%), 12-15 years old (27%) with compromised premorbid background, normal neurologic-and-behavioral development (93,3%) and average physical development (60%), more frequently in spring and summer (27% and 33% accordingly).
2. The clinical picture of disease mainly registered in moderately severe (87%) forms and are characterized by the presence of symptoms of intoxication (100%), catarrhal (73%), general cerebral (55%), hepato- or hepatolienial (40%) syndromes.
3. In peripheral blood of patients in 67% of cases registered limphocytosis, 27% - increased ESR, 20% - anemia. In half patients in urine protein is detected, in thirds - acetone.
4. In liquor of sick children moderate lymphocytic cytolysis is registered, level of sodium and calcium is decreased, level of protein, glucose, potassium and chloride is physiological.
5. 73% of patients has liquor normotension on echoencephalography; 20% - sinus arrhythmia and 13% - disorder of repolarization process on electrocardiogram.

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CHLAMYDIA INFECTION AND RESPIRATORY DISORDERS

Kharkov National Medical University, Ukraine

Abstract. *Three chlamydial organisms are pathogenic to humans: C.pneumoniae, C.psittaci, and C.trachomatis. Clinical picture of chlamidiosis determine by species of the microbe. Efficiency of the treatment depends on timely and adequate therapy.*

Key words: *Chlamydia, pneumonia, infection.*

Three chlamydial organisms are pathogenic to humans: *Chlamydomphila* (formerly *Chlamydia*) *pneumoniae*, *Chlamydomphila* (formerly *Chlamydia*) *psittaci*, and *Chlamydia trachomatis*. These are small, gram-negative, obligate intracellular organisms. All 3 species can cause pneumonia in humans.

C. pneumoniae causes mild pneumonia or bronchitis in adolescents and young adults. Older adults may experience more severe disease and repeated infections.

C. psittaci causes psittacosis or ornithosis after exposure to infected birds. Ornithosis is the preferred term, because almost any bird can transmit the organism. The clinical spectrum of *C. psittaci* infection ranges from an asymptomatic infection to a fulminant toxic syndrome. Patients with ornithosis most commonly present with pneumonia or fever of unknown origin.

C. trachomatis is an important cause of sexually transmitted diseases, including trachoma, pelvic inflammatory disease, and cervicitis. *C. trachomatis* can also cause pneumonia, primarily in infants and young children. Reports document cases of pneumonia due to *C.trachomatis* in immunocompromised adults and laboratory workers.

Classification of pneumonia:

- Mycoplasma Pneumonia

- Bacterial Pneumonia
- Viral Pneumonia
- Imaging Pneumocystis Carinii Pneumonia
- Community-Acquired Pneumonia
- Nosocomial Pneumonia
- Ventilator-Associated Pneumonia
- Pneumocystis (carinii) jiroveci Pneumonia
- Fungal Pneumonia
- Pneumonia, Immunocompromised
- Aspiration Pneumonia
- Lymphocytic Interstitial Pneumonia
- Bacterial Pneumonia
- Atypical Bacterial Pneumonia
- Viral Pneumonia

Chlamydiae initiate infection by attaching to the outer membrane of susceptible host cells. The organism subsequently produces cytoplasmic inclusions in the infected cells, which then release the matured inclusions to infect adjacent cells.

The mode of transmission is different among the 3 species (*C. pneumoniae*, *C.psittaci*, *C.trachomatis*), but all can cause systemic disease by hematogenous spread. Respiratory secretions transmit. *C.pneumoniae* from human to human, whereas infected birds transmit *C.psittaci* to humans via the respiratory route through direct contact or aerosolization [1]. Birds known to cause ornithosis include cockatiels, parrots, parakeets, macaws, chickens, ducks, turkeys, pigeons, and sparrows, among others.

When pregnant women have a *C.trachomatis* infection of the cervix, the organism is transmitted when the infant passes through the infected birth canal. *C. trachomatis* infection may cause neonatal conjunctivitis, nasopharyngitis, otitis media, and pneumonitis. The tendency to chronic inflammation is typical, and chronic persistent infection may occur if neonatal infections remain untreated.

Epidemiology. The incidence and prevalence of the chlamydial pneumonias vary with the causative organism.

C. pneumoniae pneumonia. The estimated number of cases of *C. pneumoniae* pneumonia in the United States is 300,000 cases per year, and the pathogen is estimated to cause 10-20% of community-acquired pneumonia (CAP) cases among adults [2,3]. Globally, an analysis using 2 comprehensive international databases showed that the incidence of CAP due to *C. pneumoniae* from 4337 patients was 8% in North America, 7% in Europe, 6% in Latin America, and 5% in Asia [4].

Although *C.pneumoniae* infections occur every year, epidemiologic studies suggest a 4-year cycle in the incidence of *C.pneumoniae* pneumonia. This disease is more common in males (60-90%) than in females, a difference possibly due to cigarette smoking, and the incidence of *C.pneumoniae* pneumonia is highest among elderly persons.

Although primary infection pneumonia is more common in persons aged 7-40 years, reinfection pneumonia is more common in elderly persons. Approximately 50% of young adults and 75% of elderly persons have serologic evidence of a previous infection.

C. psittaci pneumonia. Psittacosis was first reported in Europe in 1879. Anyone exposed to infected birds is at risk for infection with *C.psittaci*. This disease is found worldwide and year-round, with most cases being sporadic.

Cases of ornithosis in the United States declined after the introduction of antibiotic-laced bird feed and a quarantine period of 30 days for imported birds. From 2009-2013, 813 cases of psittacosis in humans were reported to the US Centers for Disease Control and Prevention (CDC) [5]. The Council of State and Territorial Epidemiologists revised the case definition for psittacosis in June 2009 to include more stringent laboratory criteria for confirmed and probable cases. As a result, only 4 cases of psittacosis were reported in 2010, as compared with an average of 16 (range: 9–25) cases reported from 2000-2009 [6]. Additional information about case

reporting of psittacosis can be found through the National Association of State Public Health Veterinarians.

Approximately 70% of the psittacosis cases with a known source of infection result from exposure to pet birds. The diagnosis of psittacosis can be difficult, and many more cases may occur that are not correctly diagnosed or reported.

C. trachomatis pneumonia. In infants, an estimated 12,000 cases of pneumonia due to *C. trachomatis* occur each year, and Approximately 5-22% of pregnant women are thought to have *C. trachomatis* infection of the cervix; 30-50% of neonates born to infected mothers show culture evidence of infection. Of infected neonates, 15-25% present with clinical conjunctivitis and/or nasopharyngitis that in some cases develops into neonatal pneumonitis, and approximately 11-20% of infants born to infected mothers develop symptomatic pneumonia before age 8 weeks [7]. Adult cases have been reported in immunocompromised hosts.

Clinical picture. The evaluation of patients with suspected pneumonia caused by *C.pneumoniae*, *C.psittaci*, or *C.trachomatis* is discussed in this section.

C. pneumoniae pneumonia. The incubation period of *C.pneumoniae* pneumonia is approximately 3-4 weeks, with a usually gradual onset that may be biphasic. Although most infected persons are asymptomatic, and most have relatively mild respiratory illnesses, symptoms of bronchitis or pneumonia may follow upper respiratory tract symptoms (rhinitis, laryngitis, pharyngitis, sinusitis) in 1-4 weeks.

Sputum is usually scant, but cough is prominent, with possible prolonged symptoms such as persistent cough and malaise for weeks to months despite appropriate use of antibiotics. In addition, a history of hoarseness is more common in *C.pneumoniae* infection than in mycoplasmal infection or other pneumonias. Headache occurs in as many as 58% of cases and may be important as a nonclassic pneumonia finding.

Fever is more often present in the first few days than in 1 week or later, but it is less likely to be reported, as the fever is often absent by the time of clinical examination.

Pharyngeal erythema without exudate occurs in various atypical pneumonias; however, sinus percussion tenderness is more common with *C. pneumoniae* pneumonia than with other pneumonias.

Rhonchi and rales are present even in mild disease.

C.psittaci pneumonia. Exposure to birds, especially sick ones, is a clue to the diagnosis in a patient with pneumonia and splenomegaly. Pet shop employees and poultry industry workers are also at risk. Obtain an occupational and avocational history in all patients with community-acquired pneumonia (CAP).

The incubation period of *C.psittaci* pneumonia is 5-14 days or longer. Abrupt onset of constitutional symptoms is a common presentation in symptomatic patients. The severity of disease ranges from asymptomatic to severe pneumonia with systemic illness. A nonproductive cough has been observed in 50-80% of infected patients; however, this symptom is often absent initially. Chest pain is common, but pleuritic pain is rare. Auscultatory findings may be sparse and may underestimate the extent of pneumonia.

Fever is the most common symptom and may reach 39.4-40.5°C. Some patients may present with culture-negative endocarditis or fever of unknown origin. Defervescence is usually slow.

Photophobia, epistaxis, tinnitus, deafness, gastrointestinal (GI) symptoms, and arthralgia have been reported in less than half of patients.

Physical findings that suggest ornithosis include a pulse-temperature dissociation (fever without elevated pulse), which is also seen in Q fever, typhoid fever, and Legionnaires disease [9]; somnolence; splenomegaly; and an erythematous, blanching, maculopapular rash (Horder spots) in the presence of pneumonia. Rose spots look very similar to Horder spots and are observed in persons with typhoid fever.

Signs of meningitis or encephalitis, including focal neurologic deficits and seizures, may develop. In addition, signs of hepatitis, hemolytic anemia, disseminated intravascular coagulation, meningoencephalitis, or reactive arthritis may be observed,

as well as cutaneous manifestations, including Horder spots (rare), splinter hemorrhages, superficial venous thromboses, acrocyanosis, and erythema nodosum.

C. trachomatis pneumonia. In patients infected *C.trachomatis* with, nasal obstruction and discharge, cough, and tachypnea are present. Infants are usually symptomatic for 3 weeks or more before presentation.

Most patients are afebrile and only moderately ill. Scattered crackles with good breath sounds are characteristic, but wheezing is usually absent. Conjunctivitis and middle ear abnormality are present in half the infants with pneumonia.

Differential Diagnosis. The differential diagnosis of chlamydial pneumonias includes the following conditions:

- Influenza
- Legionnaires Disease
- Mycoplasma Infections
- Pneumonia, Bacterial
- Pneumonia, Fungal
- Pneumonia, Viral
- Psittacosis
- Q Fever
- Tuberculosis
- Tularemia
- Other disorders to consider include the following:
 - *C. trachomatis* infant pneumonia
 - Respiratory syncytial virus infection
 - *Bordetella pertussis* infection
 - Infection with other respiratory viruses
- Tests in Chlamydial Pneumonias

Laboratory studies for diagnosis of the chlamydial pneumonias vary with the causative organism.

C. pneumoniae pneumonia. The commonly used serologic criteria used to evaluate *C.pneumoniae* pneumonia are an IgM titer exceeding 1:16 or a 4-fold

increase in the immunoglobulin G (IgG) titer by microimmunofluorescence (MIF) [10]. However, serologic testing is poorly standardized and studies have shown poor reproducibility [11, 12, 13]. In addition, the presence of a single elevated IgG titer may not be reliable, because elderly patients can have persistently elevated IgG titers due to repeated infections.

The absence of detectable antibodies several weeks after the onset of infection does not exclude a diagnosis of acute *C.pneumoniae* pneumonia, because the IgM antibody response may take as long as 6 weeks, and the IgG antibody response may take as long as 8 weeks to appear in primary infections.

In some laboratories, a polymerase chain reaction (PCR) assay with pharyngeal swab, bronchoalveolar lavage, sputum, or tissue can be used to seek *C pneumoniae* – specific DNA. This is the most promising rapid test but remains experimental [14].

The Film Array Respiratory Panel is a multiplex PCR that detects common respiratory viruses in nasopharyngeal specimens. In 2012, the US Food and Drug Administration approved the addition of 2 corona viruses and 3 bacteria to the Panel, including *Chlamydophila pneumoniae*, *Bordetella pertussis*, and *Mycoplasma pneumoniae*. The FilmArray Panel can now detect 17 viruses and 3 bacteria from a single sample [15]. Reported sensitivity and specificity were both 100% for *Chlamydophila pneumoniae* but fewer than 10 positive samples were available for analysis [16].

In one study, the accuracy of PCR was compared with that of MIF IgM during an outbreak of *C.pneumoniae*. PCR was less sensitive (68% vs 79%, respectively) but more specific than MIF IgM (93% vs 86%, respectively) [17].

Cell culture with oropharyngeal swabs is probably the best test to detect *C. pneumoniae*, but it requires specialized culture techniques and is performed only in research laboratories.

The white blood cell count is usually not elevated in *C.pneumoniae* infection. Alkaline phosphate levels may be elevated.

C. psittaci pneumonia. Single serum titers are insensitive and nonspecific. Confirmation with paired acute and convalescent sera is advised. Serologic tests are preferred, because culture is difficult and hazardous.

According to case definitions from the Centers for Disease Control and Prevention (CDC), a confirmed case involves any of the following [5]:

- isolation of the organism by culture. Compatible clinical illness with a 4-fold rise in CF or MIF antibodies against *C.psittaci* (to a reciprocal titer of 32 or greater by paired sera at least 2 wk apart)
- detection of an IgM titer of 16 or greater against *C.psittaci* by MIF.

The CDC defines a probable case as a compatible clinical illness that is epidemiologically linked to a confirmed case or that has a single antibody titer of 32 or greater by MIF or CF after the onset of symptoms. The CDC accepts human specimens for the diagnosis of *C. psittaci* infection [18].

A CF test can cross-react with *C.pneumoniae* and *C.trachomatis*. MIF and PCR assays can be used to distinguish *C.psittaci* infection from infection with other chlamydial species.

A third serum sample may be necessary to confirm the diagnosis, because antibiotic treatment can delay or diminish the antibody response. All serologic tests should be performed simultaneously at the same laboratory.

C.trachomatis pneumonia. Clinical findings suggest the diagnosis of *C. trachomatis* pneumonia; the presence of chlamydial inclusions or elementary bodies on Giemsa-stained smears of the conjunctivae or nasopharynx confirms the diagnosis.

Testing of the infants may show findings of elevated antichlamydial IgM titer. Peripheral eosinophilia and elevated serum immunoglobulin levels are characteristic. Screen the parents for chlamydia and other sexually transmitted diseases.

Chest Radiography. Chest radiographs of patients with *C. pneumoniae* pneumonia most commonly show a single subsegmental infiltrate that is mainly located in the lower lobes. Extensive consolidation is rare, although acute respiratory distress syndrome (ARDS) has been reported. No radiographic findings

are characteristic. Residual changes can be observed even after 3 months. Pleural effusion occurs in 20-25% of cases.

In *C.psittaci* pneumonia, consolidation in a single lower lobe is the most common finding. However, various findings have been observed, including patchy reticular infiltrates radiating from the hilum, a diffuse ground-glass appearance, and a miliary pattern. Pleural effusions are evident in as many as 50% of cases; however, the effusions are usually small and do not cause symptoms.

In cases of *C.trachomatis* pneumonia, chest radiographs show bilateral interstitial infiltrates with hyperinflation [8].

Histologic Findings. Intra-alveolar inflammation with a milder degree of interstitial reaction is a characteristic pathologic finding in the lungs of patients with chlamydial pneumonias. Alveolar-lining cells contain intracytoplasmic inclusions.

Antimicrobials in Chlamydial Pneumonias. The goals of pharmacotherapy are to eradicate infection, reduce morbidity, and prevent complications.

Tetracyclines and macrolides are the drugs of choice for chlamydial pneumonias [19]. Tetracyclines are bacteriostatic in nature; they work by inhibiting protein synthesis. As a class, tetracyclines have similar antimicrobial profiles, and cross-resistance is likely. Macrolides inhibit bacterial growth, possibly by blocking dissociation of peptidyl t-RNA from ribosomes, thus causing cessation of RNA-dependent protein synthesis.

Management of *C.pneumoniae* Pneumonia. Administer empiric treatment when mixed infections with other organisms are present (pneumococci, mycoplasmata, legionellae). The frequency of mixed infection can be as high as 60%. Clinicians must treat empirically, because rapid testing is not readily available, and antibiotic therapy is usually completed before the results of serology testing become available.

Severely ill hypoxemic patients require ventilatory support in an intensive care unit (ICU).

Drug of choice. Doxycycline is the treatment of choice, except in children younger than 9 years and in pregnant women. Treatment should be continued for at

least 10-14 days after defervescence. If symptoms persist, a second course with a different class of antibiotics is usually effective.

In inpatient settings, use doxycycline hyclate (100 mg iv). In outpatient settings, use doxycycline (100 mg per os) or tetracycline hydrochloride (500 mg per os).

Alternative drugs. Alternative agents include erythromycin (500 mg per os) and newer macrolides such as azithromycin (500 mg per os/iv for 7-10 days) and clarithromycin (500 mg - 1 g per os for 10 days). The newer macrolides are better tolerated than erythromycin, and shorter courses of the newer macrolides appear to be effective.

Telithromycin is the first antibiotic in a new class called ketolides and is approved for *C. pneumoniae* pneumonia by the US Food and Drug Administration (FDA). This agent is more expensive than doxycycline. Telithromycin is a potent inhibitor of CYP3A4 and can cause potentially dangerous increases in serum concentrations of simvastatin, lovastatin, atorvastatin, midazolam, and other drugs. If this agent is used, statins should be withheld for the duration of therapy. Hepatotoxicity (some fatal cases) has been reported. Telithromycin is contraindicated in patients with myasthenia gravis.

Fluoroquinolones, including levofloxacin (500 mg per os/iv for 10-14 days or 750 mg per os/iv for 5 days) and moxifloxacin (400 mg per os/iv for 10-14 days), also have some activity, although less than that of tetracyclines or macrolides.

Patient education and consultations. Educate patients about the possible protracted course of illness and about the need for re-treatment if symptoms recur or worsen.

Consultations with infectious disease and/or pulmonary specialists may be required if a patient needs hospitalization or does not respond to therapy.

Complications. Complications of *C.pneumoniae* infection include otitis, erythema nodosum, exacerbations of asthma, endocarditis, Guillain-Barré syndrome, and encephalitis. New-onset asthma has been also been observed. Complications

Complications of psittacosis include endocarditis, thrombophlebitis, myocarditis, thyroiditis, pancreatitis, hepatitis, renal failure, disseminated intravascular coagulation, and fetal death in infected pregnant women.

Although some studies clearly associate *C.pneumoniae* organisms with atheromatous plaques [20], multiple sclerosis, macular degeneration, Alzheimer disease, chronic fatigue syndrome, or sarcoidosis, the role of *C.pneumoniae* in the pathogenesis of these diseases remains to be established [19]. Antibiotic trials for coronary artery disease are not supportive of their role [21, 22].

Management of *C. psittaci* Pneumonia. Tetracycline (500 mg per os) or doxycycline (100 mg per os/iv) is the treatment of choice in the treatment of *C psittaci* pneumonia. Continue treatment for 10-21 days; a longer course to prevent relapse is controversial.

Azithromycin (250-500 mg per os for 7 days) is probably effective based on in vitro data and in vivo animal data.

Erythromycin is the alternative treatment, but this drug may be less efficacious in severe cases.

Severely ill hypoxemic patients require ventilatory support in an intensive care unit (ICU).

Prevention. The incidence of *C.pneumoniae* infection among military recruits during basic training is high, and weekly azithromycin prophylaxis was 58% effective in preventing the disease in this setting.

Past infection with *C.psittaci* does not confer immunity to the disease. For prevention of *C.psittaci* pneumonia, individuals should avoid dust from bird feathers and cage contents as well as avoid handling sick birds. Furthermore, imported psittacine birds must be treated for 45 days with a balanced feed containing chlortetracycline with 0.7% calcium. Refer infected birds or suspected sources to veterinarians.

Evaluate mothers of children infected with *C.trachomatis* and their sexual partners, and treat them appropriately. Repeated parental screening may be warranted in high-risk populations.

Prognosis. Outcomes in the chlamydial pneumonias depend on the causative organism and the disease severity.

C.pneumoniae pneumonia. Most cases of infection with *C. pneumoniae* are mild and usually respond to treatment in an outpatient setting. Patients with underlying disease or with concurrent infection (eg, pneumococcal bacteremia) can develop severe illness.

Treatment failure in *C.pneumoniae* pneumonia may occur more often with erythromycin [23]. Retreatment is often successful, especially with tetracyclines. Complete recovery is slow: cough and malaise may persist for weeks to months despite appropriate treatment.

C. psittaci pneumonia. *C.psittaci* infection is usually curable in 7-14 days with early diagnosis and treatment. A full recovery from *C.psittaci* pneumonia usually takes 6-8 weeks, and relapse may occur.

The mortality rate from infection with *C.psittaci* was 20% in the era before the advent of antibiotics. The mortality rate is 5% with antibiotic treatment; it is less than 1% with early diagnosis and treatment.

C. trachomatis pneumonia. Most infants with *C.trachomatis* pneumonia are only moderately ill and respond to appropriate antibiotics; if the infection is not treated, the clinical course may be protracted, and respiratory failure and prolonged spells of apnea may occur.

A higher-than-normal incidence of obstructive airway disease or asthma occurs in children who had chlamydial pneumonia before age 6 months.

Special Considerations. Avoid tetracyclines in pregnant women as well as in children younger than 9 years.

Infection with *C.pneumoniae* or *C.psittaci* can be fatal, especially in elderly patients with an underlying disease.

It is important to not only consider the diagnosis of *C.pneumoniae* infection in patients with bronchitis or community-acquired pneumonia (CAP) but also to treat with an appropriate antibiotic.

It is necessary to consider *C.psittaci* pneumonia in patients with CAP, especially those with bird exposure or fever of unknown origin, who are not responding to treatment. *C.psittaci* pneumonia must be reported to an appropriate health authority, and requests to a veterinarian should be made for evaluation and treatment of birds that are suspected sources of human infection.

In cases of infants with *C.trachomatis* infection, mothers and their sexual partners must be evaluated and treated appropriately. In younger children, *C.trachomatis* infection can also be acquired through sexual abuse.

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PECULIARITIES OF OBSTRUCTIVE BRONCHITIS IN CHILDREN OF YOUNG AGES

Kharkov National Medical University, Ukraine

Abstract. *The features of obstructive bronchitis in infants were studied. Prognostic criteria of severity was identified, the expediency of using of antibiotics was substantiated.*

Keywords. *Obstructive bronchitis, clinical symptoms, children.*

Acute bronchitis remains among the most common diseases among children [1, 3]. For children of the first years of life the development of obstruction syndrome is a particularly dangerous, aided by the anatomical-physiological characteristics of the respiratory system of the child: a much smaller diameter of the bronchi compared to that of the adults; relatively high resistance to airflow during breathing, which requires substantial muscular effort; bronchial mucosal goblet cells producing large amounts of tenacious sputum; a rich blood supply, which contributes to the rapid development of mucosal edema [2, 3]. Important contributors to the development of obstruction is the increased sensitivity of the child to adverse environmental factors, the low mobility of children in the first year of life, overweight, a tendency to allergic reactions, etc [4].

In the recent years, of great interest has been the question about the dynamics of obstructive bronchitis (OB) in children with chronic lung diseases, among which broncho-pulmonary dysplasia (BPD) occupies an important place. This pathology is characterized in very premature newborns, who had been placed on artificial respiration. We owe the increase in percentage of children with BPD to the scientific–technological progress in perinatal and neonatal intensive medicine which helps in revealing and care of children with low birth weight [5]. Broncho-pulmonary dysplasia was first described by Northway et al in 1967 as a disease of prematurity,

which is seen in children with respiratory distress syndrome who were placed on artificial lung ventilation (ALV) under high pressure and high concentrations of oxygen [6]. Previously, the pathogenic mechanisms of BPD was schematically represented as a formula by A. Philip (1975): «oxygen + pressure + time" [7]. In the recent times BPD has been considered as a poly-etiological disease, the development of which is of great importance, the presence of immature lungs in premature babies in which there is toxic effects following oxygen therapy which includes: pulmonary baro-traumas, respiratory disorders, infections, pulmonary hypertension etc. [7, 8].

As already known, broncho-pulmonary dysplasia may be one of the reasons of lethality in children and increases the incidence of sudden death syndrome in such children by 7 times [9]. Therefore, it is so important to study the course of OB in young children, including those with BPD

The purpose of the study - to determine the characteristics of the clinical manifestations of acute obstructive bronchitis in infants at the present stage.

Materials and methods. We examined 46 children 1 month -2 years aged with acute severe OB, who were treated at the regional children's infectious diseases hospital in Kharkov. Along with the study of generally accepted clinical and laboratory parameters, we conducted virological, bacteriological, serological surveys and PCR diagnosis of patients. Statistical processing of the results was performed on a PC using the program "Excel". Reliable signs were evaluated using Student's t test.

Discussion of the results. On analysis of history, it was revealed that in the vast majority (35-76,09 %) the disease begins gradually - the mother indicated the presence of occasional dry cough for $4,54 \pm 1,24$ days. In 11 children (23,91 %) we observed an acute onset of the disease, in which the clinical manifestations of obstructive syndrome (shortness of breath) were one of the first signs in combination with mucous secretions from the nose, dry cough, loss of appetite or refusal of food and disorder of general condition. In 30 children (65,22 %) on the onset of the disease fever was not observed; these children underwent symptomatic treatment at home, while in 15 (32,61 %) cases the children's parents did not seek help from pediatrician. Before admission, 14 (30,43 %) children received antibiotics, which are

dominated by three generations cephalosporins (Cefixime , Ikzyme) , macrolides (Sumamed).

Analysis of patients histories revealed that 20 children (43,47 %) had a tendency to allergic manifestations (including - hereditary), 12 (26,08 %) - overweight, 26 (56,52 %) - an early transition to mixture and mixed feeding, 29 (63,04 %) - respiratory infections in the first months of life, especially in the first six months, 22 (47,82 %) - hypoxic - ischemic CNS damage during childbirth, 6 (13,04 %) - bronchopulmonary dysplasia, which was diagnosed in the neonatal period. In the most cases one (33 - 71,73 %) smoking or both smoking parents (16-34,78 %) were found. Manifestations of atopic dermatitis on admission and during the hospital stay was observed in 8 (17,39 %) children.

The clinical picture of acute OB in all children characterized by the presence of bilateral bronchial obstruction syndrome: frequent dry cough, which later transformed into the wet with the release of viscous mucus; shortness of breath. Lung percussion noted band-box sound; auscultation depicted difficulty breathing with prolonged expiration, wheezing, dryness on both sides. Fever up to 38, 5-39,0 °C was observed in 41 (89,13 %) patients. High fever was observed in 18 (39,13 %) children. At all children (11-23,91 %) who had signs of obstructive bronchitis from the first day of the disease, the course of diseases has been very severe. These children were hospitalized in the intensive care unit where there were an average of 3,54±1,22 days; obstructive syndrome was prolonged (6,54±1,58 vs 4,84±1,23 days in patients with a gradual onset of the disease , p 0,05). In 12 (26,09 %) children prolonged course of the disease was diagnosed, characterized by the resumption of obstructive syndrome after a short (3,24 ± 0,62 days) clinical improvement. According to our data, in 4 children with BPD severe form of OB with protracted course was observed. The duration of obstruction in children with BPD was 7,54±2,46 days vs. 5,61±1,46 days, p 0,05 on average. In general, according to our findings in children with BPD obstructive bronchitis has a tendency to severe course (high probability of protracted course) accompanied by prolonged retention of obstructive syndrome.

In the study of mucus from the nasopharynx to determine the etiological factor of the disease in 13 children (28,89 %) RS-viral antigen, 11 (23,91 %) – adenoviral antigen, 7 (15,22 %) – parainfluenza antigen were found. By ELISA method in 7 (15,22 %) children high antibody titers to Chlamydia pneumonia class IgM was revealed, 4 (8,69 %) – *Mycoplasma pneumonia* antibody class IgM. We failed to define the etiology of OB in 4 (8,69 %) children by accessible for us methods of investigation.

Bacteriological examination of smears from the nasopharynx in 8 (17,39 %) patients showed *E. aerogenes*, 5 (10,87 %) - *S. epidermidis* with hemolytic properties, 4 (8,69 %) - *Strep. viridans*, 3 (6,52 %) - *S. aureus*, 3 (6,52 %) - *E. faecalis*, 2 (4,35 %) - fungi of the genus *Candida* and 1 (2,17 %) - *P. aeruginosa*. The presence of two simultaneous pathogens was found in 7 children (15,22 %). The study indicated that, despite the detection of viral antigens predominantly in patients with OB (31-67,39 %), there was a high percentage of contamination of the mucous membrane of the oropharynx with bacterial flora, which can also play a significant role in the development of the pathological process of the child.

Bacteriological study of tracheobronchial lavage tube in children who were on artificial ventilators detected *E. aerogenes* in 4 (8,69 %), *S. aureus* in 3 (6,52 %), *S. epidermidis* with hemolytic properties in 3 (6,52 %) and *Strep. Viridans* in 2 (4,35 %) patients. Comparative analysis revealed the same type of pathogen isolation coincidence only in 3 children (6,52 %), which indicates that the nasal mucosa and tracheobronchial tract were contaminated by various microorganisms.

Study of peripheral blood of patients identified that the vast majority of patients (34-73,91 %) had leukocytosis ($12,04 \pm 1,22 \cdot 10^9/L$), a shift to the left of blood formula with increased content of band ($7,05 \pm 1,34$ %) and segmented ($59,48 \pm 5,63$ %) neutrophils, accelerated ESR ($13,44 \pm 2,41$ mm/h). In 7 (15,22 %) children leukopenia ($4,05 \pm 1,55 \cdot 10^9/L$), increased lymphocytes (68,46 ± 5,74 %) and monocytes ($12,87 \pm 2,11$ %) were found. In 5 patients (10,87 %) - blood counts remained within the age norm. Noteworthy is the fact that, despite the prevalence of

viruses as pathogens of obstructive bronchitis, in most patients the changes in peripheral blood was like at a bacterial infection.

In our opinion, this is due to the activation of the bacterial flora of the upper respiratory tract. According to our research the nasopharyngeal bacterial flora was isolated in 26 children (56,52 %), which represents sufficiently high number. It can not be neglected when choosing treatment and is the reason for use antibiotics to young children with acute OB. Among the antimicrobial antibacterial preparations the most appropriate are using of macrolides, due to the sufficiently high frequency of detection of atypical flora (Chlamydia, Mycoplasma) as one of the factors of occurrence of OB.

Patients were treated according to conventional protocols and regimens for treatment of obstructive bronchitis. As is known, in the genesis of bronchial obstruction in young children predominate inflammatory edema and hypersecretion of viscous mucus. Therefore, pathogenetic and symptomatic therapies OB is anti-inflammatory, bronchodilator and mucolytic drugs, physiotherapy using inhaled, in the first place - using a nebulizer. In all children disease resolved with complete recovery.

Conclusion. Thus, in vast majority of young children (76,09 %) acute OB develops gradually. Regarding the development of symptoms in children in the first day of the disease, there appears as increased likelihood of a severe process. In infants with broncho-pulmonary dysplasia OB is characterizes the severity and unfavorable (undulating) course. The appropriateness of antibiotic therapy in children with OB was determined, primarily – macrolides. It is promising to monitor pathogens in the mucous membranes of the upper respiratory tract in OB which does not only identify the most common pathogens in this region, but will provide an opportunity to select the most appropriate treatment strategies that will prevent nosocomial infections and reduce the duration of stay in the hospital.

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PREDICTION OF UNFAVORABLE COURSE OF BRONCHOPULMONARY DYSPLASIA IN CHILDREN AT THE PRESENT STAGE

¹ *Kharkov National Medical University, Ukraine*

² *Public Health Care Institution «Kharkov Regional Clinical Children
Hospital», Ukraine*

Abstract. *The article provides the results of vasoconstrictive and adaptogenic proteinases level analysis in children with bronchopulmonary dysplasia. It was shown that proteinase-proteinase inhibitor system plays a significant role in the development of cardiovascular complications in bronchopulmonary dysplasia and it can be regarded as markers of unfavorable course of bronchopulmonary dysplasia.*

Key words: *bronchopulmonary dysplasia, unfavorable course, components of proteinase-proteinase inhibitor system.*

With the development of the technologies in special care nursery and respiratory support of premature newborns there has been noted a reduction in mortality along with an increase in frequency of bronchopulmonary dysplasia (BPD) in children [1, 2, 3].

One of the most important conditions which determine peculiarity of pathologic processes in the lungs of newborns is that they develop in one of the most critical period of a child's life during rearrangement of functional systems, first of all, respiration and blood circulation and their gradual maturation [4]. Over the period of many years bronchopulmonary dysplasia was considered to be a condition which affects newborns, premature newborns in particular. Subsequently it has been shown that the significance of BPD falls beyond the scope of neonatology [1, 5].

Due to close morphofunctional interrelation, obstructive or restrictive changes in chronic diseases of the respiratory system lead to early disorders of cardiopulmonary ratio, which result in hypoxic pulmonary vasoconstriction, mechanic narrowing of vessels and obstruction of vascular pulmonary bed, which in

its turn result in pulmonary hypertension and development of chronic cardiac insufficiency [6]. It is critical for the disease prognosis both in children and in adults.

The search for the means which could inhibit the progression of chronic pulmonary disease is at the current moment one of the main problems of pulmonology and children pulmonology in particular. That is why the search for more sensitive, delicate markers of further damage of cells and gradual decrease in lung function is still in progress. Due to this the scientists' interest to proteinases has been growing recently as its level determination is of significant clinicodiagnostic information value in many pathologic processes [7, 8].

The aim is to determine the activity of proteinases of vasoconstrictive and adaptogenic action and their participation in the development of unfavorable course of bronchopulmonary dysplasia in children.

Materials and methods. The research was carried out at the department of Pediatrics No.1 and Neonatology of KhNMU (the head of the department is Doctor of Medical Science, professor G. S. Senatorova) in the Regional Center for diagnostics and treatment of bronchopulmonary dysplasia in children Public Health Care Institution "Kharkov Regional Clinical Children Hospital" (head doctor – Candidate of Medical Science, associate professor G. R. Muratov; administrative manager – Candidate of Medical Science O. L. Logvinova).

60 children aged from 1 month to 3 years were examined, among them 29 patients were found to have classical form of BPD (1st group), 16 patients had new form of BPD (2nd group), 15 patients had BPD of mature newborns (3rd group). Bronchopulmonary dysplasia was diagnosed according to international classification of diseases 10th edition (code 27.0). Severity criteria were determined according to classification of clinical forms of bronchopulmonary diseases in children of Russian Respiratory Society (2009) [9].

The employment of high-sensitivity (10^{-9} – 10^{-10} g) enzyme method, which was elaborated in State Institution «L. T. Malaya Institute of Therapy at the Academy of Medical Science of Ukraine» (L. M. Samokhina, 1997, 2001, 2002, 2004) [10] allowed to study trypsin-inhibitory activity of α -1-inhibitor of proteinases (α -1-

P) and the activity of proteinases of vasoconstrictive action (non-trypsin-like proteinases (NTLP), chymase, tonin) and adaptogenic action (calpain) in blood serum, and also of their inhibitors – α -2-macroglobulin (α -2-MG) and trypsin-inhibitory activity. The research was carried out according to ethical principles of medical human trials stipulated by the Declaration of Helsinki.

Statistical processing of the received data was carried out with the help of statistical package of the program Statistica 7.0. Median (Me) and interquartile range (Lq – lower quartile; Uq – upper quartile) were determined for samples with distribution which doesn't correspond to normal law of errors. Non-parametric Mann-Whitney U-test (MW) was used to compare two samples. The difference in values, which was compared by two points, was considered to be statistically significant in $p < 0,05$. Kruskal–Wallis variance analysis was used in correlation of criteria which were characterized by comparison of more than 2 points and discrepancies were considered probable on the basis of Bonferonni adjustment (in $\hat{p} = p/k$, where k is the number of paired comparisons).

Results and their discussion. During the analysis of vasoconstrictive proteinases changes in the 1st group children it was determined that NTLP and tonin activity didn't significantly differ from the indices in healthy children (all $p > 0,05$), however chymase activity was definitely more significant in comparison with the control group ($p < 0,05$) (Table 1). The significant increase in α -2-MG level ($p < 0,01$) against the background of absence of changes in α -1-P ($p > 0,05$) activity can be regarded as protection, in particular, from an increase in chymase activity as this inhibitor plays a more important role in chymase inhibition than α -1-P [7]. The presence of statistically significant positive correlation relationship between α -2-MG level and activity of tonin ($r = + 0,43$, $p = 0,017$) and chymase ($r = + 0,78$, $p = 0,0000$) against the background of absence of an increase in tonin level can be indicative of a sufficient role of this inhibitor in down-regulation of the specified vasoconstrictive enzyme. An increase in chymase activity in blood serum of children with classic form of BPD demonstrates the activation of tissue pathway of angiotensin II formation,

which can contribute to the development of vasoconstrictive mechanisms of formation and progression of cardiovascular complications [7].

Table 1

Activity of vasoconstrictive proteinases in the blood serum of the examined children

Index	1 st group (n=29)	2 nd group (n=16)	3 rd group (n=15)	Control group (n=12)
	Me (Lq; Uq)	Me (Lq; Uq)	Me (Lq; Uq)	Me (Lq; Uq)
NTLP, mg/l/h.	0,095 (0,060; 0,190)	0,090 (0,071; 0,155)	0,070 (0,055; 0,160)	0,110 (0,090; 0,145)
Tonin, mcM substr/min.	0,594 (0,078; 2,673)	2,231 (0,259; 3,426)	0,344 (0,000; 2,409) [^]	2,012 (1,175; 3,107)
Chymase, 10 ⁻³ nM substr/min	3,104 (0,753; 4,264) [^]	2,184 (1,384; 2,902)	0,000 (0,000; 0,001)	0,851 (0,047; 2,869)
Calpains, g/l h.	0,107 (0,024; 0,253) ^{^^}	0,308 (0,101; 0,508)	0,063 (0,004; 0,354)	0,238 (0,161; 0,290)
α -2- G, g/l h	0,25 (0,22; 0,43) ^{^^}	0,30 (0,23; 0,49) ^{^^}	0,28 (0,20; 0,30)	0,20 (0,17; 0,29)
-1- P, g/l h	7,75 (7,30; 7,90)	7,65 (7,32; 7,71)	7,80 (7,30; 7,89)	7,67 (7,53; 7,83)

Note. [^] - in comparison with control <0,05; ^{^^} - in comparison with control <0,01

Blood serum of the 2nd group children demonstrated a statistically significant increase in only α -2- G (<0,01) level. The increase in α -2- G activity, absence of an increase in -1- P in blood serum of children with the new form of BPD, presence of statistically significant positive correlation relationship between α -2- G and NTLP ($r= + 0,48$, $\rho=0,05$) and chymase ($r= + 0,79$, $\rho=0,0002$) levels in blood serum leaves open the possibility of inhibitors participation in down-regulation of excessive proteinase activity.

The 3rd group children demonstrated a statistically significant decrease in tonin level (<0,05), a vasoconstrictive proteinase which takes part in alternative route of angiotensin II formation directly of angiotensin, without substantial changes

in the level of inhibitors as compared to the control (all $>0,05$). There has also been determined a statistically significant positive correlation relationship between the activity of chymase and α -2- G ($r = +0,50$; $p=0,05$) which, against the background of absence of an increase in vasoconstrictive proteinases activity, can be indicative of a sufficient participation of this inhibitor in down-regulation of vasoconstrictive enzymes. Besides, there has been detected a statistically significant negative correlation relationship between the activity of α -2- G and α -1- P ($r = - 0,53$; $p=0,05$). Such a character of changes in proteinase inhibitors contributes to proteolysis inhibition, especially with the participation of trypsin-like enzymes. That is, in full-term children with BPD α -2- G inhibits proteolysis in great measure without having to involve α -1- P, which is indicative of natural protection of the organism from proteolysis activation. The absence of an increase in this inhibitor activity reflects a higher possibility of NTLP participation in vasoconstrictive effects development. It is confirmed by statistically significant strong positive correlation relationship between the level of NTLP and the activity of chymase ($r = + 0,73$; $p=0,001$), which can suggest that the specified proteinases were spent on angiotensin II formation and that the possibility of their synthesis was depleted and/or tissue vasoconstrictive effects developed and released due to prolonged formation of pathologic process.

Multiple comparison of the statistical characteristics of proteinases and their inhibitors activity determined that Kruskal-Wallis test was highly significant by such indices as chymase ($F = 9,09$; $p=0,0280$) and α -2- G ($F = 8,61$; $p=0,0349$). This provides evidence that statistical characteristics of the corresponding indices of the different groups fairly differ against each other and chymase and α -2- G activity level in blood serum depends on the group to which the patients belong.

Multiple logistic regression analysis was performed to determine which factors should certainly be considered when predicting complications and unfavorable outcome of BPD. Clinical material of 63 patients has been randomly selected to develop a mathematical model for the prediction of BPD outcome in

children, among them 27 patients were found to have favorable BPD course; its criteria were chosen as follows: prolonged remission of the disease, absence of severe accompanying abnormalities and satisfactory life quality. 36 patients were found to have unfavorable BPD course, its criteria were chosen as follows: presence of severe accompanying abnormalities, frequent relapses of pneumonia or obstructive bronchitis, disability or untimely death.

Favorable ($=1$) or unfavorable BPD outcome ($=0$) was correspondingly chosen as binary dependent variable (Y). Both quantitative and qualitative factors were chosen as independent variables. Duration of artificial lung ventilation, gestation term, body mass at birth, activity of proteinase-proteinase inhibitor system components, blood pH level, P_{O_2} partial pressure, mean pulmonary arterial pressure and heartbeat rate were chosen to be quantitative factors. Clinical and anamnestic data, namely perinatal anamnesis and physical examination data, presence of accompanying abnormality, duration of the disease were considered to be independent qualitative variables. Every qualitative factor was coded as "1" if the child was noted to have this factor or "0" if this factor was not detected. Statistical significance of the obtained results (possibility that the patient will be included in the certain study group according to the factor being estimated) was determined by Wald criterion (the higher the module of this criterion (coefficient), the stronger its influence on the dependent variable). The quality of the developed model was checked by percent concordant (K). This index is equal to the part of observations which were correctly reclassified to separate groups of dependent factors by logistic regression equation. The closer this factor to 100%, the higher the quality of the obtained model. The possibility of event development for certain case was calculated by the formula:

$$P = \frac{1}{1 + e^{-z}},$$

$$\text{where } z = b_0 + b_1 * X_1 + b_2 * X_2 + \dots + b_n * X_n,$$

X_1, X_2, X_n — independent variables values, b_1, b_2, b_n — coefficients which should be calculated by binary logistic regression, b_0 — certain constant. $p > 0,5$ is indicative of a significant possibility that the event will take place (), in $p < 0,5$ this possibility is insignificant.

The procedure of multiple logistic regression allowed to separate a group of factors, which can help to predict BPD outcome with a sufficient level of statistical significance. The results of statistical analysis of multiple logistic regression are summarized in Table 2.

Table 2

Statistical characteristics of multiple logistic regression of factors, which are potentially able to influence bronchopulmonary dysplasia outcome in children

Variable	Coefficient	Standard error	Wald criterion	Statistical significance,	Confidence range _{95%} for correlation of chances
Constant	-178,894	75,30	5,643	0,01	[1,610; 2,556]
Duration of artificial lung ventilation	- 0,0819	0,04	3,846	0,05	[0,849; 1,000]
Gestation term	0,254	0,18	1,870	0,05	[0,896; 1,855]
Body mass at birth	-0,00204	0,001	3,614	0,049	[0,996; 1,000]
-2 G activity	-10,614	5,51	3,710	0,048	[0,000005; 1,205]
Tonin activity	1,821	0,75	5,839	0,01	[1,410; 27,036]
Calpains activity	-5,816	2,84	4,171	0,044	[0,00004; 0,791]
Blood	24,105	9,93	5,887	0,01	[215,337; 1,084]
β_2	0,142	0,05	6,227	0,01	[1,031; 1,289]
Heartbeat rate	-0,0342	0,01	3,325	0,047	[0,931; 1,003]
Pulmonary artery	-0,0745	0,06	1,292	0,043	[0,816; 1,055]

The quality of the developed model was checked by percent concordant (presenting factors of belonging to a subgroup (1=favorable course, 0=unfavorable course) were matched and stipulated on the basis of the developed model)).

The results of the performed analysis allowed to develop multiple regression equation:

$$\begin{aligned} \text{Logit P (z)} = & -178,894 - (0,0819 * \text{duration of ALV}) + \\ & + (0,254 * \text{gestation term}) - (0,00204 * \text{body mass at birth}) - \\ & - (10,614 * \text{ }^2 \text{ G}) + (1,821 * \text{tonin}) - (5,816 * \text{calpains}) + \\ & + (24,105 * \text{blood }) + (0,142 * \text{ }_2) - (0,0342 * \text{heartbeat}) - \\ & - (0,0745 * \text{pulmonary artery}). \end{aligned}$$

Specified mathematical models have 94,8% of specificity and 92,2% of sensitivity.

It is commonly known that BPD outcome can be influenced by a number of factors, among them is, first of all, immaturity of lung tissue, gestation term and low body mass at birth in particular. This, in its turn, results in inability of proper spontaneous respiration and children require long-term artificial lung ventilation. An increase in calpains activity in blood serum of patients with BPD can be connected with a transition to the development of structural and functional changes in lung tissue or vessels. Imbalance between proteinases of adaptogenic action and their inhibitors creates conditions for intensification of destructive processes providing other proteinases are involved and this creates conditions for pathologic process progression. The development of vasoconstrictive mechanisms of the formation and progression of cardiovascular complications in children with BPD can be associated with an increased tonin activity. An increased level of mean pulmonary artery pressure can be considered to be a manifestation of secondary pulmonary hypertension, which plays an important role in fast development of cardiovascular complications. The cause of acceleration of cardiovascular disorder development and its progression in patients with BPD can be conditioned by tissue hypoxia, which promotes activation of vasoconstrictive factors and apoptosis which by all means

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PROGNOSTIC SIGNIFICANCE OF PROINFLAMMATORY CYTOKINES IN CHILDREN WITH SHIGELLOSIS

Kharkov National Medical University, Ukraine

Abstract. *The levels of tumor necrosis factors- and interleukin-1 in the blood serum in young children with Shigellosis have been investigated. The connection between the degree indexes during acute phase and type of Shigellosis course has been discovered.*

Key words: *children, Shigellosis, cytokines.*

Intestinal infections are one of the most frequently registered groups of children diseases [2]. According to the WHO more than 2 milliard people are suffered from enteric infection every year [3]. Nearly 1 million people death of this pathology every year [4, 7]. Among of intestinal infections the Shigellosis accounts for 60-75 % [6]. Great importance in the pathogenesis of intestinal infectious diseases, such as Shigellosis, different biologically active substances have, especially - the inflammation mediators like cytokines [1]. There are proinflammatory and anti-inflammatory interleukins. These substances regulate immune and inflammatory responses in the condition of infectious pathology. Induction of cytokine synthesis begins at the first stages of pathological process. Tumor necrosis factor- (TNF) and interleukin-1 (IL1) have a special importance [5, 8].

The **aim** of the present study was to install dependency of the variant of the clinical current Shigellosis in children on the levels of proinflammatory interleukins in the blood serum.

Methods. The study was undertaken at the regional children's infectious hospital. We had observed 96 children from one month to three years with Shigellosis. Patients were divided into two groups according to the course of the disease. The first group included 65 patients with smooth-like course (SC) of the

disease, second group - 31 patients with wavy-like course (WC) of Shigellosis. The control group consisted of 20 healthy children of the similar age. The diagnosis was estimated using bacteriological and serological methods. We found that etiological factors of 47 children was *S. Flexneri* and in 49 - *S. S nnei*.

The patients came to the hospital for the first - the third day of the diseases. The manifestation of the disease characterized by a state of moderate in 38 children, and severe - 58 children. The main clinical manifestations of the disease were symptoms of intoxication (96 -100%), and dysfunction of the gastrointestinal tract: gastroenterocolitis (73 – 70.1%), gastroenteritis (9 - 8.6%), enterocolitis (16 - 21.3 %).

The concentration of tumor necrosis factor - and interleukins - 1 in the blood serum of the children during 1-3 days of the illness (the acute period of the disease), at 7-8 days of the illness (the period of recovery in smooth-like course of disease and period of improvement in wave-like course of Shigellosis), at 12-14 days of the disease with wave-like course of Shigellosis (the period of recovery) was evaluated.

The level of cytokines was determined by ELISA test. Statistical analysis of the results was performed using the "Exel" program. Reliability of the results was assessed by Student's criteria.

Results. High levels of proinflammatory cytokines (PC) in the serum in the acute phase of Shigellosis in all children were detected. The level of PC in patients significantly ($p < 0.001$) higher than the level of PC in children from the control group. (Table 1, 2). This fact can be regarded as organism's reaction to penetration of pathogenic bacteria in the gastrointestinal tract and translocations of toxin from the gastrointestinal tract into the bloodstream.

Index of IL-1 of serum in the first group was 74.2 ± 2.3 pg/ml and differed from that of the children of the second group - 39.87 ± 4.48 pg/ml ($p < 0.001$) (Table 3). The level of TNF- of patients with SC of Shigellosis amounted to 94.83 ± 1.9 pg/ml and was significantly higher than the performance of children with WC of Shigellosis (61.39 ± 3.48 pg/ml) ($p < 0.001$). The differences between the levels of

proinflammatory cytokines in the acute period indicate the hyporeactivity response of children with WC of Shigellosis at the onset of the disease.

On the seventh - eighth day of the disease (the period of early convalescence in a SC of Shigellosis and a period of improvement with WC) we found decrease of level of IL-1 in patients of the first group (48.5 ± 1.45 pg/ml) and the increase level of this index in children of the second group (57.6 ± 13.5 pg/ml), which meant about continuing inflammatory response in children with WC of Shigellosis. Also, in the patients of the first group we noted a decrease of concentration of TNF- ($68,84 \pm 1,3$ pg/ml) in comparison with level of TNF- in the acute period ($p < 0.001$). There were any dynamics of TNF- in patients of the second group (60.51 ± 1.9 pg/ml).

In children with WC of Shigellosis during early convalescence period (12 - 14 day after onset of the disease) were detected a slight decrease in the levels of proinflammatory cytokines in serum (IL-1 - $37,39 \pm 4,48$ pg/ml, TNF- - $58,43 \pm 6.1$ pg/ml) in comparison with the acute phase (IL-1 $39,87 \pm 4,48$ pg/ml TNF- $61,39 \pm 3,48$ pg/ml) and period of improvement (IL-1 $57,6 \pm 13,5$ pg/ml TNF - 60.51 ± 1.9 pg/ml). It means that process of inflammatory response in the body of patients with WC of Shigellosis is uncompleted. In our opinion, this fact is necessary to consider during rehabilitation and stage of medical follow-up.

Conclusion.

1. The increased levels of tumor necrosis factor- and interleukin-1 in the blood of patients corresponds to the acute phase of systemic inflammatory response of child's body.

2. The finding of the cytokines indexes of patients in the acute stages of Shigellosis allows to predict the course of Shigellosis in young children, and to decide the therapeutic tactics of patients.

3. The rising levels of tumor necrosis factor- and interleukin-1 in serum during stages of early convalescence indicates uncompleted inflammatory response in children's organism. In our opinion, this fact is necessary to consider during rehabilitation and stage of medical follow-up.

Table 1

Content of proinflammatory cytokines in serum of patients with smooth-like current of Shigellosis ($\pm m$, pg/ml)

Indicators	Acute stages (n=65)	Stages of early convalescence (n=65)	Control group (n=20)
L-1	74,2 \pm 2,3*' **	48,5 \pm 1,45*' **	1,62 \pm 0,35*
TNF-	94,83 \pm 1,9*' **	68,84 \pm 1,3*' **	0,87 \pm 0,13*

Note. * Reliability difference of indicators compared to the control group ($p < 0.001$)

** Reliability difference of parameters in different periods of the disease ($p < 0.001$)

Table 2

Content of proinflammatory cytokines in serum of patients with wave-like current of Shigellosis ($\pm m$, pg/ml)

Indicators	Acute stages (n=31)	Stages of improvement (n=31)	Stages of early convalescence (n=31)	Control group (n=20)
L-1	39,87 \pm 4,48*	57,6 \pm 13,5*	37,39 \pm 4,48*	1,62 \pm 0,35*
TNF-	61,39 \pm 3,48*	60,51 \pm 1,9*	58,43 \pm 6,1*	0,87 \pm 0,13*

Note. * Reliability difference of indicators compared to the control group ($p < 0.001$)

Table 3

Content of proinflammatory cytokines in serum of patients with smooth-like current and wave-like current of Shigellosis ($\pm m$, pg/ml)

Indicators	Acute stages - the first group (n=65)	Acute stages - the second group (n=31)	Early convalescence stages - the first group (n=65)	Stages of improvement second group (n=31)
L-1	74,2 \pm 2,3*	39,87 \pm 4,48*	48,5 \pm 1,45	57,6 \pm 13,5
TNF-	94,83 \pm 1,9*	61,39 \pm 3,48*	68,84 \pm 1,3**	60,51 \pm 1,9**

Note. * Reliability difference between indicators of acute period ($p < 0.001$)

** Reliability difference between indicators of early convalescence period and period of improvement ($< 0,01$).

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Kryvoruchko I.A., Povelychenko M.S., Tonkoglas A.A.

DIAGNOSTICS AND TREATMENT OF PATIENTS WITH ABDOMINAL SEPSIS

Kharkov National Medical University, Ukraine

Abstract. *Investigated 169 patients aged 21 to 78 years at abdominal sepsis is carried out and noted the following peculiarities of the main disease: the presence of at least two clinical and laboratory signs of SIRS on classification R.Bone et al. (1992), the presence of nidus of infection and enteric insufficiency. All the patients were operated in 2010-2013. Philosophy of surgical intervention in all patients included two main components: 1) source infection control (the removal or exteriorisation, drainage) and 2) the function control of damage organ. Mortality was 22.4%.*

Key words: *abdominal sepsis, diagnostics, treatment.*

Introduction. The most important and difficult problem of the modern surgery is the treatment of patients with severe abdominal infections include a wide variety of infectious processes. As usual the processes develop in the abdomen with the influence of microorganisms which colonizing the gastrointestinal tract. The problem actuality is caused by: substantial increase of patients quantity (the tendency in developing countries); increasing the number of patients with fatal complications (in Western Europe more than 500 thousand patients of intensive care wards have sepsis complications between 2% and 18%, and septic shock - about 3-4%); presence of multiple or residual nidus of infection (main: abdominal cavity, retroperitoneal space, gastrointestinal tract, additional: the pulmonary nidus, as a result of pulmonary ventilation, urinary tract, main venous catheters), polymicrobial infection and other factors. Considering the general laws of systemic inflammatory development response (SIRS) to this category of pathological processes, like other authors, refer three types of infections, joint by general term: "abdominal sepsis" (AS). Introduce: widespread purulent peritonitis arising due to destruction of the organ or perforation,

and neglected acute intestinal obstruction, postoperative peritonitis due to abscess formation, and the failure zone of previously imposed anastomosis sutures, purulent-necrotic pancreatitis due to infection of pancreatic necrosis or development septic retroperitoneal phlegmon. The problem actuality consists, that the quantity of patients with AS now has sharply increased, and the disease often complicated by multiple organ dysfunction (MODS) and accompanied by high mortality (30-80%), which show the most reputable clinics [1, 4]. The main content of the disease in these patients is the uncontrolled release of mediators of inflammation and the subsequent development of massive system damage in organs distant from the primary nidus [2]. According to recent studies just Toll-like receptors are key structures that bind to different components of microbial origin and trigger the expression of nonspecific resistance factors and SIRS. Although the fundamental treatment principles of source control, antimicrobial therapy, and restoration of a functional gastrointestinal tract (if possible) are applicable to the critically ill patient with an AS, each of these issues becomes inherently more complex in this population. Furthermore, these objectives must be met with respect to, and in conjunction with, support of organ dysfunction and mitigation of deranged immune and coagulation responses.

A new view at the pathogenesis of sepsis, including the AS, led to the other diagnostic criteria, and most support in this regard was the R.Bone et al. classification (1992), based on the simplicity of the diagnostic criteria and clinical signs of SIRS, sepsis, severe sepsis and septic shock [1].

Materials and methods. Investigated 169 patients aged 21 to 78 years at AS is carried out and noted the following peculiarities of the main disease: the presence of at least two clinical and laboratory signs of SIRS on classification R.Bone et al. (1992), the presence of nidus of infection and enteric insufficiency. All the patients were operated in 2010-2013. On the development of MODS was tried in the presence of a clinical and laboratory signs of organ dysfunction: acute respiratory distress syndrome: $RaO_2 < 70$ mm Hg, $RaO_2/FiO_2 < 175$; dysfunction of the cardiovascular system: the syndrome of “small cardiac output”, need for inotropic support; liver dysfunction: total bilirubin levels > 30 mkmol/l, increase in transaminases and

alkaline phosphatase in a 2 or more times upper limit of normal; kidney dysfunction: urine output <30 ml/h, creatinine levels > 0,15 mmol/l; dysfunction of the hemostatic system: prothrombin index <70%, platelets <150×10⁹/l, fibrinogen < 2 g/l; of CNS dysfunction: <15 points on a scale of Glasgow [5]. On the day of surgical operation received assessment of the physical condition and state of health by integrated systems APACHE II [3] for determine the risk of developing MODS.

Laboratory studies included a clinical blood tests assessment and biochemical blood tests, hemostasis system by standardized methods and indicators specific and nonspecific resistance of body. Acute phase of patients response assessed by C-reactive protein (CRP) of blood serum by test system of CARMAY (Switzerland) company, for semiquantitative analysis (56 patients). The level of IL-2, IL-6, IL-8 in serum were determined by ELISA (developer "Protein Contour", Russia, 40 patients), and the dynamics of changes in anti-LPS-IgA, IgM, IgG by ELISA with enzyme immunodetection (39 patients). Abdominal pressure monitored indirectly by using the urinary catheter by Kron I.L., et al. (1984). Bacteriological studies were performed by standardized methods.

Statistical analysis by computer programs of "Biostatistics, Russia" was done.

All the patients before surgery was performed "starting" infusion therapy by hypertonic solution (7.5% or 10%) of sodium chloride at a rate of 3.5 ml/kh/30 min in a 1:1 ratio with colloidal solutions and subsequent infusion therapy included crystalloid solutions. If necessary, for correcting disorders of hemostasis used frozen plasma, albumin was not used due to increased permeability of cell membranes in shock. In 31 patients used inotropic support by dopamine (5 - 15 mcg/kg/min), 12 - was applied intravenous nitroglycerin (5 - 15 mcg/kg/min.). Correction of the oxygen-transport function of blood was done by erythrocytic mass, wash washing RBC, with hemoglobin (below 70 g/l). Antibiotic therapy in all patients was performed in 2 phases: phase 1 - the introduction of empirical broad-spectrum antibiotics in combination with antianaerobe; phase 2 - continuation or change of antibiotic treatment based on the sensitivity of microflora. Usually appointed

fluoroquinolones in combination with ornidazol, cephalosporins of III-IV generation in combination with an aminoglycoside and ornidazol, or carbapenems with severe condition of the patients.

Philosophy of surgical intervention in all patients included two main components: 1) source infection control (the removal or exteriorisation, drainage) and 2) the function control of damage organ. Intubation of the small intestine was performed ante- or retrograde (depending on the clinical situation) using a probe that has two slits for the implementation of early enteral feeding. Source control is defined as any and all physical means necessary to eradicate a focus or infection, as well as modify factors that maintain infection, such as leaking intestinal contents. Inadequate source control at the time of the initial operation has been associated consistently with increased mortality in patients with AS. Source control was based on the following principles: the source of infection, and the intake of bacteria involved in the inflammatory process products (bile, blood, fecal matter) should be eliminated. Selection procedure depends on the anatomy of the source of infection, the degree of inflammation of the peritoneum, the severity of the syndrome of systemic inflammation reactions (SIRS) and multiple organ dysfunction (MODS), and physiological reserves patient. Antibiotic therapy was carried out taking into account the possible causative agents of abdominal infection, morbidity and other factors. Among the principles of control of functional damage is isolated by conventional measures and activities that have no advantages over the existing ones. Conventional measures: remediation of the abdomen and/or necrotic lesions with crystalloid solution (5-10 L); bowel intubation; drainage of the abdominal cavity; relaparotomy (on-demand or planned). Events that do not have the advantages of: remediation of the abdominal cavity with the use of antibiotics and antiseptics due to violation of antibacterial drugs in inflammation of the peritoneum, and because of the high risk of occurrence of local and general toxicity; radical removal of fibrin film tightly fixed on loops of intestines.

Results and discussion. All patients were identified as disturbances of blood gas transport system, the severity of which was dependent on the severity of the

disease. Also, vicious activation of the immune system and production of mediators, that is characterized by acute phase of inflammation (occurrence Immune reactions, increased cytokine, the proteins of acute phase, oxygen radicals and so on). The patients with AC, most often observed reducing IL-2 (about 70% of patients), hypersecretion of CPB (90% of patients), IL-6 and IL-8 in all 40 examined patients.

The most heavy condition was in patients with grade III of intraperitoneal pressure (>20 mm Hg) and development of abdominal compartment syndrome (ACS). Reduced anti-LPS-Ig classes in all these patients indicated the most massive arrival lipopolysaccharide complexes in the systemic blood circulation due to the most pronounced processes in the abdominal cavity, the loss of barrier function of the intestines and other reasons. Proof of this was proportional dependence to the reduction of the anti-LPS-Ig in the blood, that indicating the binding of its specific immunoglobulins.

After stabilization of hemodynamic parameters in all patients of another group, along with a saline infusion therapy to ensure iso-osmotic condition of the water sector, used a system of low-calorie food, which was a mixed or enteral (enteral and parenteral) nutrition. This method was used in 12-24 hours after surgical operations, followed by enteral tube feeding (with enzymes and probiotics) in combination (with or without) parenteral amino acid solution 500 ml/day. At the end of the fifth day in uncomplicated cases full enteral feeding was carried out with a gradual increase calorie diet to the level of the basal metabolism.

The basis for the proposed treatment technology for patients with AS the analysis of published data and data obtained during the treatment of patients of first group. As a rule, the normal barrier function of the intestine due to the following components: 1) the normal microflora; 2) mechanical factors; 3) an intact immune system; 4) the axis "gut-liver" [2, 3-8,9,11].

In cases of AS complicated by severe sepsis and septic shock, a single operation often may not be sufficient to achieve source control, thus necessitating re-exploration. Three methods of local mechanical management following initial

laparotomy for source control are currently debated: open-abdomen (also known as laparostomy); planned re-laparotomy; and on-demand re-laparotomy.

Relaparotomy on – demand strategy was carried out in an emergency (hollow organ perforation or bleeding into the abdominal cavity) and urgency (postoperative bowel obstruction, intra-abdominal opened abscess). These interventions were performed in 16 patients of 169 patients. The fault of the surgical treatment of peritonitis by on – demand strategy include the following:

- the risk of incomplete elimination of the source of peritonitis during a single operation;
- the late diagnosis of complications;
- the late decision about relaparotomy.

It is were the basis for the active development of various techniques and introduction into clinical practice of combined surgical treatment.

Planned relaparotomy were performed in 23 patients of 169 patients with AS. The intervention programs included "semi-open" approach were performed in 9 patients. The main arguments for this approach were: perforation of the colon, which can not be securely sewn or withdraw beyond the abdomen cavity; unstable hemodynamics, which requires minimization of primary interventions; abdominal tamponade due to bleeding. The main arguments for the use of the open method (laparostomy – 14 patients) were follows: diffuse infected pancreatic necrosis; large tension of the abdominal wall due to edema or fascia damage, which can lead to the development of abdominal compartment syndrome; severe injury to the loss of tissue abdominal; retroperitoneal perforation of a hollow organ; fascia poor state after multiple laparotomy. Typically, the immediate closure of the abdominal cavity technique used "sandwich". The intervention programs included open abdomen (OA) approach, conducted in 14 patients. In 1988, M. Schein et al. reported vacuum-assisted management of OA by intra-abdominal infection using a "sandwich" technique [4]. In our study, the method of temporary abdominal closure using the technique "sandwich" was used in 8 patients. In 6 patients we have chosen, with some modifications, the configuration of the vacuum pack system (VPS) made by

W.B. Brock (1995) because of its simplicity and low cost [4]. The procedure that is applied in our hospital as described below shares most of its original principles. After the initial laparotomy, a sterile 40×40 sheet of polyethylene folded over its self-adhesive side and multiperforated was placed over the peritoneal viscera (from the right paracolic sliding valve to the left) and below the parietal peritoneum of the anteriolateral abdominal wall (Figure 1-2).

In this way the formation of adhesions was decreased that hamper the mobility and subsequent closure of the abdominal wall, as well as inadvertent bowel injuries during changes in VPS. Subsequently, we placed a humid dressing of 0.9% saline in order for it to mold itself to the configuration of the wound between the polyethylene sheet and the parietal peritoneum. Two catheters (French ~ 24-26) with additional perforations were fixed to this first dressing, which were not placed in contact with the abdominal wall to prevent obstruction during aspiration. The catheters were exteriorized from the surgical wound from its superior vertex. A second dressing, dry on this occasion, was placed over the catheters, which were joined by a “Y”-connector to a latex tube. In turn this is connected to a wall system to provide continuing negative pressure of 25-150 mmHg (Figure 3).

This technique is a temporary closure of more than just the decision of containment internal organs. A layer of polyethylene, tucked between the bowel and abdominal wall, is a physical barrier preventing the formation of adhesions between the bowel and abdominal wall. In other words, while maintaining the peritoneal cavity and the delayed development of the "frozen" abdomen. Bowel loops tightly soldered together with granulation, but the space between the intestine and abdominal wall remains free and the abdominal wall is moving, expanding the time interval for the possibility of permanent closure of the abdominal cavity from a week to a month after primary surgery.

The interval between surgical interventions after the 1st surgery is usually one day, after a 2-4 interval remedial interventions specifically extend to 48 hours with

the possibility of peritoneal lavage between the operational period (patients with U-shaped drainage and eliminate the source of peritonitis), or in cases of extreme gravity condition of the patient (APACHE II > 16 points). Increasing the interval of more than 48 hours is often associated with the deterioration of the abdominal cavity - the progression of peritonitis. Except in the case of tertiary peritonitis or unliquidated its source, should be considered the best a 3-4-step relaparotom , in the subsequent risk of adverse effects increases the method of intervention and treatment effect is stabilized or regressed.

The indication for the completion of active methods of surgical treatment is the relief of inflammatory processes in the abdominal cavity. This provision is based on the intraoperative assessment of the abdominal cavity by morphological criteria. The main criteria for the end of the regime of programmable relaparotom are: removal or locating the source of peritonitis; the absence of necrosis, or may be permanently delineated multiple purulent foci; clear serous exudate; delimitation of the loops of the small intestine from the free abdominal cavity overlays are organized in the form of fibrin shell; the presence of stimulated or spontaneous motility of the small intestine; lack of widespread purulent necrotic lesions of the wound or abdominal wall, precluding the possibility of one-stage surgical correction.

Our data indicate, that between the number of reoperation on the abdomen, complications rate (group 1) and mortality (group 2) after relaparotomy established a positive relationship (Figure 4). In our study, complications occurred in 36,8% (62 patients). Major complications of reoperation: postoperative multiple organ failure, intestinal fistula, bleeding, lateral retraction of wound and formation of large defect. Mortality was 22.4% (38 patients).

Conclusion. Treatment of AS patients is a serious problem of modern surgery. The using of surgical control tactics of severe intra-abdominal infections – relaparotom on – demand strategy and planned, has its advantages and disadvantages. It remains unclear how impact of the surgical trauma to the progression of systemic inflammation and organ disorders in patients with AS, is it

possible to study the mechanisms of these disorders, depending on the number of surgical interventions, and thereby optimize treatment?. Answers to questions are identified only in single studies often are experimental in nature, which does not allow them to fully extrapolated to clinical practice. Our experience shows that planned relaparotomy need only part of this category of patients:

1) patients with sepsis and MODS, when the source of infection in them has been adequately removed during the first operation;

2) patients who wound suturing can lead to the development of abdominal compartment syndrome;

3) patients with severe combined trauma and massive intraperitoneal bleeding, to stop that requires tight tamponade with surgical swabs and towels.

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Figure 1. Placing the first multiperforated polyethylene sheet.



Figure 2. Second polyethylene sheet placed with the system under negative pressure.



Figure 3. Treatment of postoperative peritonitis by vacuum.

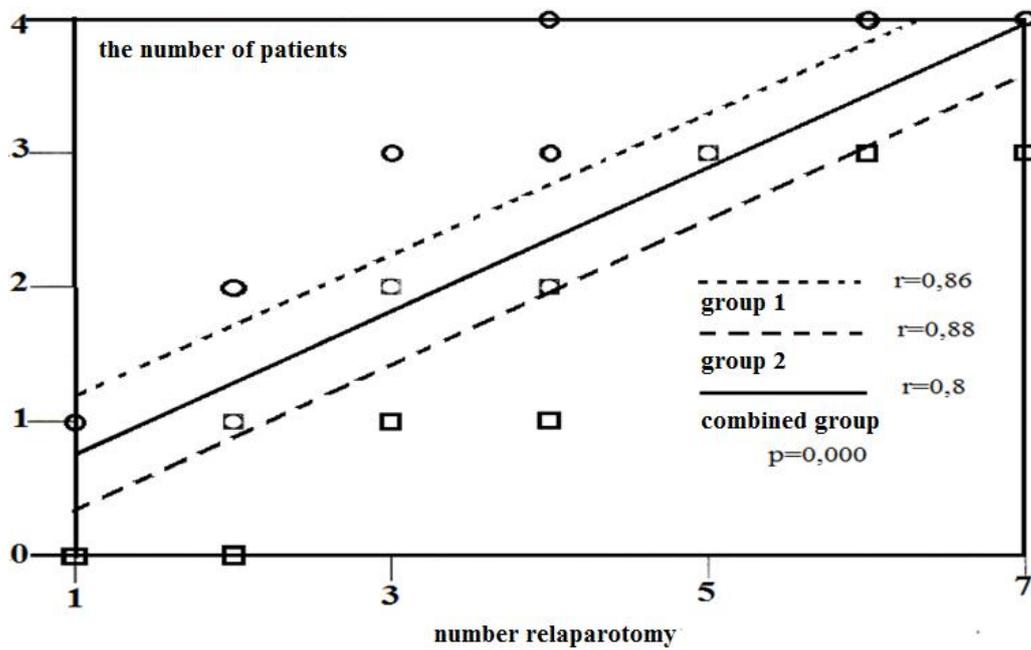


Figure 4. Relaparotomy - an independent risk factor for complications.

IMMEDIATE AND LONG-TERM RESULTS OF SURGICAL TREATMENT FOR PERFORATED GASTRODUODENAL ULCER

Kharkov National Medical University, Ukraine

Abstract. *The authors describe the methods of surgical treatment, of the patients with perforated gastric and duodenal ulcer. The role of separate techniques in diagnosis of perforated ulcer is shown. The data serving as the basis for the development individual surgical tactics in the patients with perforated ulcer are reported. Basing on the long-term results of surgical treatment of the patients with perforated gastric and duodenal ulcer, practical recommendations about the treatment of this group of patients based on the modern ideas about the etiology and pathogenesis of ulcer are given.*

Key words: *ulcer, perforation, suturing, resection, organ-preserving operations.*

In spite of the progress in diagnosis and treatment of perforated gastroduodenal ulcers, the problem of choice of the surgical technique remains disputable. The interventions used in urgent surgery do not satisfy the specialists as the former do not correspond to the contemporary demands of ulcer pathogenesis. The death rate in perforated duodenal ulcer is about 7% [1-4], while post-resection and post-vagotomy disorders are in 10 - 30% [5-8] and 10 - 15% [5,8-10] of cases respectively, that can cause a stable invalidism in these patients.

We have the data about the results of treatment of 725 patients with perforated gastric and duodenal ulcer. The distribution of the patients with gastroduodenal ulcer according to the age and sex is shown in Table 1.

It is evident from the table that the majority of the patients, 387 (53.4%) are 15 - 40 years old. The analysis of the patients with perforated gastroduodenal ulcer has demonstrated that in 208 persons (28.7%) the perforation occurred without definite signs of the disease, in 82 cases (11.3%) the disease manifested itself with

the signs of dyspepsia. The above must aim both the ambulance physician and the surgeon at thorough individual assessment of such patients.

When choosing the technique of the operation, we kept principal position. The time elapsed from the moment of the perforation to the admission, the presence and the character of peritonitis, the age of the patients and the accompanying pathology of the vital systems, the localization and the character of the ulcer; the findings of pH study of the stomach and the stomach secretion, the presence of the duodenal bulb deformity and other complications (stenosis, penetration) were taken into account.

The distribution of the patients with perforated gastroduodenal ulcer depending on the period from the moment of perforation to admission to the hospital is shown in Fig. As it is seen in the picture, 311 (42.9%) patients were admitted to the surgical department during the first two hours, 263 (36.3%) within 6 hours, 74 (10.2%) within 12 hours, 35 (4.8%) within 24 hours, 42 (5.8%) more than 24 hours.

The ulcer was localized in the stomach in 108 (14.9%) cases, in the duodenum in 617 (85.1%) patients. Of them, in 102 (14.7%) cases the ulcer was localized in a mirror-like manner both on the anterior and posterior walls. Spot-film radiography of the abdominal organs was used for diagnosis. Free air was revealed in 455 (62.8%) patients. When free air was absent (270 cases, 37.2%), pneumogastrography (83 cases), fibroesophagogastroscopy (123 cases) were performed. In doubtful cases the patients were performed laparoscopy, ultrasound study, CT (8 cases). All the patients underwent urgent surgery, in 6 the operation was put off for 8 - 5 days, which was connected with the atypical cause of the disease. Such patients were treated as those with acute cholecystitis and acute pancreatitis until the correct diagnosis was made.

The characteristic of the operative technique in the patients with gastroduodenal ulcer is given in Table 2.

The table demonstrates that suturing according to Ostrovskv or Ooppel-Polikarpov was done in 11 cases (15.3%). The indications to this kind of surgery were diffuse or generalized purulent peritonitis and complicated history. In this

group, 8 patients (7.2%) died, the cause of death was peritonitis progress, cardiopulmonary insufficiency and pulmonary embolism.

After the suturing of the perforation, great attention was paid to the measures preventing aggression by the acid stomach content using H₂-blockers and inhibitors of proton pump as well as to administration of antibacterial therapy aimed at elimination of *Helicobacter pylori* and normalization of lymph microcirculation in the zone of the damage.

As it is seen from Table 2, primary resection was performed in 40 patients (5.5%). It was done when the ulcer was located in the stomach, in repeated perforation, scar stenosis of the exit from the stomach as well as when malignancy was suspected. In this group, 3 patients died. The cause of death was inadequate evaluation of the accompanying diseases of the vital systems.

As our data demonstrate, when ulcer is localized in the duodenum, organ-preserving operations with one of the types of vagotomy are performed at present (574 patients, 79.2%). The purpose of this operation is to inhibit peptic factor which is determined with intragastric pH study before and during the operation. Selective proximal vagotomy (SPV) was done in 283 cases (38.5%), of them, in 96 (113.2%) it was accompanied by ulcer excision, in 187 (25.8%) by pyloroplasty. The excision was done in case of small infiltration around the ulcer. The indications to pyloroplasty included callous ulcer, scar deformity of the duodenal bulb as well as combination of mirror-like ulcers when the danger of pylorostenosis was present. Trunkal vagotomy (TV) was performed in 53 patients (7.3%), of them in 16 (2.2%) it was combined with ulcer excision, in 37 (5.1%) with pyloroplasty. TV was used when perforation was accompanied by hemorrhage in the patients with complicated history.

Selective vagotomy (SV) was done in 238 cases (32.9%), of them, in 55 cases (7.6%) if was combined with ulcer excision, in 183 (25.3%) with pyloroplasty. The indications to SV were the cases when Letarge's nerve verification was difficult due to infiltration of the small omentum. In this group 2 patients died: one of acute myocardial infarction, the other of early commissural ileus.

The long-term results of the surgical treatment of the patients with perforated gastric and duodenal ulcer were evaluated in 70 patients (9%) within the period of 2-5 years after the surgery at the in-patient department (Table 3). In addition to radioscopy, all the patients underwent fibrogastroscopy. Besides, the acidity was assessed, the degree of the disease development and that of Hp infection were determined.

Table 1

Distribution of the patients with gastroduodenal ulcer according to sex and age

age (years) / sex	15-30	31-40	41-50	51-60	over 60	Total
Male	191	174.	126	91	64	631
Female	10	12	16	18	23	94
Total	201	186	142	109	87	725
	27.7	25.7	19.4	15.1	12.1	100.0

Table 2

The character of surgical intervention in the patients with perforated gastroduodenal ulcer

Type of surgery	Number of patie	%
Suture according' to Ostrovsky	102	14.1
Suture according to Oppel-Polikarpov	9	1.2
Primary stomach resection	40	5.5
Exc ision of ulcer+trunkal vagotomy	16	2.2
Excision of ulcer+selective vagotomy	55	7.6
Excision of ulcer+ selective proximal vagotomy	96	13.2
Excision of ulcer with pyloroplasty+ trunkal vagotomy	37	5.1
Excision of ulcer with pyloroplasty+ selective vagotomy	183	25.3
Excision of ulcer with pyloroplasty + selective proximal vagotomy	187	25.8
TOTAL	725	100.0
Fundoplication according to Nissen	32	

All the patients were divided into three groups. The first group consisted of 15 patients (21.4%) who had been performed stomach resection. The second group included 35 persons (50.0%) who had undergone a certain type of vagotomy with the ulcer excision and pyloroplasty. The third group consisted of 20 patients (28.6%) who had been done suturing of the perforation.

Table 3

Long-term results of surgical treatment of perforated gastric and duodenal ulcer

Result	Group 1 (stomach resection)		Group 2 (ulcer excision+ vagotomy)		Group 3 (ulcer- suturing)	
	N	%	N	%	N	%
Excellent.	4	26.7	27	77.2	5	25.0
Good	6	40.0	6	17.2	8	40.0
Satisfactory	3	20.0	1	2.8	4	20.0
Bad	2	13.3	1	2.8	3	15.0
TOTAL	15	100.0	35	100.0	20	100.0

Analysis of the long-term results has demonstrated that in two patients from group 1, the outcome was poor due to stage 2-3 dumping syndrome (according to Nikolaev). In group 2, bad and satisfactory results were observed in two patients in whom light and medium diarrhea was noted. But these patients are capable of working and the complaints subsided after rehabilitation therapy. In group 3, unsatisfactory results were obtained in three patients. They were connected with ulcer relapses in two patients and decompensated stenosis of the pylorus in one patient. They underwent repeated operation and were performed stomach resection according to Bilrot-I.

Nevertheless the results in 4 patients of this were satisfactory, the patients had complaints on periodic pains in the epigastrium, eructation and heartburn. After the examination, the diagnosis of gastritis was made. These patients were referred under observation to the gastroenterologist.

Conclusions: Taking into consideration the recent achievements of gastroenterology, stomach resection and organ preserving surgery should be made under individual indications. In most cases the traditional suturing of a perforation followed by rehabilitation therapy with antisecretory therapy and Helicobacter eradication should be preferred.

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A NEW COMPLEX APPROACH FOR EVALUATION OF LIVER FUNCTION IN THE CIRRHOTIC PATIENTS

Kharkov National Medical University, Ukraine

Abstract. *The morphological and Doppler ultrasound investigations in 137 patients with liver cirrhosis were done. Three types of morphological signs of liver cirrhosis were discharged. Ultrasound characteristics of general hepatic blood circulation, state of blood vessels and portal hemodynamics for each morphological type of cirrhosis were identified.*

Keywords: *liver cirrhosis, morphometry, portal hemodynamics.*

Background. Surgical treatment of a cirrhotic patients is connected with high risk of postoperative hepatic failure [1-3, 5-8, 10-12]. Hepatic biopsy with morphological examination is a “gold” standard in evaluation of functional liver reserve while such modern noninvasive methods of examination like Doppler ultrasound can also be used to achieve this goal [4-10].

The purpose of this study is to define new criteria of functional liver reserve in cirrhotic patients in order to improve results of their surgical treatment.

Methods and results. We included 137 patients with liver cirrhosis, at whom surgical treatment was performed. In 81(59,12%) cases was performed the distal splenorenal shunt by Warren, in 56 (40,88%)– devascularization surgery. Morphological examinations with morphometry of intraoperative liver biopsies were done by V.Syplyviy method [12]. Doppler ultrasound of portal blood vessels was done at admission by Moriyasu et al. method [13]. The statistical analysis was performed by use of “Microsoft Excel 2000” and “SPSS 10.0 for Windows”.

On the basis of the analysis three (A, B, C) types of cirrhosis with statistically significant differences in area of unchanged hepatocytes, volume of dividing hepatocytes, connective tissue area, stroma to parenchyma ratio, volume of

hepatocytes in the state of necrosis and/or necrobiosis were determined. At transition of A-type cirrhosis into C-type volume of hepatic parenchyma becomes to be decreased, while volume of connective tissue becomes to be increased. This is accompanied by decrease in area of unchanged hepatocytes, increase in connective tissue area and stroma to parenchyma ratio (table 1).

Table 1.

Morphometrical characteristics of intraoperative liver biopsies in cirrhotic patients

Parameter	- type	- type	- type
Connective tissue area, μm^2	66,73±1,71	126,69±12,5*	240,16±13,4 *, **
Area of unchanged hepatocytes, μm^2	234,13±11,5	205,34±13,8	178,69±18,7*
Stroma to parenchyma ratio	0,285±0,019	0,617±0,031*	1,344±0,089*, **
Volume of hepatocytes in the state of necrosis and/or necrobiosis, %	11,21±0,74	17,32±0,63*	23,97±0,75*, **
Volume of dividing hepatocytes, %	10,23±0,57	15,43±0,48*	11,07±0,58*, **

Differences are statistically significant :*- in comparison with -type; **- in comparison with B-type.

Results of Doppler ultrasound were also different for three morphological types of cirrhosis (table 2).

At patients with A-type cirrhosis portal vein and splenic vein diameters, portal congestion index does not increase, linear portal blood velocity and volumic portal blood velocity does not decrease. At -type cirrhosis portal vein diameter increases in comparison with healthy persons and A-type cirrhotic patients ($P<0,001$), while splenic vein diameter does not enlarge. able 2.

Portal blood circulation indices and state of portal blood vessels in liver cirrhotic patients depending on type of morphological changes

Parameter	- type	- type	- type
Portal vein diameter, cm	1,13 ± 0,014	1,22 ± 0,013*	1,5 ± 0,026*,**
Splenic vein diameter, cm	0,85 ± 0,073	0,88 ± 0,012	1,32 ± 0,035*,**
Linear portal blood velocity, cm/sec	17,35 ± 0,41	14,5 ± 0,86*	10,8 ± 0,48*,**
Volumic portal blood velocity, ml/min	1055,06 ± 34,4	1024,65 ± 61,65	997,57 ± 72,11
Portal congestion index, cmxsec	0,05 ± 0,001	0,08 ± 0,005*	0,14 ± 0,015*,**

Differences are statistically significant :*- in comparison with -type; **- in comparison with B-type.

Linear portal blood velocity decreases ($P < 0,02$) with simultaneous increase in portal congestion index ($P < 0,001$). Volumic portal blood velocity decreases in comparison with A-type cirrhotic patients, but differences are statistically insignificant. These changes of portal hemodynamics can be explained by increase in connective tissue part in hepatic parenchyma at patients with -type cirrhosis.

At C-type cirrhotic patients portal vein and splenic vein diameters ($P < 0,001$), portal congestion index ($P < 0,005$) becomes to be increased, linear portal blood velocity becomes to be decreased ($P < 0,005$) in comparison with A-and B-type cirrhotic patients. Volumic portal blood velocity decreases at transition of B-type into C-type cirrhosis patients, but differences are statistically insignificant. Such changes in portal blood vessels and disturbances of portal hemodynamics corresponds to the results of liver morphometry, illustrating most expressive development of connective tissue at C-type cirrhosis.

Analysis of portal Doppler ultrasound results depending on morphological types of cirrhosis revealed that linear portal blood velocity together with portal congestion index are most significant parameters, reflecting character of pathological

liver changes. At C-type cirrhotic patients linear portal blood velocity was 1,6 times less both portal congestion index 2,8 times more than at A-type cirrhotic patients.

Analysis of factors which were predisposing for postoperative hepatic failure in cirrhotic patients, revealed, that it occurred in cases, when portal vein and splenic vein diameters with portal congestion index becomes to be increased with simultaneous decrease of linear portal blood velocity (table 3).

Table 3.

Clinical flow of postoperative period depending on indices of portal blood vessels and portal hemodynamics

Index	Patients with postoperative hepatic failure	Patients without postoperative complications
Portal vein diameter, cm	1,22±0,013	1,5±0,026*
Splenic vein diameter, cm	0,88±0,012	1,32±0,035*
Linear portal blood velocity, cm/sec	14,5±0,86	10,8±0,48*
Volumic portal blood velocity, ml/min	1024,65±61,65	997,57±72,11
Portal congestion index, cmxsec	0,08±0,005	0,14±0,015*

*-differences are statistically significant Hepatic failure occurred at 52,6 % patients with B-type and at 77,8% patients with C-type cirrhosis at portal vein diameter more than 1,5 cm, linear portal blood velocity less than 10,8 cm/sec, portal congestion index more than 0,14 cm sec. **Conclusion.** Morphological changes in liver are intercommunicated with disturbances of portal hemodynamics in cirrhotic patients.

Morphological changes in liver of the cirrhotic patients are and differs by in area of unchanged hepatocytes, volume of dividing hepatocytes, connective tissue area, stroma to parenchyma ratio, volume of hepatocytes in the state of necrosis and/or necrobiosis, that permite to divide morphology of cirrhosis in to three types – types A, B, C.

In transition of cirrhosis from A-type in to C-type, signs of portal hypertension progresses, which is accompanied by increase in diameters of portal and splenic

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ACUTE NECROTIZING PANCREATITIS: UNFAVORABLE OUTCOME RISK FACTORS

Kharkov National Medical University, Ukraine

Abstract. *There is an analysis of surgical treatment of 125 patients with severe forms of an acute pancreatitis. The indication to operation were: clinic of a peritonitis at 117 (93,6%) patients, increase of a mechanical jaundice at 4 (3,2 %) patients, a bleeding from areas of necrosis at 4 (3,2 %) patients. 80 patients had an infected pancreatic necrosis. 80 patients had an injury of retroperitoneal cellulose. 34 patients died. Factors that influence in outcome were: infected pancreatic necrosis, injury of retroperitoneal fat, cachexia, obesity, inefficiency of cardiovascular system, presence of injury of liver. Peripheral blood reaction of patients with acute necrotizing pancreatitis was studied. Prognostic value of hematological indexes was shown. Estimation of patient's state by Acute Sepsis Severity Evaluation Scale was carried out. It was shown, that Acute Sepsis Severity Evaluation Scale is objective in timely estimation of degree of severity of the state of patient with an acute pancreatitis and prognosis of flow of disease.*

Key words: *acute pancreatitis, retroperitoneal cellulose, postoperative lethality, hematological indexes, Acute Sepsis Severity Evaluation Scale*

Introduction: Severe acute pancreatitis remains one of the most difficult diseases in diagnostic and treatment [1,2,3]. The results of treatment of severe acute pancreatitis last years became better, but mortality from its destructive forms still very high on level 30-70% [4,5]. The course and prognosis of acute pancreatitis depend directly from the destruction of the pancreas, and from extrapancreatic complications - retroperitoneal fat damage and peritonitis. Retroperitoneal fat that damaged in aseptic phase of pancreatitis is the focus of developing of infection and the source of sepsis [6,4]. To prevent postoperative complications and to optimize medical tactics in patients with necrotizing pancreatitis, it is important and topical to find criteria that will quickly and accurately separate patients requiring more intensive medical tactics [1,5,6,7,8].

The purpose of research: to conduct the analysis of surgical treatment of patients with acute necrotizing pancreatitis and to identify clinical and laboratory parameters, which reflect the high probability of an unfavorable course of the disease.

Methods: There is an analysis of surgical treatment of 125 patients with severe acute pancreatitis. The age of patients ranged from 19 to 90. Men were 80 (64%), women - 45 (36%). the minimum age in men was 19 years old, maximum - 86, women - 24 and 90 years. At age 20 was 2 (1.6%) patients, from 21 to 40 - 42 (33.6%) patients, from 41 to 60 years - 35 (28%) patients, from 61 to 75 years - 31 (24.8%) patients, more than 76 years - 15 (12%) patients.

The indications to operation were: clinic of a peritonitis and parapancreatitis at 117 (93,6 %) patients, increase of a mechanical jaundice at 4 (3,2 %) patients, a bleeding from arosive vessels from necrotic areas and sequesters at 4 (3,2 %) patients.

In postoperative period 34 (27,2%) patients died. Causes of death of 26 (76.5%) patients were multiple organ failure; of 8 (23.5%) patients were heart failure.

Reaction of periphery blood by hematological indexes (one of these hematological indexes – the intoxication indicator – offered by us) [9]; estimation of severity of the patient's state by the Acute Sepsis Severity Evaluation Scale[10,11]; presents of parapancreatic fat injury; presents of concomitant diseases in dynamics of treatment of the patients also were studied.

To defining criteria that significantly affect the course of the disease; we carried out the analysis of clinical characteristics of patients with acute pancreatitis with the isolation of a group of patients who died in the hospital from complications of pancreatic necrosis.

Statistical data processing was to calculate the arithmetic mean value (M) and error (m). Parametric and nonparametric data was filed by M+m. Comparison of the signs carried out using a U-Mann-Whitney test. Assessing the statistical significance of indicators was carried out at the level of $p < 0.05$.

Results: The average age of the deceased patients was (60,5±3,56) years. In comparison with the average age of the survived patients (47,75±1,89) years. The differences are statistically significant at the level of $p < 0.05$.

Analysis of mortality by gender showed that among those women who survived were 31 (68,89 %), dead - 14 (31.11 %), among those men who survived - 60 (75 %), dead - 20 (25 %) ($p > 0.05$).

The average time from onset of illness prior to admission of patients in the surgical hospital was (5.2±2.1) days; hospitalization of patients with severe acute pancreatitis was quite late.

Criteria of severity of condition of patients with necrotizing pancreatitis are systemic inflammatory response syndrome (SIRS) and multiple organ failure.

The systemic inflammatory response syndrome detected in 75 (60 %) patients. Phenomena of acute organ failure were detected in 107 (85.6 %) patients. In 63 (58.9 %) patients of this group clinic of acute cardio-pulmonary insufficiency dominated, in 44 (41.1 %) patients clinic of renal and hepatic insufficiency dominated.

Infected necrosis revealed at 80 (64,0%) patients. Sterile necrosis revealed at 45 (36,0%) patients. In the group of died infected necrosis revealed at 30 (88,2%) patients, sterile necrosis revealed at 4 (11,8%) patients

Parapancreatic fat injury revealed at 80 (64,0%) patients. At 26 (76,5%) patients from 34 died parapancreatic fat injury revealed. Thus infected pancreatic necrosis increase lethality risk in 37,5%, parapancreatic fat injury increase lethality risk in 32,5%.

With chronic concomitant diseases in 63 (50.4%) patients revealed cardiovascular pathology; in 49 (38.0%) - gall-stone disease. Liver diseases diagnosed in 17 (13.18%) patients; chronic gastric ulcer and duodenal ulcer - in 13 (10.08%) patients. Obesity II-IV degree detected in 6 (4.8%); cachexia - in 4 (3.2%) patients. 7 (5.43%) patients had alcoholism; 7 (5.43%) patients had renal pathology; 7 (5.43%) patients had diabetes. Pathology of the respiratory system detected in 4 (3.2%) patients; 2 (1.55%) patients had malignant neoplasms; 1 (0.8%) patient suffered from syphilis.

In the analysis of concomitant diseases has been revealed that among patients with cachexia, obesity and alcoholism, the mortality rate was 100%. Our results coincide with literature facts about mortality cases frequency in patients with alcohol pancreatitis [12,13]. Among patients with chronic liver disease and kidney disease mortality rate was 54,2%, among patients with pathology of the cardiovascular system rate was 47.6% ($p < 0.05$).

It was revealed, that values of the index of organism's resistance less than 31,59; the leukocyte intoxication index more than 8,18; the reactive neutrophilic response index more than 40,77; the intoxication indicator more than 1,14 are the factors of adverse outcome of severe acute pancreatitis ($p < 0,05$). At severity of the patient's state by the Acute Sepsis Severity Evaluation Scale in a preoperative period more than 13 points lethality in a postoperative period was 51,85%, less than 13 points - 19,44%. In an early postoperative period at severity of the patient's state more than 16 points lethality was 70,59%, less than 16 points - 11,11%. At severity of the state of patient in a preoperative period more than 13 points mortality in a postoperative period was 51,85%, less than 13 points - 19,44%. In an early postoperative period at severity of the state of patient more than 16 points mortality was 70,59%, less than 16 points - 11,11%.

The analysis of individual estimations of patients by the Acute Sepsis Severity Evaluation Scale conducted. The method of cluster analysis divided patients into three clusters. The first cluster - sum of points increased at first twenty-four hours of postoperative period, decreased after. The second cluster - the sum of points decreased gradually. The third cluster- the sum of points increased progressively. The analysis of mortality in clusters conducted. Mortality was 11,11% in the first cluster, 21,43% - in the second, 50,0% - in the third.

Conclusions:

1. Postoperative mortality from complications of acute necrotizing pancreatitis is 27.2%. However infected pancreonecrosis and parapancreatic fat injury revealed at 64% of patients with acute necrotizing pancreatitis.

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Makarenko M.V., Kuzmina I.U.

PLACENTAL MORPHOMETRY AND DOPPLER FLOW VELOCIMETRY IN CASES OF CHRONIC HUMAN FETAL HYPOXIA

Kharkov National Medical University, Ukraine

Abstract: Objective: *To investigate the structural basis of abnormal Doppler waveforms in the utero-placental circulations in cases of chronic fetal hypoxia.*

Study design: *Morphometric analysis was performed on placental samples from 58 pregnancies with abnormal Doppler waveforms in the uterine, placental and umbilical circulations at 32-34 weeks, and 10 pregnancies with normal waveforms.*

Results: *The volume of placental villi reduced from 350.5 cm³ in controls to 286.4 cm³ ($P < 0.05$) in the severest cases. The volume of the fetal capillaries reduced from 59.7 cm³ to 20.5 cm³ ($P < 0.05$). These reductions were associated with increased placental infarction. The myometrial segments of the spiral arteries were severely constricted, demonstrating failure of physiological conversion secondary to deficient trophoblast invasion.*

Conclusion: *The placental vascular bed is greatly reduced in cases of chronic fetal hypoxia. We propose impaired placental perfusion causes oxidative stress and regression of the fetal vasculature, leading to fetal growth retardation and distress.*

Keywords: *Placenta; Hypoxia; Doppler ultrasonography; Morphometry; Oxidative stress.*

Introduction.

Doppler ultrasonography has become a routine non-invasive method for monitoring the functioning of the utero-placental circulations in vivo during human pregnancy. From analysis of the umbilical waveform it is possible to assess the impedance to placental bloodflow, and to accurately predict fetal hypoxia [1-3]. Various attempts have been made to correlate the Doppler abnormalities with placental structural changes in order to provide a mechanistic explanation for their origin [4-8]. The results have been varied, ranging from claims of a reduction in the number of arteries within the

supporting stem villi to a reduction in the capillary vascular bed within the terminal villi, the principal site of gaseous exchange. The underlying cause of the placental lesions is not known, although the fact that Doppler changes in the umbilical circulation are invariably seen subsequent to similar changes in the uterine arteries strongly suggests they are a secondary phenomenon. Recently, it has been proposed that the placenta is hyperoxic, rather than hypoxic as commonly assumed, in cases of severe intrauterine growth retardation [9].

This theory may explain the basis for many of the morphological changes observed, but does not account for how the hyperoxia is initiated. Here we report morphometric data demonstrating a substantial reduction in the villous capillary bed in placentas associated with severe Doppler abnormalities at 32-34 weeks of pregnancy. We propose that incomplete invasion of the endometrial spiral arteries in early pregnancy leads to poor maternal perfusion of the placenta. Periods of vasoconstriction may result in fluctuating oxygen tensions within the organ, which have been shown in vitro to generate oxidative stress within the placental vessels [10].

Subsequent regression of the capillaries would increase placental vascular resistance and also impair placental transfer, resulting in growth retardation and reduced oxygen extraction from the maternal blood. Consequently, the venous side of the placenta would become hyperoxic.

Materials and methods.

Clinical details.

Patients were selected from women attending the supraregional obstetric referral centre Delivery Unit Number 5 in Kharkov, Ukraine with the approval of the local ethics committee. A total of 58 cases of chronic hypoxia of the fetus (CHF) were identified by colour Doppler ultrasonography using a 24 MHz Prizma scanner (Diasonics International, Les Ulis Cedex B, France) with a transabdominal probe between 32 and 34 weeks of pregnancy. For each case the maximal rates of systolic (S) and diastolic (D) blood flow were

measured. From these two indices were calculated: the systolic-diastolic ratio (SDR) = S/D, and the index of resistance (IR) = (S - D)/S. The cases were classified into three groups of increasing severity (Table 1). The abnormal haemodynamics in the uterine and feto-placental circulations were the result of extra-uterine pathologies, for example idiopathic hypertension, anaemia and chronic pyelonephritis, and obstetric pathologies, such as preeclampsia and threatened miscarriage. The commonest cause of CHF was preeclampsia during the second half pregnancy, and this accounted for 78% of the cases in Group 3. CHF was sometimes associated with a small-for-dates fetus, and this was most common in Group 3 where it occurred in 40.6% of cases.

These were matched to a control group of 10 patients in which Doppler ultrasonography was within the normal range. All the pregnancies delivered a single live infant between 38 and 40 weeks, and all women gave their informed written consent to participate in the study.

Placental samples.

After delivery each placenta was weighed, and then three blocks 2 cm x 2 cm x 2 cm were removed, one from the margin of the disc, one from under the cord insertion and one equidistant between the other two. The samples were fixed in 10% formol saline, embedded in paraffin wax and sections were stained with haematoxylin and eosin.

Myometrial samples

In order to study the maternal spiral arteries small samples of the myometrium were excised at the time of caesarean section. In cases of vaginal delivery curettage of the placental bed was performed immediately after delivery. Between two and three biopsy samples per patient were fixed in 10% formol saline, embedded in paraffin wax and sections were stained with haematoxylin and eosin. Physiological conversion of individual spiral arteries was classified as 'complete' or 'incomplete' according to the histological criteria of Brosens and Renaer [11]. In order to confirm the interpretation of the arterial changes sections from three biopsy samples of the Control group and nine samples of Groups 1-3 were stained immunohisto-chemically for cytokeratin 7. Sections

(7 mm) were prepared by dewaxing, rehydration, and incubation for 15 min in 3% hydrogen peroxide (H₂O₂). Antigen retrieval was performed by microwaving in citric acid buffer pH 6.0 for 1.5 min. After blocking for 1 h in 5% horse serum, mouse anti-human cytokeratin monoclonal antibody (Dako, Ely, UK) was applied at a 1:100 dilution in 2.5% horse serum overnight at 4°C. Sections were washed in Tris-buffered saline with 0.1% Triton X-100, Tween 20 (TBS-TT), and incubated with biotinylated anti-mouse secondary antibody (Vector, Peterborough, UK) diluted 1:200 for 1 h at room temperature. After washing in TBS-TT, Vectra-stain Elite ABC reagent (Vector, Peterborough, UK) was applied for 45 min at room temperature. Slides were developed in Tris-maleate buffer, pH 7.4 with 0.5 mg/ml DAB and H₂O₂ as substrates. Sections were lightly counterstained in Gill 2 hematoxylin.

Morphometric analysis.

All estimates were made at the light microscope level by a combination of point and intersect counting using the VIDS IV system (Synoptics Ltd., Cambridge, UK). Fields of view were selected in a systematic random fashion by scanning the sections stepwise in the x- y directions, using one corner of the coverslip as a random start point. Approximately 10 fields of view were analysed per section, and three blocks were examined per placenta.

Images were overlain with a quadratic test lattice. Where the horizontal and vertical lines of the test grid met constituted a test point. The number of points falling on stem villi, intermediate and terminal villi, fetal capillaries, intervillous space, intervillous fibrin and placental infarcts were counted and expressed as a fraction of the total number of points falling on the sections.

The number of intersections the test lines made with the villous surface and with the capillary luminal margins were also counted, and so their respective surface densities could be estimated. Finally, the numbers of villous and capillary profiles were recorded, with two sides of the test lattice acting as forbidden lines, and villous and capillary length densities calculated.

Table 1

Doppler flow velocimetry data (mean \pm S.D.) for the systolic-diastolic ratio (SDR) and the index of resistance (IR) at the different sites

Parameter	Control (n = 10)		Group 1 (n =29)		Group 2 (n =18)		Group 3 (n = 11)	
	SDR	IR	SDR	IR	SDR	IR	SDR	IR
Uterine arteries	1.69 \pm 0.10	0.45 \pm 0.07	1.96 \pm 0.06*	0.49 \pm 0.01*	2.27 \pm 0.07*	0.53 \pm 0.01*	2.83 \pm 0.12*	0.68 \pm .02*
Spiral arteries	1.53 \pm 0.09	0.35 \pm 0.07	1.70 \pm 0.06*	0.40 \pm 0.02*	1.76 \pm 0.05*	0.44 \pm 0.01*	1.92 \pm 0.05*	0.47 \pm .02*
Umbilical arteries	1.88 \pm 0.10	0.47 \pm 0.03	2.56 \pm 0.10*	0.61 \pm 0.01*	2.61 \pm 0.13*	0.65 \pm 0.04*	3.07 \pm 0.09*	0.68 \pm .02*
Stem villi arteries	2.52 \pm 0.15	0.58 \pm 0.05	2.68 \pm 0.08	0.67 \pm 0.02*	3.37 \pm 0.17*	0.67 \pm 0.02*	4.03 \pm 0.20*	0.74 \pm .02*

Significant difference to control at *P* compared $<$ 0.05.

All fractions and densities were then converted to absolute values by multiplying by the overall volume of the placenta as calculated from the weight multiplied by a specific gravity of 1.05.

2Statistical analysis.

Data groups were compared by an unpaired t-test using the Statgraphics statistical programme (STSC, Rockville, Maryland, USA). Results were considered significant at $P < 0.05$.

Results.

Clinical data.

All pregnancies in the control group were delivered vaginally of a normal healthy fetus with an APGAR score of 9 or above (Table 2). By contrast, as the severity of the utero - placental vascular pathology increased, a greater number of pregnancies were delivered by caesarean section for fetal distress. Mean birthweight decreased across the groups, although there was greater variability in birthweight amongst Groups 2 and 3. These babies also had lower APGAR scores immediately after birth. By contrast, placental weight remained constant across the groups.

Placental morphometric data.

Within the placenta the volume of the intermediate and terminal villi was significantly reduced in the vascularly compromised pregnancies (Table 3),

although their surface area and length increased. This suggests a change in the topology of the villous tree, with increased branching. By contrast, the volume, surface area and length of the supporting stem villi increased (Table 3).

The total volume of the fetal capillaries within the intermediate and terminal villi was significantly reduced in Groups 1-3 compared to the controls, along with the mean capillary diameter (Table 4) (Fig. 1). Total capillary length showed no significant differences across the groups, whereas capillary surface area actually increased in Group 3 (Table 4). Despite the increase in volume of the stem villi, the total volume of their capillaries was also reduced across the groups, along with their length and surface area.

Within the intervillous space fibrin deposition and placental infarction was significantly increased in the pathological pregnancies compared to the controls (Table 5).

Myometrial histology.

In the normal pregnancies the majority (60%) of spiral arteries were of large diameter, and their walls were formed largely by fibrin, with a thin endothelial lining (Fig. 2A). Numerous invading extravillous trophoblast cells were identified within the endometrium and myometrium, and some were observed within the walls of converted vessels (Fig. 2A).

Table 2

Clinical data (mean \pm S.D.) relating to the patient groups

Group	Number caesarean deliveries	Number of forceps deliveries	Birth weight (g)	Placental weight (g)	APGAR score				
					9-10	8	6-7	<6	Still-born
Control (n= 10)	0	0	3.552 \pm 98	518 \pm 19	8	2	0	0	0
1 (n = 29)	1	2	3.048 \pm 69	463 \pm 77	8	9	11	1	0
2 (n = 18)	3	0	2.965 \pm 997	536 \pm 163	4	7	5	2	0
3(n = 11)	1	0	2.456 \pm 725	544 \pm 96	1	3	2	4	1

The incidence of full conversion was greater in the centre of the placental bed than towards the periphery. In the samples associated with abnormal Doppler waveforms only 25% of the vessels were fully converted. The majority were constricted, with several layers of smooth muscle within their walls (Fig. 2B), and often fibrin was deposited in their lumens. Invading extravillous trophoblast cells were scarce within the endometrium, and were never observed within the myometrium (Fig. 2B).

Table 3

Morphometric data (mean \pm S.D.) relating to development of the villous tree

Parameter	Control (n = 10)	Group 1 (n =29)	Group 2 (n =18)	Group 3 (n = 11)
Terminal villi:				
Volume (cm ³)	350.5 \pm 20.9	370.1 \pm 14.3	320.7 \pm 18.7	286.4 \pm 19.9
Surface area (m)	12.26 \pm 1.35	13.91 \pm 0.39*	14.12 \pm 0.49*	15.97 \pm 0.39*
Length (km)	132.8 \pm 4.5	159.8 \pm 4.8*	165,6 \pm 5.9*	187.3 \pm 6.3*
Stem villi arteries:				
Volume (cm ³)	105.1 \pm 3.4	123.6 \pm 10.1*	144.6 \pm 27.4*	143.1 \pm 27.4*
Surface area (m)	0.57 \pm 0.08	0.91 \pm 0.12*	0.77 \pm 0.02*	0.56 \pm 0.07
Length (km)	1.93 \pm 0.36	2.36 \pm 0.19*	2.66 \pm 0.11*	2.93 \pm 0.15*

Significant difference compared to control at $P < 0.05$.

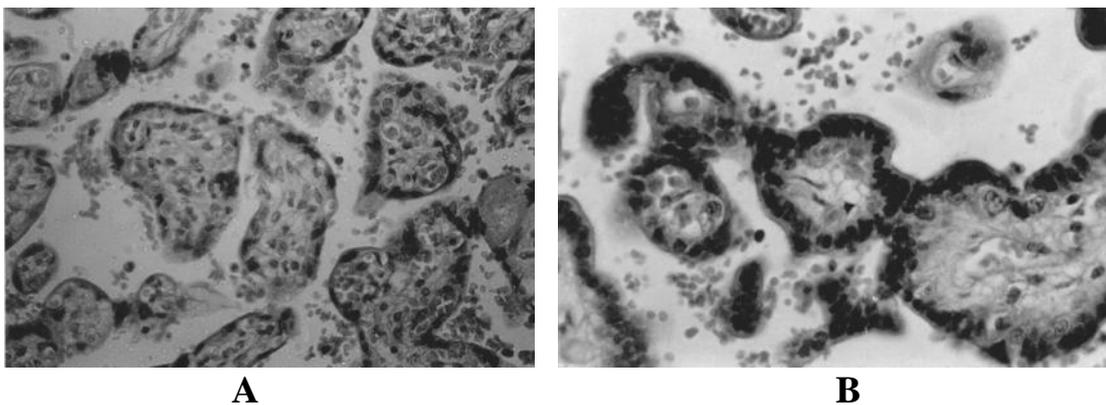


Fig. 1. Terminal villi from (A) a normal placenta displaying dilated capillaries (arrowed), compared to (B) a Group 3 placenta demonstrating the reduction in fetal capillary volume in the latter. Scale bars = 50 mm.

The results of this study are consistent with previous findings that increasing severity of abnormal Doppler waveforms in the uterine and umbilical circulations is associated with fetal distress and hypoxia [1 -3]. In the past it has been assumed that

impairment of the uterine circulation leads to decreased perfusion of the placenta and directly to fetoplacental hypoxia. However, more recently structural analyses of the placental villous tree in cases of severe intrauterine growth retardation have indicated that not all the histological changes seen can be explained on this basis. For example, several studies have shown a reduction in the extent of the intermediate and terminal villi, and a decrease in their vascularity compared to normal controls, as was the case in the present study [3,12]. Microvascular casting demonstrated that these reductions were associated with diminished branching and coiling of the fetal capillaries [13]. Equally, fewer cytotrophoblast cells than normal are present within the terminal villi [14]. As placental size, angiogenesis and cytotrophoblast proliferation are all promoted by hypoxia [15], it has been suggested that these placentas are in fact hyperoxic rather than hypoxic [9]. In this model it is recognised that there is reduced maternal blood supply to the placenta, but it is postulated that fetal extraction from the intervillous space is reduced to a greater extent. As a result, the maternal venous blood leaving the placenta contains a higher residual quantity of oxygen. Measurements taken in patients at the time of caesarean sections and in a sheep model suggest that this is indeed the case [16,17].

Table 4

Morphometric data (mean \pm S.D.) pertaining to the vascularisation of the villous tree

Parameter	Control	Group 1	Group 2	Group 3
Terminal villi:				
Capillary volume	59.7 \pm 4.2	36.9 \pm 2.9*	29.8 \pm 1.9*	20.5 \pm 1.2*
Capillary surface area (m ²)	11.90 \pm 0.87	10.69 \pm 1.04	11.59 \pm 0.94	13.20 \pm 1.27*
Capillary length (km)	557.4 \pm 0.9	463.4 \pm 0.9	421.2 \pm 1.0	463.3 \pm 1.2
Capillary diameter (mm)	12.36 \pm 0.28	12.20 \pm 0.16	11.76 \pm 0.08	10.12 \pm 0.24*
Stem villi:				
Capillary volume (cm ³)	18.6 \pm 2.4	16.7 \pm 2.2	15.3 \pm 1.9*	12.8 \pm 1.7*
Capillary surface area (m ²)	2.46 \pm 0.27	2.05 \pm 0.15*	1.51 \pm 0.09*	1.04 \pm 0.14*
Capillary length (km)	66.8 \pm 8.3	54.4 \pm 8.3	43.2 \pm 4.4*	35.2 \pm 3.1*
Capillary diameter (mm)	23.39 \pm 0.12	22.33 \pm 0.36	21.98 \pm 0.13	20.27 \pm 0.21

Significant difference compared to control at $P < 0.05$.

Whilst the evidence supports the general concept of hyperoxia in these cases, at least on the venous side of the placenta, one of the criticisms of this model has been that the severity of the fetal vascular changes is greater than might be expected on the basis of the measured rise in oxygen tension alone. In addition, when the hypothesis was put forward it was not clear what the initiating factor for the hyperoxia might be. More recent experimental work relating to oxidative stress has provided a possible explanation. Hypoxia-reoxygenation of term placental villi in vitro has demonstrated that fluctuating concentrations of oxygen can generate high levels of oxidative stress in placental tissues [10].

Table 5.

Morphometric data (mean \pm S.D.) pertaining to the intervillous space

Parameter	Control	Group 1	Group 2	Group 3
Volume of intervillous space (cm ³)	152.7 \pm 14.3	151.8 \pm 15.3	149.2 \pm 11.3	146.4 \pm 10.9
Volume of fibrin (cm ³)	4.36 \pm 0.01	16.31 \pm 0.4*	19.42 \pm 0.3*	23.89 \pm 0.3*
Volume of infarcts (cm ³)	2.87 \pm 0.13	3.02 \pm 0.06*	3.29 \pm 0.11*	4.49 \pm 0.32*

Significant difference compared to control at $P < 0.05$.

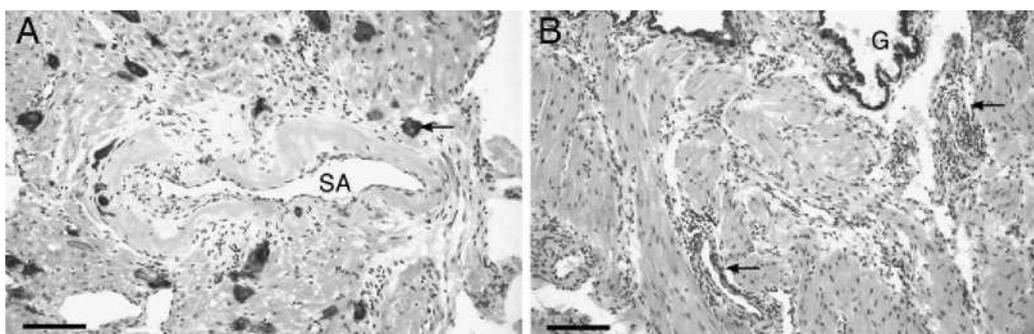


Fig. 2. Myometrial sections of spiral arteries from (A) a normal pregnancy, and (B) a pathological pregnancy immunostained for cytokeratin 7. In (A) numerous extravillous trophoblast cells (arrowed) can be seen within the myometrium, and even within the wall of a fully converted spiral artery (SA). In (B) the epithelium of the uterine glands (G) reacts positively for cytokeratin 7, but no extravillous trophoblast cells are present in either the endometrium or myometrium. As a result, the spiral arteries (arrowed)

retain the smooth muscle within their walls, and remain of small calibre.
Scale bars = 100 μ m.

Immunolabelling for nitrotyrosine residues indicating the formation of the prooxidant peroxynitrite was particularly strong in the smooth muscle cells surrounding the stem villous arteries and also in the microvascular endothelial cells. These correspond to findings in preeclamptic placentas [18,19].

As Doppler abnormalities of the umbilical circulation are rarely seen in the absence of uterine arterial abnormalities it is most likely that they are a secondary phenomenon. We propose therefore the following model for the aetiology of the fetoplacental abnormalities. Deficient trophoblast invasion for immunological or other reasons during early pregnancy leads to incomplete conversion of the spiral arteries.

These vessels remain of higher resistance than normal and this is later reflected in the uterine arterial waveform. Flow through these vessels will therefore be impaired. Predicting the effect of this on the oxygen tension within the intervillous space is difficult, as it will always be the balance between supply and extraction. It may also vary on a regional basis, as blood flow into the placenta is most likely intermittent [20]. We propose that the retention of smooth muscle within the spiral arteries exacerbates this normal contractility, resulting in longer periods of vasoconstriction and hence greater fluctuations in oxygen tension. This in turn promotes a mild ischaemia-reperfusion injury in the placental tissues, leading to oxidative stress in the fetal vasculature (Fig. 3).

Oxidative stress is a powerful inducer of endothelial cell apoptosis and repeated insults during mid-pregnancy may lead to regression of the capillaries, particularly as a high percentage are not stabilised by pericyte covering [21]. Such regression would increase vascular impedance in a reverse of the pattern seen during normal pregnancy, and so account for the changes in umbilical waveform observed. The intermediate and terminal villi are the principal sites of gaseous exchange, and decreased vascularisation will inevitably impair placental exchange.

This will lead to fetal hypoxia and growth retardation, but also reduced oxygen extraction from the intervillous space and so hyperoxia on the venous side of the placenta as a tertiary event.

Whilst this hypothesis provides a logical explanation for the placental changes observed, further work is required to test key aspects in the chain of events.

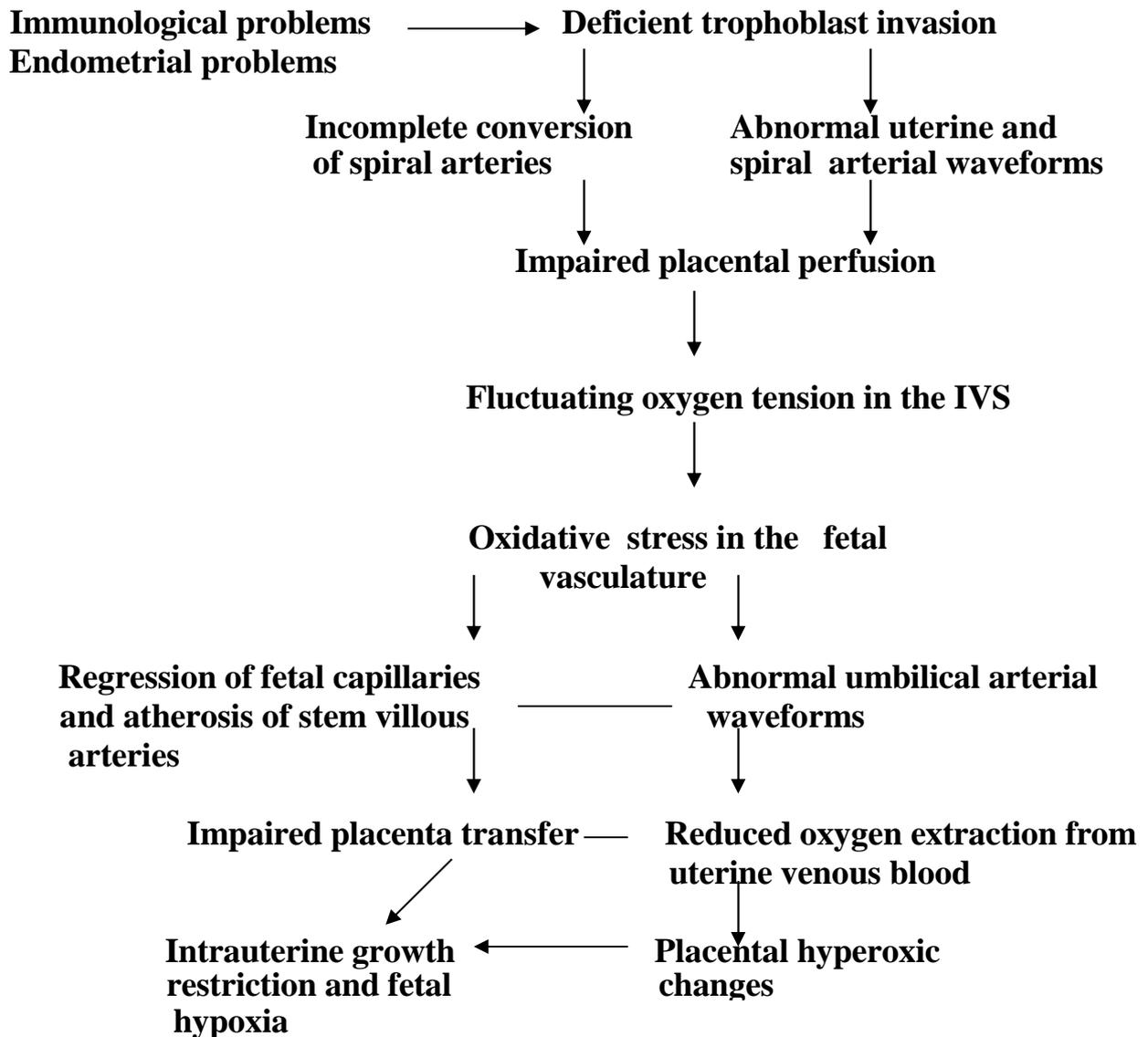


Fig. 3. Theoretical pathogenesis of placental changes in intrauterine growth retardation associated with abnormal Doppler waveforms in the uterine and umbilical circulations.

This model is compatible with the increased amount of placental infarction and fibrin deposition observed in Groups 2 and 3, which are not features of placentation under conditions of hypobaric hypoxia but are associated with ischaemia-

reperfusion in other systems. Finally, hypoxia-reoxygenation also stimulates apoptosis within the trophoblast and stromal cells in vitro [10], and so may account for the overall reduction in villous volume observed. Deportation of apoptotic fragments of syncytiotrophoblastic into the maternal circulation has been advanced as a possible stimulus for the activation of the maternal endothelial cells that underlies preeclampsia. Hence, it is perhaps not surprising that preeclampsia was associated with a high proportion of the cases in Group 3 of the present study.

Condensation

Human placental villous and vascular development is impaired in cases of chronic fetal hypoxia.

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INFLUENCE OF PERIMENOPAUSAL PERIOD ON QUALITY OF WOMAN'S LIFE

Kharkov National Medical University, Ukraine

Abstract. *The article considers the effect of menopausal period on women's quality of life. 315 women were surveyed and their quality of life was studied through simultaneous evaluation of the general condition of patients through questionnaires in 12 months after treatment of perimenopausal disorders. Four major pathological symptom complex of perimenopause were allocated: neurovegetative and psycho-emotional disorders; urogenital disorders; metabolic disorders; disorders of the musculoskeletal system. It was found that to improve physical health, psycho-emotional state and quality of life of women in perimenopausal period necessary to carry out a comprehensive examination of patients, which is appropriate to include immunological, hormonal and biochemical research, depending on the nature of perimenopausal disorders.*

Key words: *perimenopause, quality of life, perimenopausal disorders, immunohomeostasis, comprehensive survey.*

With the increase in life expectancy is currently a very important problem is the diagnosis, prevention and therapy of many functional disorders in women in perimenopausal age. According to the nomenclature of the International Federation of Gynecology and Obstetrics, this period of life is the aging process, during which a woman passes from the reproductive stage of life to non-productive.

In recent years all over the world have become increasingly interested in studying the problem of perimenopausal period.

The onset of perimenopause characterizes the beginning of a new stage in the life of a woman associated with ovarian failure and the transition of the organism to another mode of existence.

With the onset of perimenopausal age rise to new social, economic, medical and psychological problems associated with the adaptation of the female body to the ongoing restructuring of the neuroendocrine system. Changing social roles and self-

esteem, significant changes in interpersonal relationships occur with physiological characteristics of this age period. The vast majority of women at this time point changes in well-being and experiencing confusion before the upcoming changes.

WHO predicts that by 2015 46 % of the world population will reach women aged over 45 years , and by 2030 the number of women older than 50 years will be on the planet 1.2 billion [1].

Pathology of perimenopausal period significantly reduces the quality of life of working-age women at the peak of their social activity. In this regard, it is very urgent medical problem, and besides having economic importance, as discussed by I.B.Nazarova[3]. According to I.A.Shutova [4] a significant impact on pathological course of perimenopause has ecological situation. According to research of I. S. Zolotukhin [2] and co-authors in women employed in agriculture, perimenopause begins earlier and is more severe, with a predominance of vegetative- vascular disorders, rather than at employees who prevailed psycho- emotional disorders.

We examined 315 women who were divided into five clinical groups. First clinical group (control) consisted of 52 (16.5%) women with physiological perimenopausal period. In the second clinical group included 68 (21.6%) patients with neurovegetative and psycho-emotional disorders; third clinical group was represented by 72 (22.2%) patients with genitourinary disorders; fourth group consisted of 73 clinical (23.2%) women with metabolic disorders; fifth clinical group consisted of 52 women with disorders of the musculoskeletal system.

Study of quality of life was carried out by simultaneous assessment of the overall condition of the patient, using a questionnaire at 12 months after treatment of perimenopausal disorders procedure by A.A.Novick and T.I. Ions. To analyze the quality of life questionnaire used a modified SF- 36, consisting of eight scales , the maximum value of each of which is equal to 100 points, where 0 was considered for lack of health as well as 100 - full health. The analysis was conducted by comparing the integral criterion of quality of life (the sum of scores for all scales) in the study group and the comparison group using the nonparametric Mann -Whitney test, with a probability of $p < 0.05$ [5].

For realization of tasks surveyed 315 women in the age periods 45-49, 50-54 , 55-59 . Of these, 52 (16.5%) women with physiological perimenopausal period, and 263 (83.5%) - patients with various pathological manifestations of perimenopause. The entire spectrum of perimenopausal disorders based on clinical material and data analysis of the scientific literature for the purpose of systematizing perimenopausal disorders and severity of their clinical manifestations , as well as for targeted therapy of pathogenesis -based, we have allocated four major pathological symptocomplexes of pathological perimenopause. These include: neurovegetative and psycho-emotional disorders (68 patients (21.6%)); urogenital disorders (72 patients (22.2%)); metabolic disorders (73 women (23.2%)); disorders of the musculoskeletal system (52 women).

Integral indicator of the quality of life against the background of complex differential treatment in patients with neurovegetative and psycho-emotional disorders by 20.2 % higher than those obtained after conventional treatment; with urogenital disorders - 32.8%; with metabolic disorders - 31.7% , which corresponds to improve both physical and mental health component . Therefore, to improve physical health, psycho-emotional state and quality of life of women in perimenopausal period necessary to carry out a comprehensive examination of patients, which is appropriate to include immunological, hormonal and biochemical research , depending on the nature of perimenopausal disorders.

Thus, and treatment should be differentiated based on immune homeostasis, clinical form and severity of perimenopausal disorders.

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Nazaryan¹ R., Garmash¹ O., Gargin¹ V., Garmash² Ye.

INFLUENCE OF LOW BODY WEIGHT IN NEWBORNS ON MICROCIRCULATORY BED OF PERIODONTIUM

¹Kharkiv National Medical University, Ukraine,

²V.N. Karazin Kharkiv National University, Ukraine.

Abstract. *We investigated periodontium of newborn rats with experimental model of IUGR. Light microscopy showed that microcirculatory response was characterized by a pronounced decrease in vascular density ($20,9 \pm 18,2$ %); presence both contractility and dilatation of the capillary bed. Endotheliocytes of microcirculatory bed are flattened; there are signs of their desquamation. The increasing intravascular blood clotting in the postcapillary and venular portions of the microcirculatory system, along with a partial reduction of the capillary link have been observed. Perivascular space is characterized by initial sclerotic process.*

Key words: *microcirculatory bed, intrauterine growth retardation (IUGR), periodontium.*

The recent growth of somatic diseases in children can often be attributed to a violation of prenatal development or early neonatal life. The adverse consequences of intrauterine growth retardation (IUGR) is characterized by problems in postnatal adaptation, pathological development of the nervous, cardiovascular and other functional systems [1, 2, 3, 4, 5]. The frequency of IUGR varies in different countries from 12 to 39% among mature newborns [6]. Regarding this, an (IUGR) pathogenesis studies will help to develop prevention and correction of abnormal conditions of periodontal tissues on preclinical phase of pathological process.

And early correction of abnormalities and optimal rehabilitation is important not only from a medical point of view, but also for social applications. Distant consequences of IUGR are also frequently characterized by delays in oral

development, in oral pathology as overcrowding, retardation of teeth eruption, dental caries, etc [7, 8, 9, 10].

Currently there is no doubt about the fact that practically all diseases of neonatal period are accompanied by violations of the vascular system. This is due to the fact that the vascular system is an indicator of any pathological process, determining babies regulatory and adaptive mechanisms, characteristics of the connective-tissue matrix [11].

At the same time, it is known that the dystrophic and inflammatory periodontal diseases are caused by the vascular system violations, particularly at the microvasculature bed level [12, 13]. The aim of our investigation is to evaluate experimental data of morphology and function of the tissues and periodontal microvasculature bed at low birth weight.

Materials and methods. The study was conducted on rat line whose mothers had a spontaneous hypertension, which is known to be one of the most frequent causes of placental insufficiency, and, as a consequence, IUGR.

We investigated 62 full-term animals. The control group included middleweight rats, the study group included rats which body weight at birth was below the median weight (6.84×10^{-3} kg) of body of all posterity by more than 20%. The control group included 29 animals. The study group included 33 animals. Group of middleweighted animals (control group) included 16 male rats (48,48 %), 17 female rats (51,52 %). There were 17 male rats (58,62 %), 12 female rats (41,38 %) in the study group.

Immediately after birth, rats were subjected to a primary zoometric measurements: animal weighing, general and tail length measuring have been conducted. Second zoometric study of experimental animals was performed directly before the sacrifice of the experiment. It was performed in accordance with international standards of bioethics at 1, 14 and 40 days of the animal age.

Zoometric results are presented in Table. 1. This table also presents data on the number of observations in each of the subgroups.

After sacrificing, periodontal tissues of the rats were fixed in 10% formalin and

after routine proceeding produced sections that were stained with hematoxylin and eosin, by Rego, by Van Gizon. Images of stained sections of parodontal tissues were acquired by "Olympus BX-41" microscope. Morphometric study was performed by "Olympus DP-soft version 3.2" program.

Results and discussion. After examination of hematoxylin and eosin stained sections subgroup rats sacrificed at day 1 after birth, we found noticeable changes in the morphofunctional state of the microvasculature bed of parodontium in the study group compared with the control. Vascular bed of uneven blood flow, together with the empty collapsed vessels there are extremely expanded vessels filled with blood.

In addition to localized microthrombi postcapillaries and venules, small clots are present in the lumen of the vessels.

Endotheliocytes of microcirculatory bed are flattened, there are signs of their desquamation. Processes of formation of new vessels are not expressed (present).

Also, initial sclerotic processes are present in the perivascular space. Morphometric studies showed the pronounced decrease in vascular density ($20,9 \pm 18,2$ %) compared to the control group.

After examination of micropreparations stained by Rego in proper mucous plate of periodontium, areas of ischemia in each of the studied cases of low-weight rats were identified in deeper layers. In the control group, these areas of tissue were solitary. When comparing slides stained by Rego and with hematoxylin and eosin, ischemia zones are characterized by necrobiotic processes, from initial dystrophic to formation of degenerative foci of necrosis.

Our study of animal subgroups that were sacrificed at day 14 after birth, revealed quite similar pattern in the structure of microcirculatory bed in periodontal tissues. However, the study group was more homogeneous. Also, in this group, the empty dilated vessels were found along with spasmed and filled with blood vessels. In the perivascular space of these vessels, petechial (focal) hemorrhages were observed. In many cases the processes of new vessels formation in the study group were intensive focally.

Table 1.

The results of zoometric studies test animals and the number of observations in the subgroups

The study group and the subgroups	body weight (in kg $\times 10^{-3}$)	body length (m $\times 10^{-3}$)	tail length (m $\times 10^{-3}$)	number of observations
Primary zoometric study				
	5,29 \pm 0,18*	52,06 \pm 1,48*	15,82 \pm 0,56	33
	6,93 \pm 0,17	54,17 \pm 0,88	18,10 \pm 0,68	29
Secondary zoometric study				
1	5,78 \pm 0,67*	56,33 \pm 2,02*	17,05 \pm 1,52	12
1	7,60 \pm 0,24	57,58 \pm 1,23	20,33 \pm 1,06	12
14	18,13 \pm 1,90	71,77 \pm 4,69*	38,85 \pm 5,03*	13
14	22,72 \pm 1,43	88,22 \pm 8,70	52,11 \pm 4,57	9
40	42,63 \pm 3,87	108,63 \pm 7,19	74,65 \pm 5,74*	8
40	57,18 \pm 8,28	103,25 \pm 20,58	80,00 \pm 25,81	8

Where: – low-weight rats;

– middle-weight rats

A₁ – low-weight rats sacrificed at the first day after birth;

B₁ – middle-weight rats sacrificed at the first days after birth;

A₁₄ – low-weight rats sacrificed at 14 day after birth;

B₁₄ – middle-weight rats sacrificed at 14 day after birth;

A₄₀ – low-weight rats sacrificed at 35 days after birth;

B₄₀ – middle-weight rats sacrificed at the 35th day after birth;

* - The difference between a group of low-weight rats and middle-weight rats is significant (at 5% confidence level).

There were no significant difference in structure of microvasculature bed between control and study group of rats sacrificed on the 40th day after the birth. At the same time, in the perivascular space more pronounced sclerotic processes are

observed. Morphometric study showed that larger relative amount of connective tissue component in the study group compared to the control.

Our results are in a good agreement with the known facts that development of placental insufficiency is one of the most important factors leading to the formation of the syndrome of intrauterine fetal development. Immune, nutritional, endocrine and metabolic disorders along with the activation of free radical oxidation, accompanying placental insufficiency have damaging effects on the fetus. This effect depends on the duration and length of gestation. At the same time, the effects of IUGR as microvascular periodontal disorders, which underliy the development of pathological processes in the mouth further ontogeny has not been previously described.

Conclusions. Thus, low birth weight is characterized by damage to the microvasculature bed with the ischemia foci formation and initiation of the sclerosis process, which subsequently ontogeny can lead to pathological changes in the oral cavity.

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DENTAL STATUS IN BREAST CANCER PATIENTS DURING THE IV CYCLE OF CHEMOTHERAPY APPLYING PREVENTIVE MEASURES

Kharkov National Medical University, Ukraine

Abstract. *The study was focused on the impact of the preventive hygiene measures (PHM) on the manifestation of the side effects of cytostatic treatment in the oral cavity based on the evaluation of the patients' survey data and the exploration of the patients' oral mucosa status during the IV cycle of chemotherapy.*

All participants of the clinical study were divided into two groups. These groups of breast cancer (BC) patients with $T_1N_0M_0 - T_2N_1M_0$ stage included 26 and 63 patients. The patients' age ranged from 32 to 76 years in both groups.

Group 1 patients only brushed their teeth 1 time/day with any toothpaste, or didn't use any hygiene products at all. During the entire cycle of chemotherapy, Group 2 patients complied with a set of PHM, developed by us.

Fourth cycle of chemotherapy in BC patients significantly affects the condition of the oral cavity – 88.4 % of Group 1 patients showed signs of the side effects of cytostatic treatment in the oral cavity. The set of PHM was used in the comparison group during the IV cycle of chemotherapy to significantly reduce the incidence of pathological manifestations in the oral cavity in Group 2 patients to 66.7 %. The developed set of PHM contributes to a reliable decrease of only cheilitis incidence, which indicates the necessity for further improvement of methods of oral hygiene in BC patients during chemotherapy.

Key words: *breast cancer, oral cavity, mucositis, chemotherapy, preventive hygiene measures*

Advances in chemotherapy have ameliorated the results of cancer treatment. However, despite the constant improvement of cancer therapy, oral complications remain a constant problem for the majority of cancer patients [1, p. 18].

Traditional ineffective empirical schemes of assistance for chemotherapy-induced oral mucositis are gradually being revised to reflect the new paradigm of biopathology of the process and the results of clinical trials of dozens of drugs and

methods, including those focused on the newly allocated targets in the pathogenesis of oral mucositis [2, p. 44].

The incidence of various types of toxicity is diverse. Oral mucositis is recorded in 100 % of cases as a side-effect of high-dose chemotherapy for patients with hematopoietic stem cell transplantation. In non-hematological tumor localization in the course of cytostatic therapy, oral mucositis is defined in more than 30 – 40 % of cases [5]. At the same time, recent research suggests that the incidence of toxicity increases in the oral cavity to 84,6 – 96,2 % in patients, diagnosed with breast cancer [4]. This demonstrates the need for further improvement of preventive therapy methods in the oral cavity during chemotherapy in patients of this cohort.

The purpose of the current study was to examine the impact of the preventive hygiene measures on the manifestation of the side effects of cytostatic treatment in the oral cavity based on the evaluation of the survey data of patients and the exploration of the oral mucosa status of patients in the course of the IV cycle of chemotherapy.

Materials and methods. Our own clinical observations of 89 breast cancer patients (BC), who had received a comprehensive treatment of this pathology in the clinic “Grigoriev Institute for Medical Radiology of National Academy of Medical Science of Ukraine” in Kharkiv during the period from 11.2010 to 12.2013, have become the basis for this study. For the accuracy of the study’s results a homogeneous group of patients was selected: only women with malignant breast disease who have received a combined treatment (modified radical mastectomy (Madden) + radiotherapy), and 2 cycles of adjuvant chemotherapy in accordance with international healthcare standards with the same scheme [3].

The diagnosis “breast cancer” was morphologically verified in all patients.

All participants of the clinical study were divided into two groups. Patients in Group 1 only brushed their teeth 1 time/day with any toothpaste, or didn’t use any hygiene products at all. During the entire cycle of chemotherapy, Group 2 patients complied with a set of preventive hygiene measures, developed by us.

Group 1 consisted of 26 BC patients with $T_1N_0M_0$ – $T_2N_1M_0$ stage, whose age

varied in the range of 35 to 72 years. Mean age was (54.1 ± 9.2) years. The median age equaled to 55.5 years.

Group 2 included 63 BC patients with $T_1N_0M_0 - T_2N_1M_0$ stage, whose age ranged between 34 to 76 years. Mean age was (55.9 ± 1.1) years. The median age equaled to 58.0 years.

Patients' examination was performed before the start and at the end of the IV cycle of chemotherapy by common pattern: a survey, inspection, percussion, palpation, thermodiagnosics and paraclinical examination methods. The oral mucosal condition was assessed relying on the examination, noting the degree of hydration, the presence of congestion, fur, and other elements of lesions.

The manifestation of the side effects of cytostatic treatment in the oral cavity was assessed based on the patients' survey data. A questionnaire was developed and distributed between all patients, in which they denoted their complaints in detail during the IV cycle of chemotherapy.

The obtained data were put in a specifically designed unified card and subsequently used for statistical analysis. Statistical analysis of the obtained material was carried out using the software package STATISTICA.

Results

During the IV cycle of chemotherapy 23 (88.4 %) of 26 patients in Group 1 and 42 (66.7 %) ($p < 0,05$) of 63 patients in Group 2 presented various complaints.

When comparing the frequency of appearance and the nature of complaints in both groups of patients during the IV cycle of chemotherapy it was found, that the frequency of dry mouth and thirst complaints was increasing: from 30.4 to 66.7 % ($p < 0,05$) and from 39.1 to 50.0 % ($p < 0,05$), in Groups 1 and 2, respectively.

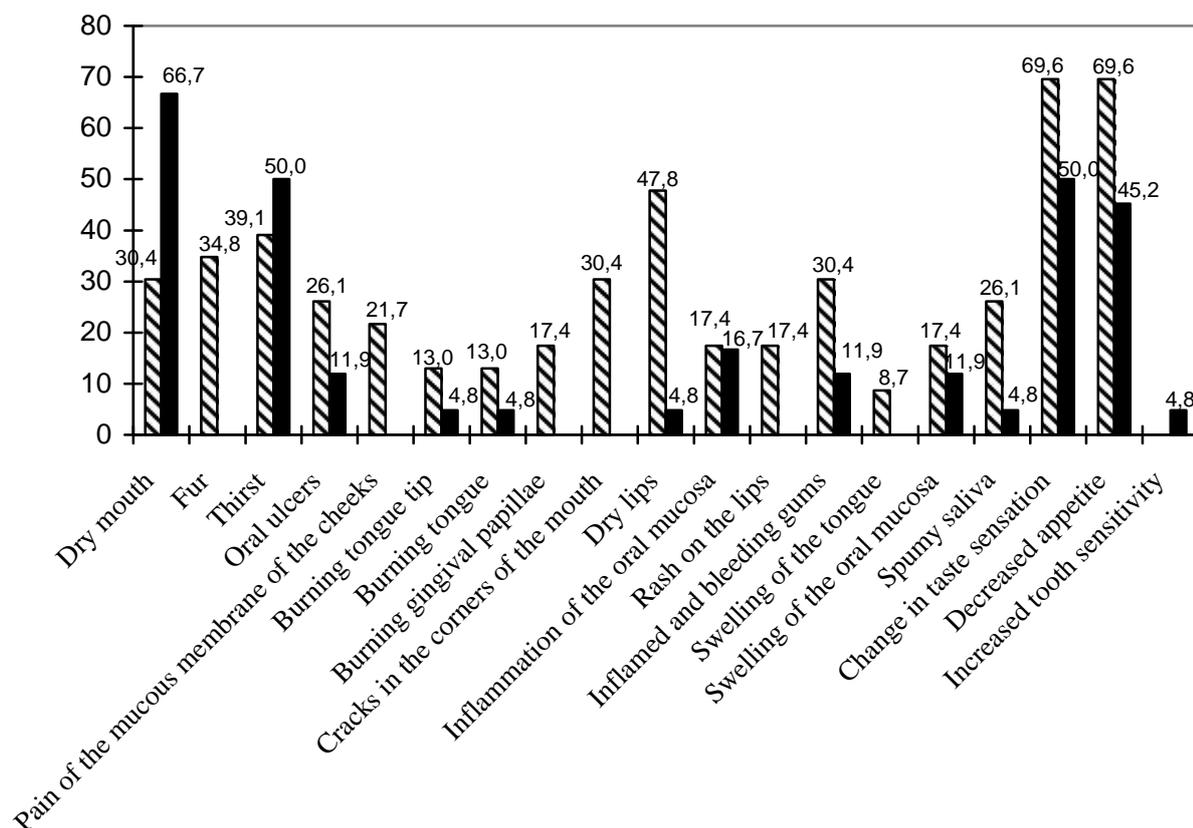


Fig. 1. Group 1 and 2 patients' complaints in the course of the IV cycle of chemotherapy

Complaints about the presence of oral ulcers in Group 2 decreased from 26.1 to 11.9 % (p 0,05), of burning tongue and its tip – from 13.0 to 4.8 % (p 0,05), dry lips – from 47.8 to 4.8 % (p 0,05), inflamed and bleeding gums – from 30.4 to 11.9 % (p 0,05), swelling of the oral mucosa – from 17.4 to 11.9 % (p 0,05), spumy saliva – from 26.1 to 4.8 % (p 0,05), change in taste sensation – from 69.6 to 50.0 % (p 0,05), decreased appetite – from 69.6 to 45.2 % (p 0,05), and increased tooth sensitivity in 2 Group 2 patients – 4.8 % (Fig. 1).

In the compared groups no differences are observed in the complaint of the inflammation of the oral mucosa – 17.4 and 16.7 % (p 0,05), in Groups 1 and 2, respectively.

It should be mentioned that during the IV cycle of chemotherapy such complaints as fur, pain of the mucous membrane of the cheeks, burning gingival

papillae, cracks in the corners of the mouth, rash on the lips and the swelling of the tongue were absent.

Objectively, in 23 patients in Group 1 and 42 patients in Group 2 were determined: dry lips in 11 (47.8) and 2 (4.8 %) patients ($p < 0,05$), isolated ulcers – in 6 (26.1) and 5 (11.9 %) ($p < 0,05$), inflammation and swelling of the oral mucosa – in 4 (17.4) and 7 (16.7 %) patients ($p < 0,05$) (Fig. 2).

No other manifestations of the side effects of cytostatic treatment in the oral cavity were found.

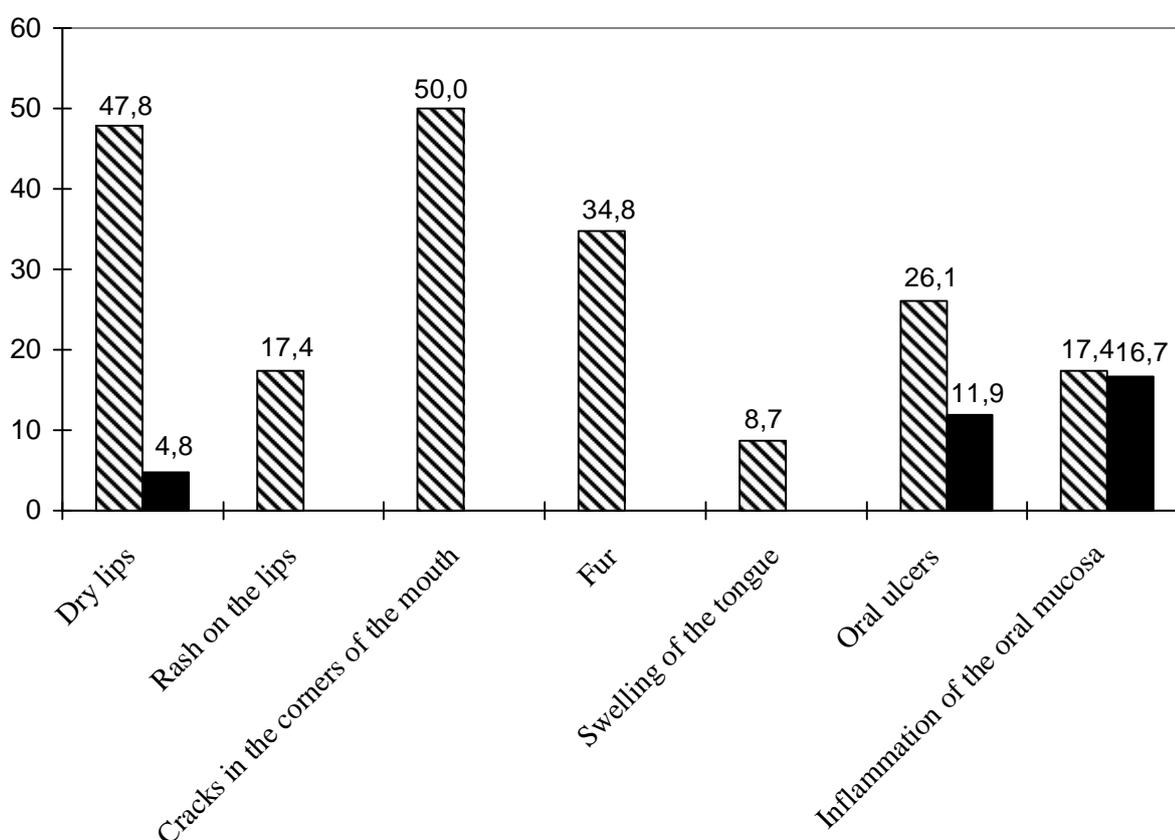


Fig. 2. Objective indicators of the side effects of cytostatic treatment in the oral cavity in Groups 1 and 2 patients in the course of the IV cycle of chemotherapy

On examination of the 3 patients in Group 1 who did not put forward any complaints, at the end of the IV cycle of chemotherapy were found such complaints as inflammation of the oral mucosa, fur on the back of the tongue, imprints of teeth on the sides of the tongue.

On examination of the 21 patients in Group 2 who also did not complain, at the end of the IV cycle of chemotherapy the condition of the oral cavity did not differ from the initial one.

Thus, the IV cycle of chemotherapy in breast cancer patients whilst complying with the set of preventive hygiene measures was accompanied by the development of cheilitis in 3.2 % (in 2 of 63 patients); mucositis of varying severity (I-II stage) – in 47.6 % (in 30 of 63 patients); and salivary gland dysfunction in 47.6 % (in 30 of 63 patients), (Fig. 3).

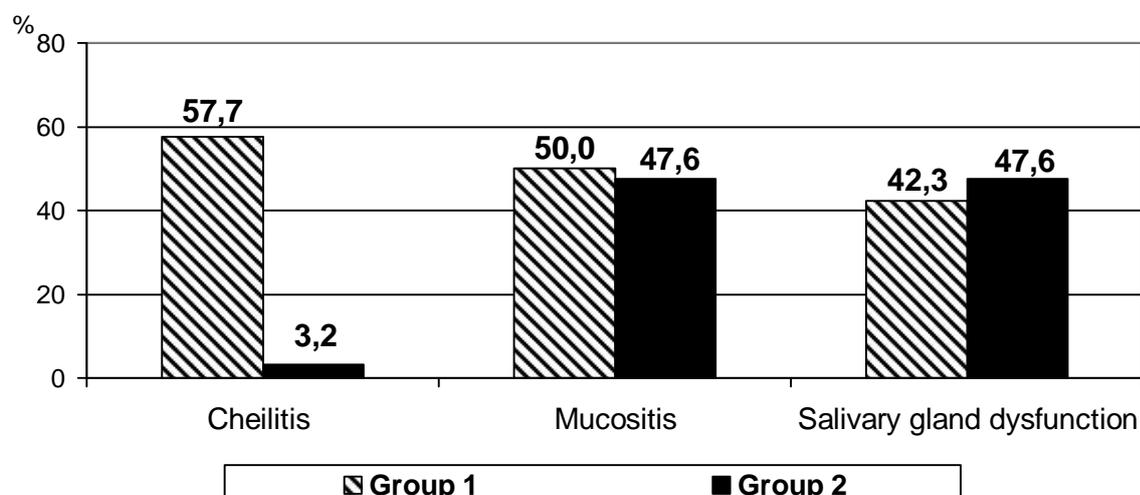


Fig. 3. Comparative analysis of the side-effects of cytostatic treatment in the oral cavity in Group 1 and 2 patients in the process of the IV cycle of chemotherapy

A comparative analysis of the pathological manifestations in the oral cavity revealed that in Group 2 the application of preventive hygiene measures contributes to a reliable reduction in the incidence of cheilitis over 18 times, but the levels of incidence of mucositis and salivary gland dysfunction did not significantly change.

Analyzing the data we can conclude that the use of the developed by us set of preventive hygiene measures during the IV cycle of chemotherapy contributes to a reliable decrease of only cheilitis incidence.

Conclusions. 1. In the course of the IV cycle of chemotherapy in 88.4 % of breast cancer patients in Group 1 we discovered signs of the significant side-effects of

cytostatic treatment in the oral cavity: cheilitis – in 57.7 %, mucositis – 50.0 %, salivary gland dysfunction – 42.3 %.

2. The set of preventive hygiene measures, developed by us and used in the comparison group, significantly reduces the incidence of pathological manifestations in the oral cavity of Group 2 patients to 66.7 %: cheilitis – 3.2 %, mucositis – 47.6 %, salivary gland dysfunction – 47.6 %.

3. The use of the developed set of preventive hygiene measures during the IV cycle of chemotherapy contributes to a reliable decrease of only cheilitis incidence, which indicates the necessity for further improvement of methods of oral hygiene in breast cancer patients during chemotherapy.

Prospects for future research

The perspective of this research lies in developing a set of therapeutic measures aimed at reducing the side-effects of chemotherapy in the oral cavity through the study of peculiarities of the oral mucosa and lips status in breast cancer patients as well as the effectiveness of applying our developed set of preventive measures.

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ORAL HYGIENE INDICES AND HARD DENTAL TISSUES CONDITION IN 9-16-YEAR OLD SCHOOLCHILDREN WITH DIFFERENT EDUCATION LOAD

Kharkov National Medical University, Ukraine

Abstract. *Over the last years scientific literature has provided the data concerning the impact of different educational forms on the health of schoolchildren. However, according to the data, provided by the current literature, there is no evidence confirming the impact of different educational load on the oral health of schoolchildren.*

That is why the aim of our research was to study oral hygiene state and hard dental tissues condition in 9-16-year old schoolchildren, who are enrolled in different education programs (children enrolled in general education program and schoolchildren enrolled in advanced study of foreign languages).

Keywords: *oral hygiene, tooth decay, various training programs, schoolchildren, children.*

Due to insufficient exploration degree of new methods of study and their impact on schoolchildren, it is necessary to investigate health condition of children in new learning environment. Comprehensive integrated study and hygienic reasoning of new education systems are required to eliminate their negative impact on child's body [1, 4, 5].

The study of education load impact, created by different education systems shows that the increase in intellectual activity volume has an influence on schoolchildren. The influence of increased load is often adverse [1, 5]. The most common data deal with negative impact of an increased educational load (lyceums, gymnasium schools, collegiums, classes with enhanced studying of particular subjects) on the impact of schoolchildren [1, 2, 3]. In the first instance this refers to

impairment of vision, musculoskeletal diseases, gastrointestinal disorders, psychosomatic disturbances etc. [4, 5].

However, according to the data, provided by the current literature, there is no evidence confirming the impact of different educational load on the oral health of schoolchildren.

The aim of our research was to investigate oral hygiene state and hard dental tissues condition in 9-16-year old schoolchildren, who are enrolled in different education programs (children enrolled in general education program and schoolchildren enrolled in advanced study of foreign languages).

Materials and methods: The research was carried out in classes with different educational load. The authors examined 90 9 – 16-year-old children without somatic diseases. This group included 60 schoolchildren who were enrolled in collegium program with enhanced study of foreign languages (first group, the main one) and 30 schoolchildren enrolled in traditional secondary education program (second group, the control one). The children were examined by standard procedure (WHO).

Index assessment for oral hygiene determination was carried out by two methods: hygiene index according to Fedorov-Volodkina and simplified oral hygiene index (OHI-S) J.C. Green, J.R. Vermillion.

Hard dental tissues were examined according to DEF-df index which analyzes the presence of decayed teeth both in deciduous bite (d) and in the permanent bite (D), the number of filled teeth in deciduous (f) and permanent (F) bite and also previously extracted teeth (excluding normal teeth shedding) (E).

Results and their discussion.

Hygiene index determination according to Fedorov-Volodkina shows that schoolchildren have different oral hygiene rates, as for instance, the rate from 1 to 1,5, which is typical for good oral hygiene, was observed in 70,0% schoolchildren, enrolled in board education program and in 80,0% children, enrolled in general education program. The index in 6,3% children in the first group and in 17,4% in the second one was found to be satisfactory. The index of unsatisfactory hygiene, which amounts from 2,1 to 2,5 points, was observed in 15,7 % board education program

schoolchildren and in 2,6 % general education program schoolchild. The index comprising from 2,6 to 3,4 points, which implicates poor oral hygiene, was found in 8,0% children of the first group. This index was completely absent in the second group children. Extremely poor oral hygiene (more than 3,5 points) was not observed neither in the first nor in the second group.

Simplified oral hygiene index data (OHI S) J. C. Green, J. R. Vermillion (Oral Hygiene Indices Simplified) revealed a similar pattern. The majority of children, 80,0% children of the first group and 90,0% children of the second group have low score (0-0,6 points), which confirmed good oral hygiene. Middle level, i.e., satisfactory oral hygiene (indices from 0,7 to 1,6 points) was observed in 10,8% board education program schoolchildren and 10,0% general education program schoolchildren. Unsatisfactory oral hygiene index was observed in 6,2% board education program schoolchildren. Extremely poor oral hygiene was found in 3,0% schoolchild of the same group, his index amounted for 2,6 points. As for general education program schoolchildren, they did not show neither unsatisfactory nor poor oral hygiene.

DEF-df index rate from 0 to 2 was determined in 67,5% schoolchildren with enhanced study of foreign languages and in 54,0% of schoolchildren enrolled in basic program. DEF-df index score from 3 to 5 was observed in 28,2% of first group schoolchildren, and in 30,6% of second group schoolchildren. And, correspondingly, DEF-df index rate more than 6 points was seen in 4,3% of schoolchildren with a higher educational load in comparison to 15,4% of schoolchildren with ordinary load.

Conclusion:

1. The results of this examination of schoolchildren with different educational load provide data that the children with enhanced study of particular subjects have healthier teeth than the children enrolled in standard school program.

2. The obtained results give a possibility to draw a conclusion that board education program schoolchildren are prone to a higher risk of oral diseases development, first of all such as gingivitis and caries.

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Chumachenko¹ T.A., Radyvonenko² O.S., Korchak² T.V., Makarova¹ V.I.

EPIDEMIOLOGICAL SURVEILLANCE SYSTEM ON THE BASIS OF THE FORECASTING INTELLECTUAL METHODS

¹Kharkiv National Medical University, Ukraine

²National Aerospace University “Kharkiv Aviation Institute”, Ukraine

Abstract. *In this paper problems of informatization in the field of monitoring and epidemiology supervision of infectious diseases are considered. The importance of a collaborative approach to the prevention and control of infections are highlighted. Time series forecasting methods are described. Basic methods of statistical, regression and fractal analysis are used. Also the problem of epidemic thresholds modeling was considered. The implementation of the fuzzy clustering procedure in the method of epidemic thresholds calculation was proposed. This feature allows exclude epidemic information from the calculation data, which will improve trueness and certainty of results substantially.*

words: *R/S analysis, forecasting, fuzzy clustering, epidemiological surveillance.*

Introduction

Globally, influenza and other acute respiratory diseases are a leading cause of morbidity and mortality worldwide, accounting for an estimated 250 000 – 500 000 deaths globally each year [1]. Seasonal influenza viruses cause annual epidemics that peak during winter in temperate regions.

Influenza occurs globally with an annual attack rate estimated at 5%–10% in adults and 20%–30% in children. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 250 000 to 500 000 deaths. An influenza epidemic can take an economic toll through lost workforce productivity and strain health services. It requires implementation of all possible prophylaxis measures for maximal diminishment of the annually inflicted hurt.

Efficiency of prevention and control these infections in the epidemic period in a great deal depends on quality of the prophylactic measures and timeliness of realization of the program of antiepidemic measures conducted in a preepidemic period. Early determination of beginning of epidemic is needed for this purpose, that is the basic task of epidemiology supervision. The common chart of the epidemiology surveillance system is depicted at the fig. 1.

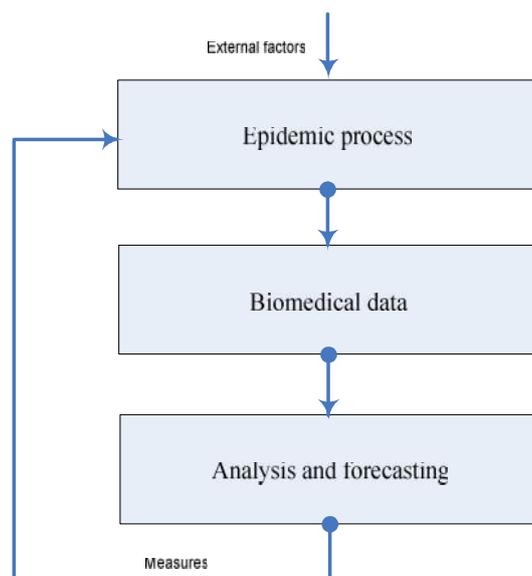


Fig.1. Epidemiology surveillance system common chart

Epidemiological service carries out the daily monitoring of level of morbidity and dynamics of development of epidemic process by means of indexes of epidemic thresholds. Epidemic thresholds are estimated on the basis of long-term indexes of morbidity for all age groups of population. Within the framework of the epidemiology surveillance a daily and weekly calculation and systematic analysis of morbidity in different age groups of population is conducted. If current morbidity exceeds the set threshold (tolerance limit for middle unepidemic morbidity), it is the sign of beginning epidemic.

To solve this problem the theory of time series analysis and forecasting has been considered. An important application of time series forecasting is to prevent undesirable events to occur by applying corrective or contention measures.

Time series analysis and forecasting methods

Analysis and forecasting methods of dynamic time series are connected with a research of the parameters isolated from each other. Each parameter consists of two elements: the deterministic forecast component and the random forecast component. If the basic tendency of evolution is certain then development of the first forecast does not represent great difficulties and its further extrapolation is possible. The forecast of the random components are more complex, as its occurrence can be estimated only with some probability.

The principal goal of time series analysis is to develop quantitative methods which allow us to characterize time series, in particular, to say quantitatively how two time series differ or how they are related.

Time series data can be considered as deterministic, random and chaotic (fig. 2).

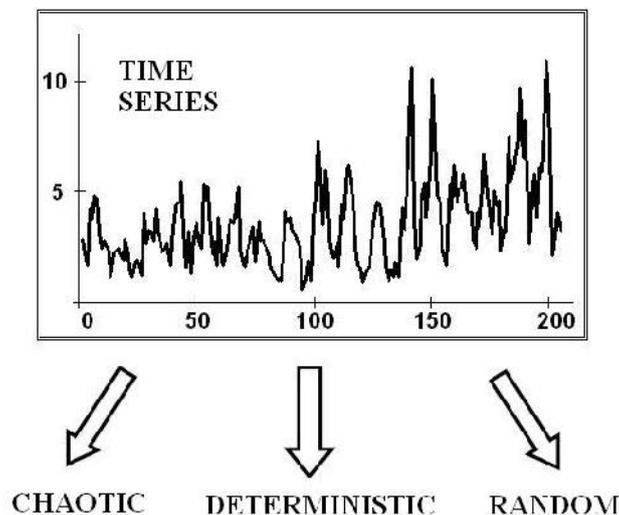


Fig.2. Time series behavior

Deterministic – can be predicted by an explicit mathematical relationship; random – the exact value of the future cannot be predicted based on the known observations. In truth, many time series lie somewhere in between strictly deterministic and random.

To define whether time series is normally distributed or not the normality test is presented. An informal approach to testing normality is to compare a histogram of the residuals to a normal probability curve. Based on the Fig. 2 hypothesis of normal distribution is rejected.

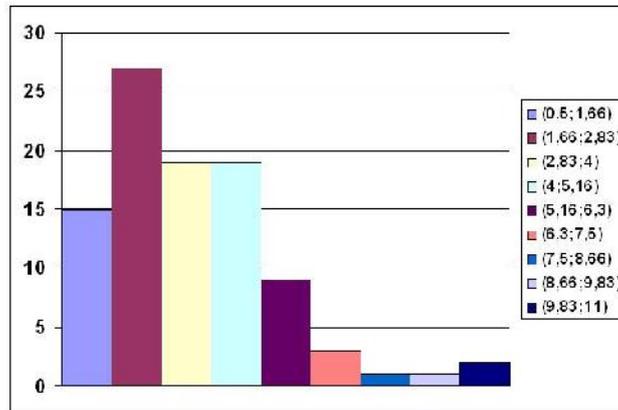


Fig.3. Histogram of the normality test

Time series data was analyzed for the autocorrelation function (Fig. 4)

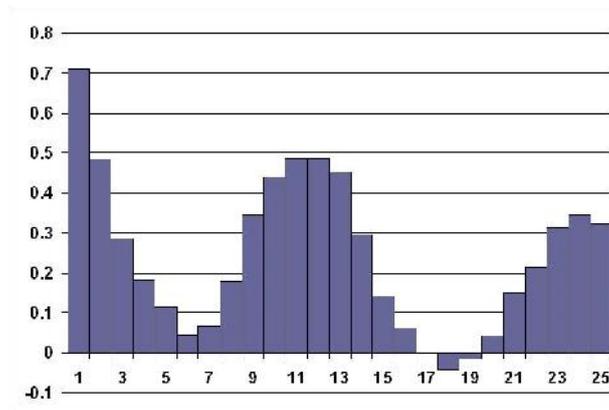


Fig.4. Histogram of the autocorrelation function analysis

R/S analysis was presented. It is non-parametric analysis, meaning there is no assumption or requirement of the shape of the underlying distribution. It was

developed by H. E. Hurst who observed an unexpected behavior of natural time series. They have become known as the Hurst phenomenon.

In [2] the algorithm of calculating of the Hurst's exponent was shown. It starts with calculating of the standard deviation:

$$S(\ddagger) = \sqrt{\frac{1}{\ddagger} \sum_{t=1}^{\ddagger} (x_t - \bar{x}_{\ddagger})^2}, \quad (1)$$

where $\bar{x}_{\ddagger} = \frac{1}{\ddagger} \sum_{t=1}^{\ddagger} x_t$.

The self-adjusted range $R(\ddagger)$ is defined

$$R(\ddagger) = \max_{t=1}^{\ddagger} X(t, \ddagger) - \min_{t=1}^{\ddagger} X(t, \ddagger). \quad (2)$$

Finally, next formula (3) defines the value that is equal to H, which is called Hurst's exponent.

$$R(\ddagger) / S(\ddagger) = \left(\frac{\ddagger}{2}\right)^H. \quad (3)$$

$H = 0.5$ implies an independent process.

$0.5 < H \leq 1$ imply a persistent time series characterized by long memory effects.

$0 \leq H < 0.5$ imply an anti-persistent time series, which covers less distance than a random process. Such behavior is observed in mean-reverting processes, although that assumes that the process has a stable mean.

Fig. 5 shows the result of calculating Hurst's exponent for the former time series.

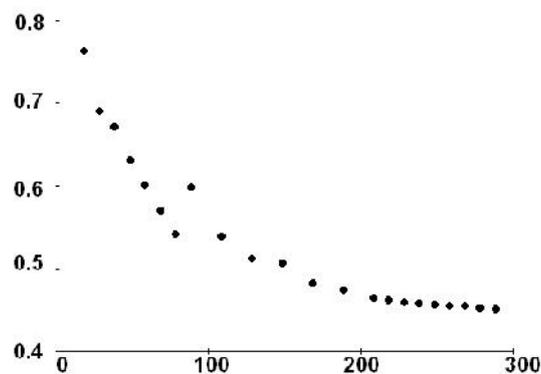


Fig. 5. Values for Hurst's exponent

Based on the time series analysis that was conducted in this work the next assumption can be provided. The former time series can be reconstructed by the next rule.

$$X = \begin{pmatrix} X^1 \\ X^2 \\ \dots \\ X^{12} \end{pmatrix} = \begin{pmatrix} x_i^1 & x_{i+L}^1 & x_{i+2L}^1 \dots x_{i+nL}^1 \\ x_i^2 & x_{i+L}^2 & x_{i+2L}^2 \dots x_{i+nL}^2 \\ \dots & \dots & \dots \\ x_i^{12} & x_{i+L}^{12} & x_{i+2L}^{12} \dots x_{i+nL}^{12} \end{pmatrix},$$

where X_i^n – state of the system in discrete time i , n – the number of years, L – lag or shift reconstructed.

The next formula (4) is used for forecast implementation.

$$X \rightarrow \begin{pmatrix} x_{i+(n+1)L}^1 \\ x_{i+(n+1)L}^2 \\ \dots \\ x_{i+(n+1)L}^{12} \end{pmatrix} \quad (4)$$

According to R/S analysis and test for normality the statement can be assumed that reconstructed time series can provide us with better forecasting result.

Forecasting approaches

Single Exponential smoothing is a very popular forecasting method for some reason:

- it is easy to use;
- requires very little computation effort;
- needs only a few data to produce future prediction.

It is recommended for short or immediate term prediction, for stationary data or when there is a slow growth or decline over time. The method bases on the following formula [3]:

$$y_t^* = \alpha y_t + (1-\alpha)y_t^*,$$

where y_t^* is a forecast, y_t is a time series, α is between zero and one.

The Holt's Three Parameters Exponential Smoothing Model is similar to Brown's model as it estimates the trend and uses it in forecasting. The equations are as follows [4]:

$$S_t = rX_t + (1-r)(S_{t-1} + T_{t-1} + R_{t-1}/2)$$

$$T_t = s dS_t + (1-s)T_{t-1}$$

$$R_t = \chi d^2 S_t + (1-\chi)R_{t-1}$$

$$dS_t = S_t - S_{t-1}, \quad d^2 S_t = dS_t - dS_{t-1}$$

Finally, the forecast can be found as:

$$F_{t+m} = S_t + T_t m + 1/2 R_t m^2$$

where m is the number of periods ahead to be forecast.

The smoothing constants r , s , χ must be specified to minimize the forecast errors over a past time horizon. During the smoothing constants selection procedure a compromise between two wishes should be taken into consideration. On the one hand it is recommended to follow changes in the pattern of the data. On the other hand a method that can distinguish between random fluctuations and changes in the basic pattern of the data is highly required.

Takagi-Sugeno models are adaptive fuzzy logic application for a forecasting problem epidemic growth of disease parameters has following advantages [5]:

- adaptive fuzzy models are easily construed after training by the person;
- some fuzzy models (Mamdani type) are less exacting to an experimental data volume, than neural networks or networks TSK;
- conflicting data can be processed by the fuzzy logic models;
- fuzzy models exactness can be improved by an addition of expert rules.

Forecast results

As a result of numerical experiments prediction methods was estimated (Table 1), where RME and MAPE – mean square error (5) and mean absolute error in percents (6), respectively.

$$RME = \sqrt{\frac{1}{T^*} \sum_{t=1}^{T^*} (y_t^* - y_t)^2} \quad (5)$$

$$MAPE = \frac{1}{T^*} \sum_{t=1}^{T^*} \left(\frac{y_t^* - y_t}{y_t} \right) \cdot 100 \quad (6)$$

where y_t – actual value of t ; y_t^* – predicted value for t ; T^* – forecasting horizon.

TABLE 1

	RME	MAPE
Braun method	1.5	27%
Adaptive ES	2.068	32%
Holt-Vinters	2.33	69%
Least square method	2.66	40
TS-models	3.94	61

As a result Fig. 6 was presented with graphs of results of used forecasting methods.

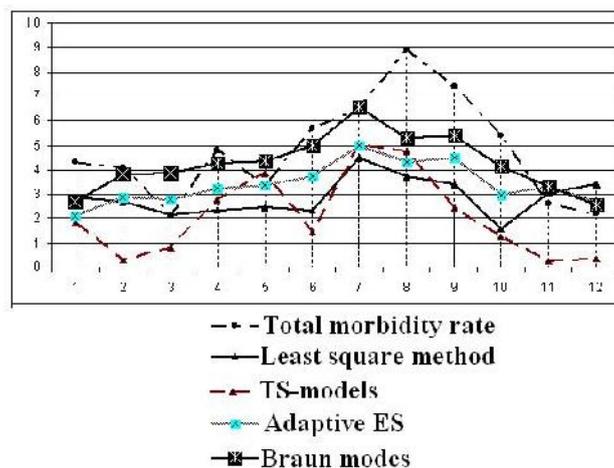


Fig. 6. Forecasting result

Epidemic thresholds calculation method

Usually, the method, based on the determination empirical series statistics is used for the estimation of epidemic thresholds [6, 7]. Epidemic thresholds are the upper tolerant limits of unepidemic morbidity.

At the sufficient number of supervisions $N_i \geq 5$ upper tolerant limit was calculated:

$$X' = \bar{X}_i + Q_{N_i-2} \sqrt{\frac{N_i - 1}{N_i - 2 + Q_{N_i-2}^2}} \cdot S_i,$$

where Q_{N_i-2} – value of the Student's test for the 95% confidence probability and

$N_i - 2$ degree of freedom, $\bar{X}_i = \frac{1}{N_i} \sum_{n=1}^{N_i} X'_n$ – mean value of morbidity for calculation

period, $S_i = \sqrt{\frac{1}{N_i - 1} \sum_{n=1}^{N_i} (X'_n - \bar{X}_i)^2}$ – standard deviation.

The approximate method with the variation coefficients calculation was used for weeks, where the number of the supervisions $N_i < 5$. Results of calculation are epidemic threshold graphs for each of age groups.

According to the mentioned methodic, it is necessary to exclude data which were represented during the period of epidemics in the city, and data, which were admitted as ambiguous from basic data. Usually, epidemiologist performs it. The using of fuzzy clustering and next aggregation of results with epidemiologist's subjective resolution allow select the class of epidemic information more accurately. As the clustering procedure, hybrid fuzzy clustering algorithm was used, described in [8]. Proposed approach is based on a fuzzy relation similarity model and supplemented with clusters merging algorithm. Application of fuzzy clustering allows remove the form and positional relationship uncertainty of clusters, quantity of clusters uncertainty and partitioning fuzziness.

Verification of results was conducted by means of real statistical information and epidemic thresholds comparison for weeks, during which the epidemic of flu was registered in the city (Fig. 7).

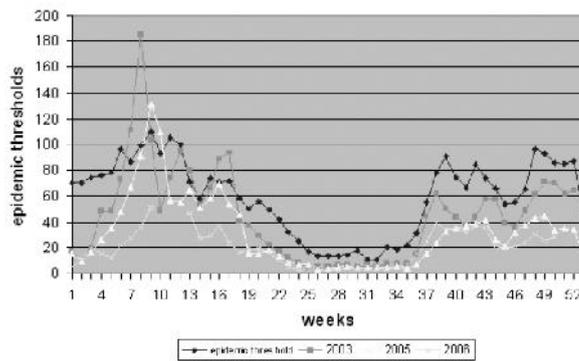


Fig. 7. Epidemic threshold and morbidity.

The computational experiments were carried out [9]. According to results, average epidemic threshold was reduced 19% in comparison with classical method (Fig. 8).

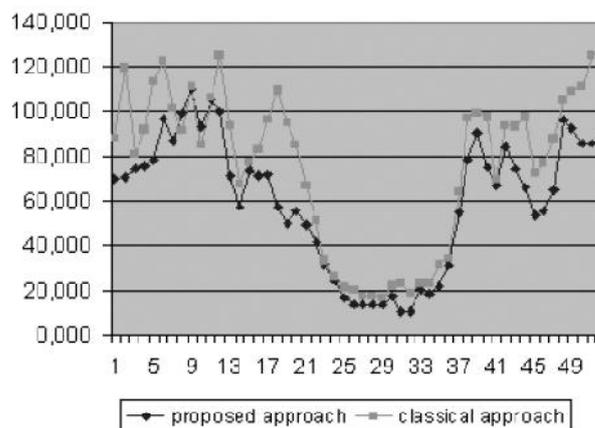


Fig. 8. Comparison results of the classical and proposed approach for an age group 7-14 years (average epidemic threshold reduction 19%).

Conclusion

In the paper comparison of fuzzy logic methods and traditional methods of time series forecasting was conducted. Computing experiments showed that not all the offered prediction approaches provide high accuracy of forecasting. Hurst's R/S-analysis provided the research with a new approach of reconstructing of the time series trajectory.

Also the epidemic thresholds calculation method using hybrid fuzzy clustering procedure was represented. The method allows exclude epidemic information from the calculation data, and demonstrates efficiency of proposed approach in comparison with classical method. The developed epidemiology surveillance information system for monitoring and analysis of epidemic morbidity allows simplify the task of doctor-epidemiologist, and reduce time for the calculation of epidemic thresholds for all of age-dependent groups.

Epidemiological surveillance system based on the forecasting intellectual methods allows for a detailed situational analysis including subgroup analysis on a daily basis.

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PREDICTING RISK OF DETERIORATING HEALTH OF THE POPULATION BASED ON THE PRINCIPLES OF MEDICINE OF BORDERLINE CONDITIONS

Kharkov National Medical University, Ukraine

Abstract. *Prenosological diagnostics is an important compound of a wider branch of modern medicine – medicine of borderline conditions. In the foundation of medicine of borderline conditions there is the working hypothesis that the development of clinical disease forms is preceded by certain bodily dysfunctions that have prenosologic character.*

Timely identification of unhealthy prenosological conditions, risk detection and elimination and medical correction are directed at health maintaining and strengthening for different population groups, regardless of age, social, professional and other attachment.

Experimental data, got in the course of the complex study, was proved that the prenosological conditions occur as the result of dysfunctions of those adaptive systems, that are currently responsible for stable body functioning.

Thereby our own observations have proved that prenosological mental conditions of students are represented by neurotic disorders of situations and risk periods against the background of certain personality accentuations.

The harmful industry workers show the prodromes of professional dust dysfunction, manifested in the disorder of pro-antioxidant system, and the prodromes of vibration pathology are the heat system disorder as the consequence of certain occupationally predetermined risk factors (occupational dust and vibrations).

Results of own theoretical and experimental research show that prenosological diagnostics has a wide application in medicine of borderline conditions. Experimental data, got in the course of the complex study, was proved that the prenosological conditions occur as the result of dysfunctions of those adaptive systems, that are currently responsible for stable body functioning, for example neurotic disorders and personality accentuations for senior pupils, disorders in thermoregulatory function for jeopardize vibration workers.

Key words: *medicine of borderline conditions, prenosological diagnostics, psychodiagnostics, correction of the functional state, risk management, occupational diseases, mental health.*

It's generally known that the persistent health deterioration of wide population groups in Ukraine that has been observed during the last few decades is immediately connected with ineffectiveness of the current primary disease prevention system. According to the opinion of the leading scientists-hygienists, representatives of Kiev, Kharkiv, Vinnitsa and Lugansk scientific schools [1, 2, 3], the solving of this urgent scientific problem consists in the introduction of hygienical prenosological diagnostics methodology into the Sanitary Epidemiological Service practice, well tested in the full-scale scientific experiments in relation to children with different social adaptation levels, students and workers of different industries.

The study of prenosological prevention issues abroad is done in several different directions. First of all, it's the use of physical activity for the prevention of both somatic and neurogenic pathology [4, 5, 6, 7]. A considerable number of researches both in the European countries and in the USA is dedicated to the study of nutrition character as a risk factor for the development of prenosological conditions [8, 9, 10]. A wide spread of neurosis-like conditions among different population groups, especially among adolescents and youth, sets conditions for absolute relevance of the study of mental health disorder prodromes and timely mental disorder prevention [11, 12]. A great number of scientists around the world have dedicated their research to this problem [13, 14, 15, 16, 17].

Besides, a lot of attention is currently dedicated to the study of bad habits proliferation and healthy lifestyle propaganda as an effective way of early disease prevention [18, 19]. An important role in the professional pathology prevention is also given to early diagnostics of premorbid conditions, stipulated by the influence of harmful working environment factors [20, 21].

According to our own experience of result generalization in theoretical and experimental research in the area of child and adolescent hygiene, industrial medicine and psychohygiene, prenosological diagnostics is an important compound of a wider branch of modern medicine – medicine of borderline conditions.

Medicine of borderline conditions is an area of medical science that studies general patterns of prenosological state formations and transitional processes of their

transformations. The goal of medicine of borderline conditions is prevention of somatic and mental diseases of different genesis by the way of early determination of prodromes and of occurrence risks followed up by the body functional state correction. In the foundation of medicine of borderline conditions there is the working hypothesis that the development of clinical disease forms is preceded by certain bodily dysfunctions that have prenosological character. Timely identification of unhealthy prenosological conditions, risk detection and elimination and medical correction are directed at health maintaining and strengthening for different population groups, regardless of age, social, professional and other attachment.

The reason for separating medicine of borderline conditions into an independent branch of medical science is the new scientific concept built on the generally acknowledged patterns of accommodation process that trace to earlier undefined physiological phenomena, generalized in the adaptive transition law: “the organism transition to adapted condition happens at the cost of energy and plastic resources, accumulated during the previous adaptation experience, through the breakup of previous useful connections in the leading biological system, that used to provide stable organism state by the way of a new dominant system formation with three main types of reactions: protection mechanisms determined by evolution, individual adaptation experience reactions, and non-specific fast reactions to the new influence”.

This law determines the connection between the temporary space characteristics of the functional life support system of an individual at a certain stage of his physical, mental and social being, exposes the mechanisms of organism existence and transformation under the influence of changing environmental factors. The principles of medicine of borderline conditions are built on the general adaptation patterns and have solely universal character.

Experimental data, got in the course of the complex study have confirmed the theoretical borderline conditions medicine principles. It was proved that the prenosological conditions occur as the result of dysfunctions of those adaptive systems, that are currently responsible for stable body functioning.

Psychodiagnostics of prenosological mental states in senior pupils

According to the results of their own research, prenosological mental states of senior pupils presented by neurotic disorders situations and periods of risk against the background of certain accentuations of personality. Features of the formation of the rising individual mental properties are separate direction of psychodiagnostic study.

We investigated the communicative and emotionally-volitional personality traits using a teenage version of the questionnaire by R. Cattell [22]. Senior pupils who are learning by innovative method of preserving and forming health in School of health promotion (study group – SHP) and senior pupils from usual comprehensive school (control group - CG) were compared (Fig. 1, 2).

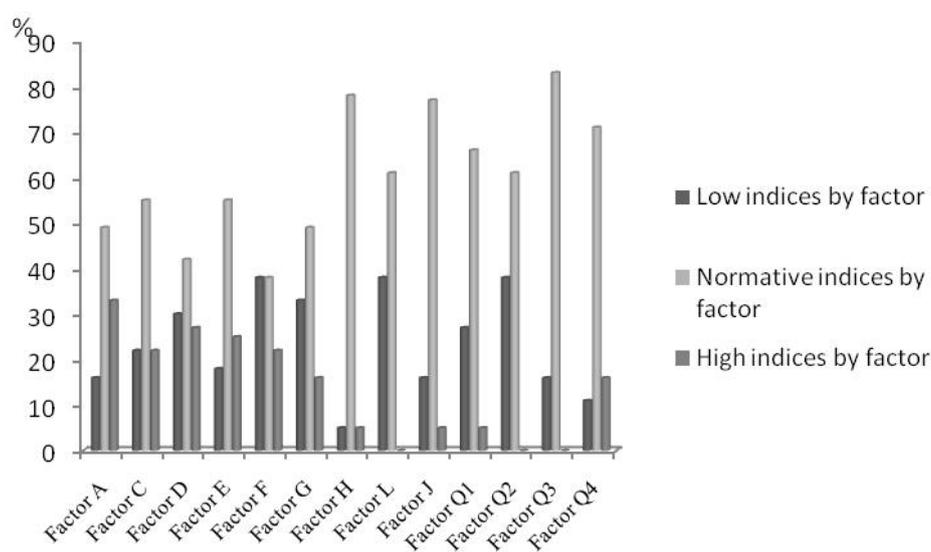


Fig.1. Emotionally-volitional communicative and personality traits of senior pupils in control group.

Regulatory emotionally-volitional traits of senior pupils were established, namely: emotional stability and restraint, normative behavior, sensitivity to others, the standard level of anxiety, operating tension. These properties belong to the typical character traits constituting psychological portrait of representatives SHP. Caution is typical communicative property of school pupil from SHP, it defines the features of interpersonal interaction.

In contrast to the study group, such emotional-volitional feature as self-regulatory is the most common personality trait in the control group. Such communicative properties as courage, conformity, self-sufficiency are more common in the control group pupils in contrast to the study group. Personality traits "closure - communicative" and "submission - domination" manifest regardless of the life conditions.

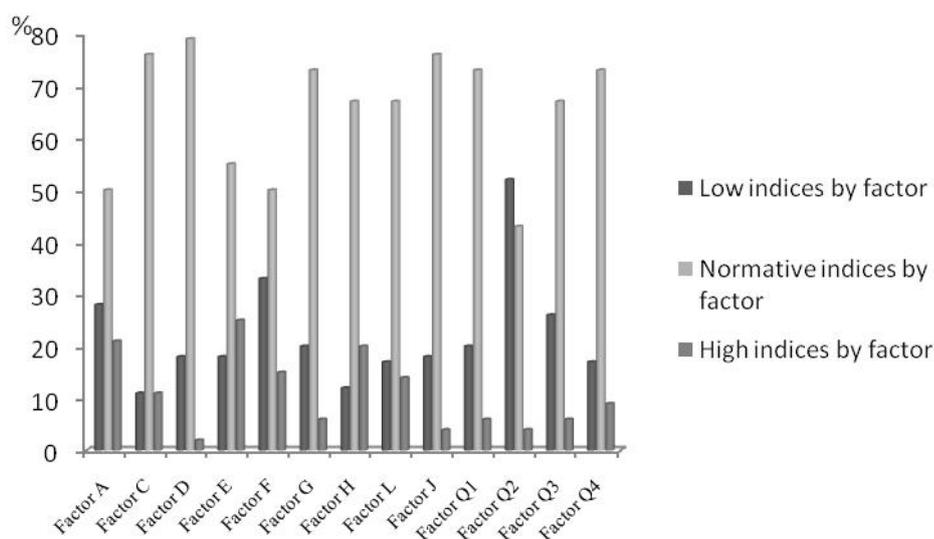


Fig. 2. Emotionally-volitional communicative and personality traits of senior pupils in SHP

Further analysis of prevalence of specific personality accentuation in the study and control groups was performed. Comparative psychodiagnostic experiment found typical personality traits, which should be subject to psychohygienic correction.

Psychological portrait of senior pupil from SHP presented by such personality traits: the individual is self-mastering, efficient, reasonable, developed emotionally and volitionally, sure of his abilities, understands the requirements of his social group, has a typical mood stability and resistance to nervous exhaustion; cautious in interpersonal relations.

Such character accentuation as unsociability and its opposite - excessive sociability, and also increased (unmotivated) caution are inherent in a particular

persons of group SHP. They have such features of psychological portrait as excessive seriousness, reasonableness, taciturnity and a tendency to complications. These features are implemented on the background of the two opposing options interpersonal interaction: 1) unsociability, reticence, rigidity and increased rigor to the estimation of people, which leads to a skeptical attitude towards others, loneliness and lack of close friends; 2) inconsistency of activities, the propensity to sociable disposition.

The data show significantly less prevalence of accentuations among of senior pupils from SHP. This can be viewed as a result of the favorable effect of social and psychological learning environment for teenagers of SHP, as well as a consequence of directional selection of students to study by the innovative pedagogical system. But, based on the potential dangers of a possible transformation of character accentuation into psychopathy, the complex of psychohygienic aid for pupils must include compulsory psychodiagnostics and psychohygienic correction of defective personality traits.

"Psycho-diagnostic questionnaire for school pupils" (own product of KhNMU department of hygiene and ecology number 1 [22]) was used to study the state of mental health by index of prenosological mental states prevalence among pupils SHP. Its questions are designed to identify abnormalities in certain cognitive function, and the cumulative diagnostic effect allows establishing signs that precede mental disorders (prenosological mental states).

Investigation of the prevalence of certain forms of prenosological states among senior pupils of SHP showed that the borderline conditions, which precede depression, are the most common ($13,4 \pm 3,5\%$), asthenia has fewer cases ($11,3 \pm 3,2\%$), hypochondria is the least common ($5,2 \pm 2,2\%$). A similar trend was observed in the control group, there were more surveyed teenagers with deviations of prenosological type: with signs of asthenia ($15,6 \pm 3,2\%$), with symptoms of depression ($18,8 \pm 4,0\%$) (Fig. 3).

Typical features of a psychological portrait of senior pupils with the specified complex of prenosological manifestations are: orientation of the individual to self-

isolation against a background of lower self-esteem and a negative attitude to their own "I", which manifests itself as boredom, depressed mood and increased anxiety (symptoms of a depressive state), exhaustion against a background of deterioration of general and intellectual efficiency with typical daytime and sleep rhythms (signs of asthenia), excessive attention to their own health with the revaluation of the negative effects of their state and its biased judgement (typical symptoms of hypochondria).

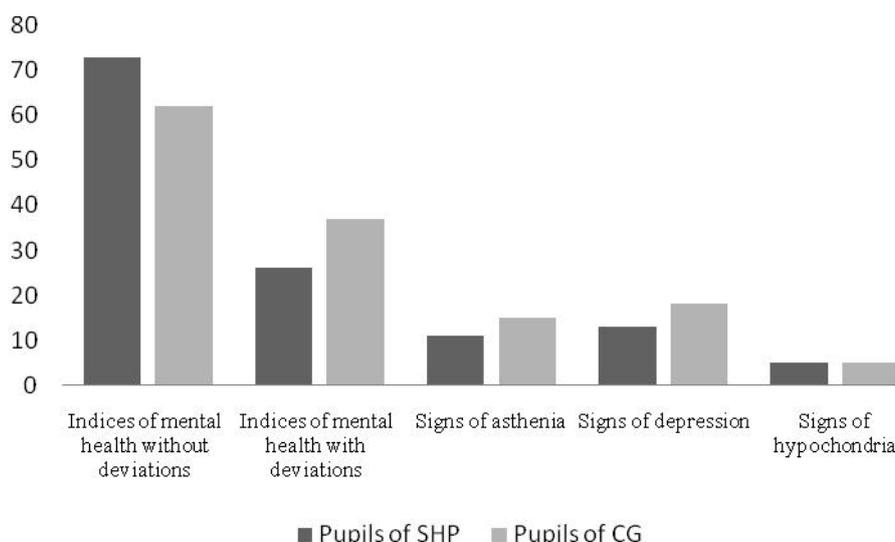


Fig. 3. Comparative characteristics of mental health of senior pupils of SHP and CG

Prenosological diagnosis of vibration disease risk among workers

The prodromes of professional dust pathology among workers in hazardous industries manifested in violation of the pro-and antioxidant systems, and primary characteristics of the vibration pathology are evident in disturbances of body thermoregulation, which are the result of the relevant professional predefined risk factors (occupational dust and vibration).

Complex of unfavorable factors of combined action acts on the body of representatives of researched professions. These factors may increase the effects of local vibration under certain conditions, namely: industrial noise (exceeding the maximum permissible level on 12 dBA), significant physical activity (transferring cargo weighing 10 to 40 kg and forced working posture for 20-80% of the time),

general vibration (boilermaker, shipbuilder, molder), unfavorable meteorological conditions (fettler, molder, fitter of machine assembly work (FMAW), insufficient lighting on work surface (boilermaker, shipbuilder, molder), occupational dust and fumes in the air (fettler, molder, FMAW).

The general regularity has been found in a elektrotermometrical study of workers with jeopardize vibration profession. It manifests itself in the dropping of skin temperature of both hands at 4°C compared to the physiological norm ($27\text{-}31^{\circ}\text{C}$) ($p < 0.001$). This indicates a persistent deterioration in thermoregulatory function of the distal parts of the upper extremities. This deterioration is the result of a long-term action of high-level local vibration. Therefore, it can be argued that the decrease in skin temperature of hand up on 4°C can be considered as one of the primary symptoms of vibration disease. These signs are objective criteria of health state for workers with jeopardize vibration profession. The presence of such symptoms, even in the absence of other symptoms, can be regarded as a preozological sign of vibration disease.

The characteristic temperature dynamics of the hand surface was found in representatives of jeopardize vibration profession in the time of the cold test. In response to cold stress temperature was varied as follows: the left hand had surface temperature before cold load ($26,80 \pm 0,27$) $^{\circ}\text{C}$ and after cold load - ($25,20 \pm 1,75$) $^{\circ}\text{C}$ ($p < 0,05$) (Fig. 4); the temperature of the right hand before the cold load was ($25,13 \pm 0,31$) $^{\circ}\text{C}$ and after cold load - ($22,64 \pm 0,27$) $^{\circ}\text{C}$ ($p > 0.05$) (Fig. 5). This shows the insufficiency of the vasomotor apparatus predominantly in left hand. However it would be necessary to pay attention to the lack of statistically significant differences between the obtained data ($p > 0.05$).

Within five minutes of monitoring the temperature of the left hand was significantly different from the start and was in the first age group - ($25,61 \pm 1,24$) $^{\circ}\text{C}$, and the second - ($24,76 \pm 0,44$) $^{\circ}\text{C}$ ($p < 0.01$). This increase of termoasymmetry with age shows typical age-related changes that occur in employees of jeopardize vibration profession.

Next, we studied the dynamics of hand temperature change after cold test, depending on the length of experience in jeopardize vibration profession.

Thus study of the dynamics of hand surface temperature using contactless thermography allowed to establish that the worker is older and more experience in his jeopardize vibration profession, so he has a lower density of infrared radiation.

In addition, by the results of cold test it was found that more negative state of the thermoregulatory system is observed in the profession "boilermaker", "FMAW" and "fettler" that is a clear example of action of unfavorable working conditions (primarily local vibration).

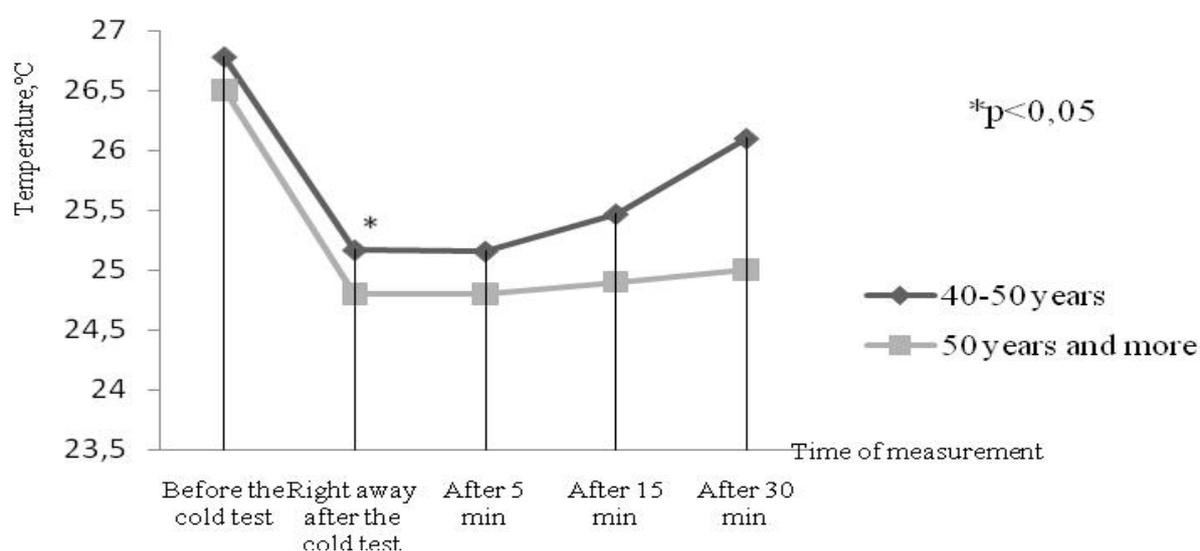


Fig. 4. Restitution of skin temperature of the left hand of employees, depending on the age

Thus, the marked affection of the distal parts of the upper extremities was noted at all test frequencies in all groups under observation. The results of observation revealed the following regularities of pathogenesis: the age of the worker and his work experience in the jeopardize vibration profession are not defining features of vibration sensitivity lowering ($p > 0.05$); however, the degree of deterioration is related to the severity of vibration disease ($p < 0.05$ - < 0.001), and

differences in professional activities (the most pronounced loss of vibration sensitivity observed in shipbuilders and FMAW, $p < 0.05$).

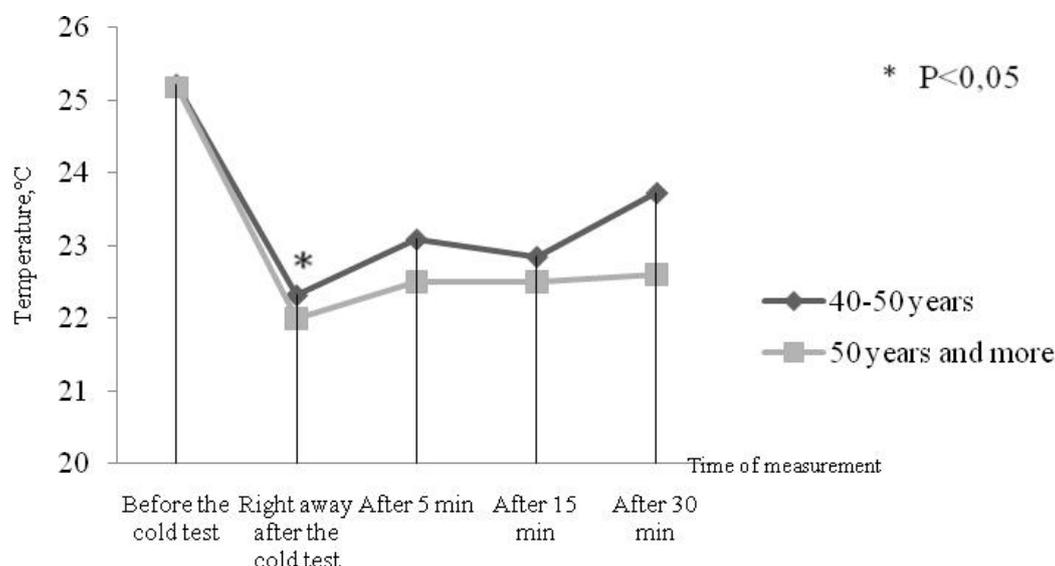


Fig. 5. Restitution of skin temperature of the right hand of employees, depending on the age

Conclusions

Thereby our own observations have proved that prenosological mental conditions of students are represented by neurotic disorders of situations and risk periods against the background of certain personality accentuations.

The harmful industry workers show the prodromes of professional dust dysfunction, manifested in the disorder of pro-antioxidant system, and the prodromes of vibration pathology are the thermoregulatory system disorders as the consequence of certain occupationally predetermined risk factors (occupational dust and vibrations).

Among different age groups of children, the prodromes of organism sensibilization are some specific disorders of immune system that manifest in the increase of immunoglobulin G in the blood serum and disorders in the clinical presentation of blood at the expense of increase in eosinophil number against the background of such risk factors as hereditary disposition to allergies. The children's

risk factors for allergic disease include: the pathology of pregnancy and delivery, the infant excess weight, presence of obligatory allergens in the nutrition, irrational immunoprophylaxis.

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RESULTS OF THE STUDY OF A MIXED EFFECT OF WORKPLACE HAZARDS ON THE STATE OF HEALTH IN MECHANICAL ENGINEERING WORKERS

Kharkov National Medical University, Ukraine

Abstract. *The necessity of studying qualitative and quantitative characteristics of a complex of workplace factors of modern mechanical engineering is substantiated. A potential possibility of a mixed effect of chemical and physical hazards on the workers' organism is found out. Higher levels of MTD, which can be caused by reduced adaptive abilities of the workers' organism, serve as the criterion for an unfavorable influence of a complex of workplace hazards (chemical pollutants, noise, vibration, electromagnetic fields, hard and strenuous work).*

Key words: *Chemical pollutants, noise, vibration, mixed effect, morbidity with temporary disability.*

Introduction. One of the main places among many factors, which affect human health and form environment, is taken by work space hazards, including unfavorable microclimate conditions, electromagnetic radiation and chemical pollutants [1]. Very widespread from the viewpoint of technological process maintenance at modern industrial plants that manufacture or use various chemicals is the equipment, which generates electromagnetic fields with different voltages. The above makes possible a mixed effect of electromagnetic fields and various chemical compounds, often potentially dangerous for the human health, on the organism of workers. At the same time the modern technological process of production is characterized by use of a wide spectrum of physical means of influence, higher or low temperatures, laser radiation, etc. [2,3].

The above facts cause formation of a complex of unfavourable work space factors with the subsequent mixed effect of chemical and physical hazards on the

organism of workers and, as result, necessitate revealing of human adaptation mechanisms for this kind of unfavourable influence.

Materials and methods. The state of work space at machine shops and foundries with assessment of working conditions of their workers and morbidity with temporary disability (MTD) in some occupational groups was studied at engineering plants of the Kharkiv Region. Work environment was studied in nine shops, where machine parts underwent chemical and mechanical treatment. The studies were carried out with standard methods and use of modern laboratory equipment [4]. At permanent and temporary work places some meteorological factors were measured, namely: air temperature, relative humidity, air flow speed, thermal radiation intensity; in some cases – temperature of heated surfaces of technological equipment and its protective covers, content of dust and harmful chemicals in air, intensity of noise and its frequency characteristics, levels of whole-body and local vibration, levels of electromagnetic fields. All in all, about 4,500 measurements of harmful work space factors were taken. Timekeeping observations of labour hours were conducted and job descriptions of workers from the main occupational groups were made.

Results. The researches, conducted in order to study working conditions at work places of engineering plants, revealed that work environment at the above shops did not satisfy sanitary and hygienic requirements by many factors. Thus, the microclimate at foundries was assessed as warming. The microclimate at all machine shops was assessed as warming in the warm season and cooling in the cold one; this thing can affect the workers' organism and provoke failures in the adaptive mechanisms of their organism.

Besides, infrared radiation at foundries in the working area of the people, who work with molten metal or shake out hot casts, exceeded permissible values several times. The temperature of heated surfaces of the main technological equipment at foundries exceeded permissible values 1.5–2 times. Dust content in the air of the working area at foundries exceeded its maximum permissible concentrations (MPC)

for relevant kinds of dust at all work places. The most dangerous dust is that one, which contains 98 or more per cent of free silicon dioxide; this is produced in processes of sand making, forming, manufacturing of cores, shaking out and cleaning of casting blocks.

The highest concentrations of dust (20.4–58.8mg/m³) were registered at work places of moulders, casting technicians, coremakers and fettlers. Other work places revealed lower concentrations (6.1 –17.7mg/m³). At machine shops, the content of dust in the working area air exceeded its permissible regulatory values too; at some places of work its concentrations were as high as 11 mg/m³ (MPC = 6 mg/m³).

Studies of the content of harmful chemicals in the working area air of foundries proved that at all their shops the values of carbon monoxide, sulphurous anhydride, manganese and nitrogen oxides and other substances were mainly within their permissible ranges, except for phenol and formaldehyde. The above substances were revealed at core areas in all work places of female coremakers. Phenol was detected in concentrations, which exceeded the permissible ones (0.1 mg/m³) 2–5.2 times; the permissible concentrations of formaldehyde (0.05 mg/m³) were exceeded 2–6.2 times. At a precision casting foundry, work places of pattern makers revealed only hydrocarbons with concentrations of 800–900 mg/m³, which exceeded MPC 2–3 times.

In the overwhelming majority of work places at machine shops, where oil and emulsion metalworking lubricants (MWL) were used, their working area air contained only small amounts of carbon monoxide, hydrocarbons and sulfur dioxide gas or did not have them at all.

Measurements of noise and vibration, taken at foundries during the work of fettling and cleaning equipment, demonstrate that parameters of these factors exceeded permissible values for noise by 13–35 dB and vibration by 20–23 dB (pneumatic hammers) or by 4–10 dB (grinding machines). The whole-body vibration on the floor of work places of casting technicians exceeded maximum permissible levels (MPL) by 11–13 dB.

Studies of noise at machine shops showed that by sound volume it exceeded MPL at all four shops on all examined work places of machine operators. By its character, the noise was mainly medium-high-frequency with prevalence of high frequencies and excess of sound volumes by 6–14 dB.

At work places with the equipment, which generated electromagnetic fields, the latter were measured, but no measurement exceeded regulatory values by either electric or magnetic components, though the above values were close to their upper permissible limits.

The conducted timekeeping studies of the work and job descriptions of 52 workers of the main occupations demonstrate a significant load with their primary and auxiliary work. A high percentage of forced breaks was observed in the majority of occupational groups, it resulting from breakdowns in the technological production cycle. The primary work of all examined occupations is connected with the influence of

workplace hazards on the workers' organism, namely: unfavourable meteorological conditions, a high dust content in the working area air, contamination of the working area air with combustion residues of organic chemicals and resins, as well as occupational noises, local and whole-body vibrations, hard physical and strenuous work.

The study of morbidity with temporary disability of workers at foundries and machine shops showed that the level of morbidity in the foundry workers was significantly higher. This difference can be explained, first of all, by a broader spectrum and a considerable excess of safe levels for the majority of hazards, as it was registered in foundry engineering, and, as a result, a higher intensity of their effect. The comparison of morbidity rates in cases for these two cohorts of workers demonstrated that the above difference caused, first of all, a higher morbidity of foundry workers with respiratory diseases (respectively, 87.0 and 30.97 cases), diseases of the nervous system and sense organs (2.53 and 1.0 cases), diseases of the alimentary organs (3.07 and 1.8 cases), diseases of the skin and hypodermic tissue (2.87 and 1.73 cases), diseases of the urogenital system (1.8 and 0.9 cases), diseases

of the musculoskeletal system and connective tissue (6.03 and 3.5 cases), as well as more poisonings and injuries (5.08 and 4.2 cases).

The supposition about a higher hazard level of the work environment at foundries is also confirmed by the fact that in foundry workers the average duration of one case of disease from a whole range of nosologic units turned out to be higher. It concerns, first of all, infectious diseases (20.3 and 11.8 days, respectively), diseases of the nervous system and sense organs (10.8 and 7.9 days), diseases of the respiratory organs (6.2 and 5.9 days), diseases of the skin and hypodermic tissue (11.7 and 10.3 days), diseases of the musculoskeletal system and connective tissue (13.7 and 11.8 days), poisonings and injuries (28.4 and 16.5 days). Besides, the connection with their service record in foundry workers was more significant than that of machine shop workers. In the both groups of shops the occupations, which were subjected to a higher influence of workplace hazards, had higher morbidity values too.

The study of the relationship between the rate of MTD in workers of some occupations at foundries and their working conditions by the results of correlation, regression and dispersion analyses made it possible to reveal close links between these indices.

Thus, the overall multiple correlation coefficient in the obtained multiple regression equation, which characterizes relations between microclimate, dust, noise, carbon monoxide and morbidity, was 0.91, the index of multiple determination being 0.82. The latter demonstrates that, beginning from morbidity at the rate of 34.85 cases in 100 workers per year, its increase by 82 % is caused by the effect of the above workplace factors. By values of the separate indices of multiple determination it was revealed that microclimate caused 34.4 % of morbidity, carbon monoxide 26.5 % and noise 19.9 %. All these coefficients and indices were statistically significant. As for the index for dust, it was negative for the general rate of morbidity, very low (0.4 %) and statistically insignificant.

The pairwise correlation analysis revealed direct relations of the rate of morbidity with working conditions in such aspects as microclimate, carbon monoxide

and noise. Pairwise correlation coefficients for these factors were, respectively, 0.70 ($p < 0.01$), 0.71 ($p < 0.05$) and 0.46 ($p < 0.05$). The pairwise correlation coefficient for dust was 0.44 and approached the statistical significance of the probability factor, which was 2.03.

Thus at foundries, beginning from the rate of 34.85 cases in 100 workers per year, the increase of MTD by 82 % was largely caused by the influence of workplace hazards, including microclimate, carbon monoxide as an indicator of combustion residues of organic substances, and noise.

The preliminary pairwise correlation analysis (calculations of pairwise correlation coefficients) of the relations between the rate of MTD in cases for 100 workers per year with indices of their working conditions made it possible to find out that only three of the five hazards, which were taken into consideration at machine shops (hard and strenuous work, effects of MWL, dust and noise), were more or less connected with the rate of morbidity; these were noise, hard work and use of MWL. The overall coefficient of multiple correlation between the general rate of MTD and the three hazards (hard work, MWL and noise), which were taken into consideration, is 0.87. The influence of all these three hazards on morbidity proved to be statistically significant ($p < 0.05$), as it is based on the fact that the sample volume at machine shops included about one thousand workers.

Conclusions.

1. Working conditions at foundries of machine shops are characterized by the influence exerted on the workers by a complex of workplace hazards; first of all, these include unfavourable microclimate, dust, harmful chemicals (products of destruction of organic compounds and polymers), noise, local and whole-body vibrations, hard and sometimes strenuous work, as well as electromagnetic radiation for workers of some occupations.

2. The levels of the majority of work space hazards on permanent work places exceed hygienic regulations or are at the level of the upper border of permissible standards.

3. By results of the conducted observations it has been found out that within 65–87 % of the time of their working shift the workers are at their permanent work places and under the influence of work space hazards with such a possible result as a failure of the adaptive mechanisms in the workers' organism.

4. When compared with machine shops, work at foundries causes a higher morbidity with temporary disability by all indices: persons, cases and days of disability, average duration of one case of disease. This difference results from more considerable values for diseases of the respiratory organs, nervous system and sense organs, alimentary organs, skin and hypodermic tissue, musculoskeletal system and connective tissue, etc.

5. The general rate of MTD of foundry workers is substantially caused by the effect of work space hazards, first of all microclimate, carbon monoxide and noise. Beginning from the rate of 34.85 cases in 100 workers per year, its further increase by 82 % is caused by the influence of the above workplace factors, including the following effects: microclimate – 34.4 %, carbon monoxide – 28.5 % and noise – 19.9 %.

6. The general rate of MTD of machine shop workers is substantially caused by the effect of work space hazards, first of all hard work, noise and MWL. Beginning from the rate of morbidity of 26.82 cases in 100 workers per year, its further increase by 76 % is caused by the influence of the above factors, where hard work increases morbidity by 33 %, use of MTD by 17 % and noise by 26 %.

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