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Philosophy of Medicine

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FROM PHYSIOLOGICAL TO PATHOLOGICAL METEOSENSITIVITY

M. I. Yabluchanskiy, O. Y. Bychkova, N. V. Lysenko, N. V. Makienko, L. O. Martimyanova, A. M. Yabluchanskiy
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This paper is dedicated to the problem of physiological and pathological meteosensitivity (meteodependency or meteopathy).We introduce and discuss the definition for individual meteodependency, define factors, mechanisms, clinical signs, diagnosis, and approaches to prophylaxy and treatment of individual pathological meteosensitivity.

KEY WORDS: weather, meteosensitivity**,** meteopathy**,** diagnosis**,** therapy

ВІД ФІЗІОЛОГІЧНОЇ ДО ХВОРОБЛИВОЇ МЕТЕОЧУТЛИВОСТІ

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Розглядається проблема фізіологічної і хворобливої метечутливості (метеозалежності або метеопатії). Розглядається індивідуальна хвороблива метеочутливість або метеопатія. Визначаються фактори, механізми розвитку, клінічні детермінанти, діагноз і підходи до профілактики та лікування індивідуальної хворобливої метеочутливості**.**

КЛЮЧОВІ СЛОВА: погода, метеочутливість, метеозалежність, діагноз, терапія

ОТ ФИЗИОЛОГИЧЕСКОЙ ДО БОЛЕЗНЕННОЙ МЕТЕОЧУВСТВИТЕЛЬНОСТИ

Н. И. Яблучанский, О. Ю. Бычкова, Н. В. Лысенко, Н. В. Макиенко, Л. А. Мартимьянова, А. Н. Яблучанский
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Излагается проблема физиологической и болезненной метечувствительности (метеозависимости или метеопатии). Рассматривается индивидуальная болезненная метеочувствительность или метеопатия. Определяются факторы, механизмы развития, клинические детерминанты, диагноз и подходы к профилактике и лечению индивидуальной болезненной метеочувствительности.

КЛЮЧЕВЫЕ СЛОВА: погода, метеочувствительность, метеозависимость, диагноз**,** терапия

The problem of meteosensitivity is new and old at the same time. It goes back to the times of Hippocrates [1]. The scientific development, however, began only in the last century, primarily in the Slavic world after the work by Chizhevsky A. «The Terrestrial Echo of Solar Storms» has been published [2]. The Western world did not pay much attention to the problem of meteosensitivity at that time, as evidenced from such manuscripts as «Oxford Companion to the Body» [3].

Meteosensitivity can be physiological and pathological. The latest, pathological meteosensitivity is also known as meteo-dependency, or meteopathy [4].

Today everything has changed and the problem of meteosensitivity, both physio-logical and Patho-logical, became very important. This became possible due to a scien-tific awareness of the direct impact of meteosensitivity on the human being and his health, which results from Earth climate and space climate changes, from space and Earth

local weather [4].The problem is exacerbated during radical climate change, and develops as a result of reckless activities of humans that put the life on Earth at the brink of survival [5]. Meteopathy is transformed from an individual to a social problem, involving larger scope of people on the continental and planetary level [4].

If social meteosensitivity is a political feature, individual meteosensitivity is a problem for everybody who is dealing with human's health, mainly for medical practitioners.

The human being is continuously connected to the nature and the reactions of his organism to the climate and weather changes thus are purely natural. These reactions are named as meteosensitivity and are realized through the adaptation to the factors of climate change.

An interface of the human's organism with weather factors is implemented in sensory system located in the skin (temperature, humidity, wind, solar activity, atmosphere electricity, radioactivity), the lungs (temperature, air purity and ionization, humidity, wind), the organs of vision, hearing, tactile and taste sensitivity (light, noise, smell, air temperature and chemical composition), etc.

In healthy human the adaptation to natural changes in climate and weather factors is physiological, and is not accompanied with deterioration of health. These conditions are termed as comfort zone.

When the health is compromised, meteo-sensitivity becomes pathological and is manifested in the deterioration of mental and/or physical health. The lesser the health resources, the more painful it is. The most susceptible to meteopathic reactions are elder people with chronic diseases. Weather change is associated with an increase in the frequency of depressive reactions, hypertensive crisis, acute coronary and cerebral events, an increase in the frequency of post-surgical complications, as well as with an increase in the frequency of anthropogenic events and catastrophes [4, 6-8].

In the economically developed countries about 38% of healthy men and 52% of healthy women show signs of compromised meteosensitivity, or in other words these people are meteopats [4].

Physiological or pathophysiological meteo-sensitivity to a large extent depends on the biological rhythms of the person, the quality and the degree of their synchronization with astronomical natural rhythms.

In healthy person the biological rhythms are physiological, and are synchronized with natural. In the pathological conditions, the rhythms are not just disturbed, but also desynchronized with natural rhythms. Pathological conditions result in the development of new additional rhythms, such as chronic disease with acute events, so called remission cycles [4, 8-10].

Biological rhythms are extremely stable, however, they are not unbreakable. Being tightly connected to external (natural) synchronizers, biological rhythms possess a spectra of stable conditions, and during the frequent change of synchronizers these rhythms transfer from one stage to another, in other words, trasnfer from one stable condition to another. This transition is realized via so called transitional processes. For daily or circadian rhythms, the duration of transitional processes could potentially take from 5 to 40 days.

The highest rate of disturbances in biological rhythms (desynchronizes) occurs during the transitional processes. Desynchronizers in many cases are a manifest-tation of clinical syndromes of many diseases. Make your conclusions yourselves [4].

The very first factor of meteopathy is a genetically determined constitutional characteristic of the human organism. Although it is impossible to avoid genetical heredity, prophylactic measures can narrow down their channel and provide an option for safer navigation between «whims of weather».

Meteopathy is a fate for «weaker» sex. Females react stronger to the weather changes. The reason for this is speculated to be found in the hormonal background; however, it is not narrowed to only one this feature.

Among the most meteodependent are children, in which it is pronounced until the regulatory and adaptation systems have not finished their development. The minimal meteodependency is observed from 14 to 20 years of age, and is further exacerbated. At the age of 50, the half of the Earth population establishes permanent meteodependency due to a decrease in the adaptation and an increase in comorbidities.

Habitants of big cities are more prone to meteopathic reactions comparing to smaller

cities populations and villagers. The main reason is found in the severe ecological environment, in the overload of air with heavy ions, shortening of the day light time, a decrease in the ultraviolet intensity, and a strong effect of technogenic, social and mental factors on the development of chronic distress. The further human is from the Nature, the stronger meteopathic reactions are.

Additional features that contribute to meteopathy include obesity; hormonal changes during puberty, pregnancy, and climax; mental state; cardiovascular diseases; trauma; acute respiratory viral and bacterial infections; a decrease in social-economic and ecological environment; etc.

Meteopathy can be recognized with foreboding the weather change and associated deterioration of health:

- decrease in physical activity,
- development of depressive states,
- discomfort (including pain) in different organs and systems,
- absence of other possible reasons for such a decrease in the wellbeing,
- an exacerbation of current disease,
- recurrence of such manifestation during change of climate and weather,
- a rapid improvement during a positive change in climate and weather.

International disease classification (IDC 10) does not have a section for meteopathy, and it is attributed to special (disadaptive) organism reactions to stress: F43.0 – Acute stress reaction and F43.2 – Adjustment disorders [11].

Meteopathy diagnosis is based on the identification of severe meteodependency in the patient and his relatives in the past, with a dynamic follow-up of his condition in the present time, and with an evaluation of the dependency from the climate and weather changes.

Preventive measures for meteopathy include healthy life style (appropriate rest, physical exercise, contrast temperatures, eating habits, and physiotherapeutic procedures if needed); tracking the weather change with an appropriate prophylactic measures; introducing the pharma-cological therapeutic measures according to the patient's state, resources, and comorbidities.

There are three types of preventive measures for meteopathy – one-time, routine, and seasonal. One-time measure is applied to people with meteodependency without chronic somatic pathology and is introduced 1-2 days prior to weather change. Routine measures are attributed to meteodependent people with chronic somatic pathologies, and start 1-2 days prior to and continue 3-5 days after the weather change. Seasonal measures are applied to meteodependent people with chronic somatic pathologies during transitional seasons and according to their physical state, weather, and reactions to weather change.

One reason for the low efficiency of the treatment of chronic diseases is underestimation of the significance of meteopathic reactions of the patient.

Pathological meteosensitivity is accompanied with a distress in the neural system, renin-angiotensin-aldosterone system, cytokine and other regulatory systems. Hence, depending on the patient's state, therapeutic approach to meteopathy can also include the use of potassium channel blockers, beta-adrenergic receptor blockers, blockers of angiotensin receptors, etc.

Physician is treating not the disease, but the patient, and the effectiveness is in many cases determined by solving the problems associated with a compromised meteosensitivity or meteopathy.

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Clinical researches

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SENSITIVITY TO ANTIBIOTICS AMONG STRAINS OF SALMONELLA CURRENT, WHICH CIRCULATES IN THE PAST 10 YEARS IN UKRAINE

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In this article the main results of the sensitivity to antibiotics on S. Typhimurium, S. strains of Salmonella Enteritidis and rare groups that circulate in Ukraine last 10 years were described. The unifying disc-fusion method determined the sensitivity of Salmonella strains to several antibiotics. Resistance to antibiotics of strains of Salmonella was caused by the lack of effective influence of drugs on salmonellosis. The obtained results revealed antibiotics with a strong antimicrobial action and a narrow focus on strains of Salmonella.

KEY WORDS: salmonellosis, S. Typhimurium, S. Enteritidis, rare Salmonella strains, antibiotics

ЧУТЛИВІСТЬ ДО АНТИБІОТИКІВ СЕРЕД АКТУАЛЬНИХ ШТАМІВ САЛЬМОНЕЛ, ЩО ЦИРКУЛЮЮТЬ НА ТЕРИТОРІЇ УКРАЇНИ ОСТАННІ 10 РОКІВ

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У статті визначені основні результати дослідження на чутливість до антибіотиків щодо S. Typhimurium, S. enteritidis та штамів сальмонел рідких груп, що циркулюють на території України останні 10 років. За уніфікованим дискодифузійним методом була визначена чутливість штамів сальмонел до ряду антибіотиків. Резистентність штамів сальмонели до антибіотиків була викликана відсутністю ефективного впливу ліків на сальмонельоз. Отримані результати дозволили виявити антибіотики з вираженою протимікробною дією і вузькою спрямованістю на штами сальмонели.

КЛЮЧОВІ СЛОВА: сальмонельоз, S. Typhimurium, S. Enteritidis, штами сальмонел рідких груп, антибіотики

ЧУВСТВИТЕЛЬНОСТЬ К АНТИБИОТИКАМ СРЕДИ АКТУАЛЬНЫХ ШТАММОВ САЛЬМОНЕЛЛ, ЦИРКУЛИРУЮЩИХ НА ТЕРРИТОРИИ УКРАИНЫ ПОСЛЕДНИЕ 10 ЛЕТ

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В статье определены основные результаты исследования на чувствительность к антибиотикам по S. Typhimurium, S. Enteritidis и штаммов сальмонелл редких групп, циркулирующих на территории Украины последние 10 лет. Унифицированным дискодифузийним методом была определена чувствительность штаммов сальмонелл к ряду антибиотиков. Резистентность штаммов сальмонеллы к антибиотикам была вызвана отсутствием эффективного воздействия лекарств на сальмонеллез. Полученные результаты позволили выявить антибиотики с выраженной противомикробным действием и узкой направленностью на штаммы сальмонеллы.

КЛЮЧЕВЫЕ СЛОВА: сальмонеллез, S. Typhimurium, S. Enteritidis, штаммы сальмонелл редких групп, антибиотики

INTRODUCTION

The frequency of infections caused by antibiotic-resistant bacteria increases among the population of the world [1-3], causing these infections are becoming animportant health-care problem [4-6]. Incorrect use of antibiotics is developing resistance to these drugs [7-9].

Application of antibiotics in farm animals allows persistent bacteria and genes of resistance be transferred through the food chain from animals to humans [10-13]. The failured treatment leads to a rise in the mortality rate, as well as to the necessity to develop new antibiotics [14-16].

RELEVANCE

At present the problem of sensitivity to antibiotics diseases is relevant to public health: each year in the European Union, more than 25,000 people die from infections caused by resistant bacteria [17, 18]. The use of antibiotics has led to the formation and spread of resistance to these drugs, which are associated with a decrease in the effectiveness of treatment and, therefore, more difficult and long duration of disease, increased frequency of hospitalization, increase the number of deaths and an increase in economic losses to society [19-21]. Microbial resistance to antibacterial agents is characterized by retention of their ability to multiply in the presence of concentrations of these substances which are administered at therapeutic doses [22-24].

The problem of stability of Salmonella to antibiotics was exacerbated in 1972, when many countries have experienced outbreaks of infections caused by S. typhi, resistant to chloramphenicol, sulfonamide, tetracycline and streptomycin, whereas ampicillin and cotrimoxazole retain activity.

After twenty years, most of the strains were resistant and so microbial agents, wherein the allocation of multidrug resistant S. typhi has become commonplace [25-27].

According to WHO, the use of fluoroquinolones in animal's food has led to the emergence of an appropriate antibiotic resistance of Campylobacter in Salmonella that cause infectious disease in humans. In diseases, caused by multi-drug resistant strains of Salmonella Typhimurium phage type specific (DT) 104 resistance to quinolones, observed treatment failure, a higher rate of hospitalization and higher risk of death [28].

Thus, resistance to antibiotics in infections has become a growing international public health problem that requires urgent attention [29-31].

The aim is to determine the sensitivity to antibiotics of current Salmonella strains circulating in Ukraine last 10 years.

MATERIALS AND METHODS

To investigate the biological properties of Salmonella used 136 strains during the period 1996-2012 years, obtained from the Museum of pathogenic microbial organism «L.V. Gromashevskiy Institute of Epidemiology and Infectious Diseases of Academy of Medical Sciences of Ukraine».

Of the 62 strains of Salmonella period 1996-2006, 24 (38 %) belonged to S. typhimurium, 38 (62 %) - to S. enteritidis, with 57 of museum culture period 2006-2012 7 (12 %) belonged to S. typhimurium, 50 (88 %) - to S. enteritidis, also for better comparison Sal-monella sampling of rare groups was formed which were isolated from the external environment in the S. java - 7 strains, S. derby - 1 strain, S. colorado - 1 strain, S. infantis - 1 strain, S. blegdam - 2 strain, S. montevideo - 1 strain, S. senftenberg -1 strain of S. haifa - 2 strain.

The study of antibiotic sensitivity was performed using a standardized Kirby Bauer Disk Diffusion Method. Getting results of diffusion in Mueller-Hinton agar was performed using paper discs and a special measuring stick that served to account for the fields of growth retardation [32]. The results are interpreted on the basis of criteria of CLSI (2010) growth inhibition zone diameter in millimeters of culture (tab. 1) and the disc manufacturer.

Depending on the diameter of growth inhibition zones around the disks were classified as resistant strains (resistant), moderately sensitive and stable. Strain of E. Coli ATCC 25922 was used as a reference and for the control; it was obtained from the Museum of pathogenic microbial organism SI «L.V. Gromashevskiy Institute of Epidemiology and Infectious Diseases of Academy of Medical Sciences of Ukraine».

Received results were treated by quantitative methods of mathematical statistics including standard deviation of sample values (M) and the mean error (m). The significance

Table 1

Standard interpretation of the results (limiting values of diameters of zones of growth delay)

Antibiotic name	Content antibiotic in disk, mcg	The diameters of zones of growth inhibition, mm		
		stable	moderately resistant	sensitive
Ampicillin	10	13	14-16	17
Gentamicin	10	12	13-14	15
Kanamycin	30	13	14-17	18
Co-trimoxazole	1,25/23,75	10	11-15	16
Nitrofurantoin	300	14	15	17
Polymyxin-B	300	11	-	12
Streptomycin	10	11	12-14	15
Sulfamethizole	300	11	12-14	15
Tetracycline	30	14	15-18	19
Ticarcillin	75	14	15-19	20
Chloramphenicol	30	12	13-17	18
Cefazolin	30	14	15-17	18
Cefoxitin	30	14	15-17	18
Cefotaxime	30	14	15-22	23
Ceftriaxone	30	13	14-20	21
Cefuroxime	30	14	15-17	18
Ciprofloxacin	5	15	16-20	21

of differences was determined using indicators Student t-test, which is defined by a table of critical points of distribution. The correlation coefficient was considered with the error probability $p < 0.05$, which was determined by comparison with the critical value from the table depending on the size of the study group, the correlation coefficients and the likelihood of errors. The data were processed using a personal computer and software for processing and analysis of statistical information «Excel 2003», included in the package «Microsoft Office 2003».

RESULTS AND DISCUSSION

Evaluation of the distribution of sensitivity to antibiotics showed that in 1996-2005, strains of S. Typhimurium were highly sensitive to polymyxin-B (100 %), cefoxitin (87,5 %), ciprofloxacin (83,33 %), cefotaxime and gentamicin (at 70,83 %), cefazolin (66,67 %), and ampicillin cefotaxime (by 62,5 %), nitrofurantoin and streptomycin (58,33 %). The most resistant strains were to sulfamethizole (83,33 %), cotrimoxazole (75,0 %), kanamycin (58,33 %), tetracycline (50,0 %).

The results of sensitivity to antibiotic resistant strains of S. Typhimurium 2006-2012 years showed significantly decreased sensitivity of cefoxitin and ceftriaxone, respectively, 73,21 and 42,26 %, tetracycline - by 31,54 %. It should be noted that strains of S. Typhimurium remained absolute sensitivity (100 %) to polymyxin-B during the whole investigated period – 1996–2012. It was found that a semisynthetic broad-spectrum penicillin - ampicillin increased its activity on 23,21 %, with a simultaneous decrease of the same level of stability during the study during the period from 1996-2005, 2006-2012 years. Among the newest synthetic antibiotic quinolones ciprofloxacin stands, the sensitivity of which was in 1996-2005, 83.33 %, and in 2006-2012 declined slightly - by 11.9 %.

Summarizing the results for the group of cephalosporins, it should be noted that almost all the members of this class, except cefazolin, lowered resistance at 2005-2012 with 1996-2005 years moderately resistant (tab. 2).

The obtained result of the distribution of sensitivity to antibiotics revealed that in 1996-2005 strains of S. Enteritidis were 100 % sensitive to polymyxin-B throughout the study from 1996 to 2012. High sensitivity was found in ampicillin (94,74 %). In 1996-2005, strains of S. enteritidis in the majority had a high

Table 2

Resistance to antibiotics of S. typhimurium strains

Antibiotic name	Distribution of sensitivity to antibiotics (M ± m), %					
	Strains 1996-2005 years (n = 24)			Strains 2006-2012 years (n = 7)		
	stable	moderately	sensitive	stable	moderately resistant	sensitive
Ampicillin	37,50 ± 9,88	0	62,50 ± 9,88	14,29 ± 13,23	0	85,71 ± 13,23
Gentamicin	4,17 ± 4,08	25,00 ± 8,84	70,83 ± 9,28	0	42,86 ± 18,70	57,14 ± 18,70
Kanamycin	58,33 ± 10,06	8,33 ± 5,64	33,33 ± 9,62	28,57 ± 17,07	0	71,43 ± 17,07
Co-trimoxazole	75,00 ± 8,84***	0	25,00 ± 8,84*	28,57 ± 17,07***	0	71,43 ± 17,07*
Nitrofurantoin	12,50 ± 6,75	29,17 ± 9,28	58,33 ± 10,06	28,57 ± 17,07	14,29 ± 13,23	57,14 ± 18,70
Polymyxin-B	0	0	100	0	0	100
Streptomycin	16,67 ± 7,61	25,00 ± 8,84	58,33 ± 10,06	14,29 ± 13,23	28,57 ± 17,07	57,14 ± 18,70
Sulfamethizole	83,33 ± 7,61***	0	16,67 ± 7,61*	28,57 ± 17,07***	0	71,43 ± 17,07*
Tetracycline	50,00 ± 10,21***	4,17 ± 4,08**	45,83 ± 10,17	14,29 ± 13,23***	71,43 ± 17,07**	14,29 ± 13,23
Ticarcillin	41,67 ± 10,06	37,50 ± 9,88	20,83 ± 8,29	14,29 ± 13,23	42,86 ± 18,70	42,86 ± 18,70
Chloramphenicol	37,50± 9,88	8,33 ± 5,64	54,17 ± 10,17	14,29 ± 13,23	0	85,71 ± 13,23
Cefazolin	12,50 ± 6,75	20,83 ± 8,29**	66,67 ± 9,62	14,29 ± 13,23	0	85,71 ± 13,23
Cefoxitin	0	12,50 ± 6,75**	87,50 ± 6,75*	0	85,71 ± 13,23**	14,29 ± 13,23*
Cefotaxime	12,50 ± 6,75	16,67 ± 7,61**	70,83 ± 9,28*	14,29 ± 13,23	57,14 ± 18,70**	28,57 ± 17,07*
Ceftriaxone	20,83 ± 8,29	16,67 ± 7,61	62,50 ± 9,88	14,29 ± 13,23	28,57 ± 17,07	57,14 ± 18,70
Cefuroxime	29,17 ± 9,28	37,50 ± 9,88	33,33 ± 9,62	14,29 ± 13,23	71,43 ± 17,07	14,29 ± 13,23
Ciprofloxacin	0	16,67 ± 7,61	83,33 ± 7,61	0	28,57 ± 17,07	71,43 ± 17,07

Note:
* - the difference in the percentage of resistant strains is likely,
** - the difference in the percentage of resistant strains conditionally probable,
*** - the difference in the percentage of susceptible strains is likely

sensitivity to the representatives of the cephalosporin group: ciprofloxacin – 94,74 %, cefoxitin – 89,47 %, cefotaxime – 78,95 %, ceftriaxone – 73,68 %, cefazolin – 68,42 %. The less sensitivity strains to cefuroxime (50,0 %) had. Low sensitivity, also, was noted in the combined antibiotic co-trimoxazole (52,63 %). High sensitivity was observed in a number of aminoglycosides - gentamicin (84,21 %), kanamycin (78,95 %), streptomycin (94,74 %). Different sensitivity was noted in the representatives of penicillin: in ampicillin – 94,74 % and ticarcillin – 39,47 %. The results of the period 2006-2012 years showed that from 18 tested antibiotics, strains S. enteritidis increased 100 % susceptibility to 11 antibiotics. Special attention deserves a slight increase in sensitivity to the cephalosporin group of strains (tab. 3). Sensitivity of the antibiotic-resistant strains of Salmonella rare groups compared with S. enteritidis 2006-2012 showed that 100 % of the sensitivity of the strains had 61,11 % of the investigated antibiotics. The most sensitive antibiotics for the period 1996-2012 years were: ampicillin, aminoglycosides (gentamicin, kanamycin, streptomycin), combined antibiotics (cotrimoxazole, polymyxin-B),

a synthetic broad-spectrum antibiotic - chloramphenicol, an antibiotic synthesized new quinolones - ciprofloxacin. Cefazolin had the absolute sensitivity from the number of cephalosporins (tab. 4).

Table 3

Resistance to antibiotics of S. Enteritidis strains

Antibiotic name	Distribution of sensitivity to antibiotics (M ± m), %					
	Strains 1996-2005 years (n = 24)			Strains 2006-2012 years (n = 7)		
	stable	moderately resistant	sensitive	stable	moderately resistant	sensitive
Ampicillin	0	5,26 ± 3,62	94,74 ± 3,62	0	0	100,00
Gentamicin	0	15,79 ± 5,92**	84,21 ± 5,92***	0	0**	100,00***
Kanamycin	10,53 ± 4,98*	10,53 ± 4,98**	78,95 ± 6,61***	0*	0**	100,00***
Co-trimoxazole	39,47 ± 7,93*	7,89 ± 4,37	52,63 ± 8,10***	0*	0	100,00***
Nitrofurantoin	0*	21,05 ± 6,61**	78,95 ± 6,61***	10,00 ± 4,87*	44,00 ± 8,05**	46,00 ± 8,09***
Polymyxin-B	0	0	100,00	0	0	100,00
Streptomycin	0	5,26 ± 3,62	94,74 ± 3,62	0	0	100,00
Sulfamethizole	55,26 ± 8,07*	2,63 ± 2,60	42,11 ± 8,01***	0*	0	100,00***
Tetracycline	2,63 ± 2,60	28,95 ± 7,36**	68,42 ± 7,54***	0	54,00 ± 8,09**	46,00 ± 8,09***
Ticarcillin	2,63 ± 2,60	57,89 ± 8,01	39,47 ± 7,93	0	46,00 ± 8,09	54,00 ± 8,09
Chloramphenicol	7,89 ± 4,37	15,79 ± 5,92**	76,32 ± 6,90***	0	0**	100,00***
Cefazolin	10,53 ± 4,98*	21,05 ± 6,61**	68,42 ± 7,54***	0*	0**	100,00***
Cefoxitin	0	10,53 ± 4,98	89,47 ± 4,98	0	22,00 ± 6,72	78,00 ± 6,72
Cefotaxime	0	21,05 ± 6,61	78,95 ± 6,61	0	16,00 ± 5,95	84,00 ± 5,95
Ceftriaxone	5,26 ± 3,62	21,05 ± 6,61	73,68 ± 7,14***	0	8,00 ± 4,40	92,00 ± 4,40***
Cefuroxime	13,16 ± 5,48*	36,84 ± 7,83	50,00 ± 8,11	0*	44,00 ± 8,05	56,00 ± 8,05
Ciprofloxacin	5,26 ± 3,62	0	94,74 ± 3,62	0	0	100,00

Note:
* - the difference in the percentage of resistant strains is likely,
** - the difference in the percentage of resistant strains conditionally probable,
*** - the difference in the percentage of susceptible strains is likely

For the treatment of Salmonella strains of S. typhimurium chloramphenicol, cotrimo-xazole, and - ticarcillin, ampicillin, amino-glycosides, cefazolin, kanamycin, sulfame-thizole are the broad-spectrum antibiotics. The resistant strains of S. typhimurium resistant to cephalosporins II and III generation, which are representatives of penicillin antibiotics group, can prevent that these strains produce betalactamase extended spectrum that can lead to future failure treating such patients by penicillins, cephalosporins I-IV and other generations of antibacterial drugs.

In this noteworthy that strains of S. typhimurium and S. enteritidis are mostly sensitive to cephalosporins, quinolones, fluoroquinolone and polymyxin. The drug nitrofuran series (nitrofurantoin), penicillin (tetracycline, ticarcillin) and cephalosporin antibiotic II generation - cefuroxime lost their effectiveness against S. typhimurium, S. enteritidis and Salmonella strains of rare groups. In most cases, antibiotic sensitivity was higher in rare strains of groups.

A characteristic feature of the use of antibiotics in patients with salmonellosis is that during the study period 1996-2005, regardless

of the type strain, the only 100% efficiency has been achieved in the treatment of polymyxin B, due, apparently, to its specific mechanism of influence on the integrity of the cytoplasmic membrane of microbial cells and its high toxicity to it.

Table 4

Antibiotic susceptibility of Salmonella strains of rare groups

Antibiotic name	Distribution of sensitivity to antibiotics (M ± m), %					
	Strains 1996-2005 years (n = 17)			Strains 2006-2012 years (n = 50)		
	stable	moderately resistant	sensitive	stable	moderately resistant	sensitive
Ampicillin	0	0	100,00	0	0	100,00
Gentamicin	0	0	100,00	0	0	100,00
Kanamycin	0	17,65 ± 9,25	82,35 ± 9,25	0	0	100,00
Co-trimoxazole	0	0	100,00	0	0	100,00
Nitrofurantoin	52,94 ± 12,11	11,76 ± 7,81	35,29 ± 11,59	10,00 ± 4,87	44,00 ± 8,05	46,00 ± 8,09
Polymyxin-B	0	0	100,00	0	0	100,00
Streptomycin	0	0	100,00	0	0	100,00
Sulfamethizole	0	0	100,00	0	0	100,00
Tetracycline	52,94 ± 12,11	47,06 ± 12,11	0	0	54,00 ± 8,09	46,00 ± 8,09
Ticarcillin	17,65 ± 9,25	35,29 ± 11,59	47,06 ± 12,11	0	46,00 ± 8,09	54,00 ± 8,09
Chloramphenicol	0	0	100,00	0	0	100,00
Cefazolin	0	0	100,00	0	0	100,00
Cefoxitin	0	29,41 ± 11,05	70,59 ± 11,05	0	22,00 ± 6,72	78,00 ± 6,72
Cefotaxime	0	17,65 ± 9,25	82,35 ± 9,25	0	16,005,95	84,00 ± 5,95
Ceftriaxone	0	0	100,00	0	8,00 ± 4,40	92,00 ± 4,40
Cefuroxime	0	52,94 ± 12,11	47,06 ± 12,11	0	44,00 ± 8,05	56,00 ± 8,05
Ciprofloxacin	0	0	100,00	0	0	100,00

CONCLUSIONS

The problem of rational use of antibiotics in the treatment of salmonellosis is among the most urgent in medicine. Strains of S. typhimurium, S. enteritidis react to cephalosporins, quinolones, fluoroquinolones. Nitrofurans, most penicillins and cefuroxime reduced their activity against S. typhimurium, S. enteritidis and Salmonella strains of rare groups. Strains of rare groups were more susceptible to antibiotics. The only current effective drug in all tested strains of Salmonella was polymyxin B.

The increase in resistance of Salmonella strains against a background of resistance to the formation of new genes produced by the microbial cells that neutralize the effect of antibiotics on their cell system. The development of resistant strains of microorganisms greatly reduces the effectiveness of antibiotic therapy.

PERSPECTIVES OF FURTHER INVESTIGAT

The development of resistance strains of Salmonella bacteria is a natural reaction, which can be controlled through the proper use of antibiotics. Advanced developments overcome resistance to antibiotics salmonellosis is to introduce the practice of rational antibiotic regimens, obtaining new types of antibiotics on the basis of known, the use of antibiotics with different mechanisms of action. For the final

solution of this problem it is expedient further research aimed at clarifying the strengths of a number of modern antibiotics against different strains of salmonella in the current economic and social terms.

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MODERN DIRECTIONS OF HERPESVIRUS INFECTIONS PHARMACOTHERAPY

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The article presents the data on the etiology, pathogenesis, clinical course, features of an immune response to human herpesvirus infections. Modern approaches to the causal treatment and principles of treatment phasing in these patients category are discussed.

KEY WORDS: Herpesvirus infection, etiology, clinical manifestations, immune response, therapy

СУЧАСНІ НАПРЯМКИ МЕДИКАМЕНТОЗНОЇ ТЕРАПІЇ ГЕРПЕСВІРУСНИХ ІНФЕКЦІЙ

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У статті представлені дані щодо етіології, патогенезу, клінічного перебігу, особливостей імунної відповіді на герпесвірусні інфекції людини. Розглянуто сучасні підходи до етіотропної терапії та принципи етапності лікування у даної категорії хворих.

КЛЮЧОВІ СЛОВА: герпесвірусна інфекція, етіологія, клінічні прояви, імунна відповідь, терапія

СОВРЕМЕННЫЕ НАПРАВЛЕНИЯ МЕДИКАМЕНТОЗНОЙ ТЕРАПИИ ГЕРПЕСВИРУСНЫХ ИНФЕКЦИЙ

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В статье представлены данные об этиологии, патогенезе, клиническом течении, особенностях иммунного ответа на герпесвирусные инфекции человека. Рассмотрены современные подходы к этиотропной терапии и принципы этапности лечения у данной категории больных.

КЛЮЧЕВЫЕ СЛОВА: герпесвирусная инфекция, этиология, клинические проявления, иммунный ответ, терапия

Current importance of herpesvirus infections (HVI) is stipulated for practically universal spreading, availability of wide spectrum of clinical manifestations and high degree of contagiousness, duration and hard consequences in case of complicated forms of the disease as well as significant material coasts on antivirus and pathogenic therapy. This category of infection is the sphere of clinical medicine being on the joint of interests of various specialties physicians: infectionists, neuropathologists, dermatovenerologists, therapeutists, gynecologists, immunologists, ophthalmologists, dentists, hematologists, oncologists. According to the data of WHO mortality as the result of diseases, stipulated for herpesvirus infection in the structure of infection pathology takes the second place after grippe [1, 2, 3].

Steady growth of HVI both in adults and in infants, high perinatal losses and birth of children with hard drain deprivations, deprivations of parenchyma organs and lungs stipulate for necessity of thorough study of HVI and elaboration of prophylaxis and treatment effective methods [1, 2, 3].

Course of HVI is often asymptomatic, which is the evidence of virus replication active control possibility outside the host immune system in spite of multiple ways of its deviation from immune response. Though further HVI can occur as recurrent or chronic with clinics specific for each virus and even be accompanied by threatening life conditions. In general both generalized form of the disease or absolute lack of clinic manifestations are most characteristic features for the whole group of herpesviruses. Among life-threatening states inflammatory CNS diseases take a special

place and particularly demyelinating encephalomyelitis which can be caused by viruses of the herpes group - CMV, HSV, EBV. Deviations in the system of virus-host interconnection stipulated for individual congenital peculiarities of host defense reactions are in the basis of unfavorable course of persistent HVI [4, 5].

Universal spreading of herpesviruses is connected with their universality, unique abilities to transform into latent state, integrate into host genome taking a qualitatively new form. Herpesviruses can migrate along the organism implicating various organs and systems into infection process and causing both light and deadly dangerous diseases with various symptomatologies [4, 6].

More than 100 representatives of herpesvirus family *(Herpesviridae)* are known by now, 8 of which are pathogenic for people. All 8 types are represented by DNC-containing viruses with unique morphology which is not differentiated by electronic microscopy. HVI pathogenesis is interconnected with clinics and epidemiology (tab. 1). Getting into the human organism herpes simplex virus (HSV) lifelong persists in it causing periodic relapses of various severities [5, 6].

Table 1

Types of herpes viruses

Name	Abbreviation (English)	Synonym	Most prominent clinical manifestation
Herpes simplex Type 1	HSV-1, HHV-1 (α-Herpesviridae)	Simple herpes, Bidwill zoster	Oral-facial deprivation, aphthous-ulcerous stomatitis, labial herpes, herpetic dermatitis, herpetiform eczema, keratitis, conjunctivitis,
Herpes simplex Type 2	HSV-2, HHV-2 (α-Herpesviridae)	Herpes genitalis	Genital mucosal deprivation, meningitis
Varicella Zoster virus, Human herpes virus Type 3	VZV, HZV, HHV-3 (α-Herpesviridae)	Herpes Zoster	Pox, shingles deprivation along sensitive nerve endings, pre- and perinatal infection
Epstein-Barr virus, Human herpes virus Type 4	EBV, HHV-4 (γ-Herpesviridae)	Virus of infection monomucleosis	Infection monomucleosis, Berkitt limphoma, nasopharyngeal carcinoma, lymphoepithelioma of salivary gland (thymoma), hepatitis
Cytomegalovirus, Human herpes virus Type 5	CMV, HHV-5 (β-Herpesviridae)	Cytomegalo-virus	Pre- и perinatal infection, teratogenic effect, immunodeficite, lever, kidneys, lungs, eyes, lymphatic nets, CNS deprivation. Inclination to infection generalization
Human herpes virus Type 6	HHV-6 (β-Herpesviridae)	Human B lymphotropic virus	Abrupt exanthesis of infants, monolucleosis-like syndrome, syndrome of chronic defatigation, encephalomyelitis, co-factor of VID- infection, oral and cervical carcinoma
Human herpes virus Type 7	HHV-7 (β-Herpesviridae)		Abrupt eczema of infants, syndrome of chronic defatigation
Kaposi's sarcoma associated herpesvirus, Human herpes virus Type 8	KSHV, HHV-8 (γ-Herpesviridae)	Human B lymphotropic virus	Kaposi's sarcoma, initial disseminated lymphoma

Distinctive feature of persistent virus infections essentially predicamenting antivirus chemical therapy conduction is an availability of latent form in them, i.e. virus, being incorporated in cell chromosomes is not only preserved for a long time but is also transformed into filial cells. Besides decrease of specific and non-specific factors of immune reactivity and sensibilization of the organism are marked in persisting virus infections. That is why the treatment of persistent virus infections accompanied by immune system

deprivation remains of current importance and demands complex approach – due consideration of both etiological factor and pathogenic peculiarities of the whole organism [1, 4].

Despite variability of remedies used for HVI treatment there are no medical preparations providing full treatment from herpes. This infection is considered a hardly controlled disease which is connected, first of all, with the variety of clinical deprivations, development of virus resistance to medications, existence of molecular mimicry in herpesviruses. That is why it is necessary to choose adequate antivirus preparation for successful treatment of HVI, its doze and duration of treatment, use the combination of various remedies. It is also necessary to include immune biological preparations into the therapy schemes which promote correction of immune status as well as pathogenic remedies improving the patient condition [5, 7].

Only patients with manifest forms of HVI are subjected to treatment. The question about reasonability of the treatment prescription moreover in clinics is defined by many factors, namely, clinical form of the disease, severity course, household conditions and character of work of a sick person. In cases when hospitalization is necessary (generalized herpes, severe herpetic gingivostomatitis or vaginal herpes) patients should be put into separate hospital ward, considering easiness of infection spreading [8, 9].

ETIOTROPIC THERAPY

At present main antivirus preparations used for various forms of HVI treatment are *aciclovir, valaciclovir, famciclovir* (tab. 2).

These remedies mechanism of activity is connected with virus DNA synthesis suppression and viruses replication by the way of competitor inhibition of virus DNA-polymerase.

Two ways of antivirus chemical preparations use are defined: episodic prescription (under HVI exacerbation if necessary) and suppressive or preventive therapy. In the first case preparation is prescribed in a short course of treatment (5-10 days), in the second – every day receiving of the preparation for some months, sometimes even years calls rate not as much cut short the relapse as prevent the development of the relapses in general. It is necessary to remember that etiotropic therapy efficacy will be maximal when the treatment is prescribed in the harbinger period or initial manifestations (in prodromal period) of the disease, during first 48 hours of virus reactivation [7, 9, 10, 11, 12].

Table 2

Antiherpetic remedies

Remedy name	Indications	Usage and dozing
Chemical preparations (abnormal nucleosides)		
Aciclovir (zovirax, heviran)	Herpetic deprivations of skin and mucosa caused by HSV, HSV relapse prophylaxis	Internally, in HSV –200 mg 5 times a day for 5-10 days; in relapse – during 5 days
Vilaciclovir (valtrex, valavir)	Herpetic deprivations of skin and mucosa caused by HSV, HSV relapse prophylaxis, infection mononucleosis	Internally, in shingles herpes –1000 mg 3 times a day (7 days), in HSV –500 mg 2 times a day; in relapse –5 days course
Penciclovir (vectavir)	Herpetic vesicular lips dermatitis	Externally. Adults and infants older than 16 years old – apply on rash every 2 hours in the daytime for 4 days
Famciclovir (famvir)	Acute and relapsing infections caused by Herpes zoster, Herpes simplex I and II	In first appeared HSV-1, HSV-2 or relapse – 250 mg 3 times a day for 5 days, for treatment of repeat episode of relapse herpes–125 mg 2 times a day for 5 days; long suppressive therapy for clinically distinct and latent relapses of herpes infection prophylaxis –250 mg 2 times a day

New and perspective antiherpetic chemical preparations are cidofovir and brivudin. These remedies have higher efficacy in comparison with aciclovir and ganciclovir, though are worse endured which limits their wide clinical use. They should be used in severe life-threatening forms of herpesvirus infections in condition of known and expected resistance to aciclovir and ganciclovir [12, 13, 16].

Antiherpetic preparations comprise about 80% of all existing antivirus preparations. Antivirus preparation existing at present cannot eliminate virus latency. As a result one and the same man can be infected, then re-infected and super-infected; autoinoculation of the virus into a new place can also occur. Early prescription of acyclic nucleosides (particularly, valtrex or famvir) can cause decrease of virus latency degree which cannot be neglected. The available remedies give good results in initial phase of the disease and relapses cutting short [14, 16].

IMMUNOTHERAPY

Individual parameters of immune status should be considered on all stages of the treatment, peculiarities of HVI clinical course, psychological sentiment and character of the patient including willingness to the treatment (compliance). In accordance with this choice and execution of immune therapy should be done, considering severity of HVI course, data of antivirus defense – interferon status, lymphocytes sub-populations as well as cytokine profile, clinical index of therapy, severity course index and concomitant diseases [8, 12, 15].

Necessary for immunotherapy: inter-ferons inductors; interferons; thymic factors; dyalised leukocytic extracts and transfer-factor preparations; vaccines; 6) immune modulators with polyvalent activity, for example: polyoxidonium, licopid, galavit, mielopid, imidazol derivatives, panavir, cagocel; substances and preparations, exerting predominant influence on non-specific (natural) resistance of the organism: adaptogenes, lizocim, vitamins, microelements, etc.

Most often the following preparations from the group of *interferons inductors* are used: amixin, neovir, cycloferon [8].

Prescription of *immunomodulators* is reasonable to those patients who are in proliferative phase of antiherpetic immune response, i.e. not earlier than the 21-st day in acute and the 14-th day in relapse process. Alpizarin, imunofan, likopid, cagocel, polyoxidonium, galavit are the most effective. Influence of immunomodulators on specific immune response in other phases of infection process is incomparably tiny in comparison with direct immunomodulating effect of herpesviruses themselves and emission of natural cytokines into hemocirculation concomitant to any virus infection. That is why hope to success should be connected with specific antiherpes preparations application which is proved by successful treatment of acute and relapse HVI forms and the use of immunomodulators is reasonable to limit by intercurrent and reparative phases of these unusual persistent diseases.

Sodium nucleate, pentoxil, metiluracil, vitamins of B group, adaptogenes of vegetable origin can be used as immunomodulating remedies (eleutherococcus, panax ginseng, yarrow).

Consequently, effective HVI treatment nowadays can be provided only in connected application of means of etiotropic and immunocorrection pathogenic therapy [8].

One more way to change the immune response to herpesviruses antigens is a *vaccinotherapy*. Principal ability of a specific antigene material to cause imperatively formation of valuable specific multicomponent and long-term immunity in organism of immunocompetent people in all cases serves a pathogenic validation of vaccinotherapy repeatedly experimentally and clinically proved under various bacterial and virus diseases. That is why vaccinotherapy is formally prescribed in severe acute HVI treatment as well as relapse processes or in prophylactics of these diseases. Thus vaccinotherapy is the only candidate on the role of populational method of HVI prophylactics and treatment [8, 14].

Nowadays the scientists efforts are directed to elaboration of 6 types of vaccines against simple herpes: killed integral virion vaccine; subisolated vaccine: henetically attenuated live vaccine; live vaccine with limited ability to replication; vaccine, containing non-pathogenic replicated vector, expressing HSV antigen; DNA-vaccines on the basis of plasmids.

Course of vaccinotherapy stipulates intradermal injection of inactivated herpetic vaccine into palm surface of the arm – 0,2 ml

of standard solution once with 3-4 days interval. It is repeated twice (in 2 weeks and 6 months).

A program of treatment and prophylactics of herpetic infection was proposed by St. Petersburg group of scientists virologists and infectionists headed by V.A. Isakov (1993) (tab. 3).

Table 3

Principles of HVI treatment and prophylactics stages

I stage: treatment in acute period of the disease(relapse)	• Antiherpetic remedies (intravenously, perorally, locally), • ncrease of the doses of chemical preparations and course and prophylactics duration in persons with immune deficit, • Natural antioxidants (vitamins E and C), course 10-14 days, • In case of pronounced exudative component prostaglan-dines inhibitors are prescribed (indometacin, etc.), course 10-14 days, • Immune-biological remedies: preparations of interferon or its inductors, immunemodulators.
II stage: therapy in the stage of remission, early convalescence	Main aim is preparation of the patient to vaccinotherapy Immune modulators, • Adaptogenes of vegetable origin, • In pronounced immune suppression – thymic hormones (timalin and others) in short course.
III stage: specific prophylactics of HVI relapses	Vaccination with the aim of cell immunity activation, its immune correction and specific desensibilization of the organism, Herpetic vaccines are used (inactivated, recombined.
IV stage: sanitarium observation and rehabilitation	Clinic-laboratory examination of convalescents every 3-6 months.

It was demonstrated that exactly complex approach to HVI treatment decreases probability of herpesvirus stable strains appearance, leads to immume-correcting effect achievement and shortens the acute period duration of the disease.

CONCLUSION

HVI therapy must be complex and prolonged. It is necessary to take into account various types of viruses differences in sensitivity to various preparations as well as peculiarities of immune status of the patient. The main aim of HVI therapy must be in suppressing virus reproduction with establishing proper control over them from the side of immune system of the patient. That is why immune therapy together with antivirus preparations is the main component of modern therapeutic schemes. Physicians of all specialties must be able to diagnose correctly and treat adequately reactivated herpesvirus infections. General scientifically reasonable principles of therapy implementation in practice will allow reaching progress in control over HVI outbreaks in human population.

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ABIFLOX EFFICACY IN COMPLEX THERAPY OF PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA

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The article presents the results of the study, during which the efficacy of levofloxacin in the treatment of patients with community-acquired pneumonia was evaluated. It was found that levofloxacin is a highly effective treatment for patients with community-acquired pneumonia.

KEY WORDS: community acquired pneumonia, antibiotic therapy, levofloxacin (Abiflox)

ЕФЕКТИВНІСТЬ АБІФЛОКСА В КОМПЛЕКСНІЙ ТЕРАПІЇ ХВОРИХ НА НЕГОСПІТАЛЬНУ ПНЕВМОНІЮ

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У статті представлені результати дослідження у якому оцінювалася ефективність левофлоксацину в терапії хворих на негоспітальну пневмонію. Встановлено, що левофлоксацин є високоефективним препаратом для лікування хворих на негоспітальні пневмонії.

КЛЮЧОВІ СЛОВА: негоспітальна пневмонія, антибактеріальна терапія, левофлоксацин (Абіфлокс)

ЭФФЕКТИВНОСТЬ АБИФЛОКСА В КОМПЛЕКСНОЙ ТЕРАПИИ БОЛЬНЫХ НЕГОСПИТАЛЬНЫМИ ПНЕВМОНИЯМИ

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В статье представлены результаты исследования, в ходе которого оценивалась эффективность левофлоксацина в терапии больных с негоспитальной пневмонией. Установлено, что левофлоксацин является высокоэффективным препаратом для лечения больных негоспитальными пневмониями.

КЛЮЧЕВЫЕ СЛОВА: негоспитальная пневмония, антибактериальная терапия, левофлоксацин (Абифлокс)

INTRODUCTION

At present the problem of antibiotic therapy of patients with community-acquired pneumonia (CAP) is one of the most important problems in pulmonology and infectology. Setting of this diagnosis is an undoubted indication to antibiotic remedies prescription. It should be mentioned that the problems of community-acquired pneumonia therapy are of current importance and the choice of antibiotic remedy practically always remains very serious and responsible decision for the physician [1, 2]. Multiresistance of microorganisms formed as a result of irrational application of antimicrobial remedies gains importance lately. [3, 4]. By now quite a great number of factors defining optimal quality of antimicrobe therapy was revealed. Maximum efficacy with minimal toxicity of preparation must combine with their correct value. Many recommendations on antibiotic remedies application need critical estimations from the point of view of therapy efficacy. The results of morbidity control centers studied prove that increase of general morbidity and mortality is considerably connected with resistance to antibiotics which leads to considerable growth of mortality risk and hospitalization duration [3, 4].

Notoriously at the beginning of the 90^{th} the concept of evident medicine came into clinical practice when treatment tactics and pharmacological remedy choice are based on the results of planned controlled studies instead of subjective experience of a physician. Noting this it is impossible to prescribe antibiotic

therapy without monitoring microorganisms resistance in specific infection stationary department.

At the present stage in pulmonological practice growing resistance to penicillin and its derivatives, tetracycline, microlides S. pneumoiae, H. influenzae, M. catarrhalis is most often overcome in the way of traditionally used antibiotics in high dozes; combined therapy with simultaneous prescription of antibiotics of various groups associations; new antibiotics [1, 5, 6].

Remedies of quinolones class which are used in clinical practice from the beginning of the 60th differ principally in activity mechanism from other antibiotics. It provides their activity towards stable strains including polyresistant ones [7, 8].

It should be mentioned that fluoroquinolones are characterized by wide antimicrobial spectrum of activity and vigorously influence a big group of gram-positive microorganisms, gram-negative aerobic bacteria, atypical pathogens. Fluoroquinolones provide bactericidal effect, inhibiting significantly important enzyme of microbe cell – DNA-gyrase and breaking the DNA biosynthesis [9, 10].

Levofloxacin, according to clinical physicians research, is indicated to the patients for respiratory tract infections treatment (acute bronchitis, pneumonia, lungs abscess, exacerbation of chronical lungs diseases etc.), kidneys infections and urinary system non-complicated infections of skin and soft tissues, infections of bone tissues and joints, infection diseases of gastrointestinal tract etc. [9, 11].

Preference of levofloxacin and other new fluoroquinolones is their improved activity towards S. pneumoniae and high effectiveness against most of pathogens of infection diseases of lower respiratory tract. Activity of the given remedy is connected with fast absorption from digestive tract, wide breakdown in tissues and creation of high concentrations in biological medium surpassing plasma concentrations. Levofloxacin is characterized by minimal metabolism, good penetration and creation of high concentrations in lung tissue, phlegm, bronchial secretion, alveolar macrophages, which is very important in treatment of patients with respiratory infections [12]. All this served as a basis for levofloxacin application as an etiotropic remedy for patients with CAP treatment.

The aim of the research became the estimation of clinical efficacy and therapeutic tolerance of levofloxacin (Abiflox) in patients with CAP.

MATERIALS AND METHODS

Patients of both sexes elder than 18 years old having roentgenologically proved CAP signs demanding hospitalization were under observation taking into account the criteria recommended for inclusion in the study.

26 patients with CAP were included in the study: 8 (69,2 %) men, 8 (30,8 %) women. Average age of the patients was between 18 and 72 years and comprised 42,1 ± 17,6. In accordance with the order of the Ukrainian MHC №128 from 19.03.2007 it is recommended to divide CAP into 4 groups depending on the severity degree of the process [2]. CAP of the 3 group in which patient with CAP of non-severe course were included and needed hospitalization according to medical and social readings was diagnosed in 80,8 % (21 patient), CAP of the 4 group in which patients with severe course of CAP were included and needed hospitalization into DRIT or ITW - in 12,2 % (5 patients).

Taking into account the fact, that isolation and identification of CAP pathogen usually needs not less than 3 days, start antibiotic therapy before Abiflox prescription was done by the remedies of various groups without desired effect (tab. 1). Average duration of antibiotic therapy before Abiflox prescription canceled because of inefficacy comprised 3,8 ± 1,2 days.

Table 1

Antibiotic remedies, the treatment by which preceded Abiflox prescription

Groups of antibiotics	Abs.	%
Ampicillin	4	15,4
Gentamicin	3	11,5
Augmentin	3	11,5
Ceftriaxone	1	3,8

Clinical symptomatologties of severe infection lesion of lower respiratory ways were found in all patients under study: cough, dyspnea, pain in thorax, high temperature and distinct signs of intoxication (tab. 2).

Table 2

Clinical manifestation of community-acquired pneumonia before the beginning of treatment by Abiflox

Disease symptoms	Abs.	%
Cough	26	100
Symptoms of intoxication	26	100
Temperature increase	26	100
Dyspnea	18	69,2
Pleura pain	12	46,1
Hemoptysis	4	15,4
Bronchial breathing	4	15,4
Weakened breathing	24	92,3
Presence of phlegm	22	84,6
Rhonchi, crepitation, noise of pleura friction	21	80,8
Unilateral deprivation	19	73,0
Bilateral deprivation	7	27,0

Hemoptysis was detected in 4 (15,4 %) patients. Percussion and auscultative signs dominated in most of the patients with CAP in clinics testified presence of lung tissue pathology. Bilateral deprivation of lungs was marked in 27,0 % (7 patients). It should be mentioned that unilateral deprivation of lung tissue was found in 19 (73,0 %) patients. Leukocytosis was found in 22 (84,6 %) patients, shift of leukocyte formula to the left was also found in 22 (84,6 %) patients. Anemia was detected in 4 (15,4 %) patients with CAP. Increase of ESR was found in 84,6 % (22 patients).

Abiflox was included into the complex therapy of the patients with CAP (mucolytic remedies, polyvitamins, metabolic). Preparation was inserted by drip intravenous infusion once a day in the doze 500 mg during 7-10 days. Such therapy was done after canceling of inefficient initial start therapy (11 patients) the rest 15 patients with CAP received Abiflox immediately after coming onto the hospital.

Clinical effectiveness of the antibiotic therapy was estimated according to the dynamics of inflammatory process in lungs activity. With this purpose the following clinical and laboratory parameters characterizing the inflammatory process activity were estimated (temperature reaction, tachycardia, respiratory rate, leukocytosis, number of immature forms of granulocytes, change of ESR), intensity of pain syndrome, roentgenological changes in lungs. Dynamics of clinical and laboratory signs were taken into account before the beginning of the treatment, in the process of treatment (3-5 days of therapy) and after treatment (efficacy) – on the 10-th day after finishing the remedy receiving. Roengenological efficacy was also estimated at the end of the therapy.

Clinical efficacy of antibacterial therapy by Abiflox was estimated as «positive» if the improvement of subjective and objective health condition of the patients was detected on the 3-rd day of the therapy, decrease and normalization of temperature, vanishing of pain syndrome, stable tendency to laboratory data normalization. Efficacy of antibacterial therapy was estimated as «satisfactory» if unstable improvement of laboratory data was detected on the background of subjective improvement of the patients health condition, subfebrile condition remained. «Unsatisfactory» results of the treatment when health condition of the patients is not improved, tendency to laboratory data normalization is absent, were not detected in our study.

Thorax organs roentgenological data results were interpreted in the following way: «improvement» – under positive dynamics or

complete disappearance of roentgenological signs of CAP, «without changes» – absence of improvement in comparison with the initial roentgenological picture.

Statistical treatment of the received results of the study was carried out with the help of the STATISTIKA program for Windows (Stat Soft Inc, USA) on the computer with Pentium II Celeron 850 PPGA processor.

RESEARCH RESULTS

Analyses of the received results of Abiflox therapy showed that clinical success was achieved in 25 (96,2 %) patients. One patient (3,8 %) with perforative ulcer of duodenum and chronical pyelonephritis against the background of Abiflox therapy was moved to surgical department for surgical treatment (Fig. 1).

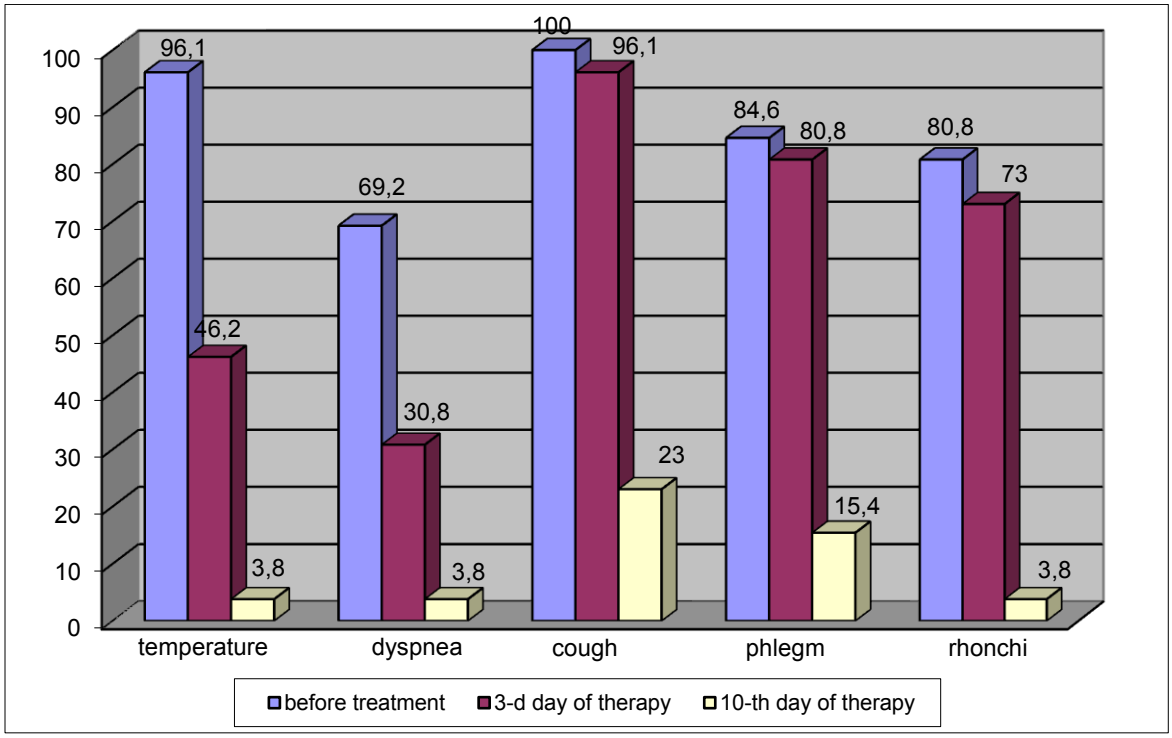

Fig. 1. Dynamics of main clinical symptoms in patients with CAP under Abiflox therapy

Positive dynamics of clinical rates were marked on the 3-rd day from the beginning of Abiflox antibiotic therapy in the way of temperature decrease, the temperature normalized practically in all patients by the 7-th day of treatment only in 1 (3,8 %) patient it remained subfebrile. The patients also mentioned about decrease of pain syndrome in this period, the signs of intoxication decreased (fig.1). Analyzing laboratory rates we authentically stated that the degree of ESR acceleration decreased in average from 26,4 ± 2,9 to 7,3 ± 0,8 mm per hour ($p < 0,05$) by the 10-12-th day of treatment; the number of leukocytes decreased from 12,5 ± 1,5 x 10^9/l to 6,2 ± 0,5 x 10^9/l ($p < 0,05$).

According to roentgenological study before the treatment and on the 10-th day of therapy absolute disappearance of infiltrative changes in lungs were marked in 7 (27 %) patients, considerable decrease of their intensity - in 18 (69,2 %) patients. Symptoms of inflammatory infiltration in lungs were absent on 15-24-th (average 15,3 ± 1,2) day after the beginning of Abiflox therapy in all patients.

It is important to mention that side effects from Abiflox provided therapy were found in 3 patients in the way of nausea and momentary diarrhea - in 1 patient. These phenomena were momentary and did not need correction and canceling of the remedy.

CONCLUSIONS

Levofloxacin (Abiflox) is a highly effective antibacterial remedy for treatment of CAP with various degree of severity. Positive dynamics

of the disease clinical manifestation was marked just on the 3-rd day from the beginning of the therapy.

Abiflox has a good therapeutic tolerance in patients with CAP. The revealed side effects were momentary and did not demand additional pharmacological correction and canceling of the remedy.

A comfortable dozing regime (500 mg intravenously once) allows keeping to the procedure of taking medication and support necessary concentration in the centre of inflammation which influences clinical and bacteriological efficacy of therapy.

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COMPARISON OF LISINOPRIL AND BISOPROLOL INFLUENCES ON REGULATORY SYSTEMS OF THE ORGANISM IN BIOFEEDBACK SERIES IN HEALTHY VOLUNTEERS

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In 15 conditionally healthy volunteers aged from 18 to 22 years influence of Lisinopril and Bisoprolol on the biofeedback in the loop of paced breathing under control of heart rate variability parameters was compared. Every volunteer underwent 3 everyday biofeedback series with 5 session in each with a 5 months gap between the series, adding oral drugs application to the 2nd and 3rd series. During the 2nd series biofeedback sessions was conducted one hour after oral application of 2,5 mg Lisinopril. During the 3rd series biofeedback sessions was conducted one hour after oral application of 2,5 mg Bisoprolol. In used protocol, it was found that Bisoprolol promotes earlier and more substantial optimization of regulatory systems in comparison with Lisinopril.

KEY WORDS: biofeedback, paced breathing, HRV, regulatory systems, BQI, Lisinopril, Bisoprolol

ПОРІВНЯННЯ ВПЛИВУ ЛІЗИНОПРИЛУ І БІСОПРОЛОЛУ НА РЕГУЛЯТОРНІ СИСТЕМИ ОРГАНІЗМУ В БІОЛОГІЧНОМУ ЗВОРОТНОМУ ЗВ'ЯЗКУ У ЗДОРОВИХ ДОБРОВОЛЬЦІВ

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На 15 умовно здорових добровольцях від 18 до 22 років порівняли вплив лізиноприлу і бісопрололу на якість біологічного зворотного зв'язку (БЗЗ) в контурі метрономізованого дихання під контролем параметрів варіабельності серцевого ритму (ВСР). Кожному випробуваному провели по 3 серії щоденних сеансів БОС на протязі 5 днів з часовим інтервалом у 5 місяців між ними, доповнюючи 2-у та 3-ю серії пероральним прийомом препаратів. В 2-й серії сеанси проводили через час після перорального прийому лізиноприлу в дозі 2,5 мг, в 3-й серії – через час після перорального прийому бісопрололу в дозі 2,5 мг. В використаному протоколі бісопролол, в порівнянні з лізиноприлом, сприяє більш ранній та суттєвій оптимізації регуляторних систем.

КЛЮЧОВІ СЛОВА: біологічний зворотній зв'язок, метрономізоване дихання, ВСР, регуляторні системи, BQI, лізиноприл, бісопролол

СРАВНЕНИЕ ВЛИЯНИЙ ЛИЗИНОПРИЛА И БИСОПРОЛОЛА НА РЕГУЛЯТОРНЫЕ СИСТЕМЫ ОРГАНИЗМА В БИОЛОГИЧЕСКОЙ ОБРАТНОЙ СВЯЗИ У ЗДОРОВЫХ ДОБРОВОЛЬЦЕВ

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На 15 условно здоровых добровольцах в возрасте от 18 до 22 лет сравнили влияния лизиноприла и бисопролола на качество биологической обратной связи (БОС) в контуре метрономизированного дыхания под контролем параметров вариабельности сердечного ритма (ВСР). Каждому испытуемому провели по 3 серии ежедневных сеансов БОС в течении 5 дней с временным интервалом в 5 месяцев между ними, дополняя 2-ю и 3-ю серии пероральным приёмом препаратов. Во 2-й серии сеансы проводили через час после перорального приёма лизиноприла в дозе 2,5 мг, в 3-й серии – через час после перорального приёма бисопролола в дозе 2,5 мг. В использованном протоколе бисопролол, по сравнению с лизиноприлом, способствует более ранней и существенной оптимизации регуляторных систем.

КЛЮЧЕВЫЕ СЛОВА: биологическая обратная связь, метрономизированое дыхание, ВСР, регуляторные системы, BQI, лизиноприл, бисопролол

RESEARCH URGENCY

The function of circulatory system is under control of regulatory systems of the organism [1]. Distress, especially chronic, has an influence on pathological states development of circulatory system that overstrains regulatory systems and causes disbalance of regulation [2].

Lisinopril (angiotensin-converting enzyme (ACE) inhibitor) and Bisoprolol (beta-blocker) have a protective effect during distress through alteration of regulatory systems of the organism [3-5]. Lisinopril and Bisoprolol are widely adopted in cardiologists practice [4-5].

Lisinopril point of application is renin-angiotensin-aldosterone system (RAAS). Blocking angiotensin I to angiotensin II conversion, Lisinopril lowers not only angiotensin II level in blood, but aldosterone level as well, lowering arginine-vasopressin and endothelin-I formation that have, in particular, vasoconstriction effect [6-7]. Additional vasodilation effect is achieved through bradykinin level saving and endogenic prostaglandins level increasing [7]. Bisoprolol, blocking beta-1 adrenergic receptors of heart, provide inhibition of sympathetic part of vegetative nervous system and, in addition, lowers renin secretion [8-9].

One of perspective ways of investigation, estimation, statusing and subsequent intervention in regulatory systems with the purpose of restoration theirs balance in organism is biofeedback series in the loop of paced breathing under control of heart rate variability (HRV) parameters [10-12].

Earlier we showed that systematic biofeedback series in the algorithm of optimal frequency of paced breathing lookup starting from physiological norm and from free breathing in healthy volunteers [10-12] and patients with hypertension [13] optimize regulatory systems of the organism through restoration sympathovagal and neurohumoral balances of regulation with a long-term (up to 3 months) saving of the results [14].

Therefore, it is interesting to compare Lisinopril and Bisoprolol influences on alterations of regulatory systems of the organism in combination with biofeedback series in the loop of paced breathing under HRV parameters control on one contingent of volunteers.

The study is conducted as a part of research project of V.N. Karazin Kharkiv National University «Development and Research of Automatic Control of Heart Rate Variability», registration No. 0109U000622.

RESEARCH OBJECTIVE

To compare Lisinopril and Bisoprolol influences on alterations of regulatory systems of the organism in combination with biofeedback series in the loop of paced breathing under HRV parameters control on one contingent of volunteers.

OBJECT AND METHODS OF THE RESEARCH

The study involved 15 conventionally healthy volunteers aged from 18 to 22 years (average age is 19,53 ± 1,55). Exclusion criteria: pernicious habits, medication taking last 3 months, heart rate less than 60 bpm at rest, blood pressure lower than 100/60 mmHg.

The study is conducted with computer diagnostic complex «CardioLab 2009» («KhAI-Medica») with special module «Biofeedback» that contains programmatically connected aural-visual breathing metronome and algorithm of HRV parameters estimation.

Biofeedback technology in the loop of paced breathing under HRV parameters control optimizes regulatory systems of the organism with a long-term (up to 3 months) saving of the results [14]. It gives an opportunity to evaluate influences of biofeedback both singly and in combination with Lisinopril and Bisoprolol on alterations of regulatory systems of the organism on one contingent of volunteers through conducting of 3 series of biofeedback sessions with a more than 3 months interval between series.

In compliance with research objective, volunteers were conducted 3 series of everyday biofeedback sessions in the loop of paced breathing under HRV parameters control for 5 days with a 5 months interval between them, adding to the 2^{nd} and 3^{rd} series oral intake of medications. Taking into account that experiment was conducted in healthy volunteers, Lisinopril and Bisoprolol was added to the 2^{nd} and 3^{rd} series of biofeedback sessions in minimal therapeutic dose. The sessions of the 2^{nd} biofeedback series were conducted 1 hour after oral intake of 2,5 mg Lisinopril. The sessions of the 3^{rd} biofeedback series were conducted 1 hour after oral intake of 2,5 mg of Bisoprolol.

HRV parameters were estimated in slide buffer for 1 minute through dynamic spectral HRV parameters were estimated in slide buffer for 1 minute through dynamic spectral decomposition by fast Fourier transform of R-R intervals sequence of lead I ECG records with 1000 Hz digitization frequency during 7-minute biofeedback session [11]. Powerfulness of low (V, up to 0,05 Hz), medium (L, 0,05-0,15 Hz) and high (H, 0,15-0,40 Hz) HRV parameters were estimated [12], then they were transformed into two-dimensional coordinate space with L/H and V/(L+H) axes, which correspond to power-fulness of sympathovagal and neurohumoral balances of regulation [15].

During biofeedback session, initialization of adaptation algorithm of biofeedback module was conducted in first 2 minutes, while volunteer breathe in his normal rhythm. After that for each following minute exact frequency of paced breathing was set through frequency rearrangement of aural-visual breathing metronome. Adaptation algorithm consists in automatic seeking of such frequency, when current L/H and V/ (L+H) values are maximally approximate to optimum zone [12].

Biofeedback quality estimation was based on optimality (O, estimation of farness of regulatory systems from optimal state during whole period of session), sensitivity (S, estimation of receptivity of regulatory systems to paced breathing), effectiveness (E, estimation of approaching range of HRV parameters to optimal physiological state during execution of optimal bioreverse control algorithm) parameters both for whole regulatory system (D) and its parts, and also on BQI integral index (parameter that reflects all qualitative changes of biofeedback process) [15]. Estimation of all values were carried out using PTC MathCad computer software.

Statistical analysis of the results for each subject was carried out using Microsoft Excel computer software. Average values (M) and standard deviation (sd) of O, S, E parameters for D, L/H, V/ (L+H) indicators of first and last records of each subject were put down in spreadsheet.

The differences reliability of each parameter between first and second sessions and in each session was determined by Wilcoxon signed-rank test.

RESULTS AND DISCUSSION

O, S, E parameters values for D, L/H, V/(L+H) indicators of 1^{st} and 5^{th} sessions of 1^{st}, 2^{nd} and 3^{rd} biofeedback series in conventionally healthy volunteers are shown in the table.Systematic biofeedback series in the loop of paced breathing under HRV parameters control optimized regulatory systems state. Biofeedback series with Lisinopril and Bisoprolol application allowed optimization process accelerating of biofeedback parameters. Optimization in biofeedback series with Bisoprolol was more expressed than with Lisinorpil.

BQI values alterations of 1^{st}, 2^{nd} and 3^{rd} biofeedback series in every volunteer, that are shown on the picture, confirm earlier and more rapid optimization of regulatory systems with Lisinopril and Bisoprolol application with a more positive influence of Bisoprolol.

These results show optimization of regulatory systems of the organism by conducting systematic biofeedback series that proofs the literature data [10-16]. Founded more effective biofeedback influence on regulatory systems of the organism with a Bisoprolol application in comparison with Lisinopril should be explained by direct Bisoprolol influence on sympathetic part of vegetative regulation, whereas Lisinopril influence is mediated through number of mechanisms of humoral systems [6-9].

In compliance with derived results, biofeedback series with supplemented application of properly selected medication should be considered as important instrument of improvement of therapeutic measures effectiveness in clinical practice not only of cardiology but other fields of medicine as well.

CONCLUSIONS:

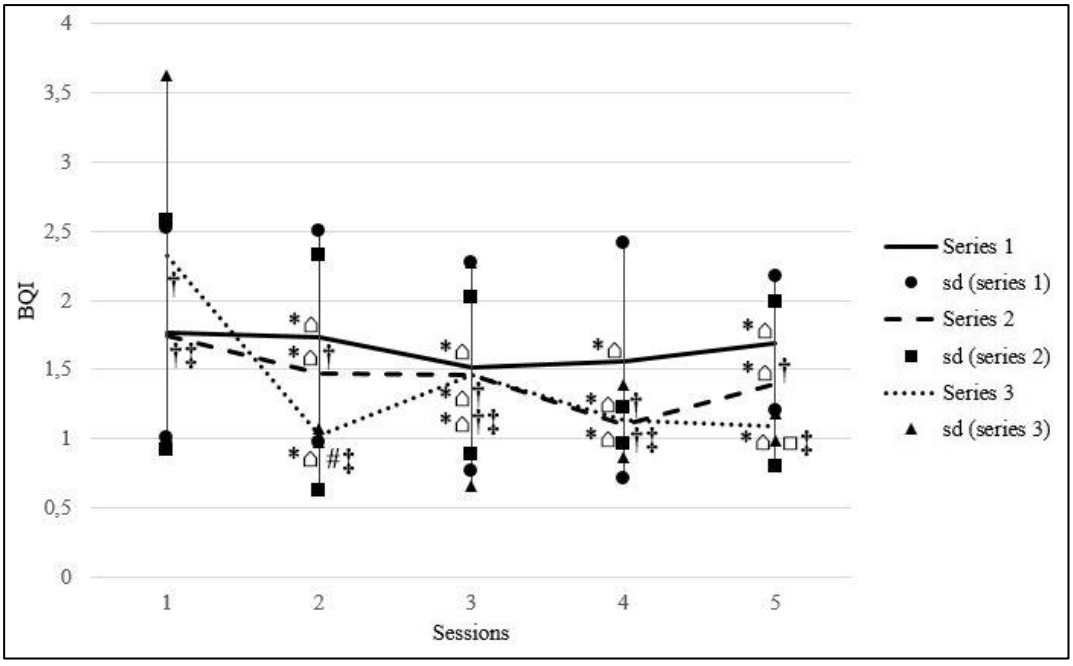
1. Systematic biofeedback sessions in the loop of paced breathing under HRV parameters control optimize regulatory systems state of the organism.
2. Biofeedback series with Lisinopril and Bisoprolol application allow achieving earlier and more rapid optimization of regulatory systems state.
3. In used protocol, it was found that Bisoprolol promotes earlier and more substantial optimization of regulatory systems in comparison with Lisinopril.

Table

O, S, E parameters values for D, L/H, V/(L+H) indicators of 1st and 5th sessions of 1st, 2nd and 3rd biofeedback series in healthy volunteers (M±sd)

Parameter		Series 1		Series 2		Series 3	
		Session 1	Session 5	Session 1	Session 5	Session 1	Session 5
D	O	-0,30 ± 4,84	-0,96 ± 2,74*	-0,71 ± 4,23†	-3,15 ± 6,10*†	-2,77 ± 4,13†‡	-0,06 ± 1,88*†‡
	S	0,91 ± 0,26	0,94 ± 0,49*	1,10 ± 0,35†	1,00 ± 0,35*†	0,62 ± 0,27†Δ	0,83 ± 0,30*†‡
	E	0,27 ± 0,25	0,46 ± 0,16*	0,43 ± 0,31†	0,31 ± 0,32*†	0,32 ± 0,26†‡	0,05 ± 0,10*□‡
L/H	O	-8,84 ± 10,84	-3,78 ± 4,03*	-5,62 ± 6,10†	-50,57 ± 49,90*†	-9,17 ± 12,66†‡	-0,51 ± 2,10*†‡
	S	6,39 ± 1,04	7,93 ± 1,88○	6,68 ± 2,04†	5,09 ± 2,39○#	4,18 ± 1,43□Δ	5,43 ± 2,83*†‡
	E	0,99 ± 0,02	1,00 ± 0,00*	0,97 ± 0,05†	0,91 ± 0,13*#	0,95 ± 0,06#‡	0,75 ± 0,50*†‡
V/(L+H)	O	-1,43 ± 1,08	-1,34 ± 0,99*	-1,08 ± 1,25†	-0,80 ± 1,28*†	-4,21 ± 0,71□◊	-3,88 ± 1,65*#Δ
	S	1,44 ± 2,14	0,60 ± 0,31*	1,65 ± 2,31†	2,18 ± 2,63*†	0,40 ± 0,04†‡	0,23 ± 0,15○#
	E	0,37 ± 0,37	0,23 ± 0,16*	0,41 ± 0,33†	0,51 ± 0,39*†	0,07 ± 0,08†‡	0,07 ± 0,05*†Δ

Notes: – p > 0,05 on sessions against base values of one series;
○ – p < 0,05 on sessions against base values of one series;
† – p > 0,05 on same session against base series;
# – p < 0,05 on same session against base series;
□ – p < 0,01 on same session against base series;
‡ – p > 0,05 on same session against adjacent series;
Δ – p < 0,05 on same session against adjacent series;
◊ – p < 0,01 on same session against adjacent series.



Pic. BQI values alterations of 1st, 2nd and 3rd biofeedback series in every volunteer

Notes: * – p > 0,05 on sessions against base values of one series;
⌂ – p > 0,05 on adjacent sessions of one series;
† – p > 0,05 on same session against base series;
# – p < 0,05 on same session against base series;
□ – p < 0,01 on same session against base series;
‡ – p > 0,05 on same session against adjacent series.

Biofeedback series with supplemented application of properly selected medication should be considered as important instrument of improvement of therapeutic measures effectiveness in clinical practice.It is interesting to study the influence of used biofeedback method in patients with different diseases of circulatory system.

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HEART RATE AND ARTERIAL PRESSURE VARIABILITY INDICES IN PATIENTS WITH ARTERIAL HYPERTENSION IN GROUPS OF TREATMENT WITH BETA ADRENERGIC ANTAGONIST, INHIBITOR OF ANGIOTENSINCONVERTING ENZYME AND THEIR COMBINATIONS AND CLASSES OF ECG QRS COMPLEX DURATION

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Studied indicators of heart rate and arterial pressure variability (HRV, AP) in patients with arterial hypertension (AH) in treatment groups of beta -blocker (BB), inhibitors of angiotensinconverting enzyme (IACE) and their combination classes and duration of the QRS complex ECG ≤ 100 and > 100 ms. 138 patients with AH of the 1-2 degrees (60 men and 78 women) at the age of 57 ± 17 years old were examined. Registration and measurement of QRS complex duration and indices of HRV ECG were done on computer electrocardiograph conducted «Cardiolab+». In groups of thera-py classes of ECG QRS complex duration <100 ms and ≥100 ms were derived. Patients were treated with lisinopril in the average daily dose of 20 mg, bisoprolol – 5 mg. Patients were assessed before, after 2 weeks, 1, 6 and 12 months after of therapy. HRV was evaluated TP, VLF, LF, HF, SAP, DAP in groups of IACE, BB and IACE + BB and classes QRS ECG. The data were processed with the help of Microsoft Excel program. In patients with AH in IACE group the best response of HRV indices ontherapy was indicated in the class of ECG QRS complex duration ≤ 100 ms and in group IACE+ B B− > 100 ms. In patients with AH of ECG QRS complex duration ≤ 100 ms in antihypertensive therapy IACE lizinopril is preferable with ECG QRS complex duration > 100 ms – combination of IACE lizinopril and BB bisoprolol.

KEY WORDS: ECG QRS complex duration, arterial hypertension, heart rate variability, inhibitors of angiotensinconverting enzyme, beta adrenergic antagonist

ПОКАЗНИКИ ВАРІАБЕЛЬНОСТІ СЕРЦЕВОГО РИТМУ І АРТЕРІАЛЬНОГО ТИСКУ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ В ГРУПАХ ТЕРАПІЇ БЕТА-АДРЕНОБЛОКАТОРОМ, ІНГІБІТОРОМ АНГІОТЕНЗИНПЕРТВОРЮЮЧОГО ФЕРМЕНТУ І ЇХ КОМБІНАЦІЄЮ ТА КЛАСАХ ТРИВАЛОСТІ КОМПЛЕКСУ QRS ЕКГ

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Вивчено показники варіабельності серцевого ритму (ВСР) і артеріального тиску (АТ) у пацієнтів з АГ в групах терапії бета-адреноблокатором (ББ), інгібітором ангіотензинперетворюючого ферменту (ІАПФ) і їх комбінацією та класах тривалості комплексу QRS ЕКГ ≤ 100 і > 100 мс. Обстежено 138 пацієнтів з АГ (60 чоловіків і 78 жінок) 1-2 ступеня і II стадії АГ у віці (50 ± 17) років. Реєстрація комплексу QRS проводилася на комп'ютерному електрокардіографі « Cardiolab + ». Виділено класи тривалості комплексу QRS ЕКГ: ≤ та > 100 мс. Пацієнти отримували лізиноприл у середній добовій дозі 20 мг, бісопролол – 5 мг . Пацієнтів обстежували до, через 2 тижні, 1 , 6 і 12 місяців від початку терапії. Оцінювали ТР ВСР, VLF, LF, HF, САТ, ДАТ у групах ІАПФ, ББ і ІАПФ + ББ та класах QRS ЕКГ. Для оцінки результатів використовували методи параметричної статистики. У пацієнтів з АГ в групі ІАПФ краща відповідь показників ВСР на терапію спостерігалася в класі тривалості комплексу QRS ЕКГ ≤ 100 мс, а в групі ІАПФ + ББ - > 100 мс. У пацієнтів з АГ в класі тривалості комплексу QRS ЕКГ ≤ 100 мс серед антигіпертензивної терапії треба віддавати ІАПФ лізиноприлу, а в класі тривалості комплексу QRS ЕКГ > 100 мс - комбінації ІАПФ лізиноприлу і ББ бісопрололу.

КЛЮЧОВІ СЛОВА: тривалість комплексу QRS ЕКГ, артеріальна гіпертензія, варіабельність серцевого ритму, інгібітори ангіотензинперетворюючого ферменту, бета адренергічні антагоністи

ПОКАЗАТЕЛИ ВАРИАБЕЛЬНОСТИ СЕРДЕЧНОГО РИТМА И АРТЕРИАЛЬНОГО ДАВЛЕНИЯ У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ В ГРУППАХ ТЕРАПИИ БЕТА-АДРЕНОБЛОКАТОРОМ, ИНГИБИТОРОМ АНГИОТЕНЗИНПРЕВРАЩАЮШЕГО ФЕРМЕНТА И ИХ КОМБИНАЦИЕЙ И КЛАССАХ ПРОДОЛЖИТЕЛЬНОСТИ КОМПЛЕКСА QRS ЭКГ

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Изучены показатели вариабельности сердечного ритма (ВСР) и артериального давления (АД) у пациентов с АГ в группах терапии бета-адреноблокатором (ББ), ингибитором ангиотензинпревращающего фермента (ИАПФ) и их комбинацией и классах продолжительности комплекса QRS ЭКГ ≤ 100 и > 100 мс. Обследовано 138 пациентов с АГ (60 мужчин и 78 женщин) 1-2 степени и II стадии АГ в возрасте (50 ± 17) лет. Регистрация комплекса QRS проводилась на компьютерном электрокардиографе «Cardiolab+». Выделены классс продолжительности комплекса QRS ЭКГ: ≤100 мс и > 100 мс. Пациенты получали лизиноприл в средней суточной дозе 20 мг, бисопролол – 5 мг. Пациентов обследовали до, спустя 2 недели, 1, 6 и 12 месяцев от начала терапии. Оценивали ТР ВСР, VLF, LF, HF, САД, ДАД в группах ИАПФ, ББ и ИАПФ+ББ и классах QRS ЭКГ. Для оценки результатов использовались методы параметрической статистики. У пациентов с АГ в группе ИАПФ лучший ответ показателей ВСР на терапию наблюдался в классе продолжительности комплекса QRS ЭКГ ≤ 100 мс и в группе ИАПФ+ ББ − > 100 мс. У пациентов с АГ с продолжительностью комплекса QRS ЭКГ ≤ 100 мс в антигипертензивной терапии преимуществами обладает ИАПФ лизиноприл и с продолжительностью комплекса QRS ЭКГ > 100 мс – комбинация ИАПФ лизиноприла и ББ бисопролола.

КЛЮЧЕВЫЕ СЛОВА: продолжительность комплекса QRS ЭКГ, артериальная гипертензия, вариабельность сердечного ритма, ингибиторы ангиотензинпревращающего фермента, бета адренергические антагонисты

Arterial hypertension (AH) prevalence according to the data of Ukrainian Medical Statistics Centre grew more than twice since 1998 to 2011 [1], which needs further improvement of prophylaxis and treatment measures.

In prescription rated in 2010 first place in AH monotherapy belonged to inhibitors of angiotensinconverting enzyme (IACE), second – to beta adrenergic antagonist (BB) and third – to these preparations combined therapy after IACE with diuretic and BB with diuretic, demonstrating significant positive dynamics comparing with 2000.

Pharmacological effects of IACE and BB are realized due to pharmacological control of renin-anhiotensine (RAS) and adrenergic systems activity connected with ECG QRS complex duration changes [2-4].

According to the data of Freminghem study ECG QRS complex elongation in patients with AH takes place in proportion to mass, walls thickness and finally-diastolic size of left ventricle (LV) increase [5-7]. ECG QRS complex duration > 120 msec is the indication to cardioresynchronizing therapy defined considering low pharmaceutical intrusion effectiveness connected with it [8, 9].

No research of heart rate variability (HRV) and arterial pressure (AP) indices were carried out in patients with AH in groups of BB, IACE and their combination therapy and classes of ECG QRS complex duration.

The research was done within the framework of scientific-research work «Elaboration and research of automatic control system of heart rate variability», state registration number 0109U000622.

OBJECTIVE AND METHODS

138 patients with AH of the 1-2 degrees (60 men and 78 women) at the age of 57 ± 17 years old were examined on the basis of city polyclinics № 6 of Moscow and city polyclinics № 24 of Kiev regions. Averaged duration of AH at the moment of examination was 7 ± 5 years. Mild AH was found in 44 patients, medium AH − in 94 patients.

Diagnosis of AH was stated according to the recommendations of the Working group on AH of Ukrainian cardiologists association (2009, 2013) [10].

Concomitant chronic ischemic heart disease (CIHD) was found in 42, sugar diabetes of the 2-nd type – in 6, ulcer of the stomach – in 12, osteoarthrosis – in 14 patients. Heart failure

(HF) of the I-st stage was in 45, of the IIA stage - in 60. FC HF (according to NYHA criteria) in 25 patients was I, in 20 − II, in 60 − III.

Patients with stable stenocardia of tension, acute coronary syndrome, HF of IIB-IV FC, AH of the I-st and III-rd stages, 3 –rd degree , ECG QRS complex duration > 120 ms, secondary arterial hypertension were not included into the study.

Limitations by ECG complex > 120 ms duration are connected with a possibility of medical beyond cardiosynchronizing therapy.

Systolic and diastolic arterial pressure (SAP and DAP) in orthostasis and clinostasis were measured by Korotkov method using tonometer Microlife BP AG1-20 on shoulder, where they were higher. Patients did not use the food products, influencing the measured parameters (strong tea, alcohol, medical preparations, etc.) the day before examination.

Registration and measurement of QRS complex duration and indices of HRV ECG were done on computer electrocardiograph «Cardiolab+» during orthostasis and clinostasis. Complex QRS duration on ECG was measured in leads II, V_I, V_5, V_6 (three consecutive complexes) with the choice of maximal values for leads registered complexes. Registration of HRV was done in orthostasis and clinostasis in 7 min intervals. General volume of spectrum (TP) was defined, volume of very low (VLF), low (LF) and high (HF) frequencies with calculation of LF/HF frequencies proportion as measures of simpatho-vagal balance on internal temporal 5 min interval.

In allocated classes of ECG QRS complex duration patients were divided into therapy groups, consequently, of IACE, BB and IACE+BB therapy. Therapy was done in accordance with the recommendations of the working group on AH of Ukrainian cardiologists association (2009, 2013) [10]. Lizinopril was used in ICAE group with average daily doze 20 mg (minimal daily doze comprised 10 mg, maximal – 40 mg), BB – bisoprolol in average daily doze 7,5 mg (minimal daily doze comprised 5 mg, maximal – 10 mg), IACE+ BB - lizinopril and bisoprolol in average daily dozes 20 mg and 5 mg, consequently (minimal daily doze comprised 10 mg and 2,5 mg, consequently, maximal – 40 mg and 10 mg, consequently). Depending on detected syndromes stains, antithrombotic preparations (acetylsalicylic acid) were prescribes if necessary.

In groups of therapy classes of ECG QRS complex duration < 100 ms and ≥ 100 ms were derived [5, 11]. Patients with QRS complex < 60 ms were absent.

Patients in which target AH was not achieved by lizonopril, bisoprolol therapy or their combination, with concomitant reactions on ICAE and/or BB in history of disease or developed during the therapy coursed were excluded from the research and converted to hypotensive preparations of other groups or their combinations.

Patients were examined up to one month, 6 and 12 months in allocated groups of therapy and classes of ECG QRS complex.

The data were processed with the help of Microsoft Excel program. Parametrical criteria were used for statistical estimation of the results (average meaning – M, standard deviation – sd). The significance of differences between the groups and classes of the patients was defined for parametrical criteria with the help of Student t-criterion, for non-parametrical – Mann-Whitney criterion. The data were accepted significant at $p < 0,05$ and $p < 0,01$ levels of significance.

RESULTS AND DISCUSSION

Indices of HRV and AP in control groups and AH group in clinostasis and orthostasis of the class of ECG QRS complex duration before and during lizinopril and bisoprolol therapy and their combination were presented in tables 1-3, consequently.

High HRV TP was observed before the therapy in control groups and AH group in the class of ECG QRS complex duration ≤ 100 ms ($p < 0,05$). In transition from clinostasis to orthostasis decrease of TP in both groups tool place which was more prominent in control group and the class of QRS duration ≤ 100 ms ─ 10 % and 13 %, consequently, against 8 % in the class > 100 ms. In both classes of ECG QRS complex duration low TP prevailed (70 % in class ≤ 100 ms and 75 % in class > 100 ms). The transition to orthostasis was not accompanied by the change of percentage correlation of TP levels in both classes of ECG QRS duration.

VLF and LF before the therapy in AH group in both classes of ECG QRS duration were lower in comparison with control group. High indices of VLF and LF were observed in

the class of ECG QRS duration > 100 ms. In transition from clinostasis to orthostasis decrease of VLF was detected in both classes of ECG QRS complex duration (6 and 4 % in classes of QRS duration ≤ and >100 ms, consequently) and its increase in control group (5 %), LF lowering in control groups (3 %) and AH group of both classes of ECG QRS complex duration (in class of ECG QRS ≤ 100 ms ─ 5 %, and ≥ 100 ms ─ 6 %).

In AH group HF was decreased in comparison with control group before the beginning of the therapy. Higher HF in AH group was observed in the class of ECG QRS complex duration ≤ 100 ms. The transition into orthostasis was accompanied by HF decrease more prominent in control group (54 %) in comparison with the classes of ECG QRS complex duration QRS ЭКГ ≤ and > 100 ms (16 % and 12 %, consequently).

The relation of LF/HF to the therapy in control group was within the limits of normal range in both classes of QRS complex duration but elevated with increase in orthostasis transition - 4 % and 6 % in classes ≤ and > 100 ms, consequently.

Higher levels of both SAP and DAP were in the AH group ($p < 0,05$) in comparison with control group, 27 % for SAP and 35 % for DAP in 12 % and 18 % in the classes of ECG QRS complex duration, consequently. Positive growth of SAP and DAP in control groups and AH group was initially detected under transition from clinostasis to orthostasis more prominent in AH group for SAP but not more than 20 % from initial indices.

Table 1

Indices of BCP and AP in control groups and AH group before therapy in classes of ECG QRS in clinostasis and orthostasis (M±sd, ms)

Groups		Position		HRV					SAP, mm Hg	DAP, mm Hg
				AD, ms^2	VLF, ms^2	LF, ms^2	HF, ms^2	LF/HF, limitless		
Control		clinostasis		2477 1807*	994 562	927 613	529 412**	1,75 1,62	122 ± 12**	75 ± 9**
		orthostasis		2229* 1323	1044 742	899 747	243 207	3,73 2,74	130 (7%) ± 9**	79 (5%) ± 8**
AH	ECG QRS complex,	≤ 100	Clino-stasis	1100 ± 890*	491 ± 197	445 ± 167	172 ± 15*	2,6 ± 1,3	146 ± 15*	84 ± 12*
			Ortho-stasis	957 ± 439	462 ± 146	423 ± 316	144 ± 10*	2,7 ± 1,9	157 (7 %) ± 10*	92 (7%) ± 19*
		>100	Clino-stasis	871 ± 611*	741 ± 305	532 ± 270	169 ± 15**	3,1 ± 2,3	165 ± 15**	88 ± 12**
			Ortho-stasis	801 ± 383*	711 ± 357	500 ± 220	149 ± 18**	2,8 ± 1,6	174(5 %) ± 18**	96 (9%) ± 16**

Comment:
* $p < 0,05$, ** $p < 0,01$ in current indices between subgroups on the research stages;
# $p < 0,05$, ## $p < 0,01$ between the meanings in subgroups on the research stages

Lowering of AD in IACE group was observed in 2 weeks of therapy in both groups of the classes of ECG QRS complex duration (11 % and 17 % in the classes ≤ 100 ms and > 100 ms, consequently) and its growth in other groups of therapy and classes of duration ($p < 0,05$). Further in 1, 6 and 12 months growth of AD was revealed in all groups in both classes of complex duration. In 12 months AD prevailed the initial meanings in 25 %, 21 % and 18 % in IACE, BB and IACE +BB groups, consequently, in class ≤ 100 ms and in 17 %, 27 % and 31 % in IACE, BB and IACE +BB groups, consequently, in class > 100 ms, approaching to moderate meanings in both classes of complex duration. In the class of ECG QRS complex duration ≤ 100 ms high and moderate AD increased in 5 %, low one decreased in 10 %, critically low AD were absent. In the class of ECG QRS duration >

100 ms high AD increased in 8 %, moderate – in 5 %, low one decreased in 8 %, critically low AD were absent. Thus redistribution of the part of the patients from the class of low and critically low AD into the class of high and moderate AD took place.

Table 2

Indices of BCP, AP and HFR in AH group in 2 weeks and 1 month of lizinopril, bisoprolol and their combinations therapy in classes of ECG QRS complex (M±sd, ms)

Therapy stages / indices		Class of ECG QRS complex duration, ms					
		≤ 100			>100		
		L	B	L+B	L	B	L+B
2 weeks	TP, ms^2	979 ± 590	1120 ± 790	1145 ± 690	722 ± 511*	981 ± 611*	1100 ± 711*
	VLF, ms^2	582 ± 297	521 ± 145	595 ± 207	741 ± 305	749 ± 215	751 ± 332
	LF, ms^2	545 ± 217	555 ± 189	494 ± 204	573 ± 159	562 ± 185	612 ± 197
	HF, ms^2	256 ± 25*	289 ± 21*	297 ± 19*	279 ± 17**	293 ± 21**	295 ± 19**
	LF/HF, dimentionless.	2,1 ± 1,3	1,9 ± 1,3	1,7 ± 1,3	2,1 ± 2,3	1,9 ± 2,3	2,1 ± 2,3
	SAP, mm HG	129 ± 13*	132 ± 17*	131 ± 16*	148 ± 15**	152 ± 15**	143 ± 15**
	DAP, mm Hg	88 ± 12*	88 ± 12*	86 ± 12*	87 ± 12	89 ± 12	80 ± 12
1 month	TP, ms^2	1080 ± 481	1144 ± 679	1259 ± 591	821 ± 511*	981 ± 611*	1100 ± 711*
	VLF, ms^2	611 ± 297	521 ± 145	595 ± 207	772 ± 299	749 ± 215	785 ± 305
	LF, ms^2	558 ± 217	562 ± 189	534 ± 114	586 ± 149	579 ± 185	637 ± 207
	LF/HF, dimentionless.	1,9 ± 1,3	1,9 ± 1,3	1,9 ± 1,3	2,0 ± 2,3	2,1 ± 2,3	2,0 ± 2,3
	SAP, mm Hg	138 ± 13*	143 ± 17*	139 ± 16*	139 ± 15**	141 ± 15**	137 ± 15**
	DAP, mm Hg	87 ± 12*	88 ± 12*	86 ± 12*	86 ± 12	87 ± 12	81 ± 12

Comment:
* $p < 0,05$, ** $p < 0,01$ in current indices between subgroups on the research stages;
# $p < 0,05$, ## $p < 0,01$ between the meanings in subgroups on the research stages;
Note:
L – lizinopril group of therapy,
B – bisoprolol group of therapy,
L + B – combination;

Growth of VLF and LF in all groups of therapy in both classes of QRS complex duration was observed in 2 weeks of the therapy. Further in 1, 6 and 12 months VLF and remained in all groups of the therapy in both classes of complex duration. In 12 months of the therapy VLF prevailed the initial indices in 14 %, 11 % and 15 % in IACE, BB and IACE +BB groups, consequently, in class ≤ 100 ms and in 8 %, 10 % and 11 % in IACE, BB and IACE +BB groups, consequently, in class > 100 ms ($p < 0,05$). In 12 months of the therapy LF prevailed the initial indices in 9 %, 8 % and 12 % in IACE, BB and IACE +BB groups, consequently, in class ≤ 100 ms and in 10 %, 12 % and 11 % in IACE, BB and IACE +Bb groups, consequently, in class > 100 ms ($p < 0,05$).

Table 3

Indices of BCP, AP and HFR in patients with AH in 6 and 12 months of lizinopril, bisoprolol and their combinations therapy in classes of QRS ECG complex (M±sd, ms)

Stages of therapy / indices		Class of ECG QRS complex duration, ms					
		≤ 100			> 100		
		L	B	L+B	L	B	L+B
6 months	TP, ms^2	1269 ± 481	1318 ± 679	1231 ± 591	1011 ± 642*	1103 ± 561*	1134 ± 624*
	VLF, ms^2	549 ± 297	497 ± 145	511 ± 207	792 ± 299	795 ± 215	812 ± 299
	LF, ms^2	558 ± 217	562 ± 189	534 ± 114	546 ± 149	551 ± 185	621 ± 207
	HF, ms^2	181 ± 25*	194 ± 21*	199 ± 19*	187 ± 17**	211 ± 21**	242 ± 19**
	LF/HF, dimensionless.	1,7 ± 1,3	1,9 ±1 ,3	1,8 ± 1,3	1,9 ± 2,3	2,0 ± 2,3	1,8 ± 2,3
	SAP, mm Hg	136 ± 13*	140 ± 17*	138 ± 16*	139 ± 15**	140 ± 15**	137 ± 15**
	DAP, mm Hg	87 ± 12*	88 ± 12*	86 ± 12*	86 ± 12	87 ± 12	81 ± 12
12 months	TP, ms^2	1375 ± 481*	1331 ± 679*	1298 ± 591*	1019 ± 642*	1106 ± 561*	1141 ± 624*
	VLF, ms^2	559 ± 297*	545 ± 145	565 ± 207	800 ± 299	815 ± 215	823 ± 299*
	LF, ms^2	485 ± 217**	480 ± 189**	498 ± 114**	585 ± 149**	596 ± 185**	590 ± 207**
	LF/HF, dimensionless.	1,7 ± 1,3*	1,9 ± 1,3*	1,8 ± 1,3*	1,9 ± 2,3	1,8 ± 2,3*	1,8 ± 2,3
	SAP, mm Hg	128 ± 13*#	131 ± 17*#	130 ± 16*#	139 ± 15**#	139 ± 15**#	136 ± 15**#
	DAP, mm Hg	88 ± 12*	88 ± 12*	84 ± 12*	86 ± 12*	87 ± 12*	81 ± 12*

Comment:
* p< 0,05, ** p < 0,01 in current indices between subgroups on the research stages;
# p < 0,05, ## p < 0,01 between the meanings in subgroups on the research stages;
Note:
L – lizinopril group of therapy,
B – bisoprolol group of therapy,
L+B – combination

Growth of HF in all groups in both classes of ECG QRS complex duration was observed in 2 weeks, 1, 6 and 12 months of the therapy. In 12 months of the therapy HF prevailed the initial indices in 19 %, 18 % and 21 % in IACE, BB and IACE +BB groups, consequently, in class ≤ 100 ms and in 15 %, 14 % and 18 % in IACE, BB and IACE +BB groups, consequently, in class > 100 ms (p < 0,01).

Lowering of LF/HF in all groups of the therapy was observed in 2 weeks of the therapy and in both classes of ECG QRS complex duration (19 %, 27 % and 35 % in IACE, BB and IACE +BB groups, consequently, in class ≤ 100 ms and in 4 %, 14 % and 4 % in IACE, BB and IACE +BB groups, consequently, in class > 100 ms). Lowering of LF/HF to the meanings of control group in all groups of the therapy and classes of complex duration was revealed on the stages of the therapy (in 12 months of the therapy LF/HF decreased in comparison with initial indices in 4 %, 3 % and 4 % in IACE, BB and IACE +BB groups, consequently, in class ≤ 100 ms and in 4 %, 2% and 3% in IACE, BB and IACE +BB groups, consequently, in class > 100 ms) (p < 0,05).

Decrease of AP in all groups of therapy and classes of ECG QRS complex duration were observed in 2 weeks of the therapy (for SAP in 11%, 9 % and in 10 % in IACE, BB and IACE +BB groups, consequently, in class ≤ 100 ms and in 11 %, 8 % and 13 % in IACE, BB and

IACE +BB groups consequently in class > 100 ms) ($p < 0,05$). Further in 1, 6 and 12 months decrease of both SAP and DAP remained (in 12 months in 12 % for SAP, 10 % and 11 % in IACE, BB and IACE +BB groups consequently, in class ≤ 100 ms and in 16 %, 16 % and 17 % in IACE, BB and IACE +BB groups, consequently, in class > 100 ms) ($p < 0,05$).

Low level of AD, HF, big indices of VLF, LF and LF/HF and levels of SAP, DAP revealed in our work are typical for the patients with AH [12-14] and connected with the deprivation of humoral link of regulation and activation of symphatic system. Positive growth of AD, VLF, HF, decrease of LF, LF/HF, DAP and mostly SAP no matter classes of ECG QRS duration found in IACE, BB and IACE +BB groups of therapy in patients with AH correspond to the given ones [15-20].

The received lower meanings of HRV AD HF, LF/HF in patients with AH in the class of ECG QRS complex >100 ms and higher ─ LF, SAP, DAP, than in the class of ECG QRS ≤ 100 ms, are new. The best response and HRV AD growth during the therapy were typical for patients in IACE therapy group in the class ≤ 100 ms, and in IACE +BB group in the class > 100 ms in comparison with the corresponding therapy groups and classes of ECG QRS. Optimal levels of AP were reached in all groups of therapy and classes of complex duration with the best indices in IACE group in the class ≤ 100 ms, in IACE +BB group in the class > 100 мms in comparison with the corresponding therapy groups and classes of ECG QRS. They can be stipulated for initially more significant misbalance of sympatho-parasympathetic regulation with the corresponding electrophysiological changes of myocardium with big levels of SAP and DAP in patients in the class of ECG QRS >100 ms, which defined their stronger response on prolonged combined antihypertensive therapy with lizinopril and bisoprolol.

CONCLUSIONS

1. In patients with AH in IACE group the best response of HRV indices on therapy was indicated in the class of ECG QRS complex duration ≤ 100ms and in group IACE+ B B− > 100 ms.
2. In patients with AH of ECG QRS complex duration ≤ 100 ms in antihypertensive therapy IACE lizinopril is preferable with ECG QRS complex duration >100 ms – combination of IACE lizinopril and BB bisoprolol.

The study of the meaning of ECG QRS complex duration is perspective in the therapy of the patients with AH by antihypertensive preparations of other pharmacotherapeutic groups.

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THE TREATMENT OF CHOLECYSTOCHOLEDOCHOLITHIASIS, COMBINED WITH JUXTAPAPILLARY DUODENAL DIVERTICULUM

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The retrospective study analysis of treatment outcomes of cholecystocholedocholithiasis, combined with juxtapapillary duodenal diverticulum (n=74), was carried out. The diagnostic and treatment algorithm was offered. It is recommended to include duodenoscopy to the complex of instrumental examination technics for patients over 50 years. When periampullary duodenal diverticulum doesn't extend to intramural part of common bile duct with the direction of papillotomy discission, the common bile duct stones are removed in a duodenoscopy transpapillary way during a postoperative period. The presence of juxtapapillary duodenal diverticulum is an indication of conversion for open or laparoscopic choledocholithotomy.

KEY WORDS: cholecystolithiasis, choledocholithiasis, juxtapapillary duodenal diverticulum, laparoscopic cholecystectomy, transpapillary choledocholithoextraction

ЛІКУВАННЯ ХОЛЕЦІСТОХОЛЕДОХОЛІТІАЗУ, ПОЄДНАНОГО ІЗ ЮКСТАПАПІЛЛЯРНИМ ДУОДЕНАЛЬНИМ ДИВЕРТИКУЛОМ

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Проведено ретроспективне дослідження результатів лікування холецистохоледохолітіазу, поєднаного з юкстапапілярним дуоденальним дивертикулом (n=74). Запропоновано діагностично-лікувальний алгоритм. Пацієнтам старше 50 років у комплекс інструментальних методів обстеження рекомендовано включення дуоденоскопії. При періампулярному дуоденальному дивертикулі без поширення на інтрамуральний відділ холедоху по напрямку папілотомного розрізу конкременти холедоха видаляються в післяопераційному періоді дуоденоскопічно транспапіллярно. Наявність юкстапапіллярного дуоденального дивертикулу є показанням до конверсії на відкриту чи лапароскопічну холедохолітотомію.

КЛЮЧОВІ СЛОВА: холецистолітіаз, холедохолітіаз, юкстапапіллярний дуоденальний дивертикул, лапароскопічна холецистектомія, транспапіллярна холедохолітоекстракція

ЛЕЧЕНИЕ ХОЛЕЦИСТОХОЛЕДОХОЛИТИАЗА, СОЧЕТАННОГО С ЮКСТАПАПИЛЛЯРНЫМ ДУОДЕНАЛЬНЫМ ДИВЕРТИКУЛОМ

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Проведено ретроспективное исследование результатов лечения холецистохоледохолитиаза, сочетанного с юкстапапиллярным дуоденальным дивертикулом (n=74). Предложен диагностико-лечебный алгоритм. Пациентам старше 50 лет в комплекс инструментальных методов обследования рекомендовано включение дуоденоскопии. При периампулярном дуоденальном дивертикуле без распространения на интрамуральный отдел холедоха по направлению папиллотомного разреза конкременты холедоха удаляются в послеоперационном периоде дуоденоскопически транспапиллярно. Наличие юкстапапиллярного дуоденального дивертикула служит показанием к конверсии на открытую или лапароскопическую холедохолитотомию.

КЛЮЧЕВЫЕ СЛОВА: холецистолитиаз, холедохолитиаз, юкстапапиллярный дуоденальный дивертикул, лапароскопическая холецистэктомия, транспапиллярная холедохолитоэкстракция

INTRODUCTION

In modern hospitals 84-95 % of patients are removed common bile duct stones with the aid of duodenoscopic transpapillary interventions [1, 2, 3].

The presence of duodenal diverticulum (DD) is one of the most important factors that prevent the endoscopic extraction of stones including contact lithotripsy [1, 4].

The patients with DD have duodenoscopy transpapillary interventions that are associated with the risk of complications which are developed at 2-6 % of cases (pancreatonecrosis, voluminous bleeding, dodecadactylon perforation into the retroperitoneal space with the development of phlegmona) and fatal outcomes (0,5-1,5 %) [1, 5]. The frequency of DD cases in population ranges from 12 to 25 % with a slight predominance among women [6, 7, 8].

DD most frequently diagnosed among people of 50-60 years old and with age this tendency increase [7, 8]. The DD detection depends on diagnostic techniques and is as follows: X-ray examination with barium meal - 0,016-6 %, endoscopic retrograde cholangiopancreaticography (ERCPG) – 9-25 % [9, 10].

About 95 % DD is located on the inner (medial) side of the descending part of the duodenum [8, 9, 10, 11]. About 70-75 % of diverticula are within 2 cm of the major duodenal papilla (MDP) [8, 9, 12].

DD is classified into extraluminal, when the mucosa and submucosa layers protrude outwards through the duodenal wall's weaknesses, and intraluminal, which are formed entirely within the lumen and covered on both sides of the mucosa layer [8].

Extraluminal DD could be – ampullary, which include MDP or interstitial part of the common bile duct and periampullary localized within 2 cm from the MDP, but not involving it. Together ampullary and periampullary DD called juxtapapillary diverticulum [3, 8, 12].

Juxtapapillary DD are usually asymptomatic, but in some cases can lead to displacement / compression of the common bile duct's lumen or pancreatic duct causing cholestasis, jaundice, pancreatitis and concretions.

In 1934, the author defined the connection between the presence of juxtapapillary diverticulum and hepatobiliopancreatic diseases as a «papillary syndrome» or Lemmel syndrome [7].

Currently, if there is appropriate medical equipment the treatment of choledocholithiasis in patients with concomitant cholecystolithiasis is provided in two stages [2, 3, 7].

The first step is the removal of common bile duct stones in a duodenoscopic transpapillary way, the next one is laparoscopic cholecystectomy.

If choledocholithiasis is detected during laparoscopic cholecystectomy it is recommended to complete the operation by cholecystectomy, followed by the removal of common bile duct stones in a duodenoscopy transpapillary way in the early postoperative period [1, 3, 4, 6, 13].

There is an open question: after laparoscopic cholecystectomy the endoscopic removal of common bile duct stones becomes impossible because of the presence of juxtapapillary DD, which is propagate on the intramural part of common bile duct. During laparoscopic cholecystectomy the intraoperation cholangiography does not allow to visualize juxtapapillary DD, that's why the patient undergoes third surgery.

As a result, the risk of intra- and postoperative complications increases [3, 6].

The aim of the study was a retrospective outcome analysis of the removal of common bile duct stones with juxtapapillary DD in order to determine the optimal diagnostic and treatment program for patients with cholecystocholedocholithiasis.

The study was carried out according to integrated research work of the department of surgical diseases of the Kharkiv National University named after V.N. Karazin «The development of minimally invasive surgical procedures with low temperatures during the treatment of patients with cholelithiasis, gastric and duodenal ulcer», the registration number is 0100U005308.

SUBSTANCES AND METHODS

The retrospective analysis has been made to 276 patients with cholecystocholedocholithiasis. The patients were at hospital treatment in surgery department of the clinical railway hospital Kharkiv STGO «SR» in the period from 2007 to 2013. Juxtapapillary DD was identified at 74 patients (26,8 %) including 32 men and 42 women at the age of 54.2 ± 6.7 years.

Ampullary DD which extend to intramural part of common bile duct with the direction of

papillotomy discission was identified at 6 patients (8,1 %), periampullary DD – at 11 patients (14,8 %), periampullary DD which is not extend to intramural part of common bile duct with the direction of papillotomy discission – at 57 patients (77,1 %).

Diagnostic program was composed of clinical and laboratory studies, ultrasound investigation, endoscopic examination of the upper gastrointestinal tract.

ERSP was carried out for patients with cholecystolithiasis, who had a suspected choledocholithiasis. The first step of choledocho- and cholecystolithiasis treatment policy was endoscopic choledocholitho-extraction; the second one was laparoscopic cholecystectomy. Open choledocholithotomy with cholecystectomy has been performed when the endoscopic removal of common bile duct stones became impossible. All transpapillary endoscopic interventions were ended by nasobiliary drain. Open interventions were ended by extrinsic drain of the common bile duct. Statistical processing of findings was made with the help of «Microsoft Office Excel 2007» and «Mathcad 14.0». The frequency of symptoms (%), universe mean value (M) of the patient's age and the standard deviation (sd) was evaluated with the help of Student t-test.

RESULTS AND DISCUSSION

The removal of common bile duct stones in a duodenoscopy transpapillary way was made for 47 patients (63,5 %) as a first step (table1.). The next step was laparoscopic cholecystectomy. The presence of periam-pullary DD was diagnosed in the preoperative diagnostic stage.

For 10 patients (13,5 %) the presence of choledocholithiasis was diagnosed during laparoscopic cholecystectomy with the help of intraoperation cholangiography, that's why the removal of common bile duct stones in a duodenoscopic transpapillary way was made in the early postoperative period.

These patients also had cholecystochole-docholithiasis, combined with periampullary DD which is not extend to intramural part of common bile duct with the direction of papillo-tomy discission. For 17 patients (23 %) the removal of common bile duct stones became impossible because of the presence in 6 cases (8,1 %) of ampullary and in 11 cases (14,9 %) of periampullary DD which was extending to intramural part of common bile duct with the direction of papillotomy discission.

For 9 of them (12,2 %) the complete diagnosis was determined in the preoperative stage, therefore open intervention with choledocholithotomy was carried out immediately.

For 8 patients (10,8 %) the presence of choledocholithiasis was diagnosed during intraoperation cholangiography with lapa-roscopic cholecystectomy. For these patients there was planned the removal of common bile duct stones in a duodenoscopic transpapillary way in the early postoperative period.

However the presence of periampullary DD which extend to intramural part of common bile duct with the direction of papillotomy discission didn't allow to carry out planned intervention and forced to subject patients to open surgery with choledocholithotomy.

Table

Patient allocation with cholecystocholedocholithiasis according to surgical measures (%)

Type of surgical measure	Localization and extension to the major duodenal papilla		
	Ampullary DD	Periampullary DD which extend to intramural part of common bile duct	Periampullary DD which is not extend to intramural part of common bile duct
Endoscopic retrograde choledocholithoextraction with performing laparoscopic cholecystectomy at the first stage	-	-	63,5
Laparoscopic cholecystectomy with performing endoscopic retrograde choledocholithoextraction at the second stage	-	-	13,5
Open cholecystectomy with choledocholithotomy	8,1	4,1	-
Open choledocholithotomy after laparoscopic cholecystectomy	-	10,8	-

The most difficult seemed to be the tactic to remove common bile duct stones which were identified for the first time at intraoperation cholangiography during laparoscopic cholecystectomy.

The reason why these patients had difficulties in preoperative diagnosis of choledocholithiasis may be associated with asymptomatic choledocholithiasis and insufficient diagnostic efficiency of used methods.

So, the sensitivity and specificity of percutaneous ultrasound investigation is 22-55 % and 80-95 %, respectively; endoscopic ultrasound examination – 89-94 % and 94-95 %, respectively; ERSP – 89-93 % and 96-100 %, respectively; computerized tomography – 65-88 % and 73-97 %, respectively; nuclear magnetic resonance imaging – 89-97 % and 95-97 %, respectively [11, 12].

The following diagnostic and treatment algorithm of case management with cholecystocholedocholithiasis was offered according to findings (fig. 1).

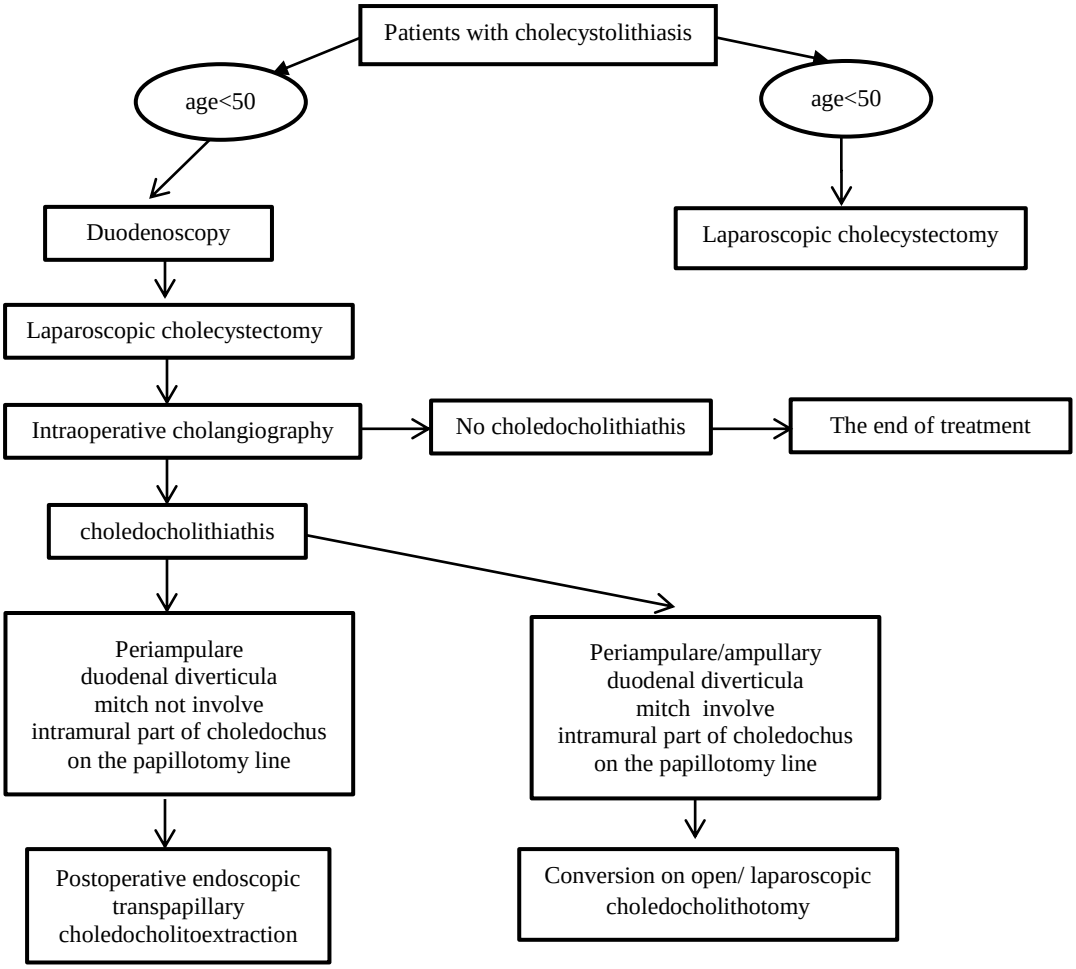

Fig. 1. Diagnostic and treatment algorithm of case management with cholecystocholedocholithiasis.

Patients over 50 years with a diagnosis of cholecystolithiasis in which the frequency of juxtapapillary DD reaches 25 % [7, 8] it is recommended to include duodenoscopy with MDP visualization which allows to reveal juxtapapillary DD in 100 % of cases. There are no studies at literary sources proposing to perform duodenoscopy in preoperative diagnostic stage.

Information which was obtained with the help of duodenoscopy about availability, location and structure of juxtapapillary DD allows to determine optimal treatment policy in case of intraoperative detection of choledocholithiasis.

In case of identifying periampullary DD which is not extend to intramural part of common bile duct with the direction of papillotomy discission, common bile duct stones are

removed in a duodenoscopic transpapillary way in the early postoperative period.

The presence of ampullary or periampullary DD which extend to intramural part of common bile duct with the direction of papillotomy discission is an indication of conversion for open or laparoscopic choledocholithotomy. In addition, in case of presence of juxtapapillary DD it is necessary to consider a question about the formation of biliodigestive anastomosis as DD can cause choledocholithiasis, that is confirmed by Kang S.K., van Basten J.P. [14, 15].

CONCLUSIONS:

1. In order to identify juxtapapillary DD and optimal treatment policy for patients with cholecystolithiasis it is required to perform duodenoscopy with MDP visualization.
2. Conversion for open or laparoscopic choledocholithotomy is indicated in case of intraoperative detection of choledocho-lithiasis combined with juxtapapillary DD which extend to intramural part of common bile duct.
3. Choledocholithiasis combined with juxtapapillary DD without extending to intramural part of common bile duct with the direction of papillotomy discission doesn't preclude the implementation of a complete endoscopic papillosphincterotomy.

FURTHER RESEARCH PERSPECTIVES

The findings show the strategy generations' prospects of the case management with cholecystocholedocholithiasis, combined with juxtapapillary DD.

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QUALITY OF LIFE IN PATIENTS WITH CHRONIC HEART FAILURE OF ISCHEMIC ETIOLOGY: ROLE OF ANXIETY AND DEPRESSIVE DISORDERS

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OBJECTIVE: To evaluate the quality of life (QoL) in patients with anxiety and depressive disorders (ADD) and chronic heart failure (CHF) of ischemic origin.

METHODS: The study involved 142 patients (85 men and 57 women, mean age 66,4 ± 10,5 years) with CHF NYHA II-IV functional class. To identify anxiety and depression were used Hospital Anxiety and Depression Scale (HADS), the scales of the Spielberger-Hanin and Beck's, QoL - Minnesota QoL Questionnaire "Living with Heart Failure» (MLHFQ) and the SF-36 questionnaire.

RESULTS: ADD prevalence in patients with CHF of ischemic etiology was 78.1 %, with the largest share in the combination of anxiety and depressive disorders. The deterioration of QoL was observed in all patients with CHF, but the most pronounced decrease in its registered patients with a combination of anxiety and depression. The obtained data was processed using the statistical suite Statistica 6.0 for Windows and presented as M ± σ (mean ± standard deviation).

CONCLUSIONS: The presence of ADD leads to a significant decrease in QoL of patients with CHF, the most significant of its deterioration observed in the combination of anxiety and depression.

The article presents the results of investigation of gastric mucosal microcirculation with the help of laser-Doppler flowmetry in acute phase of duodenal ulcer during 7 and 14-day eradication therapy. The study enabled to obtain some data on effectiveness of the two therapeutic eradication regimens as well as their impact on gastric mucosal microcirculation in the process of ulcer defects healing.

KEY WORDS: chronic heart failure, quality of life, , anxiety and depressive disorders

ЯКІСТЬ ЖИТТЯ ПАЦІЄНТІВ ІЗ ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ ІШЕМІЧНОГО ГЕНЕЗУ: РОЛЬ ТРИВОЖНО-ДЕПРЕСИВНИХ РОЗЛАДІВ

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МЕТА ДОСЛІДЖЕННЯ: оцінити якість життя (ЯЖ) пацієнтів з тривожно - депресивними розладами (ТДР) і хронічною серцевою недостатністю (ХСН) ішемічного генезу.

МЕТОДИ: обстежено 142 пацієнта (85 чоловіків і 57 жінок, середній вік 66,4 ± 10,5 років) з ХСН II - IV функціональних класів за NYHA. Для оцінки тривожності і депресії використовувалися Госпітальна шкала тривоги і депресії (HADS), шкали Спілбергера - Ханіна та Бека, ЯЖ - Мінесотський опитувальник ЯЖ «Життя з серцевою недостатністю» (MLHFQ) і опитувальник SF-36. Отримані дані оброблялися за допомогою статистичного пакету Statistica 6.0 for Windows и надавалися у вигляді M ± σ (середнє ± стандартне відхилення).

РЕЗУЛЬТАТИ: Поширеність ТДР у хворих на ХСН ішемічної етіології склала 78,1 %, найбільш питома вага припадала на поєднання тривожного і депресивного афективних порушень. Погіршення ЯЖ визначалося у всіх хворих на ХСН, однак найбільш виражене його зниження реєструвалося у пацієнтів з поєднанням тривожності і депресії.

ВИСНОВКИ: Наявність ТДР призводить до достовірного зниження ЯЖ пацієнтів з ХСН, при цьому найбільш істотне його погіршення спостерігається при поєднанні тривожності і депресії.

КЛЮЧОВІ СЛОВА: хронічна серцева недостатність, якість життя, тривожно-депресивні розлади

КАЧЕСТВО ЖИЗНИ ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ ИШЕМИЧЕСКОГО ГЕНЕЗА: РОЛЬ ТРЕВОЖНО-ДЕПРЕССИВНЫХ РАССТРОЙСТВ

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ЦЕЛЬ ИССЛЕДОВАНИЯ: оценить качество жизни (КЖ) пациентов с тревожно-депрессивными расстройствами (ТДуР) и хронической сердечной недостаточностью (ХСН) ишемического генеза.

МЕТОДЫ: обследованы 142 пациента (85 мужчин и 57 женщин, средний возраст 66,4 ± 10,5 года) с ХСН II-IV функциональных классов по NYHA. Для оценки тревожности и депрессии использовались Госпитальная шкала тревоги и депрессии (HADS), шкалы Спилбергера-Ханина и Бека, КЖ – Миннесотский опросник КЖ «Жизнь с сердечной недостаточностью» (MLHFQ) и опросник SF-36. Полученные данные обрабатывались при помощи статистического пакета Statistica 6.0 for Windows и представлялись в виде M ± σ (среднее ± стандартное отклонение).

РЕЗУЛЬТАТЫ: Распространенность ТДР у больных с ХСН ишемической этиологии составила 78,1 %, наибольший удельный вес приходился на сочетание тревожного и депрессивного аффективных нарушений. Ухудшение КЖ отмечалось у всех больных с ХСН, однако наиболее выраженное его снижение регистрировалось у пациентов с сочетанием тревожности и депрессии.

ВЫВОДЫ: Наличие ТДР приводит к достоверному снижению КЖ пациентов с ХСН, при этом наиболее существенное его ухудшение наблюдается при сочетании тревожности и депрессии.

КЛЮЧЕВЫЕ СЛОВА: хроническая сердечная недостаточность, качество жизни, тревожно-депрессивные расстройства

According to WHO, ischemic heart disease (IHD) complications including chronic heart failure (CHF) are the most common disability and death causes of working-age population in economically developed countries [1]. Despite significant advances of contemporary cardiology, the present guidelines and treatment results in IHD and CHF patients remain unsatisfactory. CHF progression shortens life, and significantly decreases its quality [2, 3]. Thereby the quality of life (QoL) improvement problem in CHF patients is highly relevant.

As multiple clinical trials signify, affective disorders can reliably worsen clinical and functional condition, decrease physical exercise tolerance and have negative influence on treatment compliance in CHF patients [4, 5]. There is an opinion that anxiety and depressive disorders (ADD), could seriously affect QoL in this group of patients [5, 6, 7].

Actually, modern life conditions increase emotional stress and psycho-emotional disorders incidence grew to epidemic numbers [8]. Wherein revealed ADD in CHF several times above its frequency in population [8, 9].

The purpose of this study was to obtain the QoL in the ischemic CHF patients with ADD.

MATHERIALS AND METHODS

142 patients were under observation (85 male and 57 female, mean age 66,4±10,5) with NYHA II-IV CHF. All patients had angina pectoris of II-III functional class, 86 of them (60,6 %) had history of myocardial infarction. Observed patients received standard CHF and IHD therapy (angiotensin converting enzyme inhibitors – 78 %, β-blockers – 63 %, diuretics – 79 %, aldosterone antagonists – 84 %, angiotensin II receptor blockers – 19 %, digoxin – 31 %, ω-3-polyunsaturated acids – 17 %, aspirin – 92 %, statins – 86 %, nitrates – 71 %).

All patients signed informed consents before the study initiation. Exclusion criteria were age less than 18, history of acute coronary syndrome in last 2 months, mental disorders, significant impairment of cognitive functions, alcohol or drug abuse, other psychoactive drug intake, severe concomitant pathology, cerebrovascular accident, decompensated diabetes mellitus, uncontrolled arterial hypertension, acquired and congenital valvular heart disease, chronic kidney or liver disease, oncologic and other severe concomitant diseases.

To detect and obtain the severity of anxiety and depression we used Hospital Anxiety and Depression Scale (HADS), Spielberger and Beck scales; for QoL – SF-36 and Minnesota Living with Heart Failure Questionnaire (MLHFQ) were used.

HADS is comprised of 14 statements and has 2 subscales – one for anxiety (even list items), another for depression (odd list items). Each statement has 4 variants of response. In interpreting the sum index of both subscales is taken to consideration and three ranges of it corresponded to: absence of anxiety/depression – 0-7 points, subclinical anxiety/depression - 8-10 points, clinically significant anxiety/depression - 11 points and over.

Spielberger scale was used to study severity of anxiety in the current study. The test results correspond of reactive anxiety level

at the particular moment and of personal anxiety as a temper trait. Personal anxiety indicates a stable tendency of an individual to perceive a large range of situations as threatening and to respond to them with anxiety. Reactive anxiety is characterized by disturbance, tension, nervousness at a particular time interval. The self-esteem scale of personal and reactive anxiety includes 20 questions-opinions. For each question, there are 4 possible answer choices of different intensity degree. Total score may range from 20 to 80 points. In interpreting of results one should focus on the following anxiety estimates: less than 30 points – the lowest, 31 - 44 points – moderate, 45 and over – severe.

Beck scale is used for self-assessment of depression and is fairly sensitive test to track dynamics of depressive disorders, which allows it to assess the effectiveness of treatment. It covers 21 symptoms of depression: low mood, pessimism, sense of dissatisfaction with themselves, frustration, guilt, self-blame, irritability, death drive, inability to work, sleep, etc. When completing the form, a patient should mark the option boxes that best fit his condition. For each question there are four possible statements that reflect different degrees of self-esteem and match score 0-3. In interpreting results the following score correspond of:

1) at least 11 points - no depression,
2) 11-19 - early signs of depression,
3) 19-26 - minimal severity of depression,
4) 26-30 - moderate depression,
5) more than 30 - severe depression.

MLHFQ, which was used in the current study, is one of the most common, relatively easy, informative and CHF-adapted questionnaires [2, 3, 6]. All its items may be divided into four subgroups. The first one – for physical abilities limitations assessment (items 2 – need for afternoon nap; 3 – ability to walk or climb stairs; 4 - ability to work at home or on a personal plot; 5 – impossibility of day trips; 6 – restful sleep; 7 - difficulties in relationships with family and friends; 9 - ability for active recreation and light sports; 12 – severity of dyspnea; 13 – fatigue effect on QoL). The second subgroup is comprised of questions which reflect emotional factors, (items 17 - feeling like a burden to family; 18 – feeling of helplessness; 19 – feeling anxiety; 20 - inability to concentrate and memory loss; 21 – feeling depressed). Items 8 (inability to earn a living) and 10 (impossibility of normal sexual life) comprise the third subgroup because of the lack of a clear link with the other parameters and each other. The fourth subgroup of factors consists of items 1 (edema), 14 (need in hospitalization), 15 and 16, related to the cost of treatment and its adverse effects. A patient responds to 21 questions, marking a column corresponding to his or her perception of the state. 0 points for the answer that the particular complication of the condition is not remarcable, and 5 points mean the most significant complication for the last month. Scores are added, 0 points correspond to the best health, 105 points – to absolute critical illness.

At the same time such a good technique as MLHFQ is cannot assess all QoL components [8]. In this regard, current study also used common international practice questionnaire SF-36. It consists of 11 sections and allows you to evaluate the patient's satisfaction to his or her physical and mental well-being, social functioning, self-esteem and QOL reflects the severity of pain. SF-36 questionnaire consists of 36 questions. Results are presented as scores of 8 scales, higher score indicates better QoL (100 – full health). The following indices are quantified:

1. PF — physical functioning which reflects the degree of health limitation of physical activities (such as self service, walking, climbing stairs, weightlifting, etc.);
2. RP — role physical functioning, reflects the impact of physical condition on role functioning (job, casual activities);
3. BP — physical (body) pain, pain intensity and its ability to affect casual activities such as housekeeping etc.;
4. GH — general health, gives an evaluation of the patient’s health status in the present and treatment perspective;
5. VT — vitality (means feeling full of energy, or, on the contrary, exhausted);
6. SF — social functioning; determined by the degree to which physical or emotional condition restricts social activities and communication;
7. RE — role emotional functioning — influence of emotional state on the role functioning; involves an assessment of the extent to which emotional state interfere with work or other daily activities (including big

time waste, reducing the amount of work, reduction of its quality, etc.);

8. MH — mental health, evaluates mental health, characterizes by mood (for depression, anxiety, overall positive emotions). The scales group into two separate indices – «physical health component» and «psychological health component».

The obtained data was processed using the statistical suite Statistica 6.0 for Windows and presented as M ± σ (mean ± standard deviation). The significance of differences between independent groups was determined by Student's t-test. Minimal acceptable statistical significance was at $p<0.05$.

RESULTS AND DISCUSSION

According to the total index of HADS, Spielberger and Beck questionnaires ADD were revealed in 111 (78,1 %) patients, 23 (16,2 %) of them had isolated anxiety, 32 (22,5 %) – isolated depression, and 56 (39,4 %) had both anxiety and depression (Fig. 1).

Incidence of ADD among females was statistically higher than in males (93,0 % and 83,5 %, respectively).

Patients with ADD (n=111) were included in group 1, those without affective disorders (n=31) formed the 2nd group.

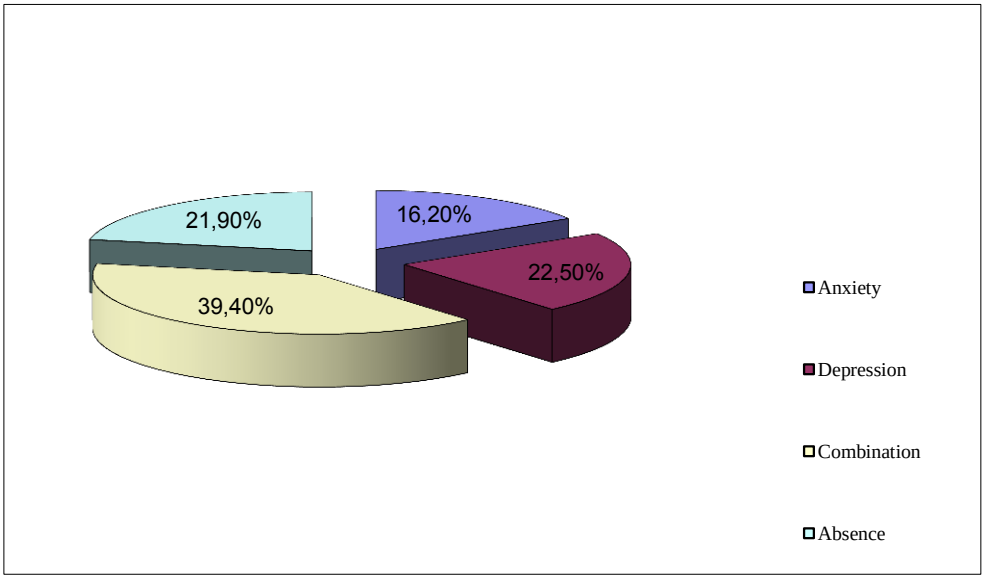

Fig. 1. ADD incidence in observed patients

ADD severity according to HADS, Spielberger and Beck questionnaires is presented in tab. 1

Table 1

Anxiety and depression severity (GPA) in the CHF patients with revealed ADD (M±sd)

ADD type	Used questionnaires, mean score		
	HADS	Spielberger	Beck
Anxiety	13,8 ± 2,5	41,6 ± 5,4 - personal 42,3 ± 4,8 - reactive	-
Depression	14,10 ± 3,7	-	27,2 ± 6,3

According to the scale of the Spielberger anxiety disorders were found in 77 (54,2 %) patients, 68 (47,8 %) had levels of both reactive and personal anxiety of «moderate» degree, 4 (2,8 %) had moderate personal and high reactive, 1 (0,7 %) - low personal and moderate reactive, and 5 (3,5 %) - high both personal and reactive anxiety.

When analyzing Beck scale survey depresssive disorders were detected in

83 (58,5 %) patients, and the minimal level of depression was detected in 7 (4,9 %), moderate - in 68 (47,8 %), severe - in 8 (5,6 %) patients.

The MLHFQ score of Group 1 patients averaged 62,4 ± 10,7, in Group 2 - 44,2 ± 9,5 ($p < 0.001$), indicating a significant decrease in QoL in patients with ADD compared with patients without affective disorders. QoL according MLHFQ in patients with various types of ADD and in their absence, is shown in Fig. 2.

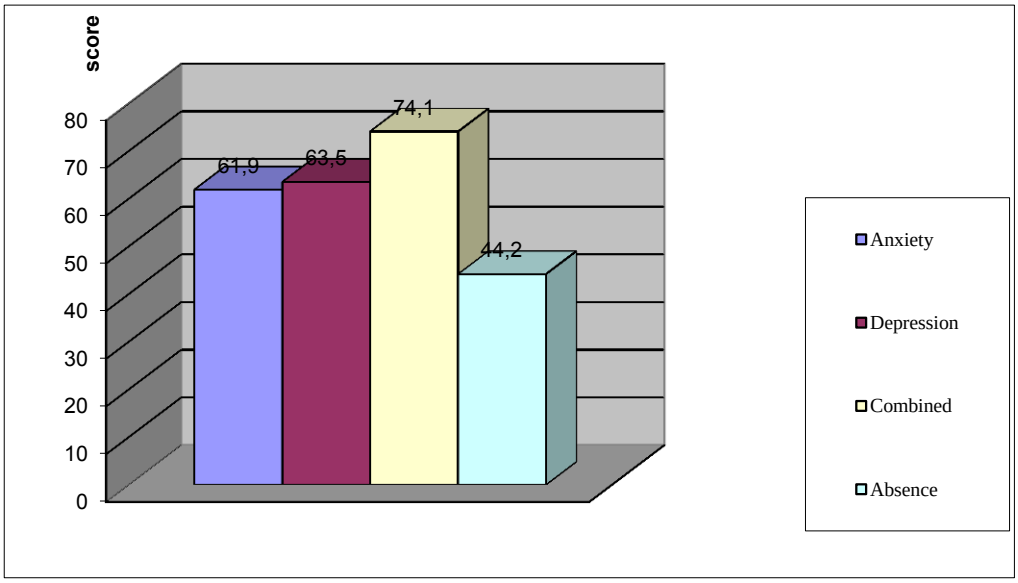

Fig. 2. QoL (according to MLHFQ) in patients with different types of ADD and in their absence

Thus, QoL indices in CHF patients with isolated anxiety were 61,9 ± 12,8, with isolated depression - 63,5 ± 14,1, in patients with a combination of anxiety and depression - 74,1 ± 15,2 points, those without mood disorders - 44,2 ± 13,3 points. Hence, QoL in patients with anxiety and depression alone or in combination was significantly worse ($p < 0.05$ all), than in patients without mental disorders. QoL study results based on SF-36 questionnaire are presented in tab. 2.

Table 2

QoL (by SF-36) in the patients with and without different ADD (M±sd)

Scale	Patients with anxiety (n=23)	Patients with depression (n=32)	Patients with anxiety and depression (n=56)	Patients without ADD (group 2) (n=31)
Physical functioning	45,3 ± 14,5*	42,0 ± 15,1*	36,8 ± 14,9**	61,9 ± 17,2
Role physical functioning	32,4 ± 9,7*	29,3 ± 11,88	22,6 ± 10,4**	52,3 ± 12,0
Physical pain	47,3 ± 11,7	46,8 ± 13,0	39,9 ± 10,1*	53,8 ± 14,2
Total health condition	40,5 ± 10,4*	41,3 ± 11,5*	34,0 ± 9,9**	51,4 ± 13,2
Vitality	47,7 ± 11,8	42,4 ± 13,2*	33,5 ± 14,7**	54,6 ± 13,3
Social functioning	51,8 ± 12,0*	50,3 ± 14,1*	43,2 ± 11,8**	67,2 ± 10,9
Role emotional functioning	45,8 ± 10,7*	46,5 ± 11,3*	29,4 ± 12,3**	65,9 ± 14,4
Mental health	49,4 ± 13,7*	48,0 ± 12,6*	42,3 ± 10,2*	62,5 ± 11,5

* - differences are statistically significant when compared to group 2, $p < 0,05$,
** - differences are statistically significant when compared to group 2, $p < 0,01$

The QoL deterioration was observed in all patients with heart failure, but the most pronounced its decrease was registered in patients with a combination of anxiety and depression. In patients without ADD, it was most significant in the scales of «role-physical functioning», «physical pain», «general health» and «vitality». The QoL scales of «role-physical functioning» and «general health» prevailed in the group of patients with anxiety alone; scales of «role- physical functioning0187», «general health» and «vitality» were predominant in the patients with isolated depression. A significant decrease in the scales of «role-physical functioning», «general health», «vitality» and «role-emotional functioning» in the analysis of QoL in patients with a combination of anxiety and depression was remarkable.

Thus, the prevalence of ADD in patients with CHF of ischemic etiology was 78,1 %, with the largest share in the combination of anxiety and depressive mood disorders group. The presence of ADD was associated with a significant decrease in QoL of patients with CHF, the most significant of its deterioration was observed in its combination with anxiety and depression.

The mechanisms of ADD negative impact on QoL in patients with CHF are complex and not fully understood. It is known that anxiety and depression come as additional factors in the reduction of their physical, mental and social activity, which are important components of QoL. In addition, the presence of physical symptoms that is directly caused by ADD (sleep disorder, loss or gain of weight, weakness, fatigue, etc.), also plays a role in the deterioration of QoL in these patients [10].

Importantly, the presence of ADD is associated with reduced efficiency of CHF treatment too, which could be explained by negative attitude of a patient to the therapy. It is shown that such patients have a low lifestyle and drug therapy compliance [11, 12].

The deterioration of QoL in the cohort of patients may also be due to the exacerbation of clinical manifestations of heart failure caused by the direct influence of anxiety and depression [13, 14]. The negative impact of ADD on the course and prognosis of CHF is implemented by a variety of pathophysiological mechanisms, among which activation of the hypothalamic-pituitary-adrenal axis, hyperproduction of proinflammatory cytokines, endothelial and platelet dysfunction are [15]. It is known that the activation of the hypothalamic-pituitary-adrenal axis, which is observed in anxiety and depression is often accompanied by rising levels of corticotrophin-releasing factor and adrenocorticotropic hormone production by the pituitary gland. It increases the production of cortisol and norepinephrine, increases heart rate and blood pressure, increases myocardial oxygen demand, reduces heart rate variability, promotes sodium and water retention, which paves the way for the progression of heart failure and the occurrence of life-threatening arrhythmias [9].

An equally important role in the negative impact of ADD on the cardiovascular system is played by overproduction of proinflammatory cytokines under their influence. In particular, patients with depression were found to have unusually high levels of interleukin-1, interleukin-6, tumor necrosis factor, C-reactive protein, which can also contribute to the progression of CHF, because of their accelerating effect on pathological remodeling of the left ventricle and its contractile dysfunction deterioration [15].

Thus, pathophysiological conditions accompanying anxiety and depression, undoubtedly contribute to the progression of CHF severity. On the other hand, the progression of CHF, in turn, exacerbates the patient's ADD, thus completing «vicious» cycle and contributing to the further worsening of their QoL.

CONCLUSIONS

The presence of ADD is associated with a significant decrease in QoL of patients with CHF, the most significant of its deterioration observed in the combination of anxiety and depression

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THE INTERNET ADDICTION OF PATIENTS WITH PSYCHOPATHOLOGICAL CONSEQUENCES OFCRANIOCEREBRAL INJURY

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Based on the Kharkov Regional Clinical Psychiatric Hospital № 3 examined 100 male patients aged 38,35 ± 0,96 years, with psychopathological consequences of craniocerebral injury (TBI). The control group consisted of 73 healthy male volunteers aged 36,97 ± 1,73 years. The frequency of different degrees of Internet use was assessed by using AUDIT-like test INTERNET-UDIT (Internet Use Disorders Identification Test) and calculation of addictive potential in groups.

In patients with psychopathological consequences of craniocerebral trauma, despite the high prevalence of lack of experience «usage» of the Internet, high degrees of addiction and dependence were reported. The addictive potential of the Internet addiction in the study group exceeded 32 % of that of the control group.

KEY WORDS: internet addiction disorder (IAD); AUDIT-like tests; addictive potential; psychopathological consequences of craniocerebral injury

ІНТЕРНЕТ-АДДИКЦІЯ У ПАЦІЄНТІВ ІЗ ПСИХОПАТОЛОГІЧНИМИ НАСЛІДКАМИ ЧЕРЕПНО-МОЗКОВОЇ ТРАВМИ

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На базі Харківської обласної клінічної психіатричної лікарні № 3 обстежено 100 пацієнтів чоловічої статі у віці 38,35 ± 0,96 років с психопатологічними наслідками перенесеної черепно-мозкової травми (ЧМТ). Групу порівняння склали 73 здорових добровольця чоловічої статі у віці 36,97 ± 1,73 років. У групах вивчалася частота зустрічальності різних ступенів захопленості інтернетом за допомогою INTERNET-UDIT (Internet Use Disorders Identification Test) та визначення адиктивного потенціалу.

У пацієнтів з психопатологічними наслідками перенесеної ЧМТ, незважаючи на значне переваження відсутності досвіду «вживання» інтернету, зареєстровані високі ступені пристрасті та залежності. Аддиктивний потенціал інтернет-залежності перевищував на 32 % відповідний показник контрольної групи.

КЛЮЧОВІ СЛОВА: інтернет-аддикція, AUDIT-подібні тести, аддиктивний потенціал, психопатологічні наслідки черепно-мозкової травми

ИНТЕРНЕТ-АДДИКЦИЯ У ПАЦИЕНТОВ С ПСИХОПАТОЛОГИЧЕСКИМИ ПОСЛЕДСТВИЯМИ ЧЕРЕПНО-МОЗГОВОЙ ТРАВМЫ

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На базе Харьковской областной клинической психиатрической больницы № 3 обследовано 100 пациентов мужского пола в возрасте 38,35 ± 0,96 лет с психопатологическими последствиями перенесенной черепно-мозговой травмы (ЧМТ). Группу сравнения составили 73 здоровых добровольца мужского пола в возрасте 36,97 ± 1,73 лет. В группах изучалась частота встречаемости различных степеней увлечённости интернетом с помощью INTERNET-UDIT (Internet Use Disorders Identification Test) и определения аддиктивного потенциала.

У пациентов с психопатологическими последствиями перенесенной ЧМТ, несмотря на значительное преобладание отсутствия опыта «употребления» интернета, зарегистрированы высокие степени пристрастия и зависимости. Аддиктивный потенциал интернет-зависимости превышал на 32 % таковой в контрольной группе.

КЛЮЧЕВЫЕ СЛОВА: интернет-аддикция, AUDIT-подобные тесты, аддиктивный потенциал, психопатологические последствия черепно-мозговой травмы

The Internet addiction disorder (IAD), or, more broadly, Internet overuse, problematic computer use or pathological computer use is excessive computer use that interferes with daily life [1]. Study of Internet addiction in different countries is widely reported in the literature [2, 3, 4].

In several studies, where the authors have identified signs of depending which fulfill the criteria DSM-IV: the uncontrolled use, a significant stress effect, conjugation financial problems, social and educational difficulties, provocation of symptoms that characterize hypomania, - researchers operated extremely small samples and did not use clinical and experimental psychological research methods [5, 6].

Using AUDIT-like test INTERNET-UDIT (Internet Use Disorders Identification Test - test for detecting disorders related to passion for the Internet) showed its effectiveness in survey of addictive behavior among young people in Ukraine [7, 8].

The frequency of different degrees of the Internet addiction among patients with psychopathological consequences of craniocerebral injury still has not been studied.

OBJECTIVE

To study the frequency of different degrees of the Internet addiction among patients with psychopathological consequences of cranio-cerebral injury.

MATERIALS AND METHODS

The research work was carried in two groups. The study group consisted of 100 male patients aged 38,35 ± 0,96 years, with psychopathological consequences of craniocerebral injury who were examined at the Kharkov Regional Clinical Psychiatric Hospital № 3. The control group consisted of 73 healthy male volunteers aged 36,97 ± 1,73 years.

The research was conducted by using AUDIT-like test INTERNET-UDIT (№ 29 597, 27.07.2009) and calculation of addictive potential (the ratio of the number of people who have experience of the «usage» dependency object was accompanied by the formation of the corresponding dependence of the total number of persons who had experience of this «usage», expressed as a percentage, i.e. quantitative measure of the ability of the Internet to cause addiction) [7, 8].

Interpretation of the results of the test carried out on the basis of calculation of received grade points: number of points in the range of 1 to 7 were classified as Internet surfing (Zone I), from 8 to 15 - as an predilection to the internet (Zone II), from 16 to 19 - predilection to the Internet at the stage of formation of addiction (Zone III), from 20 to 40 – formed addiction (dependence) (Zone IV).

Mathematical and statistical analysis of received grade points was performed using the software Microsoft Office XL 2010 with the calculation of the percentage (P) and its error (sp). Valid data were recognized with the significance level $p < 0.01$. The indicator was calculated using Microsoft Excel and SPSS 15.0 for Windows.

RESULTS AND DISCUSSION

In patients with psychopathological consequences of craniocerebral trauma, compared with healthy individuals of the control group, despite the high prevalence of lack of experience «usage» of the Internet (35 %), there was enthusiasm for the Internet by 63 % less while the predilection to the internet was recorded at 4 % more, predilection to the Internet at the stage of formation of addiction revealed by 6 % more, formed addiction (dependence) registered 18 % more than in the control group of healthy volunteers. The addictive potential of the Internet addiction in the study group exceeded 32 % of that of the control group (33 % vs 1 %). The frequency of different degrees of the Internet addiction among patients with psychopathological consequences of craniocerebral injury is presented in tab. 1.

Table 1

The frequency (P±sp) of different degrees of the Internet addiction among patients with psychopathological consequences of craniocerebral injury

Degrees of Internet addiction	**Study group**	**Control group**	**comparison**
noexp.	42 ± 6%	7 ± 3%*	+35%
Zone I	16 ± 4%	79 ± 5%*	-63%
Zone II	14 ± 4%	10 ± 3%	-4%
Zone III	9 ± 3%	3 ± 2%	-6%
Zone IV	19 ± 5%	1 ± 1%*	+18%

*p ≤0,01 - in current values versus the control group

According to published data, the prevalence of the internet addiction ranges from 1 to 5 % of the population [4-6].

The received data of frequency of the internet addiction among healthy population in our study correspond to those described in [4-6, 9-13].

The obtained data of frequencies of the internet addiction among patients with psychopathological consequences of craniocerebral injury are new. However, it is known that traumatic brain injury (TBI) may cause emotional, social, or behavioral problems and changes in personality [14-17], that allows to speak that the craniocerebral injury increases the tendency to form depending conditions, changing additive status of persons with traumatic brain lesions compared with their healthy peers.

CONCLUSIONS:

1. The frequency of Internet useamong patients with psychopathological consequences of craniocerebral injurywas 35 % less than in the control group.

2. Despite the high prevalence of lack of experience «usage» of the Internet (35 %), the Internet addiction among patients with psychopathological consequences of craniocerebral injury on the level of internet dependence registered 18 % more than in the group of healthy volunteers.

3. The addictive potential of the Internet addiction among patients with psychopathological consequences of craniocerebral injury exceeded 32 % of that of the control group.

PERSPECTIVES FOR FUTURE RESEARCH

Using AUDIT-like test INTERNET-UDIT in study the frequency of occurrence of various degrees of the Internet addiction for developing and improving diagnostic and therapeutic protocols of care patients with psychopathological consequences of traumatic brain injury.

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Clinical case

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PRINZMETAL ANGINA PECTORIS IN CLINICAL PRACTICE: POSSIBILITY OF CHRONO-THERAPEUTIC APPROACH AND LIMITATIONS OF COMORBIDITY

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Prinzmetal Angina (synonyms: vasospastic angina, variant angina) in accordance with the definition of, it is caused by coronary artery spasm which occurs during sleep at night, between midnight and early morning and manifested with ST segment elevation on the ECG.

Frequent «attachment» to the attacks of a certain period of the sleep period, gives you the opportunity to use chronomedical approaching the treatment of patients suffering from it, as demonstrated by our observation.

On the other hand, for adulthood comorbidity is characteristic, and Prinzmetal is no exception, which we wanted to show, studying the clinical case.

KEY WORDS: prinzmetal angina, vasospasm, ST segment elevation, chronotropic effects, dysregulation

СТЕНОКАРДІЯ ПРИНЦМЕТАЛА В РЕАЛЬНІЙ КЛІНІЧНІЙ ПРАКТИЦІ: МОЖЛИВІСТЬ ХРОНОТЕРАПЕВТИЧНОГО ПІДХОДУ ТА ОБМЕЖЕННЯ КОМОРБІДНОСТІ

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Стенокардія Принцметала (синоніми: вазоспастична стенокардія, варіантна стенокардія) викликається спазмом коронарної артерії, виникає вночі під час сну, у проміжку між серединою ночі і рано вранці та проявляється підйомом сегмента ST на ЕКГ.

Часта «прихильність» нападів до певного проміжку періоду сну дає можливість використовувати у лікуванні пацієнтів хрономедичний підхід, що демонструється нашим спостереженням.

З іншого боку, для дорослого віку характерною є коморбідність, і стенокардія Принцметала не є винятком , що ми також показали , розглядаючи клінічний випадок.

КЛЮЧОВІ СЛОВА: стенокардія Принцметала, вазоспазм, елевація сегмента ST, хронотропія, порушення регуляції

СТЕНОКАРДИЯ ПРИНЦМЕТАЛА В РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКЕ: ВОЗМОЖНОСТЬ ХРОНОТЕРАПЕВТИЧЕСКОГО ПОДХОДА И ОГРАНИЧЕНИЯ КОМОРБИДНОСТИ

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Стенокардия Принцметала (синонимы: вазоспастическая стенокардия, вариантная стенокардия) вызывается спазмом коронарной артерии, возникает ночью во время сна, в промежутке между полуночью и ранним утром и проявляется подъемом сегмента ST на ЭКГ.

Частая «привязанность» приступов к определенному промежутку периода сна дает возможность использовать в лечении страдающих ею пациентов хрономедицинский подход, что демонстрируется нашим наблюдением.

С другой стороны, для взрослого возраста характерной является коморбидность, и стенокардия Принцметала не является исключением, что мы также хотели показать, рассматривая клинический случай.

КЛЮЧЕВЫЕ СЛОВА: стенокардия Принцметала, вазоспазм, элевация сегмента ST, хронотропность, нарушение регуляции

INTERVIEW DATA

Female, 43 years old, employee at wagons' depot, date of admission: 10.10.12.

Complaints of pain in the heart pressing nature, radiating to the left arm, left shoulder, chin, arising during sleep between 3 and 3,30 am and accompanied by a feeling of anxiety, sweating, severe weakness, shortness of breath when walking fast, recurrent headaches in occipital region, a feeling of disruption of heart rhythm not associated with physical activity. Recurrent pain in the neck and the right upper extremity. Numbness of the 4-5 fingers of the left upper extremity; constant cough in the morning with expectoration of scanty sputum.

She has been suffering from hypertension since 2009. An increase in blood pressure to 170/90 mm Hg is noted. Usual blood pressure - 120/80 mm Hg. She was treated in the outpatient department with antihypertensive drugs taken regularly. She can not specify names of the drugs taken.

In 7.10.12 in the afternoon, after a psychological and emotional load, she felt pain behind the breastbone for the first time, which radiate to the left arm, left scapula, accompanied by sore throat, blackout, and sweating and lasted 15-20 minutes. The ambulance arrived with the squad. No abnormalities were registered on ECG. On 10.08.12 she began to feel these complaints at night but she took no action.

On 10.10.12, she went to a doctor and was sent to the 5-th Central Clinical Hospital for examination and treatment.

According to life history of the patient: frequent childhood respiratory diseases, in 2 or 3 years of age - with bilateral pneumonia. Chronic bronchitis - about 15-20 years. In 2012 received medical treatment for vertebral sided cervico-brachial neuralgia. Tuberculosis, diabetes, viral hepatitis patient denies. She hasn't undergone any operations. Gynecological history: chronic left-sided salpingitis. Family history is not burdened. Allergies to medications, food, purged household chemicals, are absent. She has been smoking 8-10 cigarettes a day for 20 years. No abuse of alcohol.

Objectively, clear consciousness, active position. Overweight, height is 1. 67 m, weight - 80 kg BMI = 34.8 kg/m2, waist circumference of 91 cm, skin is of normal color, the thyroid gland and peripheral lymph nodes were not enlarged visual, painless on palpation. Respiratory system: percussion - sounds over the light lung; auscultation - hard breathing, no wheezing. Circulatory system: percussion - offset to the left border of the relative dullness of 2 cm from the left mammilar line in the 5th intercostal space; auscultation: muffled heart sounds, rhythmic. HR 60/min. Pulse 60 beats/min, regular, satisfactory filling, BP 110/70 mm Hg on both hands (on a background of antihypertensive therapy). No peripheral edema. Tongue is moist, abdomen is soft, painless. Pasternatsky's symptom is negative on both sides. Marked tenderness at paravertebral points in the cervical-thoracic spine. Left humerus is painless, active and passive movements are maintained.

RESULTS OF LABORATORY AND FUNCTIONAL STUDIES

Complete blood count: polycythemia ($4.75x10^{12}$ g/l), leukocytosis (11.6×10^{9} g/l), relative lymphocytosis (44 %). Increased ESR (20 mm/h).

Urinalysis: figures in the normal range.

Biochemical analysis of blood: increased ALT (38 U/L).

Analysis of lipid: hyperlipoproteinemia type 2b according to Fredrickson criteria.

ECG showed sinus rhythm, regular, left ventricular hypertrophy. Heart rate 59 beats/min.

Echocardiography: moderate thickening of the left ventricular (thickness of the posterior wall of the left ventricle 11.34 mm). First degree of mitral regurgitation. Akinesia zones not found, valves are intact. EF – 79 %.

Veloergometry: negative.

Coronary angiography: right type of coronary blood supply. Left coronary artery – the eccentric atherosclerotic plaque up to 20 %

of the distal portions of the trunk. Local concentric atheroma up to 30 % in the middle segment of the left anterior descending artery. Atheroma to 15 % at the mouth of the circumflex artery. Right coronary artery - without visible atherosclerotic lesions.

1st. Holter ECG monitoring (16.10.12): sinus rhythm, average heart rate - 70 beats / min, maximum heart rate - 124 beats / min (at 20:12), minimum heart rate - 49 beats / min on background AV block II stage (Mobitz 2) at 03:27. Circadian index - 1.26. In 03:25-03:29 registered episode of ST elevation by 3 mm, accompanied by the development of AV block of the I stage (maximum PQ 288 ms) in the future with the addition of AV block II stage (Mobitz 2). Episode coincided with an attack in the night, noted in the patient diary.

2nd. Holter ECG monitoring (17.10.12): Against the backdrop of the main sinus rhythm recorded: average heart rate during the day 73 beats/min, at night 61 beats/min, maximum heart rate 109 beats / min at 06:55, minimum heart rate 46 beats / min at 01 41. Circadian index – 1,19; episode of ST segment elevation greater than 2 mm in the night between 1:38-1:44 and 3:21-3:26. In the period following ischemia detected arrhythmias. Singles premature beats (5 in total) on the background of bradycardia (1 episode). Sinus tachycardia, heart rate 104 beats/min (1 episode). AV block I stage and AV block II stage (Mobitz 2) (1 episode 1).

Spondylography: On digital spondylograms thoracic spine in the frontal and lateral projections: Bone-destructive changes are not detected. Right-sided scoliosis with the apex of the arc at the level of Th 7.The initial manifestations of osteochondrosis more in the lower part. Paravertebral soft tissue without features.

At neurology: bilateral muscle-tonic cervico-brachial neuralgia, dorsalgia due to degenerative disc disease, relapsing course, the stage of the protracted deterioration, severe pain.

Consultation of gynecologist: chronic left-sided salpangitis in remission.

CLINICAL DIAGNOSIS

Underlying disease: coronary artery disease. Vasospastic angina. Coronary atherosclerosis (CVG from 19.10.12). Hyperlipoproteinemia type 2b according to Fredrickson's criteria. Transient AV block I stage, II stage (Mobitz 2). Single supraventricular extrasystoles. Arterial hypertension stage II, 2 degree. Hypertensive heart. Risk 3. 1st stage of heart failure, 1st functional class with preserved systolic function.

Comorbidities: COLD. Obesity I degree. Chronic left-sided adnexitis in remission. Osteochondrosis of the cervical-thoracic scoliosis of the thoracic spine, functional failure of joints 0. Bilateral muscular-tonic cervico-brachial neuralgia, dorsalgia recrudescence.

RECOMMENDED TREATMENT

Lifestyle modification

Smoking cessation. Reduction in body weight (diet restriction of animal fats, carbohydrates, salt).Physical activity (therapeutic exercises, jogging, swimming). In the period of remission of osteochondrosis - massage cervical-thoracic spine.

Medication:

- Amlodipine 10 mg at bedtime,
- Nitroglycerin (1tab) under the tongue for relief of pain attack (allowed up to 5 tablets for 5 minutes),
- Atorvastatin 10 mg per day,
- Enalapril maleate 10 mg per day,
- Cardiomagnyl 75 mg per day during the meal.

Planned hospitalization 23.04.13: satisfactory condition. Blood pressure 130 /90 mm Hg, pulse 68 beats/min. Slowing to 2-4 attacks of heart pain per month, reducing the intensity of pain. ECG showed sinus rhythm, regular, HR 73 beats/min deviation of electrical axis of heart to the left. Echocardiography: heart cavity is not an extension, moderate thickening of the walls of the left ventricle (Thickness of posterior wall of left ventricle 11.26 mm), Akinesia zones not found, valves are intact. EF = 79 %. Holter ECG monitoring (23.04.13): circadian index of 1.17. Found: 6 tachycardias, the total duration of 8 minutes 40 second. Single supraventricular arrhythmias. Episodes of ST elevation not detected. Noted a significant positive trend.

Prinzmetal angina usually occurs in adulthood, usually at night, often in women [1], which corresponds to our observation. Present atherosclerotic plaques exceed 30 % of the lumen of the coronary arteries and do not provoke attacks during the day, not counting the very first episode, which, after a demonstration was not repeated. Of the risk

factors spasm, including circadian dysregulation, physical and mental distress, the medication (ephedrine, ergonovine, bromocriptine, 5-fluorouracil, propofol), smoking, cocaine use, our patient had two - circadian dysregulation (circadian index 1, 19), and smoking. Characteristic of the development of attack rhythm disturbances in the form of transient atrioventricular and intraventricular blocks, frequent ventricular arrhythmia of high grade, paroxysmal tachycardia and ventricular fibrillation [2] in our case were atrioventricular block of 1st and 2nd degree. Isolated supraventricular extrasystoles and paroxysmal sinus tachy-cardia. The European Society of Cardiology recommended methods of diagnosis [3] (ECG during an attack , coronary angiography for evaluation of coronary vessels, intracoronary provocative tests for the identification of coronary spasm , Holter ECG monitoring to detect shifts of ST segment), we used coronary angiography and Holter ECG monitoring . Also, following the recommendations of the European Society of Cardiology [3], we have assigned therapy with calcium antagonists and nitrates.

CONCLUSION

Clinical case is interesting primarily by chronotherapeutic approach in the treatment, when the occurrence of spasms around the same time of night sleep (about 3-3:30 am) allowed to assign amlodipine once a day at bedtime with significant positive dynamics in the quality of life and decrease in the frequency of attacks to 2-4 per month with a decrease in pain intensity.

It is important to pay attention to comorbidity with other diseases in the case of Prinzmetal angina (atherosclerosis, obesity, hypertension, low back pain, circadian disorders) that might provoke attacks and aggravate its course and intervention which contributed to a better clinical outcome.

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DIAGNOSIS AND CHOICE OF THE MANAGEMENT STRATEGY IN PATIENT WITH CARDIAC RESYNCHRONIZATION THERAPY IN CASE OF CHRONIC HEART FAILURE WITH MULTIMORBIDITY

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The importance of correct diagnosis and appropriate treatment is illustrated by the example of a clinical case in patient with multimorbidity. The diagnosis was confirmed in accordance with the modern diagnostic criteria and classifications. The pacemaker with dislocated electrode was replaced and cardiac resynchronization therapy device was implanted because of chronic heart failure with medical therapy optimization.

KEY WORDS: chronic heart failure, cardiac resynchronization therapy, multimorbidity

ВСТАНОВЛЕННЯ ДІАГНОЗУ І ВИБІР ТАКТИКИ ВЕДЕННЯ ПАЦІЄНТА З ІМПЛАНТОВАНИМ КАРДІОРЕСІНХРОНІЗУЮЧИМ ПРИСТРОЄМ З ПРИВОДУ ХРОНІЧНОЇ СЕРЦЕВОЇ НЕДОСТАТНОСТІ В УМОВАХ МУЛЬТІМОРБІДНОСТІ

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На прикладі клінічного випадку проілюстрована значущість постановки вірного діагнозу і проведення адекватного лікування у пацієнтів з мультіморбідної патологією. У пацієнта уточнюється діагноз у відповідності з діючими критеріями діагностики та класифікаціями, замінюється електрокардіостимулятор з електродом, що дислокувався на пристрій для кардіоресинхронизації у зв'язку з хронічною серцевою недостатністю і оптимізується медикаментозна терапія.

КЛЮЧОВІ СЛОВА: хронічна серцева недостатність, кардіоресінхронізірующая терапія, синдром преекзітації, мультіморбідность

ПОСТАНОВКА ДИАГНОЗА И ВЫБОР ТАКТИКИ ВЕДЕНИЯ ПАЦИЕНТА С ИМПЛАНТИРОВАННЫМ КАРДИОРЕСИНХРОНИЗИРУЮЩИМ УСТРОЙСТВОМ ПО ПОВОДУ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ В УСЛОВИЯХ МУЛЬТИМОРБИДНОСТИ

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На примере клинического случая показана значимость постановки правильного диагноза и проведения адекватного лечения у пациентов с мультиморбидной патологией. У пациента уточняется диагноз в соответствии с действующими критериями диагностики и классификациями, заменяется электрокардиостимулятор с дислоцированным электродом на кардиоресинхронизирующее устройство в связи с хронической сердечной недостаточностью и оптимизируется медикаментозная терапия.

КЛЮЧЕВЫЕ СЛОВА: хроническая сердечная недостаточность, кардиоресинхронизирующая терапия, синдром преэкзитации, мультиморбидность

Cardiac resynchronization therapy (CRT) is a firmly established method for treatment of chronic heart failure (CHF). In accordance withthe recommendations [1, 2], CRT is indicatedin patients with left ventricle ejection fraction (EF) ≤ 35 %, QRS ≥ 120 ms and FC III-IV CHF, who are undergoing optimal medical therapy without any positive effect. The recommend-dations, however, do not take into account multimorbidity factors which can affect the pharmacological strategy after cardiac resynchronization therapy device implantation [1, 3, 4].

This clinical case represents the full range of diagnostic and therapeutic applications.

Our patient was 62 years old male, chief specialist in the sphere of energy. Diagnosis of the establishment which had directed was the following:

Primary: Dilated cardiomyopathy (DCM). Secondary pulmonary hypertension syndrome. Hypertensive heart disease, degree II, stage 2, high cardiovascular risk. Mitral and tricuspid valves relative failure. CHF II B, FC III (with reduced left ventricular function (EF – 17 %)). Status after implantation of cardiac resynchronization DDD (RV) pacing. Dislo-cation of left ventricular electrode.

Comorbidities: Chronic obstructive pulmonary disease (COPD). Gout, gouty arthritis, remission stage. Ankylosing spondylitis, central form, clinical stage III, FC II.

On admission, the patient complained of general weakness, decreased working ability, dyspnea with non-significant physical exertion (climbing on the second floor, walking about 500 m) – that grows in horizontal position, especially at night; of cough with scanty white sputum at night, feet and legs pastosity, pain in the left first metatarsophalangeal joint with the swelling and redness, lower thoracic and lumbar spine pain and restriction, crunch during movements, especially just after a state of rest and at night, morning stiffness; with weight loss being 20 kg (May-August 2013) due to severe distress, and futher rapid weight gain becoming 7 kg in September-October 2013.

THE HISTORY OF THE DISEASE

The patient has been feeling sick since February 2002, when angina was diagnosed. He took the following medications: aspirin, nitroglycerin, atenolol, nadroparin calcium.

In April 2007 the condition of the patient deteriorated. Echocardiography: Calcification of posterior flap of the aortic valve with its limited mobility (perhaps because of the nature of atherosclerotic transferred valvulitis). The slight acceleration of blood flow in the aortic valve, aortic valve regurgitation, degree 2. Dilatation of left heart chambers. The relative failure of the mitral valve, degree 2. The relative failure of tricuspid and pulmonary valves. Diffuse decrease in contractile function of the left ventricular myocardium, postcapillary pulmonary hypertension, degree 1. Echo features of the aortic defect. Cardiomyopathy. The therapy was the following: aspirin, captopril, carvedilol, indapamide.

In April 2009, the therapy was made again by the medical establishment. Drug therapy included: ivabradine, spironolactone, torasemide, ramipril, enoxaparin sodium.

In March 2010, the diagnosis was the following:

Dilated cardiomyopathy of unknown etiology. Secondary pulmonary hypertension syndrome. Hypertensive heart disease, degree II. CHF II B, FC IV (with reduced left ventricular systolic function (EF – 23 %)), with acute left ventricular failure attacks. Bilateral pleural effusion. Therapy: ivabradine, spironolactone, ramipril, apixaban.

In September 2012, the diagnosis included:

Small ischemic stroke in the vertebralbasilar pool with atactic-vestibular syndrome, left-sided pyramidal insufficiency. Cerebral atherosclerosis. Encephalopathy, degree II. Coronary heart disease (CHD). Ischemic dilated cardiomyopathy. Left bundle branch block. CHF II A (with left ventricular systolic dysfunction (EF – 23 %)), QRS complex 160 ms, refractory to medical therapy, the negative dynamics of echocardiography, the presence of cardiac dyssynchrony echocardiography markers. Cardiac resynchronization therapy device implantation was recommended. Therapy: crystalloid plasma, L-lysine, citicoline, actovegin, heparin, metoclopramide, dexamethasone.

In October 2012, pacemaker implantation (Medtronic Vitatron) in DDD (RV) mode was made. The electrode localization was the following: atrial – in the right atrial, right ventricular electrode – interventricular septum, left ventricular electrode – a side

wall of the left ventricle. Therapy: cefuroxime, ramipril, furosemide, spironolactone. After pacemaker implantation, QRS complex duration was 120 ms, EF – 32 %.

In June 2013, the patient was hospitalized into cardiological department with complains of dyspnea, decreasing exercise tolerance. Chest X-ray – dislocation of left ventricular electrode. QRS – 138 ms, EF – 17 %.

The patient was transferred to the cardiothoracic surgical department of the SI «Zaytsev V.T. Institute of General and Emergency Surgery NAMS of Ukraine», for the surgery – replacement pacemaker and cardiac resynchronization therapy. The device was disconnected.

LIFE HISTORY

Gout, gouty arthritis, activity 0, since 2007 (allopurinol 100 mg/day).

Ankylosing spondylitis, central form, activity 0. FJI III, since 2008.

COPD. Chronic obstructive bronchitis. PF, stage 1, since 2013.

Diabetes, infectious disease, rheumatism, tuberculosis, sexually transmitted diseases are denied.

Smoking, alcohol abuse, taking drugs are denied.

Allergic history is not burdened.

ADMISSION OBJECTIVE STATUS

The patient's general condition is characterized as of an average severity. Consciousness is clear. Skin is pale. During percussion lungs border were normal. Lungs auscultation – a weakened vesicular breathing. Cardiac percussion – border of the relative cardiac dullness is extended: the right – in the i/c space III to 1.5 cm outside of L. parasternalis dextra, left – in the i/c space V to 1.5 cm outside on L. clavicularis media, upper – in i/c space III on L. parasternalis sinister. Heart sounds are rhythmic, muffled at all points of auscultation. Tone I weakened at the top. Tone II strengthened on the aorta and the pulmonary artery. Systolic murmur at the apex. Heart rate (HR) = pulse = 52 beats / min. BP – 110/70 mm Hg on both hands. Abdomen was soft and painless in all regions during palpation. The liver enlarged for 2 cm under the costal margin, the spleen not palpable. Kurlov's liver dimensions 11 cm x 10 cm x 9 cm. Legs and feet with peripheral edema. Negative sign of a beating from both sides. Normal stool and urine output.

THE LABORATORY STUDIES

Complete blood count and urinalysis within the physiological range.

Biochemical analysis of blood: total bilirubin (41,9 mmol/l), direct bilirubin (13,5 mmol/l), urea (18,7 mmol/l), creatinine (0,204 mmol/l), ALT (72,174 U/L) were increased.

Coagulation: recalcification time was increased to 130 seconds.

THE INSTRUMENTAL METHODS

Chest X-ray (09.10.2013): transparent tissue of the lungs, pulmonary diffuse pattern is strengthened by the veins, the roots are not changed, sinuses are free, heart was expanded in diameter at the expense of the left atrium and ventricle, aortosclerozis.

ECG (11.10.2013): sinus rhythm, regular, LBBB, heart rate = 62 beats / min, QRS = 138 ms.

Echocardiography (11.10.2013): sclerotic changes in the aorta, dilatation of the left and right atrial cavity, marked hypertrophy of the left ventricle, moderate pulmonary hypertension, a small aortic and mitral valves, the electrodes in the right cavities of the heart. LV systolic dysfunction. EF – 17 %.

Ultrasonography of the abdomen (11.10.2013): indirect signs of stagnation in the systemic circulation. Free fluid in the abdominal cavity.

The main clinical symptoms are:

- combined heart defect
- arterial hypertension
- congestive heart failure
- cardiomegaly
- encephalopathy
- cytolysis
- cholestasis
- articular syndrome
- left ventricular electrode dislocation

THE DIAGNOSIS

Diagnostic criteria for dilated cardiomyopathy (L. Mestroni, 1992) [5]: the patient has criteria that exclude this pathology: arterial hypertension (systolic blood pressure >160 mm Hg and diastolic blood pressure 100 mm Hg), documented and confirmed by

repeated measures and/or the presence of organ – target coronary artery disease, systemic disease (gout).

Classification of hypertension by blood pressure level [6]: hypertension, degree 2 (systolic blood pressure (SBP) 160-179 mm Hg and diastolic blood pressure (DBP) 100-109 mm Hg), very high risk due to organ damage (minor ischemic stroke, 2012), stage III (small ischemic stroke, 2012).

Classification of chronic heart failure [7]: stage III – final, dystrophic circulatory failure, severe hemodynamic instability, persistent changes in metabolism and function of irreversible changes in the structure of tissues and organs, III FC – significant limitation of physical activity, systolic dysfunction of the left ventricular ejection fraction of 40 % or less.

Among the characteristic clinical and laboratory parameters for the COPD, the patient has only cough, dyspnea, decreased exercise tolerance. These complains developed as a result of stagnation in the vessels of the pulmonary circulation on the background of chronic heart failure. Hence there is no reason to confirm the diagnosis of COPD [8].

Ankylosing spondylitis. Roman diagnostic criteria (International Congress, 1961, Rome) [9] – there are 2 diagnostic criteria of 6, which is not enough to confirm this diagnosis.

Criteria for diagnosis of gout (SL Wallace et al., 1977) [10] – 6 of 12 diagnostic criteria allowing a large base suspected gout.

Clinical classification of gout (Institute of Rheumatology, 1995) [10]: primary gout, gouty arthritis, intermittent flow with the defeat of the left first metatarsophalangeal joint. Activity 0. Functional joint insufficiency (FJI) 0.

Criteria for diagnosis of osteoarthritis of the American Rheumatism Association (New York, 1995) [11] – 5 of 10 diagnostic criteria which allow establishing the likely osteoarthritis.

Clinical classification of osteoarthritis (recommended by the Association of Rheumatology Ukraine, 2000) [12]. The secondary osteoarthritis. Osteochondrosis of the lower thoracic and lumbar spine. FJI 0.

CLINICAL DIAGNOSIS

Primary: Atherosclerosis of the aorta, cerebral arteriosclerosis.

Complication: Combined aortic defect with predominance of the disease (degree 2), relative mitral insufficiency (degree 2), tricuspid valve, the relative pulmonary valve insufficiency. Arterial hypertension stage III, degree 2, very high cardiovascular risk. Cardiomegaly. CHF III stage, FC III (with reduced left ventricular systolic function (EF=17 %)). Small ischemic stroke in the vertebral-basilar pool with atactic-vestibular syndrome, left-sided pyramidal insufficiency (2012). Encephalopathy, degree II. Status after implantation of cardiac resynchronization DDD (RV) pacing device. Dislocation of left ventricular electrode.

Comorbidities: Gout, gouty arthritis, intermittent flow with the defeat of the left first metatarsophalangeal joint. Activity 0. Secondary osteoarthritis. Lower thoracic and lumbar spine osteochondrosis. FJI 0.

MEDICAL ADVICE

Further examination: lipidogram, Nechyporenkos' urine test, ophthalmologist consultation, thoracic and lumbar spine X-ray, radiographs of the left first metatarsophalangeal joint, monitoring of the blood uric acid level.

THE TREATMENT PLAN

Interventional procedure

Replacing of DDD (RV) pacemaker by the cardiac resynchronization device was carried out (21.10.2013): atrial and right ventricular electrode were located on the previous sites, left ventricular electrode was replaced on the vein of smaller diameter. Characteristics of pacemaker (Medtronic Consulta CRT-P): synchronous atrio-ventricular pacing, QRS 126 ms, the lower HR limit was 55 beats/minute, the top HR limit – 130 beats/minute, the AV delay was 180 ms, VV delay was 20 ms, the atrial electrode was unipolar, left ventricular – multipolar (LV tip – LV ring).

The condition of patient improved after pacemaker replacement. ECG (23.10.2013) bipolar stimulation was detected, QRS 126 ms, on echocardiography (23.10.2013) EF – 25 %.

Therapeutic interventions

Lifestyle modification: restriction of salt and fat intake (especially animal fats), increasing the consumption of fruits, vegetables, protein in the diet, regular physical activity (30 minutes, 5–7 days a week).

DRUG THERAPY ADVICE

- cancellation of torasemide, valsartan, procoralan , trimetazidine dihydrochloride
- appointment of bisoprolol 5 mg in the morning, spironolactone 50 mg in the morning, lisinopril 2.5 mg at night, atorvastatin 20 mg/day, allopurinol 100 mg/day, non-steroidal anti-inflammatory drugs topically (patch, ointment, gel diclofenac sodium).

Findings

- multimorbidity is aggravating factor for diagnosis, course and treatment of the underlying disease, which is clearly shown by this clinical case.
- cardiac resynchronization therapy reduces the severity of chronic heart failure, improves the patient's quality of life, makes the addition, but does not substitute medical treatment, which should be tailored according to the patient's overall health and the information about multimorbidity.
- the doctor does not treat the disease, but does treat the patient.

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CLINICAL CASE OF PERSISTENT ATRIAL FLUTTER IN PATIENT WITH COMORBID PATHOLOGY

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Clinical case of persistent atrial flutter in combination with comorbid pathology is presented. Clinical diagnosis, choice of optimal interventional and drug therapy are discussed. Catheter ablation was considered as the optimal method for radical treatment of the atrial flutter. A modification of drug therapy is required according to the condition of the patient after the catheter ablation.

KEY WORDS: atrial flutter, anticoagulation therapy, dabigatran, catheter ablation

КЛІНІЧНИЙ ВИПАДОК ПЕРСИСТУЮЧОЇ ФОРМИ ТРІПОТІННЯ ПЕРЕДСЕРДЬ ПАЦІЄНТА З КОМОРБІДНОЮ ПАТОЛОГІЄЮ

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Розглянуто клінічний випадок ведення пацієнта з персистуючою формою тріпотіння передсердь у поєднанні з коморбідною патологією. Описана діагностика, постановка клінічного діагнозу і вибір оптимальної інтервенційної та медикаментозної тактики. Вирішальним у виборі тактики лікування стало радикальнее усунення причини тріпотіння передсердь методом катетерної абляції. Після виконання абляції потрібна модифікація медикаментозної терапії, яку приводять відповідно до стану пацієнта і його змінами.

КЛЮЧОВІ СЛОВА: тріпотіння передсердь, антикоагулянтна терапія, дабігатран, катетерна абляція

КЛИНИЧЕСКИЙ СЛУЧАЙ ПЕРСИСТИРУЮЩЕЙ ФОРМЫ ТРЕПЕТАНИЯ ПРЕДСЕРДИЙ У ПАЦИЕНТА С КОМОРБИДНОЙ ПАТОЛОГИЕЙ

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Рассмотрен клинический случай ведения пациента с персистирующей формой трепетания предсердий в сочетании с коморбидной патологией. Описана диагностика, постановка клинического диагноза и выбор оптимальной интервенционной и медикаментозной тактики. Решающим в выборе тактики лечения явилось радикальное устранение причины трепетания предсердий методом тактики лечения явилось радикальное устранение причины трепетания предсердий методом катетерной абляции. После выполнения абляции требуется модификация проводимой медикаментозной терапии в соответствии с состоянием пациента и его изменениями.

КЛЮЧЕВЫЕ СЛОВА: трепетание предсердий, антикоагулянтная терапия, дабигатран, катетерная абляция

Atrial flutter is one of the most commonly encountered disturbances of cardiac rhythm, which accounts for close to 10 % paroxysms of ventricular tachyarrhythmias [1].

Atrial flutter remarkably reduces the patient's quality of life, however, most danger is due to its complications, such as stroke and other consequences of thromboembolism in the systemic circulation, development and progression of heart and kidney failure [2].

Special difficulties are presented by occurrence of combined atrial flutter with comorbid pathologies, this requires coordinated interventions and medical treatment.This article dedicated to one such case.

CLINICAL CASE

Patient V, an 81 year old female, came to the hospital with complaints of breathlessness on exertion (walking more than 500m), and bending of the trunk, feelings of increased heart rate and heaviness in the area of the heart, edema of the legs, dizziness, episodes of loss of loss of consciousness, general weakness and easy fatigability.

HISTORY OF DISEASE

In 1975, 1st registered episode of increased blood pressure 200/110 mm Hg. Treatment: Enalapril, Acetylsalicyclate. 2007 - transitory ischemic attack (TIA). 2008 - complaints of breathlessness, feelings of heaviness in the area of the heart, dizziness. Coronary ventriculography did not detect any pathology of the coronary arteries. On echocardiography - stenosis of bicuspid aortic valve. 2008 - implantation of prosthetic aortic valve in the A.N Bakuleva RAMN Scientific Center for Cardiovascular Surgery (Biological prothesis «Biolab-26»). In the post operative period (20 days), she was placed on warfarin. Condition stabilized after the surgery. August 2012 – complaints of acute dizziness and loss of consciousness, discovered syndrome of bradycardia-tachycardia. During attacks of the bradycardia took zelenin drops with a positive effect. June 2013 - deterioration of patient's condition, once more complaints of dizziness, loss of consciousness, feeling of increased heart rate. On electrocardiogram (ECG) - atrial flutter, complete blockade of right bundle branch of His. Therapy: amiodarone 200mg 2 times a day. Therapy continued twice a month, condition did not improve, reported to Central Clinical Hospital Ukrzaliznitsi. Diagnosis of atrial flutter was confirmed. Therapy: bisoprolol, valsartan, dabigatran, atorvastatin, furosemide, consultation and of intervention cardiologist, recommended surgical correction of the arrhythmia.

MEDICAL HISTORY

Childhood infections: diphtheria, measles, pneumonia. Transmissible infections: tropical malaria (1947). Acute thrombophlebitis of the deep veins of the left lower limb, thromboembolism of the small pulmonary arteries - Pulmonary embolism (1980). In the postmenopausal period (1985), in connection with uterine hemorrhage, curettage of the uterine cavity was performed. In 2008 she was diagnosed with diabetes mellitus type 2, placed on gliclazide 30 mg a day along with monitoring of diet. In 2013 was diagnosed with euthyroid autoimmune thyroiditis.

Viral hepatitis, tuberculosis, venereal diseases, HIV are absent. Hereditary diseases not detected. No allergies. Patient does not smoke or drink.

PHYSICAL EXAMINATION

General condition satisfactory. Clear consciousness. Patient is active. Body type – normosthenic. Skin and mucosa clean, pale and dry. Skin is flabby and wrinkled, turgor is reduced. Subcutaneous fat is evenly distributed. On the chest wall is a scar from previous thoracotomy. Peripheral lymphatic nodes are not enlarged. Shape of neck is not changed. Palpable enlargement of the halves of the thyroid gland on swallowing. Musculoskeletal and respiratory system without abnormalities. Borders of the heart expanded to the left by 2 cm. Arrhythmic heart activity with weakened tones. Systolic murmur over the aortic projection and diastolic murmur over the mitral valves. Blood pressure 150/76 mm Hg (on the background of antihypertensive medication), pulse 72 bpm, no pulse deficit. Edema of the lower extremities from the shins to the level of knee joint. The gastrointestinal and renal systems are without abnormalities.

DIAGNOSIS OF REFERRING HOSPITAL

Atrial flutter, persistent form. Arterial hypertension stage 3, very high risk. Chronic heart failure Stage IIB, functional class II. Diabetes Mellitus type 2. Euthyroid auto-immune thyroiditis.

RESULT OF LABORATORY AND INSTRUMENTAL EXAMINATIONS

Complete blood count: erythrocytoses 4.86 x 10^6/L (T/L), thrombocytopenia 148,000/L.

Urinalysis: all results within normal ranges.

Protein electrophoresis: increased α2 globulin 15.31 %.

Biochemical analysis of blood: ALT increased to 46u/L, Hyperglycemia (8.6mmol/L).

International Normalization Ration (INR): increased to 2.02.

Coagulogram: increased Soluble Fibrin Monomer Complex to 13.0x 10^{-2}g/L.

Lipid profile: all results within normal ranges.

Blood Analysis for Thyroid hormones: All results within normal ranges.

Analysis for antibodies to thyroglobulin: result within normal range.

Echocardiogram: sclerotic changes of aortic walls and leaves of the mitral valve. Dilatation of both atria. Condition after prosthetic aortic valve implantation. Mitral regurgitation I-II stage. Moderate hypertrophy of myocardium of the left ventricle. Mild pulmonary hypertension (pressure at the mouth of the pulmonary artery 21.7mm Hg). Ejection fraction (EF)-62 %.

ECG: Atrial flutter, irregular form, heart rate 62 bpm. Complete blockade of the right bundle branch of His (complete RBBB). Hypertrophy of the myocardium of the left ventricle. Disturbance of the process of myocardial repolarization.

24hr ECG Holter monitoring: Length of monitoring- 13 hrs 53 minutes. On the background of atrial flutter with heart rate ranging from 49 to 115 (day average-68, night average-49) bpm. 57 single ventricular extrasystoles, 4 pauses with intervals RR 2019 -2237 ms. Ischemic changes of ST-segment not detected.

24hr monitoring of blood pressure: average day BP 139/73 mm Hg, average BP during active period 147/77 mm Hg and passive period 139/67 mmHg (group «Non-dipper» according to systolic BP).

Ultrasonography of Abdominal Organs: diffuse changes of parenchyma of the liver with increase d size typical of Fatty liver. Calculi in the gallbladder. Diffuse changes of the pancreas without its enlargement. Micro-lithiasis.

Ultrasonography of the Thyroid gland: hyperplasia stage II-III, with nodal changes of the parenchyma - focal type, with mixed structures in both halves.

Chest X-Ray: focal and infiltrative changes in the lungs not detected. Root structures not widened, sinuses are free. Diaphragm clearly outlined. Heart has aortal configuration and is widened to the left, aorta has no changes.

RECOMMENDATIONS FOR FURTHER EXAMINATION

Further examination of the patient to determine the stage of damage to the kidneys: determine glomerular filtration rate (GFR), creatine clearance, Nechiprenko urinalysis, Zimnitski urinalysis, bacterial culture of urine.

Further examination to determine the stage of compensation of diabetes mellitus: determine glycylated hemoglobin $HbA1_C$.

Examination by a gastroentologist for gallstone disease, decide further treatment tactics. Consultation by a cardiologist with the aim of correction of the antihypertensive therapy and selection of optimal doses for achieving the target systolic blood pressure. Observation by an endocrinologist with the aim of control of hormone levels and staging hyperplasia of the thyroid gland, and also to simultaneously control the diabetes mellitus and determine any complications.

BASIC CLINICAL SYNDROMES

- Syndrome Disturbance of activation and conduction
- Syndrome of Bradycardia-tachycardia
Syndrome of Arterial Hypertension
- Syndrome Chronic Heart failure
- Edema Syndrome
- Syndrome of Hyperglycemia
- Syndrome of Nodular goiter
- Cholelithiasis

STAGING OF CLINICAL DIAGNOSIS

Classification of atrial flutter [3]: according to duration - persistent form, by condition of AV conduction- irregular form, by rate of ventricular contraction - normosystolic variant.

Classification of arterial hypertension [4]: according to degree - severe hypertension (degree 3), by damage to target organs - III stage (heart failure, transient ischemic attack in the history).

Stratification of risk with arterial hypertension [4]: 3rd stage combined with

associated clinical status (i.e heart failure and history of TIA) - very high cardiovascular risk.

Classification of chronic heart failure [5]: by stage - IIB, by functional class (FC) (NYHA) - IIFC, by variant - II variant (EF 62 %).

Classification of Diabetes Mellitus [6]: by severity – moderate (II stage) severity, by stage of compensation of glucose tolerance - sub-compensation.

Classification of goiter [7]: by stage - I stage.

Classification of nodular goiter [7]: multinodular goiter.

Classification of gallstone disease [8]: by stage of disease - asymptomatic, by clinical form - latent («stone carrier»).

CLINICAL DIAGNOSIS

Primary disease:

Atrial flutter, persistent type, normosystolic variant. Condition after prothesis of aortic valve «Biolab 26» (2008) due to stenosis of the bicuspid aortic valve. Arterial hypertension stage 3, degree 3. Very high cardiovascular risk. Heart failure IIB stage, II FC, with retention of systolic function (EF 62 %)

Basic Complications:

TIA (2007).

Accompanying Conditions:

Diabetes Mellitus type 2, stage of sub-compensation, moderate severity.

Multinodular goiter, stage I, Euthyroid.

Gallstone disease, latent form.

PATIENT MANAGEMENT

Relief of atrial flutter can be achieved by medications, transesophageal pacing and catheter ablation. Considering the high probability of recurrence of attacks of atrial flutter with the use of the first two methods, the patient has been recommended catheter ablation (in agreement with HRS/EHRA/ECAS expert Consensus Statement on the catheter and surgical ablation of atrial fibrillation, 2012, class evidence IIa, level B) [9].

In preparation for the operation requires additional laboratory information (clinical analysis of blood, coagulogram, biochemical analysis of blood), ECG, echocardiogram for exclusion of fresh thrombi in the heart cavities as this is an absolute contraindication for performing catheter ablation [10].

LIFESTYLE MODIFICATION

Present recommendations are control by physical exercise, reduced intake of easily digested carbohydrates and animal fat products, salt (4-6 g/day), limit calorie-rich foods with exclusion of rations of products with high content of highly digestible proteins, fibers and vitamins C, E, mineral and adequate intake of fluid. Also recommended limiting intake of legumes (beans, peas) and coffee.

MEDICATION THERAPY

Amiodarone 200-400mg/day and bisoprolol 5mg/day with correction of dosage after relief of atrial flutter, dabigatran 110-220 mg/day, enalapril 10mg/day, furosemide 10mg twice a week, atorvastatin 10 mg/day, gliclazide 30 mg/day.

Anticoagulant therapy (Dabigatran) taken for prophylaxis of stroke, systemic thromboembolism and reduce the risk of cardiovascular death [11, 12].

Patient sent for catheter ablation in Scientific Center of Cardiovascular Surgery a.n. Bakyleva RAMN, as a citizen of the Russian Federation.

CONCLUSION

Comorbidity is the hallmark of elderly patients. It is an evidence of the systemic character of impairment of functioning of the organism and worsening of severity of their condition and prognosis of life.

This clinical case is interesting in that the patient with persistent form of atrial flutter with comorbid pathologies was placed on a complex medical therapy and intervention of elimination of arrhythmic pathways by catheter ablation.

After performing catheter ablation, it is required to conduct a modification of medication according to changes in the patient's condition.

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Review

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OBSTRUCTIVE SLEEP APNEA-HYPOPNEA SYNDROME. MODERN VIEW ON THE PROBLEM

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Obstructive sleep apnea syndrome is a common chronic syndrome that significantly affects the quality of life of patients and often requires lifelong care. This review deals with modern ideas about the prevalence, causes, clinical presentation, diagnosis and treatment of obstructive sleep apnea syndrome. Using modern methods of diagnosis and the correct approach to such patients helps prevent unwanted effects and significantly improves quality of life.

KEY WORDS: obstructive sleep apnea-hypopnea, sleep disorders

СИНДРОМ ОБСТРУКТИВНОГО АПНОЕ-ГІПОПНОЕ СНУ. СУЧАСНИЙ ПОГЛЯД НА ПРОБЛЕМУ

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Синдром обструктивного апное сну є поширеним хронічним синдромом, яке значно погіршує якість життя пацієнтів і часто вимагає довічного догляду. У цьому огляді розглянуто сучасні уявлення про поширеність, причини, клінічну картину, діагностику та лікування синдрому обструктивного апное сну. Використання сучасних методів діагностики і правильний підхід до такого роду пацієнтів дозволяють запобігти небажаним наслідкам і значно поліпшити якість життя.

КЛЮЧОВІ СЛОВА: синдром обструктивного апное, порушення сну

СИНДРОМ ОБСТРУКТИВНОГО АПНОЭ-ГИПОПНОЭ СНА. СОВРЕМЕННЫЙ ВЗГЛЯД НА ПРОБЛЕМУ

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Синдром обструктивного апноэ сна является распространенным хроническим синдромом, которое значительно ухудшает качество жизни пациентов и часто требует пожизненного ухода. В настоящем обзоре рассмотрены современные представления о распространенности, причинах, клинической картине, диагностике и лечении синдрома обструктивного апноэ сна. Использование современных методов диагностики и правильный подход к такого рода пациентам позволяют предотвратить нежелательные последствия и значительно улучшить качество жизни.

КЛЮЧЕВЫЕ СЛОВА: синдром обструктивного апноэ, нарушения сна

People spend about 30 % of their lives asleep. Sleep is essential for a variety of restoration and biochemical processes in the body, such as tissue repair, growth of the organism, recovery of immune reserves, synthesis of anabolic hormones, ontogeny, information processing, formation of memory and knowledge[1-3]. Sleep plays a vital role in good health and well-being throughout life. Getting enough quality sleep at the right times can help protect mental health, physical health, quality of life, and safety [4, 5].

In 1965, independently of one another the German and French researchers have described many detrimental effects of sleep disorders related to sleep apnea and snoring [6].

Snoring not only creates certain social problems, but also is a harbinger and one of the main symptoms of obstructive sleep apnea-hypopnea (OSAHS) [7-9]. In severe forms of OSAHS up to 400-500 pauses in breathing per night can be observed for a total duration of 4-5 hours, which leads to acute and chronic deficiency oxygen saturation during sleep [10]. This, in its turn, greatly reduces the quality of life of the patient, significantly increases the risk of developing metabolic syndrome, erectile dysfunction, hypertension, cardiac arrhythmias, myocardial infarction, stroke and sudden death during sleep [11, 12].

Unfortunately, today in Ukraine insufficient attention is paid to the diagnosis of sleep-related breathing stops. Moreover, these patients do not complain of sleep apnea, snoring is considered a symptom that unworthy of attention of the doctor, patients do not report the relevant complaints. Severe forms of OSAHS often remains undiagnosed and untreated, which significantly affects the quality of life and prognosis in these patients.

DEFINITION

OSAHS is a condition wherein a patient has multiple, repeated respiratory standstills because of complete or partial narrowing of the airways in the throat accompanied by cessation of pulmonary ventilation during sleeping with continued respiratory efforts characterized by the presence of snoring, decrease of oxygen level in blood, coarse fragmentation of sleep with frequent awakenings and excessive daytime sleepiness [13]. Herewith awakening serves as a protective mechanism in which the activation of the muscles - upper airway dilators occurs and warns of asphyxia from OSAHS [14, 15].

PREVALENCE

The prevalence of the OSAHS is 5–7 % of the total population over 30 years (predominantly male). Severe forms of the syndrome occur in about 1–2 % from above [16-18]. Frequency of occurrence of this syndrome increases with age. In persons older than 60 years occurrence of occurrence OSAHS is about 30 % in men and 20 % women; In persons older than 65 years - about 60 % [19]. These figures exceed the prevalence of the bronchial asthma [20].

The prevalence of clinically significant OSAHS is 15 % for patients in the therapeutic profile hospitals [21-23]. In cardiac patients the prevalence of OSA is even higher. In patients with systemic arterial hypertension, the figure is 30 % [24], and in refractory forms of hypertension reaches 83 %. [19, 25]. In patients with nocturnal bradyarrhythmia OSAHS is detected in 68 % of cases [26]. In patients with coronary heart disease (CHD) and heart failure II-IV functional NYHA class, OSAHS prevalence reaches 43 % [27]. Frequency of occurrence of ischemic cerebral stroke in patients with OSAHS is 2-10 times higher than in the general population and have a higher risk of car accidents in 4-6 times compared with the average data [19]. The prevalence of OSA is also very high in obese patients with metabolic syndrome, diabetes mellitus, hypothyroidism. [28].

AETIOLOGY AND PATHOPHYSIOLOGY

The basis of the syndrome is a periodic cessation of breathing due to subsidence of airways on the level of the pharynx. The airways can be completely occluded and then develops into apnea. Apnea is a cessation of airflow (pulmonary ventilation) for 10 seconds or more. With a partial loss patency of the respiratory tract patients have hypopnea. It is a significant reduction in air flow (over 50 % from baseline), accompanied by a decreased arterial oxygen saturation of 3 % or more [29]. In severe forms of OSAHS, breathing may be missing for 5 hours per night which leads to a dramatic lack of oxygen during sleeping. If the rate of oxygen in the blood is 96-98 %, episodes of obstructive apnea during sleeping could cause severe intermittent hypoxia and retention of CO_2, with a fall in arterial oxygen saturation during the pauses to less than 60 % i.e. development of prohibitive hypoxia (according to resuscitators, reduction
of saturation below 50 % for 2 minutes causes the death of the cerebral cortex). In intensive care where the oxygen level in blood is less than 80 % doctors make intubation and mechanical ventilation [30].

Acute shortage of oxygen in arterial blood leads to the stress response, accompanied by activation of sympathetic nervous system and the rising in blood pressure [15, 30].

Eventually the negative information from different organs and systems causes a partial awakening of brain (micro activation). The brain regains control over the pharyngeal muscles and opens airways quickly. Then person snorts loudly and makes few deep breaths [31]. The normal oxygen content restored in the body, the brain calms down and falls asleep again. The patient falls asleep, and these events repeat again, breaking sleeping continuity [32].

The causes of the oropharynx collapse are a significant reduction of pressure in the upper inspiratory airway and the inability of the muscles which extend the throat to keep it open [33]. The reduction of muscle tone of the upper airway during sleeping and weakening of their reflex reaction on the fall of airway pressure plays a decisive role [34].

Most people have structural abnormalities of upper respiratory tract. Sometimes it's rough anatomical changes for example adenoids, curvature of the nasal septum, polyps, macroglossia, retrognathia (underdevelopment and rearward displacement of the upper and / or lower jaw), but basically there is just a slight reduction of the oropharynx size [35, 36].

A number of diseases promote the narrowing of the upper airway:

- obesity – the deposition of fat in the soft tissues of the pharynx or squeezing of the throat by massive subcutaneous tissue of the neck;
- hypothyroidism- weight gain, global decrease in muscle tone and edema of visceral tissues with lower thyroid function;
- acromegaly- disproportionate growth of individual organs and the tongue that causes narrowing of the throat at the base of the tongue, etc. [19].

Muscle relaxants (hypnotics, alcohol) often provoke the collapse of the oropharynx. As they cause selective relaxation of these muscles and prevents activation which interrupts each apnea [37]. Smoking also has different negative impacts on upper respiratory tract which foster the development of respiratory disorders during sleeping [38].

CLASSIFICATION

There are three types of sleeping apnea: central, obstructive and mixed (CSA, OSA and MSA). Airway collapse during ongoing respiratory effort is observed in obstructive sleep apnea (respiratory center function maintained).With central sleep apnea (Cheyne-Stokes and other forms) there is a decrease of function or stoppage of the respiratory center and the cessation of respiratory effort. Thus airways are still open. The concept of mixed apnea includes the features of both above types [39].

Standard criteria of classifying of OSAHS are the frequency of apneas and hypopneas per hour - the apnea / hypopnea index (AHI). It is inappropriate to count separately the number of apneas and hypopneas, as they carry on similar risks to the development of cardiovascular disease and other complications. Currently, the majority of international consensus and clinical guidelines adhere to the following classification of the severity of OSAHS in adults based on IAG: mild form - from ≥ 5 to < 15; Mild (moderate) form - from ≥ 15 to < 30, Severe ≥ 30 [40].

The additional criteria for classifying the severity of OSAHS may be the amount of desaturation on the background of episodes of apnea / hypopnea index, the degree of structural failure of a night's sleeping, cardiovascular complications associated with respiratory disorders (myocardial ischemia, arrhythmias and conduction, hypertension) and the severity of cognitive deficits [41].

SYMPTOMS AND SIGNS

Generally, symptoms of OSAHS begin insidiously and are often present for years before the patient is referred for evaluation. The characteristic symptom of OSAHS is excessive daytime sleepiness, also known to be a common predisposing factor for accidents, reduced productivity, neurocognitive impairment and interpersonal and/or social problems [42]. Snoring is one of the main symptoms of OSAHS, which is usually loud, habitual, and bothersome to others. Also patients commonly experience repeated awakenings from sleep, feelings of choking or gasping, flailing or thrashing during sleep, restless sleep, with patients often experiencing frequent arousals and tossing or turning during the night, decreased capacity for concentration, impaired functioning in daily activities, morning headaches and sexual dysfunction. Deteriorations in quality of life and affect, which can include irritability, depression, and anxiety, are common among patients with OSAHS [43].

Every stoppage of breathing leads to a sharp deterioration of the quality of sleeping.

The patient may wake up from the effects of long pauses with a sense of heart, rapid breathing, breathlessness, anxiety, profuse sweating. Headache, increased blood pressure, angina may disturb in the morning [44, 45]. Marked hypersomnia throughout the day and also irritability, poor mood [46]. The attacks of severe drowsiness are especially dangerous while driving. The risk of traffic accidents may increase because of this [47]. Memory and attention become worse, body weight increased, libido decreased and impotence develops [48].

DIAGNOSIS

The presence or absence and severity of OSAHS must be determined before initiating treatment in order to identify those patients at risk of developing the complications of sleep apnea, to guide selection of appropriate treatment and to provide a baseline to establish the effectiveness of subsequent treatment. Diagnostic criteria for OSAHS are based on clinical signs and symptoms determined during a comprehensive sleep evaluation, which includes a sleep oriented history and physical examination, and findings identified by sleep testing [49].

The diagnosis of OSAHS starts with a sleep history that is typically obtained in one of three settings: first, as part of routine health maintenance evaluation, second, as part of an evaluation of symptoms of obstructive sleep apnea, and third, as part of the comprehensive evaluation of patients at high risk for OSAHS. High-risk patients include those who are obese, those with congestive heart failure, atrial fibrillation, treatment refractory hypertension, type 2 diabetes, stroke, nocturnal dysrhythmias, pulmonary hypertension, high-risk driving populations (such as commercial truck drivers), and those being evaluated for bariatric surgery [50].

The physical examination can suggest increased risk and should include the respiratory, cardiovascular, and neurologic systems [51].

Particular attention should be paid to the presence of features that may suggest the presence of OSAHS include obesity (body mass index: > 30 kg/m^2), an enlarged neck circumference (men: > 43 cm; women: > 37 cm), and hypertension [52]. Other clinical pointers may include craniofacial and soft tissue enlargement associated with upper airway resistance such as retrognathia, deviated nasal septum, low-lying soft palate, enlarged uvula and base of the tongue, congenital narrowing of upper airway can be detected radiographically or by acoustic pharyngometry [53, 54].

A diagnosis of OSAHS must be established by an acceptable method. The two accepted methods of objective testing are; in-laboratory polysomnography (PSG) and home testing with portable monitors (PM). The American Academy of Sleep Medicine guidelines for the indications and performance of PSG include the following [55]: electroencephalogram (EEG), electrooculogram (EOG), chin electromyogram, airflow (using both a thermal sensor and a nasal pressure transducer), oxygen saturation, respiratory effort (using inductance plethysmography), and electrocardiogram (ECG) or heart rate. Additional recommended parameters include body position and tibialis electromyogram (EMG) derivations. The breathing pattern is analyzed for the presence of apneas and hypopneas as per definitions standardized by the American Academy of Sleep Medicine [40].

A PM records airflow, respiratory effort, and blood oxygenation. PM for the diagnosis of OSAHS should be performed only in conjunction with a comprehensive sleep evaluation. PM may be used to diagnose OSAHS when utilized as part of a comprehensive sleep evaluation in patients with a high pretest likelihood of moderate to severe OSAHS. PM testing is not indicated in patients with major comorbid conditions including, but not limited to, moderate to severe pulmonary disease, neuromuscular disease, or congestive heart failure, or those suspected of having a comorbid sleep disorder [56]. PM testing may also be indicated for the diagnosis of OSAHS in patients for whom in-laboratory PSG is not possible by virtue of immobility, safety or critical illness and to monitor response to non-continuous positive airflow pressure (CPAP) therapies [57].

The multiple sleep latency test (MSLT) is not routinely indicated in the initial evaluation and diagnosis of OSAHS or in an assessment of change following treatment with nasal CPAP. However, if excessive sleepiness continues despite optimal treatment, the patient may require an evaluation for possible narcolepsy, including the MSLT. The MSLT has a reasonably high test-retest reliability over periods of months in normal subjects. However, the MSLT is very cumbersome, time

consuming and expensive to perform. It takes all day, both for the subject and the polysomnographer and is not easy to justify as a routine test for all patients [58].

There are other methods of assessment of sleep disorders. The Stanford sleepiness scale (SSS) is a quick and simple test. It involves the subject's own reports of symptoms and feelings at a particular time. Visual analogue scales (VAS) of sleepiness/alertness have also been used, however, these tests do not attempt to measure the general level of daytime sleepiness, as distinct from feelings of sleepiness at a particular time [59]. The Epworth sleepiness scale (ESS), designed to measure sleep propensity in a simple, standardized way. The scale covers the whole range of sleep propensities, from the highest to the lowest and is a validated method of assessing the likelihood of falling asleep in a variety of situations. The Scale should be completed independently by both the patient and their partner as the patient may underestimate the severity of their sleepiness due to its insidious onset, or in order to hide concerns over driving ability [60].

Thus, by questioning patients with high confidence a diagnosis of OSAHS can be made, and for diagnosis objectification patient should be send to the sleep laboratory.

OUTCOMES AND COMPLICATIONS

Frequent episodes of breathlessness and severe hypoxemia in conjunction with disruption of the structure of sleeping could cause the development of cardiovascular diseases [44], metabolic, endocrine, neurological and psychiatric disorders [48, 61].

Acute and chronic lack of oxygen increases the risk of development of cardiac arrhythmias, the development of acute myocardial infarction, acute stroke, sudden death during sleeping [60]. Frequent respiratory arrest leads to a sharp deterioration of the quality of sleeping and disruption of sleeping structure. As a result, there are frequent nocturnal awakenings, loss of deep stages of sleeping, restless sleeping, excessive daytime sleepiness, irritability, poor concentration, loss of memory [62].

It is proved that OSAHS is an independent risk factor for hypertension [63-66], 50 % patients with hypertension have OSAHS [67, 68]. In the 7-th Report of the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) sleeping apnea is at the first place among all causes of secondary hypertension, this highlights the high prevalence and clinical significance of hypertension caused by OSAHS [69]. Patients with OSAHS have absence of blood pressure reduction at night («non-dipper») or even its excess over the daily pressure («night peaker») [70]. Increase in blood pressure (mainly diastolic) in the morning has been also marked [71]. Significant reduction of the blood pressure in 20-30 minutes after waking up without any medical intervention is an interesting feature which patients with OSAHS have. According to Logan and co-authors [25] 41 patients with refractory hypertension (blood pressure > 140/90 mm Hg), who are not treatable with three or more drugs had obstructive sleeping apnea (AHI > 10 per hour) in 83 % of cases. So you should always assume the presence of OSAHS in patients with predominantly nocturnal and morning hypertension, especially refractory to treatment.

After 12 years observation it was noted a threefold increase in fatal and 4-5-fold increase in non-fatal cardiovascular events among patients with untreated severe OSAHS. In fact, the risk of dying or getting a heart attack or stroke was 50 % during the 12 years of observation. Patients who had constant CPAP therapy for OSAHS had the same frequency of complications as the patients without OSAHS [72].

Wisconsin cohort study showed an increased risk of cardiovascular mortality by 5,2 times during the 18 year follow-up of patients with untreated OSAHS [48]. During the observation 35 % of patients with untreated severe OSAHS compared with 7 % in the group without OSAHS died. Another study demonstrated that for moderate and severe forms of OSAHS risk of death from any cause within 14 years of observation is 6,24-fold higher ($p < 0,002$) compared with the control group, comparable in age, gender, body mass index, mean blood pressure, smoking, coronary heart disease and diabetes, the level of total cholesterol and high density lipoproteins. [37].

OSAHS is a cause of progression of visceral obesity and the metabolic syndrome by disrupting hormone production during the night, such as cortisol and insulin, thus in patients with metabolic syndrome prevalence

of OSAHS is approximately 50 %, and with the Pickwick syndrome – 90 % [73].

Impaired Peaks in the production of growth hormone and testosterone secretion which are found in the deep stages of sleeping develops in severe forms of OSAHS. When patient has OSAHS he practically doesn't have deep stages of sleeping which leads to their lack of production. The mobilization of fat from the depot and its transformation into energy and muscle mass is one of the functions of growth hormone in adults. With a lack of the hormone a person begins to gain weight, and any effort either diet or medications aimed at weight loss give poor results , and fat at the neck leads to further narrowing of the airways and the progression of OSAHS. Lack of testosterone in the body leads to impotence and reduction of men's libido [74].

Negative impact of OSAHS on beta cell function and insulin sensitivity is proved. The prevalence of OSAHS in patients with type 2 diabetes is 36 %. With this in mind, the International Diabetes Federation published clinical guidelines, which urged health professionals working with patients with type 2 diabetes or OSAHS, in the case if a patient has one of the diseases not to exclude the possibility of the other disease [75].

MODERN APPROACHES TO THERAPY:

Approach to the treatment of patients with snoring and OSAHS should be comprehensive and flexible [76]. Modern guidelines for the management of such patients include the following categories:

1. Patient Education

Sleep hygiene. An integral component of the treatment of all forms of sleep disorders is the culture preparation for sleep, which includes the following recommendations [77]:

- go to bed and get up at the same time;
- exclude naps, especially in the afternoon;
- do not eat at night tea or coffee;
- reduce stress, mental workload, especially in the evening;
- arrange for physical activity in the evening, but not later than 3 hours before bedtime;
- regularly use water treatments before bedtime;
- exclude watching television for 2 hours before bedtime.

Positional therapy. Body position greatly affects the number and severity of episodes of obstructive sleep apnea, with at least twice as many apneas occurring in people who lay on their back as in those who sleep on their side. This may be due to the effects of gravity, which cause the throat to narrow when a person lies on the back. A special pillow that helps to stretch the neck may reduce snoring and improve sleep for people with mild sleep apnea. Sleeping in an upright position may improve oxygen levels in overweight people with sleep apnea. Elevating the head of the bed may help. Some people are helped by special oral appliances to keep the airway open during sleep [78-80].

Weight loss. All patients with obstructive sleep apnea who are overweight should attempt a weight-reducing program. Weight loss certainly reduces snoring and apnea/hypopnea episodes in many people, sometimes stopping it completely. It also improves sleep and significantly reduces daytime sleepiness [81-83].

Smoking, alcohol and drugs.

- Smokers should quit, since smoking worsens apnea. Smoking causes chronic chemical trauma of airway at the throat, which leads to their swelling and decrease in muscle tone at the level of the pharynx, and this in turn contributes to the progression of snoring and OSAHS [35].
- Avoid sedatives and sleeping medications. Most of these drugs have a muscle relaxant and depressing influence of respiratory function, that impairs breathing disorders during sleep [84].
- Avoid alcohol within 4 hours of sleep. Alcohol has a double negative effect in OSAHS. First, it acts as a muscle relaxant and that leads to the relaxation of the pharyngeal muscles and more frequent collapse airways. Secondly, ethanol increases the threshold of the brain's response to adverse stimuli. In this situation, respiratory arrest last longer and develop more severe hypoxemia [85].

Exercise. Training tongue muscles and lower jaw is also advisable to apply. If the muscles are trained, even in a relaxed state (in a dream), they maintain a certain tone, providing an increase in the lumen of the pharynx and reducing snoring. Training can be carried out by a course of special set of exercises or by electrical stimulation of upper pharyngeal muscles [86].

2. Medication

To alleviate uncomplicated snoring there are pharmacological agents based on essential oils with methyl salicylate, which have a local tonic, anti-inflammatory and antiseptic action, they are sprayed directly on the back of the throat and uvula, but the effectiveness of their use remains controversial [87]. There are also studies on the use of glucocorticoids in patients with sleep apnea amid allergic rhinitis [88]. Pharmacologic therapy is generally not a part of the primary treatment recommendations. Acetazolamide, medroxyprogesterone, fluoxetine, and protriptyline have been used to treat OSAHS; however, these medications are not recommended. Modafinil is approved by the US Food and Drug Administration (FDA) for use in patients who have residual daytime sleepiness despite optimal use of CPAP [89, 90].

3. Treatment with the equipment

Treatment for OSAHS depends on the severity of the problem. At this time, the most effective treatments for sleep apnea are devices that deliver slightly pressurized air to keep the throat open during the night. There are a number of such devices available [35].

The best treatment for obstructive sleep apnea is a system known as CPAP. It is safe and effective for people of all ages, including children [91].

The device itself is a machine weighing about 3 pounds that fits on a bedside table. A mask containing a tube connects to the device and fits over just the nose.The machine supplies a steady stream of air through a tube and applies sufficient air pressure to prevent the tissues from collapsing during sleep [92].

The standard CPAP machine delivers a fixed, constant flow of air. Variations on CPAP include:

Autotitrating positive airway pressure (APAP) devices automatically respond to changes in the sleeper's breathing patterns by adjusting and varying the air pressure flow throughout the night. Some patients find this makes CPAP easier to tolerate [93].

Bilevel positive airway pressure (BPAP) systems deliver two different pressures, a higher one for inhalation (breathing in) and a lower one for exhalation (breathing out) [94].

For patients with OSAHS, CPAP therapy is usually prescribed as first-line treatment, a recommendation supported by high-level evidence for efficacy of CPAP in preventing upper airway collapse and relieving symptoms such as daytime sleepiness and mounting data suggesting that CPAP therapy may favorably impact cardiovascular outcomes and reduces mortality [95-97].

4. Surgery

Surgical modifications of the upper airway have been performed for decades as a treatment for OSAHS.Yet, the role of such procedures in the management of OSAHS remains controversial [98]. Critics point to the lack of high-level, controlled studies in the surgical literature and the absence of standardized criteria to define surgical «success,» while proponents cite ethical and logistical limitations to controlled surgical studies and contend that the «all or none» principle of eradication of OSAHS (an apnea-hypopnea index < 5) as the standard of care is flawed and impractical for many patients [99, 100].

All patients with OSAHS should have ongoing, long-term management for their chronic disorder. Those on chronic therapy should have regular, ongoing follow-up to monitor adherence to therapy, side effects, development of medical complications related to OSAHS, and continued resolution of symptoms. Those with elimination of OSAHS should be monitored for continued risk factor modification and to look for return of symptoms.

CONCLUSION

Obstructive sleep apnea syndrome is an actual problem in modern medicine because of the high prevalence in the population, increasing the risk of cardiovascular, neurological and metabolic complications of this syndrome, as well as a significant deterioration in the quality of life of patients.

At the moment the doctor informed about this issue, has the ability to accurately diagnose this potentially lethal syndrome. Designated timely treatment can in most cases prevent unwanted effects and significantly improve the quality of life of the patient.

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THE SIGNIFICANCE OF HEART-TYPE FATTY ACID BINDING PROTEIN AMONG PATIENTS WITH ACUTE CORONARY SYNDROME

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With increasing numbers of patients with acute coronary syndrome (ACS) it is very important to have reliable biomarkers for early diagnostics and treatment. The role of heart-type fatty acid binding protein (H-FABP) is investigated to confirm patients with ACS and to evaluate the long-term prediction of complications and death. H-FABP allows to define myocardial infarction with changes on ECG and without ST elevation, it helps to differentiate unstable angina. H-FABP sensitivity is higher than troponin, myoglobin and other biomarkers, at the same time H-FABP has a high specificity. Increasing of the H-FABP level is an independent prognostic factor in the long-term prediction in patients with suspected ACS. H-FABP definition, especially in combination with other biomarkers, has the important value, when the diagnosis of ACS is difficult against the background of the atypical clinical picture, the absence of typical ECG changes.

KEY WORDS: acute coronary syndrome, heart-type fatty acid binding protein

ЗНАЧЕННЯ СЕРЦЕВОГО БІЛКА, ЩО ЗВ'ЯЗУЄ ЖИРНІ КИСЛОТИ У ПАЦІЄНТІВ З ГОСТРИМ КОРОНАРНИМ СИНДРОМОМ

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З урахуванням зростання кількості хворих з гострим коронарним синдромом (ГКС) дуже важливо мати для ранньої діагностики і тактики ведення надійні біомаркери. Для підтвердження у пацієнтів ГКС та оцінювання довгострокового прогнозу ускладнень і смерті вивчається роль серцевого білка, що зв'язує жирні кислоти (СБЗЖК). СБЗЖК дозволяє визначити інфаркт міокарда зі змінами на ЕКГ і без підйому ST, допомагає диференціювати нестабільну стенокардію. Чутливість СБЗЖК вище ніж у тропонінів, міоглобіну та інших біомаркерів, в той же час СБЗЖК має високу специфічність. Підвищення рівня СБСЖК є незалежним прогностичним фактором довгострокових прогнозів у пацієнтів з підозрою на ГКС. Визначення СБЗЖК, особливо в комбінації з іншими біомаркерами, має важливу цінність, коли діагностика ГКС ускладнена на тлі атипового клінічного перебігу, відсутності характерних змін на ЕКГ.

КЛЮЧОВІ СЛОВА: гострий коронарний синдром, серцевий білок, що зв'язує жирні кислоти

ЗНАЧЕНИЕ СЕРДЕЧНОГО БЕЛКА, СВЯЗЫВАЮЩЕГО ЖИРНЫЕ КИСЛОТЫ У ПАЦИЕНТОВ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ

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С учётом роста количества больных с острым коронарным синдромом (ОКС) очень важно иметь для ранней диагностики и тактики ведения надежные биомаркеры. Для подтверждения у пациентов ОКС и оценивания долгосрочного прогноза осложнений и смерти изучается роль сердечного белка, связывающего жирные кислоты, (СБСЖК). СБСЖК позволяет определить инфаркт миокарда с изменениями на ЭКГ и без подъёма ST, помогает дифференцировать нестабильную стенокардию. Чувствительность СБСЖК выше чем у тропонинов, миоглобина и других биомаркеров, в то же время СБСЖК имеет высокую специфичность. Повышение уровня СБСЖК является независимым прогностическим фактором долгосрочных прогнозов у пациентов с подозрением на ОКС. Определение СБСЖК, особенно в комбинации с другими биомаркерами, имеет важную ценность,

когда диагностика ОКС затруднена на фоне атипичного клинического течения, отсутствия характерных изменений на ЭКГ.

КЛЮЧЕВЫЕ СЛОВА: острый коронарный синдром, сердечный белок, связывающий жирные кислоты

Mortality among patients with cardiovascular disease (CVD) is high and it tends to increase. One of the most important CVD is acute coronary syndrome (ACS), that may be divided into unstable angina (UA) and myocardial infarction (Ml) with the typical ECG progression with ST-elevation (STEMI) or non-ST-segment elevation (NSTEMI).

CVD is the reason of over 4 300 000 deaths a year in Europe, and it is 48 % of all cases of death. According to American College of Cardiology (ACC) there is about 1100000 MI per year in USA, and about 40 % of patients die [1, 2, 3].

There are a lot of patients with CVD in Ukraine. It is about 47,8 % of the population of the country. And CVD is the reason about 62,5 % of all cases of death. There was more then 50 000 cases of MI per year in Ukraine in 2010, and 10031 patients died [4].

CVD and ACS are caused more frequently by atherosclerosis of coronary arteries. So it is very important to identify healthy people and people with high risk, to influence modified risk factors, and to conduct primary and secondary prevention [4, 5].

With increasing numbers of patients with ACS it is very important to have reliable biomarkers for early diagnosis, to identify ACS and to optimize further tactics of patients management and prediction of the risk of recurrent ischemic damage and mortality.

Acute myocardial infarction (AMI) leads to cardiomyocytes necrosis because of lengthy ischemia, unlike UA. One of the main reason of high AMI mortality is untimely diagnostics [6-9].

The most frequent complaint in patients with ACS is chest pain. Chest pain is pressing or squeezing, it does not stop after taking nitrates (sublingually) or renew for a short time.

However, ACS patients may have atypical clinic and ACS may be present with nonspecific symptoms, such as weakness, dizziness, shortness of breath, or altered mental status or pain may be in neck, the lower jaw, shoulder, under the left shoulder-blade or in the epigastric region. Sometimes, it may be with the lack of air; heart palpitation; a feeling of discomfort in the left half of the chest; shortness of breath, generalized weakness, nausea, anxiety/fear. 20-30 % of patients with ACS have no pain, especially the elderly, patients with diabetics or hypertension [4-10]. At least every third patient has nonspecific complaints, such as weakness, dizziness, shortness of breath, or altered mental status. Factors, against that atypical manifestations of ACS are often observed, are older age, female gender, diabetes mellitus, arterial hypertension, and heart failure in history [8].

Furthermore, chest pain may also be observed in diseases of the cardiovascular system (pulmonary embolism, pericarditis, myocarditis, hypertension, etc.), stomach (GERD, stomach ulcer and 12 duodenal ulcer, acute pancreatitis, etc.), respiratory system (pneumonia, pleurisy, pneumothorax, etc.), nervous system (neurosis, neuralgia), musculoskeletal disorders (osteochondrosis of cervical and thoracic spine, Tietze syndrome), oncological diseases, that also requires timely differential diagnosis [8, 11, 12].

Diagnosis of ACS may be hampered by the presence of ECG changes (Bundle Branch Block, cardiosclerosis), or non-ST segment elevation [7, 8, 10].

According to ACCF/AHA recommendations, features of UA low probability are: age less than 70 years, the duration of pain less then 20 minutes, slow increasing of the pain, normal or unchanged ECG, no cardiac markers elevation [1].

Clinical examination provides minimal information for the evaluation of the ACS and it is often no diagnostic. Risk factors of ACS are old age, male sex, diabetes, MI, a history of previous episodes of stable angina and smoking. However, neither presence of them, nor absence of them does not exclude the possibility of ACS [8].

Standards of myocardial damage diagnosis and the main criterion for NSTEMI diagnosis are biochemical markers, which are very important for early verification, for risk stratification, for the selection of treatment and for the control of the disease progression

and for the treatment efficacy in patients with ACS.

Now the most widely used biomarkers in the diagnosis of ACS are cardiac troponins, that have high sensitivity with a slight myocardial injury and almost absolute specificity for myocardial damage.

Cardiac troponins are more specific and sensitive than traditional cardiac enzymes, such as creatine kinase (CK), its MB isoenzyme (CK-MB), and myoglobin [6-9, 13, 14]. However, cardiac troponin I (cTnI) can be discovered at least in 4-6 hours after the beginning of AMI; moreover, its level is not increased after 12 hours after the start, it is not optimal for the identification of patients with ACS without ST raising on ECG (NSTEMI) [6, 15-17]. 2 hours after AMI more highly sensitive cTnT compared with cTnI. However, cTnT analysis reflects the cell membrane permeability, not clinical threat of AMI [16].

Alternative markers are elaborated for patients with possible ACS. New biochemical markers reflect the different phases of the pathophysiological abnormalities in patients with ACS and, therefore, they can identify particular pathological processes to determine the specific therapy. Also more and more evidence of the multimarker approaches benefits are elaborated in patients with ACS [18].

The alternative marker is heart-type fatty acid binding protein (H-FABP), the role of which is actively investigated to confirm patients with ACS and to evaluate of the long-term prediction. H-FABP can predict a 6-year mortality after acute coronary syndrome [9, 18, 19].

H-FABP confirms the acute cardiomyocytes necrosis and also myocardium ischemia. H-FABP allows to define STEMI and NSTEMI, helps to differentiate unstable angina.

H-FABP is small size molecule (14 kDa) (in comparison with troponins, with the size 21-27 kDa and myoglobin with the size 17.2 kDa), that promotes more rapid exit of H-FABP than troponins from the cells. H-FABP is involved in fatty acids transport [4, 11, 20].

H-FABP is water-soluble protein. It contains in the cytoplasm of the cardiac myocyte. H-FABP is found in abundance in cardiomyocytes but is also expressed (to a lesser extent) in skeletal muscle, distal tubular cells of the kidney, specific parts of the brain, lactating mammary glands and placenta. H-FABP is approximately ten times more abundant in the cardiac myocyte than skeletal muscle [6, 8].

The main biological function of H-FABP is to facilitate intracellular translocation of long-chain fatty acids, which is usually hampered by the very low solubility of these compounds in aqueous solutions [21]. Mechanisms, that initiate and maintain increase free fatty acids (FFA) concentration after ischemia, are not clear. Some reasons are suggested: increased blood catecholamines in association with ischemia cause increasing FFA concentrations and then increased FFA release through adipose lipolysis, and although ischemia activates lipid hydrolysis within the heart [22].

After dissociation from plasma albumin, fatty acids are translocated through the lipid bilayer via passive diffusion, membrane-associated proteins, or a combination of both. The membrane-associated fatty acid transporters: fatty acid-binding protein (FABPpm), fatty acid translocase (CD36), and fatty acid transport protein (FATP) are involved. Intracellular fatty acids are bound to cytoplasmic H-FABP (FABPc) and, after activation to fatty acyl-CoA, to acyl-CoA–binding protein (ACBP). After dissociation from plasma albumin, fatty acids are translocated through the lipid bilayer via passive diffusion, membrane-associated proteins, or a combination of both. The membrane-associated fatty acid transporters fatty acid-binding protein (FABPpm), fatty acid translocase (CD36), and fatty acid transport protein (FATP) are involved. Intracellular fatty acids are bound to cytoplasmic H-FABP (FABPc) and, after activation to fatty acyl-CoA, to acyl-CoA–binding protein (ACBP) [21].

Although H-FABP include participation in signal transduction pathways, such as regulation of gene expression by mediating fatty acid signal translocation to peroxisome proliferator–activated receptors, and putative protection of cardiac myocytes against the detergent-like effects of locally high concentrations of long-chain fatty acids, particularly during ischemia [21].

H-FABP release into the blood as early as 30 minutes after cardiomyocytes injury, detectable in the circulation as early as 1-3 hours and return to baseline within 12-24 hours [14, 20]. The greatest significance of H-FABP

determination is within 12 hours. H-FABP is also found in urine as early as 1-2 hours following an ischemic damage [6, 8].

Normally H-FABP level is 0-6 μg/l, with myocardial ischemia 6-20 μg/l, with necrosis of cardiomyocytes 6-2000 μg/l [21].

The sensitivity of H-FABP testing is higher then troponin testing every time period after beginning of ACS [23].

First hours H-FABP sensitivity was higher then troponin at 18-32 %, and H-FABP specificity was almost the same, but if there was no ECG changes or Bundle Branch Block, H-FABP has higher sensitivity and specificity compared with troponins [14, 19, 23, 24].

H-FABP is not only independent prognostic marker, but it identifies high-risk patients who are troponin negative. H-FABP predicts long-term mortality and recurrent MI at troponin-negative patients with suspected acute coronary syndrome.

The peak of H-FABP is associated with increased risk of death and major negative cardiac events in patients with ACS and is not dependent for other installed clinical risk prediction and biomarkers.

Furthermore, elevated H-FABP levels were associated with increased risk of MI or recurrent ischemia within 30 days, especially in unstable angina patients, when they were determined the negative troponin I.

H-FABP for confirming AMI has a higher significance and sensitivity, compared with myoglobin, troponin, CK-MB elevation, and at the same time H-FABP has a high specificity [11].

H-FABP definition for the diagnosis of myocardial damage was effective without depending on sex, age and localization of myocardial injury. Thus, localization of MI does not affect the validity of the results, H-FABP sensitivity was higher for Q-positive MI than for Q-negative MI [10].

For practical using H-FABP determination express-methods are significant, they are based on immunochromatographic method that helps carry out a qualitative or quantitative assessment of the level of H-FABP, but not immunoassay, that allows conducting quantitative determination of H-FABP. Advantages of rapid tests are easy for techniques, compactness, efficiency of obtaining results [23].

When H-FABP, troponin I, myoglobin and B-type natriuretic peptide were estimated simultaneously, the degree of increased H-FABP worsen the prediction regardless of biomarkers values. The more H-FABP increasing was, the higher risk of cardiovascular complications was. Moreover, the level of H-FABP had the greatest predictive value within 48 hours after the onset of chest pain [18, 25-27].

Furthermore, predicting of mortality depends from increased levels of H-FABP, but it does not depend on the level of troponin [19].

Multimodal regression approach confirmed that the age, prior MI, heart rhythm disorder and the concentration of H-FABP remained statistically significant, as independent factors of development-term complications [18].

Also high H-FABP concentration is associated with a risk of cardiovascular complications, including heart failure, recurrent myocardial infarction, sudden cardiac death.

Furthermore, high H-FABP concentration worsen ventricular contractility, by disordering the splitting of mitochondrial proteins that impairs the production of energy by the mitochondria [19].

There is a gradient of increasing risk with elevated H-FABP concentration ($p < 0.001$). During the study of O'Donoghue M. et al. was confirmed that there was the correlation between the level of H-FABP and the risk of subsequent adverse clinical events, according to which the patients are divided into three groups, depending on the level of H-FABP: low risk (< 8 ng/mL), medium (from 8 to 16 ng/mL), and high (> 16 ng/mL). The relationship was established between the level of H-FABP and risk of death, recurrent MI, chronic heart failure, and these values [18].

Moreover, the elevated H-FABP level within 30 days also was associated with the risk of recurrent ischemia [18]. Normal levels of troponin and H-FABP were associated with very low risk of death [19].

During the study of Kilcullen N. et al. mortality within 1 year in patients with unstable angina in patients with H-FABP level < 5,8 micrograms/l was 2,1 %, and in patients with higher H-FABP levels was 22,9 % [19].

Determination of biochemical markers is not only the method, that complement methods of verification of the diagnosis of ACS, but it is an independent criterion in making a decision about invasive treatment strategy in the early

hours of NSTEMI. Combining of highly sensitive cardiac troponin and H-FABP significantly increases diagnostic accuracy of ACS, with greater sensitivity and specificity [11, 26].

CONCLUSIONS

Thus, H-FABP allows to differentiate ACS in the early period and also to assess prognostic significance for patients with ACS and further adverse complications. H-FABP has sensitivity higher than troponins and other biomarkers, furthermore it has high specificity. Definition H-FABP, especially in combination with other biomarkers, has the important value, when the diagnosis of ACS is difficult against the background of the atypical clinic, the absence of typical ECG changes, or presence of myocardial disorders. Increased H-FABP level is an independent prognostic factor in the long-term prognosis in patients with suspected ACS, especially among troponin-negative patients, even in combination with high sensitivity troponin tests.

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ANTIHYPERGLYCEMIC THERAPY FOR PATIENTS WITH DIABETES MELLITUS TYPE 2

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The article describes the main classes of oral antihyperglycemic drugs, the mechanism of action, administration details, indications and contraindications. The innovative incretin-directed therapy was also covered. Rational algorithms of patients' treatment with diabetes mellitus type 2 were presented.

KEY WORDS: diabetes mellitus type 2, oral antihyperglycemic drugs, biguanides, sulfonylurea medications, incretin mimetics

ЦУКРОЗНИЖУВАЛЬНА ТЕРАПІЯ У ПАЦІЄНТІВ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

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У статті розглянуті основні класи пероральних цукрознижувальних препаратів, механізм дії, показання та протипоказання до їх використання, особливості застосування. Висвітлена інноваційна інкретин-спрямована терапія. Наведено раціональні алгоритми лікування пацієнтів з цукровим діабетом 2 типу.

КЛЮЧОВІ СЛОВА: цукровий діабет 2 типу, пероральні цукрознижувальні препарати, бігуаніди, препарати сульфанілсечовини, інкетіноміметики

САХАРОСНИЖАЮЩАЯ ТЕРАПИЯ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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В статье рассмотрены основные классы пероральных сахароснижающих препаратов, механизм действия, показания и противопоказания к их использованию, особенности применения. Освещена инновационная инкретин-направленная терапия. Приведены рациональные алгоритмы лечения пациентов с сахарным диабетом 2 типа.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 2 типа, пероральные сахароснижающие препараты, бигуаниды, препараты сульфанилмочевины, инкретиномиметики

According to World Health Organization experts, in economically developed countries about 4 % of the population suffers from diabetes mellitus (DM) [1, 2]. Altogether 5-6 % of the population suffers from DM and every 10-15 years the number of diabetic patients is doubly increased [1, 3]. The epidemiology of diabetes in general is defined by DM type 2 (DM-2), as it is about 90-95 % of all sickness cases [1-4]. The control over the DM progression is a pressing question because DM is one of the most frequent causes of disability and patients' mortality (is ranked third after cancer and atherosclerosis). For patients with DM the life expectancy is reduced by 10-15 % [2, 3]. In the course of DM treatment there should be made some modifications in the patients' lifestyle such as nutritional care and physical activities, smoking cessation, reducing of alcohol ingestion or it renunciation, patient teaching, self-control, psychological support and glycemic control [1-5].

Oral antihyperglycemic drugs (OHGD) are assigned to patients with DM-2 in cases when dietary interventions and increasing of physical activities didn't lead to fasting glucemic goals [1, 3-5].

According to the mechanism of action the OHGD can be divided into main groups [3-6]: drugs that reduce insulin resistance – sensitizers; drugs that stimulate insulin release by B-cells – secretagogues; drugs that reduce intestinal glucose absorption; innovative drugs – innovative incretin-directed therapy (incretin mimetics).

1) Drugs that reduce insulin resistance include biguanides and thiazolidinediones (tab. 1) [3].

Table 1

Drugs that reduce insulin resistance – sensitizers

Drug	Daily dose, mg	Dosage frequency, mg per day	HbA1c Reduction, (%)	Characteristic
Biguanides				
Methylbiguanide (Metformin)	500-3000	1-3	1,0-2,0	Counter-indicative at: GFR < 60 ml/min/1,73m^2; in cases when creatinine >115 mole/l there is a risk of lactic acidosis
Thiazolidinediones (glitazone)				
Pioglitazone	15-45	1	0,5-1,4	Counter-indicative at: hepatic disorders; edema of any origin; HF I-IV FC; in combination with insulin's or nitrate intake; ketoacidosis; pregnancy and lactogenesis

Dimethylbiguanide – metformin is the only biguanide that is used at present.

Basic mechanisms of metformin's antihyperglycemic effect are caused by:

- increasing of peripheral glucose disposal (muscular tissue is in the first flight) by anaerobic glycolysis activation;
- decreasing hepatic glucose output;
- partly – by decreasing of jejunum's glucose absorption.

Metformin is a drug of the first-line therapy for patients with DM-2 and with body mass index (BMI) of 30 kg/m^2 or more, i.e. for overweight patients [5]. The metformin's usage for monotherapy is able to reduce HbA1c by 1.5 %. The initial metformin's daily dose is 500 mg (with food in the evening or for a night). Metformin's antihyperglycemic effect is most effective while the dose is 2000-2500 mg/d. Such indices are achieved by dose titration of metformin 500 mg weekly (to minimize adverse effects at intestinal tract) [1, 5-7]. In contrast to the sulfonylurea medications (SUs), metformin does not stimulate pancreas' insulin secretion and that's why doesn't lead to hypoglycemia progression. In other words, the metformin's effect isn't hypoglycemic but antihyperglycemic. Metformin has quite frequent but transient adverse effect such as diarrhea [3, 6-7]. Metformin's contraindications are: pregnancy and lactation, severe renal failure (GFR < 60 ml/ min/1 73 m2), severe hypoxia (heart failure III-IV function classes by NYHA classification, respiratory failure and anemia), alcohol abuse. Although metformin is just slightly lead to lactic acid accumulation (because of anaerobic glycolysis' hyperactivation), but the risk of lactic acidosis increases with renal failure. That's why metformin isn't recommended for patients with serum creatinine level > 115 mmoll/l. If it is necessary to make a radiographic contrast study, metformin should be temporarily put off due to the risk of contrast-media induced nephropathy [3, 5].

Thiazolidinediones (glitazone) have a favorable metabolic profile:

- decrease insulin resistance;
- low risk of hypoglycemia;
- hypolipidemic effect.

Rosiglitazone is forbidden to use and removed from sale because of close relationship between the drug intake and the increased rate of cardiovascular deaths [5, 7]. Pioglitazone – is the only acceptable pioglitazone. Glitazones are able to reduce HbA1c by 1.5 %. Pioglitazone can be added to OHGDs in cases when the OHGDs in the form of monotherapy was ineffective. A daily dose

of pioglitazone in the form of monotherapy is – 15-45 mg, as a part of combined therapy – 15-30 mg. Pioglitazone should be taken as a single dose without regard to timing of food ingestion.

Glitazones' adverse effects such as water retention and edema are more common in patients who receive TZDs with insulin. Patients with HV II – IV FC and those with hepatic impairment should not receive TZDs [3, 5-7].

2) Drugs that stimulate insulin release by B-cells.

This group includes SUs and meglitinids (glinides), which are mainly normalize a postprandial blood glucose. SUs are bind to specific receptors of pancreas' β-cells-surface that leads to closure of ATF-dependent potassium channels and cell membrane's depolarization that causes the calcium channels opening. Calcium inside β-cells causes degranulation and insulin release into the blood [3, 5, 6]. All the SUs are sulphonylurea derivatives and differ from each other by the type of additional conjugations, which were included to the main group, that define the SUs' pharmakokinetics and act habits (tab. 2).

Table 2

Drugs that stimulate insulin release by B cells – secretagogues

Drug	Daily dose, mg	Dosage frequency, mg per day	HbA1c Reduction, (%)	Characteristic
SUs				
Glibenclamid	2,5-20	1-2	1,0-2,0	Has the most pronounced antihyperglycemic effect
Micronized glibenclamid	1,75-14	1-2	«—»	
Glipizide	2,5-30	1-2	«—»	Low risk of hypoglycemia
Glipizide -retard	2,5-30	1	«—»	Drug effect - over a day
Glimepiride	1-8	1	«—»	Drug effect - over a day, wide therapeutic index
Gliclazide	80-240	1-3	«—»	The lowest risk of hypoglycemia, angioprotective effect
Gliclazide MR with modified release	30-120	1	«—»	Drug effect - over a day
Gliquidone	30-120	1-3	«—»	In 95 % of cases is secreted by intestinal tract, that allows to prescribe this drug for patients with early renal failure
Meglitinids (glinides)				
Repaglinide	0,5-16	3-4	0,5–1,5	Risk of weight gain
Nateglinide	120-480	3-4	«—»	Decreasing risk of hypoglycemia

According to the recommendations of International Diabetes Federation 2005, the SUs are drugs of the first-line therapy for patients with DM-2 and with BMI of 30 kg/m^2 or more. The SUs treatment is started with minimum dose and gradually under the glucose profile's control the dose is increasing. Antihyperglycemic therapy isn't recommended to start with SUs that have the highest risk of hypoglycemia progression, i.e. with glibenclamid [5-7]. In cases when chosen SUs are poorly effective it isn't recommended to use it in combination with other SUs or with glinides. SUs reduce HbA1c as effective as biguanides – by 1,5 %. A frequent adverse effect of SUs is hypoglycemia, that occurs in cases of overdose, accumulation (renal failure), carbohydrates' shortfall (meal absence) or

overrun (alcohol ingestion, physical activities). Glinides include repaglinide (a benzoic acid derivative) and nateglinide (a phenylalanine derivative) which stimulate insulin secretion like the SUs, although they bind to a different site within the sulfonylurea receptor. They have a shorter circulating half-life than the sulfonylureas and must be administered more frequently. As the result a blood glucose is briefly increasing. Glinides should be taken about 10-20 minutes before meals, 3-4 times per day. A daily dose of repaglinide is – 0,5-16 mg, nateglinide – 120-480 mg. Glinides' contraindications are similar to the SUs. Repaglinide is almost as effective as biguanides and SUs, decreasing HbA1c levels by 1,5 %. The risk of weight gain is similar to that for the SUs, but hypoglycemia may be less frequent, at least with nateglinide [3, 5-7].

3) Drugs that reduce intestinal glucose absorption – α-glucosidase inhibitors.

This group includes acarbose, which reversibly blocks α-glycosidase of jejunum. As the result, the polysaccharides' absorption slows down , the rate of resorption and glucose admission in the jejunum decreases and the postprandial blood glucose level reduces. The drug has no systemic effects, does not cause hypoglycemia and mainly reduces postprandial blood glucose. The drug is taken immediately before the meal. The initial daily dose is 150 mg and it should be taken three times per day. In the future it is possible to increase the dose up to 300 mg per day. In comparison with biguanides and SUs, acarbose is less effective in reducing blood glucose level. It is able to reduce the level of NbA1s by 0.5-0.8 %. The flatulence and diarrhea are the main adverse effects of acarbose. The main reason of such effects is admission of not absorbed carbohydrates to the colon. [3, 5-7].

4) Incretin mimetics.

Searching for the DM's optimum treatment, based on the study of a new regulating mechanism of glucose homeostasis, led to the creation of drugs with the incretin effect [5-8]. After a meal incretin-hormones, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagonlike peptide (GLP) are synthesized in intestinal mucosa. Such hormones are easily destroyed (about 2-7 minutes) by dipeptidyl peptidase-4 enzyme (DPP-4) [8-10]. Incretins exert multiple effects on the exocrine pancreas, but their main mechanism is connected with potentiation of insulin release by B cells. The fundamental point is that the insulinotropic effect of GLP-1 is glucose-dependent. In other words, GLP-1 stimulates insulin secretion only with hyperglycemia, insulin stimulating effect is leveled down during the normalization of blood glucose level at least less than 6,0 mmol/l. Whereas, GIP with a glucose level above 7,8 mmol/l has a little effect on insulin secretion and doesn't suppress the glucagon synthesis [11]. In turn, GLP-1 is also suppressed glucagon secretion according to the blood glucose level. The physiological mechanism of insulin secretion «on demand» and glucose-dependent suppression of glucagon secretion under the action of GLP-1 prevents the progression of hypoglycemic states [10, 11]. One of the positive properties of GLP-1 is the fact that it affects the regulation of postprandial hyperglycemia by lowering the motor and secretory activity of the stomach and intestines. Moreover, in cases, when GLP-1 has an effect on nuclei in the hypothalamus, it promotes rapid saturation and, as a consequence, reduces body weight. The additional effects of GLP-1 are shown in the suppression of hepatic gluconeogenesis and glucose escape in muscle and adipose tissue (resolves insulin resistance of peripheral tissues). The experiments demonstrated that GLP-1 prevents the progression of osteoporosis and osteopenia [11]. Presumably GLP-1 has an additional advantage in terms of conservation mass of β-cells pancreas [8].

The effective investigation of incretin metabolic approach led to the creation of two drug groups (tab. 3):

1. Agonists of GLP-1 (aGLP-1);
2. Medications, that prevent the destruction of GLP-1, DPP-4 inhibitors (iDPP-4).

Incretin-mimetics took a worthy place in the treatment of patients with DM- 2 due to the following advantages: physiological mechanism of insulin secretion «on demand» with a low risk of hypoglycemia, glucose-dependent suppression of glucagon hypersecretion, the improving of beta-cell function, the ability to control body weight [11].

Table 3

Incretin-mimetics

Drug	Daily dose, mg	Dosage frequency	HbA1c reduction, (%)	Characteristic
aGLP-1				
Exenatide	0,5 – 1,0	1 – 2	1,5	Injected subdermally, there is no information on long-term efficacy and safety
Liraglutide	0,6 – 1,8	1	1,1 – 2,5	
iDPP-4				
Vildagliptin	100	1 – 2	0,5 – 1,4	Is not recommended in the cases when the activity of ALT or AST is increasing > 2,5 times; Dosage modification in moderate and severe renal failure
Sitagliptin	100	1	0,6 – 1,4	
Saxagliptin	5	1	0,7 – 0,8	
Linagliptin	5	1	0,4 – 1,2	Excreted mainly via the intestine, that's why there is no need of dosage modification according to the renal function

GLP-1 receptor agonists are injected subdermally the abdominal zone, femora or antibrachium. Exenatide is recommended to inject 2 times a day within 60 minutes, prior to breakfast and dinner. After a month of therapy the dose can be increased to 1,0 mg two times a day [5, 7, 11].

Liraglutide is a first analog of human GLP-1, is injected once a day. It does not cause hypoglycemia, reduces body weight (in overweight patients) and blood pressure. The initial dose of Liraglutide is 0,6 mg per day and can be increased to 1,2 mg in a week, but the excess more than 1.8 mg is not recommended. Patient's body weight is reduced to 4 kg during the aGLP-1's chronic administration. The most common adverse effects (30-40 % of patients) of this drugs group are nausea and vomiting, that have transient effect. It is contraindicated in case of renal failure (GFR less than 30 ml/min/1.73 m^2); liver function abnormality; cardiac failure of III-IV functional class. This drug should be carefully prescribed to patients with relapsing pancreatitis [7, 11].

The iDPP-4 ' medications are gaining popularity in the DM-2 treatment. Published research results shows the efficacy and safety of the iDPP-4, both as the monotherapy and in the combination with other antihyperglycemic drugs [5, 7, 9, 12, 13].

The iDPP- 4 class, in view of its efficacy and safety, was included to all current recommendations of the DM-2 treatment [5, 12-14]. Besides the proved antihyperglycemic effect, indisputable advantage of the iDPP-4, compared to the traditional drugs, is a minimum hypoglycemia's risk, lack of weight gain, that is especially important for patients with particular risk group. So, the iDPP-4 should be prescribed for overweight patients, patients with excess body weight and for elderly people with high hypoglycemia's risk. Upper respiratory infections (6,8 %), nasopharyngitis (4,5 %) and diarrhea(3,0 %) are the most frequent adverse effects during a chronic administration of DPP-4 inhibitors [5, 13, 14].

Drugs are not recommended for patients with severe renal (GFR less than 30 ml/min/1,73 m^2) and hepatic failure. The drug should be carefully prescribed for patients with anamnestic indications of relapsing pancreatitis. In general, the inhibitor therapy is assessed as a safe one, but the greatest benefits are for patients with high cardiovascular risk factors [5, 13-16]. The concept of the target achievements in the DM-2 treatment is changing with the rise of new antihyperglycemic drugs, their introduction into clinical practice and the data capture of formerly used medicines. As the result, there are regular renewals of international and national hypoglycemic therapy algorithms [5, 7, 13-17].

A joint algorithm of American Diabetic Association (ADA) and the European Association for the Study of Diabetes (EASD) is one of the most recognized international algorithms of DM-2 treatment, which was first proposed in 2006 and amended in 2009 [6, 7]. Due to this algorithm the DM-2 therapy is represented as two tiers: well-validated core therapies (tier 1) and less well-validated

therapies (tier 2). The aim of hypoglycemic therapy is to achieve and maintain the level of glycosylated hemoglobin (HbA1c) <7,0 % in all patients.

Tier 1: well-validated core therapies

Metformin and lifestyle interventions are recommended as the initial pharmacological therapy for patients with DM-2. If lifestyle intervention and the maximal tolerated dose of metformin fail to achieve HbA1c >7 %, another antihyperglycemic medication (the SUs or basal insulin) should be added within 2–3 months of the initiation of therapy. Insulin is the more effective glycemia-lowering agent for patients with HbA1c >8.5 % or with symptoms to hyperglycemia. If glycaemic targets aren't achieved, the next step should be to start, or intensify insulin therapy.

Tier 2: less well-validated therapies

To a basis metformin therapy and lifestyle interventions may be added aGLP-1 or glitazone. If these interventions, after 3 months therapy, are not effective in achieving HbA1c target, the insulin therapy or addition of a sulfonylurea could be considered.

Weaknesses of ADA/EASD algorithm (2006, 2009) [5, 6, 7]:

1. One target level of HbA1c for all patients (< 7,0 %);
2. Basal control value of carbohydrate metabolism with a limited choice of initial therapy isn't taken into account;
3. High rate of therapy' s intensification;
4. There are no modern incretin-mimetics – iDPP-4.

The results of ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease-Preterax and Dimicron Modified Released Controlled Evaluation) and VADT (Veteran Affairs Diabetes Trial) study are demonstrated that factors such as age, risk of hypoglycemia and the presence of concomitant diseases need to be considered for every patient before choosing the individual HbA1c target level [5, 7]. The algorithm of the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE, 2009) takes into account the above disadvantages [7].

New AACE/ACE-2009 recommendations:

- choosing initial therapy, the HbA1c target level is taken into the account;
- there are modern incretin mimetics – iDPP-4;
- there noted that taking sulfonylureas is associated with a high risk of hypoglycaemia and during a long-term treatment its effectiveness decreases.

Due to AACE/ACE-2009 recommendations, the experts of the Russian Association of Endocrinologists (RAE) built up a Consensus for therapy optimization of DM-2 [5]. In the RAE recommendations the emphasis laid on individualization, safety and efficacy of treatment.

General provisions of RAE Consensus for initiation and intensification of DM-2 antihyperglycemic therapy [5]:

The individual glycemic control target's determination on HbA1c level (tab. 4).

Table 4

The individualized choice's algorithm of the HbA1c target level

Severe complicationsand/or risk of severehypoglycemia	**Age**		
	Juvenile	**Median**	**Elderly and/or LE* < 5 years**
Present	<6,5%	<7,0%	<7,5%
Epsent	<7,0	<7,5%	<8,0%

* life expectancy

In addition the doctor should pay attention the motivation and treatment compliance, interaction with already obtained drugs.

1. The stratification of treatment strategy depending on the HbA1c initial level.

Regardless of the HbA1c initial level, the first main recommendation is a lifestyle modification. But taking into account the low compliance to the non-drug treatment, it is necessary to prescribe the hypoglycemic therapy at the beginning of the disease.

If the initial HbAlc level is about 6,5-7,5 %, it is recommended to start with the monotherapy. But if HbA1c targets are not

achieved, it is necessary to prescribe the combined therapy, which includes 2 or 3 drugs.

If the initial HbAlc level is 7,6–9,0 % it is recommended to start with the combined therapy. If the treatment is not effective it is possible to combine three OHGDs or to conduct insulin therapy.

If the the initial HbAlc level is more than 9,0 % it is necessary to prescribe insulin as a monotherapy or in the combination with OHGDs. In the case of reaching HbA1c targets it is possible to start the treatment with tableted antihyperglycemic drug.

2. The ability to make allowances to previously prescribed therapy schemes.

It is recommended to measure therapy outcomes every 3 month, and, if it is necessary, to intensify therapy not later than 6 months, or in cases of patient's deterioration.

Therapeutic management with the initial HbA1c level 6.5-7.5%.

Before choosing the clinical management of the patient it is necessary to determine the individual target level of HbA1c (Table 4). If it is below the initial level for a particular patient, it is necessary to recommend the diet therapy and regular doctor's following up. In the case when the initial level of HbA1c is above the target, it is recommended to start with OHGD therapy.

Step 1 –therapy initiation.

First-line drugs: biguanides, the iDPP -4 or aGPP-1.

Metformin is the most studied in terms of efficiency and safety drug in monotherapy. It does not cause hypoglycaemia and weight gain. Therefore its prescribing to the overweight patients is justified. The drugs from iDPP-4 and aGPP-1 group also should be prescribed to the patients who need weight reducing, and individuals with a high risk of hypoglycaemia. The choice between first-line drugs depends on the risk of possible adverse effects of a particular patient.

Alternative medications for therapy initiating are: OHGD, glinides, glitazones, alpha-glucosidase inhibitors.

If the initial HbA1c level is 6,5–7,5 % OHGD , glinides are not considered as a first-line agents, because of hypoglycemia's risk. The OHGD and glinids' prescribing is justified in case when there are contraindications to first-line drugs. It can be prescribed to patients with normal body weight (lack of insulin secretion dominates). Pioglitazone can also be recommended to individuals with normal body weight without cardiovascular diseases, if taking the first-line drug is contraindicated.

If the initial HbA1c level is 6,5–7,5 %, insulin therapy is not prescribed as starting treatment. It is possible only in cases of suspected latent autoimmune diabetes in adults (LADA), when the insulin secretion deficiency symptoms are expressed (massive weight loss, thirst, polyuria).

If individual HbA1c targets are achieved or there is a decrease of HbA1c to more than 0.5 % for 6 months, it is necessary to follow the monotherapy option.

Step 2 - therapy intensification.

The step of therapy intensification can be started within 6 months from the monotherapy beginning, if the HbA1c target isn't achieved or it's decreasing is less than 0.5 %. At this step the combination of two complementary medicines is prescribed.

Rational combination of antihyperglycemic drugs:

- Metformin + the iDPP-4;
- Metformin + aGPP-1;
- Metformin + SUs or glinides.

These combinations reduce insulin resistance and at the same time stimulate the secretion of insulin. At the same time a combination of metformin + iDPP-4/aGPP-1 has a minimal risk of hypoglycemia and lack of weight gain, and the combination with aGPP-1 decreases its level. The prescribing of two fixed different drug combinations is a possible variant. If the targets of glycemic control are achieved, the chosen combination scheme of 2 antihyperglycemic drugs should be continued.

Step 3 - further therapy intensification.

If the double scheme proved to be ineffective, even using the most effective doses of both components, than it is necessary to start taking the triple combination, or adopt the insulin therapy. The decision on further intensification must be taken not later than 6 months from the start of step 2 beginning. Meformin continues to be a major component of any combination, even during the insulin therapy. At the triple combination, the second and third components can be incretin mimetics or SUs/glinides, in some cases, glitazones, except irrational schemes.

The list of irrational and/or unauthorized combinations of antihyperglycemic drugs:

1. SUs + glinides,

2. iDPP+ aGPP-1,
3. Two representatives of SUs,
4. Glitazones + insulin,
5. aGPP-1/iDPP-4 + glinides,
6. Short-acting insulin + SUs/aGPP-1/iDPP-4/glinides.

It is necessary to carry out the insulin therapy, if the three-part treatment is ineffective. If there are no metformin contraindications, the combination of metformin with insulin is quite safely. The iDDP-4 and aGPP-1 drugs can be taken only in combination with basal insulin. Taking glitazones in combination with insulin increases the risks of: edema, weight gain, and cardiac decompensation. So, the combination of these drugs isn't recommended. The combination of insulin with SUs or glinides is dangerous and can become a cause of hypoglycemia.

Therapeutic management with the initial HbA1c level 7,6–9,0 %.

Step 1 – therapy initiation.

If the target level of HbA1c is above the initial level, it is recommended to prescribe a minimum dose of medications with low risk of hypoglycemia (metformin and iDPP-4), in addition to diet therapy.

If the target level is below the initial HbA1c level, it is recommended to start therapy with a combination of two drugs, which act on various links of the DM-2 pathogenesis (insulin secretion and its sensitivity to peripheral tissues).

The combination of basic drug (Metformin) with iDPP-4 or aGPP is more appropriate For overweight patients, patients with excess body weight and high hypoglycemia's risk. For patients with more than 8.5 % NbA1c, that indicates the presence of serious decompensation of carbohydrate metabolism, the metformin combination with SUs or insulin is more appropriate. The other combinations are possible, but it depends on the individual drug tolerance profile, adverse effect and contra indications.

The chosen scheme of hypoglycemic therapy should be continued in case when the target level of HbA1c was achieved or decreased at more than 1,0 % from the initial level within six-month period.

Step 2 - therapy intensification

In case when HbA1c is<1,0%, the obtained therapy can be intensified after 6 months from its beginning or in case of the patient's deterioration it can be intensified even earlier. In such case it is recommended the 3 drugs' combination with the main component (metformin) and with possible insulin taking.

Step 3 - further therapy intensification.

It is recommended to start insulin therapy in case when within 6 months triple therapy the level of HbA1c wasn't decreased to the target level.

Therapeutic management with the initial HbA1c level more than 9,0 %.

Step 1 – therapy initiation.

If the patient has not previously received glucose-lowering therapy and has the initial HbA1c> 9 %, the glucose toxicity should be urgently removed by insulin treatment. If the level of HbA1c within 6 month insulin therapy decreases by more than 5 %, it is possible to start a 2-3 antidiabetic drugs combination.

If there are any strong indications of decompensation (progressive weight loss, polyuria, polydipsia), the alternative 2-3 components scheme can be prescribed even at onset of disease. The basis of such combinations should be the drug with a maximum insulin secretory capacity (DMC) and metformin (if there are no contraindications). The insulin should be prescribed, if the HbA1c target level is not reached. If within 6 months of insulin therapy the HbA1c level decreases less than 1.5 % or its targets will not be reached, insulin therapy should be intensified (steps 2, 3).

Thus, the RAE Consensus encourages to individualize the treatment of patients with DM-2, starting out from the initial state of metabolic control, choosing safe and effective therapy [5, 17].

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Lecture

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ANKYLOSING SPONDYLITIS

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Etiologic, epidemiologic, pathogenic and clinical description of ankylosing spondylitis are discussed in the lectures. Basic approaches to diagnostics, medical treatment and prophylaxis of disease are represented.

KEY WORDS: ankylosing spondylitis, etiology, clinics, diagnostics, medical treatment and prophylaxis

АНКІЛОЗУЮЧИЙ СПОНДИЛІТ

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У лекції представлена етіологічна, епідеміологічна, патогенетична і клінічна характеристика анкілозуючого спондилоартриту. Висвітлено основні підходи до діагностики, лікування та профілактики захворювання.

КЛЮЧОВІ СЛОВА: анкілозуючий спондилоартрит, етіологія, клініка, діагностика, лікування та профілактика

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В лекции представлена этиологическая, эпидемиологическая, патогенетическая и клиническая характеристика анкилозирующего спондилоартрита. Освещены основные подходы к диагностике, лечению и профилактике заболевания.

КЛЮЧЕВЫЕ СЛОВА: анкилозирующий спондилоартрит, этиология, клиника, диагностика, лечение и профилактика

Chronic lumbar pain is the problem of current importance in modern clinical medicine. More frequently it has an inflammatory character and is determined by spondyloarthropathies [1].

Spondyloarthropathies is a group of interconnected inflammatory arthritis which includes ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis, Crohn's disease, undifferentiated spondyloarthropaties and juvenile spondylitis [2, 3].

AS (rheumatoid spondylitis, Bechterev-Shtrumpel-Marie disease) is a system inflammatory disease of connective tissue with predominant deprivation of the joint ligamentous apparatus of the spine and periphery joints with the involvement of internal organs (heart, aorta, kidneys) [4, 5].

Archeological digging revealed the remains of the spine skeleton of the Egyptian mummy 5000 years of age with the features of «bamboo rod» [6].

AC was first described by anatomist and surgeon Realdo Colombo in 1559 [7] in his treatise «Anatomy». In 1691 Bernar Connor [8] gave the description of the human skeleton with the signs of scoliosis in which sacrum, pelvic bone, lumbar vertebra and 10 thoracic vertebras with ribs are merged in single bone.

The disease called «spine numbness with curvature» was first described by V.M. Bechterev in 1892 [9, 10]. In 1897 A.Strumpell [11] gave to it the definition «chronic inflammation of spine and sacral-iliac joint», and in 1898 P. Marie [12] described one of its forms – spine deprivation with involvement of

hip and shoulder joints into the process and called it rhysomyelitic spondylitis.

EPIDEMIOLOGY

Prevalence of AS comprises 0,01 – 6 % of the population. It more often affects men (90 %) at the age of 20-40 years old. Possibly the morbidity of women is understated because of less expressed symptomatic.

Social significance of AS dictated by the development of the disease in young productive age and progressive course of it with the development of disability [13, 14].

RISK FACTORS, ETIOLOGY, PATHOGENESIS

Genetic predisposition, sex (men suffer more frequently), age (20-40), overcooling, presence of chronic infection in the organism belong to AS risk factors.

The connection of HLA-B27 with AS was first descried in 1973 [15, 16], though it does not explain the cause of the disease**.** More than 90 % of Europeans with AS are the carriers of HLA-B27, though most of HLA-B27-positive people remain healthy, thus prompting the idea, that there are other genes, taking part in the development of susceptibility to the disease. Thus carriage of HLA-B27 is the risk factor of AS development only in 20-50% [17, 18]. Identification of new genes - ARTS1, IL23R and IL1A gave the ground to suppose that susceptibility to AS development can also be connected with genes which are not included into the main complex of human histocompatibility [19, 20].

Three hypothesis of AS pathogenesis are defined:

- molecular mimicry between amino acid successiveness of infection agents and HLA-B27 (got no acknowledgement);

- receptor (HLA-B27 and virus antigens form circulating immune complexes possible to cause pathologic reactions, providing for AS clinics);

- changed HLA-B27 (some microorganisms can change molecular structure of HLA-B27, which activated T-killers for its destruction). More thorough study of AS pathogenesis is necessary for improvement of modern methods of treatment and increase of the patients' quality of life [21, 22];

Inflammation usually begins in sacroiliac junctioning and spreads on upper section of the spine. Later reflex spasm of paravertebral muscles appears which strengthens pain syndrome and causes blood circulation disorder. In time inflammation in intervertebral junctions causes the development of ankylosis with ossification of joint apparatus and degenerative changes of hyaline layers and bodies of the vertebra.

CLASSIFICATION

LCH 10

M45 Ankylosing spondylitis.

M45.1 Ankylosing spondylitis: Localization – Occipital section, first and second neck vertebras

M45.2 Ankylosing spondylitis: Localization – Neck section

M45.3 Ankylosing spondylitis: Localization – Cervical-thoracic section

M45.4 Ankylosing spondylitis: Localization – Thoracic section

M45.5 Ankylosing spondylitis: Localization - Lumbar-thoracic section

M45.6 Ankylosing spondylitis: Localization – Lumbar section

M45.7 Ankylosing spondylitis: Localization - Lumbar-sacral section

M45.8 Ankylosing spondylitis: Localization – Sacral and sacral-coccyx section

M45.9 Ankylosing spondylitis: Localization – Unknown localization

Clinical classification Masurov V. I. 2008 [23].

Course:

1. Slowly progressing,
2. Slowly progressing with exacerbation periods,
3. Quickly progressing,
4. Skeptical variant.

Stages:

1. Minimal signs of sacroileitis – tiny areas of erosion and sclerosis without joint fissure width change,
2. Signs of the 1 stage but in connection with join fissure contraction,
3. Defined signs of sacroileitis: moderate or pronounced sacroileitis, occurring by erosions, prominent sclerosis, expansion, contraction or partial ankylosis of the joint fissure,
4. Complete ankylosis.

Inflammatory process degree of activity:

1. minimal – tiny stiffness and spinal pains in the morning, ESR – to 20 mm per hour, CRP – more than 6 g/l;

2. moderate – constant spinal and joints pain, morning stiffness for some hours, ESR – to 40 mm/h, CRP – more than 12 g/l;

3. pronounced – strong constant pains, stiffness for the whole day, subfebrile temperature, visceral manifestations, ESR – more than 40 mm/h, CRP - more than 12 g/l.

Degree of functional joints deficiency (FJD):

1. change of physiological spine flexures with the limitation of spine and joints mobility;

2. sufficient limitation of spine and joints mobility which causes the patient to change the profession;

3. ankylosis of all spine and joints regions, causing absolute loss of employability;

AS forms:

1. - central – only spine is affected

а) kyphosis of the spine thoracic region, hyperlordosis of the neck region (kyphosis look),

б) absence of lumbar region lordosis, back looks like a board (rigid look);

2. - rhysomielitic – besides spine root (shoulder and hip) joints are affected;

3. – periphery – periphery joints (knee and ankle) and spine are affected;

4. – Scandinavian – wrist and feet joints, spine are affected.

European Spondyloarthropathy Study Group (ESSG) classification criteria for spondyloarthritis (sensitivity of 75 %) [24].

Inflammatory spinal pain or synovitis (asymmetrical, predominantly in lower limbs), and any one of the following:

Positive family history
Psoriasis
Inflammatory bowel disease
Alternate buttock pain
Enthesopathy

ESSG criteria were created as a classification and cannot be widely used in clinical practice. Their sensitivity in patients with the history of the disease less than 1 year comprises less than 70 % [25]. Alternative scheme classification was suggested by Amor et al. [26] and is considered more sensitive and specific (up to 90 %) because it takes also into account manifestations beyond the joints.

Amor classification criteria for spondyloarthropathy

Clinical symptoms or past history of:

Lumbar or dorsal pain at night, or lumbar or dorsal morning stiffness = 1

Asymmetrical oligoarthritis = 2

Buttock pain (buttock pain = 1, alternating buttock pain = 2)

Sausage-like finger or toe = 2

Heel pain = 2

Iritis = 2

Non-gonococcal urethritis or cervicitis accompanying, or within 1 month before, the onset of arthritis = 1

Acute diarrhea accompanying, or within 1 month before, the onset of arthritis = 1

Presence of history of psoriasis and/or balanitis and/or of inflammatory bowel disease (ulcerative colitis, Crohn's disease) = 2

Radiological findings

Sacroileitis (grade >2 if bilateral, grade >3 if unilateral) = 3

Genetic background

Presence of HLA-B27 and/or family history of ankylosing spondylitis, reactive arthritis, uveitis, psoriasis or chronic inflammatory bowel disease = 2

Response to therapy

Definite improvement of musculoskeletal complaints with non-steroidal anti-inflammatory drugs (NSAIDs) in less than 48h or relapse of the pain in less than 48h if NSAIDs discontinued = 2

A patient is considered as having a spondyloarthropathy if the sum of the scores is 6 or more.

CLINICAL PICTURE

In 75 % of cases AS begins with sacral and spine pains, in 20 % - with pains in periphery joints, in 5 % - with eyes affection (iritis, iridocyclitis). In most cases A begins imperceptibly withc lumbar-sacral and/or neck regions of the spine affection. The beginning often coincides with hypothermia or acute virus infection.

Several variants of AS beginning are defined:

- AS starts from constant appearance of typical pains of inflammatory character in the region of sacro-iliac junctioning under initial localization of the process, pains can become stronger and combine with pains in junctions;

- only subacute monoolygoarthritis often asymmetric and unstable can be observed under initial junctions affection (often in youth) in debut phenomena of sacroileitis join later;

- the beginning with migrating pains sometimes with tiny swelling in periphery joints is possible in children and adults which

is necessary to differentiate with acute rheumatic fever;

- seldom AS begins with acute fever syndrome, arthritis join only in 2-3 weeks;

- the beginning is possible from eyes affection (iritis, iridocyclitis) or from, aothitis or carditis (seldom) in connection with high indices of inflammatory process activity, in this case joint syndrome and symptoms of sacroileitis appear only in some months.

Early features of spine affection are pains irradiating into inguinal area which can disturb either under physical loading or weather change or appear under lasting stay in one stable position at rest. Sometimes pains in the heal bone, ligaments are marked, migrating pains in various (shoulder, knee) junctions, often on the background of subfebrile temperature.

Some patients mention morning stiffness of the spine which disappears during the day. Weakness, loss of body mass, raised fatigue and appetite lowering can disturb. The disease is diagnosed in some years after the beginning because of tiny complaints.

At the beginning of the disease abnormalities from physical norms are not marked in the condition of intact periphery joints under the patient examination the walk can be gentle in condition of strong pains. Painfulness of sacroilial, sternocleidal, sternocostal junctionings in the places of tendon attachments can appear under palpation.

Kushlevsky symptoms testify about sacroiliac junctions affection. In this purpose the patient is put down on the back, one leg is asked to be maximally withdrawn aside and bent in knee junction and put the heel on the forward area of the knee junction of the other leg which is not bent. Pains appear under the pressure of one hand on the bent knee junction and another hand – on the ridge of iliac bone from the opposite side on the side of withdrawn leg.

Under involvement of thoracic section of spine into pathological process intercostals neuralgia begins to disturb with circular pains in ribcage which become stronger in breath and cough. Pains can irradiate into stomach region, kidneys and heart.

In the later stage of AS all regions of the spine are involved into pathological process. Pain syndrome becomes less prominent but constant especially under physical loading. Lasting rest is worsening the AS symptoms which are the main difference from other arthritis the symptoms of which weaken at rest.

The ability to work sharply decreases, dyspnea is disturbing especially after meals because of breathing excursion decrease of the chest as a result of inflammatory process and further costovertebral junctions ankylosis.

Typical posture changes pay attention at later stages of the disease. Kyphosis or kyphoscoleosis of thoracal region, hyperlordosis of the neck region of the spine, smoothness of lumbar lordosis are detected. The patient moves with the legs set wide apart and shaking his head because of the pronounced atrophy of the back muscles. A «supplicant pose» is typical for AS under which the body is fixed in the bending position and the head is lowered.

Zatsepin samples (pressing on X, XI, XII ribs to vertebras places of fixation causes pain) and Verschakovsky samples (pressing by the кистью into the space between lower ribs and iliac ridge bone causes resistance of stomach muscles and back because of inflammation in intervertebral joints) are directed to the objectivities of pain syndrome. When neck section of the spine is involved into pathological process pain and activity limitation disturb while head turning and cause neck fixation in the bending forward position. In this case the head is immersed and the chin touches the chest.

Neck section of the spine is estimated according to the ability of the patient to press the chin to the chest (normally there is no distance between them) and prominence of neck kyphosis like the distance between the wall and the occipit when the patient is standing tightly pressed to the wall.

While AS progressing limitation of the thoracic wall excursion with the decrease of life capacity of lungs is marked. Maximal breathing excursion of the thoracic wall in intervertebral space on the chest circumference change becomes less than 5 sm the breathing range – less than 2,5 sm.

The thoracic section of the spin mobility is estimated according to Otte symptom. In this purpose two points are marked in the patient in vertical position of the body: first on the level of VII neck vertebra and the second - 30 sm lower. Then the distance change between the points under maximal body bending is measured. In healthy people it

increases up to 34–35 sm, while in patients with AS it sharply decreases or remains stable.

Estimation of the lumbar section of spine function was done with the use of Schober symptom. Two points are marked in the patient in vertical position of the body – over V spinous process, lumbar vertebra and 10 sm higher. While bending in healthy people the distance between the points grows in 4–5 sm and changes insufficiently in the patients.

Spine and junctions can be affected in various sequences. Hip and knee junctions are affected more often. The hardest affection is chronic coccsitis with the following ankylosis which causes disability.

The number of affected junctions in one patient can change with mobility limitation in one and ankylosis in other junctions.

In women AS has some peculiarities, it usually starts imperceptibly and develops slowly with improminent pains in junctions. Inflammation of ileo-sacral junctionings demonstrates tiny painfulness in sacrum area under palpation. Prominent deformation of the spine is absent on roentgenograms. Its function preserves for a long time. In AS other organs and systems can be involved into the process.

Very often affection of vegetative nervous system can be observed in the patients, which is manifested by the appearance of skin paleness and high sweating. Patients are nervous, emotionally labile, subjected to depression. Affection of periphery nerves most often is manifested in the way of secondary radiculitis – neck, chest or lumbar. Subluxation of atlant-axial joint can meet in destruction of transverse atlant ligament. Fracture of neck vertebra after a tiny trauma with paralysis development can appear as a result of pronounced osteoporosis of neck section of the spine. The syndrome of "horse tail" can be met more seldom as a result of spine hard envelope affection which leads to the affection of hip organs functions.

Mialgias, muscular contractures and further muscular atrophies occur from the part of muscular system.

Inflammation of upward aorta section is often found in AS which leads to dilatation and aorta valve insufficiency. Violation of conductance can occur up to absolute transversal heart blockade.

Lungs are seldom affected in AS.

Affection of kidneys is manifested by amyloidosis, developing under high inflammatory process activity with hard progressive course of the disease. Kidneys amyloidosis leads to hard kidneys insufficiency and uremia.

Eyes affection in AS results in iritis, uveitis, episcleritis, iridocyclitis. Eyes symptoms are manifested in about 2 -11 % of the patients some years before the beginning of pathological process development in spine and joints.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis in later stages of AS is not difficult at all, but early diagnostics is difficult because of poor clinical picture and often atypical or asymptomatic course. Identification of pains under loading on sacral-iliac junctions is of great importance. Such rear symptoms as arthralgia or arthritis in sternoclavicular and sternocostal junctions, iritis, pain in heels, muscles tension in lumbar section, smoothness of lumbar lordosis, feeling of difficulty in bending in lumbar section are very important.

Radicular pains, posture affection («supplicant pose» or «straight disk-shaped back»), arthritis of hip (or) knee joints, tension of back muscles («bowstring» symptom) or their atrophy, limitation of chest mobility in deep breathing are recently detected. Bilateral ankylosis of sacroiliac junction and intervertebral joints, syndesmophytis of spine are detected roentgenologically.

Diagnostical criteria are used in diagnosis detection [27].

Modified New York Criteria for AS (1984) [28].

Clinical criteria:

Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest;

Limitation of motion of the lumbar spine in both the sagittal and frontal planes;

Limitation of chest expansion relative to normal values correlated for age and sex;

Radiological criterion

Sacroileitis grade $\geq$ 2 bilaterally or grade 3–4 unilaterally.

Definite AS is present if the radiological criterion is associated with at least one clinical criterion.

The Assessment of Spondylo-Arthritis International Society (ASAS) worked out the

criteria for axial spondyloarthropaties in patients with or without roentgenological signs of sacroileitis (fig. 1) [29]. The given diagnostical criteria were based on the analyses of 649 patients data with chronic pain in spine in the history of disease (not less than 3 months), which debuted before 45 years old under presence of periphery symptoms or without them. As well as on the basis of the analysis of 226 patients data without pain in spine but with periphery manifestations of the disease (arthritis, enthesitis), appeared at the age of 45 new criteria were worked out for periphery spondiloartritis (fig. 2) [30, 31, 32].

IN PATIENTS WITH ≥ 3 MONTHS BACK PAIN AND AGE ≤ 45 YEARS

acroilsiitis on imaging[a] plus ≥1 SpA feature[b]	HLA-B27 plus ≥2 other SpA features

a sacroiliitis on imaging ✓ active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA ✓ definite radiographic sacroiliitis according to modified New York criteria	**b** SpA features IBP arthritis enthesitis (heel) uveitis dactylitis psoriasis Crohn's / colitis good response to NSAIDs family history for SpA HLA-B27 elevated CRP

IBD –inflammatory bowel disease, SpA –spondyloarthritis,
CRP –C-reactive protein, IBP –inflammatory back pain,
MRI – magnetic resonance imaging, NSAID – nonsteroidal anti-inflammatory drug

Fig. 1. ASAS classification criteria for axial spondyloarthritis

ARTHRITIS OR ENTHESITIS OR DACTYLITISPLUS

PLUS

≥1 SpA feature ✓ uveitis ✓ psoriasis ✓ Crohn's / colitis ✓ preceding infection ✓ HLA-B27 ✓ sacroiliitis on imaging	**OR**	≥2 other SpA features ✓ arthritis ✓ enthesitis ✓ dactylitis ✓ IBP (ever) ✓ positive family history for SpA

SpA –spondyloarthritis, IBP –inflammatory back pain

Fig. 2. ASAS classification criteria for peripheral spondyloarthritis

Besides olygoarthritis monoarthritis was included as well as genetic marker HLA–B27 for sensitivity diagnostic criteria. «Abaissment» of the patients with disease debut in 45 years of age and absence of clearness in the question of the participation

level of axial skeleton affection in patients with periphery form of the disease and vice versa can be carried to innovation failures. Modification of the given criteria particularly isolation of axial and periphery spondyloarthropaties is important for the given pathology diagnostics [33].

Laboratory diagnostics

In general blood analysis the increase of ESR can be revealed in 50-60 % of the patients. Level of CRP is more sensitive and specific marker of the process activity and increases in 75 % cases.

In 15 % of patients moderate normocytar normochrome anemia and increase of lysosomal enzymes increase are found (alkaline phosphatase, acid protease).

Antinuclear factor and rheumatoid factor in AS are negative.

HLA-B27 carrying is correlated with more severe AS course.

Instrumental and functional diagnostics

On suspicion on AS it is necessary to de roentgenological examination. Roughness or fuzziness of joint surfaces can be referred to initial changes in sacroiliac junctions. Pseudoexpansion of joint space can be observed due to subchondral osteoporosis. Further it becomes narrower and at the final stage this process is finished by partial or absolute sclerosis of sacroiliac junctions.

There are three roentgenological stages of sacroileitis [34]:

I – expansion of sacroiliac joint fissure junctions due to osteoporosis, focal subcartilage osteosclerosis along the joint fissure;

II – contraction and fuzziness of joint fissure, its usuration (subcartilage osteosclerosis and partial ankylosis);

III – complete bone ankylosis of sacroiliac junctions.

In the initial stages of AS erosions in upper and lower forward longitudinal corners of vertebra bodies are revealed, further – ossification of the forward longitudinal junction (symptom of «vertebra quadrization»). Spine typical changes like «bamboo rod» determine bone bridges between the vertebra.

Signs of enthesopaties with destruction centers in the places of junctions attachment to processus spinosus, kneepans, collar bones and heel bones, ischiatic tubers, trochanter of femoral bones can be observed.

MRT has diagnostic and prognosis importance for spondyloarthropaties especially for «axial» affection [35, 36].

Scyntigraphy with technetium pyrophosphates shows the increase of its accumulation just in the initial sacroileitis which can be observed in other diseases (rheumatoid arthritis, spondylosis of lumbar and sacral section of the spine, metabolism disease).

AS level of activity is estimated with the use of summary Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [37], which consists of fatigue estimation, axial pain, periphery pain, stiffness and entesopaties according to VAS (0 – 100 mm). the index allows to estimate the AS level of activity in average meaning of the sum of 5 clinical signs: pain in spine, pain in joints, duration and prominence of stiffness in spine (average meaning), fatigue and level of uncomfortable feelings, appearing in touching to any painful sections. The index volume varies from 1 to 100. Activity is considered high under BASDAI >40.

BASFI (Bath Ankylosing Spondylitis Functional Index) [38] is used for prominence of functional affections in AS estimation. It includes 10 points, allowing to estimate the patient's ability to fulfill everyday activity. Every point is presented in the way of VAS (0 – 100 mm). It is calculated as an average sum of 10 indices from 1 to 100. Functional affections are considered prominent under BASFI index > 40.

Differential diagnoses of AS is done with such diseases as spondilosis, rheumatoid arthritis, Forestier hyperstosis and other seronegative arthropaties.

Difficulties if differential diagnostics appear in early stages of AS when there is no clear clinical picture and typical roentgenological signs are absent. First of all it is concerned AS differentiation with spondylosis (dystrophic affection of spine) which develops preferably after 30-40 years of age. Pains in AS become stronger at rest or in long term keeping of one position especially in the second part of night. In spondylosis, on the contrary, they appear or become stronger after physical loading at the end of working day. In spondylosis in comparison with AS the movement

limitation occurs on the top of pain and radiculitis development, and is the pain is removed spin mobility restores. Roentgenological research in dystrophic process can reveal typical changes more often in thoracal section of spine while in AS early changes are found in sacroiliac junctions. Besides in AS signs of inflammatory process are found in blood in AS which are absent in spondylosis.

Spine affection is often preceded by periphery joints affection that is why it is necessary to differ early stage of AS from rheumatoid arthritis. Presence of morning stiffness in joints, their symmetric affection (preferably hands), stable joints changes with fast development of muscular atrophy, contractures, rheumatoid nuts, rheumatoid blood factor, early roentgenological changes are typical for the last one which is more often met in women.

Signs of inflammatory activity and sacroileitis are absent in Forestiye hyperostosis (ossification of junctions of spine in elderly people).

Symmetry of sacroileitis and spreading of pathological process on all spine sections are typical for AS in comparison with other arthropaties.

TREATMENT

Main principles of AS treatment assume prompt beginning with maximally possible preservation and rehabilitation of spine and junctions function.

Way of life modification

It is necessary to flatly refuse smoking.

Moderate tempering procedures are useful.

The bed of the patient must be hard. Pillow and under neck cushion must be removed (for neck lordosis not to develop). Later thin pillow is possible.

Emotional comfort, sufficient sleeping in comfortable position, sanitation of chronical infections centers are indicated.

Diets

Food ration must be balanced and compensate organism losses. Weight should be controlled because its raising can increase the loading on spine and junctions of lower limbs. Sufficient use of protein food is obligatory, preference is given to dishes from fish, milk products.

Medical treatment

Basic therapy of AS is directed on prophylaxis of structural changes progressing or existing lowering of their development rates.

Sulfasalazine is widely used as a basic preparation in daily doze 2-3 g for not less than 3-4 months [39, 40]. Methotrexate is also used, though its positive effect is typical only for a small number of patients [41, 42]. The preparations demonstrate higher efficacy on periphery arthritis symptomacy and lower – on inflammatory process in spine that is why they are preferable to be used in periphery or rhysomelic form of AS, preferably under short remoteness of the disease.

Bisphosphonates (pamidronate), having anti-inflammatory potential and being inhibitors of osteoclast-indirect resorbtion of the bone are used lately in basis therapy of AS. Treatment by bisphosphonates leads to inflammation decay and improvement of joints and spine function (according to BASDAI and BASFI indices) [43, 44].

Inhibitors ФНО-α are lately used in AS treatment, allowing to get sufficient and stable effect with high AS activity, if traditional preparations are ineffective [45].

Inhibitors of timorous necrosis factor alpha (ITN–a) are an additional means to methotrexate – infliximab [46, 47], etanercept [48, 49] adalymumab [50, 51], holymumab [52].

Symptomatic therapy of AS is directed to coping with the pain and suppression of inflammation and includes nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GK), simple analgetics and miorelaxants.

NSAIDs facilitate pain and allow keeping working ability [53]. Lowering of pain intensity promotes decrease of muscles hypervitality which form typical spine deformation together with structural changes. Preparations of changes are COX-2 NSAIDs (celexosib), due to decrease of side effect appearance risk [54, 55]. Pronounced pains in joints and spine in some patients are impossible to cope by the only NSAIDs and then they are supplemented with simple analgetics [56]. It should be mentioned that according to some data [57] in spite of high efficacy of NSAIDs in pain syndrome they do not stop further disease progress.

Local infections. GK are used in arthritis of peripheral joints and entesites. They are prescribed orally if necessary (uveitis, carditis and aortitis, fever, non stopping while receiving NSAIDs) [58]. Duration of GK receiving in these cases must be short (weeks, seldom - months). According to the study results intrajoint injections of triamcinolone acetate give good effect is sacra-iliac joints in the group of patients with NSAIDs intolerance [59, 60, 61].

System application of GK is grounded on patients with AS with multiple joints affection and system manifestations with brightly pronounced exudative phenomena, refractive to other types of medical therapy as well as in persistent coxite, long term persistence of high concentrations of acute phase proteins, maximal activity of inflammatory process for three and more further months. The doze in calculation on prednisolone must not usually exceed 10–15 mg a day. Puls-therapy leads to frequent and sufficient decrease of inflammatory process in periphery joints and in less degree – in spine. But positive effect keeps for a short period, but in three months indices of inflammatory activity reach the former level, that is why the question about its use remains controversial [62, 63].

Myorelaxants are used in prominent muscles rigidity.

Physyotherapeutical treatment envisages hydrocortisone phonophoresis on inflammatory periphery and sacroiliac junctions, lasermagnetotherapy on the region of hip junctions, ionophoresis of lithium chloride in growing concentration (from 5 % to 10 %) on spine, biodynamic and sinusoidal–dynamic currents.

Surgical treatment

It is necessary to consider the variant of operative treatment under pronounced spine deformations in the way of correcting osteotomy with the distraction of back elements of one or more vertebras and setting the spine in more beneficial position. Endoprosthesis is done in severe forms of joints affection [64].

Rehabilitation

Rehabilitation program helps to decrease pain and inflammation, improve the spine flexibility and solidity, it helps to cope with everyday activity being the prophylaxis of deformations caused by AS [65]. The patients are recommended to stand, sit and walk with maximally rectified back and avoid long term bents. Therapeutic physical training course (TPT) is necessary the change every 4-6 weeks. Regular TPT allows keeping relatively good functional state and ability to work for a long time, no matter the severity of the disease.

Aims of therapeutic physical training under AS are:

1. decrease of ankylosis progressing;
2. deformations prophylaxis;
3. treatment of existing deformations;
4. increase of muscles strengthy of the weakened group of muscles;
5. decrease of muscle spasm and pain syndrome;
6. development of correct compensation, correct functional stereotype;
7. increase of breathing ability of lungs

Sanitary treatment is indicated.

Prognosis depends on AS form, stage and timeliness of the started treatment. As for disability the prognosis is usually unfavorable as for the life it worsens in cases of internal organs deprivation, especially kidneys.

MEDICO-SOCIAL EXAMINATION

Work connected with hard and moderate physical labor, forced position of the body, frequent bending, body vibration, demanding acute and tiny actions under periphery and Scandinavian forms of the disease, with long term standing on feet, in unfavorable meteorological conditions are counterindicated to the patients with AS.

Criteria of disability groups:

In employment with qualification decrease or shortening of the work volume to the persons occupied in professions with contraindicated factors the III-rd group of disability is defined. Under pronounced limitation of viability and employment under I and II stages of the disease, quick progressing of the disease course, with frequent and prolonged exacerbations, process activity of II and III degree, joints and spinal function violation of the II and III degrees, deprivation of internal organs, accompanied by organic insufficiency the II-nd group of disability is defined. The definition of the I-st group of disability is connected with severity and irreversibility of the joints (IFS of the IV degree) and spinal

changes (III stage of the disease). More often such patients are reverted to the bed and need constant care.

PROPHYLAXIS

At the expense of the fact that genetic factors play one of the main roles in AS development there is no specific prophylaxis. Though, knowing risk factors and first symptoms of AS, it can be identified on the early stage and the treatment can be prescribed in time which can help to keep physical activity for a long time under correct way of life as well as postpone the development of degenerative changes in spine and joints.

EXAMPLES OF CLINICAL DIAGNOSIS FORMULATING

1. Ankylosing spondylitis, central form, slowly progressing course, 1 stage, I stage of activity, FJF I.
2. Ankylosing spondylitis, visceral form, aortic valve insufficiency, myocardiodystrophy H0, iridocyclitis, II stage, II stage of activity, quickly progress, FJF II.

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